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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.

Keywords

Clostridium difficile; *C. difficile*; Loop ileostomy and colonic lavage; Colectomy; Total abdominal colectomy

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

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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 $\geq 38.5^{\circ}\text{C}$, ileus or significant abdominal distension, altered mental status, white blood cell count $\geq 15,000$ cells/mm³ or <2000 cells/mm³, 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 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 ileostomy was reversed. This patient had recurrent severe, complicated CDI in the immediate postoperative period which was successfully eradicated with three rounds of FMT delivered via colonoscopy.

All six patients who underwent loop ileostomy and colonic lavage and survived for over one year postoperatively had successful colon preservation and five (83%) of these patients later had return of intestinal continuity with ileostomy reversal. In contrast, only three (43%) of the surviving colectomy patients had return of intestinal continuity. A summary of all postoperative outcomes can be found in Table 2.

4. Conclusions

In this retrospective review of all patients who underwent surgical treatment of CDI, we found less convincing evidence to support loop ileostomy with colonic lavage than the initial Neal study demonstrated in 2011. In our much smaller cohort of patients utilizing the same treatment protocol, 30% died within 30 days compared to 23% in the total colectomy group. In the Neal study, the 30-day mortality was 19% (8/42) for the loop ileostomy group and 50% (21/42) for the historically matched colectomy patients, showing a survival advantage for the loop ileostomy cohort ($p = 0.006$).¹⁰ While our institution's data does not show a similar improvement in mortality for those undergoing loop ileostomy and lavage, our 30-

day mortality after total abdominal colectomy appears to be substantially lower than the Neal results. These differences may be attributable to small sample size and improvements in management of *C. difficile* patients between the time of the two studies. The two surgical groups in our study also had similar 1-year mortality (40 vs 46%, $p = 1.00$), and we therefore have concluded that there is no short- or long-term mortality benefit of loop ileostomy and colonic lavage over total abdominal colectomy in the treatment of severe, complicated CDI.

The rate of CDI recurrence in loop ileostomy patients who survived more than 30 days was remarkably high at our institution, with 57% experiencing at least one episode of recurrent CDI. The Neal study reported a very low rate of CDI recurrence, with only one patient (2.4%) experiencing recurrent symptoms two months after loop ileostomy and colonic lavage.¹⁰ In a similarly surprising outcome, 30% of our total abdominal colectomy patients experienced a second episode of CDI after surgery, detected either in the ileostomy effluent or rectal stump output. Our high recurrence rate in both groups may represent a higher overall rate of CDI or may suggest a more virulent strain of *C. difficile* in our hospital system.

Of all patients undergoing loop ileostomy and colonic lavage in our study, there were no patients who required subsequent colectomy, representing a 100% colon salvage rate. Further, 83% of these patients had restoration of normal intestinal continuity with ileostomy reversal in the follow-up period. Both of these results closely match those obtained by Neal et al. Preservation of the colon is a major benefit of this alternative surgical treatment strategy, as patients avoid the morbidity and inconvenience of a permanent ileostomy.

There are several limitations to this study including the study design itself. Because this is a single hospital center's review of the surgical treatment of CDI, the application of these results to a broader population is clearly limited. As in any retrospective review, the analysis is subject to bias. The choice of procedure to be performed for a given patient was left entirely to the attending surgeon on call and therefore no randomization was possible. Additionally, the 23 identified CDI surgeries were performed by 14 different attending surgeons, subjecting the data to performance bias. Finally, the small sample size of patients undergoing the two surgical treatments underpowered our data, preventing any definitive conclusions about the benefit of loop ileostomy and colonic lavage over total abdominal colectomy.

Although Neal et al. described the novel technique of loop ileostomy and colonic lavage for the treatment of CDI over five years ago, follow-up data in support of their exciting results has yet to be published. After review of our institute's experience with the surgical treatment of severe, complicated CDI, we have shown similar results in the rate of colon preservation and restoration of intestinal continuity. Our data does not, however, suggest that there is a mortality benefit, either short- or long-term, when compared to the standard surgical treatment of severe, complicated CDI. Larger, prospective and perhaps multi-institutional studies are warranted to further study outcomes after loop ileostomy and lavage in the treatment of this common and potentially life-threatening disease.

Discussion

Hallowell, P. T.; Fashandi, A. Z.; Martin, A. N.; Wang, P. T.; Hedrick, T. L.; Friel, C. M.; Smith, P. W.; Hays, A. R.

DR. AMBER LINNELL TRAUGOTT (Columbus, Ohio): I want to commend you on this data, which are only going to add to the controversy surrounding loop ileostomy versus total abdominal colectomy for severe C. diff infection. And as you pointed out, there's very little in the literature at this point and we really still lack a good understanding about how to select patients, which might be better with one approach versus the other. I do have a few questions for you. In the Neal study, they theorized that because the loop ileostomy procedure seemed to be safe with colon sparing and had, in their group, lower postoperative mortality, they suggested that we should be performing loop ileostomy preferentially and earlier in the patient's clinical course. I have a couple questions about your data related to that. Do you have any evidence or understanding that that assertion made by the authors of that study influenced the surgical decision making by your surgeons? Were they taking the patients they intended to perform loop ileostomy on to the OR earlier in their clinical course than the ones that ultimately had a colectomy? And then as a related question, there weren't any statistically significant differences in the variables you measured related to severity of preoperative illness. I noticed you didn't measure any validated composite scores of illness severity like the APACHE score, and I was wondering if you could comment on why you chose the variables that you did. My second question is about the postoperative recurrence after 30 days postop. We had one patient at our institution who we did a loop ileostomy and lavage on who did well initially and then developed fulminant c. diff infection in the postoperative period after the ileostomy takedown where the only antibiotic exposure was the surgical prophylaxis for the ileostomy takedown. That patient ended up going for an emergent colectomy. So while the numbers that you showed are not statistically significant, that was also true in the Neal study, in both cases you had more patients with late recurrent C. diff infections in the ileostomy group, and I was wondering if you could comment on whether you think that's clinically significant. And then the third question I have is why do you think that the mortality benefits seen in their study was not borne out in your data?

DR. FASHANDI: So first to address your question about whether or not our patients were taken to the OR sooner for loop ileostomy and lavage, I do not actually believe that they were. Probably this is similar for most institutes, but about 80–90 percent of these patients were actually admitted to a medical service and not a surgical service. So surgery was not actually involved in the care of these patients until they were already, for the most part, in an ICU and critically ill. Looking at the time from date of consult to the time to the surgical procedure, the groups were pretty much equivalent. The loop ileostomy/lavage group was about 1.6 days, although almost all of these patients went either the day of consult or the following day. And the same with the colectomy group, the average time from consult to surgery was about 0.8 days. So, again, both groups were pretty similar, I think, because they were critically ill. Our surgeons did a pretty good job of getting these patients in the OR in an expedited manner and got them treated with what they needed. Regarding critical illness scores, the Neal paper did use APACHE II scores, which we know are calculated in the first 24 hours of ICU admission. Ideally we would have done the same just to have a little bit

easier way to compare the two papers, although not all patients were admitted to the ICU in our study, plus since this was retrospective, all 12 of the variables of the APACHE score were not available to us in many patients so many patients would have had to have been thrown out, and comparing the two groups with just a couple patients in each group wouldn't have been terribly informative. We, therefore, used more descriptive variables, like how many were on vasopressors, how many required intubation, what their white count was, just as a more visual indication of their degree of critical illness that we know these are not validated, and ideally we would use a more validated scoring system for critical illness. I do appreciate that you brought up your episode of recurrence after ileostomy takedown. This project actually started after Dr. Hallowell and I had a similar patient who was referred to our hospital after having the initial index procedure just for ileostomy reversal, and he, unfortunately, died within three days of ileostomy reversal in a very quick critical illness. Even despite total abdominal colectomy, he ended up passing away. We've actually had two further patients after that who have had recurrence of fulminant C. diff who were successfully rescued with fecal transplantation from our GI colleagues, so I do think that that's an important thing to keep in mind. So as to whether the recurrent is clinically significant after loop ileostomy and lavage, I definitely think it is, although in such a small group, you know, we had four of our seven surviving patients, which is 57 percent, had a recurrence, I'm not sure that that is likely to be the recurrence rate across the country that high, but I do think that it's something to keep in mind and that we should all be aware of. And then, finally, your last question was about why we did not see the difference in mortality for these two surgeries. I think our main problem was probably that of sample size. The Neal paper had 42 patients in each arm of their surgical groups, so we had 10 and 13. So I think just the small sample size alone was going to prevent us from seeing any real differences between the groups. Additionally, with our study design, they had a protocol in place to set up for these patients who underwent loop ileostomy and lavage, and we did not. This is all retrospective. They also had one patient or one doctor who took care of all their patients who had loop ileostomy lavage, making everything kind of more protocolized, whereas we had six patients or six attendings who took care of our loop ileostomy patients and ten who did the total abdominal colectomies, so a lot more variability. So I think going forward if we were able to expand our groups possibly with a multi-institutional look at this procedure, that would be one way to benefit and see if there is actually a mortality difference.

DR. SCOTT R. STEELE (Cleveland, Ohio): So it has been five years since the Pittsburgh paper. Yours is the second one, and you have ten patients, seven of which survived. Why do you think that is and what do you think the actual role of this procedure for this particular clinical situation is eventually going to be? Is it going to go by the way or is it actually we are going to get data to be able to support this procedure?

DR. FASHANDI: So I think if we are going to find the data to support the procedure, it's definitely going to need to be on a larger scale. At least at our institution, with having so few patients with this procedure, having undergone this procedure, anyway, I think you would need a multi-institutional look to get the numbers. However, I do think there's a role for this procedure, just based on colon preservation alone and eventual ability to return to normal intestinal continuity.

I know as a patient, I would probably prefer that, and so, therefore, as it's definitely not a more dangerous procedure. I think it definitely has a role. It's just not able to be studied as easily as they did in Pittsburgh with just such small numbers.

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Table 1

Preoperative risk factors stratified by procedure.

	TAC, N = 13	Loop ileostomy, N = 10	P-value^a
Age (in years), Median (IQR)	63.2 (59.4–72.4)	59.7 (56.4–63.4)	0.54
Female sex, N (%)	7 (54)	7 (70)	0.67
Preoperative WBC, Median (IQR)	21 (9.8–43.4)	39.3 (24.5–49.5)	0.35
Preoperative albumin, Median (IQR)	2.2 (1.9–2.8)	2.0 (1.8–2.7)	0.44
Preoperative ICU, N (%)	11 (85)	9 (90)	1.00
Preoperative intubation, N (%)	6 (46)	2 (20)	0.38
Preoperative vasopressor use, N (%)	6 (46)	5 (50)	0.86
Immunosuppression, N (%)	2 (15)	2 (20)	1.00
Treated with metronidazole and/or oral vancomycin, N (%)	13 (100)	10 (100)	N/A
Treated with rectal vancomycin, N (%)	6 (46)	7 (70)	0.40

TAC = total abdominal colectomy; IQR = interquartile range; ICU = intensive care unit.

^aP-value for continuous variables calculated using Mann-Whitney *U* test; p-value for categorical variables calculated using Chi-squared or Fisher's exact tests, where appropriate.

Table 2

Outcomes following total abdominal colectomy versus loop ileostomy for CDI.

	TAC, N = 13	Loop ileostomy, N = 10	P-value ^a
30-day mortality, N (%)	3 (23)	3 (30)	1.00 ^b
1-year mortality, N (%)	6 (46)	4 (40)	1.00 ^c
CDI recurrence, N (%)	3 (23)	4 (40)	0.57
CDI recurrence in >30-day survivors, N (%)	3 (30)	4 (57)	0.35
Colon preservation in >1-year survivors, N (%)	–	6 (100)	–
Return of intestinal continuity in >1-year survivors, N (%)	3 (43)	5 (83)	0.27

TAC = total abdominal colectomy; CDI = *Clostridium difficile* infection.^aP-value for continuous variables calculated using Mann-Whitney *U* test; p-value for categorical variables calculated using Chi-squared or Fisher's exact tests, where appropriate.^bOdds ratio = 0.70, 95% CI: 0.11–4.54, p = 0.71.^cOdds ratio = 1.29, 95% CI: 0.24–6.83, p = 0.77.