The always evolving diagnosis and management of *Clostridioides difficile* colitis: What you need to know

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ABSTRACT: The diagnosis, pharmacologic management, and surgical options for *Clostridioides difficile* infection (CDI) are rapidly evolving, which presents a challenge for the busy surgeon to remain up to date on the latest clinical guidelines. This review provides an evidence-based practical guide for CDI management tailored to the needs of surgeons and surgical intensivists. Historically, the diagnosis of CDI relied on slow cell culture cytotoxicity neutralization assays, but now, the rapidly resulting nucleic acid amplification tests and enzyme immunoassays have become mainstream. In terms of antibiotic therapy, metronidazole and oral vancomycin were the main "workhorse" antibiotics in the early 2000s, but large randomized controlled trials have now demonstrated that fidaxomicin produces superior results. Regarding surgical intervention, total abdominal colectomy was once the only procedure of choice; however, diverting loop ileostomy with colonic lavage is emerging as a viable alternative. Finally, novel adjuncts such as fecal microbiota transplantation and targeted therapy against toxin B (bezlotoxumab) are playing an increasingly important role in the management of CDI. (*J Trauma Acute Care Surg.* 2025;98: 357–367.

KEY WORDS: *Clostridioides difficile*; *Clostridium difficile*; colitis; total abdominal colectomy; diverting loop ileostomy.

Clostridioides difficile, formerly known as *Clostridium difficile*, is a gram-positive, anaerobic bacterium responsible for *C. difficile* infection (CDI),[1] which can range from mild diarrhea to fulminant colitis[2] and, rarely, enteritis.[3] CDI poses a formidable challenge in health care, particularly for surgeons who are often at the forefront of managing severe and complicated cases. Over the past few decades, significant advancements have been made in understanding the pathophysiology, epidemiology, and risk factors of CDI. Concurrently, diagnostic techniques and therapeutic interventions have evolved, offering more precise and effective management options. The goal of this review is to provide surgeons with a practical, evidence-based, and up-to-date overview of CDI, emphasizing the evolving nature of its diagnosis and management to ensure improved patient outcomes through timely and appropriate interventions.

PATHOPHYSIOLOGY, EPIDEMIOLOGY, AND RISK FACTORS

Pathophysiology and Epidemiology

C. difficile produces exotoxin A (toxin A) and exotoxin B (toxin B), which have both cytopathic (e.g., increased epithelial permeability) and cytotoxic (e.g., induction of apoptosis) effects.[4–6] These toxins disrupt the normal function of the intestinal mucosa, causing excessive fluid secretion and cell death in the colonic lining. The resulting cellular debris, along with necrotic immune cells, mucus, and fibrin, combines to form the characteristic pseudomembrane (Fig. 1). Some strains also produce a binary toxin (CDT), although its role in clinical disease remains unknown.[7] Of note, the microbe's presence does not always lead to CDI.[8] Nearly 10% of hospitalized patients may be asymptomatic carriers of the disease, and only a minority of them will go on to develop CDI.[9]

C. difficile is spread via the fecal-oral route, and health care workers are in part responsible for its transmission.[10] This underscores the importance of good hand hygiene. A prospective randomized controlled trial demonstrated the superiority of soap and water hand washing over the use of alcohol-based hand sanitizer in preventing the spread of *C. difficile*.[11] The number of CDI cases is decreasing in the United States from an estimated 476,400 cases in 2011 to 462,100 cases in 2017.[12] The decrease in CDI cases mirrors that of other health care-associated infections and is likely due to increased infection control protocols and awareness. Interestingly, the COVID-19 pandemic did not hasten the decline in CDI.[13] Although this time period was marked with hyperawareness of infection prevention, it is possible that resources including personal protective equipment, sanitization supplies, and staffing were diverted toward patients with COVID-19.

Risk Factors

Risk factors for CDI can be categorized into three main groups: antibiotic usage, decreased host defenses, and recent therapeutic interventions for other conditions.

The most widely recognized and modifiable risk factor for CDI is antibiotic use, leaving patients at increased risk of CDI for up to 3 months after stoppage. Among all antibiotics, the most commonly cited antibiotic associated with CDI is clindamycin, which was first linked to the infection in the

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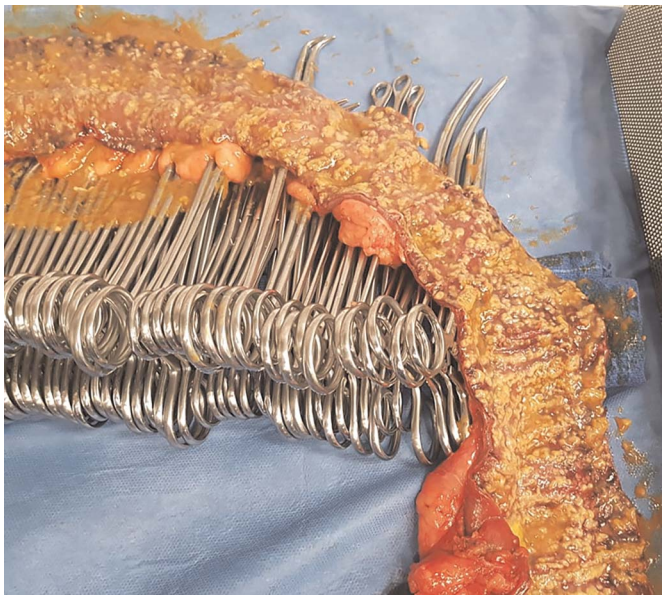

Figure 1. The opened colon specimen reveals typical pseudomembranous colitis features, with numerous yellowish-white plaques scattered across the mucosa. These pseudomembranes consist of fibrin, inflammatory cells, and necrotic debris. The intervening mucosa is erythematous and edematous, indicative of extensive inflammation. The cobblestone appearance of the mucosal surface, caused by the pseudomembranes, suggests significant colonic wall structural damage (courtesy of Irene Yu, MD).

1970s.[14] Since then, it has become evident that exposure to nearly any antibiotic can disrupt the gut microbiome, thereby creating an environment conducive to *C. difficile* colonization and infection. Specifically, clindamycin, third-generation cephalosporins, penicillins, and fluoroquinolones are particularly associated with a higher risk of CDI.[15] It should be noted that CDI can also occur without antibiotic use, especially in patients with compromised immune systems. Furthermore, proton pump inhibitors (PPIs) have also been epidemiologically linked to an increased risk of CDI. The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines recommend discontinuing unnecessary PPIs only upon CDI diagnosis, as there is insufficient evidence to support PPI discontinuation for the primary prevention of CDI.[16]

The second group of risk factors pertains to decreased host defense mechanisms, which are generally nonmodifiable. These include increased age (65 years or older), generalized debility, inflammatory bowel disease (IBD), renal failure, leukemia, and diabetes.[17] Consequently, patients with these underlying conditions who present with symptoms such as diarrhea, abdominal pain, or an acute flare of their disease should be considered for *C. difficile* testing.

Lastly, certain recent therapeutic interventions performed for other medical conditions may also elevate the risk of CDI. These interventions include abdominal surgery, mechanical ventilation, and nasogastric tube placement.[18] However, it is important to note that further research is needed to fully elucidate the extent of these risks.

DIAGNOSIS AND SEVERITY

Diagnosis

An accurate diagnosis of CDI relies on clinical manifestations and laboratory confirmation of the *C. difficile* organism and/or its toxin in a diarrhea stool sample. Common clinical pictures of CDI include diarrhea (three or more unformed stools within 24 hours), abdominal pain, cramps, abdominal distension, ileus (signs of severe disruption of bowel function), and toxic megacolon on imaging studies. However, we have observed instances where *C. difficile* testing was ordered based on a single episode of large loose stool without abdominal pain. This practice should be discouraged.

C. difficile diarrhea typically manifests as mushy or porridge-like stool rather than completely liquid stool. Occasionally, it may exhibit a green tint, although this characteristic is not exclusive to *C. difficile* and can also occur with other bacterial infections. In some cases, stools may contain blood, mucus, or pus. Moreover, a distinctive odor is often associated with *C. difficile* diarrhea. It has been reported that nursing staff can identify CDI patients by this characteristic smell alone.[19] They describe the odor as unusually strong and oddly sweet, potentially because of increased levels of bile acids and unique volatile organic compounds in the stool.[19,20] However, other studies have shown that relying on stool odor for CDI detection has poor predictive value.[21]

Since *C. difficile* can colonize the normal intestinal tract without causing infection, confirmation testing of CDI should only be performed on the preferred target population with three or more unformed stools in a 24-hour period without another explanation (e.g., IBD flair, enteral tube feeding, chemotherapy, or laxative use within 48 hours).[16,22] However, some have challenged aspects of this recommendation by the IDSA/SHEA which is based on low-quality evidence. First, many patients with antecedent laxative use have CDI.[23] Precluding patients with possible alternative explanations for their diarrhea may lead to patient harm because of delay of workup for and treatment of CDI. In practice, many patients with unformed stools who had received enteral tube feeding, chemotherapy, or laxatives within the preceding 48 hours are tested for CDI despite the IDSA/SHEA guidelines.[24] Second, ileus could be a marker of fulminant CDI because of the severe disruption of bowel function. Patients with fulminant CDI may not have three or more unformed stools in a 24-hour period precisely because of the severity of the condition.[15] Therefore, surgeons should be using patient-specific judgment when initiating testing for CDI while considering other possible explanations for their symptoms. In the case of severe leukocytosis and multiorgan failure without a clear source, a diagnosis of CDI should be considered, even in the absence of bowel movements.[25] It is crucial to differentiate between the absence of bowel movements and the absence of diarrhea. The former can result from inhibited bowel motility due to ileus, while the latter implies the production of formed stools. Since CDI is characterized by a toxin-mediated inflammatory response in the intestinal epithelium, a *C. difficile* confirmatory test is not necessary for patients who presents with leukocytosis and abdominal pain while still producing formed stools; in such cases, an alternative diagnosis should be pursued. Detecting the *C. difficile* toxin genes alone cannot differentiate between CDI

and asymptomatic carriers. As a result, testing formed stool may yield false-positive results in individuals without symptoms, leading to unwarranted antibiotic treatment. However, for patients with similar clinical symptoms but no diarrhea due to ileus, a perirectal swab for a CDI polymerase chain reaction test for *C. difficile* toxin–producing genes should be performed to confirm the diagnosis.[15] One study reported that the sensitivity, specificity, positive predictive value, and negative predictive value of perirectal swab testing reached 95.7%, 100%, 100%, and 99.1%, respectively.[26]

Although CDI typically refers to colitis, enteritis resulting from *C. difficile* has been documented. It is a rare entity with no specific treatment guidelines. Surgeons should consider this possibility when managing patients with unusual ileostomy output or an unexplained systemic inflammatory response. Early diagnosis can be facilitated by sending the bowel content for confirmation of the infection. Generally, the treatments for *C. difficile* colitis are applied to enteritis.[27] In severe cases, small bowel resection may be required.

Laboratory Testing

The laboratory confirmatory test has been evolved over time. Historically, toxigenic culture was regarded as the gold standard for diagnosing CDI. Toxigenic culture identified *C. difficile* organisms and tested the colonies for toxin production. However, it fell out of favor because of its extended processing times and inability to detect toxins directly in stool samples. Subsequently, a two-step process using cell culture cytotoxicity neutralization assays was recommended. This involved testing cells for toxin-induced cytopathic effects, followed by a neutralization assay specific to *C. difficile* toxins.[28] This test also became less popular because of slow turnaround times and inconsistent sensitivities and specificities.

Currently, there are now two main types of laboratory tests commonly used for the detection of CDI, each with its own limitations.[15]

Nucleic Acid Amplification Tests for Toxigenic Genes

Nucleic acid amplification tests (NAATs) use polymerase chain reaction to detect *C. difficile* toxin-producing genes including *tcdA* (toxin A gene), *tcdB* (toxin B gene), and *cdt* (binary toxin gene) depending on the specific assay.[28] While NAATs have a relatively high sensitivity (80–100%) and high specificity (87–99%) for the detection of the microbe, they do not discriminate between active disease and asymptomatic colonization.[29] These tests take from 30 minutes to 4 hours to complete.[30]

Enzyme Immunoassays for Toxins and Antigen

Enzyme immunoassays (EIAs) detect toxin A, toxin B, or glutamate dehydrogenase (GDH) directly. GDH is produced by the microbe in larger amounts relative to toxins A and B. Enzyme immunoassays typically yield results in less than 30 minutes.[31] Specifically, GDH EIA tests have a sensitivity of 80% to 100% and a specificity of >90%, but similar to NAATs, they also do not differentiate active disease from colonization.[15,28,32] Enzyme immunoassays that detect toxin A and toxin B directly reflect active disease, but they have low sensitivity (32–99%) and high specificity (84–100%). Therefore, guidelines recommend multistep algorithms starting with a high sensitivity test (NAATs or GDH EIAs) followed by a high specificity test for active disease (toxin EIAs).[33]

Of note, even with multistep diagnostic algorithms, biochemical workup can be completed within hours.[28,34] Patients should be placed in contact isolation while awaiting biochemical testing if the tests will not result on the same day.[16] Although empiric treatment is generally initiated in practice, this approach is discouraged because of the risk of overtreatment, except in cases of strong suspicion for fulminant CDI.[15,16]

Our algorithm for the diagnosis of CDI based on prior clinical guidelines is shown in Figure 2.[15,16] First, if patients have a positive NAAT or GDH and subsequent positive toxin EIA, the diagnosis of CDI is made. Second, if patients have a negative NAAT or GDH, CDI is unlikely, although, if there is a strong clinical suspicion, another high sensitivity test such as NAAT or GDH EIA can be performed to arbitrate. Third, interpreting a positive NAAT or GDH followed by a negative toxin EIA can be complex, as it may indicate either CDI or asymptomatic carrier status. Generally, NAAT- or GDH-positive/toxin EIA-negative patients with CDI have milder symptoms than patients who are NAAT or GDH positive/toxin EIA positive. Nevertheless, they may have similar rates of complications, and some even require surgical intervention.[35,36] However, at the population level, others have demonstrated similar outcomes in treated versus untreated NAAT- or GDH-positive/toxin EIA–negative patients and have called the utility of multistep algorithms into question in favor of solely toxin testing.[37] Ultimately, the consensus for multistep testing is driven by low sensitivity of toxin EIA.[30,33] As the sensitivity of toxin EIA tests improve, a move toward toxin EIA testing alone may ensue.

It should be noted that biochemical testing for cure is discouraged as spores and/or toxins remain detectable in 7% of patients at the end of treatment and more than half of patients with the infection continue to test positive following symptomatic

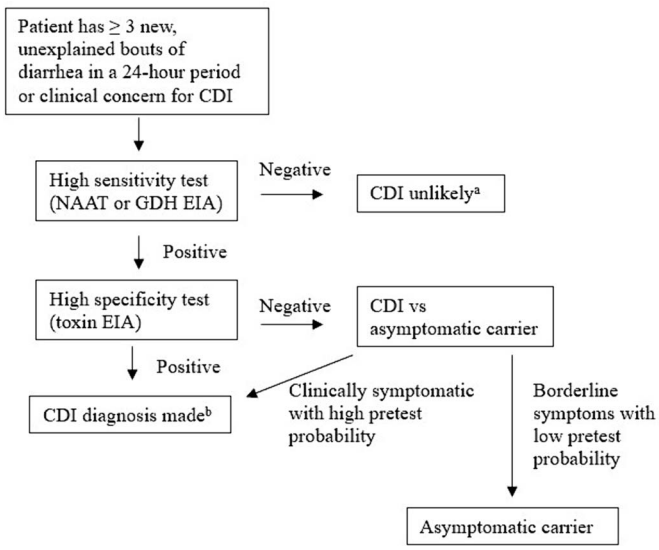

Figure 2. Diagnostic algorithm. [a]If strong clinical suspicion, can consider performing another high sensitivity test to corroborate. [b]Computed tomography, ultrasonography, and endoscopy are useful adjunct imaging studies in select cases including of diagnostic uncertainty.

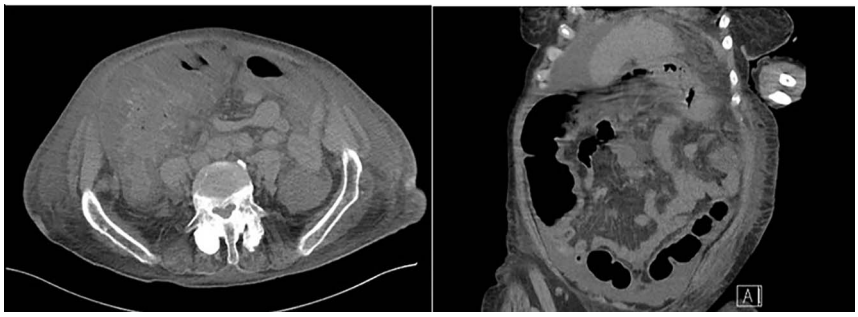

Figure 3. (Left) Axial CT scan of the abdomen without oral contrast demonstrates marked diffuse edematous wall thickening of the colonic wall with hyperdense nodular haustral thickening producing the so-called "thumbprinting sign." The normal haustra become thickened at regular intervals appearing like thumbprints projecting into the aerated lumen. (Right) Coronal view CT scan of the abdomen through the pelvis shows marked thickening of the wall of the colon with pericolonic stranding indicating pancolitis.

resolution.[38] Repeat testing following a negative result should only be performed with a change in clinical symptoms and at least 1 week from the first test.[15,16]

Adjunct Imaging Studies

Imaging tests including computed tomography (CT), ultrasonography, and endoscopy may aid in the workup of CDI, but none should be used as a screening tool.[15]

CT Scan

Computed tomography scans are preferred for imaging in cases of suspected CDI, especially when pseudomembranous colitis, CDI complications, or other intra-abdominal pathology is a concern. This imaging technique can help evaluate related complications, such as ileus, toxic megacolon, or perforation, especially when the patient experiences severe abdominal pain. However, there are no pathognomonic findings of CDI on CT imaging. Patients with CDI may show various findings on CT imaging, including colonic bowel thickening (Fig. 3) with thumbprinting (most common), accordion signs (best seen with oral contrast), pericolonic stranding, loss of haustral markings, or unexplained ascites. It is important to note that the sensitivity (52%) and negative predictive value (67%) of these findings are low.[39] As such, routine CT scan is not necessary for mild to moderate cases, and CT findings might not reliably distinguish CDI from other colonic diseases.

Ultrasound

Ultrasound can serve as a valuable tool for detecting colonic wall thickening and ascites with a positive predictive value of 80% and a negative predictive value of 90%.[40] This makes ultrasound a valuable diagnostic modality for assessing complications of CDI when more advanced imaging like CT scans is not available in resource-constrained environments.

Endoscopy

The role of flexible sigmoidoscopy has evolved the most. Before more sophisticated diagnostic tests were available, the diagnosis of CDI was often first made by visualizing pseudomembranes directly.[14] However, it is not a sensitive diagnostic test in patients with milder presentations. The risk of colonic perforation with colonoscopy is less than 0.1% overall and can still be safely performed in cases of active colitis in the hands of an experienced operator.[41,42] Currently, endoscopy

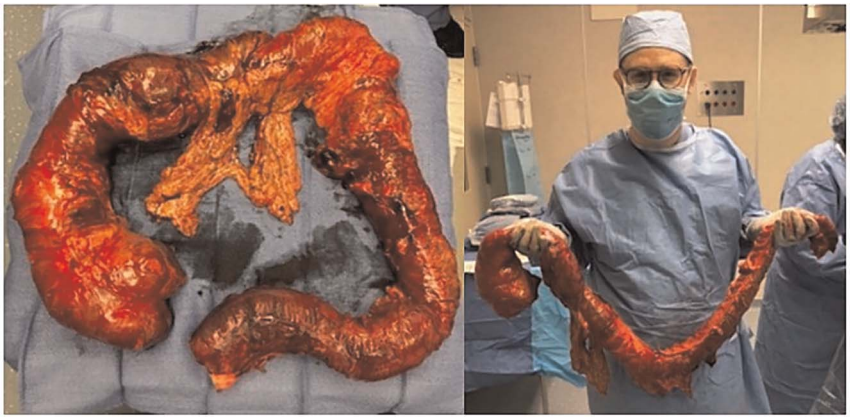

Figure 4. (Left) The colon specimen, removed from a patient with fulminant *C. difficile* colitis, appears markedly distended and edematous, consistent with toxic megacolon. The serosal surface is dull and exhibits areas of hemorrhage. The colonic dilation and thickened walls are indicative of severe inflammatory change and colonic paralysis. This presentation is characteristic of advanced and life-threatening CDI. (Right) The colon specimen held by surgical resident Dr. Thomas Langen, MD, to illustrate its relative enlargement (courtesy of Molly Moore, MD).

TABLE 1. Antibiotics Regimen for CDI

	IDSA/SHEA[16,51]	ACG[49]	ESCMID[50]
Nonsevere	*2017* VAN 125 mg qid × 10 d (strong/high) or FDX 200 mg bid × 10 d (strong/high) or MTZ 500 mg TID × 10 d if other agents not available (weak/high) *2021* FDX 200 mg bid × 10 d over VAN 125 mg qid × 10 d (conditional/moderate)	FDX 200 mg TID × 10 d (strong/moderate) or VAN 125 mg qid × 10 d (strong/low) or MTZ 500 mg TID × 10 d for low-risk patients (strong/moderate)	FDX 200 mg bid × 10 d (strong/moderate) or VAN 125 mg qid × 10 d if FDX unavailable (strong/high)or MTZ 500 mg TID × 10 d if FDX and VAN unavailable (strong/moderate)
Severe	*2017* VAN 125 mg qid × 10 d (strong/high) or FDX 200 mg bid × 10 d (strong/high) *2021* FDX 200 mg bid × 10 d over VAN 125 mg qid × 10 d (conditional/moderate)	VAN 125 mg qid × 10 d (strong/low) or FDX 200 mg bid × 10 d (conditional/very low)or FMT if refractory to abx (strong/low)	FDX 200 mg bid × 10 d or VAN 125 mg qid × 10 d and if deteriorating tigecycline 50 mg bid (weak/very low)
Fulminant	*2017* VAN 500 mg qid oral (strong/moderate) and if ileus VAN 500 mg in 100 mL NS q6h rectal (weak/low) and VAN 500 mg × q8h IV (strong/moderate)	VAN 500 mg qid × 2–3 d (strong/very low) and VAN 500 mg q8h IV (conditional/very low) and if ileus VAN 500 mg q6h (conditional/very low) or FMT if refractory to abx (strong/low)	FDX 200 mg bid × 10 d or VAN 125 mg qid × 10 d and if deteriorating tigecycline 50 mg bid (weak/very low)
1st Recurrence	*2017* VAN 125 mg qid × 10 d if MTZ was used for the initial episode (weak/low) or prolonged tapered and pulsed VAN regimen if a standard VAN regimen was used for the initial episode (weak/low) or FDX 200 mg bid × 10 d if VAN was used for the initial episode (weak/moderate) *2021* FDX 200 mg bid × 10 d or extended-pulsed regimen (conditional/low) or VAN 125 mg qid × 10 d or VAN tapered and pulsed regimen	Tapered and pulsed VAN after an initial course of FDX, VAN, or MTZ (strong/very low) or FDX after an initial course of VAN or MTZ (strong/moderate)	FDX 200 mg bid × 10 d if VAN or MTZ was used for the initial episode (strong/low) or bezlotoxumab added to VAN or FDX (weak/moderate) or tapered and pulsed VAN if FDX is unavailable (weak/very low)
≥2 Recurrences	*2017* VAN in a tapered and pulsed regimen (weak/low) or VAN 125 mg qid × 10 d followed by RIF 400 mg TID × 20 d (weak/low) or FDX 200 mg bid × 10 d (weak/low) or FMT (strong/moderate) *2021* FDX 200 mg bid × 10 d or extended-pulsed regimen (conditional/low) or VAN 125 mg qid × 10 d followed by RIF 400 mg TID × 20 d or VAN tapered and pulsed regimen or FMT	n/a	FMT after antibiotic pre-treatment (weak/moderate) or bezlotoxumab in addition to standard regimen (weak/low)

The parenthesis contains the systematic weight of the (strength of recommendation/quality of evidence) using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system.

ACG, American College of Gastroenterology; VAN, vancomycin; FDX, fidaxomicin; MTZ, metronidazole; RIF, rifaximin; FMT, fecal microbiota transplantation; bid, twice a day; tid, three times a day; qid, four times a day; q6h, every 6 hours; q8h, every 8 hours.

is most useful to confirm the diagnosis when clinical suspicion is high despite inconclusive stool testing or to rule out other etiologies, especially in patients with prior organ transplantation.[43,44] In critically ill ICU patients with potential fulminant CDI and a long list of differential diagnoses, lower endoscopy may be particularly useful for rapid diagnosis by identifying pseudomembranes in the colonic mucosa while providing therapeutic decompression rather than waiting hours for laboratory testing or proceeding directly to surgical intervention. However, pseudomembranes are seen in only about half of patients with CDI.[44] If pseudomembranes are not visualized, CDI cannot be ruled out. Surgeons should then develop a patient-specific plan for this case in advance of the procedure. If clinical suspicion is low, for example, because of a lack of known risk factors

and the presence of an alternative underlying cause of severe illness, waiting for biochemical testing to return may be justified. However, if clinical suspicion is high, early surgical intervention is warranted regardless of the presence or absence of pseudomembranes.

Severity of the Disease

Once CDI is suspected or diagnosed, assessing the severity of the disease is crucial for determining whether medical management or surgical intervention is needed. *CDI* severity can range from mild to highly complicated and fulminant. Clinical definitions of the disease spectrum have been defined by the IDSA/SHEA guidelines.[16] According to these guidelines, nonsevere disease is quantified as white blood cell count of ≤15,000/mm^3 and a serum creatinine level of <1.5 mg/dL. Severe disease is defined as white blood cell count of ≥15,000/mm^3 or a serum creatinine level of >1.5 mg/dL. Fulminant disease, which has previously been called severe or complicated CDI, is characterized by hypotension, shock, ileus, or toxic megacolon (Fig. 4). However, these definitions alone sometimes create diagnostic uncertainty. For example, it can be challenging to differentiate between severe and fulminant CDI in patients who are critically ill because of their underlying disease process, as they may present with the same laboratory abnormalities or clinical signs.[45] Nearly all surgical intensivists will face this dilemma, as CDI occurs in 2% of ICU patients and in 11% of ICU patients with diarrhea.[46]

TREATMENTS

Pharmacologic Therapy

In terms of antibiotic therapy for CDI, the optimal regimen has evolved significantly over the past two decades. Historically, metronidazole and oral vancomycin were the main treatment for CDI. However, metronidazole fell out of favor because of its association with higher rates of treatment failure in two large randomized control trials published in 2007[47] and 2014.[48]

The current recommendations for antibiotic treatment of CDI are summarized in Table 1. While the American College of Gastroenterology still lists metronidazole as one of three options for an initial episode of nonsevere CDI in low-risk patients,[49] the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and IDSA/SHEA recommend using metronidazole only when vancomycin and fidaxomicin are not available or feasible.[50] Consequently, IDSA/SHEA guidelines (2017) recommend oral vancomycin (125 mg four times a day for 10 days) or oral fidaxomicin (200 mg twice a day for 10 days) as first-line therapy for both nonsevere and severe initial episodes.[16]

In light of accumulating evidence favoring fidaxomicin[52–55] for its sustained therapeutic response in pooled analysis, the IDSA/SHEA (2021) and ESCMID recommend oral fidaxomicin over vancomycin for initial and recurrent episodes of nonsevere and severe CDI.[51] A standard vancomycin regimen remains an acceptable alternative for initial and recurrent episodes if fidaxomicin is not available, given its high cost.[56] When oral route is not possible or reliable for severe disease, one should also consider rectal delivery, with or without intravenous (IV) metronidazole or tigecycline according to ESCMID.[50]

Despite the evolution toward fidaxomicin for nonsevere and severe disease, oral vancomycin (500 mg four times daily) is still recommended for fulminant CDI.[16,49] Of note, the 2021 IDSA/SHEA update states that their previous recommendation of vancomycin for fulminant disease holds. The studies on fidaxomicin excluded patients with fulminant disease; therefore, there are no robust data to support its use in these patients.[51] However, a recent case report described a patient with fulminant CDI refractory to oral vancomycin and IV metronidazole who had a rapid recovery within 24 hours of starting fidaxomicin, indicating its potential application in these patients.[57] In case of ileus where the absorbability of oral drugs is uncertain, rectal vancomycin should be considered.[16,51] In fulminant cases, intravenously administered metronidazole (500 mg every 8 hours) together with oral or rectal was also recommended, particularly if ileus is present.[16]

In cases of recurrent disease, either a standard dose or extended-pulsed regimen of fidaxomicin or vancomycin is acceptable. Other alternatives to recurrences include a pulsed and tapered vancomycin regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation (FMT).[51]

Surgical Intervention

Indications for Surgery

While only 1% of all patients with CDI will require surgical intervention, this number climbs to 30% among those with severe disease.[58] Surgical intervention is typically indicated for patients with fulminant CDI who progress to systemic toxicity and complications. Major life-threatening complications such as toxic megacolon and bowel perforation, regardless of etiology, unequivocally require emergency surgical intervention. These conditions are well-known to surgeons and necessitate immediate action. Toxic megacolon is defined as a cecal diameter greater than 12 cm or a colonic diameter greater than 6 cm on radiological imaging.[59] Other absolute indications for surgery include full-thickness ischemia, peritonitis with a worsening abdominal examination, abdominal compartment syndrome, hemodynamic instability with escalating dosage of vasopressors, acute respiratory failure requiring mechanical ventilation, and worsening end-organ damage especially renal failure (Table 2).[60] A relative indication for surgical intervention is the failure of medical management, although there are no official guidelines defining this threshold.

Timing of Surgical Intervention

Relying solely on hemodynamic instability as the indicator for surgical intervention presents a significant pitfall, as these

TABLE 2. Absolute Indications for Surgical Intervention in a Patient With CDI

Indication
Colonic perforation
Full-thickness ischemia
Peritonitis with a worsening abdominal examination
Abdominal compartment syndrome
Hemodynamic instability requiring vasopressors
The need for mechanical ventilation
Worsening end-organ damage

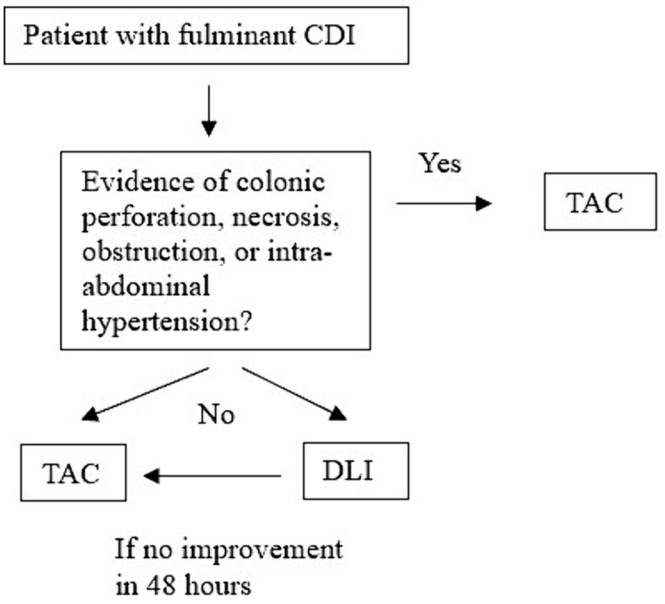

Figure 5. Management algorithm.

conditions are often late indicators of severe illness and correlated with poor outcomes.[61] Offering surgery at such a late stage may be futile, because of high mortality rate.[62,63] Therefore, early surgery, as opposed to relying solely on medical management, has been shown to improve survival rates in fulminant disease cases.[15] Specifically, performing surgery before the onset of vasopressors requirements reduces mortality, particularly in elderly patients.[64] A retrospective analysis of 4,796 patients with *C. difficile* revealed that those patients had higher surgery rates but lower mortality when admitted to a surgical team compared with a nonsurgical team, highlighting the critical role of early surgical intervention in reducing mortality.[64]

Currently, there are no definitive clinical or laboratory markers to predict the need for surgical intervention reliably. However, several studies provide valuable insights that may aid in clinical decision-making.

Independent Risk Factors for Surgical Intervention

Multivariate analyses have identified several independent risk factors for surgical intervention, including the following[65–67]:

- Advanced age
- Symptoms of abdominal pain, diarrhea, and distension
- IBD
- Recent CDI
- Use of antiperistaltic medications
- Prior intravenous immunoglobulin treatment
- Recent surgical interventions
- Hemodynamic instability
- Leukocytosis
- Megacolon or colonic perforation

Despite these data, the mechanism driving some of these associations remains unknown. For instance, the immunomodulatory and antimicrobial agents used to treat IBD disturb the gut microbiome, which may leave it susceptible to CDI, yet how this relates to an increased need for surgical intervention is unclear.[68]

Risk Scoring System

A risk scoring system has been developed to identify high-risk patients requiring surgical intervention based on factors such as age, severe leukocytosis or leukopenia, cardiorespiratory failure, and diffuse abdominal tenderness. The scoring system allocates points as follows[67]:

- Age older than 70 years: 2 points
- White blood cell count of ≥20,000/μL or ≤2,000/μL: 1 point
- Cardiorespiratory failure: 7 points
- Diffuse abdominal tenderness: 6 points

A total score of 6 points is used as the threshold to differentiate between low-risk (scores <6) and high-risk (scores ≥6) patients.

What Surgery Should Be Performed

Once the decision has been made to pursue surgical intervention, the options for the specific patient should be determined. Our algorithm for the surgical management of CDI based on prior clinical guidelines is shown in Figure 5.[15,16] Patients with CDI who require surgical intervention can undergo a total abdominal colectomy (TAC)/subtotal abdominal colectomy with end ileostomy, a diverting loop ileostomy (DLI) with colonic lavage (Fig. 6), or segmental colectomy. Historically, the only option was TAC with end ileostomy. The major society guidelines still state that TAC is the standard treatment for fulminant colitis, yet DLI can be considered and may lead to improved outcomes.[15,16,69]

The protocol for DLI was originally described by Neal et al.[70] from the University of Pittsburgh. The procedure included an assessment of colonic viability followed by creation

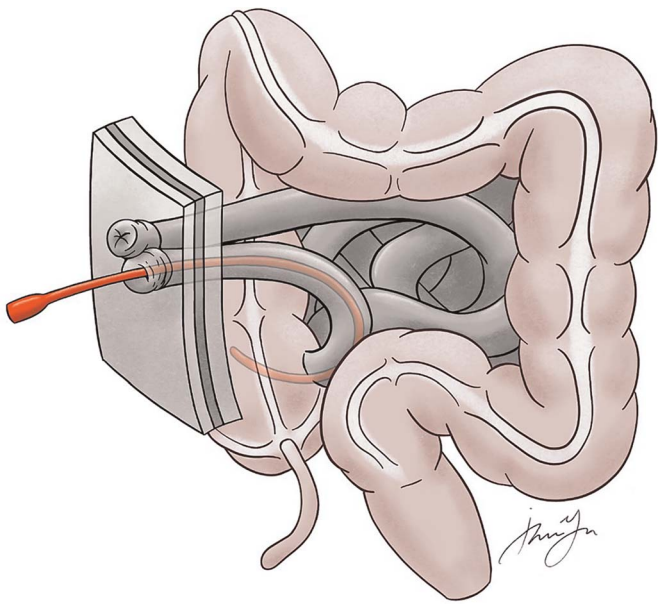

Figure 6. Surgical technique of diverting loop ileostomy with colonic lavage for the treatment of *C. difficile* colitis. The procedure involves creating a loop ileostomy proximal to the ileocecal valve, followed by the insertion of a urinary catheter into the efferent limb for colonic irrigation with a polyethylene glycol solution. Postoperatively, vancomycin flushes are administered through the catheter (illustration courtesy of Irene Yu, MD).

of a DLI 20 to 40 cm from the ileocecal valve. A 26- to 30-French urinary catheter is then inserted into the efferent limb of the ileostomy, with the tip positioned in the cecum or ascending colon. The colonic lavage is performed by instilling 8 L of warm polyethylene glycol solution into the colon via the catheter, which is then collected through a rectal tube. Postoperatively, patients received 500 mg of vancomycin flushes (500 mg in 500 mL of lactated Ringer solution) delivered into the efferent limb of the ileostomy every 8 hours for 10 days and 500 mg of metronidazole IV every 8 hours for 10 days.

Their initial case series of 49 patients who underwent DLI with colonic lavage as an alternative to TAC showed significantly lower 30-day mortality in the DLI (19%) group compared with a matched, historic control group who underwent TAC (50%).[70] An Eastern Association for the Surgery of Trauma-sponsored retrospective multicenter trial of 10 institutions found no difference in mortality: 23.8% for DLI patients (n = 21) and 33.8% for TAC patients (n = 77).[71] However, after adjusting for preoperative confounders, they determined that there was a mortality benefit to DLI over TAC (17.2% vs. 39.7%, respectively).

Despite initial excitement for DLI, other studies have not uniformly demonstrated a similar benefit. Four meta-analyses were published in 2020. All included the same five studies[70–74] and came to the same conclusion: there was no difference in mortality between procedures.[75–78] Notably, a randomized controlled trial comparing DLI and TAC was planned but not completed because of low patient enrollment.[79] Nevertheless, the proportion of patients undergoing DLI increased from 11% in 2011 to 25% in 2015.[74]

Proponents of DLI emphasize its minimally invasive nature and higher reversal rate compared with end ileostomy (79% vs. 19% at 6 months),[70] leading to better functional outcomes. However, critics point out that not resecting the inflamed colon can prolong systemic inflammation and critical illness, causing slower recovery and fluctuating clinical conditions. In addition, recurrent CDI is possible without resection, although specific recurrence rates are unknown.

Segmental colectomy has generated less enthusiasm than TAC and DLI.[80] However, a small, single-institution study[81] and two large retrospective database reviews[82,83] have found no difference in complications or mortality between patients who underwent TAC compared with segmental colectomy. There is no prospective or multicentered trial to support the use of segmental colectomy and it should be avoided in most patients.

Ultimately, patients whose colon is not salvageable because of colonic perforation, colonic necrosis, colonic obstruction, and intra-abdominal hypertension should undergo TAC.[84] Some have anecdotally suggested that patients who fail to improve within 48 hours of DLI should be considered for conversion to TAC, but there is no formal evidence to suggest when a patient has failed DLI.[84]

In patients who undergo a subtotal colectomy, there is no evidence to support routine vancomycin irrigations into the rectal stump.[85] However, if a patient has copious discharge from the rectal stump, vancomycin irrigations (125 mg in 30 mL of irrigation for 7 days) should be considered.[86] In patients who undergo DLI, reversal can be discussed when the patient has recovered from their initial bout of disease and has returned to their normal day-to-day activities.[84] However, fatal recurrences of CDI following DLI and subsequent ileostomy reversal have been reported.[87] Fecal transplantation prior to reversal may be a viable option to reduce the risk of recurrence.[88]

Ancillary Treatment Strategies

Discontinuation of the Inciting Antibiotic

Discontinuation of the inciting antibiotic therapy is generally recommended for patients with CDI;[16] however, in cases where it is essential to treat other infections, continuation of antibiotic therapy may be unavoidable. In such instances, choosing antimicrobial agents less commonly associated with antibiotic-associated CDI is advisable. These include parenteral aminoglycosides, sulfonamides, macrolides, vancomycin, or tetracycline/tigecycline. Preferably, the intravenous route for continued antibiotic therapy is considered superior, as it minimizes disruptions to the gut microbiome.

Management of Diarrhea

Antimotility agents (e.g., loperamide, diphenoxylate-atropine) have traditionally been avoided in CDI, but the evidence regarding their potential harm is inconclusive. Based on current data, antimotility agents should be avoided in untreated CDI and in patients with severe infection.[89] However, once anti-CDI therapy has been initiated, they can be safely considered for patients experiencing difficulty maintaining fluid balance, provided there is no ileus or colonic distention.[49,89]

Probiotics

The disruption of gut microbiota because of CDI has sparked interest in the potential benefits of probiotics in the past. These probiotics are intended to help recolonize the gut and restore microbial diversity after it has been disrupted by antibiotic treatment and the overgrowth of *C. difficile*. However, there is limited direct evidence to support the routine use of probiotics for the primary prevention of CDI outside of clinical trials. Probiotics may hinder the reconstitution of the microbiome following antibiotic therapy,[90] and there are ongoing concerns about potential adverse effects, as highlighted by increased mortality rates in a pancreatitis trial.[91]

Fecal Microbiota Transplantation

Fecal microbiota transplantation involves the transfer of donor stool from a healthy individual to another with the intent of restoring a normal gut microbiome.[92] Stool can be delivered via upper gastrointestinal routes or lower gastrointestinal routes, although enema or colonoscopic delivery may be more effective.[93] In 2011, the Fecal Microbiota Transplantation Workgroup described three indications for using FMT to treat CDI: (1) recurrent CDI, (2) CDI not responding to standard therapy for at least 1 week, and (3) severe CDI with no response to standard therapy for 48 hours.[94] Guidelines have evolved with current recommendations suggesting consideration of FMT in cases of second or subsequent CDI recurrences.[16] Fecal microbiota transplantation can be highly effective with efficacy ranging from 84% for single FMT and 91% for multiple FMT on recent meta-analysis.[95]

Immunization Therapy (Antitoxin Agents)

In 2016, the US Food and Drug Administration approved bezlotoxumab, a monoclonal antibody against toxin B, for

CDI.[96] This agent is administered as a one-time intravenous solution at a dose of 10 mg/kg during administration of antibiotic therapy. Two phase III randomized controlled trials (MODIFY I/MODIFY II) demonstrated that the addition of bezlotoxumab reduced CDI recurrence rates and reduced CDI-associated 30-day hospital readmissions but did not reduce mortality.[97] Patients with risk factors for recurrent disease (age 65 years or older, history of CDI, immunocompromised state, severe CDI, and a high-risk strain) derived the most benefit on secondary analysis.[98] Studies outside of clinical trial data have found supporting results.[99] In their 2021 update, the IDSA/SHEA recommended the use of bezlotoxumab for patients with a recurrent CDI episode in the previous 6 months and the first CDI episode in a patient with high risk of recurrence, resource permitting.[51]

CONCLUSION

The diagnosis, pharmacologic management, and surgical options for CDI have evolved substantially, even since the turn of the century, necessitating that surgeons stay abreast of the latest developments. From the nuanced understanding of pathophysiology and risk factors and to advancements in diagnostic technologies and novel treatment modalities, the shift toward more sophisticated, evidence-based practices is evident. With the advent of NAATs and EIAs, the use of cell culture cytotoxicity neutralization assays has fallen to the wayside. In the early 2000s, CDI was treated with metronidazole and oral vancomycin, but now, fidaxomicin has emerged as a superior. Surgically, while TAC was the procedure of choice for CDI patients requiring surgical intervention, DLI with colonic lavage may be a useful alternative and is increasing in popularity. In addition, the introduction of FMT and immunization therapy as adjunct therapies underscores the ever-evolving nature in CDI management. The landscape of CDI diagnosis and management is continually evolving, and staying informed is essential for effective surgical intervention and improved patient outcomes.

AUTHORSHIP

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DISCLOSURE

Conflicts of Interest: Author Disclosure Forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E54).

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