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CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Clostridium difficile in the ICU

The Struggle Continues

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***Clostridium difficile* infection (CDI) management has become more daunting over the past decade because of alarming increases in CDI incidence and severity both in the hospital and in the community. This increase has concomitantly caused significant escalation of the health-care economic burden caused by CDI, and it will likely be translated to increased ICU admission and attributable mortality. Some possible causes for difficulty in management of CDI are as follows: (1) inability to predict and prevent development of severe/complicated or relapsing CDI in patients who initially present with mild symptoms; (2) lack of a method to determine who would have benefited a priori from initiating vancomycin treatment first instead of treatment with metronidazole; (3) lack of sensitive and specific CDI diagnostics; (4) changing epidemiology of CDI, including the emergence of a hypervirulent, epidemic *C difficile* strain associated with increased morbidity and mortality; (5) association of certain high-usage nonantimicrobial medications with CDI; and (6) lack of treatment regimens that leave the normal intestinal flora undisturbed while treating the primary infection. The objective of this article is to present current management and prevention guidelines for CDI based on recommendations by the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America and potential new clinical management strategies on the horizon.**
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Abbreviations: CDI = *Clostridium difficile* infection; EIA = enzyme immunoassay; IBD = inflammatory bowel disease; IVIG = IV immunoglobulin; MIC_{90} = minimal inhibitory concentration of 90%; PPI = proton pump inhibitor

Clostridium difficile is the leading cause of hospital-associated infectious diarrhea, and *C difficile* infection (CDI) is now considered a public health emergency in the United States, Canada, and Europe. According to the Centers for Disease Control and Prevention, the number of cases of CDI in patients discharged from acute-care facilities exceeded 300,000 in 2005 (from 149,000 in 2001).[1] Our own recent analysis of the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project indicated that this number has continued to rise, with 348,950 patients discharged from acute-care facilities who received the diagnosis of CDI in 2008.[2] Hospital-acquired CDI has surpassed methicillin-resistant *Staphylococcus aureus* infections in some hospitals as the leading cause of health-care-associated infection.[3] The attributable CDI mortality rate for all patients typically ranges from 5.5% to 6.9% but can be as high as 16.7% during severe outbreaks.[4-7] The burden on the US health-care system is substantial, with attributable costs ranging from $2,871 to $4,846 per case of primary CDI and from $13,655 to $18,067 for recurrent or relapsing infection.[4,8] In ICU patients, the gross cost was $11,353 for CDI compared with $6,028

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without CDI in one study.[9] A 5-year retrospective study of the Healthcare Cost and Utilization Project data found an increased association between CDI and colectomy, with or without gastric and small bowel resection, with an increase in charges of > $77,000 due to greater length of stay and an inability to prevent mortality.[10] The annual CDI economic cost for the United States has been estimated to be $1.1 to $3.2 billion per year.[4,11,12]

Risk Factors

In general, infectious causes of diarrhea in the ICU are of major concern because there is an increased likelihood of patients developing complications and because the causative agent can be transmitted between patients and health-care workers. It is essential to consider an infectious etiology in an ICU patient with diarrhea, especially if the patient has >3 bowel movements per day, blood or mucus in the stool, vomiting, severe abdominal pain, and fever. Patients are at increased risk for developing diarrhea in the hospital, and as many as 40% to 90% of ICU patients are affected.[13] However, most diarrheas are noninfectious. Approximately 80% of antibiotic-associated diarrhea is not caused by *C difficile* but may be due to carbohydrate and bile salt malabsorption or laxative usage. Rarely, antibiotic-associated diarrhea has been attributed to other pathogens such as *S aureus*, *Klebsiella oxytoca,* or *Clostridium perfringens*.[14]

Risk factors for CDI (Table 1) can be thought of as encompassing three categories, although there is some overlap among categories. The first, perturbation of the endogenous intestinal flora/mucosa or immune system by exogenous factors, can occur as a result of medications, procedures, or radiation therapy. Of hospitalized patients with CDI, it is well known that in the majority, antibiotic exposure will have occurred within the past 30 days. The most common culprits are fluoroquinolones, cephalosporins, and clindamycin, which are identified in >90% of hospitalized patients who develop CDI, although most antibiotic classes have been implicated. Disruption of normal competitive bowel flora allows overgrowth of *C difficile* and toxin production. In addition, increased CDI in some hospitals is related to the emergence of fluoroquinolone resistance in *C difficile* in patients treated with this antibiotic class. It is generally believed that the increase in Canadian *C difficile* outbreaks were due to selection of a fluoroquinolone-resistant BI/NAP1/027, the epidemic strain, in conjunction with high fluoroquinolone usage.[5,6] The outbreaks did not appear to be related to the type of quinolone.[15,16]

In addition to antibiotics, it has recently been recognized that gastric acid suppressant agents, such as proton pump inhibitors (PPIs) and H_2-receptor antagonists, are associated with increased risk of primary and recurrent CDI.[17-20] However, studies have yielded conflicting results, including no increased risk of CDI with gastric acid suppressants, increased risk with PPIs alone associated with a dose response, or increased risk with both PPIs and H_2-receptor antagonists.[21] The pathophysiologic mechanism of increased resistance of *C difficile* to gastric acid suppression is not clear. In laboratory studies, vegetative forms of *C difficile* can survive longer in the presence of oxygen in gastric contents that had been neutralized to pH >5 by acid-suppressing agents.[22] However, it is more likely that patients have ingested the acid-resistant spores of *C difficile* because the vegetative forms typically die within 15 min of exposure to ambient air. Some other explanations for increased CDI risk are that gastric acid suppression can lead to alterations in competitive flora of the upper GI tract and, subsequently, in the lower GI tract. Conversely, gastric acid suppression may be a marker for increased severity of illness or comorbidities that are associated with CDI. Regardless, as many as 50% of patients on gastric acid suppression therapy do not have an indication for it. For patients with primary or recurrent CDI, consideration should be

Table 1—*Risk Factors Associated With CDI*

Variable	Risk Factors
Perturbation of the intestinal flora/mucosa or immune system	
	Antibiotic treatment
	Fluoroquinolone-resistant BI/NAP1/027
	Proton pump inhibitors and H_2-receptor antagonists
	Chemotherapy (hematopoietic stem cell and solid organ transplants)
	Glucocorticoids
	Radiation treatment
	Intestinal stasis (medications)
	Abdominal surgery
	Nasogastric tubes and enemas
Environmental contamination	
	Length of stay in hospital or long-term care facility
	Possible: food contamination, pets, and farm animals
Host factors	
	Age >65 y
	Multiple comorbidities
	Peripartum women and children
	Inflammatory bowel disease
	HIV
	Chronic kidney disease requiring hemodialysis

CDI = *Clostridium difficile* infection.

given to discontinuation of gastric acid suppressants unless the patient's risk for GI bleeding outweighs the risk of CDI treatment failure.

Chemotherapy, immunosuppressant medications, and radiation presumably increase the risk of CDI by disrupting the normal intestinal mucosal barrier and local immunity in stem cell hematopoietic patients and solid organ transplant recipients. Increased risk of severe CDI in these populations has increased since 2000,[23-27] which might be due to frequent use of antibiotics altering the gut flora, immunosuppressives, or the occurrence of graft vs host disease, creating an inflammatory bowel disease (IBD)-like condition. Certain medications that cause intestinal stasis, such as opiates and loperamide, may increase risk of CDI, but the pathophysiology is not certain. It is advised not to administer loperamide to a patient with *C difficile* diarrhea. In addition, nasogastric tubes and enemas also are associated with increased CDI risk. Abdominal surgery is noted to increase CDI risk, and presumably this is due to perioperative antibiotic exposure, a single dose of which can lead to CDI.[28,29]

The second category of CDI risk relates to environmental exposure to *C difficile* spores. Patients become infected primarily from spores present on the hands of health-care workers (see "Infection Prevention and Control" section). Length of stay in a hospital or long-term care facility increases the risk of CDI,[30,31] probably because of an increased likelihood of being exposed to *C difficile* as the length of stay increases in addition to being a marker for patients who are sicker and are more likely to be exposed to antibiotics. CDI pressure is a risk factor for CDI.[32] CDI pressure is analogous to colonization pressure where the more patients with CDI in a given patient care area, the greater the risk that other patients will develop CDI. The intensivist also should recognize that there is an increase in community-associated CDI in patients with no recent exposure to the health-care system in Canada, England, and some regions of the United States.[33] Certain *C difficile* strains, including the epidemic BI/NAP1/027 strain, have been found in prepared foods, retail ground meat, pets, and farm animals.[15,34-36] It is not known yet to what extent these exposure sources have contributed to the increase in CDI both in the community and in hospitalized patients.

The third category includes certain host factors that are associated with increased CDI risk and is perhaps the most poorly understood. Age >65 years is well recognized as a risk for both CDI and development of severe disease. This could be due to the increased presence of multiple comorbidities in association with antibiotic usage or to immune senescence. Such patients are living longer in general and have more exposure encounters in the health-care setting, especially in the ICU. The Agency for Healthcare Research and Quality found that the top four comorbidities associated with CDI are sepsis, pneumonia, urinary tract infection, and skin infection where, not surprisingly, patients have received antibiotics.[37] In addition, hospitalized patients with 10 conditions were at increased risk for CDI compared with six conditions in patients without CDI.

Intensivists also should be aware that CDI is considered an emerging threat to the formerly thought low-risk groups of peripartum women and children. CDI can be particularly severe and has been associated with ICU admission, colectomy, and maternal and fetal death. Rouphael et al[38] found that although most of the women received antibiotics during delivery, some did not have traditional risk factors, including antibiotics and prior hospitalization. In one series of 10 peripartum women who developed severe CDI, 64% had the epidemic BI/NAP1/027 strain.[39] Thus, it is prudent to include CDI in the differential of peripartum women with diarrhea.

Patients with IBD are believed to be at increased risk for developing severe CDI because of frequent antibiotic treatment during exacerbations, use of immunosuppressive medications, and altered gut mucosal immunity.[40-43] CDI that is superimposed on an IBD exacerbation can contribute to a more fulminant course. Recognition of CDI in patients with IBD is important because treatment of IBD exacerbation, such as with glucocorticoids, may allow CDI to progress more rapidly. Patients with IBD may not develop pseudomembranes, making it more difficult to establish the diagnosis by endoscopy. In addition, patients with IBD and CDI reportedly have an increased need for colectomy.[41]

Some studies have shown that patients with HIV/AIDS or chronic kidney disease requiring hemodialysis are at increased risk of CDI.[44,45] This increased risk may be due in part to increased exposure to the health-care setting and decreased ability to mount an effective neutralizing antibody response to *C difficile* toxins.

Pathophysiology and Clinical Manifestations

C difficile primarily affects the colon where its toxins A and B disrupt the actin cytoskeleton of enterocytes, leading to opening of tight junctions, fluid release into the intestinal lumen, and cell death.[46,47] The toxins also come into contact with the submucosa where they elicit upregulation of proinflammatory mediators from the lamina propria, leading to an intense inflammatory response. This is characterized by massive neutrophilic infiltration and inflammatory debris.[48] In severe CDI with pancolitis, the lamina

propria can become severely inflamed because of the systemic inflammatory response. If this severe inflammation of the colon progresses, it can lead to inflammatory dysregulation and severe sepsis complicated by fulminant colitis and death. In the gnotobiotic piglet infection model, severe disease and toxemia was associated with elevated levels of IL-8, a neutrophil chemokine.[49] Toxin B also causes cardiotoxicity in the embryonic zebrafish model.[50] These animal studies suggest that complications of severe CDI such as multiple organ dysfunction, abdominal compartment syndrome, and ARDS might be due to toxemia and abnormal modulation of the inflammatory response.[51-53]

Symptoms of CDI range from a mild self-limited diarrhea to life-threatening colitis. CDI should be suspected in patients with recent health-care exposure and aged > 2 years with unexplained diarrhea or if ileus is present. Common symptoms of CDI include a watery, distinctive-smelling diarrhea (horse barn-like odor), nausea, and mild abdominal pain or cramping. About 30% of patients with CDI are febrile, and 50% have a leukocytosis.

A WBC count > 20,000/μL may herald a patient at risk for rapid progression to fulminant colitis with the systemic inflammatory response syndrome and shock. It is important to recognize that presentation of fulminant CDI colitis may be atypical, especially if the patient is immunosuppressed or elderly, and may not be necessarily associated with antibiotic usage.[54] Pseudomembranous colitis and toxic megacolon are pathognomonic of severe CDI, especially in the absence of IBD. However, pseudomembranes are present in only 50% of patients with *C difficile* colitis.

Fulminant disease is a dreaded complication of CDI, occurring in 3% to 5% of patients with *C difficile* colitis, and colectomy in this group can be life saving.[55] Unfortunately, hospital mortality in this group of patients ranges from 34.7% to 57%.[55-59] Although diarrhea is the hallmark for symptomatic CDI, severe abdominal pain and lack of diarrhea could indicate that the patient has ileus with toxic megacolon. High mortality in fulminant colitis is largely due to lack of timely recognition, which in turn could be due to the lack of a good prediction tool for who will progress to fulminant colitis. The inflammatory process in fulminant colitis is usually too far progressed for good outcome after the initiation of vasopressors.[58] It is for this reason that the intensivist and surgeon should jointly evaluate and manage patients with CDI in order to identify fulminant disease in a timely manner so that colectomy and its timing can be optimized. Table 2 provides indications for colectomy in patients with more fulminant forms of CDI.

A rare manifestation of CDI is small bowel enteritis. Backwash ileitis can occur in patients with cecal involvement, but isolated small bowel disease is exceedingly uncommon. When it does occur, it typically presents in patients with a prior colectomy for reasons unrelated to CDI.[60-62] It is possible that these patients develop colonic metaplasia with expression of receptors not normally found on enterocytes through which *C difficile* toxins can gain entry into the cell. The cases of small bowel enteritis reported are generally fulminant with high mortality, possibly because of lack of recognition of CDI in patients without a colon and resultant treatment delays (60%-83%).[62]

Table 2—*Indications for Surgery/Colectomy in CDI*

	Indication
Immediate surgery/colectomy	
	Bowel perforation
	Fulminant colitis
	Refractory shock
	Peritonitis with impending perforation
Surgery after 12-24 h of medical therapy	
	Lack of clinical improvement
	Development of toxic megacolon (> 6 cm)
	Severe colitis in older adults (age > 65 y)
	Coexisting inflammatory bowel disease
	Progressive organ dysfunction

During calculation for surgery, appropriate antimicrobial treatment (see Table 3) and hemodynamic resuscitation should occur. See Table 1 legend for expansion of abbreviation.

There are no validated methods to identify patients at risk for poor outcomes due to CDI, but some factors include advanced age, acute renal insufficiency, WBC count > 20,000/μL, immunosuppression, hypoalbuminemia, and at least one organ system failure.[56,57] Independent predictors of mortality for fulminant *C difficile* colitis in one study were age > 70 years; WBC count > 35,000/μL, < 4,000/μL, or bandemia > 10%; and cardiorespiratory failure (intubation or vasopressors).[58] An active area of research is whether certain biomarkers of the inflammatory response can predict severe disease or death in CDI. Candidate biomarkers, such as fecal IL-8 (a neutrophil chemokine) and mitogen-activated protein kinase 2 (a stimulator of IL-8), are reported to be significantly associated with CDI.[63,64] Because some studies indicate that patients with severe CDI are more likely to respond to oral vancomycin treatment compared with metronidazole, it would be beneficial to be able to predict a priori who should preferentially be started on vancomycin or IV immunoglobulin (IVIG) (see "Treatment" section) by using biomarkers to predict disease progression.[65]

A particularly troublesome manifestation of CDI is relapsing or recurrent infection, which occurs in

up to 30% of patients who were treated successfully initially, regardless of whether the initial antibiotic choice was vancomycin or metronidazole.[66] Relapsing infection can occur as soon as 3 days after treatment cessation or as long as 2 months later. This could be due to reinfection with the same endogenous strain or from a different strain acquired exogenously. Patients with a prior episode of recurrent CDI have a 50% to 65% chance of repeated episodes. A meta-analysis found reexposure to antimicrobials, gastric acid suppression, and older age to be associated with an increase risk of recurrent CDI.[67]

Most patients who acquire toxigenic *C difficile* remain asymptomatic. It is unclear whether these patients have developed a neutralizing antibody response to the toxin or whether natural gut substances, such as defensins, play a role in protection.[68] As many as 20% of hospitalized patients are carriers, and the carriage rate may reach 50% in long-term care facilities.[69-71] Of note, studies prior to the changes in CDI epidemiology found asymptomatic carriage to be protective against the development of CDI.[67] Whether this has changed is unknown.

Laboratory Diagnosis

There are a variety of methods to detect the presence of toxigenic *C difficile* in stool, all with advantages and limitations (Table 4). These include toxin enzyme immunoassays (EIAs), cytotoxicity cell assay, nucleic acid amplification tests, glutamate dehydrogenase EIAs, and toxigenic culture. It is important to note that use of these assays alone is insufficient in the diagnosis of CDI. First and foremost, a patient must have a clinical syndrome compatible with CDI, which is important because 40% to 60% of patients colonized with *C difficile* in the hospital setting are asymptomatic carriers, which can result in a positive test for *C difficile* in the absence of CDI. Unfortunately, the existing *C difficile* diagnostic literature does not include patient presentation. As a result, it is unclear how sensitive or specific these assays are for the diagnosis of CDI. We recently conducted an assay comparison that assessed the impact of including patient symptoms in the interpretation of the assay results.[72] The specificity of the more sensitive tests decreased when symptoms were included, indicating that many of the additional positive tests were from patients who were asymptomatic carriers. Two methods recommended to minimize the chance of having a false-positive test result for CDI are to not test patients who have formed stools and to not automatically repeat tests if previous tests were negative.[73] A patient with formed stools by definition does not have CDI. Automatic repeat testing increases the probability of a false-positive test because the prevalence of CDI decreases in patients with a prior negative test. Because it is not clear how the decrease in toxin EIA sensitivity to detect the presence of toxigenic *C difficile* in stool correlates with patients with CDI, clinical judgment may need to override a negative assay in patients for whom there is a high index of suspicion for CDI. Intensivists should be familiar with which test is offered in their institution and interpret the laboratory results in the context of epidemiology, clinical presentation, radiographic evidence of colitis or bowel wall thickening, toxic megacolon or perforation, and pseudomembranes by endoscopy. When clinical suspicion for CDI is high, the intensivist should initiate empirical therapy for CDI regardless of the diagnostic test results. Of note, rectal swabs have been used in studies of *C difficile* colonization in adults and infants.[74-76] It is recommended that a rectal swab also be sent for diagnostic testing if a patient does not have diarrhea because of an ileus.[73] Unfortunately, a swab specimen is not compatible with some assays, particularly EIAs and cytotoxicity cell assays.

Treatment

Supportive therapy with fluid and electrolytes repletion should be provided. In addition, it is recommended to discontinue the offending antibiotic if possible because this may reduce the risk of CDI recurrence. Recently published guidelines recommend specific anti-*C difficile* treatment based on CDI severity and recurrence[73] (Table 3). Metronidazole 500 mg po tid is used for mild or moderate CDI, and vancomycin at 125 mg po qid is recommended for severe or multiply recurrent CDI. In a prospective, randomized, blinded, placebo-controlled trial, there was no difference between metronidazole and vancomycin for clinical cure of nonsevere CDI.[65] However, vancomycin was associated with increased cure in severe disease. There was no difference for either drug in preventing recurrent CDI.[65] A caveat to treatment selection based on CDI severity is that there are no validated methods to reliably detect which patients with mild disease will progress to severe disease and thus benefit from oral vancomycin a priori. In addition, the benefit of vancomycin in severe disease is small.[70]

It is recommended to administer both IV metronidazole and a higher dose of oral vancomycin for patients with CDI who are hemodynamically unstable. There are no data to indicate that synergy exists between metronidazole and vancomycin or data to suggest that a higher dose of vancomycin is any better than the standard 125-mg dose, which achieves levels of vancomycin 500 to 1,000 times the minimal inhibitory concentration of 90% (MIC_{90}) of *C difficile* in stool. Rather, the rationale behind this recommendation

is to get therapeutic antibiotics to the colon as quickly as possible in these acutely ill patients while recognizing the possibility that metronidazole may be inferior to oral vancomycin for treatment of severe CDI. It is also recommended that a surgical consult be obtained for these patients because the patient may require a therapeutic colectomy (Table 3). Vancomycin retention enemas of 250 mg in 250 mL of normal saline qid should be considered if the patient has an ileus.

IVIG at 200 to 500 mg/kg for one to three doses has been used as well in patients with fulminant colitis. Antitoxin A/B antibodies have been detected in IVIG, so it may provide passive immunity by neutralizing *C difficile* toxins. In addition, IVIG has many antiinflammatory properties, one of which is inhibition of the proinflammatory/apoptotic cytokine tumor necrosis factor. In theory, IVIG may be beneficial by interrupting the sepsis cascade in these extremely ill patients. However, uncontrolled studies have reported conflicting results. A retrospective, propensity score-matched case-control study failed to demonstrate benefit of IVIG for severe CDI. Potential reasons no benefit was found are that time from symptom onset to administration of IVIG was not controlled for and that the dose of IVIG was relatively low.[77,78] In our experience, timing of IVIG administration is similar to timing for colectomy in that it is important to administer it before further deterioration occurs. The importance of timely administration of IVIG is further supported in a mouse model of *C difficile* toxemia.[79] Maximal benefits (ie, 100% survival) occurred when mice received IVIG at the same time as toxin injection compared with giving IVIG at later time points after toxin infusion. Survivors demonstrated decreased vascular permeability, apoptosis, and mucosal damage, suggesting that maximal benefit of IVIG in fulminant colitis may be time dependent. At this point, there is insufficient evidence for IVIG as a standard therapy, and its use should be limited to patients with fulminant disease or for salvage therapy.

Table 3—*Treatment Guidelines Based on Clinical Severity and Number of Recurrences*

Presentation	Treatment and Cautions
Initial infection with mild to moderate infection	Metronidazole 500 mg po q8h 10-14 d; multiple and prolonged courses can cause irreversible peripheral neuropathy
Severe infection without complications[a]	Vancomycin 125 mg po q6h 10-14 d
Severe infection with complications	Vancomycin 500 mg po q6h or nasogastric tube plus metronidazole 500 mg IV q8h; vancomycin 250 mg q6h per rectal retention enema for ileus Surgical consult for possible subtotal colectomy
First recurrence	Same as initial infection based on disease severity
After a second relapse within 30-90 d or if the patient significantly worsens after treatment cessation	Vancomycin taper or pulse dosing
	Taper: week 1, 125 mg po q6h; week 2, 125 mg q12h; week 3, 125 mg daily; week 4, 125 mg every other day; week 5-6, 125 mg every 3 d Pulse dosing: up to 125-500 mg po every 2-3 d for 3 weeks

[a]Complications include toxic megacolon, ileus, bowel perforation, systemic inflammatory response syndrome, or sepsis.

For patients with multiple CDI recurrence, defined as at least the third episode of CDI, the recommended treatment is tapered oral vancomycin. Vancomycin is initially administered at 125 mg po qid for 10 to 14 days and then one dose per day is removed one week at a time until the patient is taking one dose every 2 to 3 days. The rationale for this regimen is that as the doses are spaced out, the colonic flora have time to regenerate. IVIG also has been used to treat relapsing CDI. Many patients who develop recurrent CDI have a poor IgG response to *C difficile* toxins. In a small unmatched study of relapsing CDI cases, IVIG along with 500 mg vancomycin po tid was used, and a durable response was reached at 3 months in most of the patients.[79]

There are numerous adjunctive treatments for CDI in the literature, with poor quality of data to support their use. The efficacy of tigecycline has had mixed results for treatment of severe, refractory CDI, and nitazoxanide for metronidazole treatment failures.[80] Anion-exchange resins, such as cholestyramine (4 g three to four times daily) and colestipol (5 g every 12 h), have been used for recurrent CDI based on case reports and case series. These agents have been found to be inferior to vancomycin and no better than placebo for the treatment of CDI. These resins do bind vancomycin, so it is advisable to administer them at least 2 h before oral vancomycin for severe CDI if they are used. Probiotics also have not been found to be of benefit when treating an acute episode of CDI or for preventing recurrent CDI when studied in randomized trials. In addition, ICU patients may be at increased risk for infections because of probiotic organisms, especially if immunosuppressed. However, in a randomized, double-blind, placebo-controlled study in ICU patients, significant reductions in CDI and days of antibiotics occurred in patients treated with enteral *Lactobacillus rhamnosus* GG as primary prophylaxis for ventilator-associated pneumonia compared with placebo, with no adverse events.[81]

Table 4—Clostridium difficile *Diagnostic Tests: Advantages and Limitations*

Test	Advantages	Limitations	Other
GDH EIA[a]	Triage tool if for screening, inexpensive	Need confirmatory test, sensitivity varies	Nontoxigenic also positive
Toxin A/B EIA[b]	Inexpensive, rapid, relatively little expertise	Wide variation in sensitivity and specificity	Toxin A negative strains exist, so use A/B EIA
Toxin B PCR	Several hours, relatively little expertise	Expensive, not validated, may be overly sensitive	Occasional toxin B PCR positive but strain not cytotoxic[c]
Direct stool cytotoxicity[d]	High specificity	48-96 h, tissue culture facility, low sensitivity, expensive, technical expertise	
Cytotoxigenic culture[e]	Gold standard, epidemiologic studies of strain type	48-96 h, anaerobic and tissue culture facility, expensive, technical expertise	Could be mixture of toxin positive and negative strains

EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; PCR = polymerase chain reaction.
[a] GDH followed by a more sensitive test, such as PCR or cytotoxicity.
[b] EIA must include A and B.
[c] L. Bobo, MD, PhD, unpublished data.
[d] Tissue culture of stool.
[e] Anaerobic culture of stool followed by tissue culture on isolate.

Several investigational agents also show some promise. Fidaxomicin (also known as OPT-80 and PAR-101) is a new narrow-spectrum macrocyclic antibiotic that is not absorbed systemically, achieves very high levels in the stool, and has a good safety profile. It has good anti-*C difficile* activity (MIC_{90}, 0.25 μg/mL), whereas normal, competitive intestinal microflora, such as *Bacteroides* species, which may be protective against CDI, have high-level resistance (MIC_{90} > 1,024 μg/mL).[82,83] Metronidazole and vancomycin are associated with marked alteration of the commensal bowel flora and with recurrent infection once these antibiotics are stopped. In a phase 3 trial, fidaxomicin had increased efficacy for global cure of CDI by decreasing the relapse rate, and it was noninferior to oral vancomycin for initial response.[84] The results suggest that fidaxomicin may prevent repeat hospitalizations. Efficacy for preventing ICU admissions in patients with CDI who do not initially present with fulminant CDI or toxic megacolon is unknown because patients with fulminant CDI were specifically excluded from the study.

Fully humanized monoclonal antibodies to toxins A and B (Medarex/Merck CDA1+CDB1; Merck & Co, Inc; Whitehouse Station, New Jersey) have completed phase 2 study trials.[85] The recurrence rate was 7% in the monoclonal antibody group compared with 25% in the placebo group when administered in addition to standard treatment of CDI.[64] Severity of CDI and days of hospitalization were not different between the two groups; rehospitalization was significantly different in the monoclonal (9%) vs placebo (20%) group. The data suggest that this approach might prevent rehospitalization or possibly decrease admissions to the ICU.

Bacteriotherapy using fecal transplantation from healthy donors by various routes for recurrent CDI is reported to be associated with improved response or clinical cure in up to 80% in anecdotal studies.[86] This therapy is believed to work by the reintroduction of normal intestinal flora from the donor into the recipient and can produce a durable modification of colonic flora to a presumably more protective type.[87] It is debatable whether bacteriotherapy would be effective for ICU patients with severe CDI who are taking concurrent multiple antibiotics, which could kill the desirable bacteria being transferred.

Finally, colectomy should be considered for patients with fulminant or refractory disease (Table 2). Surgical intervention should occur after initial antibiotic treatment and resuscitation. The timing of surgery requires close cooperation between the intensivist and the surgeon to ensure that the patient's condition is optimized prior to surgery and that unnecessary delays do not occur that could contribute to worse clinical outcome. Most surgical series support an advantage to total colectomy with ileostomy compared with segmental colectomy.[88,89] Additionally, small bowel enteritis can occur after total colectomy, requiring antimicrobial treatment. This diagnosis should be suspected if the patient experiences a high ileostomy output postoperatively.

Infection Prevention and Control

The approaches for preventing acquisition of CDI in the hospital are to decrease patients' risk of exposure and to prevent transmission to other patients. Decreasing the risk of CDI involves antimicrobial stewardship because the first line of defense against CDI is healthy intestinal flora. By decreasing the numbers of patients taking antimicrobials and decreasing high-risk antimicrobial exposures, the number of patients at risk for CDI is decreased if *C difficile*

exposure occurs. Up to 25% of antibiotic usage is not needed, and this is true even in the ICU setting.[90]

C difficile transmission is through the fecal-oral route, and infected patients can excrete large numbers of spores that contaminate the environment. The spores are transmitted by contamination of the hands of health-care workers. Health-care worker hands are just as likely to be contaminated when leaving the room of a patient with CDI, whether the patient was touched. Strategies to interrupt transmission involve using contact precautions and environmental cleaning. Quaternary ammonium disinfectants commonly used to clean patient rooms are not sporicidal, so using sporicidal hypochlorite-based disinfectants on surfaces is recommended in outbreak settings.[71] Use of sporicidal agents to clean the environment is not routinely recommended in nonoutbreak settings because they do not appear to be associated with reductions in CDI outside of an outbreak.[91] The infection prevention and control department and the hospital epidemiologist should determine whether an outbreak or increased CDI rate is occurring.

Despite the fact that alcohol does not kill *C difficile* spores and that alcohol-based hand hygiene products are less effective than handwashing with soap and water at removing spores from the hands of volunteers, it is still not recommended to preferentially wash hands with soap and water after caring for a patient with CDI in nonoutbreak settings.[73] Seven studies have failed to demonstrate an increase in CDI with the use of alcohol-based hand hygiene products, and no studies have demonstrated a decrease with soap and water.[73] Potential explanations for these findings are that gloves are effective at preventing health-care worker hand contamination, poor adherence to hand hygiene when soap and water is the preferred method, and contamination of hands after gloves are removed by the health-care worker using the same sink as the patient. Although there are no studies that demonstrate the effectiveness of soap and water at preventing CDI, it is recommended to preferentially use soap and water for hand hygiene in outbreak settings because of the concern that alcohol-based hand hygiene products do not remove *C difficile* spores. With regard to these issues, the intensivists should be guided by their local infection prevention and control policies and procedures.

The use of a bundled approach to prevent CDI based on local surveillance data for CDI of a given institution has been shown to work.[92] The components of the bundle include the following: (1) early recognition of CDI through appropriate surveillance case-finding methods and microbiological identification, (2) implementation of contact precautions in addition to standard precautions and patient placement, (3) establishment and monitoring of adherence to environmental controls, (4) hand hygiene measures, (5) patient and family education, (6) evidence-based methods for patient treatment and management of disease, (7) antimicrobial stewardship, (8) education of healthcare workers, and (9) administrative support.[1]

Conclusions

The implications of the increases in CDI and severity of disease and the successful management of CDI mandate the combined expertise of intensivists, surgeons, infectious disease physicians, pharmacists, infection prevention and control personnel, and the laboratorian. Patients in the ICU setting frequently have multiple risk factors for CDI and may be at increased risk for adverse outcomes due to CDI. The ideal method to diagnose CDI is still not known, but testing should be limited to patients with a compatible clinical syndrome, and automatic repeat testing should be avoided. Oral vancomycin is recommended to treat patients with severe CDI per Society for Healthcare Epidemiology of America and Infectious Diseases Society of America guidelines, but there are several promising new agents being evaluated. CDI is preventable though antimicrobial stewardship and adherence to contact precautions.

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