Chapter 25
Indications for Surgery in Patients with Severe Clostridium Difficile Colitis

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Introduction

Clostridium difficile colitis (CDC) is the leading cause of nosocomial diarrhea in the United States, with a broad spectrum of symptoms ranging from mild diarrhea to fulminant colitis which can lead to multisystem organ failure and death. For the majority of cases, surgical therapy is unnecessary as CDC responds to antibiotic therapy. Medically refractory colitis carries a high morbidity and mortality, and often necessitates surgical intervention which may also be associated with poor outcomes. The timing of surgery in the setting of CDC is critical; surgical intervention early in the course of disease may lead to an unnecessary colectomy with ileostomy when medical therapy may have been sufficient, but delaying surgical therapy in fulminant colitis commonly leads to a fatal outcome.

Recommendations for intervention requires is based on the severity of disease. Mild disease is characterized by diarrhea without any systemic symptoms. Endoscopic findings in mild disease show non-specific diffuse or patchy erythematous colitis, and pseudomembranes are usually not found. Imaging shows no evidence of colitis. Moderate disease is associated with more severe diarrhea, and mild systemic signs such as fever, leukocytosis, nausea and general malaise. Pseudomembranes, though not specific for CDC, are likely to be noted on endoscopy. Severe disease is progressively worsening CDC with hypoalbuminema (<3 g/dL) in the setting of worsening leukocytosis (>15,000 cells/mm^3) or abdominal tenderness. Fulminant colitis is a rare but life-threatening progression of severe CDC characterized by segmental or total colonic distention with signs of systemic toxicity (fever,

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leukocytosis, distention, tenderness, hemodynamic instability, and organ dysfunction) and clinical deterioration with peritonitis and sepsis. Unfortunately, a clear algorithmic approach to surgical management is difficult as the ability to categorize the severity of the disease is challenging. Most of the studies addressing indications for surgery are limited by small sample sizes, retrospective analysis, and inconsistent criteria in distinguishing severe from fulminant colitis.

Non-surgical options include treatment with antibiotics, fecal microbiota transplant (FMT) and intravenous immunoglobulin (IVIG) transfers. Antibiotic therapy includes single agent therapy with oral metronidazole or vancomycin for mild to moderate disease, and dual coverage with metronidazole and vancomycin for severe disease. Nitazoxanide and fidaxomicin have also been used, but their utility in severe CDC needs to be more fully addressed. FMT is the transfer of stool from a heathy donor to a patient with CDC to remedy the decreased colonic diversity that is thought to drive CDC [1]. Instillation can be done by colonoscopy, upper endoscopy, per nasogastric tube, or by retention enemas. Lower GI tract instillations are associated with better outcomes.

Surgical options for the management of fulminant colitis include segmental colectomy, total or subtotal abdominal colectomy (TAC) with a stoma, or a diverting stoma with lavage of the distal bowel [2]. Of these, TAC with end ileostomy is the gold standard [3] which eliminates the diseased colon while avoiding the added morbidity of a pelvic dissection. Diverting stoma and lavage of the distal bowel markedly decreases the magnitude of the surgical procedure and diminishes the likelihood of a permanent ileostomy.

Search Strategy

The MEDLINE database was searched using the following MeSH headings: “Clostridium difficile”, “surgery”, and “outcome.” The time interval of the retreived articles was limited to 2005–2015. Non-english language publications were excluded. Information obtained was graded according to published GRADE guidelines. In general, the strength of the evidence is moderate to low, as it has been difficult to initiate large randomized controlled trials to evaluate the role of surgery in severe Clostridium difficile colitis. Meta-analyses, case reports, and reviews not containing original data were also excluded (Table 25.1).

Table 25.1 PICO table

P (patient population)	I (intervention)	C (comparator)	O (key outcomes)
Patients with severe Clostridium difficile colitis	Surgery	No surgery	Morbidity, mortality, quality of life

Results

The overall quality of the evidence is very low. Of the articles which met the search criteria, there were no randomized controlled trials, and only one was a prospective study (Table 25.2). Note that the data in the table shows some studies which included all patients with CDC while others show patients who underwent an intervention for CDC.

The mortality for surgical intervention was 19–67 % in the included studies (Table 25.2). Koss et al. showed that 80 % of those undergoing a segmental colectomy died, while mortality was significantly lower in those undergoing total abdominal colectomy; 6 of the 9 patients who underwent a TAC eventually had re-establishment of continuity [4]. Kenneally et al. studied CDC patients in the intensive care setting (ICU) [5]. The overall 30-day mortality was 36.7 % and the surgical mortality was 33.3 %. This study is limited by the selection of the population: patients in the ICU setting who were more likely to have other co-morbidities and likely at a greater risk of hospital mortality. Lamontagne et al. studied CDC in the ICU setting and noted that patients undergoing surgery had fewer co-morbidities, higher leukocytosis and increased probability of sepsis, but lower mortality [6]. Ali et al. studied factors associated with survival after colectomy and noted higher mortality with delaying surgical intervention, worsening leukocytosis, multisystem organ failure and the preoperative use of pressors [7].

Byrn et al. showed increased mortality with mental status changes, vasopressor requirement and delayed surgical therapy [8]. Hall et al. reported a lower mortality after colectomy in the absence of preoperative vasopressor requirement and ventilator support [9]. Hermensen et al. reported that in patients considered candidates for surgery, mortality was 46 %, while all patients who declined surgery died [10]. Pepin et al. showed that mortality after surgery increased with age, preoperative lactic acidosis, leukocytosis and hypoalbuminemia [12]. Sailhamer et al. studied patients with fulminant CDC and noted a decreased mortality with surgical intervention [13]. Age greater that 70 years, severe leukocytosis, leukopenia or bandemia, and cardiopulmonary failure were associated increased mortality (57 % when all three were noted, but 0 % in the absence of all three factors). Care on the surgical service was associated with higher operative intervention and better survival. Seder et al. also noted increasing age, acute respiratory failure and acute renal failure to be associated with increased mortality [14]. Dudukgian et al. noted that among the patients with CDC who died, 12.2 % underwent surgery while 87.8 % did not. Non-survivors who were medically managed had a longer pre-CDC hospital stay and more co-morbidities. Halabi et al. reviewed the Nationwide Inpatient Sample and noted an inpatient mortality of 30.7 % in patients undergoing colectomy [20]. Delaying surgery was associated with worse outcomes.

In assessing overall mortality, there are few studies comparing surgical to medical therapy for severe disease [22]. Two studies show a decrease in mortality with surgical intervention in the setting of severe CDC [6, 13]. Lamontage et al. identified patients in the ICU with CDC and noted a significant decrease in mortality with surgical inter-

Table 25.2 Summary of studies

Year	Study	Design (quality)	Study size (N)	Surgery (N)			Mortality (%)		
				Total	TAC	Other	Overall	Surgical	Medical
2006	Koss et al. [4]	Retrospective (very low)	3472	14	9	5	–	36	–
2007	Kenneally et al. [5]	Retrospective (very low)	278	6	–	–	37	33	37
2007	Lamontagne et al. [6]	Retrospective (very low)	165	38	35	–	53	34	58
2008	Ali et al. [7]	Retrospective (very low)	36	36	28	8	–	47	–
2008	Byrn et al. [8]	Retrospective (very low)	5718	73	63	10	–	34	–
2008	Hall and Berger [9]	Retrospective (very low)	3237	36	34	2	–	36	–
2008	Hermsen et al. [10]	Retrospective (very low)	7588	13	13	–	–	46	–
2009	Chan et al. [11]	Retrospective (very low)	15	15	12	3	–	67	–
2009	Pepin et al. [12]	Retrospective (low)	130	130	124	6	–	37	–
2009	Sailhamer et al. [13]	Retrospective (low)	4796	75	69	6	35	24	45
2009	Seder et al. [14]	Retrospective (very low)	6841	69	68	1	–	42	–
2010	Al-Abed et al. [15]	Retrospective (very low)	528	20	17	3	–	40	–
2010	Dudukgian et al. [16]	Retrospective (very low)	398	14	11	3	–	36	–
2010	Gash et al. [17]	Retrospective (very low)	1398	17	16	1	–	53	–
2010	Perera et al. [18]	Retrospective (very low)	35	35	32	3	–	46	–
2011	Markelov et al. [19]	Retrospective (very low)	13	13	12	1	–	46	–
2011	Neal et al. [2]	Prospective (low)	42	42	–	42	–	19	–
2013	Halabi et al. [20]	Retrospective (low)	2,773,521	19,374	3900	–	–	31	–
2015	van der Wilden et al. [21]	Retrospective (very low)	100	100	100	–	–	25	–

vention [6]. Sailhamer et al. reviewed all patients with severe CDC at their institution, and noted a trend towards decreased mortality with surgery [13]. Care on the surgical service was associated with a significantly lower mortality rate (12.8 % vs 39.3 %).

When comparing TAC with a segmental resection, several studies show the inferiority of segmental resection, need for additional intervention and ultimately, the increased mortality [4, 8, 9, 12, 14–16, 18, 19]. Interestingly, segmental colectomy as the first intervention was associated with a slightly lower mortality as noted on two meta-analyses [3, 23]. However, when corrected for re-intervention and an eventual completion colectomy in patients undergoing a segmental resection, the relative risk of a TAC trended lower [23]. Of the patients who undergo a segmental colectomy, 15.9 % need an eventual re-operation to decrease the disease burden [3].

A less aggressive alternative to a subtotal colectomy was studied prospectively, and involved the creation of a loop ileostomy, washout of the colon with warm polyethylene glycol 3550, and postoperative antegrade colonic vancomycin flushes [2]. When compared to historical controls, a lower mortality (19 vs 50 %) was noted and preservation of the colon was achieved in 93 % of subjects. However, selection and management bias cannot be ruled out as this was a small study cohort with no randomization and retrospective comparison to historical controls.

Several studies show that delaying surgical intervention is associated with worse outcomes. Respiratory failure [4, 8, 9, 13, 14, 20], renal failure [4, 9, 14, 20], and vasopressor requirement due to hemodynamic instability [4, 7–10, 12–14, 18–20] were associated with increased mortality. Ali et al. showed that survivors had surgery at a mean of 3.2 days vs. 5.4 days [7]. Sailhamer et al. similarly showed that the mean time to surgery was lower for survivors at 1.9 days vs. 3.9 days [13]. Halabi et al. reviewed a large administrative database and noted that surgical intervention more than 3 days after admission for CDC was associated with poorer prognosis [20].

Antibiotic treatment of patients after TAC for CDC was addressed by van der Wilden et al. who noted that intravenous metronidazole or enteral vancomycin for no more than 7 days was sufficient [21]. Mortality did not improve with antibiotic usage more than 7 days. Studies on the long-term follow-up of patients after colectomy for CDC are limited. Though Koss et al. [4] showed a 67 % re-establishment of continuity in survivors after colectomy, Miller et al. noted that the 5-year survival rate after colectomy was 38 % and intestinal continuity was re-established in only 20 % of the patients [24].

Recommendations Based on the Data

Mortality rates attributable to CDC remain high and even with surgery are as high as 19–67 %. The judgement for surgical intervention is empirical, and no clear evidence exists due to the lack of prospective, randomized controlled studies. Compounding the decision to intervene surgically is the lack of data on the timing of the intervention. Overall, the quality of the data is low, but most patients and all clinicians would place a high value on the reduction in mortality; despite the adverse

effects of surgery (for example on quality of life), surgical intervention in complicated severe CDC warrants a strong recommendation.

Patients with complicated severe CDC benefit from early surgical intervention, as delaying definitive surgery will increase the morbidity and mortality. Intervention should be considered prior to the onset of cardiopulmonary collapse (need for ventilator assistance or the use vasopressors) and renal failure. Transfer to or admission to the surgical service may be prudent for closer monitoring and quicker intervention. Intervention within 3 days of medically refractory severe disease may be warranted to improve outcomes.

Of all the surgical options, TAC with ileostomy has the best outcome. Long-term prognosis of the patients who undergo colectomy for CDC is limited. A retrospective study of 61 patients from a single institution estimated a mean survival of 18.1 months [25]. The cause of death could not be distinguished between CDC, colectomy for CDC, or comorbid diseases.

A diverting loop ileostomy with colonic lavage is a more palatable approach and may enable both the medical and surgical teams to intervene more quickly as there is less fear of a permanent ileostomy and a major abdominal operation. However, the evidence supporting this approach is limited, and extreme caution is warranted when proceeding with diversion and lavage alone.

Personal View of the Data

Our approach to a patient with severe CDC has always been to assess the risk vs. benefit of the surgery, be aggressive about the approach, and if uncertain, proceed with surgical resection. Patients with severe CDC are transferred to our service in the ICU. Close hemodynamic monitoring, serial abdominal exams, laboratory evaluations and computed tomography (CT) imaging are obtained. Immunosuppressed patients or those in whom a reliable abdominal exam cannot be obtained are more likely to undergo TAC with ileostomy. Early signs of hemodynamic compromise such as fluid responsive hypotension, decreasing urine output, labored breathing or subtle mental status changes warrant surgery. Worsening leukocytosis, hypoalbuminemia, or lactic acidosis also decrease the threshold for surgery. Patients with severe comorbidities who may not survive a TAC with ileostomy are considered candidates for a diverting loop ileostomy and colonic lavage. Survivors after TAC will more than likely need disposition to long-term care facilities, and prolonged recuperation prior to consideration of ileosigmoid or ileorectal anastomoses.

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