Clostridium Difficile and Inflammatory Bowel Disease

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The past decade has seen an alarming increase in the burden of disease associated with Clostridium difficile.\textsuperscript{1–4} Studies from North America have demonstrated a doubling of incidence during this time period.\textsuperscript{3,4} The estimated economic costs associated with C difficile infection (CDI) range from $436 million to $3 billion in the United States annually.\textsuperscript{5,6} Initially considered to play a key role in the development of antibiotic-associated pseudomembranous colitis,\textsuperscript{7} C difficile is now known to cause a wide range of disease presentations ranging from asymptomatic carriage to fulminant colitis, toxic megacolon, sepsis, multiorgan failure, and death. Recent antibiotic exposure or hospitalization were previously considered key in the acquisition of CDI but recent data suggest an increasing number of CDI not associated with antibiotic use and infections being acquired in the community.

Inflammatory bowel diseases (IBD; Crohn disease [CD], ulcerative colitis [UC]) are chronic, lifelong, immunologically mediated inflammatory disorders of the gut that present typically with symptoms of abdominal pain, diarrhea, or rectal bleeding.\textsuperscript{8} Several studies have now demonstrated an increasing incidence of CDI in patients with IBD with a more severe course of disease compared with the non-IBD population.\textsuperscript{9–14} The similarity in symptoms between the two conditions (CDI and an IBD flare) but markedly divergent treatment plans (specific-antibiotic therapy and potential reduction of immunosuppression for CDI in the setting of IBD compared with escalation of immunosuppressive therapy for an IBD flare) makes it essential for treating physicians to be aware of the impact of CDI on patients with IBD, have a high index

KEYWORDS
- Clostridium difficile
- Inflammatory bowel disease
- Crohn disease
- Ulcerative colitis
- Colectomy

This article originally appeared in Gastroenterology Clinics of North America, Volume 38, issue 4.

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doi:10.1016/j.mcn.2009.08.013
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of suspicion, and institute early diagnostic testing and appropriate therapy to ensure optimal outcomes.

This article summarizes the available literature on the impact of CDI on IBD and discusses the various diagnostic testing and treatment options available. Also reviewed are clinical situations that may be specific to patients with IBD that are important for the treating physician to recognize.

PATHOGENESIS OF CDI

*Clostridium difficile* is a gram-positive spore-forming anaerobe that exerts its effect on tissue through active toxin production. There are two toxins associated with *C difficile* (toxin A and toxin B), which are coded by the *tcd A* and *tcd B* genes, respectively.15,16 These loci are located on a 19.6-kb base locus, the pathogenicity locus. The toxins act by binding to receptors on the enterocyte with subsequent endocytosis. This leads to pore formation, which further facilitates intracellular entry of the toxins. This is followed by glycosylation of Rho and Ras proteins leading to disruption of the epithelial cytoskeleton. As a result, there is loosening of the intercellular tight junction, increasing secretory losses, and voluminous diarrhea.15–22 In addition, toxin A also exerts a cytotoxic effect. Although most of the strains causing CDI produce both toxins A and B, a small fraction of CDI is caused by strains that either produce toxin A (11% of infections) or toxin B alone (7% of infections).23,24 Up to six other toxins are produced by *C difficile*. Important among these is a recently identified toxin, the binary toxin,25–27 which may be associated with more severe disease. The exact role of the binary toxin in the pathogenesis of CDI has not yet been defined.

**NAP1/027 Epidemic Strain of Clostridium difficile**

Between 2002 and 2005, outbreaks of CDI were identified in the province of Quebec, Canada.4 The strain of *C difficile* associated with these outbreaks demonstrated greater virulence than previously described strains. Over 150 ribotypes of CDI have been described so far. This epidemic strain of hypervirulent *C difficile* was identified to be the BI/NAP1/027 strain (restriction-endonuclease analysis group BI; pulsed-field gel electrophoresis type NAP1 [North American pulsed-field gel electrophoresis type 1]; and polymerase chain reaction ribotype 027).28,29 This strain carries the binary toxin in addition to producing 16 times the amount of toxin A and 23 times the amount of toxin B compared with typical strains.30 This epidemic strain has also been identified subsequently from several countries, forming an increasingly important cause of regional outbreaks of *C difficile*. The specific impact of this epidemic strain on patients with IBD is still unknown. Bossuyt and colleagues10 in examining the rising IBD-associated CDI in their institution did not find it to be disproportionately caused by the epidemic strain, but did not describe a prevalence of BI/NAP/027 ribotype among all their cases of CDI.

PREVALENCE OF CDI IN PATIENTS WITH IBD

Two decades ago *C difficile* was believed to be an infrequent infectious complication in patients with IBD. More recent reports have noted higher rates of infection, however, but more importantly, a rising temporal trend in CDI complicating the course of patients with IBD across several institutions and study populations.9–11,13,14 Rodemann and colleagues14 in a single center retrospective study identified a doubling of the incidence of CDI in patients with CD (from 9.5 to 22.3 per 1000 admissions) and a tripling in incidence among UC patients (from 18.4 to 57.6 per 1000 admissions) from 1998 to 2004. At the Medical College of Wisconsin, the authors identified a similar
rise in the proportion of *C difficile* cases complicating IBD from 1.8% in 2004 to 4.6% in 2005.\textsuperscript{11} The data from these single-center reports have been corroborated by larger studies using nationwide representative hospitalization population sampling in the United States.\textsuperscript{9,13} In a study using the Agency for Healthcare Research and Quality’s Nationwide Inpatient Sample from the United States, Ananthakrishnan and colleagues\textsuperscript{9} identified similar increases in CDI complicating hospitalization for IBD occurring nationally (UC, from 24 per 1000 to 39 per 1000; CD, from 8 per 1000 to 12 per 1000) between 1998 and 2004. Extending this study to 2006 reveals a continuing increase in the proportion of IBD hospitalizations being complicated by CDI (Fig. 1). The similar frequency estimates in the previously mentioned single-center and national studies suggest that the issue of CDI complicating hospitalizations in patients with IBD is widespread and not restricted to specific hospitals, tertiary referral centers, or regions within the United States.

Although these studies used the entire United States inpatient IBD cohort as the denominator in calculating the rates of infection, the frequency of *C difficile* complicating disease course in IBD patients who present with typical symptoms of colitis or disease flare, such as diarrhea and rectal bleeding, is much higher. Early reports found CDI infrequently in this population. Rolny and colleagues\textsuperscript{31} identified *C difficile* in only 5% of patients admitted for a flare. Subsequent reports placed the frequency of CDI between 5% and 18% among patients presenting with disease flare.\textsuperscript{32–35} More recently, among 99 patients who were admitted to Mount Sinai hospital with symptoms of a UC flare and had stool testing for *C difficile* toxin, 47% were positive, emphasizing the importance of a high index of suspicion for CDI in IBD patients presenting with typical symptoms.\textsuperscript{12} Adult IBD patients are not the only cohort impacted by *C difficile*. A recent study from Italy identified *C difficile* in 24.7% of patients with diarrhea or abdominal pain from within their pediatric IBD cohort.\textsuperscript{36} Although most studies on *C difficile* in IBD have focused on the hospitalized population, the prevalence of *C difficile* identified through stool culture was as high as 8.2% in an asymptomatic outpatient IBD cohort.\textsuperscript{37} Whether this represents asymptomatic

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**Fig. 1.** Trends in *Clostridium difficile* infection complicating hospitalizations in patients with inflammatory bowel disease in the United States. Data from the Nationwide Inpatient Sample 1998–2006.
colonization or has true disease-modifying effect by affecting the future disease course of IBD is still unclear. The rising frequency of CDI complicating IBD has paralleled the alarming increases in *C difficile* seen in the non-IBD population. In some institutions, the rate of increase of *C difficile* in the younger, healthier patients with IBD has outpaced that in the older non-IBD population with a greater comorbid burden, a traditionally higher-risk cohort.

**RISK FACTORS FOR CDI**

*Environmental Risk Factors*

Environmental exposure is the most common route of acquisition of CDI, which is frequently the result of person-to-person transfer of infectious spores. Exposure to a health care environment including recent hospitalizations increases the risk for nosocomial acquisition of CDI, the most common source of infection. Health care personnel are both at a greater risk for acquisition of infection and potentially transferring infection between patients if appropriate infection control measures are not followed.

Prior antibiotic exposure remains a key risk factor for the acquisition and development of CDI. Emerging data suggest, however, it no longer remains the only or even a necessary risk factor. Clindamycin was the antibiotic initially associated with CDI but since then multiple other antibiotics have been identified to confer a higher risk for CDI. These more commonly include broad-spectrum antibiotics, particularly fluoroquinolones, but the risk is not restricted to any specific antibiotic class. *C difficile* has even been described during the use of such antibiotics as vancomycin and metronidazole, agents typically used to treat CDI. The mechanism through which antibiotic use seems to increase the risk for CDI may be through the disruption of the normal intestinal flora and a subsequent proliferation of *C difficile*, a more resistant organism. Antibiotic use seems to be less essential for development of CDI in the IBD population. Antibiotic use within 3 months before CDI was seen in only 40% of IBD patients compared with 69% in the non-IBD population in one study, whereas another study was not able to identify any recent antibiotic exposure in 39% of IBD patients developing *C difficile*.

Immunosuppression is another well-recognized risk factor for acquisition of *C difficile* with greater frequency of CDI recognized in cancer patients undergoing chemotherapy or patients with organ transplantation on immunosuppression. Being chronic immunologically mediated inflammatory diseases, both CD and UC require long-term immunosuppressive therapy in a significant proportion of patients. Issa and colleagues identified maintenance immunosuppression to be associated with twofold risk of CDI (odds ratio [OR] 2.58; 95% confidence interval [CI], 1.28–5.12), a finding corroborated by a second study from Belgium. One other study failed to demonstrate this association, but may have been limited by a small sample size. Aminosalicylates (5-aminosalicylic acid compounds, such as mesalamine) have not been associated with CDI.

Other potential offending drugs that have been proposed include gastric acid suppressive therapy, such as with proton pump inhibitors. Some initial studies demonstrated a higher risk of development of CDI with proton pump inhibitor therapy but this finding has not been universally demonstrated. Recent studies of CDI in IBD populations also did not confirm this association of proton pump inhibitors with CDI.

Nosocomial or health care associated–infection is the most common modality of acquisition of CDI. Several recent studies in IBD population have shown, however, that a significant proportion of CDI in this cohort is community acquired.
recent health care environment should also not deter the treating physician from suspecting CDI.

**Host Risk Factors**

Increasing age and greater comorbid burden increase the risk of CDI in the IBD and non-IBD populations. IBD patients who develop CDI tend to be younger, however, than the corresponding non-IBD population who develop CDI. Nguyen and colleagues from an analysis of the Nationwide Inpatient Sample demonstrated a 13% greater risk of CDI with each 1 point increase in the Charlson’s comorbidity burden index. In addition to immunosuppressive medication, host immunity may play a role in determining susceptibility to CDI with patients who are able to mount a greater antibody response against the toxin being less likely to develop overt disease.

**IBD-specific Risk Factors for CDI**

Recent studies have shown that underlying IBD itself seems to be a risk factor for the development of CDI. Among IBD patients, involvement of the colon (compared with small bowel disease) seems to be a risk factor for CDI. Several studies have documented a greater rate of *C difficile* complicating UC compared with CD. Issa and colleagues identified colonic involvement in nearly 93% of IBD patients with CDI; on multivariate analysis, colonic disease conferred threefold greater risk (OR 3.12; 95% CI, 1.28–5.12) for CDI. Among CD, patients within colonic involvement seem to be at a greater risk for CDI than those with isolated small bowel disease. Also, among the subgroup of patients with colonic disease, left-sided or pancolonic involvement is more frequently complicated with CDI than those with limited colonic involvement. This suggests that extent of colonic disease may also be an additional risk factor. Patients with a greater disease activity may also be at a higher risk for CDI. Whether this elevated risk in colonic IBD is attributable to the extent of disruption of the mucosal barrier, alteration in gut flora, or other mechanisms has not yet been well defined. Because most studies on this topic have been retrospective, it has been difficult to tease out whether these associations represent true causation and are risk factors, or actually represent a consequence of the CDI complicating IBD. Further prospective studies are essential to identify if there are any IBD-specific risk factors that may increase the risk for CDI.

**CLINICAL FEATURES**

**Symptoms and Signs**

CDI typically presents with symptoms of diarrhea, lower abdominal pain, and tenderness. Although CDI itself presents with voluminous, watery diarrhea without gross blood or mucous, in the setting of underlying active IBD colitis overt rectal bleeding may not be infrequent. Patients may also have systemic symptoms, such as fever, malaise, and anorexia, and in the right setting these symptoms should raise suspicion for *C difficile* in the absence of an alternative explanation, even if diarrhea is not a prominent symptom. Laboratory evaluation may reveal leukocytosis with left shift; anemia (caused by bleeding or chronic inflammation); or hypoalbuminemia. Stool microscopy can reveal the presence of polymorphonuclear leukocytes and is also essential to rule out other bacterial or parasitic causes of diarrhea.

The frequency and impact of asymptomatic carriage of *C difficile* in patients with IBD remains under investigation. Between 1% and 4% of healthy adults may carry *C difficile*. In a study of 122 outpatients with quiescent, mild IBD not on
immunosuppression, Clayton and colleagues identified asymptomatic carriage of *C. difficile* (by stool culture) in 8.2% of the cohort; this was statistically higher than the rate in their control population of healthy volunteers. They identified no clinically evident CDI during a follow-up of 6 months, but whether the same lack of clinical CDI holds true in patients with greater severity of underlying IBD including those on maintenance immunomodulatory or biologic therapy has not yet been defined and merits future investigation.

**Radiologic Evaluation**

Radiologic evaluation is not required in most patients with CDI but it can be an important tool to aid in the assessment of complications of severe CDI. Plain abdominal radiography or abdominal CT scans may demonstrate colonic dilatation, wall thickening, or overt perforation and free air in those with complications or severe CDI, with CT scans being the more sensitive of the two modalities. Abdominal imaging can also help in the diagnosis of toxic megacolon or reveal alternative etiology to the patients’ symptoms, such as partial small bowel obstruction or internal penetrating disease.

**Endoscopy**

Lower gastrointestinal endoscopic evaluation is a key modality for assessment of CDI. The classic endoscopic appearance of CDI, described in about 50% of patients, is the pseudomembrane formation caused by sloughing and necrosis of the mucosa with ulceration. Histologic examination of this pseudomembrane may reveal a “volcano” lesion, focal ulceration with an eruption of necrotic debris and inflammatory cell infiltrate through the area of ulceration. The use of endoscopy in differentiating active colitis related to IBD from CDI has remained disappointing, however, because of the lack of typical features of pseudomembranous colitis in many patients with CDI associated with IBD. Both Issa and colleagues and Bossuyt and colleagues identified no pseudomembranes in any of the IBD patients with CDI who underwent endoscopic evaluation. In the right clinical scenario, the absence of pseudomembranes on lower gastrointestinal endoscopy should not deter the treating clinician from entertaining the diagnosis of CDI in IBD patients. Given the low discriminatory power of endoscopy in distinguishing active IBD colitis from CDI, the authors do not tend to evaluate patients endoscopically solely for the purpose of diagnosis CDI. In patients with fulminant disease, endoscopic evaluation may help objectively assess disease activity and look for other complicating infections, such as cytomegalovirus colitis. In this situation, the authors also obtain stool samples for *C. difficile* toxin testing using suction and a collection trap.

**DIAGNOSIS OF CDI**

The diagnosis of CDI relies on the demonstration of the organism by stool culture or the identification of the toxins in the stool. The most commonly performed and widely available test for *C. difficile* is the stool ELISA for toxins A and B. Although the first-generation ELISA tests detected only toxin A, more recent ELISA tests detect both toxins. This has improved sensitivity because in a small group of patients, CDI is caused by strains producing only toxin B. A minimum of 100 to 1000 pg of either toxin is required for detection by ELISA. The false-negative rate is between 10% and 20% with some studies demonstrating sensitivity as low as 66%. Stool culture is the most sensitive method for the identification of *C. difficile* and is the gold standard but fails to differentiate toxin-producing from nontoxigenic strains.
It requires additional testing for toxins A and B with either cell cytotoxicity assays or ELISA. In addition, it has a prolonged turnaround time of 48 hours and is not widely available. Stool cultures have the advantage of allowing for antibiotic susceptibility testing and molecular typing (especially in outbreak investigations). Cell cytotoxicity assays have sensitivity and specificity approaching 98% and detect much lower levels of toxin than the ELISA. Similar to stool culture, however, they too require significant laboratory support and have a turnaround time of 24 to 48 hours precluding their widespread adoption in routine clinical practice.

It is also important for the treating clinician to recognize the need for testing of multiple consecutive samples because a single sample, particularly with ELISA, may fail to have adequate sensitivity to diagnose CDI. In the authors’ experience, the initial stool ELISA for toxins A and B identified only 54% of cases with the second, third, and fourth specimens identifying 75%, 78%, and 92% of cases, respectively.

COMPLICATIONS AND OUTCOMES

**Short-term Outcomes**

Important and life-threatening complications of CDI include toxic megacolon, colonic perforation, and peritonitis with sepsis. Complicating the clinical picture, many patients who acquire CDI may do so during prolonged hospital stays and have significant underlying comorbid illness, contributing to the higher risk of death associated with CDI.

There are now several single-center and nationwide studies defining the short-term impact of CDI on patients with IBD. Although some studies found shorter hospital stays related to CDI in IBD compared with non-IBD patients, in contrast other studies found similar or longer duration of hospitalization among IBD patients with CDI compared with those with isolated CDI or IBD-related hospitalizations. In one study, CDI-IBD was associated with a 3-day longer hospital stay compared with IBD hospitalizations not complicated by *Clostridium difficile* (3 days; 95% CI, 2.3–3.7 days) and $11,406 higher adjusted hospitalization charges.

Studies have reported varying rates of colectomy for CDI in the setting of IBD. One study reported low rates for urgent or semiurgent colectomy after CDI (1 of 15 patients). Jodorkovsky and colleagues, however, found a 23% rate of emergent colectomy in their CDI-UC population with the indications being toxic complications (4 of 11) or medically refractory disease (7 of 11). This rate was higher than in the *Clostridium difficile*-negative IBD population. In the authors’ center, the rate of colectomy in hospitalized IBD patients with CDI was similarly high at 45% in 2004, but decreased to 25% in 2005 despite similar rates of requirements for hospitalization. Analysis of the nationwide inpatient sample corroborated these single-center studies demonstrating that underlying IBD was associated with sixfold (OR 6.6; 95% CI, 4.7–9.3) greater risk of bowel surgery compared with patients with CDI without underlying IBD.

**Long-term Outcomes**

Despite this information on the short-term outcomes of IBD patients with CDI, there are far more limited data on the long-term outcomes following CDI in IBD patients. A report from Mount Sinai hospital demonstrated worse outcomes in IBD patients with associated CDI for as long as 1 year after the initial infection, although this study was limited by its inability to tease out recurrent CDI versus a true change in the behavior of underlying IBD. In the previously mentioned study, UC patients with CDI had a significantly higher number of hospitalizations for UC-related causes (58 vs 27; *P* = .001) or emergency room visits at 1 year following the initial
hospitalization for *C difficile*. They also had a twofold (OR 2.38; 95% CI, 1.01–5.6) higher risk for colectomy at 1 year. At the authors’ institution, they performed a case-control study comparing the disease course for 1 year before and 1 year after the initial infection in 81 patients with IBD who developed *C difficile*. They found that the mean difference in hospitalizations between the year prior and the year following CDI was 0.89 (95% CI, 0.51–1.27). Forty patients (46%) had at least one more hospitalization in the year following *C difficile* infection (range 1–9) compared with the year prior. Over half the patients with IBD and CDI required an escalation in the medical therapy for IBD after treatment of *C difficile* (46 patients, 52.9%). This included new initiation of biologic therapy (23 patients); escalation of current biologic (seven patients); escalation or initiation of azathioprine and 6-MP (10 patients); or methotrexate (six patients). There were 10 documented cases of recurrent *C difficile* documented by positive toxin assay in this cohort.

The limitations of these retrospective studies remain, however, specifically in teasing out if underlying disease severity is a confounding factor, predisposing to these worse outcomes. It remains undefined whether more severe IBD is associated with acquisition of *C difficile* and subsequent CDI, although the study by Issa and colleagues indirectly suggested that the use of maintenance immunosuppression and potentially more severe illness was associated with the development of CDI. Likewise, it is unknown if CDI itself truly exerts a disease-modifying effect in patients with IBD.

**TREATMENT**

*General Measures*

Entertaining a high suspicion for *C difficile* and initiating early and appropriate testing is essential in the management of CDI. Infection control measures, such as hand washing and contact isolation for hospitalized patients, help in preventing patient-to-patient transfer of infection and prevent transfer through health care providers. Among patients who develop CDI in the setting of antibiotic use, a small proportion (10%–20%) may respond completely simply with the cessation of the offending antibiotic. Bossuyt and colleagues found that in 18% of IBD patients with CDI, this approach resulted in resolution of symptoms. Most patients, however, require specific directed antimicrobial therapy in addition to the previously mentioned steps.

**MEDICAL THERAPY**

*Metronidazole*

Metronidazole has historically been the first choice for the treatment of CDI, including infection in the setting of IBD. Despite the lack of Food and Drug Administration approval for this indication, several small randomized controlled trials have demonstrated success rates with metronidazole in the range of 75% to 90% and it remains a widely used antibiotic for treatment of CDI. Guidelines from the Infectious Disease Society of America recommend a dose of 500 mg orally three times daily for 10 days. In patients unable to take oral agents, metronidazole is also the only agent that can be administered intravenously (in doses of 500 mg four times daily) and attain sufficient concentration in the colon following biliary excretion for the treatment of CDI. Metronidazole also offers several advantages over vancomycin, namely a lower cost and less likelihood for the development and spread of vancomycin-resistant enterococci. Peripheral neuropathy, pancreatitis, and gastrointestinal side effects, however, including a metallic taste are not uncommon with metronidazole and limit its tolerability.
More recently, other important concerns have arisen regarding the use of metronidazole and its use in CDI.\textsuperscript{59} Failure rates before the emergence of the epidemic*C diffi-
cile* BI/NAP1/027 strain were 16\%, but more recent failure rates are alarmingly high at 35\%.\textsuperscript{57,60} Although it has efficacy comparable with vancomycin in the treatment of mild*C diffi-
cile*–associated diarrhea, it is inferior for severe*C diffi-
cile*–associated diar-
rrhea\textsuperscript{61} and should not be used as first-line therapy in such circumstances. This is an
important consideration for hospitalized IBD patients, who face a double challenge of infec-
tion and concomitant exacerbation of their idiopathic inflammatory colitis. Its
efficacy specifically in the IBD population with CDI is unknown, but one study reported
that just less than one quarter of the IBD patients with CDI required to be initiated on
oral vancomycin because of lack of sufficient response with metronidazole.\textsuperscript{10}

**Vancomycin**

The only Food and Drug Administration approved agent for the treatment of CDI,
vancomycin is typically dosed at 125 mg orally four times daily for a 10-day
course.\textsuperscript{15,39,57,62} Alternate dosing schedules include doses of 250 or 500 mg orally
every 6 hours, with a trial by Fekety and colleagues\textsuperscript{63} demonstrating equivalent effi-
cacy with both the 125- and 500-mg doses. It is important for clinicians to remember
that intravenous vancomycin has no role in the treatment of CDI because it fails to
achieve a sufficient concentration in the colon. Numerous clinical trials have docu-
mented efficacy of vancomycin in treating CDI with the relative risk of initial symptom-
atic resolution compared with placebo of 6.75 (95% CI, 1.16–48.43).\textsuperscript{64} Vancomycin is
the agent of choice in patients unable to tolerate oral metronidazole, pregnant or
lactating patients, and those with recurrent episodes or CDI refractory to metronida-
zole therapy. Overall, vancomycin is as effective as metronidazole in terms of
achieving initial symptomatic resolution or bacteriologic cure, and slightly inferior to
teicoplanin.\textsuperscript{64} A recent randomized trial has demonstrated superiority of vancomycin
over metronidazole, however, in the treatment of severe CDI.\textsuperscript{61} In that study, severity
of CDI was assessed by giving a score of 1 point each for age greater than 60 years,
a temperature of greater than 38.3°C, albumin level greater than 2.5 mg/dL, and WBC
count of greater than 15,000 cells/mm\textsuperscript{3}, and 2 points each for pseudomembranous
colitis or hospitalization in the intensive care unit. Patients with a severity score of
2 or more were considered as having severe CDI. In patients with mild disease (N =
81), vancomycin (125 mg four times a day) and metronidazole (250 mg four times
a day) had similar clinical cure rates of 98\% and 90\%, respectively (P = .36), but in
those with severe*C diffi-
cile*–associated diarrhea (N = 69), vancomycin had a superior
cure rate of 97\% compared with only 76\% with metronidazole (P = .02). Given the
demonstrated higher rate of adverse outcomes with CDI in the IBD compared with
a non-IBD population, it has not yet been defined how underlying IBD affects this
severity stratification. Physicians involved in treating IBD patients must recognize
the potential compounding effect of these conditions and promptly consider switching
therapy to vancomycin if there is no response to metronidazole in 2 to 3 days, partic-
ularly in patients requiring hospitalization.

Vancomycin is available in pill formulation, but this formulation is often more expen-
sive and poses challenges for patients with inadequate health care coverage. An alter-
native solution is to use parenteral formulations of vancomycin that are routinely
available for hospitalized patients as an orally ingested solution. For outpatients,
this strategy can also be arranged, typically through the assistance of hospital-based
pharmacies to provide the medication, at significant cost savings. The unpalatability of
oral vancomycin solution can be lessened with the oral dosing being followed by apple
juice or alternatively having the patient rinse their mouth with mouthwash to diminish drug aftertaste.

Although it is appropriate to wait for the confirmation of CDI with a positive C. difficile toxin assay in most patients before starting therapy, there are a few situations where the authors consider starting empiric therapy on suspicion of underlying CDI while waiting for the stool toxin assay and testing of multiple samples after an initial negative result. These include patients with fulminant colitis, especially those who remain unresponsive to steroids, or in those with unexplained clinical deterioration despite previously stable, mild disease in the right setting. In ambulatory patients with mild CDI, therapy is started with oral metronidazole. In most IBD patients with CDI severe enough to require hospitalization, the authors start treatment with oral vancomycin, typically 125 to 500 mg four times a day. In hospitalized patients with ileus or inability to consistently take oral antibiotics, they add intravenous metronidazole for severe CDI.

A more difficult issue has been the management of ongoing immunosuppressive therapy in the setting of IBD complicated by CDI with limited data on this topic. In most patients with CDI, the authors tend to not escalate immunosuppressive therapy during the acute CDI episode while the patient is being treated with metronidazole-vancomycin, and sometimes even decrease the dose of corticosteroids. Patients who have persistent disease activity after an episode of CDI who have documented negative toxin assays after completion of antibiotic course, however, may merit escalation of their immunosuppression. For hospitalized, fulminant IBD colitis patients this may involve initiation of anti–tumor necrosis factor-α therapy with infliximab. The rationale for the use of infliximab stems from concern regarding the broad immunosuppressive effect of high-dose intravenous corticosteroids, which may exert an inhibitory effect on humoral immunity, which is required to effectively clear the C. difficile infection. In addition, C. difficile infection elicits a tumor necrosis factor-α response in the gut, and this inflammatory mechanism may be targeted with the use of an anti–tumor necrosis factor-α antibody rescue strategy for hospitalized, severely ill IBD patients.

Probiotics

One proposed theory for the development of CDI has been disruption of the normal gut flora by the inciting antibiotics with subsequent proliferation of C. difficile. Probiotics are nonpathogenic microorganisms that theoretically may help restoration of gut flora, and decrease the incidence of CDI and potentially may be used in the treatment of CDI. There are several studies that have examined the role of probiotics in this setting. Interpretation of these studies is limited by small sample sizes, however, or variation in either the types of microbes studied or study population. The most promising results have been for Saccharomyces boulardii, with two studies demonstrating efficacy in the treatment of initial infection or recurrent disease. A recent Cochrane review concluded, however, that there was insufficient data to recommend use of probiotics either as the sole agent or in conjunction with antibiotics for the treatment of CDI.

Other Agents

Rifaximin is a nonabsorbed rifamycin-derived antibiotic that is used in the treatment of travelers’ diarrhea and has good in vitro activity against C. difficile. There are no randomized double-blind controlled trials yet examining its efficacy in the treatment of CDI. A single open-label trial comparing rifaximin with vancomycin demonstrated an efficacy of 90% in the treatment of CDI. Several studies have also demonstrated
in vitro resistance of *C. difficile* to rifaximin, however, particularly among the epidemic BI/NAP1/027 strain.\(^{18,57,58,68,69}\)

Teicoplanin is a glycopeptide antibiotic that has shown comparable or slightly superior efficacy than oral vancomycin in the treatment of CDI.\(^{57,64}\) It is not commercially available, however, in the United States. Other antibiotics that have demonstrated efficacy in treatment of CDI include nitazoxonide, fusidic acid, and bacitracin with none of the agents being used widely.

Anion-binding resins, such as cholestyramine and colestipol, may bind to the *C. difficile* toxin and be used in conjunction with antibiotic therapy.\(^{39}\) It is important to give these agents at least 2 to 3 hours apart from other oral agents to prevent binding to the antibiotics.

**SURGICAL TREATMENT**

In patients with CDI refractory to medical therapy or fulminant disease, surgery may be required for management.\(^{70,71}\) Surgery for CDI may have increased temporally over the past decade with a greater proportion of severe disease. Studies have also demonstrated a greater need for colectomy in patients with IBD and CDI compared with those without underlying IBD.\(^{9}\) Early involvement of surgeons with experience in the management of fulminant colitis is essential to ensure optimal outcomes. Total colectomy is the procedure of choice for patients requiring surgical treatment with inferior outcomes after hemicolecctiony or limited resection. The optimal timing of surgery in IBD patients has not yet been well-defined. Patients with toxic megacolon or perforated bowel require emergent surgery. Patients who do not improve with medical therapy within 3 to 5 days with worsening symptoms may also require more urgent surgery.

**SEVERE OR REFRACTORY CDI**

Metronidazole or vancomycin achieve clinical and bacteriologic cure in most patients with CDI, but a small cohort of patients may not respond and have refractory disease. Vancomycin has superior efficacy compared with metronidazole in the treatment of severe CDI.\(^{61}\) A combination of oral vancomycin and intravenous metronidazole can also be tried in patients who do not respond to either antibiotic or have adynamic ileus as a means of ensuring adequate colonic antibiotic concentration.\(^{15,57,58}\) There are no randomized trials, however, of intravenous metronidazole in the treatment of CDI. In patients with severe CDI, intraluminal administration of vancomycin by intracolic delivery or rectal administration using a retention enema administered through a Foley catheter has shown success in a small number of patients.\(^{15,57}\)

Intravenous immunoglobulin (IVIG) has been used successfully for the treatment of CDI in a series of 14 patients,\(^{72}\) all of whom had failed a median of three courses of treatment with either vancomycin or metronidazole. They were administered a single dose of IVIG in doses ranging from 150 to 400 mg/kg. Six patients responded with a median time to response of 10 days. This success has been replicated in another small series and is a therapeutic option in this cohort of patients. IVIG may have a more important role in a subset of patients who develop IBD as a complication of an underlying congenital immunodeficiency state, such as hypogammaglobulinemia or common variable immunodeficiency. In patients with a history suspicious for common variable immunodeficiency, the authors check quantitative immunoglobulins and in patients with low levels, consultation with an allergy or immunology specialist and an initiation of an immunoglobulin replacement regimen may help treat the underlying colitis. They also check quantitative immunoglobulin levels in hospitalized
patients who are unresponsive to standard CDI therapy and use IVIG to treat refractory disease in patients with low immunoglobulin levels. Rectal infusion of feces obtained from healthy hosts (fecal biotherapy) has shown benefit in some patients. Early surgical consultation is essential for patients with severe or refractory CDI.

**RECURRENT CDI**

After a single episode of CDI, patients may either develop a relapse (if symptoms recur within 7–14 days of cessation of therapy) or a true recurrence if symptoms reappear at a more distant time interval. Recurrence may be seen in 15% to 35% of patients after an initial episode, with this rate rising to 35% to 65% after the first recurrence. Some recurrences may last for several months. A recent meta-analysis of 12 studies including 1382 patients identified continued use of non–C difficile antibiotics after diagnosis of CDI (OR 4.23; 95% CI, 2.10–8.55; \textit{P}<.001), concomitant receipt of antacid medications (OR 2.15; 95% CI, 1.13–4.08; \textit{P} = .019), and older age (OR 1.62; 95% CI, 1.11–2.36; \textit{P} = .0012) to be risk factors for recurrent disease.74 There are limited data on CDI recurrence rates in an IBD population. At the authors’ center, among 81 IBD patients who had a positive stool \textit{C difficile} toxin assay in 2005 to 2006, 10 patients had documented toxin positive recurrence within the subsequent year.75

There are several treatment options available for the treatment of recurrent disease. Patients with the first recurrence after treatment with metronidazole can be treated with a course of vancomycin, whereas those who fail vancomycin may be tried on a second course. For multiply recurrent disease, there are several nonrandomized series documenting efficacy of various treatment regimens. A longer course of vancomycin administered with gradual taper over 6 weeks was effective in a small cohort of patients. Higher doses of vancomycin (500 mg four times a day) may be effective but may also be associated with a high rate of relapse. IVIG may be useful in patients with accompanying hypogammaglobulinemia. One study reported on use of rifaximin in eight patients with more than three recurrences each. Oral vancomycin was used until symptomatic cure followed by a 2-week course of rifaximin. This regimen achieved success in seven of eight patients. There are limited data on treatment of recurrent disease in IBD patients. In a study from the authors’ center of 14 IBD patients, rifaximin was administered at a dose of 200 mg three times a day for 2 weeks, followed by 200 mg once daily for 2 weeks and 200 mg every other day for the final 2 weeks of the taper. They were able to prevent recurrent CDI in all patients with this regimen. Probiotics have also shown a benefit in preventing recurrent CDI with two randomized studies showing a benefit with the addition of \textit{S boulardii} to standard treatment.

In patients with recurrent CDI, in addition to the previously mentioned therapeutic options, it is important to remove potential external sources of reinfection. Cessation of the offending antimicrobial agent, if possible, is important. Use of more targeted antimicrobial therapy may decrease disruption of gut flora. The treating physician should also inquire about all potential environmental sources of recurrent disease including exposure to a health care setting or patients who may be caregivers to people who are carriers of \textit{C difficile}. All patients should be instructed on the importance of strict hand hygiene measures.

**INFECTION CONTROL AND PREVENTION**

\textit{Clostridium difficile} is transmitted through spores that are relatively resistant to environmental degradation. The spores can persist for as long as 5 months on hard
surfaces. One study found *C. difficile* in 49% of sites in rooms occupied by those with CDI. Commonly used quaternary-ammonium–based or surfactant-based detergents may not adequately eradicate *C. difficile* spores and may actually increase sporulation. In addition, the epidemic BI/NAP1/O27 epidemic strain may hyper-sporulate, producing more spores than other *C. difficile* strains. A 10% sodium hypochlorite solution has been shown to have good efficacy in decreasing environmental spore burden and reducing the number of cases of CDI.

In addition to environmental precautions, hand washing and hygiene are keys in preventing transmission of *C. difficile*. Soap-and-water hand washing effectively mechanically dislodges spores. Alcohol-based hand gels do not eradicate spores or reduce transmission with a mean of 30% of spores being transferred by a handshake even after use of these gels. Although institution-wide use of alcohol-based gels has not been shown to increase the rate of CDI, experts suggest use of soap-and-water hand washing techniques after the care of patients with CDI. Contact isolation may help prevention of patient-to-patient transfer of infection within hospitals and healthcare institutions. The use of gloves and gowns in the care of patients with CDI may also help prevent transmission and reduce cases of CDI. Standard endoscope decontamination procedures may be followed after lower gastrointestinal endoscopy in patients with CDI.

**CDI in Special Situations in IBD**

**Clostridium difficile Enteritis**

Infection with *C. difficile* has been reported in the small bowel in patients with colectomy. Such infection may carry high morbidity and mortality in the range of 60% to 93%. The authors reported a series of six patients with *C. difficile* enteritis from 2004 to 2006. All patients had undergone colectomy for severe UC and had developed high-volume ileostomy output (six of six), fever and leukocytosis (four of six), and ileus (five of six) in the postoperative period. Ileostomy output tested positive for *C. difficile* toxin and there were no other likely explanations for the patient’s symptoms. All patients responded to treatment with oral and intravenous metronidazole or oral vancomycin.

**Clostridium difficile Pouchitis**

Total proctocolectomy with ileo-anal pouch anastomosis is the procedure of choice in patients with severe UC who require surgery for dysplasia or refractory medical disease. The ileal pouch is also susceptible to infection with *C. difficile* and may be associated with either *C. difficile* enteritis above the reconstruction or *C. difficile*–associated inflammation of the pouch. Because as many as half the patients develop acute or chronic pouchitis after ileo-anal pouch anastomosis and require treatment with antibiotics, this may predispose them to developing CDI. There are now several reports of infection with *C. difficile* causing pouchitis that is refractory to broad-spectrum antibiotic therapy. Administration of oral vancomycin in such patients with a positive *C. difficile* toxin assay has shown benefit in some. A recent study of 115 patients with ileo-anal pouch anastomosis from the Cleveland Clinic identified 21 patients (18.3%) to be positive for *C. difficile* toxin by ELISA. Male gender (OR 5.12; 95% CI, 1.38–20.46) and preoperative left-sided colitis (OR 8.4; 95% CI, 1.25–56.4) were independent risk factors for *C. difficile* infection. Interestingly, there was no difference in antibiotic or immunomodulator use between the two groups, again serving to emphasize that prior antibiotic use should not be considered essential to entertain a suspicion for *C. difficile* infection in IBD patients.
*Clostridium difficile* infection has also been reported in segments of diverted bowel and responds to topical therapy with metronidazole or vancomycin.

**DIRECTIONS FOR FUTURE RESEARCH**

Although there are growing data on the incidence and impact of CDI on patients with IBD, there are several areas that have yet remained undefined. Most studies have been retrospective in design, which has precluded moving identifying associated factors to defining true causative risk factors. The studies have also focused on hospitalized cohorts of IBD patients, an important subgroup given the higher rate of adverse outcomes in this cohort. Further research is essential, however, to examine the impact of CDI in those with milder IBD or ambulatory cohorts to truly define the impact of CDI on IBD. There is need for research on the role of asymptomatic carriage of *C difficile* and examination of longer-term outcomes of CDI in IBD. There are preliminary data suggesting that an episode of CDI can affect disease activity for even as long as 1 year after the initial infection. This needs to be examined prospectively, however, with better identification of recurrences, standard protocols of measuring disease activity at periodic intervals after the initial infection, and using an appropriate control population. There is also a significant dearth of data on the therapeutic efficacy of various treatment regimens for CDI including recurrent and refractory disease in the setting of underlying IBD. Multicenter cohorts and randomized trials in the IBD population are essential to satisfy this need.

**SUMMARY**

Infection with *C difficile* is an increasingly common complication in patients with IBD and can have severe consequences in some patients. There has been a temporal escalation of burden of CDI over the past decade with higher rates of surgery and mortality in the IBD population compared with the non-IBD cohort. A high index of suspicion should be maintained even in the absence of traditional risk factors, such as antibiotic use or health care exposure, and should be followed by testing including testing of multiple stool samples in appropriate clinical situations. Directed antibiotic therapy should be initiated early after a positive test; in select patients with severe presentation, empiric antibiotic therapy should be considered. Comanagement with surgeons is a key in those with severe disease.

**REFERENCES**


