Management of *Clostridioides difficile* Infection

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CLINICAL RELEVANCE *Clostridioides* (formerly *Clostridium*) *difficile* infection is among the most identified causes of health care–associated infections in US hospitals and remains a major public health problem. The incidence and severity of *C difficile* infection are high among critically ill patients. Treating critically ill patients is challenging; treatment failure is especially common because of comorbidities and the continued need for antibiotic therapy for other infections. Because of the high risk of *C difficile* infection recurrence and high mortality rate associated with the disease, intensive research has taken place over the last decade to improve patient outcomes. This research has resulted in new drugs indicated for *C difficile* infection and new information on existing drugs. The 2010 clinical practice guidelines for *C difficile* infections have been updated on the basis of this new information.
PURPOSE OF PAPER To review the 2017 update of the clinical practice guidelines from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America.
CONTENT COVERED The updated recommendations for the treatment of *C difficile* infection, the clinical pharmacology of old and new drugs for treating the infection, and the role of critical care nurses in minimizing the risk of *C difficile* infection for their patients. (*Critical Care Nurse*. 2019;39[5]:e1-e12)

*C*lostridioides **(formerly *Clostridium*) *difficile* infection (CDI) is the leading cause of health care– associated diarrhea in the United States.**[1,2] According to the Centers for Disease Control and Prevention Emerging Infections Program, a national resource for population-based surveillance of emerging infectious diseases, an estimated 453 000 cases of CDI and 29 000 deaths associated with CDI occurred in 2011.[3] For surveillance purposes, the Centers for Disease Control and Prevention classifies CDI according to the setting in which it occurs: health care facility onset; community onset, health care facility associated; and community associated.[4] Health care facility–onset CDI (HO-CDI) describes cases in which the positive stool specimen is collected more than 3 days after admission or the patient is a resident in a long-term care facility. In contrast, community-onset, health care facility–associated (CO-HCFA) CDI describes cases in which the positive stool specimen is collected either in the outpatient

setting or within 3 days after a patient is admitted to the hospital with a documented overnight stay in a health care facility in the preceding 12 weeks.[2] Community-associated CDI describes cases in which the positive stool specimen is collected in the outpatient setting or within 3 days of hospital admission; the patient has had no overnight hospitalization in the past 12 weeks.[2]

Although rates are declining in parts of Europe, CDI remains a public health concern in the United States, with annual CDI-related costs estimated at $6.3 billion.[5] Rates of community-acquired CDI and antibiotic-resistant CDI have been increasing, and *C difficile* has become the most common cause of health care–associated infection in the United States (until recently, the most common cause was methicillin-resistant *Staphylococcus aureus*).[6]

> Complications associated with CDI include colitis, toxic megacolon, and paralytic ileus.

Although hospitals have made efforts to reduce the burden of HO-CDI, its clinical and economic impacts continue to worsen. Health care resource use and costs attributable to primary CDI and recurrent CDI are substantial. In a retrospective database study, cumulative hospitalized days attributable to primary CDI and recurrent CDI over a 6-month follow-up period were 5.20 days and 1.95 days, respectively.[7] The health care costs attributable to primary CDI and recurrent CDI over the 6-month follow-up period were $24 205 and $10 580, respectively.[7]

The incidence and severity of CDI are high for patients in intensive care units across the United States.[8]

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Critically ill patients are at high risk of *C difficile* acquisition and are more likely than others to have prolonged hospitalization, risk of recurrent disease, complicated surgery, and death.[9] Signs and symptoms of CDI include diarrhea, fever, nausea, vomiting, loss of appetite, and abdominal pain. Complications associated with CDI include colitis, toxic megacolon, and paralytic ileus. Toxic megacolon results from the accumulation of *C difficile* toxins and is a life-threatening complication of CDI. Other complications include dehydration, electrolyte imbalances, bowel perforation, hypotension, renal failure, and sepsis.[1,4]

Clostridioides difficile is an anaerobic, gram-positive bacillus transmitted person to person via the fecal-oral route.[2] This pathogen can exist in either spore or vegetative form, with the spore form responsible for the transmission of *C difficile* and the vegetative form responsible for toxin production and infection. Because *C difficile* spores can survive extreme conditions, they are difficult to eliminate from contaminated surfaces. Asymptomatic carriers are thought to be a significant source of transmission.[2]

Although many ribotypes have been identified, a virulent strain of *C difficile* known as NAP1/BI/027 is a major concern. The NAP1/BI/027 strain is associated with increased severity and mortality of CDI due to fulminant colitis.[2] According to the 2015 Annual Report for the Emerging Infections Program, 133 distinct ribotypes were identified within 35 counties in 10 US states, with the virulent NAP1/BI/027 ribotype accounting for 9% of health care–associated CDI and 8% of community-acquired CDI.[10] This strain is classified by increased production of toxins A and B, the presence of binary toxin, and increased fluoroquinolone resistance.[2] Fluoroquinolone antibiotics, such as ciprofloxacin and levofloxacin, are commonly used to treat infections of the respiratory and urinary tracts and are considered the drugs of choice for prostatitis. Patients who are infected by the NAP1/BI/027 strain of *C difficile* and have other comorbid conditions requiring fluoroquinolone antibiotics are likely to experience worse outcomes.

Risk Factors

Previous hospitalization has been found to be the main risk factor for CDI.[11] Duration of hospitalization and advanced age are important risk factors for CDI because these factors are often associated with increased

severity of illness and number of comorbidities.[12,13] Additional risk factors include chemotherapy, gastrointestinal surgery, and HIV infection.[1]

Antibiotic exposure is the most important modifiable risk factor for CDI. Because of the suppression of normal intestinal flora during antibiotic therapy, which allows *C difficile* to grow, almost all antibiotic agents have been associated with CDI.[2] Specific antibiotic agents associated with higher risk are third- and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and clindamycin.[14-16] The risk of CDI is increased during antibiotic therapy and may persist for up to 3 months after antibiotic exposure.[15] Acid-suppressing medications, such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists, are commonly administered to hospitalized patients. The concomitant administration of PPIs and antibiotics has been shown to increase the risk of developing CDI, regardless of the antibiotic agent used.[17] In addition, an independent association has been observed between intensive acid-suppressing therapies and increased risk of CDI.[18]

Specific risk factors for subpopulations can predict complicated disease, recurrence, and mortality. Risk factors specifically associated with fulminant CDI, previously known as complicated CDI, include older age, leukocytosis (white blood cell count > 20 000/μL), renal failure, and comorbidities.[19] Comorbidities include chronic renal or pulmonary disease, diabetes mellitus, and inflammatory bowel disease. Risk factors for recurrence include age of 65 years or greater, antibiotic exposure following CDI treatment, PPI use following CDI treatment, *C difficile* strain ribotypes 027/078/244, exposure to fluoroquinolones, immunocompromised status, severe CDI, prior CDI episode(s), and chronic renal insufficiency.[20,21] Risk factors associated with increased mortality from CDI include advanced age, hypoalbuminemia, leukocytosis, acute renal failure, and infection with the NAP1/BI/027 strain.[19]

Diagnostic Testing

Rapid diagnosis is crucial for proper management of CDI. Nurses are critical in identifying patients with suspected CDI. To prevent unnecessary laboratory testing, only samples that meet the criteria suggested by the guidelines should be tested. The 2017 guidelines recommend diagnostic testing for CDI in patients with new,

unexplained onset of 3 or more unformed stools within 24 hours.[2] Potential causes of diarrhea include enteral tube feedings, inflammatory bowel disease, antibiotic exposure, laxatives, and chemotherapy.[1] Asymptomatic patients and patients who have received laxatives within the previous 48 hours should not be tested.[2]

Several laboratory tests are used to diagnose CDI, but because of discrepancies in test performance and limited comparability between studies, there has been controversy over which method performs best. Current laboratory methods include *C difficile* cytotoxin assay, enzyme immunoassays for toxin A and toxin B, enzyme immunoassay for the *C difficile* common antigen glutamate dehydrogenase, and nucleic acid amplification testing.[2]

The updated guidelines include new recommendations for the diagnosis of CDI. The initial step of diagnosis depends on the institution's practice regarding patient stool submissions. In institutions that submit samples for laboratory analysis according to the criteria set forth by the guidelines (patients who have 3 or more unformed stools in 24 hours and are not taking laxatives), nucleic acid amplification testing alone is satisfactory for CDI diagnosis. In institutions that do not have predetermined criteria for patient stool submission, a 2-step diagnostic process is recommended. The 2-step processes suggested by the guidelines are nucleic acid amplification testing plus toxin immunoassays or glutamate dehydrogenase plus toxin immunoassays. If the results of glutamate dehydrogenase and toxin immunoassays are discordant, the results should be arbitrated by nucleic acid amplification testing.[2]

A new formulation of vancomycin hydrochloride has become available as a powder for oral solution and can help overcome the barrier of cost.

Classifications of Disease Severity

The 2017 guidelines revised the classifications of disease severity from the previous guidelines, which classified CDI as either mild to moderate, severe, or severe and complicated.[4] The 2017 guidelines define CDI episodes as either initial or recurrent, with initial episodes further classified as nonsevere, severe, or fulminant (Table 1). The 2010 guidelines used a serum creatinine level of 1.5 times baseline in the classification of disease severity, whereas the updated guidelines use a serum creatinine

Table 1 Disease severity of initial *Clostridioides difficile* infections[2]

Classification	Clinical presentation
Nonsevere	WBC ≤15 000/μL and serum creatinine <1.5 mg/dL
Severe	WBC ≥15000/μL or serum creatinine >1.5 mg/dL
Fulminant	Hypotension/shock, ileus, or megacolon

Abbreviation: WBC, white blood cell count.

level of 1.5 mg/dL. This revision was made because baseline serum creatinine levels are not always available.

Review of Nonoperative Therapies
Metronidazole

Metronidazole is a nitroimidazole antibiotic that inhibits nucleic acid synthesis in microbial cells and exerts a bactericidal effect.[22] Because of its activity against most obligate anaerobes, including *C difficile,* metronidazole alters normal gastrointestinal flora and is associated with treatment failure and high recurrence rates.[23]

The most serious adverse reactions associated with metronidazole treatment are convulsive seizures and peripheral neuropathy.[22] Peripheral neuropathy is characterized by numbness or paresthesia of an extremity. Treatment with metronidazole should be limited to 1 course because prolonged or repeated courses have been associated with persistent peripheral neuropathy.[22] Although the overall incidence of metronidazole-associated neuropathy is unknown, one study found that the incidence was greater in patients receiving a total metronidazole dose of more than 42 g within a span of 4 weeks.[24] Metronidazole should be discontinued in patients who experience neurological symptoms, and most patients experience complete symptom resolution after discontinuation. In addition to neurotoxicity, metronidazole has been associated with nausea and an unpleasant metallic taste in the mouth.[22]

Metronidazole should be used with caution in patients receiving warfarin therapy because metronidazole may increase the serum concentrations of warfarin and other oral coumarin anticoagulants.[22] Close monitoring of the international normalized ratio is necessary in patients receiving both metronidazole and warfarin. Patients receiving metronidazole at the time of hospital discharge should be educated on the importance of avoiding alcohol during and for at least 3 days after the course of metronidazole therapy. Metronidazole inhibits aldehyde dehydrogenase and when administered with alcohol can result in accumulation of acetaldehyde in the blood. This accumulation can result in a disulfiram-like reaction, characterized by flushing, abdominal cramps, nausea, vomiting, and headaches. Metronidazole should also be avoided in patients who have been treated with disulfiram within the previous 2 weeks.[23]

Vancomycin

Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis by preventing polymerization of cell wall components, resulting in cell death.[25] When administered intravenously, it is clinically useful against a variety of gram-positive bacteria, including methicillin-susceptible and methicillin-resistant *S aureus*. Intravenous and oral/enteral vancomycin have different indications for use. Because of its poor bioavailability, oral vancomycin is not indicated for systemic infections and can be used only to treat CDI. Intravenous vancomycin is used to treat systemic gram-positive bacterial infections such as skin and soft-tissue infections, pneumonia, osteomyelitis, bacteremia, sepsis, and meningitis. Intravenous vancomycin is not indicated for the treatment of CDI.[26]

In the past, some clinicians preferred metronidazole over vancomycin for the treatment of initial CDI episodes. This was partially because of concern about promoting the colonization of vancomycin-resistant *Enterococcus* strains as well as the barrier of cost associated with branded vancomycin capsules. Although vancomycin-resistant *Enterococcus* is resistant to most antibiotics and presents a major problem in health care, oral metronidazole has also been shown to promote vancomycin-resistant *Enterococcus* colonization when used to treat mild to moderate CDI.[27] A new formulation of vancomycin hydrochloride has become available as a powder for oral solution and can help overcome the barrier of cost.[25]

Treatment with vancomycin is generally well tolerated. The most common adverse effects of oral vancomycin are nausea, abdominal pain, and hypokalemia.[25] Intravenous vancomycin has been associated with more severe adverse reactions, such as an infusion-related reaction called red man syndrome and nephrotoxicity, but these reactions do not occur with oral vancomycin.[25,26]

Table 2 Agents used to treat *Clostridioides difficile* infections[22,25,26,28,31,32]

Agent	Mechanism of action	Adverse reactions	Drug interactions (selected)	Cost of therapy (10 days)
Metronidazole	Inhibits bacterial nucleic acid synthesis	Convulsive seizures, peripheral neuropathy, nausea, headache, anorexia, vomiting, metallic taste in mouth	Warfarin Disulfiram Alcohol	Oral tablets, $7-$20
Vancomycin	Inhibits bacterial cell wall synthesis	Nausea, abdominal pain, hypokalemia	None known	Oral capsules, $1250 Solution for oral/enteral administration, $100
Fidaxomicin	Inhibits bacterial RNA polymerase	Nausea, vomiting, abdominal pain	None known	Oral capsules, $4420
Rifaximin	Inhibits bacterial RNA synthesis	Headache, peripheral edema, nausea, dizziness, fatigue, ascites, increased alanine aminotransferase level	Warfarin P-glycoprotein inhibitors such as amiodarone, verapamil, and azithromycin	Oral tablets, $2760
Bezlotoxumab	Binds to and neutralizes *Clostridioides difficile* toxin B	Nausea, pyrexia, headache	None known	$3192 (1-dose course for 70-kg patient)

Fidaxomicin

Fidaxomicin is a macrocyclic antibiotic that acts as an RNA polymerase inhibitor.[28] It was approved by the Food and Drug Administration (FDA) in 2011 for treatment of CDI. Fidaxomicin acts locally in the gastrointestinal tract, with clinical activity against *Clostridia* species only. Because of its minimal absorption, fidaxomicin can be taken with or without food. Fidaxomicin may also be crushed to form an aqueous suspension for administration via a nasogastric tube.[29] Compared with treatment with vancomycin, treatment with fidaxomicin has been associated with lower CDI recurrence rates, possibly as a result of its minimal effect on normal intestinal flora.[30] Because of fidaxomicin's high acquisition cost compared with other available agents for CDI, its use in practice is currently limited.

Treatment with fidaxomicin is generally well tolerated, with the most common adverse reactions being nausea, vomiting, abdominal pain, gastrointestinal hemorrhage, anemia, and neutropenia.[28] Acute hypersensitivity reactions, such as angioedema, dyspnea, pruritis, and rash, have been reported. Treatment with this agent should be discontinued in patients who experience a hypersensitivity reaction. No known drug interactions are currently associated with fidaxomicin.[28]

Rifaximin

Rifaximin inhibits bacterial RNA synthesis by binding to DNA-dependent bacterial RNA polymerases.[31] Rifaximin is not approved by the FDA for the treatment of CDI, but it is used off label as an adjunctive treatment following a standard course of vancomycin therapy. Its use should be considered only to treat second or subsequent recurrences; high-quality data supporting its use are limited and cost remains an issue (Table 2).[2]

Adverse effects observed with rifaximin include headaches, peripheral edema, nausea, dizziness, fatigue, ascites, and increased serum alanine aminotransferase level.[31] Prolonged used of rifaximin should be avoided because it may result in opportunistic infections. Rifaximin should be used cautiously in patients with severe hepatic impairment (Child-Pugh class C) because increased systemic exposure has been observed in these patients, although dose adjustments are not recommended.[31]

Rifaximin should be used with caution in patients receiving warfarin therapy. Through an unclear mechanism, rifaximin can decrease the anticoagulant effect of warfarin.[31] Patients receiving both warfarin and rifaximin should be monitored closely for changes in the international normalized ratio and for signs or symptoms of thrombosis. Significant dose adjustments of warfarin may be necessary, especially in patients with conditions associated with increased gastrointestinal permeability. Rifaximin should also be used in caution in patients receiving concomitant therapy with P-glycoprotein inhibitors, such as amiodarone, verapamil, and azithromycin. P-glycoprotein inhibitors significantly increase the systemic exposure of rifaximin, especially in patients with hepatic impairment.[31]

Bezlotoxumab

Bezlotoxumab was approved by the FDA in 2016 as an adjunctive therapy for patients receiving antibiotic treatment for CDI.[32] This recommendation was not included in the 2017 guidelines because of the timing of approval. Bezlotoxumab is a human immunoglobulin G1 monoclonal antibody that binds to and neutralizes *C difficile* toxin B. Toxins A and B are responsible for the toxic effects of *C difficile*. Circulating antibodies against toxin A and toxin B are thought to protect against primary and recurrent CDI. Although it does not provide protection against toxin A, bezlotoxumab has been shown to be more effective than placebo in preventing recurrent CDI and has a similar safety profile.[33] Bezlotoxumab is effective when administered at any time during treatment with antibiotics.[33]

> Metronidazole is no longer recommended for the treatment of initial nonsevere and severe CDI unless vancomycin and fidaxomicin are unavailable.

Bezlotoxumab should be administered at a dose of 10 mg/kg as an intravenous infusion over 60 minutes.[32] Other medications should not be coadministered through the same infusion catheter. The infusion solution should be at room temperature before administration.

Although bezlotoxumab is usually well tolerated, an infusion reaction including nausea, pyrexia, and headache can occur.[32] Patients with heart failure before bezlotoxumab treatment had higher mortality rates because of cardiac failure, infection, and respiratory failure.[32] Therefore, bezlotoxumab should be used in patients with heart failure only if the benefits of therapy outweigh the potential risks. These patients should be monitored for symptoms of worsening heart failure, infection, and respiratory failure. Bezlotoxumab has no currently known drug interactions.[33]

Probiotics

One effect of antibiotic therapy is the elimination of a patient's natural protective gut flora. This elimination leaves room for colonization by *C difficile*. One proposed method to combat this issue is to provide patients with probiotics alongside antibiotic therapy. Probiotics are live organisms such as bacteria or yeast that can help prevent *C difficile* colonization. By restoring the natural protective gut flora, probiotics replenish a healthy balance of gut organisms. Probiotics can directly inhibit *C difficile* growth and neutralize its toxins. Studies also indicate that probiotics modulate the gut's inflammatory response to more effectively combat CDI.[34] Despite the promise of probiotics in treating CDI, the 2017 guidelines state that there is insufficient data to recommend using probiotics for primary prevention of CDI.[2] Although evidence from probiotic clinical trials displays a trend toward CDI reduction, the quality of such evidence is limited. Limitations include a large variability in probiotic formulations studied and vast differences in probiotic treatment regimens, definitions of CDI, study follow-up durations, and patient inclusion criteria.[2] In addition, there is concern about the potential for organisms in probiotics to cause infection, especially in critically ill patients who have a central venous catheter, be immunocompromised, or have compromised intestinal integrity, increasing the risk for translocation.

Treatment Recommendations

Empiric antibiotic therapy is recommended when laboratory confirmation is expected to be delayed for longer than 48 hours or in cases of fulminant CDI. In cases of nonsevere or severe CDI, antibiotic therapy should be initiated in patients only after a confirmed CDI diagnosis. Systemic antibiotic agents should be discontinued in patients with confirmed CDI as soon as clinically appropriate because their continued use has been associated with treatment failure and CDI recurrence.[35] Treatment recommendations for *C difficile* infection in adults and recommended dosages can be found in Tables 3 and 4.

The administration of antimotility agents, such as loperamide, for symptomatic relief in patients with CDI is discouraged because of the risk of toxic megacolon, or colonic dilation.[2] Some data suggest that antimotility agents may be safe when used as adjunctive therapies along with specific antibiotic treatment for *C difficile*, but no randomized controlled trials support this recommendation.[2,36] Therefore, the use of motility agents in patients with CDI remains discouraged.

Treatment of Initial Nonsevere CDI and Initial Severe CDI

Important revisions have been made regarding the management of initial CDI episodes. Metronidazole is no longer recommended for the treatment of CDI unless

Table 3 Treatment recommendations for initial *Clostridioides difficile* infections in adults[2]

Disease severity	First-line treatment	Comments
Nonsevere	Vancomycin 125 mg by mouth/enterally 4 times daily for 10 days OR Fidaxomicin 200 mg by mouth/enterally twice daily for 10 days	Metronidazole 500 mg by mouth 3 times daily for 10 days can be considered when first-line options are unavailable.
Severe	Vancomycin 125 mg by mouth/enterally 4 times daily for 10 days OR Fidaxomicin 200 mg by mouth/enterally twice daily for 10 days	
Fulminant	Vancomycin 500 mg by mouth/enterally 4 times daily PLUS Metronidazole 500 mg intravenously every 8 hours	Consider vancomycin 500 mg in 100-500 mL normal saline every 6 hours via retention enema (30-60 minutes) in the presence of ileus.

Table 4 Treatment recommendations for recurrent *Clostridioides difficile* infections in adults[2]

Agent used for initial episode	First recurrence — Treatment recommendations	Second or subsequent recurrence — Treatment options
Metronidazole	Vancomycin 125 mg by mouth/enterally 4 times daily for 10 days	Prolonged and tapered oral/enteral vancomycin regimen OR Vancomycin 125 mg by mouth/enteral 4 times daily for 10 days, followed by rifaximin 400 mg by mouth 3 times daily for 20 days OR Fidaxomicin 200 mg by mouth/enterally twice daily for 10 days OR Fecal microbiota transplant
Vancomycin	Fidaxomicin 200 mg by mouth/enterally twice daily for 10 days OR Prolonged and tapered oral/enteral vancomycin regimen (eg, 125 mg 4 times daily for 10-14 days, twice daily for a week, once daily for 1 week, then every 2-3 days for 2-8 weeks)	

oral or enteral vancomycin and fidaxomicin are unavailable.[2] This is a major change from the 2010 guidelines, which recommended metronidazole as the preferred agent for the treatment of mild to moderate CDI.[4] This revision is a result of evidence supporting the superiority of vancomycin over metronidazole. In 2007, the first prospective, randomized, double-blind, placebo-controlled trial comparing metronidazole and vancomycin for the treatment of CDI was conducted. Patients were stratified on the basis of disease severity. The investigators concluded that the 2 agents had equally effective clinical cure rates for mild disease but found that vancomycin was superior to metronidazole for patients with severe disease.[37] This finding led to the preference for metronidazole as a

first-line agent because metronidazole was significantly more affordable. However, the study was in a single center, which is an important limitation. A later study (in 2014) involving 2 multinational randomized controlled trials found vancomycin to be superior to metronidazole for clinical success in both mild and severe disease.[38] Furthermore, a retrospective study published in 2016 found vancomycin to be superior to metronidazole for initial treatment of mild to moderate CDI in terms of rate of treatment response and recurrent episodes.[39] As a result, the guidelines now recommend metronidazole as an alternative agent for treatment of nonsevere CDI when preferred agents are not available because of cost or lack of access.[2]

The guidelines now recommend initial treatment with vancomycin or fidaxomicin for nonsevere or severe CDI because of the ability of these agents to sustain resolution of symptoms for up to 1 month.[2] Ten-day treatment courses are effective, but treatment duration can be extended to 14 days if signs and symptoms have not fully resolved.[1] Fidaxomicin was approved by the FDA in 2011 for the treatment of CDI and was not included in the 2010 guidelines. Fidaxomicin has been shown to be as safe and effective as vancomycin, with the additional benefit of sustained cure rates.[40,41] Cost remains a significant barrier to fidaxomicin therapy; as a result, its use may be reserved for patients at high risk of CDI recurrence.

Treatment of Initial Fulminant CDI

Treatment recommendations for fulminant CDI, previously known as severe and complicated CDI, include higher doses of oral/enteral vancomycin. Vancomycin therapy should be supplemented with intravenous metronidazole, especially in the presence of ileus.[2] Ileus can interfere with the ability of orally administered vancomycin to reach the colon, but intravenous metronidazole can still reach therapeutic concentrations in an inflamed colon. In an observational study of 88 critically ill patients with CDI, patients were given either oral vancomycin as monotherapy or oral vancomycin with intravenous metronidazole combination therapy.[42] The authors of the study found that the addition of intravenous metronidazole to oral vancomycin therapy was associated with significantly decreased mortality rates.[42]

Fecal microbiota transplant is the only recommendation for the treatment of recurrent CDI that is supported by high-quality evidence.

Rectal administration of vancomycin should be considered in the presence of ileus. Vancomycin 500 mg may be prepared in 100 to 500 mL of normal saline and administered as a retention enema for 30 to 60 minutes.[1,26,43] The volume of the enema may depend on the length of colon affected. Because patients with fulminant disease may require therapy delivered orally/enterally, intravenously, and rectally, careful coordination between the nursing and pharmacy departments is required to ensure that products are clearly labeled with the intended route of administration and instructions for administration.[44]

Randomized controlled trials investigating the safety and efficacy of fidaxomicin included patients with severe disease but excluded those with fulminant disease. The limited data on the use of fidaxomicin in critically ill patients suggest that the drug produces comparable responses in critically ill patients and non–critically ill patients.[45]

Early surgical management can be lifesaving for some patients. Patients who present with megacolon, colonic perforation, acute abdomen, or septic shock and associated organ failure should be evaluated for surgery. In addition, patients with a white blood cell count of 25 000/μL or greater or a lactate level of 45 mg/dL or greater should be evaluated for early surgery because these signs have been associated with high mortality.[2]

Treatment of Recurrent CDI

An estimated 20% to 30% of patients with CDI will experience a recurrent episode after initial treatment, and 50% of those patients will experience additional recurrences.[2] Guidelines suggest treating first recurrences on the basis of the agent used to treat the primary episode. If metronidazole was administered for the first infection, then a standard 10-day course of vancomycin should be given for the first recurrence. If a standard course of vancomycin was used for the first infection, then either a standard course of fidaxomicin or a tapered and pulsed vancomycin regimen should be given for the first recurrence. Tapered and pulsed dosing of vancomycin allows time for the restoration of normal flora, which may reduce recurrence rates.[2]

Second or subsequent recurrences of CDI can be the most difficult to treat. The guidelines recommend several options, including a tapered and pulsed regimen of vancomycin, a standard regimen of fidaxomicin, vancomycin followed by rifaximin, or fecal microbiota transplant.[2] Data regarding the use of fidaxomicin to treat multiple recurrent CDI episodes are limited. Standard vancomycin regimens can be followed by antibiotic treatment with rifaximin.[2] Rifaximin is not FDA approved to treat CDI, but a small randomized clinical trial showed that this regimen resulted in fewer CDI recurrences than did placebo.[35] Stronger evidence for the use of rifaximin is lacking.

The recommendation for fecal microbiota transplant is 1 of the major additions to the treatment recommendations in the 2017 update. In addition, it is the only recommendation in the guidelines for the treatment of

recurrent CDI that is supported by high-quality evidence. Fecal microbiota transplant should be considered in patients in whom antibiotic treatment has failed for at least 2 CDI recurrences.[2] The transplant of stool from a healthy donor into the intestinal tract of a patient with CDI restores normal flora and induces colonization resistance. Fecal microbiota transplant has been shown to be successful for the management of recurrent CDI regardless of the route of instillation, with the highest success rates (80%-100%) associated with instillation of feces via the colon.[2] Induction courses of oral vancomycin 3 to 4 days before fecal microbiota transplant have been given to patients not currently receiving antibiotic therapy for CDI.[46] Despite the success rate of fecal microbiota transplant, its widespread adoption is limited for many reasons, including the requirement that prescribers obtain an investigational new drug application from the FDA for each use, questions regarding the ideal donor and formulation, and the ability of the hospital and pharmacy to prepare and deliver the sample.

Patients at high risk for recurrent CDI may also benefit from the addition of bezlotoxumab as an adjunct to antibiotic therapy for CDI.[2] Bezlotoxumab was approved by the FDA in 2016 and is indicated to reduce recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at high risk for recurrence.[32]

The safety and efficacy of bezlotoxumab was evaluated in the MODIFY trial, which included adults with primary or recurrent CDI who were receiving standard-care antibiotics (metronidazole, vancomycin, or fidaxomicin, chosen by the treating physician) for 10 to 14 days. The primary end point of the trial was the proportion of participants with recurrent CDI, defined as a new episode of CDI during a 12-week follow-up period after initial clinical cure of the baseline episode. The results demonstrated that treatment with bezlotoxumab was associated with a significantly lower rate of recurrent CDI compared with placebo.[33] Although participants in the MODIFY trial were not stratified according to disease severity, analysis of prespecified subpopulations of participants showed that patients at high risk for recurrent CDI who received bezlotoxumab experienced lower rates of recurrent infection than did those who received placebo.[33] Specifically, patients with certain risk factors for recurrence (age 65 years or greater, compromised immunity, and severe CDI) were less likely to have recurrence

when treated with bezlotoxumab than when treated with placebo.[21] Although bezlotoxumab may be beneficial for the prevention of recurrent CDI, cost remains a limitation to its use in clinical practice.

Prevention

Contact Precautions

Recent evidence has shown that only a small percentage of HO-CDI cases can be linked to inpatients with symptomatic CDI, suggesting that asymptomatic carriers are a significant source of new CDI cases in hospitals.[47] Asymptomatic carriers of *C difficile* can spread spores to health care workers, fomites, the environment, and other patients. Therefore, nurses play an important role in the operational aspects of caring for patients with CDI by ensuring proper sanitary contact precautions. Precautions should begin immediately when test results for CDI are pending and should continue for 48 hours after diarrhea has resolved. If hospital CDI rates are high despite standard infection control policies, precautions should continue until discharge.[2] Ideally, patients with CDI should be placed in a private room with an assigned toilet. Patients colonized by the same strain of *C difficile* can share a room when few rooms are available. Disposable medical equipment should be used whenever possible when treating patients with CDI. Nondisposable equipment must be cleaned with a sporicidal disinfectant. All persons must wear disposable gloves and gowns upon entering the room of an infected patient and must wash their hands with soap and water upon entering and exiting. Washing the hands with soap and water is time-consuming, difficult to enforce, and not completely effective at eliminating contaminant spores. Requiring universal gloving of everyone in contact with an infectious patient may be more effective. Significant decreases in rates of CDI have been noted in hospitals implementing such gloving procedures.[47]

Hospitals with the highest CDI rates are now at risk of incurring financial penalties imposed by the Hospital-Acquired Condition Reduction Program.[48] To address the increasing burden of CDI, hospitals have implemented multiple *C difficile* interventions into a *C difficile* bundle.

> Patients at high risk for recurrent CDI may also benefit from the addition of bezlotoxumab as an adjunct to antibiotic therapy for CDI.

The optimal bundle for CDI prevention is unknown because multiple inventions are usually given simultaneously. A recent study found that daily cleaning with sporicidal disinfectant and *C difficile* screening at admission were the most effective single-intervention strategies, reducing HO-CDI rates by 68.9% and 35.7%, respectively.[6] Screening admitted patients who present with diarrhea can help identify those with community-acquired CDI. *Clostridioides difficile* screenings upon admission can mitigate outbreaks and have been associated with a definitive decline in HO-CDI rate over a 10-month period.[49] Screening all inpatient admissions can be expensive and taxing for hospital workers and patients alike. One way to alleviate this problem is to develop a focused process that screens only high-risk patients with known CDI risk factors such as prior hospital admissions and recent antibiotic use.

Proton Pump Inhibitor Restriction

Proton pump inhibitors are pharmacological agents that suppress acid secretion in the stomach and are frequently administered to hospitalized patients. Under normal conditions, the low pH of the stomach protects the gastrointestinal tract from ingested bacteria. Therefore, patients receiving PPIs are at increased risk of CDI development.[18] Although insufficient evidence supports discontinuing PPI use solely to prevent CDI, the benefits of discontinuing PPIs that are administered without an appropriate indication should be considered.[2] Therefore, the FDA has issued a safety announcement recommending using the lowest dose and shortest duration of PPI to decrease the risk of CDI.[50]

> Patients with penicillin allergies have a 26% higher risk of CDI. Up to 95% of patients who report an allergy to penicillin do not have a true hypersensitivity reaction.

Because stress ulcers are a common concern for critically ill patients, critical care nurses should be familiar with pharmacologic stress ulcer prophylaxis. Nurses should be able to identify patients at high risk for gastrointestinal bleeding. Clinical characteristics of high-risk individuals are mechanical ventilation for over 48 hours, coagulopathy, history of gastrointestinal ulceration or bleeding in the past year, and at least 2 of the following risk factors: sepsis, intensive care unit stay of more than 1 week, occult bleeding lasting 6 days or more, and use of high-dose corticosteroids. High-dose corticosteroid therapy is classified as more than 250 mg per day of hydrocortisone or its equivalent. Alternative acid-suppressing medications such as histamine-2 receptor antagonists can achieve prophylactic results against stress ulcers similar to those of PPIs, with a lower risk of CDI. Clinicians must weigh the risks and benefits of the various treatment options after identifying critically ill patients in need of stress ulcer prophylaxis.

Antibiotic Stewardship

Antibiotic use is a major risk factor for the development of CDI. Antibiotic exposure often results in clearance of the normal gut flora that offers protection against infections. Without such protection, *C difficile* can overpopulate the gastrointestinal tract and increase a patient's susceptibility to developing CDI. Because inappropriate antibiotic use increases patients' risk of developing CDI, hospitals should establish effective antibiotic stewardship programs. Antibiotic stewardship programs use multidisciplinary teams of medical professionals to eliminate unnecessary antibiotic use and decrease the frequency and duration of use of antibiotics that increase the risk of CDI. Antibiotic agents associated with increased risk of CDI include fluoroquinolones, clindamycin, carbapenems, and cephalosporins.[14-16] The Centers for Disease Control and Prevention recommends that all hospitals have an antibiotic stewardship program to address *C difficile* infections and antibiotic resistance.[51] Nurses are important members of antibiotic stewardship programs because they provide a pivotal point of communication between medical staff and patients.

Drug allergy is one subject nurses can focus communication efforts on to help decrease the occurrence of CDI. Patients with an allergy to penicillin are of particular importance because this is one of the most common drug allergies reported in the United States. Patients with penicillin allergies are prescribed alternative antibiotics that are more frequently associated with CDI. Studies have shown that a documented penicillin allergy is associated with an approximately 26% increased risk of CDI.[52] Up to 95% of patients who report an allergy to penicillin do not have a true drug hypersensitivity reaction, such as urticaria, angioedema, hypotension, or dyspnea. More common reactions include idiopathic reactions such as maculopapular rash. Obtaining a

complete history of a patient's use of β-lactam antibiotics, such as penicillins and cephalosporins, and the type, severity, and timing of reactions is paramount to determining if a true hypersensitivity exists. Patients with mild allergic penicillin reactions, such as rash, are likely able to tolerate other β-lactam antibiotics. A simple and relatively quick skin test can determine if patients have a true penicillin allergy and help determine the most effective course of antibiotic treatment. By communicating directly with their patients, nurses can identify candidates for this skin test to determine if they can tolerate treatment with β-lactam antibiotics and avoid exposure to alternative antibiotics that increase the risk of CDI.[53]

Conclusion

Clostridioides difficile infections are the leading cause of health care–associated infections and are associated with high morbidity and mortality. Critically ill patients are at increased risk of treatment failure and recurrent infection. Rapid diagnosis and treatment of CDI are especially crucial for these patients. Nurses play an important role in the management and prevention of this disease and can help reduce the morbidity and mortality associated with it. CCN

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To learn more infection control, read "Disinfection of Blood Pressure Cuffs and Electrocardiographic Telemetry Leads With 0.5% Hydrogen Peroxide Wipes" by Risteen et al in the *American Journal of Critical Care,* July 2018;27:322-327. Available at **www.ajcconline.org.**

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