Surgical Management of *Clostridium difficile* Colitis

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Abstract

Keywords

- *Clostridium difficile*
- pseudomembranous colitis
- colectomy

Clostridium difficile infection (CDI) will progress to fulminant disease in 3 to 5% of cases. With the emergence of hypervirulent, multidrug-resistant strains, the incidence and severity of disease are continuing to rise. Prompt identification, early resuscitation, and treatment are critical in preventing morbidity and mortality in this increasingly common condition. Discontinuation of antibiotics and treatment with oral vancomycin and intravenous or oral metronidazole are first-line treatments, but complicated cases may require surgery. Subtotal colectomy with ileostomy remains the standard of care when toxic megacolon, perforation, or an acute surgical abdomen is present, but mortality rates are high. Recognition of risk factors for fulminant CDI and earlier surgical intervention may decrease mortality from this highly lethal disease.

Objectives: Upon completion of this article, the reader should be able to (1) understand the pathogenesis and evolving epidemiology of *Clostridium difficile* colitis, (2) identify predictors of fulminant disease and mortality, and (3) describe medical and surgical management options and expected outcomes.

Since the identification of *Clostridium difficile* as the causative agent in pseudomembranous colitis in 1978, *Clostridium difficile* infection (CDI) has reached epidemic proportions.^{1,2} It is the most common cause of hospital-acquired diarrhea and has become a major cause of morbidity in hospitalized patients, reaching 250,000 cases in inpatient care facilities in the United States in 2005.³

The spectrum of disease in CDI can range from benign, self-limited diarrhea to fulminant pseudomembranous colitis, toxic megacolon, perforation, shock, or even death. Fulminant disease can be seen in 3 to 5% of patients and can result in mortality in up to 34 to 80%.^{4,5} In the early 2000s, a hypervirulent, multidrug-resistant strain was identified in epidemics across North America and Europe, and eventually in Asia. These outbreaks were associated with dramatically increased morbidity and mortality. Since that time, outbreaks of hypervirulent strains have persisted. As the severity of disease has increased over the past decade, surgical intervention for CDI

has similarly increased. Despite greater awareness of the disease and increasing colectomy rates, mortality remains high.

Prompt diagnosis, early resuscitation, and directed treatment are critical in preventing morbidity and mortality. Understanding risk factors for fulminant disease and death can help identify patients who may benefit from early surgical intervention. In this article, we will discuss epidemiology and pathogenesis, predictors of mortality, current medical management, and the role of surgery in patients with fulminant *C. difficile* colitis.

Pathogenesis and Epidemiology

Clostridium difficile is an anaerobic, Gram-positive, spore-forming rod that can produce toxins that are damaging to the colonic mucosa and are capable of causing a marked systemic inflammatory response.^{4,6} Bacteremia from *C. difficile* is rare, and morbidity from infection is due to a direct cytotoxic effect on the colonic mucosa.

Colonization with the metabolically inactive spore occurs in 2 to 3% of healthy adults and 20 to 50% of hospitalized patients.⁷ Symptomatic infection results from transformation of the spores into active bacteria, which can occur in the

setting of microbial disruption following antibiotic administration.

Although many strains have been identified, only strains that produce toxins A and B cause symptomatic disease. These toxins cause apoptosis and hyperpermeability of the colonic epithelium by inactivating GTPases within the cells, thereby disrupting critical cell signaling pathways and causing degradation of the actin cytoskeleton.⁷ Both toxins cause neutrophilic infiltration and fluid secretion and stimulate production of inflammatory cytokines including tumor necrosis factor- α , interleukin-8, substance P, and macrophage inflammatory protein 2.⁴ Toxin B has long been considered the primary virulence factor, but recent data demonstrate that both toxins A and B can cause colitis and play an important role in the disease process.⁸

Up to six other toxins have been identified, including binary toxin, or *C. difficile* transferase, which may be an important virulence factor for CDI. It is an ADP-ribosyltransferase that similarly alters the actin cytoskeleton in colonic epithelial cells, and is associated with hypervirulent strains and may cause increased mortality.⁹ Together, these toxins cause cell necrosis and sloughing, creating an exudate of cellular debris and inflammatory cells that make the pseudomembranes characteristic of the disease.

Since 2000, there has been a dramatic rise in the incidence and severity of CDI. Because CDI is not a reportable disease, comprehensive statistics are not available, but studies from individual centers consistently report increasing incidence, morbidity, and mortality over the past decade. From 1997 to 2005, incidence rates grew from 3.8 up to 9.5 cases per 10,000 patient-days in a survey of Canadian hospitals.¹⁰ Recent data from Michigan show an increase in CDI from 463.1 to 1096.5 discharges per 100,000 over the period from 2002 to 2008.¹¹ Incidence can increase four- to fivefold during outbreaks.^{12,13} Overall directly attributable mortality of up to 6.9% has been reported.³

NAP1/B1/027 (North American pulsed-field type 1, PCR ribotype 027) is a highly fluoroquinolone-resistant, hypervirulent strain that produces binary toxin and levels of toxins A and B in vitro that are 16 to 23 times higher than historical strains.¹⁴ Since 2002, this strain has been associated with epidemics in the United States, Canada, Europe, and Asia, where morbidity and mortality had risen dramatically. Although NAP1/B1/027 is the most well-known hypervirulent strain, other genotypes including PCR-ribotypes 018, 056, and 078 have also been implicated in severe outbreaks.¹⁵

Relapse rates for CDI are high—up to 20%. Relapses are associated with continued use of broad-spectrum antibiotic and hypoalbuminemia, and like primary infection, can progress to fulminant disease.^{16,17}

Risk Factors for Development of CDI

The strongest risk factor for the development of CDI is antimicrobial exposure, with up to 98% of patients having had at least one dose of antibiotics in the preceding 2 weeks. When the disease was first described, clindamycin was the primary agent associated with infection.¹ Over the past two

decades, cephalosporins and fluoroquinolones have played a dominant role in pathogenesis, but a wide range of antimicrobial agents continues to be implicated in CDI.¹⁸ Although broad-spectrum antibiotics are more likely to cause disease, patients with any antibiotic exposure, including a single perioperative prophylactic dose, can develop CDI.

CDI has long been considered a hospital-acquired disease. Incidence increases with prolonged hospital stays, and higher rates of infection are also seen in long-term care facilities. Although hospital-acquired infections have been the primary source of CDI, community-acquired infections now account for up to 41% of cases. Community-acquired CDIs tend to occur in younger, healthy patients and are less likely to be severe. A greater number of these cases are not associated with antibiotic exposure.^{3,19}

Infection is also more prevalent, and often more severe, in older patients. Age-adjusted rates of CDI are several times higher in patients > 64 years old compared with younger patients.¹⁰ Immunosuppressed patients, including those with chronic steroid use, chemotherapy, or immunosuppression after transplantation, are more likely to develop CDI and have increased risk of fulminant disease, but in some cases mortality from severe disease may be lower. It is unclear why this is the case, but a heightened level of suspicion, early intervention, lower threshold for surgery, and limited ability to mount an inflammatory response to toxins may be factors. Patients with severe comorbidity and postoperative patients following cardiothoracic, vascular, transplantation, and gastrointestinal procedures also have increased rates of CDI.^{4,16,20,21}

Role of proton pump inhibitors (PPIs) in the development of CDI remains controversial. PPIs suppress the secretion of gastric acid, thereby potentially limiting the natural antimicrobial effect of stomach. Gastric acid suppression does not seem to affect the spore form of *C. difficile*, which is already resistant to low pH, but the vegetative form may be more likely to remain viable through the gastrointestinal tract in patients using PPIs. This effect seems to be muted by the concurrent use of antibiotics.^{22–24}

Patients with inflammatory bowel disease (IBD) are particularly susceptible to CDI and have a poorer prognosis from infection. CDI has been shown to affect up to 4.6% of IBD patients.²⁵ These patients not only have worse outcomes from CDI, but are shown to have escalation in medical therapy, higher rates of colectomy, and increased mortality for up to a year after infection.^{26,27} Patients can even develop infection after total proctocolectomy, as CDI has been documented in the ileum of patients with ileostomy or ileoanal pouch.

Signs, Symptoms, and Diagnosis

Although CDI classically presents with watery diarrhea, patients with severe forms of the disease have additional nonspecific toxic manifestations including abdominal pain, severe bloating, profuse diarrhea, fever, tachycardia, sepsis, and/or shock. It is noteworthy that 16 to 37% of patients with severe colitis have no diarrhea due to ileus or fulminant disease.^{4,5,16,28,29} Patients may progress rapidly to fulminant

disease or can develop severe symptoms days to weeks into their clinical course.

Because bacterial or viral infections, Crohn's or ulcerative colitis, ischemic colitis, autoimmune and inflammatory colitis can appear similar in their most severe forms, the initial diagnosis should be guided by objective data, either by laboratory confirmation of *C. difficile* toxin, toxigenic culture, or endoscopic findings of pseudomembranes. *C. difficile* toxin gene testing by polymerase chain reaction (PCR) allows prompt diagnosis that is highly sensitive, similar to the historical gold standard of toxigenic culture, which takes up to 48 to 96 hours. Enzyme immunoassays to detect toxins A and/or B are easy to perform and widely available, but have a lower sensitivity (63–94%) and specificity (75–100%) than gene testing or culture.¹⁰ A shift toward the more sensitive PCR test may allow for improvements in targeted clinical care.

In addition to testing for *C. difficile*, comprehensive physiologic assessment for patients with suspected CDI should include a complete blood count, electrolyte levels, lactate level, and arterial blood gas. Patients can develop a leukemoid reaction with white blood cell count elevations from 30,000 to 50,000/microliter with bandemia.⁴ Hypoalbuminemia may be present due to the protein-losing enteropathy caused by the presence of the toxin. Stool examination for ova and parasites and pathogenic bacteria will rule out most additional infectious sources.

Endoscopy is not mandatory if CDI has been confirmed, but is useful in diagnosing or ruling out other causes of colitis. Minimal insufflation will reduce the risk of iatrogenic perforation. Pseudomembranes are diagnostic of CDI, although not all patients with CDI will have pseudomembranes present. If pseudomembranes are seen, no biopsies need to be taken.

Moderate to severe abdominal pain or peritoneal findings including rebound and guarding should prompt further imaging. An upright abdominal plain film can demonstrate free air, identify mucosal edema or thumbprinting, and assess for colonic dilation. In stable patients, a computed tomography scan may demonstrate continuous or segmental colonic thickening, pericolic stranding, and ascites (→Fig. 1). Findings of severe colonic distention, extraluminal air, or pneumatosis may indicate perforation or impending perforation and lead to earlier surgical intervention.

Management of Complicated CDI

The term “complicated CDI” has been used to describe cases with shock, megacolon, perforation, need for intensive care unit (ICU) admission, emergency colectomy, or death within 30 days of diagnosis.⁷ Initial management of severe disease is to stabilize the patient with isotonic fluid resuscitation. Inciting antibiotics should be stopped, if possible, and any antidiarrheal medications should be discontinued, as these may potentiate the effect of the toxins. In severe cases of colitis where CDI is suspected, empiric treatment should be initiated while confirmatory tests are pending.

Metronidazole (oral and intravenous [IV]) and vancomycin (oral) have been the mainstays of treatment since the initial description of *C. difficile* colitis in 1978 and remain the

Figure 1 Computed tomography scan showing colonic thickening, edema, and pericolic stranding.

treatment of choice today. In mild cases of CDI, a 10- to 14-day course of oral metronidazole is the first-line therapy. Low-dose oral vancomycin (125 mg every 6 hours) is preferred in cases of severe CDI where diarrhea and leukocytosis are present, and combination IV metronidazole and higher dose oral vancomycin (500 mg every 6 hours) should be used in cases of complicated CDI.¹⁰ Rectal infusion of vancomycin may be helpful in cases of severe ileus.

Systematic reviews of clinical trials comparing various antimicrobial agents have failed to demonstrate any antibiotic that was clearly superior, although recent trials examining a new agent are promising for prevention of recurrent disease.^{3,10,30} Two recent randomized controlled trials evaluated the efficacy of fidaxomicin, a selective antimicrobial with high fecal concentration, poor systemic absorption, and minimal activity against normal gastrointestinal flora. Results from these studies showed fidaxomicin to be similar in efficacy to vancomycin in initial clinical cure and more effective in preventing recurrence (15% vs 25%, $p = 0.005$,³¹ 13% vs 27%, $p = 0.0002$ ³²). Fidaxomicin has recently been approved for the treatment of CDI in the United States, and is available, albeit at significant cost. In three small studies, teicoplanin (not currently available in the United States) was found to have an initial bacteriologic response and cure that was superior to vancomycin and metronidazole, but concerns about study size and potential for bias limited interpretation of these results. Rifampin and metronidazole in combination were shown to have a significantly higher mortality than with metronidazole alone. Vancomycin is found to have significantly higher rates of bacterial or toxin clearance than bacitracin.^{3,30}

Other proposed treatments have targeted control or elimination of the toxin to disrupt the pathogenesis of the disease. One small study showed that *C. difficile* immune whey binds toxin A and has been shown to have similar efficacy to metronidazole in the treatment of recurrent CDI.³³ Colestipol

is similar to placebo in the treatment of CDI. Toxin-binding therapy is currently not recommended for widespread clinical use.

Probiotics have been disappointingly ineffective in the prevention and treatment of primary and recurrent CDI. No advantage is shown to adding probiotics to antibiotic treatment, and they are contraindicated in critically ill patients who are at risk developing fungemia, a potentially life-threatening side effect of probiotic administration.³

There has been a renewed interest in fecal transplantation in the treatment of recurrent CDI. Donor stool is administered by direct infusion during colonoscopy. Recent reports show 70 to 92% success in treating relapsing CDI. There is currently no role for this technique in severe, acute disease.^{34,35}

Operative Management

Patients with an acute surgical abdomen require emergent colectomy. As these patients may not have an established diagnosis, intraoperative colonoscopy may help to establish the diagnosis. Intraoperative findings may be nonspecific as this is a mucosal-based disease. Colonic serosa may appear normal or thickened.

Deciding when to intervene in medically managed patients is more difficult. Because of the nature and severity of disease, few high-quality studies directly comparing surgical and medical management exist and there are no prospective, randomized studies to evaluate the role of colectomy in the management of complicated CDI. Many recent studies attempt to identify risk factors for fulminant disease, although they are heterogeneous and most have a small sample size.

There is evidence that early surgical intervention can prevent deaths. Patients with fewer than 6 days of medical therapy prior to surgery have been shown to have lower mortality. Lamontagne et al showed that patients undergoing emergent colectomy were less likely to die than patients treated medically (AOR [adjusted odds ratio] 0.22, 95% confidence interval [CI] 0.07–0.67).¹⁴ Postoperative patients, who are under the close watch of a surgical team, and those cared for in the surgical intensive care unit setting, tend to fare better. This may suggest that patients receive more timely surgical intervention.

However, even in patients undergoing colectomy, mortality remains as high as 34 to 57% (► **Table 1**).^{4,5,16,21,28,36–41} Understanding the risk factors for mortality following colectomy for complicated CDI can help identify which patients may benefit from early surgical intervention. Data consistently identify markers of multiorgan failure as predictors of mortality, including vasopressor requirement, hemodynamically instability, need for mechanical ventilation, and renal failure. These findings may be even more relevant in elderly patients, who have been found to have a higher rate of mortality from complicated CDI and from emergent colectomy. Once these signs develop, the window of opportunity for surgical intervention may have closed.

Laboratory markers have been identified that are associated with higher mortality in complicated CDI and may help

in quickly risk-stratifying patients. Leukocytosis $> 50,000/\mu\text{L}$, lactate $\geq 5 \text{ mmol/L}$, and hypoalbuminemia, may identify patients with impending shock and hemodynamic collapse.³⁹ Urgent colectomy should be considered in these patients.

Subtotal Colectomy with End Ileostomy

Subtotal colectomy with end ileostomy is the procedure of choice for patients requiring surgery for severe colitis or toxic megacolon. Subtotal colectomy allows for control of disease, stabilization of the patient, and preserves reconstruction options for the future. Segmental colectomy has generally been associated with higher mortality and does not address the pancolonic nature of the disease. Similarly, ileostomy alone, colostomy, and nontherapeutic laparotomy have generally shown increased mortality.

An open approach is the standard of care in most severely ill patients. Careful mobilization of the abdominal colon is performed to prevent perforation and intraabdominal contamination. Vascular ligation near the colonic wall will minimize collateral injuries during a difficult dissection. In cases of severe colonic inflammation, ligating vessels first may minimize inflammatory response. As mentioned above, intraoperative colonoscopy is indicated if there is any question about the diagnosis.

The colon can be divided at the distal sigmoid or rectosigmoid junction. Several options for the Hartmann pouch are possible. A longer Hartmann pouch can be brought up as a mucous fistula and matured at the bedside postoperatively or can be sewn to the inferior portion of the fascia. These methods for control of the stump help minimize complications resorting from a rectal stump blowout. Some surgeons advocate lavage of the rectal stump with vancomycin irrigation to help control inflammation in the Hartmann pouch. Data for this technique is limited. A Penrose drain positioned transanally may help to decompress the stump and prevent leak.

Diverting Loop Ileostomy and Colonic Lavage

Although subtotal colectomy with end ileostomy remains the standard operation for fulminant CDI, new alternatives for treatment are emerging. Neal et al treated all patients who presented with severe, complicated, fulminant *Clostridium difficile*-associated disease over an 18-month period ($n = 42$) with laparoscopic exploration with diverting loop ileostomy and colonic lavage with 8 L of warm polyethylene glycol intraoperatively. This was followed by 10 days of vancomycin antegrade enemas and 10 days of IV metronidazole. Mortality was 19% and only three required subsequent total abdominal colectomy. End ileostomy or colostomy has been associated with high mortality in the past, but the authors attribute their success to the dilution of toxins through colonic lavage followed by appropriate antibiotic treatment.⁶ Although promising, these results have not been duplicated at other institutions and should be interpreted with caution.

Table 1 Outcomes of Colectomy for *Clostridium difficile* Infection (CDI): Predictors of Mortality

Author	Publication Year (Study Period)	CDI with Colectomy/ Total CDI	Mean Age	Mortality	Predictors of Mortality on Multivariate Analysis (Odds Ratio, 95% CI)
Dallal et al ⁴	2002 (1989–2000)	44/2334 (1.9%)	65	57%	Advanced age Vasopressor [†]
Koss et al ³⁸	2005 (1996–2003)	14/3472 (0.4%)	64	35.7%	Segmental (80% mortality) vs subtotal colectomy (11%) [‡]
Ali et al ⁴⁰	2008 (1995–2006)	36/ [*]	70	47%	WBC $\geq$ 37,000 (based on ROC curve, area under the curve = 0.727, $p < 0.01$)
Hall and Berger ³⁷	2008 (1998–2006)	36/3237 (1.1%)		36%	Preoperative intubation (7.2, 1.2–39.8) Vasopressor requirement (6.0, 1.08–33) Recent surgery (improved outcome) (0.1, 0.02–0.52)
Byrn et al ²⁸	2008 (1994–2005)	73/5718 (1.3%)	68	34%	Vasopressor requirement (5.0, 1.1–22.2) Mental status change (12.6, 2.45–64.7) Length of medical treatment (1.4, 1.1–1.64)
Seder et al ²¹	2009 (2000–2007)	69/6841 (1%)	71	42%	Age $>$ 65 (6.8, 1.4–32.3) ARF (5.4, 1.6–18.1) Acute respiratory failure (3.8, 1.1–13.1)
Pepin et al ³⁹	2009 (1994–2007)	130/ [*]	71.5	37%	Age per year (1.03, 1.00–1.06) Lactate $\geq$ 5 mmol/L (10.32, 2.59–41.07) WBC $\geq$ 50,000 (3.68, 0.92–14.80) Albumin $\leq$ 15 g/L (6.57 (1.31–33.06)
Sailhamer et al ⁵	2009 (1996–2007)	75 [§] /4796 (1.6%)	68	32%	(Includes medical and surgical patients) Age $\geq$ 70 (2.2 1.0–4.8) WBC $\geq$ 35,000 or $<$ 4000 (4.2, 1.9–9.1) Neutrophil bands $\geq$ 10% (2.8, 1.3–6.5) Preoperative intubation (4.7, 2.1–10.5) Vasopressor requirement (4.0, 1.9–8.5) Preoperative oral vancomycin (improved outcome) (0.25, 0.11–0.55)
Dudukgian et al ⁴¹	2010 (1999–2006)	14/398	59	36%	(Includes medical and surgical patients) Higher APACHE II score and ASA class Renal failure Pulmonary failure Steroid use

WBC, white blood cell count; ROC, receiver operating characteristic; ARF, acute renal failure.

^{*}Total number of CDI cases unknown.

[†]Mann-Whitney rank sum; no odds ratio data available.

[‡]Fisher exact test; no odds ratio data available.

[§]Includes patients requiring intensive care unit admission with and without colectomy.

Conclusion

Fulminant CDI is a highly morbid and often fatal disease. Appropriate and timely treatment may help to reduce mortality. Vancomycin and metronidazole remain the primary antibiotic treatments of choice, although fidaxomicin shows potential for an alternate agent. Early surgical intervention in elderly patients, patients with severe leukocytosis, elevated lactate, hypoalbuminemia, and/or signs of hemodynamic collapse or organ failure may help to reduce mortality for complicated CDI.

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