Clostridium difficile disease: Diagnosis, pathogenesis, and treatment update

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Clostridium difficile infections are the leading cause of health care–associated infectious diarrhea, posing a significant risk for both medical and surgical patients. Because of the significant morbidity and mortality associated with C difficile infections, knowledge of the epidemiology of C difficile in combination with a high index of suspicion and susceptible patient populations (including surgical, post-colectomy, and inflammatory bowel disease patients) is warranted. C difficile infections present with a wide spectrum of disease, ranging from mild diarrhea to fulminant colitis or small bowel enteritis and recurrent C difficile infections. Early implementation of medical and operative treatment strategies for C difficile infections is imperative for optimal patient outcomes. National and international guidelines recommend early operative consultation and total abdominal colectomy with end ileostomy and preservation of rectum. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and intracolonic vancomycin administered via the efferent limb of the ileostomy should be considered as an alternative to total colectomy in selected patients. New and emerging strategies for C difficile infection treatment include monoclonal antibodies, vaccines, probiotics, biotherapeutics, and new antibiotics. A successful C difficile prevention and eradication program requires a multidisciplinary approach that includes early disease recognition, implementation of guidelines for monitoring adherence to environmental control, judicious hand hygiene, evidence-based treatment and management strategies, and a focused antibiotic stewardship program. Surgeons are an important part of the clinical team in the management of C difficile infection prevention and treatment. (Surgery 2017; j:j-j.)

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A 64-YEAR-OLD MAN developed pneumonia after emergency repair of an incarcerated inguinal hernia (small bowel incarcerated, but no intestinal resection required). He was treated with broad-spectrum intravenous antibiotics for pneumonia. He then developed increasing abdominal distention and increasing leukocytosis (maximum white blood cell count 80,000/uL) and obstipation. Abdominal radiographs confirmed evidence of intestinal ileus and abdomen/pelvis computed tomography (CT) imaging confirmed pancolitis and ascites (Fig 1). Laboratory testing confirmed Clostridium difficile, and medical management was initiated with intravenous metronidazole and enteral and rectal vancomycin. He failed to improve with medical management and required loop ileostomy with antegrade vancomycin instillation. He fully recovered and subsequently underwent closure of ileostomy without complication.

As in this patient case, C difficile infection (CDI) is a common problem in surgical patients and can present with ileus and obstipation or with diarrhea. We provide an update regarding diagnosis, epidemiology, pathogenesis, and clinical treatment in this review.1,2

EPIDEMIOLOGY

It has been conservatively estimated that CDI is responsible for over 500,000 enteric infections, the majority of which are hospital acquired.3 Over the past decade, there has been a significant increase in both the incidence and economic burden associated with CDI. Estimates of the annual economic burden ranges from $436 million to $3 billion dollars in the United States.4,5 The morbidity associated with this disease process is significant, with
more than 9% of hospital admissions for CDI resulting in death.⁸

In the United States, *C. difficile* is the most frequently reported health care–associated pathogen, and CDI rates continue to rise.⁹,¹⁰ Community-associated CDI is also increasing, and disease onset outside of the hospital setting has increased as well. Nursing home–onset CDI saw approximately 113,000 infections in the United States in 2012, representing approximately one-quarter of all US CDI cases, and was associated with a 19% recurrence rate and 8% 30-day mortality rate.¹¹

Epidemiologic data document that CDI is increasing in US surgical patients and is most prevalent after emergency operations and intestinal resection.¹² In 2006–2010, compared with the prior 5 years, the *C. difficile* colitis rate increased by 47%, and a 32% increase in the rate of colectomies for CDI was noted in the Nationwide Inpatient Sample.¹³

The spectrum of CDI ranges from mild diarrhea to toxic megacolon, fulminant colitis, colonic perforation, multiple organ failure, and ultimately death.¹⁴ Patients with severe CDI manifest a severe systemic inflammatory response, which differs significantly from mild/moderate infection.¹⁵ The majority of all-cause gastroenteritis deaths are associated with CDI.¹⁶ Infection with *C. difficile* is an independent predictor of increased intensive care unit and hospital duration of stay, total charges, and mortality rate after operative care and represents a considerable burden to both patients and hospitals.

There has also been a significant increase in morbidity and mortality related to CDI, in part related to new hypervirulent strains (*C. difficile* BI/NAP1/027 clones that produce binary toxin [*C. difficile* transferase toxin] in addition to toxins A and B), causing increased mortality and increased use of colectomy since CDI was refractory to medical management. The BI/NAP1/027 strain is characterized by high-level fluoroquinolone resistance, efficient sporulation, markedly high toxin production,¹⁷,¹⁸ and a mortality rate 3-fold higher than less virulent strains, such as the 001 or 014 ribotypes.¹⁹,²⁰ Rates of CDI caused by BI/NAP1/027 remain high in the United States, where 28.4% of 2,057 recent *C. difficile* isolates were NAP1.²¹ It is important to understand *C. difficile* epidemiology and transmission because it has a significant impact on the clinical management of CDI.²²

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**Fig 1.** CT scan of abdomen/pelvis. Scout with colonic ileus (A). Marked diffuse colonic wall thickening (B, C, and D) compatible with infectious pancolitis. Ascites, moderate to large amount (C). No pneumatosis, no free intraperitoneal gas. Patent central mesenteric vessels without portal venous gas. No intra-abdominal abscess.
The first description of a C difficile–associated disease (CDAD)-like process was recorded in a surgical patient at Johns Hopkins University in 1892. The patient was a 22-year-old woman who underwent operative care by Dr William Osler for resection of a tumor in the gastric pylorus. Early in the postoperative period, she developed severe diarrhea and died on the 15th postoperative day. The postmortem revealed a pseudomembranous “diphtheritic membrane” in the small bowel which upon cytological examination presented with the key inflammatory features of CDAD.

After the introduction of antibiotics in the late 1940s and early 1950s, case reports of pseudomembranous enterocolitis became much more numerous with Staphylococcus aureus implicated as the causative organism based on routine stool cultures. In 1974, clindamycin was linked to a series of patients who developed fulminant diarrhea while being treated for anaerobic infections. In a subsequent prospective study, 21% of patients who received clindamycin developed diarrhea with 50% of patients demonstrating pseudomembranous lesions on endoscopy. The characterization of the disease process and toxigenic nature of the pseudomembranous colitis was verified by investigators at the University of Michigan and in the United Kingdom. Eventually, several investigators were able to isolate C difficile from the stool of patients with pseudomembranous colitis.

Table I. Risk factors for initial, recurrent, severe, and BI/NAP1/027 CDI

<table>
<thead>
<tr>
<th>Initial CDI</th>
<th>Recurrent CDI</th>
<th>Severe CDI</th>
<th>BI/NAP1/027 CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic exposure</td>
<td>Any prior episodes of CDI</td>
<td>White blood cell count &gt;15,000/µL</td>
<td>Age &gt;65 years</td>
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<tr>
<td>Increased patient age</td>
<td>Additional antibiotic use</td>
<td>Serum creatinine level greater than 1.5× baseline</td>
<td>Fluoroquinolone antibiotic exposure</td>
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<tr>
<td>Prior hospitalization</td>
<td>Advanced age</td>
<td>Low serum albumin level</td>
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<tr>
<td>Severity of underlying illness</td>
<td>Prolonged or recent stay in health care facility</td>
<td>Increased C-reactive protein level</td>
<td></td>
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<tr>
<td>Proton pump inhibitors and H2 blocker use</td>
<td>High severity of Horn Index for underlying illness</td>
<td>Infection with NAP7-8-9/BK/078 and NAP1/B1/027 C difficile strains</td>
<td></td>
</tr>
<tr>
<td>Abdominal operation</td>
<td>Proton pump inhibitor use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>Infection with NAP1/B1/027 strain type</td>
<td></td>
<td></td>
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<tr>
<td>Long duration of hospitalization</td>
<td>Absence of an antitoxin A antibody response</td>
<td></td>
<td></td>
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<tr>
<td>Long-term care residency</td>
<td>Absence of an antitoxin B antibody response</td>
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<td>IBD</td>
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<tr>
<td>Organ transplantation</td>
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<td>Chemotherapy</td>
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<td>Chronic kidney disease</td>
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<td>Immunodeficiency</td>
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Adapted from Gerding et al.148

HISTORY

The first description of a C difficile-associated disease (CDAD)-like process was recorded in a surgical patient at Johns Hopkins University in 1892. The patient was a 22-year-old woman who underwent operative care by Dr William Osler for resection of a tumor in the gastric pylorus. Early in the postoperative period, she developed severe diarrhea and died on the 15th postoperative day. The postmortem revealed a pseudomembranous “diphtheritic membrane” in the small bowel which upon cytological examination presented with the key inflammatory features of CDAD.

After the introduction of antibiotics in the late 1940s and early 1950s, case reports of pseudomembranous enterocolitis became much more numerous with Staphylococcus aureus implicated as the causative organism based on routine stool cultures. In 1974, clindamycin was linked to a series of patients who developed fulminant diarrhea while being treated for anaerobic infections. In a subsequent prospective study, 21% of patients who received clindamycin developed diarrhea with 50% of patients demonstrating pseudomembranous lesions on endoscopy. The characterization of the disease process and toxigenic nature of the pseudomembranous colitis was verified by investigators at the University of Michigan and in the United Kingdom. Eventually, several investigators were able to isolate C difficile from the stool of patients with pseudomembranous colitis.

RISK FACTORS FOR CDI

Clinicians must be aware of the risk factors for CDI (Table 1), because this will assist them in having a high index of suspicion in making an early diagnosis. Antibiotic use is the most common risk factor for initial and recurrent CDI. Although all antibiotics are associated with increased CDI risk, clindamycin, fluoroquinolones, and second-generation and higher cephalosporins are associated with the highest CDI risk. Proton pump inhibitors were identified as risk factors in some studies but not confirmed in others. Other risk factors include increased age, nasogastric tube, and kidney disease.

Abdominal operations, specifically colorectal operations, are a significant CDI risk factor. A recent study examined risk factors and variation associated with the development of nosocomial CDI among patients undergoing colorectal resection in New York State from 2005–2013. Of 150,878 colorectal resection patients, 3,323 (2.2%) developed CDI. This study documented that colorectal surgery patients are at high risk for CDI. There was an approximately 5-fold difference in adjusted CDI rates across hospitals (0%-11.2% among surgeons; 0%-6.8% among hospitals), confirming significant variation unexplained by patient, surgeon, and hospital factors.

Solid-organ transplant recipients are at increased risk for hospital-onset CDI, 5-fold higher than among general medicine patients (209 vs 40 per 10,000 hospital discharges from the University...
Further efforts to detect, prevent, and manage CDI among transplant recipients are needed.

**PATHOGENESIS**

The gastrointestinal tract is a complex ecosystem exposed to a constant flow of microbial populations, many of which transit through the length of the bowel without establishing residency or causing disease. This microbial population of the gastrointestinal tract represents great genetic and ecologic diversity with an estimated 15,000 to 36,000 different species of bacteria residing within the lumen and on the mucosal surfaces.

Clostridia are a heterogeneous group of organisms that exist in both the lumen of the bowel and on the epithelial brush-border surface of the large intestines. *C. difficile* colonizes the intestinal tract in approximately 1% to 15% of healthy adults, and it has been estimated that colonization in newborns can approach 80%, but rarely does the organism cause disease in this population.

In healthy adults, the intrinsic combination of a competent (intact) normal intestinal flora and the production of antibodies to toxin A protect against *C. difficile* colonization and infection. Antitoxin IgG has been found to be more common in asymptomatic carriers than patients with active disease. It has been hypothesized that individuals who are colonized early in life most likely develop an immune memory, which has a protective effect through adulthood but wanes in the sixth or seventh decade.

**Microbial virulence.** The principal virulence factors (Table II) associated with CDAD are 2 large molecular weight cytotoxins, toxin A and toxin B, which have enterotoxicogenic and cytotoxic activity. Both toxins can cause significant colonic inflammation and disruption of the epithelial mucosal surface. These toxins are coded in the region of the genome called the pathogenicity locus (*PaLoc*).

The mechanistic action of toxin A (*TcdA*) and B (*TcdB*) most likely begins with the binding of the toxin C-terminus to one or more target receptors present on the colonic epithelial cell surface. Upon binding to the receptor, the toxins are endocytosed, where the toxins are acidified prior to translocation into the cell cytosol. Once inside the cell, a host cytoplasmic inositol hexaphosphate induces autocleavage of the toxin mediated by a *C. difficile* aspartate protease, resulting in a biologically active toxin. Upon entry into the cell, the toxins target Rho GTPases, which play a central role in a multitude of cellular processes, including organization of the actin cytoskeleton, controlling epithelial barrier function, and the signaling and motility of host immune cells.

The cumulative effect of this intoxication is the eventual loss of the intestinal barrier function. The normal tight junctions between individual epithelial cells are disrupted, allowing the migration of cells, such as neutrophils, into the intestines, which play a role in the inflammatory response that is typically seen with colitis. The loss-of-barrier function leads to increased intestinal permeability and fluid accumulation followed by diarrhea.

Two additional genes, which are not on the *PaLoc*, encode the binary toxin. Another potential virulence loci includes *slpA*, a gene that codes the S-layer proteins (adherence and inflammatory stimulation); genes that code for the extracellular matrix-binding domain; a collagen protease gene; a gene for the surface anchor protein required for covalent attachment to peptidoglycan; a pilus biosynthesis locus involved in fimbrial biosynthesis; and a cluster of genes involved in extracellular polysaccharide synthesis. The nontoxicigenic *C. difficile* strains lack the *PaLoc* gene locus.

In 2003, a severe outbreak of CDAD occurred in both the United States and Canada, which was caused by a clone that was designated as BI/NAP1/027. Studies have demonstrated that this strain (027) produces both toxins A and B faster and in large quantity (hyperproduction). These clones are also capable of producing an actin-ADP-ribosylating toxin, called binary toxin (*C. difficile* transferase toxin), which is not encoded on the *PaLoc* and contributes to CDAD by cytotoxic activity, inducing the formation of thin microtubules on the outer surface of the epithelial cell (colonicocyte), leading to increased clostridial adherence. This strain also expresses resistance to the fluoroquinolones, levofloxacin, and moxifloxacin. In many geographical areas of the United States, BI/NAP1/027 accounts for >50% all strains recovered from CDI.

An interesting finding in a recent study found that isolates recovered from relapse cases show a significantly higher germination rate compared to isolates recovered from single cases. Whether this higher germination rate has an impact on disease recurrence is unknown. Although our primary knowledge of the microbial virulence of *C. difficile* hinges on deciphering the genetic components of the *PaLoc* and its toxigenic variations, other virulence factors, such as adherence and motility, are likely to emerge as we further probe the biology of this significant health care pathogen.
GDH-positive specimens are then confirmed using a toxin EIA. From stool is strongly predictive of the absence of toxigenic culture from anaerobic culture remains the gold standard for laboratory diagnosis owing to its high sensitivity (94%–100%) and high specificity (99%). While extremely sensitive and specific, the toxigenic culture test is time consuming and laborious, taking 2 to 5 days.56

The addition of GDH as a screen increased the sensitivity for C difficile testing was a 2-step algorithm combining GDH with toxin EIA testing. The first step involves a GDH EIA to screen stool samples for GDH activity. Positive GDH EIA results are then confirmed using a toxin EIA or C difficile NAAT (Fig 2).

An additional challenge of selecting C difficile testing is an increasing requirement for public health agencies to monitor the emergence and spread of C difficile infections and to assess the effectiveness of interventions to control transmission. The 2010 Society for Healthcare Epidemiology of America (SHEA) guidelines established specimen collection requirements and recommendations for optimal C difficile testing based on existing evidence.64 The SHEA guidelines recommend that C difficile testing only be performed on diarrheal (unformed) stool, unless ileus due to CDI is suspected. The proper stool specimens should be watery and take the shape of the collection container. Although swab specimens are not considered acceptable, newer molecular probe technology is in development that will allow swab samples to be analyzed in the future. Testing of formed stools and asymptomatic patients is discouraged because a significant proportion of the hospitalized population will be colonized with C difficile.

A recent study has documented that exclusive reliance on molecular tests for CDI diagnosis without tests for toxin or host response is likely to result in overdiagnosis, overtreatment, and increased health care costs.65 When the current SHEA guidelines were published, the optimal method with sufficient evidentiary support for C difficile testing was a 2-step algorithm combining GDH with toxin EIA testing. The addition of GDH as a screen increased the sensitivity for C difficile but alone was not specific enough to sufficiently exclude nontoxigenic strains. This led to the development of the 2-step algorithm wherein GDH-positive specimens are confirmed using an assay that specifically detects toxin or the toxin genes (polymerase chain reaction [PCR]).

Nucleic acid amplification (NAAT) is the newest commercially available method for the diagnosis of CDI. Current NAATs are formatted in PCR, DNA microarray, and loop-mediated isothermal amplification methods. A result (positive or negative) is reported within 2 hours. NAAT sensitivity ranges from 84% to 96% and specificity ranges from 94% to 99% depending on the gold standard used.52,63

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Table II. Selective microbial virulence factors for Clostridium difficile

<table>
<thead>
<tr>
<th>Virulence factor</th>
<th>Target effect on host cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin A (PaLoc-TdA gene)</td>
<td>Cytotoxic loss of gastrointestinal cell barrier function</td>
</tr>
<tr>
<td>Toxin B (PaLoc-TdB gene)</td>
<td>Synergistic interaction with toxin A</td>
</tr>
<tr>
<td>Variant toxin A–/B+</td>
<td>Cardiotoxic-multiorgan failure</td>
</tr>
<tr>
<td>Binary toxin</td>
<td>Increases clostridial adherence to intestinal cell surface-fluoroquinolone resistance</td>
</tr>
<tr>
<td>S-layer protein</td>
<td>Gene encoding cell surface adherence-stimulates inflammation</td>
</tr>
<tr>
<td>S-anchor protein</td>
<td>Mediates covalent attachment to cell wall peptidoglycan</td>
</tr>
<tr>
<td>Sporulation/germination</td>
<td>Outer spore coat protein that induces inflammation</td>
</tr>
</tbody>
</table>

Adapted from Badger et al.2
reporting of *C. difficile* rates. A potential downside of public reporting is a lack of adjustment for case mix and testing methodology.66 Institutions that have implemented PCR screening for *C. difficile* have reported 2- to 3-fold increases in CDI positivity rates. If public reporting does not allow for rate adjustments based on testing methodology and population prevalence, hospitals may be disadvantaged when performing the most sensitive testing methodologies.

**RADIOLOGIC DIAGNOSTIC IMAGING**

Diagnostic imaging can assist in making an early diagnosis of CDI. Plain radiography of the abdomen can demonstrate polypoid mucosal
thickening, “thumbprinting” (wide transverse bands associated with haustral fold thickening), or gaseous distention of the colon (ileus). CT scan imaging is most commonly used to evaluate patients with CDI to determine the severity of disease. Common CT findings include wall thickening, low-attenuation mural thickening corresponding to mucosal and submucosal edema, the “accordion sign,” the “target sign” (“double halo sign”), pericolonic stranding, and ascites (Fig 3). Pneumatosis intestinalis (affecting both the small and large intestine) has also been reported in patients with CDI. Familiarity with these imaging characteristics may allow early diagnosis and treatment and prevent progression to more serious pathologic conditions.

CLINICAL PRESENTATION

Acquisition of *C difficile*, like most enteric pathogens, results in a wide spectrum of clinical manifestations including intracolonic and extracolonic. The clinical features can vary from asymptomatic presentation to fulminant colitis and peritonitis due to perforation of the colon.

Intracolonic disease manifestations. Asymptomatic carriers. Most individuals who are culture positive for toxin producing *C difficile* are asymptomatic carriers. Asymptomatic carriage is very common in hospitalized patients. Symptomatic disease is less often seen in carriers despite the observation that most *C difficile* isolates exhibit toxin production. Asymptomatic carriage can be influenced by certain clinical factors, such as recent antibiotic exposure or previous occurrence of CDAD.

*C difficile* diarrhea. This manifests as mild to moderate diarrhea, often associated with cramps and abdominal pain. Although patients will often exhibit malaise and fever, it is not a common component of disease presentation. Symptoms usually occur during or shortly after antibiotic therapy but sometimes may be delayed for several weeks. *C difficile* toxins are normally detected in stool samples even though endoscopic and
histologic features may be normal in patients with mild disease.\(^7^6\)

**C difficile colitis.** This is the most common clinical manifestation of CDI. This is generally a more serious illness, and patients present with mild to moderate abdominal pain, nausea, anorexia, and watery diarrhea. Dehydration, low-grade fever, and systemic polymorphonuclear leukocytosis may occur in selected patients. A nonspecific diffuse or patchy erythematous colitis without pseudomembranes may be seen with sigmoidoscopy.\(^7^7\)

**Pseudomembranous colitis.** Symptoms of pseudomembranous colitis are similar to *C difficile* colitis but often more severe. Diarrhea is often profuse, and patients have intense abdominal pain (left or right lower quadrants). Endoscopy will often reveal pseudomembranes that appear as raised yellow plaques, measuring about 2 to 10 mm in diameter, scattered over the colorectal mucosa. Most patients with pseudomembranous colitis have involvement of the rectosigmoid colon, and many will also have involvement of the proximal large bowel. There is often marked leukocytosis (white blood cell count >20,000), and hypoalbuminemia of 3.0 g/dL or lower may be observed in severely ill patients.\(^7^8\)

**Fulminant colitis.** Fulminant colitis (FC) is the most feared presentation of CDI and occurs in 2% to 3% of patients. FC accounts for most of the serious CDI complications, including ileus, megacolon, colonic perforation, and death.\(^7^9\) In some cases, patients presenting with benign symptoms will suddenly and rapidly progress to shock. Contributory factors associated with disease severity and patient death include age, immune status, patient comorbidities, microbial virulence factors, and perhaps antimicrobial resistance.\(^8^0\)

Patients with FC complain of severe lower quadrant or diffuse abdominal pain, distension and diarrhea, or ileus. Diarrhea is minimum in patients with ileus, since secretions accumulate in the dilated atonic colon. FC may lead to toxic megacolon. The small bowel can also exhibit dilated segments with air-fluid levels simulating intestinal obstruction or pseudo-obstruction. The high morbidity and mortality associated with FC can be mitigated by early aggressive diagnosis and therapy.

**Recurrent CDI.** Recurrent CDI manifests as reappearance of diarrhea/ileus and abdominal symptoms usually within a few weeks after completion of treatment for CDI.\(^8^1\) The pathophysiology of recurrent CDI has not been well described, but it is likely related to a persistently altered fecal flora in combination with *C difficile* sporulation and an impaired host immune response to *C difficile* and/or its toxin. Recurrent CDI develops in approximately 5% to 20% of patients treated for CDI. In older patients, acute confusion or altered mental state may be the first symptom of recurrent CDI. Other nonspecific signs of infection may include weakness and lethargy, frequent falls, anorexia, and loss of physical functional capacity.\(^5\)

**Extracolonic disease manifestations.** Extracolonic manifestation of CDI in a variety of organ systems includes small bowel infection, bacteremia, reactive arthritis, and other infectious processes (cellulitis, necrotizing fasciitis, and osteomyelitis). Small bowel CDI is often seen after a previous operation and is associated with high mortality and is also observed in patients with inflammatory bowel disease (IBD) who have undergone total colectomy.

**Impact of CDI in IBD.** Current clinical and epidemiologic findings document a significant increase in the burden of CDI in the IBD patient population over the last decade. One study reported that the rate of CDI-IBD-associated CDI as a proportion of institutional burden increased from 7% in 2005 to 16% in 2006 (\(P < .01\)). The majority of patients contracted CDI as outpatients. Antibiotic exposure in the CDI-IBD patients was found to be 61%. Univariate and multivariate analysis revealed that maintenance immunomodulation and colonic involvement were independent risk factors for CDI.\(^4\)

In a retrospective study of CDI in IBD patients over 7 years, there was a doubling of CDI in Crohn’s patients (9.5 to 22.3/1,000 admissions) and a tripling of CDI in ulcerative colitis patients (18.4 to 57.6/1,000 admissions).\(^9^2\) In a study of patients who underwent colectomy for severe ulcerative colitis, many developed high-volume ileostomy output (clostridial toxin positive), fever, leukocytosis, and ileus in the postoperative period.\(^8^3\) In data obtained from the US Healthcare Cost and Utilization Project Nationwide Inpatient Sample, hospitalized patients with concurrent CDI and IBD had a 4-fold or greater risk of mortality than patients admitted for either CDI or IBD alone. CDI-IBD patients also had longer hospital stays and a higher rate of gastrointestinal operations and endoscopic evaluations than patients with CDI alone.\(^6\)

IBD patients who acquire CDI share many of the risk factors (environmental acquisition, prior antibiotic exposure, immunosuppressive therapy, and gastric acid suppressive therapy) associated with non-IBD patient populations. An interesting
epidemiologic finding associated with CDI acquisition in IBD patients is that in the majority (>75%) of IBD patients, C. difficile acquisition occurs in the community. This is in direct contrast to many of the CDIs that are acquired within the hospital environment. The reason for this finding is unknown.

A recent study suggested that a subset of IBD patients in remission has a higher carriage rate of C. difficile than healthy individuals, and that C. difficile carriage appears unrelated to antibiotic exposure or immunosuppressive therapy. The role of immunomodulation may be a significant risk factor in IBD patients because these drugs (azathioprine, 6-mercaptopurine, methotrexate, and infliximab) have all been associated with an increase in CDI in IBD patients, with almost 50% of the patients taking 2 immunosuppressive agents for maintenance therapy.

IBD patients may develop C. difficile enteritis and C. difficile pouchitis. C. difficile small bowel enteritis is rare but associated mortality is high (60%–83%). The clinical presentation includes diarrhea followed by ileus with fluid-filled loops of small bowel and sepsis. C. difficile associated pouchitis is responsive to medical management. Potential treatment with inhibitory bile acids may be a future nonantibiotic therapy for CDI pouchitis, as the restoration of secondary bile metabolism may be the key mechanism underlying the success of fecal microbiota transplantation in treating recurrent CDI. Clinicians should have a high index of suspicion of postoperative CDI in any patient who has a history of IBD, particularly with history of CDI prior to colectomy. Most patients will respond to rapid and aggressive therapy.

**MEDICAL TREATMENT STRATEGIES**

Initial management of CDI should always be discontinuation of antimicrobial agents that may have led to CDI. Antibiotic treatment of CDI is the mainstay of therapy, and specific antibiotic treatment guideline recommendations are based on the severity of CDI disease. Although initial systematic reviews documented that no antimicrobial agent was clearly superior for the initial cure of CDI, additional analyses stratified by disease severity identified that vancomycin provided improved initial clinical and sustained cure rates in patients with severe CDI compared with metronidazole. In a study of quantitative bacterial cultures of fecal samples, vancomycin treatment consistently reduced C. difficile counts to the limit of detection, whereas metronidazole was associated with C. difficile counts 1.5 to 2 log higher at 10 days of treatment. Based on these results, vancomycin is considered first-line therapy for severe and complicated CDI (Table III).

Additional antimicrobials that have potential efficacy for CDI treatment include rifaximin, tigecycline, ramoplanin, and nitazoxanide. Small trials of these agents have been encouraging, but additional studies are warranted.

**Fidaxomicin.** Fidaxomicin is a member of a new class of antibacterials (macrocycles) and has beneficial properties, including in vitro activity 8 times greater than vancomycin against clinical C. difficile isolates, minimal systemic absorption, and limited activity against the normal gut flora. Based on data from 2 phase 3 trials (n = 1,164), clinical cure rates were similar for fidaxomicin and vancomycin, but CDI recurrence (relative risk [RR] 0.47, 95% confidence interval [CI] 0.34–0.65) was significantly lower and sustained cure rates (RR 1.75, 95% CI 1.35–2.27) were significantly higher for fidaxomicin than vancomycin. A significant limitation of fidaxomicin compared to other antibiotics for CDI is its high cost.

**Intravenous immunoglobulin.** Intravenous immunoglobulin is another potential treatment strategy for CDI. Few case reports are available, and current guidelines state the following: “Intravenous immunoglobulin may be helpful in patients with hypogammaglobulinemia (strong recommendation, low quality of evidence)”—see AJG guideline, page 488, right column.

**Monoclonal antibodies.** Antibody-based immunotherapies for CDI are emerging. Monoclonal antibodies active against toxins A and B administered by intravenous (IV) infusion were superior in reducing rates of recurrent CDI when administered with antibiotics compared to antibiotics alone (7% vs 25% recurrent CDI) in a phase 2 randomized controlled trial that enrolled 200 adult patients with CDI. The mechanism of the monoclonal antitoxin antibodies is through direct neutralization of the toxins and does not appear to involve host effector functions.

Bezlotoxumab, a fully human monoclonal immunoglobulin G1/kappa antibody that binds to and neutralizes C. difficile toxin B, was an efficacious adjunctive therapy for the prevention of recurrent CDI. Two global, phase 3, double-blind studies were conducted to evaluate bezlotoxumab, either alone or in combination with actoxumab (a fully human monoclonal antibody against C. difficile toxin A), compared to placebo for the prevention...
of recurrent CDI in patients on standard of care antibiotics for a primary or recurrent CDI. The MODIFY (monoclonal antibodies for \textit{C} \textit{difficile} therapy) I study enrolled 1,452 patients (median age 65 years) in 19 countries, and the MODIFY II study enrolled 1,203 patients (median age 67 years) in 17 countries. The studies were conducted in both hospital and outpatient settings, and the primary end point for each study was evaluated through 12 weeks after study drug administration.

In the MODIFY I study, patients receiving standard-of-care antibiotics for \textit{C} \textit{difficile} were randomized to receive a single, 1-time infusion of either bezlotoxumab (10 mg/kg) \((n = 403)\), actoxumab (10 mg/kg) \((n = 242)\), the combination of bezlotoxumab and actoxumab (10 mg/kg each) \((n = 403)\), or placebo \((n = 404)\). The actoxumab arm was stopped for efficacy and safety reasons after an interim analysis. In the MODIFY II study, patients receiving standard-of-care antibiotics for \textit{C} \textit{difficile} were randomized to receive a single, 1-time infusion of either bezlotoxumab (10 mg/kg) \((n = 407)\), bezlotoxumab and actoxumab (10 mg/kg each) \((n = 397)\), or placebo \((n = 399)\).

In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12, the primary efficacy end point, was significantly lower in the bezlotoxumab arms (17.4\%, \(P = .0003\)) and (15.7\%; \(P = .0003\)) and the combination bezlotoxumab and actoxumab arms (15.9\%, \(P < .0001\)) and

### Table III. Medical treatment recommendations for CDI based on severity of illness

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
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<tr>
<td>Mild/moderate CDI</td>
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<tr>
<td>Diagnosis of CDI</td>
<td>Metronidazole 500 mg PO TID for 10–14 days</td>
</tr>
<tr>
<td>None of the criteria in &quot;severe&quot; or &quot;complicated&quot; CDI</td>
<td>In patients with metronidazole allergy, pregnant, nursing, or on warfarin therapy: Vancomycin 125 mg PO QID for 10–14 days</td>
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<tr>
<td>Severe CDI</td>
<td>Vancomycin 125 mg PO QID for 10–14 days</td>
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<tr>
<td>WBC ≥15K</td>
<td></td>
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<tr>
<td>Cr ≥1.5×baseline</td>
<td></td>
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<tr>
<td>Age ≥65 years</td>
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<tr>
<td>ANC ≤500</td>
<td></td>
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<tr>
<td>ALB ≤2.5 g/dL</td>
<td></td>
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<tr>
<td>SOT/BMT &lt;100 days</td>
<td></td>
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<tr>
<td>Chronic GVHD (BMT)</td>
<td></td>
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<tr>
<td>Treatment of rejection in the preceding 2 months (SOT)</td>
<td></td>
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<tr>
<td>Small bowel CDI</td>
<td></td>
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<tr>
<td>Complicated CDI</td>
<td>Vancomycin 500 mg PO QID</td>
</tr>
<tr>
<td>Septic shock–sepsis with persistent hypotension, requiring vasopressors to maintain MAP ≥65 mm Hg and serum lactate level ≥2 mmol/L despite adequate fluid resuscitation</td>
<td>Metronidazole 500 mg IV every 8 hours, and Vancomycin enema 500 mg in 1,000 mL of normal saline every 8 hours (in patients with ileus, bowel obstruction or toxic megacolon).</td>
</tr>
<tr>
<td>Sepsis–life-threatening organ dysfunction caused by a dysregulated host response to infection. Suspected or documented infection and an acute increase of ≥2 SOFA points</td>
<td>Consult infectious diseases and surgery to assist in management including possible surgical intervention. Operative management strategies for CDI may include exploratory laparotomy, diverting loop ileostomy with lavage, total or subtotal abdominal colectomy with end ileostomy.</td>
</tr>
<tr>
<td>Ileus or bowel obstruction</td>
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<tr>
<td>Toxic Megacolon</td>
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<tr>
<td>Peritonitis</td>
<td></td>
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<tr>
<td>Bowel perforation</td>
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</table>

ANC, Absolute neutrophil count; ALB, albumin; BMT, bone marrow transplant; Cr, serum creatinine; GVHD, graft versus host disease; MAP, mean arterial pressure; SOFA, sequential organ failure assessment; SOT, solid organ transplant; WBC, white blood cell count.
(14.9%, \( P < .0001 \)) compared to the placebo arms (27.6%) and (25.7%), respectively. In both studies, the rate of CDI recurrence was lower in the bezlotoxumab arms compared to the placebo arms in patient subgroups known to be at high risk for CDI recurrence, including patients with any prior episodes of CDI within the previous 6 months, patients infected with the BI/NAP1/027 strain, patients with severe CDI (Zar score \( \geq 2 \)), patients 65 years of age or older, and patients with compromised immunity.

These subpopulation analyses were prespecified in the protocol for each study. Rates of serious adverse reactions and deaths assessed through 12 weeks after infusion were comparable across the treatment arms. Treatment with the combination of bezlotoxumab and actoxumab did not provide added efficacy over bezlotoxumab alone. Furthermore, actoxumab alone provided no benefit in the prevention of CDI recurrence compared with placebo.

Clinical cure of the initial CDI episode, however, was lower for both actoxumab/bezlotoxumab (74.7%; \( P = .0057 \)) and bezlotoxumab (77.5%; \( P = .0622 \)) compared with placebo (82.8%) in MODIFY I. In MODIFY II, clinical cure of the initial CDI episode was numerically lower for actoxumab/bezlotoxumab (72.3%) compared with placebo (77.8%). In contrast, clinical cure was numerically higher for bezlotoxumab (82.5%) compared with placebo. Neither of these comparisons was statistically significant (\( P = .0801 \) and \( P = .0973 \), respectively).

Based on these results, bezlotoxumab (administered IV as a single dose of 10 mg/kg over 1 hour) was recently approved by the Food and Drug Administration (FDA) for the prevention of CDI recurrence in patients aged 18 years or older who are receiving antibacterial drug treatment for CDI.\(^{107,108}\)

Vaccines. Despite numerous scientific and operational challenges, there are vaccine candidates in late-stage clinical development for CDI, and 3 \( C \) difficile vaccines have progressed to phase 2/3 clinical trials.\(^{109}\) Some observations suggest that recurrent CDI is associated with failure to develop an adequate immune response to \( C \) difficile toxins. Immunization could therefore be beneficial in high-risk patients.

A phase 3 clinical trial with an estimated primary completion date of December 2017 is evaluating a vaccine (Cdifffense) that contains toxins A and B for induction of an immune response against toxins A and B.\(^{110}\) The Cdifffense study is enrolling 2 patient cohorts: (1) those who have had at least 2 hospital stays and received systemic antibiotics in the 12 months prior to enrollment and (2) those scheduled for an inpatient hospitalization (>72 hours) for a planned operative procedure (kidney, bladder, urinary system, musculoskeletal system, respiratory system, circulatory system, central nervous system) within 60 days of enrollment. Patients will be randomized to the \( C \) difficile vaccine at days 0, 7, 30 or to normal saline placebo.

The European Union is funding a 3-year initiative to develop an oral (sublingual) \( C \) difficile vaccine; the intended strategy is to use harmless bacterial spores that carry the antigen and boost immunity by targeting the protein needed for the infection to take hold.\(^{111}\) The candidate \( C \) difficile vaccine has been well tolerated by patients. To date, no \( C \) difficile–targeted vaccine has been approved by the FDA, although an agent is currently under clinical development by Pfizer Inc (PF-06425090).\(^{112,113}\)

NEW AND EMERGING MEDICAL TREATMENT STRATEGIES

New approaches to CDI prevention and treatment are needed (Fig 4). Antibiotics under development include cadazolid and ridinilazole. Suromycin has had disappointing phase 3 results. Multiple live biotherapeutics are being developed, including freeze thawed and encapsulated versions of fecal microbiota transplantation to improve the practicality of treating patients with recurrent CDI. Alternatives to fecal microbiota transplantation that aim to improve safety, including a microbial suspension (RBX2660) and a complex spore formulation (SER-109), have progressed to phase 2 studies. A nontoxigenic \( C \) difficile strain has also shown promise to prevent recurrent CDI.\(^{114,115}\)

OPERATIVE TREATMENT STRATEGIES

Operative consultation should be considered early in the course of severe and complicated CDI (Fig 5), as operative consultation may be beneficial.\(^{116,117}\) High mortality rates have been reported with operative treatment for CDI, likely related to significant delay in operative intervention.\(^{118}\) But operative therapy for severe CDI can indeed be lifesaving. A systematic review of 510 patients with fulminant \( C \) difficile colitis reported decreased mortality comparing operative treatment with medical therapy (RR 0.70, 95% CI 0.49–0.99).\(^{119}\)

Subtotal colectomy, end ileostomy with preservation of rectum has been a standard recommended operative treatment, particularly for fulminant colitis. A systematic review of 31 studies (\( n = 1,442 \)
of patients undergoing emergency operation for CDI documented that 1.1% of all patients with CDI and 29.9% with severe CDI underwent emergency operation. The most commonly performed operation was total colectomy with end ileostomy in 89% of patients. In patients who underwent partial colectomy, reoperation to resect additional colon was required in 15.9% of patients. The 30-day mortality rate was high (41.3%), and the strongest predictors of postoperative death were preoperative intubation, acute renal failure, multiple organ failure, and shock requiring vasopressors.120

A review of the Nationwide Inpatient Sample 2001–2010 documented over 2.7 million discharges with a diagnosis of CDI in the United States over this decade, and colectomy was performed in 19,374 cases (0.7%), with an associated mortality of 30.7%. Predictors of mortality after colectomy included coagulopathy, age >60 years, acute renal failure, respiratory failure, sepsis, peripheral vascular disease, and congestive heart failure. Importantly, operative treatment more than 3 days after admission was associated with higher mortality rates.13

Similarly, a review of the American College of Surgeons National Surgical Quality Improvement Program database from 2005–2010 identified 335 open colectomies for CDI with an overall mortality rate of 33% and a median time to death of 8 days. Risk factors for postoperative mortality included age >80 years, preoperative shock, preoperative dialysis dependence, chronic obstructive pulmonary disease, thrombocytopenia, coagulopathy, and renal insufficiency.121

Recent experience with a minimally invasive, colon-preserving approach as an alternative to total colectomy has proven to be successful in select patients. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and vancomycin administered via the efferent limb of the ileostomy (n = 42) is an accepted alternative to total colectomy in the treatment of severe complicated CDI with reduced mortality (19% vs 50%) compared to a historical total colectomy cohort (n = 42) in a single-institution (University of Pittsburgh) report.122

This strategy led to colon preservation in 39/42 patients; 3 patients subsequently required total
colectomy, either for abdominal compartment syndrome or for continued sepsis. The advantage of this approach is that it can be considered early if patients are failing medical management, and it can be done laparoscopically in many patients. This approach, however, should not be considered in patients with abdominal compartment syndrome or concern for colonic ischemia, necrosis, or perforation (Fig 6).

National and international guidelines recommend total abdominal colectomy with end ileostomy and preservation of rectum. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and vancomycin administered via the efferent limb of the ileostomy should be considered as an alternative to total colectomy in selected patients (Table IV). The 2014 Eastern Association for the Surgery of Trauma practice management guidelines for operative treatment of CDAD strongly recommended that adult patients with CDI undergo early operative care, before the development of shock and need for vasopressors, and
conditionally recommended total or subtotal colectomy (versus partial colectomy or other operation) as the procedure of choice.

If the diverting loop ileostomy and colonic lavage procedure are planned, it is important to have an institutional protocol to facilitate prompt performance of this procedure because the supplies required may not be readily available in the operating room. We have created a 1-page document that allows our operating room staff to obtain all supplies needed and provides the steps of the operative intervention in a clear, concise approach to achieve success with this operative procedure (Fig 7).

**SMALL BOWEL CDI**

Small bowel involvement in CDI (enteritis) is uncommon; however, increasing case reports and series have been published, some leading to fatal outcome. Small bowel CDI is more commonly associated with abdominal operations and particularly among patients with IBD and with total abdominal colectomy. CT imaging features of CDI of the small bowel include mesenteric or
<table>
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<th>Guideline</th>
<th>Operative consultation recommended</th>
<th>Operative treatment</th>
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<tbody>
<tr>
<td>SHEA/IDSA Guidelines 2010</td>
<td>“Severely ill patient”</td>
<td>Subtotal colectomy, end ileostomy with preservation of rectum</td>
</tr>
<tr>
<td>American College of Gastroenterology (ACG) Guidelines 2013</td>
<td>Surgical consultation should be solicited in all severe-complicated CDI cases with 1 or more of the following: hemodynamic instability requiring vasopressors, clinical sepsis with organ failure, changes in mental status, extreme leukocytosis (≥50,000 cells/µL), elevated lactic acid (≥5 mmol/L), or evidence of treatment failure after 5 days of conservative therapy (strong recommendation, moderate quality evidence).</td>
<td>Subtotal colectomy, end ileostomy with preservation of rectum. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and vancomycin administered via the efferent limb of the ileostomy; alternative to total colectomy in selected patients</td>
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<tr>
<td>European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2014</td>
<td>Patients with “systemic inflammation and deteriorating clinical condition despite maximal antibiotic therapy (with) toxic megacolon, acute abdomen, and severe ileus”</td>
<td>Subtotal colectomy, end ileostomy with preservation of rectum. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and vancomycin administered via the efferent limb of the ileostomy; alternative to total colectomy in selected patients</td>
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<tr>
<td>EAST Practice Management Guidelines 2014</td>
<td>No recommendation</td>
<td>Subtotal colectomy, end ileostomy with preservation of rectum</td>
</tr>
<tr>
<td>WSES Guidelines for Management of Clostridium difficile infection in surgical patients 2015</td>
<td>18) Patients with severe CDI who progress to systemic toxicity should undergo early surgical consultation and be evaluated for potential surgical intervention (Recommendation 1 C). “patients with fulminant colitis”</td>
<td>19) Resection of the entire colon should be considered to treat patients with fulminant colitis (FC) (Recommendation 1 B). 20) Diverting loop ileostomy with colonic lavage may be a useful alternative to resection of entire colon (Recommendation 2 C).</td>
</tr>
<tr>
<td>Practice parameters for the management of Clostridium difficile infection. American Society of Colon and Rectal Surgeons, 2015</td>
<td>“There is no high-grade evidence regarding the optimal timing of surgical intervention, but it appears that surgical consultation early in the course of disease may be beneficial.”</td>
<td>Subtotal colectomy with ileostomy is typically the operative procedure of choice for C difficile colitis. Grade of recommendation: strong recommendation based on low-quality evidence, 1C. Diverting loop ileostomy with colonic lavage may be an alternative to total abdominal colectomy for the treatment of severe C difficile colitis. Grade of recommendation: weak recommendation based on low-quality evidence, 2C.</td>
</tr>
<tr>
<td>Australasian Society for Infectious Diseases (ASID) 2016</td>
<td>Indications for surgery are toxic megacolon, bowel perforation, or severe deterioration in spite of first-and second-line medical therapy.</td>
<td>Subtotal colectomy, end ileostomy with preservation of rectum. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and vancomycin administered via the efferent limb of the ileostomy; alternative to total colectomy in selected patients</td>
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retroperitoneal fat stranding, ascites, small bowel distention and mural thickening with the terminal ileum being the most affected, pneumatosis intestinalis (gas within the wall of the small bowel), and intrahepatic portal venous gas.69

The largest case series of ileal CDI (12 cases in 5 years) also included a report of fatal ileal CDI in a 61-year-old man admitted for radical prostatectomy with lymphadenectomy for prostate adenocarcinoma with no prior antibiotic use. He was discharged on postoperative day 4 but was readmitted with severe diarrhea; he received oral and intrarectal vancomycin and intravenous metronidazole for treatment, but died 2 days later of multiple organ failure. Autopsy confirmed C difficile enteritis in the ileum but not in the colon;
toxigenic *C difficile* was isolated from ileal tissue but not colonic tissue. This case depicts the potential rapid trajectory of disease in ileal CDI. A patient with possible ileal CDI should be treated with oral vancomycin (not metronidazole) because it results in reliable therapeutic concentrations in the small bowel.

Recommendations for treatment for small bowel CDI include IV metronidazole 500 mg IV 18 hours, by mouth, orally (PO) vancomycin 500 mg every 6 hours (q6h) if evidence of resolution of ileus, and if ileostomy present initiate retrograde vancomycin flushes (500 mg in 100–500 mL normal saline q6h) via the ileostomy to reduce luminal toxin. If severe ileus is still present, consideration of retrograde polyethylene glycol lavage via the ileostomy to flush out the intestinal luminal toxin (similar to the strategy used for loop ileostomy and colonic lavage) may be helpful.

**RECURRENT CDI TREATMENT**

Recurrent CDI affects 15% to 35% of patients with primary CDI, and additional patients go on to develop chronic relapsing CDI. Prolonged vancomycin oral taper is the initial treatment strategy for recurrent CDI. For the first recurrence, use of the same regimen used in the first episode is recommended, unless the severity of disease dictates a switch from metronidazole to vancomycin. For the second recurrence and all subsequent recurrences, vancomycin is typically recommended in tapering and pulsed doses (eg, vancomycin 125 mg 4 times a day for 14 days, 125 mg twice daily for 7 days, 125 mg daily for 7 days, 125 mg every other day for 7 days, and 125 mg PO every third day for 2–8 weeks). Spores are only susceptible to killing by antibiotics when they are in a fully vegetative form, and by pulsing vancomycin intermittently, spores are allowed to germinate, thus making them susceptible to killing. The repetitive cycle of antibiotic-free periods also allows an opportunity for the normal colonic flora to reestablish itself.

For patients with multiple CDI recurrences who break through a tapering/pulsed vancomycin treatment strategy, the use of a fidaxomicin “chaser” (200 mg PO twice a day for 10 days) has been shown to be effective in some patients, but randomized comparative data are not available. Bezlotoxumab (administered IV as a single dose of 10 mg/kg over 1 hour) was approved (October 2016) by the FDA for the prevention of CDI recurrence in patients aged 18 years or older who are receiving antibacterial drug treatment for CDI.

**Fecal microbiota transplant.** In patients with recurrent CDI, fecal microbiota transplant (FMT) aims to restore the normal composition of the gut microbiome and is recommended when antibiotics fail to resolve CDI. The efficacy of FMT in recurrent CDI had previously been limited to case series and open-label trials. The first randomized controlled double-blind clinical trial enrolled 46 patients who had 3 or more recurrences of CDI and received a full course of vancomycin for their most recent acute episode in 2 academic medical centers. FMT with donor or autologous stool was administered by colonoscopy with the primary end point of resolution of diarrhea without need for anti-CDI therapy during the 8-week follow-up. This study demonstrated that donor FMT was more efficacious (90.9% clinical cure) than autologous FMT (62.5% clinical cure) in prevention of additional CDI episodes.

Although FMT is a highly effective treatment for recurrent or refractory CDI, 10% to 20% of patients fail to achieve a cure after a single FMT. Risk factors for FMT failure have been identified and include severe and severe-complicated indication, inpatient status during FMT, and increased number of previous CDI-related hospitalizations. A prediction model based on these risk factors had good discrimination for identification of patients at high risk of failure after FMT therapy. FMT is associated with primary and secondary cure rates of 88% and 94% in patients with severe or complicated CDI, respectively.

The National Institute of Allergy and Infectious Diseases of the National Institutes of Health has provided funding to launch the American Gastroenterological Association Fecal Microbiota Transplantation National Registry, the first national registry to track short- and long-term outcomes in patients who have undergone the gut-microbiome–based therapy. The American Gastroenterological Association plans to put a formal infrastructure into place for physicians and patients to report information that will standardize best practices for FMT while offering insight into the gut microbiome and its role in human health and disease.

**Probiotics.** The use of probiotics to restore balance to colonic microbiota either in the treatment or prevention of CDI has been investigated. An updated Cochrane systematic review and meta-analysis of 23 randomized controlled trials, including 4,213 patients (moderate quality evidence), suggests that probiotics are both safe and effective for preventing *C difficile*-associated...
Table V. Prevention strategies for CDI

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<th>Strategy</th>
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<tr>
<td>Handwashing</td>
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<tr>
<td>Contact precautions</td>
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<tr>
<td>Antibiotic stewardship</td>
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<tr>
<td>Chlorhexidine gluconate bathing</td>
</tr>
<tr>
<td>Hydrogen peroxide vapor for terminal room cleaning</td>
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<tr>
<td>Pulsed xenon ultraviolet light for terminal room cleaning</td>
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<tr>
<td>Daily cleaning with hydrogen peroxide disposable wipes</td>
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<tr>
<td>Probiotics</td>
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Diarrhea. The SHEA/Infectious Diseases Society of America treatment guidelines do not recommend probiotics for CDI treatment due to limited data and potential risk for bloodstream infection.

Of the probiotics studied, *Saccharomyces boulardii* has the most data as a potential adjunctive treatment agent in recurrent CDI in adult patients. A recent cost-effectiveness analysis conducted in Canada evaluated the impact of oral probiotics on the incidence and cost of CDAD among hospitalized adult patients. The preventive intervention involved the administration of one oral dose (capsule) in any formulation with the course of antibiotics and continuing for 5 days after the completion of therapy (the control group received no probiotics). The study documented a reduced risk of CDAD and a cost savings of $518 per patient treated.

In the operative patient population, a single dose of antibiotic prophylaxis is often sufficient to stimulate the development of CDAD. If we extrapolate to a population undergoing an operative procedure that would most likely require a single prophylactic antibiotic dose, conservatively estimating that number to be 25 million, the projected saving to the US health care system for reducing the risk of CDAD using a probiotic agent would approach $13 billion. Further studies are warranted in selective surgical patient populations to validate the cost-effective and risk-reduction benefits associated with probiotic prophylaxis for CDI.

INFECTION CONTROL STRATEGIES AND PREVENTION

The challenges posed by CDI represent one of the most difficult patient care issues confronting health care workers and infection control personnel. All efforts to prevent and control CDI should be implemented (Table V). Early recognition of patients who are suspected of having or who are diagnosed with CDI is the primary step in preventing the spread of this epidemiologically significant organism. *C. difficile* can spread by direct or indirect contact with the patient or his/her environment. CDI patients should be placed in Contact Precautions as recommended by the Healthcare Infection Control Practices Advisory Committee/Centers for Disease Control and Prevention guidelines for isolation precautions. Strict adherence to the components of Contact Precautions will help to break the chain of infection, making a significant impact on limiting the spread or cross-contamination of this organism.

The following infection control strategies have documented efficacy when applied in an appropriate manner.

(I) **Patient placement:** Ideally, CDI patients should be kept in a private room with a bathroom or commode solely dedicated for their use.

(II) **The use of personal protective equipment:** Incorporating effective and consistent barrier precautions is deemed critical to preventing transmission of spores from patient to health care providers and subsequently to other patients. It is important that personal protective equipment (gown and gloves) be donned before entering the patient’s room and discarded before leaving the patient room. High-touch surfaces like bed railings, doorknobs, and light switches are often highly contaminated with *C. difficile* spores. Consequently, gloves must be donned before contact with patients or their environment and throughout the period of direct or indirect patient care.

(III) **Patient transport:** Unless it is absolutely necessary, transport of CDI patients from their rooms should be limited as much as possible. Individual persons involved in this transport should be aware of the patients’ status and use appropriate personal protective equipment.

(IV) **Patient care equipment, instruments, devices, and patient care environment:** *C. difficile* spores will contaminate patient care equipment and devices through fecal shedding or through contaminated hands of the patient or health care providers. *C. difficile* spores can persist for months within the health care environment and be transmitted to patients over a long period of time (months). Fecal contamination of surfaces, devices, and materials, such as commodes, thermometers, and blood pressure equipment may provide a reservoir for *C. difficile* spores to disseminate, leading to transmission throughout the environment.
health care environment. Disinfectant products with approved Environmental Protection Agency registration should be used for daily routine cleaning in the health care setting and hypochlorite-based disinfectants used for environmental surface disinfection in those patient-care areas where surveillance and epidemiology data indicate ongoing transmission of *C difficile*. The Centers for Disease Control and Prevention currently recommend that hospital rooms be terminally cleaned with bleach when patients are discharged or transferred. The use of selective spectrum ultraviolet light and hydrogen peroxide vapor have demonstrated in both laboratory and clinical trials to reduce (or eliminate) *C difficile* (vegetative cells and spores) from inert, contaminated surfaces. \(^\text{140}\)

**Hand hygiene.** Health care providers’ hands are often contaminated with *C difficile* after patient contact. After gloves are removed, health care providers should wash their hands with soap and water rinse. Although alcohol hand gel products are effective against vegetative cells, they are ineffective against clostridial spores. \(^\text{141}\) Numerous studies have documented that judicious compliance with appropriate hand hygiene practice is an effective strategy for reducing the risk of dissemination and acquisition of *C difficile* within the health care environment. \(^\text{142}\)

**Antibiotic stewardship.** Judicious and appropriate use of antibiotics under an antimicrobial stewardship program plays an important role in prevention strategies for *C difficile*. \(^\text{143}\) CDI can often be linked to prior antibiotic use. Virtually all antibiotics produce disruption of the host normal colonic flora but differ in their capability to cause collateral damage to the patient’s gastrointestinal flora. There are 2 key considerations when evaluating the risk for CDI: (1) the level of risk conferred by antibiotics, categorized as low, intermediate, or high risk; and (2) the number of days the patient will be at risk for CDI.

A patient who receives a narrow-spectrum antibiotic for less than 1 day will be considered to have a low risk and a short duration of risk. Alternatively, for a patient who receives operative prophylaxis with an unnecessary broad-spectrum antibiotic, the level of risk for developing CDI would move from low to high without any additional clinical benefit from the inappropriate drug. \(^\text{144}\)

A recent case-controlled clinical trial found that ertapenem operative prophylaxis was significantly associated with postoperative CDI (*P* < .028). \(^\text{145}\) Furthermore, an analysis of morbidity and mortality outcomes in postoperative CDI in Veterans Affairs hospitals found that administration of 3 or more classes of antibiotics in a 60-day preoperative period was one of several significant risk factors. \(^\text{146}\) Implementation of an effective antimicrobial stewardship program would assist in the development of institutional policies that address inappropriate antimicrobial use and lowering the potential for collateral damage. \(^\text{147}\)

In conclusion, *C difficile* infections are the leading cause of health care–associated infectious diarrhea, posing a significant risk for both medical and surgical patients. Because of the significant morbidity and mortality associated with CDI, knowledge of the epidemiology of *C difficile* in combination with a high index of suspicion and susceptible patient populations (including surgical, postcolectomy, and IBD patients) is warranted.

CDI presents with a wide spectrum of disease, ranging from mild diarrhea to fulminant colitis or small bowel enteritis and recurrent CDI. Early implementation of medical and operative treatment strategies of CDI is imperative for optimal patient outcomes. National and international guidelines recommend early operative consultation and total abdominal colectomy with end ileostomy and preservation of rectum. Diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and intracolonic vancomycin administered via the efferent limb of the ileostomy should be considered as an alternative to total colectomy in selected patients.

New and emerging strategies for CDI treatment include monoclonal antibodies, vaccines, probiotics, biotherapeutics, and new antibiotics. A successful *C difficile* prevention and eradication program requires a multidisciplinary approach that includes early disease recognition, implementation of guidelines for monitoring adherence to environmental control, judicious hand hygiene, evidence-based treatment and management strategies, and a focused antibiotic stewardship program. Surgeons are an important part of the clinical team in management of CDI prevention and treatment.

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