Surgical aspects of fulminant Clostridium difficile Colitis

Parag Butala, M.D., Celia M. Divino, M.D., F.A.C.S.*

Department of Surgery, Mount Sinai School of Medicine, New York, NY, USA

Abstract

BACKGROUND: Clostridium difficile–associated disease (CDAD) is responsible for the majority of nosocomial diarrhea, and fulminant C difficile colitis can have mortality upwards of 80%. Early identification and treatment of fulminant C difficile colitis is critical to patient care, but timing of surgical intervention remains difficult. This review summarizes the epidemiology, predictors of development, and management of fulminant C difficile colitis.

METHODS: A literature search was conducted between January 1989 and May 2009 using the keywords “clostridium difficile colitis” or “fulminant clostridium difficile colitis” and “surgery.” Articles not in English, those not involving human subjects, and case reports were excluded. A total of 29 studies were identified, none of which were randomized controlled trials. Studies were assessed for total number of cases, surgical mortality, and significant variables affecting mortality. Additionally, results of diagnostic modalities assessing for active infection were tabulated.

CONCLUSION: Early diagnosis and treatment with subtotal colectomy and end ileostomy is critical in reducing the mortality associated with fulminant colitis. Patients who have a history of inflammatory bowel disease (IBD), recent surgery, prior treatment with intravenous immunoglobulin (IVIG), vasopressor requirements, leukocytosis, or increased lactate should have early surgical consultation and operative intervention.

© 2010 Elsevier Inc. All rights reserved.

KEYWORDS:
Fulminant Clostridium difficile colitis; Surgery

Clostridium difficile–associated disease (CDAD) accounts for the majority of nosocomial cases of diarrhea, and with the recent upsurge of multidrug-resistant strains, morbidity and mortality from C difficile have been increasing. The most severe form of C difficile colitis, known as fulminant C difficile colitis, has been associated with mortality as high as 80%. For these severe forms of infection, early diagnosis and definitive treatment are essential for survival of patients; despite this, there is a lack of data on factors that guide a clinician regarding surgical management. This article reviews the epidemiology and predictors of development of fulminant C difficile infection with a focus on the surgical treatment and outcomes.

Methods

A literature search was conducted between January 1989 and May 2009 using the keywords “clostridium difficile colitis” or “fulminant clostridium difficile colitis” and “surgery.” Articles not in English, those not involving human subjects, and case reports were excluded. A total of 29 studies were identified, none of which were randomized controlled trials. Studies were assessed for total number of cases, surgical mortality, and significant variables affecting mortality. Additionally, results of diagnostic modalities assessing for active infection were tabulated.

Epidemiology

Clostridium difficile is the leading cause of nosocomial diarrhea, with more virulent and drug-resistant strains spreading through hospitals in the past decade. The bacteria are a normal component of gastrointestinal flora in up to 3%
of healthy adults and up to 20% of those who are on antibiotic treatment. As many as 10% of patients hospitalized for more than 2 days are found to have C difficile colitis. In a study by McFarland et al in which rectal swab specimens were serially cultured, approximately 8% of patients who did not have C difficile on admission were found to have developed C difficile–associated diarrhea during their hospitalization, and a far larger percentage of the patient population was found to have become asymptomatic carriers of the bacteria.1

The prevalence of C difficile infection within hospitalized patients has been rising and, more recently, virulent strains isolated throughout North America have become more widespread, thereby raising the morbidity and mortality of C difficile infection. Recent studies reviewing the prevalence of C difficile have found that the number of hospital discharges for C difficile colitis have increased from 261 cases per 100,000 discharges to 546 cases per 100,000 discharges in the years between 1993 and 2003.2 In Pittsburgh, a significant increase in the incidence of C difficile colitis was noted in the years 1999 and 2000, with an increase in diagnoses from 206 to 343.3 In a retrospective analysis of data from the Agency for Healthcare Research and Quality’s National Inpatient Sample Database, Zerey et al found a 34% increase in the incidence of CDAD among a sampling of surgical patients in 2002. These patients were also more likely to have a longer length of stay (18.0 days vs 4.0 days) and higher in-hospital mortality (13.5% vs 2.4%) when compared with patients who did not develop C difficile colitis. Predictably, patients undergoing colon, small bowel, or gastric resection were at highest risk of developing CDAD.4

This recent upsurge in infection rates correlates with the onset of outbreak of BI/NAP1/027, a more virulent form of C difficile.5,6 Outbreaks in the United States, France, Japan, United Kingdom, Netherlands, and Belgium have all identified this strain. Approximately 50% of the isolates found among patients in recent outbreaks in Pennsylvania and Maine have been of this virulent strain. This epidemic strain has multiple toxigenic factors, including upregulation of toxins A and B and a resistance to fluoroquinolones, and has been associated with an increased mortality compared with older strains of C difficile.7,8

While most patients respond to oral metronidazole or oral vancomycin as treatment of CDAD, some are prone to progression of the disease to a more severe form, known as fulminant C difficile colitis, which carries a mortality ranging from 35% to 80%. These patients develop systemic symptoms of hypotension, oliguria, and tachycardia secondary to bacterial toxin-induced release of inflammatory mediators, and they frequently require surgery to prevent worsening sepsis and complications such as colonic perforation.5 Recently, published reports suggest that mortality from C difficile colitis is worsening substantially. In 1993, the total mortality rate was 20.3 per 100,000 discharges. This more than doubled to 50.2 deaths per 100,000 in 2003. Among patients with the principal diagnosis of C difficile colitis, the mortality increased from 2.32 to 4.26 per 100,000 in the years between 1993 and 2003.2 The incidence of fulminant symptoms at one institution increased from 0.48% in 1999 to 3.2% in 2000. Within 1 year, their incidence of colectomy for fulminant colitis increased from 0.48% to 2.6%.3 Similar increases were noted nationally at other institutions, with reports recording an increase of abdominal colectomy rate from 1.8 per 1,000 in 1993 to 6.4 cases per 1,000 in 2003 in Minnesota, and an increase in operative intervention from 0.3% to 1.4% between 2000 and 2007 in Michigan.2,9

Predictors and Management of Fulminant Clostridium difficile Colitis

The ability to predict the risk factors that differentiate the patients who will progress to fulminant C difficile colitis is critical to reducing the associated mortality. Prior studies have shown that patients are taken to the operating room when they have signs of systemic toxicity and are refractory to medical therapy. While the average length of medical treatment has varied per study, overall mortality was lower when medical treatment before surgery was less than 6 days.10–17 Among the studies assessing the length of medical treatment among patients with fulminant colitis before operative therapy, investigators reported the highest mortality and longest delay before operative intervention. Mortality was notably decreased in those studies in which patients had no more than 6 days of medical treatment. Of note, diarrhea is not necessarily a common finding in this patient population, and up to 20% of patients may not have any diarrhea.3,18

Over the past 20 years, a number of studies have attempted to assess the predictors of fulminant colitis. From their results, broad conclusions can be drawn, which suggest that peritoneal signs, failure of improvement to antibiotic therapy, and signs of multi-organ failure are all indicators of the need for surgical intervention.10,19–22 The largest of these series reviewed the records of 67 patients undergoing colectomy at Veterans Affairs Medical Centers nationwide over a 4-year period. While their results corroborate other studies in suggesting that systemic toxicity and failure of antibiotic therapy are indications for operative management, Longo et al fail to provide a more detailed quantitative assessment of the factors that contribute to fulminant colitis.13

More recently, several studies in the past 3 years have provided insight into predictors of fulminant colitis. In a recently published study, Greenstein et al describes 75 patients who had undergone colectomy for the diagnosis of fulminant C difficile colitis of which 35 met the study inclusion criteria of having undergone medical therapy for C difficile for at least 3 days before colectomy. Severity of disease was similar to results of prior studies, as the cohort had a 31% rate of admission to the intensive care unit and an overall mortality of 40%. By adjusting for confounding
factors and performing a multivariate logistic regression analysis, Greenstein et al demonstrated that 4 factors were significantly associated with progression to fulminant *Clostridium difficile* colitis. These were leukocytosis greater than 16,000 cells/µL, surgery within the past 30 days, a history of inflammatory bowel disease (IBD), and a history of past intravenous immunoglobulin (IVIG) treatment.\(^\text{15}\)

While the presence of leukocytosis with colitis is not surprising given that most patients with fulminant colitis have substantial leukocytosis, the significance of a leukocyte count greater than 16,000 cells/µL at the start of therapy is a useful prognosticator of those patients likely to need operative intervention. Additionally, while it would be expected that some patients may have undergone treatment with IVIG as one of the final medical therapies available for refractory colitis, the pre-existing comorbidities of recent surgery and of having IBD are valuable identifiers for the development of fulminant colitis. Patients with IBD are well known to have a higher incidence and recurrence of *C difficile* colitis than other hospitalized populations. The incidence at one institution increased from 1.8% to 4.6% between 2004 and 2005. Additionally, 20% of IBD patients with colitis required colectomy, suggesting the increased incidence of progression to fulminant *C difficile* colitis among these patients.\(^\text{23,24}\)

Likely due to their immunocompromised state, patients with IBD warrant particular attention when faced with *C difficile* infection.\(^\text{25}\) A limitation in the Greenstein study design is that by excluding those patients who went directly to the operating room for colectomy before receiving antibiotic therapy, the sickest patients may have been excluded from the study, thereby affecting the results of the multivariate analysis.

Lamontagne et al performed a logistic regression analysis on patients undergoing colectomy for *C difficile* during a recent outbreak in Quebec. By comparing 38 patients who had colectomy for *C difficile* colitis with 127 controls who had an admission to the intensive care unit but had not undergone surgery for *C difficile* colitis, the authors were able to draw several pertinent conclusions that were corroborated by Greenstein et al. When compared with controls that had not undergone surgery, patients who had a colectomy had a 78% reduction in the odds of mortality. It was also shown that up to 95% of patients with a white blood cell count greater than 50/L × 10^9/L or with lactate greater than 5 mmol/L died within 30 days of admission without a colectomy. In particular, patients with a leukocyte count greater than 20,000 cells/µL and patients older than 75 years of age demonstrated a survival benefit from colectomy. Additionally, Lamontagne et al found that colectomy in patients with a peak lactate between 2.2 and 4.9 improved survival when compared with medical therapy. In this study, Lamontagne et al demonstrated both the advantage of colectomy and provided cutoffs for surgical intervention. Lastly, while their study does not comment on the use of IVIG or the presence of IBD, this is likely to be related to characteristics of the patients at Greenstein’s and Lamontagne’s specific institutions.\(^\text{26}\)

A number of other studies have followed the precedent of Lamontagne et al and have developed predictors of mortality to aid in timing of surgical intervention. Byrn et al identified 73 patients who had undergone colectomy for fulminant *C difficile* colitis over 11 years and who had an in-hospital mortality rate of 34%. Among these patients, a multivariate analysis showed that mortality was increased among patients with vasopressor requirements, mental status changes, and longer length of medical treatment (6.4 days vs 3.0 days) before surgery. Therefore, multisystem organ failure and a delay in surgical intervention were strongly correlated to mortality among these patients. While the increased mortality associated with vasopressor requirements is in concordance with the results of Lamontagne et al, although elevated lactate was a significant predictor of mortality in Byrn’s univariate analysis, it did not maintain significance on multivariate analysis. Leukocytosis was also not found to be significant in predicting mortality.\(^\text{16}\)

A similar study by Ali, et al, reviewing data from 36 patients who had undergone colectomy for fulminant *C difficile* colitis at a single institution also showed that leukocytosis was a significant predictor of mortality on multivariate analysis. Additionally, while vasopressor requirement was not a predictor of mortality on multivariate analysis, it was a significant predictor on univariate analysis, with 47% of nonsurvivors requiring vasopressors compared with 16% of survivors.\(^\text{17}\) Hall and Berger also conducted a single-institution study assessing predictors of mortality among 36 patients undergoing colectomy for fulminant colitis and found that vasopressor requirement and preoperative intubation indicated increased mortality.\(^\text{27}\)

A recently published study assessed 69 patients undergoing surgery for fulminant colitis over a 7-year period found results corroborating previous studies. In the study by Seder et al, multivariate analysis found that the predictors of mortality were age greater than 65 years, respiratory failure, and renal failure.\(^\text{27}\) Vasopressor requirements, however, were not predictive of mortality. Some of the most convincing evidence is from the largest study published involving 199 patients, which suggests that leukocytosis, age, and cardiorespiratory instability are predictive of mortality.\(^\text{28}\)

While it is difficult to reconcile some of the conflicting data among these studies, a possible explanation is that the population evaluated by Byrn et al, of which 16% had IBD, had a predisposition to mounting a lower leukocyte response. Additionally, as suggested by Seder et al, those patients may have undergone surgery early within their disease process before the development of a more substantial leukocytosis. Limitations in the current literature are clear and account for some of the discrepancy between studies. Due to the nature of the disease, no randomized controlled trials exist, and there is likely a selection bias inherent to the retrospective data as patients more likely to survive may have received more aggressive surgical treat-
ment. How these patients would have responded to medical treatment therefore remains unclear.

All recent studies, however, propose that multi-organ damage, whether evidenced by vasopressor requirements, lactic acidosis, or renal insufficiency, is ominous in patients with fulminant colitis. By viewing these results more broadly within the context of indicators of multisystem organ damage, one can better determine which patients infected with \textit{C difficile} colitis will progress to fulminant colitis. Table 1 summarizes the results of the reported literature. Given that the current mortality of \textit{C difficile} colitis is between 35\% and 80\%, it is imperative that fulminant colitis be diagnosed early. In summary, using prognostic predictors for early diagnosis, combined with predictors of mortality, a patient population can be identified that would benefit from early surgical intervention.

Two points are important to note regarding the diagnosis and treatment of fulminant colitis. Although there has been debate regarding the operation of choice, most studies have demonstrated the benefits of subtotal colectomy over segmental colonic resection for fulminant colitis.\textsuperscript{14,16,19,29} Presumably from the pancolonic nature of the infection, a segmental resection has a higher risk of leaving residual disease in what may appear to be unaffected colon.\textsuperscript{13}

Secondly, it is important to note that when diagnosing fulminant colitis, characteristic findings in patients with \textit{C difficile} colitis, such as diarrhea, may not be as readily apparent.\textsuperscript{30} The results of a number of studies analyzing different diagnostic modalities suggest early use of computed tomography (CT) scanning is highly effective in determining whether patients have fulminant colitis.\textsuperscript{31} While the false negative rate of CT scan varies from 0\% to 22\%,\textsuperscript{3,13,16,17,26} 4 of these studies show a rate of less than 10\% (Table 2). Typical CT findings include colonic wall thickening, dilation, “accordion sign,” which consists of thickened haustral folds and trapped contrast material, ascites, and pericolonic stranding.\textsuperscript{32,33} Stool toxin titer and endoscopy are also useful diagnostic modalities; however, time lag in attaining results may delay treatment.

### Conclusions

From data shown in multiple recent studies, it is apparent that \textit{C difficile} infection has become an international problem with epidemic proportions. With new more virulent strains identified, and with an increasing incidence and severity of disease, prevention through basic hygiene among healthcare workers and others in contact with patients has become essential. Although most patients who develop colitis respond to traditional antibiotic therapy, a small percentage of patients proceed to develop fulminant \textit{C difficile} colitis.

The lack of level I data make clear recommendations difficult. Without randomized trials one cannot conclusively determine the benefit of early colectomy compared with medical management with delayed colectomy; however, the body of level II data suggest that early diagnosis and treatment through subtotal colectomy can reduce the mortality associated with fulminant colitis. With the results of recent studies, clinicians have basic parameters that they can use to

### Table 1  Recommendations and level of evidence

<table>
<thead>
<tr>
<th>Predictors of mortality</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoalbuminemia</td>
<td>B</td>
</tr>
<tr>
<td>High ASA class</td>
<td>B</td>
</tr>
<tr>
<td>Lactate &gt;5 mmol/L</td>
<td>B</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>B</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>C</td>
</tr>
<tr>
<td>Length of medical treatment</td>
<td>C</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>C</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>B</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>C</td>
</tr>
<tr>
<td>WBC count &gt;35,000/µL</td>
<td>C</td>
</tr>
<tr>
<td>WBC count &lt;4,000/µL</td>
<td>C</td>
</tr>
<tr>
<td>Neutrophil bands &gt;10%</td>
<td>C</td>
</tr>
<tr>
<td>Vasopressor requirement</td>
<td>B</td>
</tr>
</tbody>
</table>

### Table 2  False negative rates of diagnostic studies (%)

<table>
<thead>
<tr>
<th>First author</th>
<th>CT</th>
<th>Sigmoidoscopy</th>
<th>Colonoscopy</th>
<th>\textit{C difficile} stool toxin titer</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrn\textsuperscript{15}</td>
<td>0</td>
<td>24</td>
<td>25</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>Lamontagne\textsuperscript{19}</td>
<td>22</td>
<td>—</td>
<td>13</td>
<td>8</td>
<td>46</td>
</tr>
<tr>
<td>Longo\textsuperscript{18}</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Dallal\textsuperscript{3}</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>12.5</td>
<td>—</td>
</tr>
<tr>
<td>Ali\textsuperscript{16}</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grundfest-Broniatowski\textsuperscript{27}</td>
<td>—</td>
<td>—</td>
<td>33</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\textit{CT} = computed tomography.
guide their diagnostic strategy. For patients who have a history of IBD, recent surgery, or prior treatment with IVIG, there should be a high index of suspicion for the development of refractory colitis and surgical consult should be sought very early in the patient’s admission. For other patients, colitis associated with signs of organ dysfunction such as vasopressor requirements and increased lactate, with the addition of leukocytosis greater than 16,000/μL should be parameters that indicate the need for operative intervention. Additionally, early use of CT scan over other diagnostic modalities can provide a diagnosis and guide surgical therapy. As demonstrated from the evidence of recent investigations, studies in the future that use these specific prognosticators to predict disease progression and perform early surgical intervention should yield results that lower the mortality of fulminant C difficile colitis.

References