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## Key Concepts

- More virulent strains of *C. difficile* such as ribotype 027 are associated with severe clinical infection.
- CDI in IBD patients should be treated with vancomycin.
- CDI is often associated with an exaggerated leukocytosis.
- Fecal transplant is effective therapy for recurrent CDI.

## Introduction

*Clostridioides* (formerly *Clostridium*) *difficile* is an anaerobic, Gram-positive rod bacterium, which often is part of normal colonic flora, but can become a pathogenic organism under the appropriate circumstances when the microbiome is altered. While this was once an uncommon clinical entity, *Clostridium difficile* infection (CDI) is now responsible for at least 20% of the cases of antibiotic-associated diarrhea, and its incidence continues to steadily rise [1]. As the incidence of this disease has increased, the emergence of more virulent strains, such as ribotype 027, has led to increasingly severe clinical presentations [2–4]. As we have seen evolutions in the *Clostridium difficile* bacterium, management strategies have drifted away from the older recommendation of metronidazole as a first-line agent to newer strategies using vancomycin or fidaxomicin [5–9]. This chapter will discuss the epidemiology of CDI and the most pertinent clinical risk factors. We will discuss current microbiological nomenclature and the evolving testing strategies. Finally, we will discuss the current best recommendations for medical and surgical treatment of this disease, as well as the evolving

role for fecal microbiota transplantation (FMT) [10] as an alternative to classical medical and surgical options for CDI.

## Epidemiology

Evidence is mounting that both the incidence and severity of CDI are increasing [11–13]. In fact, recent evidence suggests that in many hospital settings, CDI has now become the most common cause of hospital-acquired infection, surpassing methicillin-resistant *Staphylococcus aureus* (MRSA) infection [14, 15]. Data from the Centers for Disease Control and Prevention (CDC) suggested a fourfold increase in CDI from 1993 to 2009, while the incidence in those over age 65 increased by over 200% [16].

In addition to an overall increasing incidence, there appears to be an increasing severity as well. At least one ribotype (ribotype 027) has been associated with >15 times the production of toxins A and B compared to other strains, as well as producing a third toxin called binary toxin. This strain has been associated with a higher incidence of toxic colitis and increased mortality [17, 18]. A study by Falcone examined clinical response to antibiotic treatment in 027<sup>+</sup> vs. 027<sup>-</sup> subtypes. Overall, metronidazole monotherapy (HR 2.38, 95% CI 1.55–3.60,  $p < 0.001$ ) and immunosuppressive treatment (HR 3.11, 95% CI 1.91–5.09,  $p < 0.001$ ) were associated with recurrent CDI in ribotype 027-positive patients [4]. The authors advocated for vancomycin as primary treatment over metronidazole in cases where ribotype 027 is identified.

The increasing incidence of this condition is both clinically and financially important. A recent meta-analysis by Nanwa examined studies from 1988 to 2014 to determine the economic impact of CDI. The main outcome was the total direct cost attributable from hospital stays for CDI. Attributable direct costs of CDI ranged from \$8911 to \$30,049 [19]. A second study by McGlone agreed with these estimates for cost of a hospitalization and extrapolated to an

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annual US economic burden of \$496 million (hospital perspective) and \$547 million from a third-party payer perspective [20]. When both estimates from an inpatient and outpatient perspective are considered, the cost to the US healthcare system has been estimated to be a staggering \$3 billion [21]. Given the increasing incidence and cost of CDI, it is important to fully understand the most current risk factors, diagnostic testing, and treatment strategies.

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## Clinical Risk Factors

### Advanced Age

Though increasing age is commonly cited as a risk factor for CDI [22–25], patients of any age may be affected. The majority of the literature on age in CDI suggests that both young and older patients with CDI have similar clinical presentations and comorbidities, indicating that medical comorbidities rather than age may be the most important risk factors predisposing to CDI [22, 24]. Lee compared patients younger than 65 to those older than 65 and found more severe colitis in older patients and more frequent failure of first-line treatment, suggesting the need for more aggressive initial treatment in older patients hospitalized with CDI [23]. Louie randomized patients to be treated with vancomycin or fidaxomicin for severe CDI. Compared to patients age 18–40, clinical cure rate was lower, and clinical recurrence was higher for each successive decade [25].

### Antibiotic Treatment

The most consistent and potentially modifiable risk factor for the development of CDI is antibiotic use. Though the most commonly reported antibiotics implicated are clindamycin, fluoroquinolones, carbapenems, and cephalosporins [26–34], it appears that almost any antibiotic, used over any period of time, can be associated with the development of CDI. A recent systematic review compared the impact of different classes of antibiotics on the development of CDI in the setting of randomized trials. The results compared all classes of antibiotics and quantified individual risks of CDI. Clindamycin and carbapenems appeared to be the most strongly associated antibiotics with CDI [28]. Another contemporary review by Slimings of 13 heterogeneous studies indicated that second-, third-, and fourth-generation cephalosporins (OR 3.2), clindamycin (OR 2.8), and fluoroquinolones (OR 1.6) were the most commonly cited agents [35]. Though these studies are quite heterogeneous and it is difficult to assess the impact of antibiotics in comparison of the other myriad of risk factors, it does serve to remind us that antibiotics should be used judiciously in both the prophylac-

tic and therapeutic settings and that inciting antibiotics should be discontinued as soon as possible once CDI is diagnosed [26, 28–34]. Though it is postulated that antibiotics cause changes in colonic bacterial flora leading to susceptibility to CDI, most of the available data is descriptive in nature. Certain species of bacteria such as *Bacteroides*, *Bifidobacteriae*, and *Lachnospiraceae* seem to be the most prevalent among species which confer resistance to *C. difficile* colonization [36].

There is some degree of controversy as to whether probiotics should be used for primary prevention of CDI when a course of antibiotic therapy is prescribed. There are meta-analyses suggesting that probiotics could decrease the incidence of CDI when given to patients on antibiotics with no prior history of CDI [37–39]. Arguments against this strategy suggest that the incidence of CDI in hospitalized patients > age 65 on antibiotics tends to be <3% even without probiotics [40]. Additionally, the meta-analyses contained some studies with higher than expected incidence of CDI; excluding these studies makes the magnitude of effect of probiotics much less impressive. Additionally, due to the heterogeneity in types of probiotic and the numerous clinical confounding factors, it is difficult to say at this time whether these agents should be used as a means of primary prevention of CDI.

### Contact with a Healthcare Facility

CDI is common both in acute care and longer-term health facility stays. This is likely due to a concentration of patients with the typical risk factors for CDI, as well as the transmission from patient to patient via the fecal-oral route. In addition to the usual clinical risk factors, hospital-related factors such as increasing bed occupancy have been associated with an increased risk of developing CDI [41]. It is increasingly clear that hospitals need to be aware of the potential to transmit CDI among patients and to have proper infection control practices in place [42]. These practices include antibiotic stewardship, contact precautions in the appropriate setting, hand washing, disinfection practices, and CDI treatment protocols. Though literature has shown decreased incidence in CDI when proper disinfection practices [43], antibiotic stewardship [30, 44], and hand washing with soap rather than alcohol-based disinfectants [42, 45] decrease the incidence of CDI, not all hospitals follow these practices. A recent study by Aquina used a New York statewide database to study 150,878 patients in New York having either a segmental colectomy or proctectomy. *C. difficile* incidence ranged from 0% to 11.3% among surgeons and 0% to 6.8% among hospitals. Importantly, patient factors only explained 24% of the variation, while approximately 70% of the variation was from unexplained hospital factors [46]. This highlights the

need to be vigilant when caring for hospitalized patients, as the risks for CDI transmission are significant.

### Immunocompromised States

Regardless of the cause, compromise of the immune system appears to be associated with the development of CDI. It remains unclear whether immunosuppression alone is sufficient for the development of CDI, or whether immunocompromised patients frequently become hospitalized and have several of the other clinical risk factors for CDI. HIV patients seem to be at risk to develop CDI, with several of the common risk factors for infection also being cited such as low serum albumin, clindamycin use, prolonged hospital stay, and proton pump inhibitor use [47–50]. The strongest risk factor for CDI in HIV patients appears to be a CD4 count  $\leq 50/\text{mm}^3$ , with an adjusted odds ratio of 5.2–27.6 [48, 51]. There are many reports in the literature of CDI in other settings of immunocompromise such as general oncology patients [52], solid organ transplant recipients [53, 54], or stem cell transplant recipients [55–57]. Although these patients do have compromised immune systems, most of them seem to exhibit the classic risk factors for CDI as well such as prolonged hospitalization and antibiotic use [52, 54, 55, 57].

### Inflammatory Bowel Disease

CDI has been increasing in inflammatory bowel disease (IBD) patients and may be associated with increased morbidity, mortality, and need for surgery [58, 59]. Patients with both Crohn's disease and ulcerative colitis both appear to be at risk, and clinical presentation with CDI most often happens during an acute disease exacerbation. There is some evidence that specific genetic polymorphisms may be associated with the development of CDI. One such study noted that the TNFRSF14 locus was associated with a sixfold increase in development of CDI [60]. Some of the clinical risk factors for the development of CDI in the setting of IBD are low serum albumin, hemoglobin level below 9 g/dl, active colitis from IBD, biologic use, and antibiotic use [61, 62].

Though most studies consistently show a relationship between active colitis, steroid use, and antibiotic use with CDI, some studies failed to show an association between biologic medication use and CDI [63]. Testing for CDI is recommended in patients with IBD and severe colitis. Though the evidence supports the early administration of vancomycin to treat the CDI [64], these patients need close clinical monitoring in the hospital, as at least one study has estimated a sixfold increase in the need for colectomy in this setting [65].

### Perioperative Prophylactic Antibiotics and Mechanical Bowel Preparation

In preparation for elective colectomy, patients for several decades have typically received a combination of mechanical and oral antibiotic bowel preparation [66]. This was thought to minimize infectious complications by decreasing both the load of stool and bacteria in the colon. For many years, bowel preparation was used less and less, as the oral antibiotic preparation was abandoned. Recently, many studies have highlighted improved outcomes with mechanical bowel preparation and oral antibiotics including decreased surgical site infection (SSI) and anastomotic leak [67–71]. Some data also suggests that even in the absence of a mechanical bowel preparation, oral antibiotics may still decrease the incidence of SSI following colectomy [72]. It is possible that beneficial changes in the microbiome may be responsible for these improved surgical outcomes [73, 74]. However, there are some concerns that changes in the colonic microbiome may make a patient more susceptible to pathogens such as *C. difficile*. Literature on this topic is quite sparse. While on one hand, a single study by Morris noted that 9.5% of CDI patients had only preoperative oral antibiotic utilization as the only clinical risk factor [75], this likely does not outweigh the benefits of these agents in reducing SSI and potentially anastomotic leak. Further, the comparative data described above actually showed that patients receiving mechanical bowel preparation with oral antibiotics had a *lower* incidence of CDI postoperatively.

Likely the most important factor in reducing CDI is the appropriate adherence to guidelines and cessation of perioperative antibiotics as soon as feasible. A study by Balch showed that patients who had perioperative antibiotics continued for greater than 24 hours had a 6.7-fold increase in the incidence of CDI compared to those who received 24 hours of therapy alone [27].

### Proton Pump Inhibitors

There appears to be a clinical association between proton pump inhibitors and CDI, though it is difficult to directly attribute causation owing to the numerous other clinical risk factors that are often present. The exact mechanism for this association remains unclear, but at least one recent *in vitro* study by Stewart indicated that omeprazole stimulated the production of *C. difficile* toxins in both acidic and basic environments [76]. Since many conflicting studies have been published, there were 4 recent meta-analyses performed, combining data on over 300,000 patients [77–80]. These analyses were limited due to significant heterogeneity of data, and two of the studies noted publication bias. Combined

studies suggest an odds ratio of 1.6–1.7 for the development of CDI for hospitalized patients on PPIs [77–80].

One observational study by Chitnis examined 984 cases of community-acquired CDI. In this population, 36% had not received antibiotics. The most common risk factor was use of PPI medication, which was present in 31% of patients [81]. Though there appears to be a clinical correlation between use of PPIs and development of CDI, the quality of the evidence is poor. Randomized clinical studies with proper consideration of other clinical risk factors are lacking. Though this does not support the global discontinuation of PPIs in hospitalized patients, physicians should be encouraged to use these medications judiciously, when there is a clinical indication to do so. Many patients are routinely placed on PPI medication as a means of “prophylaxis” or for other questionable clinical indications [82]. The risk of CDI could be a reason to call these practices into question.

### Nomenclature and Genetics of *C. difficile* Infection

The proper genus designation for this pathogen is *Clostridioides* and not *Clostridium*. This change in terminology, introduced in 2016, was prompted by phylogenetic studies indicating that the genus *Clostridium* should be restricted to *Clostridium butyricum* and similarly evolutionarily related species that shared genetic and functional characteristics common to *Clostridium* cluster [83–85]. Despite being an anaerobic, spore-forming, Gram-positive rod, *Clostridioides* has more in common with genus *Peptoclostridium*. Its official reassignment to this genus never occurred, however, due to concerns that the pathogen’s former name recognition would make the introduction of such a different moniker a source of confusion and generate a significant financial burden to research and medical fields due to re-labelling costs. Therefore, a new genus was proposed (*Clostridioides*), one similar enough to the former name to allow continued broad recognition and one clever enough to allow the continued use of the term “*C. difficile*.”

CDI is clinically characterized by a colitis that is, in large part, mediated by bacterial envenomation. The genetic basis for *C. difficile* toxin production includes a 19.6 kb region known as the pathogenicity locus (PaLoc) that contains the genes for clostridial toxins A (*tcdA*) and B (*tcdB*) [86, 87]. These toxin genes, and the regulatory genes that increase and decrease their expression, are actually of bacteriophage (viral) origin [88, 89]. With successive replicative errors, loss of portions of these previously viral genes, under selective pressure, resulted in their retention as bacterial genes that increase the fitness of *C. difficile* [90]. Some, though not all, strains of *C. difficile* can produce an additional toxin known as binary toxin (*CDT*) encoded by genes outside of the

*PaLoc*. Toxins A (308 kDa) and B (269 kDa) are classified as large clostridial toxins due to their larger molecular weight [91]. Both of these toxins initiate monoglucosylation of a variety of intracellular Rho GTPases that result in depolymerization of cytoskeletal elements, with resultant cytopathy of colonocytes [92]. Binary toxin has an ADP-ribosyltransferase function that requires internalization by colonocytes; to promote this internalization, binary toxin is able to induce colonocytes to alter the apical aspect of their cell membrane to produce microtubular protrusions, increasing the membrane surface area up to fivefold and promoting the adherence of both *C. difficile* and its toxins, promoting further mucosal damage [93, 94]. Although updated studies are needed, the most current data suggests that binary toxin is present in up to 6% of all *C. difficile* isolates [95]. In virtually all symptomatic infections among humans, toxins A and B will be present.

### Ribotype and Clinical Severity

Although more frequently incorporated into research than clinical care, efforts at characterizing the dominant *C. difficile* strain on the basis of bacterial genotype have most commonly involved a process called ribotyping, a process using restriction enzymes to characterize the heterogeneity of the bacterial ribosomal intergenic spacer region [96, 97]. The most frequently identified ribotype associated with severe forms of *C. difficile* infection is ribotype 027 [98]. Though there are exceptions to the following, several associations between this ribotype and the clinical characteristics of CDI have emerged [99]. Ribotype 027 is the most frequently encountered strain among patients admitted from long-term healthcare facilities, with one study identifying an odds ratio of 4.87 for 027 being present compared to patients admitted with CDI from a private residence [100]. This may be a reflection of this ribotype having a selective advantage in terms of colonization and the promotion of a carriage state. Ribotype 027 is able to outcompete endemic bacteria for resources while producing larger volumes of bacterial toxins and producing higher rates of symptomatic infections; this strain also frequently has the ability to produce binary toxin in addition to toxins A and B [101]. Investigations focused on comparative bacterial genomics reveals that ribotype 027 has more than 200 genes not found in other strains of *C. difficile*, with many of these genes having a plausible role in promoting virulence [102, 103]. Other ribotypes, such as 078, represent potentially virulent strains that also have a zoonotic link between human and animal CDI. *C. difficile* as a pathogen has soil, animal, and human reservoirs, creating an important interaction between humans and their environment in terms of the emergence of new virulent strains of this bacteria [104, 105].

## Diagnosis of *C. difficile* Infection

CDI is a disease capable of producing both toxin-mediated and toxin-independent forms of colitis (160), and thus the hallmark of symptomatic infection is diarrhea. The term “*C. difficile* infection” should be kept distinct from carrier states, defined as patients without symptoms of infection who nonetheless also have a positive stool test for *C. difficile*. The exact incidence of carrier states in the general population is not known, though small studies of patient populations at risk for CDI suggest the incidence is not small. In 1 study of geriatric patients without diarrhea, 43 (16.4%) out of 262 consecutive patients tested positive for toxin B based on PCR stool testing. Of those 43 patients, 7 (16.3%) eventually developed symptomatic CDI, confirming that carrier states are both more common among patients with frequent health-care facility contacts and predispose patients to symptomatic infection [106]. Studies have suggested that patients who are able to form antibodies to *C. difficile* toxin A are more likely to remain asymptomatic carriers compared to patients who develop symptoms of CDI [107].

Diarrhea, which is typically grossly non-bloody in this disease, is the primary symptom of CDI. Depending on the severity of CDI, other findings will include abdominal distention, abdominal pain that is frequently colicky due to colitis, tachycardia, and hypotension. In fulminant cases, localized or generalized peritonitis may develop, which serves as an indication for surgery. CT findings include colonic wall thickening and pericolic fat stranding, as would be observed with any form of colitis. Colonic wall thickening is characteristic of severe forms of CDI and can provide a heightened index of suspicion for CDI prior to the results of stool testing. Transudative ascites is frequently associated with more severe forms of colitis. Pneumoperitoneum and portal venous gas are rarer radiographic findings and are generally encountered in patients with fulminant forms of the infection with septic shock and the need for vasopressors; the patients often develop non-viable colon due to severe mesenteric vasoconstriction.

## Diagnostic Tests for CDI

In general, the diagnosis of CDI is founded on a clinical suspicion with support from specific laboratory testing. The original confirmatory test for CDI was bacterial culture, which proved to be both difficult and was plagued by a lengthy time interval to final results. This technique was replaced by the cell culture cytotoxicity neutralization assay (CCCNA). This approach uses a filtrate of patient stool applied to a monolayer of one of various cell lines. After a 24–48-hour incubation period, cells are evaluated for evi-

dence of cytopathy attributable to *C. difficile* toxins. If cytopathic changes are observed, a neutralization assay is then performed to assure that these changes are due to *C. difficile* toxins. Historically, this technique was considered to be the gold standard; but with sensitivities as low as 65%, this test has been replaced by more sensitive tests that provide more expeditious results and do not require technical expertise that may limit generalizability [108].

Another, now outdated, method involves toxigenic culture. Though there are multiple methods to accomplish this test, all of them focus on isolating *C. difficile* from stool samples and confirming the presence of its toxin. There were numerous steps and difficulties with this approach. First, there is no one superior approach to isolating *C. difficile* from candidate stool samples. Secondly, once *C. difficile* colonies are isolated, those colonies have to be evaluated for their ability to produce toxin. This technique is considered by some to be a gold standard in terms of serving as a reference for new testing methods, though in terms of current practice, it has been supplanted by simpler, quicker, and less exacting approaches.

A current method of testing involves immunoassays that detect glutamate dehydrogenase (GDH), a conserved metabolic enzyme ubiquitous among *C. difficile*. As it is present among toxigenic and non-toxigenic forms of *C. difficile*, GDH alone lacks specificity for clinical purposes. Therefore, GDH is a useful screening test that, when positive, must be followed by a confirmatory test, which generally involves a toxin enzyme immunoassay (EIA). This approach allows for the use of a GDH as a high sensitivity test (80–100%) with an excellent negative predictive value, with limited cost and limited requirement for expertise and with rapid turnaround. When combined with toxin EIA, the cost per test remains less than PCR-based diagnostics while providing rapid results (<24 hours) and excellent sensitivity.

Nucleic acid amplification tests (NAATs) are a collection of PCR-based diagnostics that are designed to amplify highly conserved *C. difficile* genes, such as those related to toxins A (*tcdA*) and B (*tcdB*). The sensitivity of these tests is greater than EIA and possibly GDH-EIA combinations, though their cost is two to three times greater than GDH-EIA, and NAATs may require longer result times depending on the particular test considered. To leverage sensitivity, specificity, and cost-related issues, many hospitals have adopted an algorithmic approach, where diarrheal stools are first tested using a GDH assay. A negative result marks the end of the testing algorithm, while a positive GDH assay is followed by a confirmatory test, usually a toxin EIA. A positive GDH assay followed by a positive toxin EIA in patients with symptoms of CDI is treated as a case of CDI. A stool that is GDH positive and toxin EIA negative is tested using a NAAT. Routine retesting with NAATs to confirm resolution of CDI is not recommended, given the potential for bacterial DNA to linger for

as long as 30 days resulting in patients who no longer have CDI but who test positive for this infection.

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### Clinical Measures of Severity

Several clinical severity scoring systems are available, though none has emerged clearly superior to the others. Perhaps the two most commonly utilized are the 2017 Infectious Disease Society of America (IDSA) guidelines [109] and those published by the American College of Gastroenterology (ACG) [21]. In the IDSA schema, initial episodes are classified as (1) non-severe, if a patient's white blood cell count is <15,000 cells/mL and if their serum creatinine is <1.5 mg/dL; (2) severe, if a patient's white blood cell is >15,000 cells/mL and if their serum creatinine is >1.5 mg/dL; or (3) fulminant, if the patient demonstrates evidence of cardiovascular shock, ileus, or megacolon. The ACG schema defines severe CDI as patients with a white blood cell count of  $\geq 15,000$  cells/mL or a serum albumin of <3 g/dL. Fulminant disease is then defined as any patient requiring ICU admission, with a temperature of  $\geq 38.5$  °C, ileus, significant abdominal distention, altered mental status, a white blood cell count of >35,000 cells/mL or <2000 cells/mL, a serum lactate of >2.2 mmol/L, or any evidence of organ dysfunction. Using scoring systems such as these offers the potential advantages of standardizing patient assessments across providers and institutions.

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### Antibiotic Therapy for CDI

For more than 20 years, the two principal antibiotics used to treat CDI were metronidazole and vancomycin. Data has accumulated to suggest that vancomycin is the superior treatment option compared to metronidazole. For example, in a 2007 randomized, prospective, double-blind, placebo-controlled trial by Zar, 150 patients with either mild or severe CDI were randomized to either oral metronidazole (250 mg 4 times daily) or vancomycin (125 mg 4 times daily). While no significant difference in clinical cure rates was noted among patients with mild disease, for study subjects with severe disease, vancomycin was associated with a significantly higher cure rate (97% versus 76%;  $p = 0.02$ ) [110].

Additionally, retrospective data specifically focused on the treatment of mild disease suggests that vancomycin is superior to metronidazole in these cases as well, with one study reporting that compared to vancomycin, metronidazole was an independent risk factor for treatment failure [110]. Given these data, the most recent IDSA recommendations state "Use of oral metronidazole, however, should be restricted to an initial episode of nonsevere CDI in cases where other therapies are contraindicated or not available,

and treatment should be limited to one course due to case reports of neurotoxicity with prolonged or repeated use." Between these two drugs, vancomycin has emerged as the recommended drug for mild and severe forms of CDI [109].

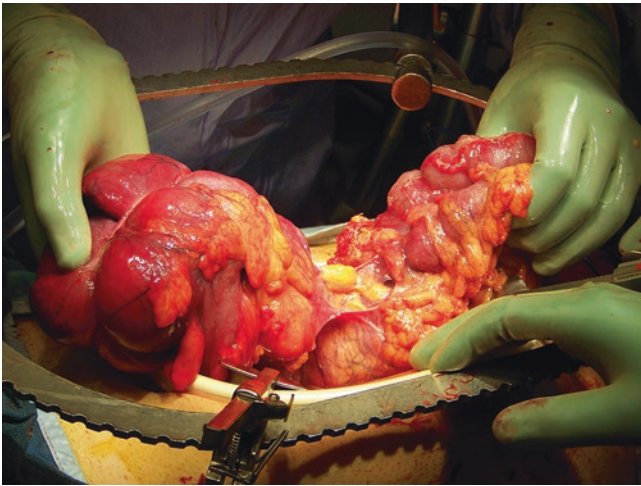
Fidaxomicin is a macrocyclic drug designed to exhibit a narrow antibiotic spectrum mediated through inhibition of the sigma subunit of RNA polymerase. The first Phase III study comparing fidaxomicin to vancomycin enrolled 629 subjects, demonstrating that fidaxomicin was non-inferior to vancomycin with respect to clinical cure rates [111]. Additionally, lower recurrence rates were noted with fidaxomicin, though only with strains that were not NAP-1 (a nomenclature of strains associated with more virulent infections). A more recent study (the EXTEND study) evaluated 364 patients randomly assigned to either vancomycin or extended pulsed fidaxomicin. Fidaxomicin was associated with an 11% improvement in clinical cure at 30 days after the end of treatment compared to vancomycin [112]. Further, fidaxomicin was just as safe as vancomycin, with no difference in treatment-related adverse events. A recent Cochrane Database Systematic Review evaluated 22 studies representing a total of 3215 patients. This study concluded that "moderate quality evidence suggests that vancomycin is superior to metronidazole and fidaxomicin is superior to vancomycin. The differences in effectiveness between these antibiotics were not too large and the advantage of metronidazole is its far lower cost compared to the other two antibiotics" [113].

For a first episode of non-severe CDI, the best available evidence supports the use of either vancomycin 125 mg orally every 6 hours or fidaxomicin 200 mg every 12 hours, either for 10 days. For fulminant cases, the most effective treatment remains the use of oral vancomycin 500 mg every 6 hours. In many instances, patients with fulminant CDI will develop an ileus, potentially decreasing the safety and efficacy of orally administered drugs. Therefore, for patients with fulminant CDI with concerns regarding the appropriateness of orally administered therapies, vancomycin can be administered as a retention enema (500 mg diluted in 100 cc of normal saline every 6 hours) [114], though the quality and strength of clinical data supporting vancomycin enemas is weak. In the setting of fulminant CDI, the Infectious Diseases Society of America also recommends administering 500 mg of parenteral metronidazole every 8 hours in conjunction with oral or rectal vancomycin, as the risks and side effects of a limited course of metronidazole are small in comparison to the risk of progressively worsening CDI.

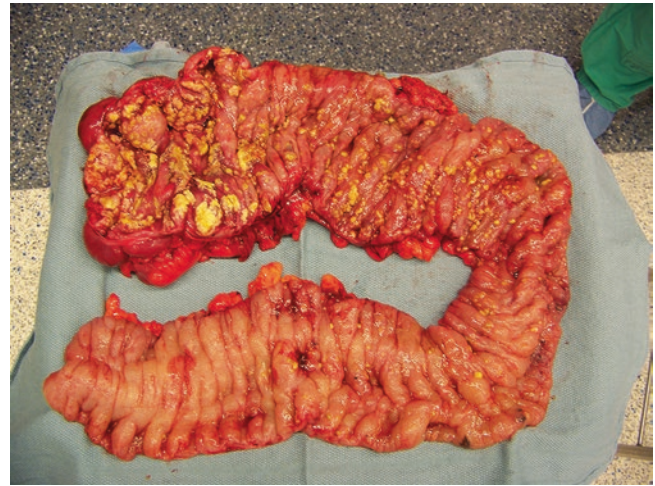
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### Surgery for CDI

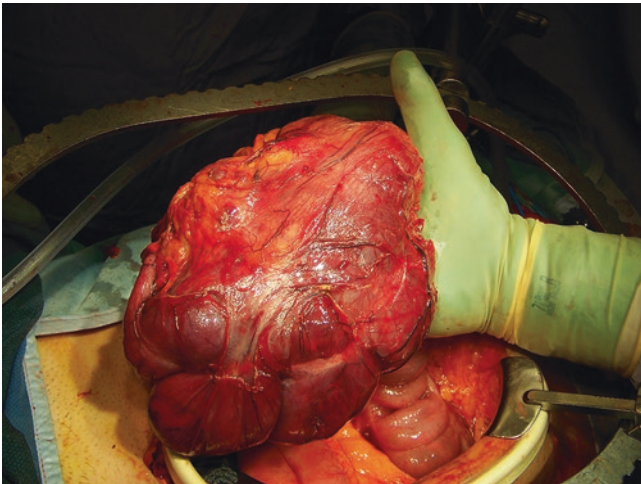
The incidence of patients who undergo surgery (Figs. 52.1, 52.2, and 52.3) for CDI has been estimated to be as high as 10% [115–117]. Inherent in these estimates are decisions



**Fig. 52.1** Patient with fulminant CDI with a dilated and thickened colon, with telangiectasias and serositis indicative of severe, transmural inflammation mediated by *C. difficile* toxins



**Fig. 52.3** Gross findings of mucosal thickening, inflammation, and pseudopolyps, consistent with severe CDI



**Fig. 52.2** Non-confluent regions of transmural ischemia observed in a patient with fulminant CDI. The combination of bacterial toxins as well as septic shock can produce non-viable large intestine

assessing whether a patient has received maximal medical therapy for CDI with surgery remaining as the only option, as well as selecting which patients might meet this qualification but are not considered to be candidates for surgical intervention. Multiple series indicate that only a small percentage of patients with fulminant CDI will undergo surgery; this suggests that the majority of CDI patients will not develop medically refractory disease severe enough to warrant surgery [115–117]. With the more recent introduction of diversion and colonic lavage [115], if it becomes more commonplace, it may increase the incidence of surgical intervention for CDI as it may be considered a “more survivable” surgery than total colectomy, which serves as the traditional procedure of choice.

There are two systematic reviews that compare the survival benefit of total abdominal colectomy to continued medical therapy in the setting of fulminant CDI, although the particular vantage points by which they evaluate this question differ in important respects. In a review by Bhangu, 31 studies were included in an effort to compare survival rates among patients with fulminant CDI who either underwent colectomy or who continued with medical therapy. In the surgical cohort, 89% of patients underwent a total colectomy, but patients who underwent a partial colectomy were also included. Findings from this review included a statistically significant association between preoperative clinical findings of septic shock and the incidence of postoperative mortality. Of interest, patients who underwent a partial colectomy experienced a 16% reoperation rate with resection of an additional length of colon. This review provided support for a survival benefit for surgical intervention in cases of fulminant CDI, with total colectomy arguably the preferred form of surgery compared to partial colectomy [118].

A second systematic review described outcomes among 510 patients for the purpose of evaluating whether total colectomy was associated with a survival benefit in the setting of medically refractory, fulminant CDI. The pooled odds ratio for mortality was significantly lower in patients undergoing total colectomy (OR = 0.70) [119]. Importantly, this study excluded patients undergoing partial colectomy.

In 2011, Neal described an alternative to total colectomy, involving the construction of a diverting loop ileostomy allowing for intraoperative colonic lavage with 8 liters of polyethylene glycol, followed by postoperative intraluminal vancomycin provided per stoma. In this study, 42 patients with fulminant CDI were treated with intestinal diversion, and their outcomes were compared to a historical control group of patients treated with colectomy and an end ileos-

tomy. The colectomy and diversion populations demonstrated similar preoperative APACHE scores as well as preoperative clinical indices, suggesting similar degrees of CDI severity. The group undergoing diversion was observed to have a significantly lower postoperative mortality (19% versus 50%) and shorter length of surgery, and 83% of the patients undergoing diversion had their surgeries completed laparoscopically [115]. This study provided the first modern description of diversion for life-threatening colitis of an infectious etiology, providing ostensibly superior survival utilizing a much smaller and more tolerable surgery that would also offer a higher likelihood of restoring gut continuity.

Since the study by Neal and colleagues, a number of primarily retrospective studies on diversion for fulminant CDI have been published using either institutional- or population-level data. One such study was undertaken in 2017 by the EAST Multi-Center Trials Committee that collected data from ten participating centers [120]. Certain details, such as the definition of CDI and the form of stool testing used at the participating centers, were not described. Comparing patients who underwent total colectomy to those who underwent diversion, there were no statistically significant differences in median vital sign measurements, white blood cell counts, lactate levels, INRs, or APACHE scores.

There were no differences between the surgical cohorts with respect to postoperative outcomes such as the rate of any complication, pneumonia, acute renal failure, sepsis, and acute respiratory distress syndrome. Just as importantly, there was no difference in rates of overall as well as unplanned reoperations, while ventilator days, ICU, and hospital lengths of stay were also similar between these groups. Unadjusted mortality was comparable between the cohorts (23.8% in the diversion cohort and 33.8% in the colectomy cohort;  $p = 0.44$ ). The authors of this study also performed calculations for what they termed adjusted mortality, which involved an inverse probability of treatment weights propensity score analysis. With this adjustment, mortality was significantly lower among the diversion group (17.2% versus 39.7%;  $p = 0.002$ ) [120].

A 2019 study using data from the Nationwide Inpatient Sample suggests that more surgeons are adopting diversion as the surgery of choice for fulminant CDI. In a retrospective review of this dataset from 2011 to 2015, 2408 patients were identified as undergoing surgery for CDI. Of these, 613 patients (approximately 20% of the study population) underwent diversion with a loop ileostomy; during the study period, the use of this procedure increased from 11% in 2011 to 25% in 2015 [121]. Although important details regarding the severity of CDI and the management of study subjects were not available using this data source, the authors also reported that in-hospital mortality did not significantly differ between these cohorts. One important limitation with the

data source used for this study was the inability to identify the selection criteria used for choosing the form of surgical intervention, which has implications for the measured outcomes such as mortality rates.

In summary, patients with severe, complicated/fulminant CDI should be managed in a multidisciplinary fashion. Surgical consultation is recommended when CDI of this severity is first recognized, in an effort to allow for surgical intervention at the earliest appropriate time. CDI is frequently associated with organ failure, including hematologic failure characterized by an exaggerated leukocytosis that is often  $>30,000$  cells/mm. It is critical that patients are euvolemic when assessing severity of sepsis, with a greater emphasis on trending organ function than on absolute cut-off values for laboratory abnormalities. De-escalating or discontinuing antibiotics that are not *C. difficile* targeted is also important; though the data is limited [122], CDI outcomes are worse when the inciting antibiotics are continued while CDI is being treated. While de-escalation of antibiotics is not always appropriate, certain infections (mild bladder infections) that are not life-threatening can have their treatment deferred, while life-threatening CDI is first addressed.

When patients are deemed to be too ill to allow for ongoing medical therapy, or demonstrate continued deterioration, surgery should be recommended for patients who are candidates for surgery. The largest body of evidence supports the use of total abdominal colectomy with an end ileostomy; partial colectomies have an extremely limited utility given a significantly higher incidence of reoperation due to postoperative fulminant CDI. Loop ileostomy has enough data at this juncture to be an acceptable alternative to total colectomy, though as described in a letter to the editor [123] in response to the recent EAST study [120] on loop ileostomy, there are several unanswered questions regarding this newer surgery. In the EAST study, diversion provided no advantage compared to total colectomy in terms of postoperative sepsis, renal failure, acute lung injury, overall mortality, and mortality related to unplanned reoperation. This may indicate that the particular strain of *C. difficile*, which is information frequently missing from the surgical literature on CDI, may influence postoperative outcomes, especially when a diverting stoma is created and an infected colon is left in situ.

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## Fecal Microbiota Transplant (FMT)

With access to commercially screened and prepared stool from vendors, FMT in either a liquid form for endoscopic or nasogastric application, or in capsule form for oral consumption, is now more readily available for inpatient use than in earlier times when providers had to collect, screen, and prepare stool from donors. FMT is extremely effective for treating recurrent CDI, with cure rates greater than 80% routinely



described [124]. FMT for fulminant CDI has the least exploration of all FMT applications, though the few studies on this topic are promising [125, 126]. One of the challenges with FMT for fulminant CDI is that of disease recrudescence and a measurable mortality from that disease recurrence. The incorporation of vancomycin in addition to FMT for fulminant cases appears to be important for ensuring reliable cure rates [127].

FMT is no longer an experimental therapeutic for outpatients, or inpatients, with CDI. Its cure rates for recurrent forms of CDI are superior to conventional antibiotics, leading some to question whether FMT should be the first intervention to address the recurrence of this infection. Of note, FMT does not currently represent the first-line therapy for a primary case of FMT. The availability of commercial vendors who can provide screened and prepared transplant material has simplified the process of FMT, making it more accessible for clinicians. The use of inpatient FMT for inpatient cases of CDI has increased in recent years, though physicians continue to treat the majority of cases of this infection with conventional antibiotics. At this time, there is insufficient data to recommend the routine use of FMT for the treatment of fulminant CDI; though there are limited numbers of small series that suggest safety and efficacy with FMT, more data in this patient population is required before FMT can be recommended for patients with life-threatening CDI.

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