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An institutional comparison of total abdominal colectomy and diverting loop ileostomy and colonic lavage in the treatment of severe, complicated *Clostridium difficile* infections

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ABSTRACT

Background: Total abdominal colectomy (TAC) is the standard surgical treatment of *Clostridium difficile* infection (CDI). An alternative therapy, loop ileostomy and colonic lavage (IL), was described in 2011, but the results have never been validated.
Methods: Patients treated surgically for CDI between April 2011 and June 2015 were included. Bivariable analysis was used to compare 30-day mortality, 1-year mortality, CDI recurrence, colon preservation and ileostomy reversal.
Results: Ten IL patients and thirteen TAC patients were identified. 30-day mortality (30% vs 23%, $p = 1.0$) and 1-year mortality (40% vs 46%, $p = 1.0$) were similar. Four IL and three TAC patients (57% vs 30%, $p = 0.35$) experienced recurrent CDI. All six surviving IL patients had successful colon preservation; five underwent ileostomy reversal compared to three in the TAC group (83% vs 43%, $p = 0.27$).
Conclusions: Although IL allowed colon preservation and return of intestinal continuity in most patients, IL did not decrease mortality or recurrent CDI when compared to TAC.

1. Background

Clostridium difficile is an anaerobic, gram-positive rod bacterium and the leading cause of infectious diarrhea in hospitals in the developed world.[1] The incidence and severity of *C. difficile* infection (CDI) have been increasing since the turn of the 21st century, placing a large burden on the American healthcare system and costing an estimated 4.8 billion dollars annually.[1,2] The American Journal of Gastroenterology published guidelines for the diagnosis, treatment and prevention of CDI in 2013. The guidelines defined severe and complicated *C. difficile* infection as CDI with any of the following symptoms that can be attributed to the infection: admission to an intensive care unit, hypotension with or without required use of vasopressors, fever of ≥38.5 °C, ileus or significant abdominal distension, altered mental status, white blood cell count ≥35,000 cells/mm^3 or <2000 cells/mm^3, serum lactate >2.2 mmol/l, or end organ failure (mechanical ventilation, renal failure, etc.).[3] The recommended treatment for severe, complicated CDI is oral vancomycin and intravenous (IV) metronidazole plus rectally-instilled vancomycin, if the patient has signs of ileus or significant abdominal distension. Additionally, early surgical consultation is suggested as many of these severely ill patients will have disease that is refractory to antibiotic treatment alone.[3] If surgery is required, total abdominal colectomy with end ileostomy formation has been considered the gold standard treatment.[1,4] Though systematic review suggests colectomy provides survival advantage over medical management alone in these patients, mortality has remained high after this salvage therapy, with reported mortality rates ranging from 32 to 80%.[5–9]

In 2011, Neal and colleagues published the novel technique of performing diverting loop ileostomy with intraoperative colonic lavage and postoperative, antegrade vancomycin enemas in patients with severe CDI.[10] This simpler, less-invasive surgical approach resulted in preservation of the colon in 93% of trial patients as well as reduced mortality (19% vs 50%, odds ratio 0.24) when compared to matched historical patients who were treated

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with total abdominal colectomy. At the time of initial publication, fifteen of the nineteen surviving patients (79%) had undergone reversal of their ileostomy.[10]

Despite encouraging results, the Neal study has been met with some trepidation with critics citing concerns over study design and small study group as well as the fact that these results have not yet been reliably replicated.[1] There has been only one follow-up study published since the Neal paper was released, though it was a small, four patient cohort.[11] Given the lack of follow-up evidence in support of loop ileostomy and colonic lavage, we chose to review our institution's experience with the surgical treatment of severe, complicated CDI during the time period since the Neal study was first published. Our goal was to compare outcomes in patients treated with this novel approach to those in patients treated with the current operation of choice, total abdominal colectomy and end ileostomy.

2. Methods

2.1. Study design and intraoperative detail

A retrospective review was conducted of all adult patients who were treated surgically for severe, complicated *C. difficile* infection at the University of Virginia between April 2011 and June 2015. The Institutional Review Board of the University of Virginia reviewed the study proposal and determined it to fall under "quality improvement" guidelines. Patients with concurrent inflammatory bowel disease or whose final pathology did not show pseudomembranous colitis were excluded. All patients treated with total abdominal colectomy underwent open surgery with creation of an end ileostomy. Those patients who underwent loop ileostomy creation with intraoperative colonic lavage were treated with either laparoscopic or open surgery. The perioperative surgical protocol used in the Neal paper was followed. Briefly, once the colon viability was assessed and a loop ileostomy was created, 8 L of warmed polyethylene glycol 3350/electrolyte solution (GoLytely; Braintree Laboratories) was infused into the colon via catheter in the efferent limb of the ileostomy. The catheter was left in place in the efferent limb and the patient was taken to the intensive care unit for continued monitoring. Postoperatively, patients received antegrade vancomycin boluses (500 mg every 8 h) via the catheter in the efferent limb of the ileostomy. Patients were additionally continued on IV metronidazole (500 mg every 8 h). Patients were monitored in the intensive care unit until their hemodynamic status improved and they were deemed stable for transfer to the acute care floor.

2.2. Outcome measures and statistical analysis

The primary outcome of the study was occurrence of 30-day mortality. Secondary outcome measurements included 1-year mortality, *C. difficile* infection recurrence, colon preservation and return of intestinal continuity. Preoperative risk factor data for patients were summarized and stratified according to type of surgery received and includes age, sex, preoperative white blood cell (WBC) count, preoperative albumin level, preoperative intubation and/or vasopressor use, immunosuppression as defined by chronic steroid or immunosuppressant use, and treatment with antibiotics, including IV metronidazole, oral vancomycin, or rectal vancomycin. This information is reported as a median with interquartile range or a percentage (%). Statistical analysis for continuous variables was calculated using Mann-Whitney *U* test; analysis for categorical variables was calculated using Chi-squared or Fisher's exact tests, where appropriate. The threshold for statistical significance was set at an alpha of 0.05. STATA version 14.4 (StataCorp LP, College Station, TX, USA) was utilized for statistical analysis of all study data.

3. Results

Twenty-seven patients with severe, complicated *C. difficile* infection were treated surgically during the 51-month study period. Four patients treated with total abdominal colectomy were excluded for concurrent inflammatory bowel disease or final pathology that did not show pseudomembranous colitis. Of the remaining twenty-three patients, thirteen (56.5%) underwent total abdominal colectomy. Ten (43.5%) underwent loop ileostomy creation and colonic lavage and seven of these (70%) were completed laparoscopically. As in the Neal study, all patients underwent postoperative, antegrade vancomycin colonic flushes via the efferent limb of the loop ileostomy in addition to continued IV metronidazole infusion. The two cohorts were similar in age, gender and degree of critical illness (all p-values >0.35, Table 1). The median WBC count was higher in the loop ileostomy patients, though this difference was not statistically different. A majority of patients in both the loop ileostomy and colectomy groups required preoperative ICU care (90 vs. 85%, $p = 1.00$).

Of the patients who underwent total abdominal colectomy and end ileostomy creation, three (23%) died within 30 days of surgery, compared to three (30%) in the loop ileostomy and colonic lavage group ($p = 1.00$). The odds ratio for 30-day mortality was lower in the colectomy patients, though this did not reach statistical significance (OR = 0.70, 95% CI: 0.11–4.54, $p = 0.71$). One-year mortality was also similar between the two groups; six (46%) patients in the colectomy cohort died compared to four (40%) in the loop ileostomy cohort ($p = 1.00$). The odds ratio for 1-year mortality was higher in the colectomy group, though this was, again, not statistically significant (OR = 1.29, 95% CI 0.24–6.83, $p = 0.77$). Among the three colectomy patients who died more than 30 days following surgery, one died of metastatic cancer and one died from causes unrelated to CDI. The third was placed on comfort care and expired after multiple readmissions for abdominal bacterial infections, including vancomycin resistant enterococcus and a *C. difficile* positive perisplenic abscess. The only additional death that occurred after 30 days from surgery in the loop ileostomy and colonic lavage cohort was a patient who had been discharged to hospice after surgery given her poor clinical condition.

Three (23%) of the patients who underwent total abdominal colectomy experienced at least one CDI recurrence, compared to four (40%) of those who underwent loop ileostomy and colonic lavage ($p = 0.57$). If the patients who died within 30 days of surgery are removed from these groups, three (30%) of all surviving colectomy patients and four (57%) of all surviving loop ileostomy patients had a recurrent CDI episode ($p = 0.35$). The three colectomy patients had recurrences 0–5 months after surgery. One was treated with oral metronidazole and vancomycin. One was treated with oral metronidazole but had a second recurrence requiring oral vancomycin and IV metronidazole treatment. The last colectomy patient also had two recurrences, both occurring after he had undergone ileostomy reversal. The first was treated with oral vancomycin and IV metronidazole but no documentation of treatment regimen for the second recurrence was reported in the medical record. Among the loop ileostomy and colonic lavage group, the recurrent CDI episodes occurred 2–7 months after surgery. One was not treated because the patient was in hospice care. Two patients were treated with vancomycin instilled through the efferent limb of their existing ileostomies; one of these patients experienced an additional recurrent CDI episode which was treated with fecal microbiota transplantation (FMT) via the ileostomy. The last CDI recurrence in this cohort did not occur until after the patient's