Management of Severe *Clostridioides difficile* Infection

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KEYWORDS

• *C difficile* • Severe • Fulminant • Colectomy • Ileostomy

KEY POINTS

- Severe *Clostridioides difficile* infection can lead to mortality or the need for surgical intervention as an exigent treatment if medical therapy fails.
- Appropriate resuscitation, de-escalation of nonessential antibiotics, and appropriate difficile-directed antibiotics are important both for treating severe *C difficile* infection, as well as being vital to assessing whether medical therapy has truly been maximized.
- Surgery as a life-saving measure should only be required in a small percentage of patients but can include the creation of a diverting ileostomy or a total colectomy with an end ileostomy.

INTRODUCTION

Hospital-acquired *Clostridioides difficile* infection (CDI) has surpassed methicillin-resistant *Staphylococcus aureus* as the highest incidence hospital-acquired infection in the United States.[1] CDI accounts for approximately 300,000 annual hospitalizations, with mortality rates as high as 16.7% during outbreaks[2] and contributes to billions of dollars in annual health care costs.[3] Thus, CDI represents a major burden on health care systems, posing a risk for any patient requiring hospital contact and/or antibiotic exposure, including both patients presenting for medical and surgical care.

The incidence of fulminant or life-threatening CDI has not been the frequent subject of population level, epidemiologic investigations. Most studies that provide a measurement of the incidence of the most severe forms of CDI do so as single-institution, retrospective studies that are frequently focused not on disease epidemiology but on the role of surgery as an exigent intervention. While their methodologies

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Infect Dis Clin N Am 39 (2025) 653–662
https://doi.org/10.1016/j.idc.2025.07.006 **id.theclinics.com**

Abbreviations	
CDI	*Clostridioides difficile* infection
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IL	interleukin

include weaknesses such as a lack of consistent and evidence-based criteria for what constitutes fulminant disease, as well as a lack of established criteria for which patients should undergo surgery, these studies collectively suggest that no more than 10%[4,5] of patients with CDI are likely to require surgical intervention. While only a minority of patients with CDI will have disease so severe that surgery will need to be considered, the mortality of this form of CDI, the morbidity of surgery, the potential for a patient to require a permanent stoma as a result of surgery, and uncertainties as to whether surgery reliably reduces mortality from fulminant CDI are the questions that form the basis of this article.

DEFINING FULMINANT DISEASE

One of the challenges in synthesizing the literature on managing fulminant CDI is navigating the divide in study questions and outcomes of interest between medical and surgical investigators studying the same disease. In the case of surgeons, a narrower focus on surgical outcomes but with broader, often ill-defined, inclusion criteria for what is considered fulminant disease and what constitutes failure of medical therapy is a feature of this literature. In particular, the majority of surgical studies report outcomes based on retrospective reviews of medical records. Furthermore, establishing the optimal timing of surgery represents decision-making for which a retrospective methodology limits the ability to guide that decision-making.

The Infectious Diseases Society of America (IDSA)[6] has produced, perhaps, the simplest and arguably the best-known criteria for grading CDI severity. In this schema, a severe episode is defined by a leukocytosis of 15,000 cells/mL or greater or a serum creatinine level greater than 1.5 mg/dL. A fulminant episode is distinguished by the additional presence of hypotension/shock, ileus, or megacolon; while it may be possible for these findings to occur in the setting of a white count and renal function that would be considered otherwise nonsevere, fulminant disease is typically accompanied by acute renal failure and a significant white count elevation. The IDSA criteria are easy to remember, and there is potential value in terminology agreed upon to describe severe or fulminant disease among providers and specialties to avoid ambiguity. A post hoc analysis of 2 randomized controlled trials[7] by Bauer and colleagues included 1105 patients with CDI. Leukocytosis (defined as a leukocyte count $>15 \times 10^9$ leukocytes/L) and renal failure (defined as a 50% creatinine level increase with a fixed value of a serum creatinine >1.5 mg/dL) were both associated with antibiotic treatment failure. This study observed that median leukocyte counts and creatinine levels were significantly higher in patients with treatment failure, with median creatinine levels also being significantly higher in patients who developed recurrent CDI. Interestingly, different cutoffs for leukocyte counts and creatinine levels, assessed by receiver operating characteristics, did not improve the predictive performance for predicting either treatment failure or recurrent CDI. Several studies have noted an association between hypotension, shock, ileus, and megacolon, and both the need for a colectomy and risk of inpatient mortality.[8,9]

One limitation of the IDSA system is that definitions of severe disease are inclusive of an incredibly large and heterogeneous group of patients with CDI. These definitions

are based entirely on minimum laboratory abnormalities that are not specific to CDI, as opposed to calibrating the definition of severity based on risk estimates for adverse outcomes specific to CDI. This methodological weakness, in part, explains why the IDSA severity classification has been criticized[10,11] as a poor predictor of serious adverse events such as inpatient mortality, the need for intensive care unit (ICU) admission due to sepsis, and the need for colectomy. Stevens[10] and colleagues reviewed Veterans Affairs data (2006–2016) to investigate whether IDSA criteria for severity correlated with "poor outcomes," which were defined as hospital or intensive care admission within 7 days of diagnosis, colectomy within 14 days, or 30 day all-cause mortality. The authors noted that areas under the curve predicting adverse outcomes were poor, though negative predictive values were greater than 0.80, thereby indicating that the IDSA classification may be more reliable in identifying low-risk patients who are less likely to experience a poor outcome, rather than identifying high-risk patients. The methodology of this study was unable to comment on the predictive value of individual fulminant criteria such as hypotension and ileus. This reflects how a finding such as hypotension can represent a correctable abnormality such as under-esuscitation, as opposed to sepsis that is medically refractory and requires surgery.

The majority of patients with CDI will not require surgery, and therefore, there is a difference between defining severe or fulminant disease and identifying a point in the care of a patient with CDI when surgery should be considered. One of the unique features of CDI is its ability to elicit a significant leukocytosis; white counts greater than 30,000 or 50,000 cells/mL are not uncommon. In virtually any other disease where surgery is a treatment option, a leukocytosis of this degree would typically prompt surgical intervention. In CDI, a different "range" of white counts acceptable during a period of close observation and goal-directed resuscitation is important to consider to avoid a potentially unnecessary intervention. While previous studies[7] have shown that leukocytosis is predictive of treatment failure, no established cutoff to serve as an independent trigger for surgery is available, which makes incorporating white counts into this decision difficult by virtue of a nullity of reliable data in the surgical literature on this specific point.

There has been little direct investigation into why some patients with CDI mount such an unusually elevated white blood cell count. From these limited data, bacterial envenomation appears to elicit the migration of neutrophils from bone marrow into both the systemic circulation and to the colon, which is potentially mediated by increases in proinflammatory cytokines (interleukin [IL]-1, IL-6, and tumor necrosis factor-alpha) and an increase in granulocyte colony-stimulating factor.[12] Although it has been assumed in clinical practice that this leukemoid response predicts treatment failure, the need for surgery, and mortality, it has yet to be proven through prospective study.[13] An exaggerated immune response leading to very elevated white counts may represent a form of host–pathogen response[14] that could be associated with a greater degree of inflammation (colitis), which may in turn result in a higher incidence of disease-related adverse events.

In summary, providers, especially surgeons, must remember that CDI has the ability to induce a leukocytosis that is unusually elevated compared to most other diseases that surgeons evaluate and treat. The literature provides suggested cutoffs for defining severe versus nonsevere CDI, but there is not an established white count to serve as an independent indicator of medical failure or the need for surgery. Although challenging, the white count requires interpretation in conjunction with assessing vital signs and the function of organ systems, preferably noting the trend of these measures as a more holistic judgment of the efficacy of medical therapy. This approach is the best that can be supported by the currently available literature, though it invites a

degree of best judgment for determining an indication of surgery, which both explains the heterogeneity of surgical patients in the CDI literature and it anticipates that such heterogeneity in patient selection and timing for surgery will continue.

SURGERY—TOTAL COLECTOMY VERSUS DIVERSION AND LAVAGE

The conventional surgery performed for fulminant CDI failing medical therapy involves a total abdominal colectomy with an end ileostomy. Although case series generally more than 20 years in the past included segmental colectomies in their descriptions,[15–17] segmental colectomy is no longer routinely performed given higher complication rates and generally worse outcomes compared to total colectomy. These complications include a higher incidence of patients requiring unplanned reoperation due to colon ischemia and colonic perforation. There are multiple studies, all from single institutional retrospective reviews, which have evaluated the survival benefit and complication rates of total colectomy with an end ileostomy for fulminant CDI; the majority suggest a survival benefit, though the bias introduced by varying patient selection among these studies is a significant limitation.

Of more value than individual, retrospective studies in evaluating the role of total colectomy in CDI are 2 systematic reviews that have evaluated the survival benefit of total colectomy. Bhangu[18] and colleagues reviewed 31 studies that allowed a comparison of outcomes between surgery and ongoing medical therapy. Among surgical patients, 89% underwent a total colectomy, with the remainder having received a partial colectomy. A statistically significant improvement in survival for patients undergoing surgery was reported; among patients undergoing a partial colectomy, 16% required an unplanned reoperation involving the resection of additional colon, which, compared to a partial colectomy, supports total colectomy as being the surgery of choice for fulminant CDI. One additional observation from this study was the association between preoperative septic shock with multiorgan failure and a higher rate of postoperative mortality, again underscoring the importance of patient selection and timing of surgery. A second systematic review described the outcomes of 510 patients,[19] with the main study outcome being survival benefit comparing total colectomy (partial colectomies were not included) and medical therapy for fulminant CDI. The pooled odds ratio for mortality was lower (odds ratio [OR] = 0.70) for patients undergoing surgery. Though a major surgery, with some series reporting a perioperative mortality as high as 80%,[20] these systematic reviews suggest that a total colectomy should be expected to provide greater odds of survival than continuing a failing course of medical therapy in patients with CDI whose sepsis is not improving as indicated by ongoing clinical deterioration.

Many surgeons are understandably reticent to perform a total colectomy in patients who, in addition to having fulminant CDI with multiorgan failure, are often of advanced age. In the pursuit of a potentially safer alternative to offer patients whose medical therapy not preventing worsening sepsis, a 2011 case series[21] was published describing the outcomes of 42 patients (2009–2011) treated for what the authors termed, “severe, complicated” CDI. These patients underwent the creation of a loop ileostomy and received an intraoperative colonic lavage with warmed polyethylene glycol via the ileostomy, with postoperative antegrade instillation of vancomycin flushes per ileostomy. The authors compared these surgical patients to a historical control group, finding no statistically significant differences between the 2 groups in terms of APACHE II scores. A total of 35% of surgical patients were able to undergo a laparoscopic procedure, despite their poor physiologic status, with surgery being associated with less mortality (OR = 0.24) compared to the control group. The authors

reported that 93% of surgical patients did not require colonic resection, which allows for the possibility of restoration of gut continuity with greater ease than when considering the closure of an end ileostomy with the creation of an ileorectal anastomosis. Of note, the primary endpoint of this study was not survival, but rather, resolution of CDI. Additionally, the use of historical controls introduces the possibility that different strains of CDI may have affected the 2 patient groups, along with differences in medical therapy and the lower likelihood of patients in the historical control group being offered surgery, given the prevailing view of CDI management at that earlier time. Nonetheless, proof of concept was provided in support of a surgical intervention in the setting of life-threatening CDI that offered a minimally invasive approach involving a lower magnitude surgery that is better tolerated by acutely ill patients, and that offers the possibility of both greater survival and the potential closure of the stoma.

A series of studies with stronger methodologies followed the seminal report by Neal, adding further support for diversion and colonic lavage. In 2017,[22] the Eastern Association for the Surgery of Trauma reported on the results of a 10 center retrospective study (2010–2014) for patients receiving either a total colectomy or a diverting ileostomy for CDI. A total of 98 patients were included, with no significant differences between the 2 groups in terms of their antibiotic exposures, preoperative laboratory test results, or the incidence or severity of preoperative organ failure. Interestingly, despite the difference in magnitude between the 2 surgeries, there were no significant differences between the groups in terms of their length of ICU and hospital stays, reoperation rates, fluid and vasopressor requirements for 24 hours following surgery, or the incidence of all-complications. The diversion cohort was noted to have a lower intraoperative blood loss, with no advantage for diversion in terms of unadjusted mortality rates. When adjusted for preoperative variables (age, lactate, timing of operation, vasopressor use, and acute renal failure), the authors reported significantly lower mortality in the loop ileostomy group (17.2% vs 39.7%). In the ileostomy group, 5 patients required an unplanned reoperation, one of which involved a total colectomy; none of these 5 patients died from reoperation. In the total colectomy group, 11.7% of patients required an unplanned reoperation, with no effect on mortality.

A 2023 review of data[23] (2016–2019) from the Nationwide Inpatient Sample compared total colectomy to diversion with a loop ileostomy. The primary outcome of this study was postoperative inpatient morbidity with secondary outcomes including postoperative inpatient mortality, complications, length of stay, and cost. A total of 886 patients were included, and following adjustment for preoperative risk variables, the authors reported no difference between these groups in terms of morbidity or mortality. Those undergoing a total colectomy were noted to have lower hospital costs and shorter lengths of stay, with the latter being a likely driver of the former. The authors concluded that while diversion did not appear to provide either an advantage or a disadvantage in terms of complications and mortality compared to a total colectomy, diversion may result in greater hospital resource use.

A 2020 meta-analysis provided by Felsenreich[24] and colleagues also compared total colectomy to diversion with a loop ileostomy, with 30 day postoperative mortality being the primary outcome of interest and secondary outcomes including a variety of perioperative complications. The authors included 5 observational studies with a total of 3683 subjects. Postoperative mortality was reported as 31.3% following total colectomy and 26.2% following the creation of a diverting ileostomy, which was not a statistically significant difference. Evaluating the rates of various complications between these groups was nuanced and often required the inclusion of fewer than all 5 studies; there was no statistically significant difference in the incidence of postoperative venous thromboembolisms, urinary tract infections, respiratory complications, or

unplanned reoperations. Surgical-site infections were significantly lower in the loop ileostomy group (4.5% vs 11.5%). A comparison of a composite postoperative adverse event rate was significantly lower in the loop ileostomy group (37.3% vs 59.2%; $P = .001$). Stoma reversal rates were higher in the ileostomy group (80% vs 25%), which represented a statistically significant difference. This meta-analysis concluded that diversion for CDI provides similar survival rates compared to total colectomy, with a reduced incidence of surgical-site infection rates, and with a higher likelihood that the stoma would be reversed.

An additional meta-analysis comparing diverting loop ileostomy to total colectomy for fulminant CDI was published in 2024 by Aljaafreh[25] and colleagues. Seven studies were included, totaling 7048 patients, with 1728 individuals undergoing the creation of a diverting loop ileostomy. Patients undergoing diversion were noted to have a statistically significant lower incidence of postoperative mortality and a higher rate of stoma reversal, with no significant difference between the surgical groups in terms of postoperative complications such as thromboembolic events, surgical-site infections, urinary tract infections, renal failure, and pneumonia.

In summary, the literature regarding surgical outcomes for fulminant CDI indicates that patient selection is an important element in determining postoperative mortality. Due to its lower magnitude, its lesser operative time, and the potential for a minimally invasive approach, the currently available data suggest that mortality following the creation of a diverting loop ileostomy is equivalent to or superior to that afforded by the much lengthier and more physiologically taxing total colectomy. The consensus of current data indicates that diversion is associated with equivalent or lower rates of complications compared to total colectomy, while the total cost of care may be higher for patients undergoing diversion depending on length of stay. Postoperative length of stay may not reflect the physiologic cost of diversion as much as age-related comorbidities and the convalescence that reflects the severity of sepsis from CDI prior to surgery.

PRINCIPLES OF SURGICAL EVALUATION OF PATIENTS WITH FULMINANT *CLOSTRIDIOIDES DIFFICILE* INFECTION

Surgeons are typically asked to consult on patients with CDI who have severe or fulminant infections. This makes the initial consultation a time-sensitive evaluation to determine if further efforts at medical therapy would be safe. There are several principles that are helpful in expeditiously assessing such patients (**Fig. 1**):

- If the patient has been admitted for more than 24 hours, reviewing vital signs and laboratory test results is helpful for providing a trend of the patient's response to medical therapy. Most patients requiring surgical consultation will have at least one organ system in a dysfunctional state; the more organ systems that fail, the less safe ongoing medical therapy becomes.
- Assess fluid administration to ensure that the patient is being adequately resuscitated. Inadequate fluid administration is a confounder for interpreting vasopressor requirements and acute renal failure as an indication for surgery, while also representing a modifiable risk factor for adverse events at the time of anesthesia induction.
- Review *difficile*-directed antibiotic treatment. For fulminant patients with CDI, expert consensus[8] favors the use of oral vancomycin using 500 mg dosing, and the addition of parenteral metronidazole can be considered for this patient population.
- Review all antibiotics indicated for infections other than CDI. The decision to de-escalate or discontinue antibiotics for these other conditions is a difficult one,

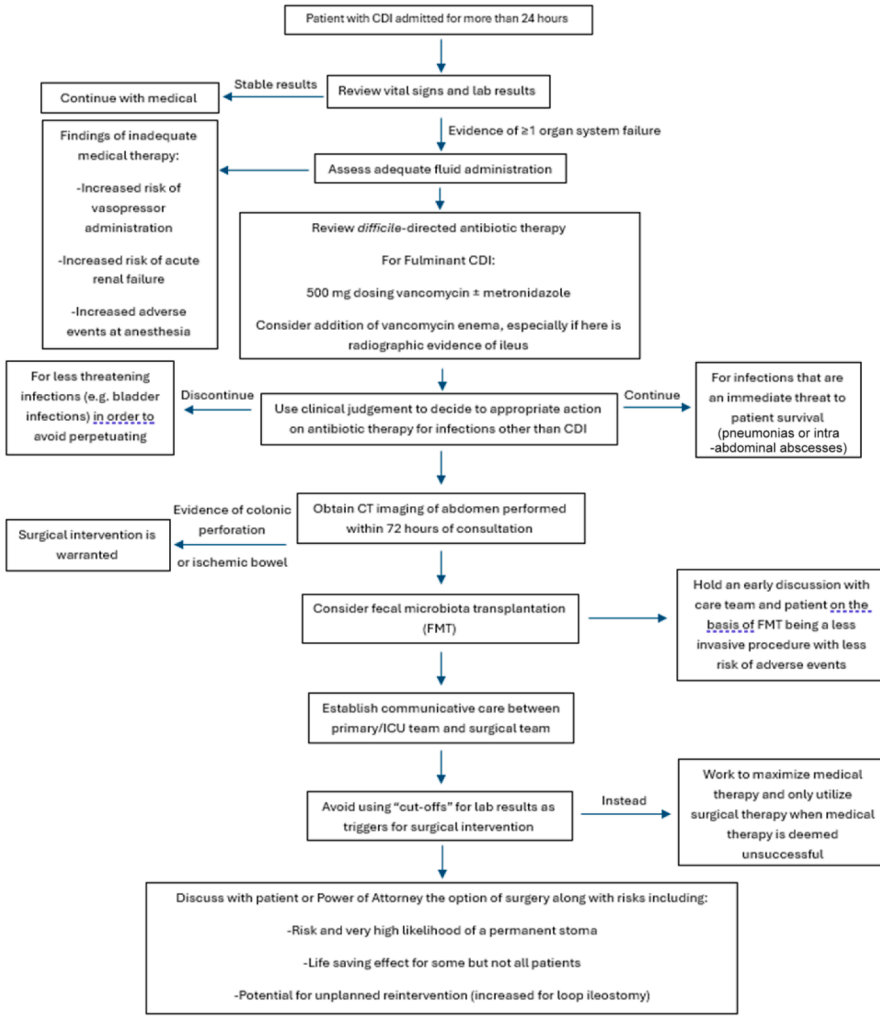

Fig. 1. Algorithm for surgical assessment of patients with fulminant CDI.

and there is currently no data to guide such decisions, leaving them to best judgment. While certain types of infections, such as pneumonias or intra-abdominal abscesses, are more likely to require ongoing antibiotic therapy due to their threat to patient survival, others such as bladder infections may allow for discontinuing antibiotics in an effort to avoid perpetuating the intestinal dysbiosis that represents a significant causal factor in perpetuating CDI. Vancomycin enemas can be considered in conjunction with oral agents, especially if there is radiographic evidence of an ileus, though the data supporting this intervention comes from lower quality studies with small numbers of patients.

- Ensure that there is recent (within 72 hours of consultation) computed tomographic imaging of the abdomen and pelvis. For fulminant CDI patients in shock, medical imaging is particularly important not to diagnose fulminant CDI, but to ensure the absence of a colonic perforation and/or ischemic colon as complications of this

disease that cannot be managed with medical therapies and thus require surgery if salvage is still in view.

- Although not available at many centers, as an alternative to both failing medical therapy *and* possible surgical intervention, a discussion regarding fecal microbiota transplantation should be undertaken. The application of fecal microbiota transplant (FMT)[26] via colonoscopy represents a less-invasive and a lower overall risk for periprocedural adverse events than does any kind of surgery, and thus, this discussion represents a different branch point in decision-making than whether or not to perform surgery. Since FMT can also be appropriately administered at time points earlier than would be appropriate for surgery, if FMT is available at the patient's facility, discussing its use would preferably occur prior to surgical consultation, and certainly should occur at the time a surgeon becomes involved in the care team.
- A discussion between the primary/ICU team and the surgical team is helpful to both ensure consistent communication to the patient and their family as well as to ensure shared definitions of "improvement" and "deterioration." This latter element is important given the ease with which information can be sequestered between primary and consulting service lines.
- Avoid single laboratory measurements as "cutoffs" or triggers for surgery but instead focusing on defined goals between care teams regarding resuscitation and antibiotic management, with serial laboratory measurements allowing for frequent reassessment of the patient to offer surgery in circumstances where medical therapy is maximized but unsuccessful. This promotes surgery being offered in a manner that is timely and yet not premature.
- Early discussions with the patient or, when necessary, their power of attorney to discuss the option of surgery. Surgery should be described as involving the creation of a stoma that has a very high likelihood of being permanent, especially for older patients and for those with poor baseline health. Surgery should also be described as having data to support its life-saving effect for some but not all subjects, and the potential need for unplanned reoperation should be emphasized for patients undergoing the creation of a loop ileostomy.

In conclusion, surgery for fulminant CDI represents an intervention that only a minority of patients with this infection should require. Best current data suggest that diversion with a loop ileostomy and colonic lavage provides an advantage compared to total colectomy, though the lower magnitude of diversion does not guarantee a shorter length of depending on the patient's preoperative comorbidities and the severity of their sepsis. Assessing patients for failed medical therapy that may warrant surgery requires trending organ function while ensuring that medical therapy is truly being optimized. The preponderance of data suggests that surgical intervention has a reasonable likelihood of extending life for patients with no other options.

DISCLOSURE

Neither author has any financial or commercial disclosures, and no conflicts of interest to disclose.

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