ORIGINAL ARTICLE

Predictors of Mortality After Colectomy for Fulminant *Clostridium difficile* Colitis

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Objectives: To present, to our knowledge, the largest experience with colectomy for fulminant *Clostridium difficile* colitis and to propose factors significant in predicting mortality.

Design: Retrospective medical record review.

Setting: University teaching hospital.

Patients: Seventy-three patients undergoing colectomy between 1994 and 2005 for *C difficile*–associated pseudomembranous colitis.

Main Outcome Measures: Preoperative predictors of in-hospital mortality.

Results: Seventy-three of 5718 cases (1.3%) of *C difficile* colitis required colectomy. Mean age was 68 years. In-hospital mortality was 34% (n=25). Eighty-six percent (n=63) of patients received a subtotal colectomy. Patients presented with diarrhea (84%; n=61), abdominal pain (75%; n=55), and ileus (16%; n=12). Mean duration of symptoms was 7 days followed by 4 days of medical treatment prior to colectomy. On univariate analysis, an admitting diagnosis other than *C difficile* ($P=.049$), vasopressor requirement ($P=.001$), intubation ($P=.001$), and mental status changes ($P<.001$) were significant predictors of mortality. Arterial lactate level (4.9 vs 2.4 mmol/L; $P=.007$) was significantly higher and length of medical management (6.4 vs 3.0 days; $P=.006$) was significantly longer in the mortality group. Platelet counts (169×10^3/μL vs 261×10^3/μL [to convert to $\times10^9$/L, multiply by 1]; $P=.04$) were significantly lower in the mortality group. On multivariate analysis, vasopressor requirement ($P=.04$; odds ratio, 5.0), mental status changes ($P=.002$; odds ratio, 12.6), and treatment length ($P=.002$; odds ratio, 1.4) remained significant predictors of mortality.

Conclusions: Colectomy for *C difficile* colitis carries a substantial mortality regardless of patient age and white blood cell count. Preoperative vasopressor requirement, mental status changes, and length of medical treatment significantly predict mortality.

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THE INCIDENCE AND SEVERITY of *Clostridium difficile* infection is reaching epidemic proportions.[1,2] The often self-limiting infection can evolve into a fulminant process ending with toxic megacolon in susceptible hosts for unclear reasons.[3-6] Patients with fulminant infection require surgery in up to 20% of cases, carrying a mortality of 35% to 80%.[7-9] Studies of the surgical management of *C difficile* infection have been limited by small sample size and the lack of a standard definition of fulminancy and further confounded by population-specific immunocompromise. We present, to our knowledge, the largest single-institution experience over a 12-year period with colectomy for fulminant *C difficile* colitis and propose factors significant in predicting mortality.

See Invited Critique at end of article

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METHODS

After approval by the Mount Sinai School of Medicine institutional review board, an institutional pathologic database (Tamtron PowerPath system; IMPAC, Columbus, Ohio) was used to search all pathologic diagnoses between 1994 and 2005 for "pseudomembranes" and "pseudomembranous colitis." Seventy-three colectomy specimens were identified with *C difficile*–associated pseudomembranous colitis as the final pathologic diagnosis. Within the same period, 5718 cases of nosocomial and community-acquired *C difficile* colitis were diagnosed by stool *C difficile* cytotoxin assay (enzyme-linked immunosorbent assays toxins A and B).

Table 1. Patient Demographics and Medical History

Characteristic	No. (%)		
	Mortality Group (n=25)	Survivor Group (n=48)	All Patients (n=73)
Age, y, mean	71	66	68
Sex, M/F	12/13	21/27	33/40
Ulcerative colitis	0	8 (17)	8 (11)
Crohn disease	0	4 (8)	4 (5)
Diabetes mellitus	3 (12)	17 (35)	20 (27)
Chronic obstructive pulmonary disease	2 (8)	4 (8)	6 (8)
Coronary artery disease	10 (40)	14 (29)	24 (33)
Hypertension	14 (56)	24 (50)	38 (88)
End-stage renal disease	2 (8)	3 (6)	5 (7)
Immunosuppression	9 (36)	23 (48)	32 (44)
Previous diagnosis of *Clostridium difficile*	7 (28)	10 (21)	17 (23)
Treated with antibiotics within last 2 mo	24 (96)	43 (90)	67 (92)

Hospital and operative records were retrospectively reviewed for patient demographics, clinical presentation, medical history, antibiotic therapy, preoperative course and workup, operative management, and in-hospital mortality. All laboratory values were recorded from the patient records timed closest to the operation. Because *C difficile* colitis was not always recognized preoperatively as the indication for colectomy, fulminant *C difficile* is defined in cases where the attending surgeon felt emergent exploration and colectomy were indicated and subsequent pathologic diagnosis identified pseudomembranous colitis.

Predictors of in-hospital mortality were determined using multiple logistic regression. Variables to be included in the model were selected using the *t* test for continuous variables and the χ^2 test for categorical variables. All significant ($P<.05$) predictors of mortality on univariate analysis plus commonly held clinically significant predictors were used in the multivariate model (SPSS 14.0; SPSS Inc, Chicago, Illinois). Predictors were deemed significant when $P<.05$. Both nosocomial and community-acquired cases of *C difficile* were used to calculate the incidence of fulminancy because we did not exclude operative cases based on preoperative location or timing of *C difficile* infection.

RESULTS

Seventy-three patients undergoing colectomy for fulminant pseudomembranous colitis were identified of 5718 diagnosed cases of *C difficile* (incidence, 1.3%). Mean age of patients was 68 years, with a 55% female majority. Mean length of stay was 45 days with an in-hospital mortality rate of 34% (n=25). There was a single intraoperative mortality. A summary of patient characteristics and medical history is provided in **Table 1**. None of these characteristics were predictors of mortality.

Mortality and incidence were further considered over time and by admitting service. From 2000 to 2005, there were 45 operative cases of fulminant colitis of 3917 *C difficile* diagnoses (incidence, 1.2%). The in-hospital operative mortality rate during this period was 33%. From 1994 to 1999, there were 28 operative cases of 1801 *C difficile* diagnoses (incidence, 1.5%), with a 36% in-hospital operative mortality rate. These incidences and mortality rates were not significantly different ($P>.05$).

Table 2. False-Negative Rates of Diagnostic Studies

Diagnostic Study	No. (%) of Patients With False-Negative Findings
Computed tomography (n=35)	0
Sigmoidoscopy (n=29)	7 (24)
Colonoscopy (n=12)	3 (25)
Clostridium difficile stool toxin titer (n=47)	5 (11)

Furthermore, mortality was not significantly different when considering admitting service (surgery, 47% vs nonsurgery, 30%; $P>.05$).

Forty-four percent of patients were immunosuppressed (n=32). Conditions associated with immunosuppression included corticosteroid treatment for inflammatory bowel disease (n=12) or other conditions (n=5) and carcinoma with or without chemotherapy (n=8). Nine percent of the immunosuppressed patients (n=3) were transplant recipients (heart, 2; kidney, 1). Four patients (12.5%) were human immunodeficiency virus positive. One transplant recipient (heart) died postoperatively.

Forty-four percent (n=32) of patients were admitted with *C difficile* colitis or with symptoms later attributed to their pseudomembranous colitis. Thirty-six percent of patients (n=26) were diagnosed with *C difficile* colitis as inpatients while recovering from surgery. Common procedures performed prior to diagnosis with *C difficile* colitis included cardiothoracic (n=16), abdominal (n=6), and vascular (n=3) procedures. The most common presenting symptoms included diarrhea (84%; n=61), abdominal pain (75%; n=55), and ileus (16%; n=12). A mean of 7 days elapsed between onset of symptoms and institution of medical treatment, with an additional 4 days of medical management prior to colectomy. Fourteen percent of patients (n=10) received no medical treatment prior to colectomy, 18% (n=13) received only intravenous metronidazole, and 5% (n=4) received only oral vancomycin hydrochloride. The remaining 49% of patients (n=36) received a combination of antibiotic therapies. No differences in mortality were observed between different antibiotic regimens.

Table 2 illustrates the false-negative rates of the diagnostic studies used in our series. Forty-eight percent of patients (n=35) underwent computed tomographic (CT) scanning as part of their preoperative workup and 56% of patients (n=41) underwent endoscopy. All CT scans illustrated at least segmental colitis (n=11) while most cases showed pancolitis (n=24). Additional findings included ascites (n=6) and free intraperitoneal air (n=5). Seventy-one percent (n=29) of endoscopies were completed to the level of the sigmoid colon while the remainder were complete colonoscopies (n=12). Documentation of *C difficile* stool toxin titer results was available for 47 patients. Four of 5 patients with titers negative for toxin survived (mortality, 20%).

Mean preoperative laboratory and clinical values are summarized in **Table 3**. At the time of surgery, 32% of patients (n=23) required vasopressors, 41% (n=30) were intubated, and 52% (n=38) had exhibited documented mental status changes.

Table 3. Selected Laboratory and Clinical Values[a]

	All Patients	Mortalities	Survivors	*P* Value[b]	95% Confidence Interval of Difference
Selected laboratory value					
White blood cell count, /μL	28 000	27 300	28 300	.23	−9.4 to 11.4
Arterial lactate level, mmol/L	3.5	4.9	2.4	.007	−4.15 to −0.75
Platelet count, $\times 10^3$/μL	230	169	261	.04	3130 to 182 400
Mean plasma creatinine, mg/dL	2.10	2.34	1.99	.36	−1.09 to 0.39
Mean albumin, g/dL	2.1	2.0	2.2	.30	−0.18 to 0.57
Selected clinical value					
Length of medical treatment, d	4.15	6.4	3.0	.006	−5.8 to −1.01

SI conversion factors: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001; platelet count to $\times 10^9$/L, multiply by 1; creatinine to micromoles per liter, multiply by 88.4; and albumin to grams per liter, multiply by 10.

[a] Values are expressed as means.

[b] From univariate analysis.

- Age
- Sex
- History of previous *Clostridium difficile* diagnosis
- Surgery on hospital admission
- Admitting service, nonsurgery vs surgery
- Immunosuppression
- Antibiotic regimen used
- Presenting symptoms of diarrhea, abdominal pain, and ileus and duration
- Computed tomographic findings
- Completeness of endoscopy or findings
- Accuracy of *C difficile* titer
- White blood cell count
- Plasma creatinine level
- Plasma albumin level
- American Society of Anesthesiologists score
- Estimated blood loss, transfusion requirements, operating room time

Figure. Nonsignificant predictors of mortality ($P>.05$ by univariate analysis).

Table 4. Predictors of Mortality by Univariate Analysis

Predictor	*P* Value	Odds Ratio (95% Confidence Interval)
Admitting diagnosis other than *Clostridium difficile*	.049	2.0 (0.96-4.2)
Mental status changes	.001	9.57 (2.82-32.5)
Vasopressor requirement	.001	5.52 (1.89-16.1)
Need for mechanical ventilation	.049	5.72 (1.99-16.42)

Table 5. Predictors of Mortality by Multivariate Analysis

Predictor	*P* Value	Odds Ratio (95 % Confidence Interval)
Mental status changes	.002	12.6 (2.45-64.7)
Vasopressor requirement	.04	5.0 (1.1-22.2)
Length of treatment	.002	1.4 (1.1-1.64)

Eighty-six percent of patients (n=63) received subtotal colectomy with end ileostomy. There were an additional 4 right hemicolectomies and 5 left hemicolectomies. One of the patients who underwent left hemicolectomy had recently undergone a right hemicolectomy, making the left hemicolectomy a completion abdominal colectomy. One patient underwent an ileocolic resection with primary anastomosis. This patient ultimately died, accounting for the only segmental colectomy mortality. The minority of patients were found to have necrosis (n=8) or perforation (n=6) during exploration. There was no significant difference in the mortality rates of the patients who underwent segmental or subtotal colectomies (10% vs 38%, respectively; $P>.05$).

The **Figure** summarizes the nonsignificant predictors of mortality on univariate analysis ($P>.05$). **Table 4** summarizes the significant results from the univariate analysis of our data. An admitting diagnosis other than *C difficile* ($P=.049$), vasopressor requirement ($P=.001$), intubation ($P=.001$), and mental status changes ($P<.001$) were significant predictors of mortality. As shown in Table 3, arterial lactate level (4.9 vs 2.4 mmol/L; $P=.007$) was significantly higher in the mortality group and platelet counts were significantly lower (169×10^3/μL vs 261×10^3/μL [to convert to $\times10^9$/L, multiply by 1]; $P=.04$) in this group. The mortality group had a significantly longer trial of medical management (6.4 vs 3.0 days; $P=.006$) than the survivor group (Table 3). On multivariate analysis (**Table 5**), vasopressor requirement ($P=.04$; odds ratio, 5.0), mental status changes ($P=.002$; odds ratio, 12.6), and treatment length ($P=.002$; odds ratio, 1.4) remained significant predictors of mortality.

Although not statistically significant, 47% (14 of 30) of patients diagnosed with *C difficile* colitis as inpatients recovering from surgery died, while 26% (11 of 43) of nonpostoperative patients ultimately died ($P=.06$). Forty-five percent (5 of 11) of patients presenting with ileus and 50% (4 of 8) of patients with end-stage renal disease ultimately died. No patients with Crohn disease (0 of 4) or ulcerative colitis (0 of 8) died postoperatively.

COMMENT

Fulminant C difficile is a poorly defined term in the surgical literature. Fulminancy has been assigned to patients with *C difficile* who develop toxic megacolon, as well as for patients clinically requiring colectomy without the development of toxicity.[3,10-12] Confounding the literature is the relatively frequent occurrence of patients presenting with an "acute abdomen" without a clear etiology. These patients are operated on emergently only

to find pathologic evidence of pseudomembranous colitis after the specimen has been removed from the body. Endoscopy and stool toxin titers both have reported false-negative rates, further blurring the accurate diagnosis and treatment of the critically ill patient with *C difficile* infection.[10,13] For this study, we defined "fulminancy" retrospectively for patients with a pathologic diagnosis of pseudomembranous colitis where the operative indications for colectomy were *C difficile* colitis or clinical toxic megacolon.

Multiple small series have addressed the surgical management of fulminant *C difficile* colitis.[7-9,11,12,14-16] Although these studies have described conflicting results, they have brought attention to an increasingly important surgical disease. Furthermore, many of the trends observed in these smaller studies have been confirmed in larger reviews.[10,17] In our patients, we observed several trends consistent with the literature. Our mortality (34%) is at the low end of reported ranges (35%-80%) and the mean age (68 years) of our patients is consistent with the literature.[7-10] Recent exposure to antibiotics (92% of our patients) and a previous *C difficile* diagnosis (23% of our patients) are also well documented in the literature.[4-6] The percentage of our patients with *C difficile* colitis as the admitting diagnosis (44%) and the percentage of inpatient postoperative presentations (41%) are not uncommon.[10,17] Furthermore, as seen in our series, cardiothoracic procedures have been reported to be most commonly associated with fulminant *C difficile*.[3,10] Lastly, as occasionally observed in the literature, a significant minority of our patients presented with ileus (16%).[10,17,18]

Endoscopy, when performed preoperatively, has been shown to be highly reliable in small series.[7,11,16] However, in larger patient populations, failure to produce a diagnosis increasingly occurs, with false-negative rates approaching 10%.[10] In our study, the false-negative rate for endoscopy was nearly 25% regardless of whether a sigmoidoscopy or full colonoscopy was performed. Computed tomographic scan, on the other hand, produced significant findings in 100% of our patients. This extremely high sensitivity is consistent with the literature.[10,17,19] Published false-negative rates for stool toxin assays are 10%.[13,20] Although our results (11%) were consistent with these rates, documentation of toxin assay completion was only found in 64% of patients (n=47).

As recommended in the literature, the majority of our patients underwent subtotal colectomy with end ileostomy.[10,17] The minority of patients who did undergo segmental resections, however, had an acceptable 10% mortality rate. The single patient who underwent a segmental colectomy and ultimately died also was the only patient to undergo a primary anastomosis. Although patients who underwent segmental colectomy were not proven to have a higher mortality in this series, likely because of sample size, a subtotal colectomy with end ileostomy remains our recommended procedure. Clearly, if segmental colectomy is attempted, diversion is necessary.

Several novel trends were also observed in our series. The majority of patients in this series were female whereas most literature exhibits a male preponderance.[7,10,11,16] Inflammatory bowel disease (IBD) and fulminant *C difficile* colitis, generally a topic of case reports, were prominent in our series.[21,22] Clinical and pathologic diagnoses were able to definitively attribute the acute colitic episode to *C difficile*, supporting literature that refutes an association between IBD exacerbation and *C difficile* infection.[23,24] Despite being well represented in our series, no patients with IBD were counted among the mortalities. Although this mortality difference was not statistically significant, the trend toward lower mortality in the IBD group may be explained by a lower mean age (47 years vs 72 years). The mean length of stay, however, of the IBD group was longer than in patients without IBD (13.8 vs 5.6 days) and the mean length of treatment was similar (4.4 vs 4.2 days). Considering the small number of patients with IBD, no strong conclusions can be drawn from our series regarding the effect of a concomitant IBD diagnosis on fulminant *C difficile* colitis postcolectomy mortality.

Patient immunosuppression is commonly cited as a predisposing factor in the development of fulminant *C difficile* colitis. Our series was not different, with 44% of patients considered immunosuppressed. What was unique in our series was the low number of immunosuppressed organ transplant recipients (n=3) relative to patients with other causes of immunosuppression (Table 3). This discrepancy from the literature is most likely institution specific. Furthermore, it has been suggested that lung transplant has a higher rate of fulminant *C difficile* infection than kidney or kidney-pancreas transplant, which, considering the relative paucity of lung transplant compared with kidney transplant at our institution, would explain our low rate of transplant-related fulminant *C difficile* infection.[10,25,26]

Fourteen percent of our patients went to surgery without receiving medical management beyond routine preoperative prophylactic antibiotics, and half of patients received combined antibiotic regimens. Most studies show that the majority of patients receive at least some medical therapy, although significant variability exists regarding the exact regimen.[7,16] Such treatment variability is not supported by the literature where the standard remains oral metronidazole.[4,5,13,20] These results illustrate a lack of consistent institution-wide treatment policies. The explanation for not instituting medical management in patients may be 2-fold. First, patients presenting with peritonitis are promptly taken to the operating room for surgery, often without a clear preoperative diagnosis. Second, the occasional patient may be misdiagnosed, leading to surgery without an adequate trial of medical treatment for *C difficile* infection.

Although dissection of patient trends may help us understand the characteristics of the patient population, clear predictors of mortality are of greater clinical value. Vasopressor requirement and mental status changes, while predicting mortality in our series, are also general indicators of severe illness. From this, we conclude that when managing a critically ill patient with *C difficile* infection it is imperative to operate prior to the development of multisystem organ failure. The significantly longer length of medical treatment in the mortality group may support this conclusion in that patients not improving while receiving medical treatment continue to deteriorate between 3 and 7 days with a corresponding increase in mor-

tality. This is further supported by significant literature stating that patients with *C difficile* infection should respond to antibiotic therapy within 4 days.[13]

Our study was unable to predict the failure of medical management and the progression of *C difficile* colitis to multisystem organ failure. Understanding the factors that predispose medical management to fail will require prospective studies investigating patients with *C difficile* colitis not requiring surgery. The role of CT scan is of specific interest, considering the highly sensitive ability to detect changes consistent with fulminant colitis as seen in our results.

In conclusion, colectomy for fulminant *C difficile* colitis carries a significant mortality. Vasopressor requirement, mental status changes, and length of medical treatment are significant predictors of mortality. These findings suggest that mortality after colectomy can be reduced with prompt surgical intervention once medical management has failed. Conclusion regarding the failure of medical management, however, cannot be drawn from our series. Further prospective studies investigating predictors of medical management failure and the role of CT in predicting fulminancy are warranted.

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Author Contributions: Dr Byrn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Byrn, Maun, Gingold, Baril, Ozao, and Divino. *Acquisition of data:* Byrn, Maun, and Gingold. *Analysis and interpretation of data:* Byrn, Gingold, Baril, and Divino. *Drafting of the manuscript:* Byrn, Maun, Gingold, Baril, Ozao, and Divino. *Critical revision of the manuscript for important intellectual content:* Byrn, Maun, Baril, and Divino. *Statistical analysis:* Byrn, Maun, Gingold, and Baril. *Obtained funding:* Divino. *Administrative, technical, and material support:* Byrn, Maun, Gingold, Baril, Ozao, and Divino. *Study supervision:* Baril and Divino.
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