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Prolonged non-operative management of clostridium difficile colitis is associated with increased mortality, complications, and cost

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ABSTRACT

Background: We aim to investigate the effects of delaying surgery on outcomes and cost in patients admitted with severe clostridium difficile infection (CDI).
Methods: The Vizient database was queried for patients with CDI who underwent open total abdominal colectomy (TAC). Patients operated on the day of admission were excluded. Chi-square, Fisher's exact, student T-test, and logistic regression were performed with $\alpha = 0.05$.
Results: Logistic regression analyses using days from admission to surgery (DATO), age, race, and gender demonstrated that increased DATO was associated with higher 30-day mortality (OR 1.022, 95% CI 1.001−1.044, $p = 0.040$), overall complications (OR 1.034, 95% CI 1.014−1.054, $p = 0.001$), and infectious complications (OR 1.040, 95% CI 1.018−1.062, $p < 0.001$) compared to age for all three outcomes. Total length of stay (LOS), intensive care unit LOS, and direct cost increased in conjunction with DATO ($p < 0.001$).
Conclusions: Early surgical intervention in appropriately selected patients should be considered when there is a high suspicion for prolonged non-operative treatment.

Introduction

From 2001 to 2010, more than 2.7 Million patients were discharged with a diagnosis of clostridium difficile infection (CDI), and of these, more than 19,000 underwent colectomy.[1] During this period, the incidence of CDI and frequency of operative intervention were noted to have increased by 47% and 32%, respectively.[1] In certain regions of the United States, CDI has now surpassed methicillin-resistant staphylococcus aureus as the most common type of hospital acquired infection.[2] Many patients with CDI are successfully treated with metronidazole, vancomycin, or fidaxomicin; however, up to one-third of patients may become persistent carriers who are at risk for recurrent disease. Additionally, resistant strains of C *difficile* (i.e. BI/NAP1/027) have been identified and contribute to non-operative treatment failure.[3,4] Patients with CDI frequently require extended inpatient treatment with intravenous antibiotics, and an increasing number of patients are ultimately requiring surgical intervention with mortality rates varying from 19% to 80%.[5–7]

The increasing incidence of CDI and its emergence as a surgical disease is a relatively recent event and little data has been published to support early versus late operative intervention. The high mortality rate associated with surgical intervention in patients with CDI may be partially attributable to advanced age and medical comorbidities; however delayed surgical intervention may also contribute.[1] Non-operative treatment of CDI is often continued until the patient either recovers or acutely decompensates in the intensive care unit; however, the latency period between diagnosis and decompensation can extend for a prolonged period.[7] The outcomes associated with prolonged non-operative treatment have largely not been investigated, yet it remains a relevant clinical question. We aim to determine the effects of prolonged non-operative management on morbidity, mortality, and cost in patients who undergo rectal-sparing total abdominal colectomy and end ileostomy (TAC) for CDI. Improving patient selection and timing of surgical intervention may help lower the markedly high mortality rate associated with surgical intervention in patients with CDI.

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Materials and methods

Database description

We have previously described the Vizient Clinical Database as it relates to surgical outcomes research.[8] The Vizient Clinical Database uses the All Patients Refined Diagnosis Related Groups (APR-DRG) classification system to assign a severity of illness (SOI) score to each patient using a validated algorithm that is calculated using several patient demographics, comorbidities, and diagnoses. A SOI score of 1–4 is assigned to each patient for minor, moderate, major, or extreme SOI, respectively.[9,10] For our purposes, "high-risk" operative candidates had SOI scores of either three (major) or four (extreme).

Study design

The Vizient Clinical Database was queried for patients who were admitted urgently or emergently with a primary admission diagnosis of colonic CDI (ICD-9-CM diagnosis code of 8.45) and a SOI score of three or four who underwent total abdominal colectomy and end ileostomy (ICD-9-CM procedure code 45.82) from October 2008 to October 2015. Patients <18 years of age were excluded as were patients with high outliers (>95th percentile) for total hospital length of stay (LOS) or days from admission to operation (DATO). Patients who underwent surgical intervention on the day of admission (DATO = 0) were also excluded in order to best capture patients who underwent a meaningful attempt of non-operative intervention. Regarding the definition of outcomes analyzed in this study, "infectious complications" were reported as a single outcome and were inclusive of 1. aspiration pneumonia; 2. catheter-associated urinary tract infection; 3. nosocomial pneumonia; 4. wound infection; 5. Sepsis; 6. post-operative infection; 7. post-operative shock. Similarly, "cardiovascular complications" were inclusive of 1. acute myocardial infarction occurring during hospital stay; 2. cardiac abnormalities except acute myocardial infarction; 3. hospital acquired acute myocardial infarction.

Statistical analysis

Descriptive statistics were performed for patient demographics including age, gender and race. Continuous data were reported as mean ± standard deviation (SD). Descriptive analyses, Kruskal-Wallis one-way ANOVA, and logistic regression were performed using IBM SPSS v.23.0.0, with $\alpha = 0.05$ and parametric tests were performed according to the Central Limit Theorem. Data were stratified according to DATO quartile including Quartile 1 (Q1, DATO = 1), Quartile 2 (Q2, DATO 2–4), Quartile 3 (Q3, DATO 4–9) and Quartile 4 (Q4, DATO >9).

Results

Patient characteristics

A total of 10,679 patients ≥18 years of age underwent TAC during this period. Of these, 1590 patients had a primary admission diagnosis of CDI. Patients with SOI scores of 1 or 2, LOS or DATO greater than 95th percentile and those who underwent non-emergent surgery were excluded ($N = 358$). Of the remaining 1232 patients, 173 (14%) underwent surgery on the day of admission (DATO = 0) were thus excluded, yielding a total of 1059 patients which were included in our analysis. Stratification of patients by DATO quartile yielded 254 patients in Quartile 1 (DATO = 1), 356 patients in Quartile 2 (DATO 2–4), 215 patients in Quartile 3 (DATO 5–9), and 234 patients in Quartile 4 (DATO >9). A slight majority of patients were Female (53.4%, $N = 565$) and mean age for all patients was 64 years. Thirty-day mortality rate for the entire cohort was 29.2% ($N = 309$). Of patients who survived, 25.5% ($N = 191$) experienced a 30-day readmission. Mean age for survivors versus non-survivors was 62.7 years vs. 66.2 years, respectively ($p < 0.001$). Forty percent ($N = 424$) of patients experienced at least one post-operative complication.

Compared to older patients, younger patients underwent operative intervention on later admission days. We observed that 34% of patients <55 underwent TAC after the ninth inpatient day compared to only 14% of patients >76 ($p < 0.001$). Similarly, only 19% of patients <55 years of age underwent surgical intervention on the day after admission compared to 31% of patients >76 years of age ($p = 0.003$) (Table 1). Females and Caucasian patients tended to undergo earlier operative intervention; however, these trends did not reach statistical significance (Table 1).

Perioperative outcomes and cost

Patients in DATO Q4 were 50% more likely to suffer a complication compared to DATO Q1 (49% vs. 33%, $p = 0.002$). Patients in DATO Q4 were two- and ten-times more likely to sustain two or three complications compared to patients in DATO Q1, respectively (9.8% vs. 4.7% and 3.8% vs. 0.4%, $p = 0.007$). Strokes were six-times more common in DATO Q4 compared to DATO Q1 (4.7% vs. 0.8%, $p = 0.004$). Infectious complications were twice as common in DATO Q4 compared to DATO Q1 (30% vs. 16%, $p = 0.001$) and gastrointestinal hemorrhage, while observed in 3.4% of patients in DATO Q4, was not observed for any patient in DATO Q1 ($p = 0.001$) (Table 2). On univariate analysis, other complications of interest were not significantly different among DATO quartiles (all $p > 0.05$) (Table 2). Both total hospital LOS and ICU LOS increased in conjunction with DATO quartile (both $p < 0.001$). Patients with prolonged non-operative management prior to surgery (DATO >9 days) had a total hospital LOS double those who underwent operative intervention on the first full day of admission (DATO = 1) (33 days vs. 16 days, respectively, $p < 0.001$) (Table 3). Similarly, these patients had longer ICU admissions (16 days vs. 9 days, respectively, $p < 0.001$) (Table 3). Patients who underwent surgery after the ninth admission day accumulated a mean of $84,717 ± $63,529 in direct charges, double that of patients operated on the first full admission day ($p < 0.001$, Table 3).

Table 1
Patient characteristics stratified by duration of non-operative management.

	Days from admission to operation								*p*-value
	Quartile 1 (DATO = 1)		Quartile 2 (DATO 2–4)		Quartile 3 (DATO 5–9)		Quartile 4 (DATO >9)		
	N	%	N	%	N	%	N	%	
Total patients	254	24.0%	356	33.6%	215	20.3%	234	22.1%	N/A
Age (years)									**<0.001**
<55	48	18.9%	78	21.9%	49	22.8%	80	34.2%	
55-66	72	28.3%	92	25.8%	60	27.9%	68	29.1%	
67-76	56	22.0%	95	26.7%	57	26.5%	54	23.1%	
>76	78	30.7%	91	25.6%	49	22.8%	32	13.7%	
Gender									0.072
Male	101	39.8%	169	47.5%	105	48.8%	119	50.9%	
Female	153	60.2%	187	52.5%	110	51.2%	115	49.1%	
Race									0.091
White	201	79.1%	275	77.2%	160	74.4%	160	68.4%	
Black	23	9.1%	49	13.8%	29	13.5%	42	17.9%	
Other	26	10.2%	27	7.6%	21	9.8%	30	12.8%	
Unknown	4	1.6%	5	1.4%	5	2.3%	2	0.9%	

Table 2
Perioperative outcomes stratified by duration of non-operative management.

	Days from admission to operation								*p*-value
	Quartile 1 (DATO = 1)		Quartile 2 (DATO 2–4)		Quartile 3 (DATO 5–9)		Quartile 4 (DATO >9)		
	N	%	N	%	N	%	N	%	
Total patients	254	24.0%	356	33.6%	215	20.3%	234	22.1%	N/A
≥1 complication	83	32.7%	147	41.3%	79	36.7%	115	49.1%	**0.002**
Number of complications									**0.007**
0	171	67.3%	209	58.7%	136	63.3%	119	50.9%	
1	70	27.6%	113	31.7%	56	26.0%	83	35.5%	
2	12	4.7%	28	7.9%	20	9.3%	23	9.8%	
3	1	0.4%	5	1.4%	2	0.9%	9	3.8%	
4	0	0.0%	1	0.3%	1	0.5%	0	0.0%	
Individual complications									
Stroke	2	0.8%	3	0.8%	5	2.3%	11	4.7%	**0.004**
Pneumonia	27	10.6%	33	9.3%	24	11.2%	26	11.1%	0.858
Infectious	40	15.7%	90	25.3%	57	26.5%	71	30.3%	**0.001**
Cardiovascular	10	3.9%	17	4.8%	5	2.3%	7	3.0%	0.444
Gastrointestinal hemorrhage	0	0.0%	2	0.6%	1	0.5%	8	3.4%	**0.001**
Reopening of wound	9	3.5%	19	5.3%	8	3.7%	18	7.7%	0.144
Coma or stupor	1	0.4%	5	1.4%	2	0.9%	2	0.9%	0.648
Adverse anesthetic events	0	0.0%	0	0.0%	0	0.0%	1	0.4%	0.317
30-day readmission	39	15.4%	64	18.0%	47	21.9%	41	17.5%	0.333
30-day mortality	85	33.5%	92	25.8%	55	25.6%	77	32.9%	0.069

Independent predictors of complications

Patient age, DATO, gender, and race were analyzed using logistic regression analyses to determine if any were independently associated with 30-day mortality, 30-day readmission, the occurrence of at least one postoperative complication, and postoperative infectious rates. We found that patient gender and race were not significantly associated with any outcome of interest (all $p > 0.05$); however, DATO was associated with a higher risk of 30-day mortality (OR 1.022, $p = 0.040$), any complication (OR 1.034, $p = 0.001$), and infectious complications (OR 1.040, $p < 0.001$). Similarly, patient age was associated with a higher risk of 30-day mortality (OR 1.016, $p < 0.001$), any complication (OR 1.013, $p = 0.002$), and infectious complications (OR 1.015, $p = 0.002$), but to a lesser extent than DATO (Fig. 1). Patient age was found to be protective against 30-day readmission (OR 0.984, 95% CI 0.974–0.993, $p = 0.001$); however, DATO was not significantly higher or lower risk ($p = 0.721$) (Fig. 1).

Discussion

We have demonstrated that earlier operative intervention has the potential to lower morbidity, mortality, and cost in patients with CDI who ultimately require operative intervention.

Patient age is frequently considered when deciding if, and at what point, surgically intervention should be performed; however, the duration of non-operative management is less frequently discussed in this setting. This is particularly relevant considering that 41% of all deaths in this study occurred in younger patients with age ≤66 years (median age for all patients). Earlier operative intervention may rescue some of these patients; however, the decision to do so should be weighed against the patient's preferences and ability to care for what could be a permanent end ileostomy. Additionally, while earlier operative intervention may reduce the cost of the initial hospitalization, it should be considered that survivors will accumulate stoma-related charges and may elect to have their ileostomy reversed in the future, both of which have associated morbidity and costs that we were unable to measure in this study. Permanent ileostomies are associated with decreased quality of life; however, for many patients, living with an ileostomy may be preferable to the alternative.[11] As such, attempts should be made to lower the unacceptably high mortality rate associated with surgical treatment of CDI. This could be achieved by 1) accurately identifying patients not salvageable with surgical intervention; 2) identifying medical treatment options that negate the need for surgery; 3) identifying patients who do not want extraordinary interventions and adhering to their wishes; and 4) surgically intervening earlier to preserve the patient's ability to physiologically recover from both medical and surgical insults.

Surgical intervention for CDI most often includes TAC and formation of an end ileostomy.[12] In some cases, the colon may grossly appear normal, prompting partial colectomy; however, this approach has been associated with increased mortality, and is not recommended.[13,14] In 2011, Neal and colleagues published single-institution results demonstrating that loop ileostomy for antegrade colonic lavage may be an alternative surgical approach that allows for colonic preservation without an increase in mortality. A clinical trial (NCT02347280) is currently accruing patients that aims to determine the relative safety of this approach; however no high-quality evidence currently supports this less invasive approach. As

Table 3
Length of stay and direct cost stratified by duration of non-operative management.

	Days from admission to operation				*p*-value
	Quartile 1 (DATO = 1)	Quartile 2 (DATO 2–4)	Quartile 3 (DATO 5–9)	Quartile 4 (DATO >9)	
ICU LOS (days)	9.2 ± 9.1	10.0 ± 9.6	10.0 ± 10.4	15.6 ± 13.6	< **0.001**
Hospital LOS (days)	16.3 ± 12.1	18.0 ± 11.0	21.9 ± 10.4	32.5 ± 11.8	< **0.001**
Direct cost	$42,124 ± $30,535	$44,068 ± $30,904	$53,105 ± $36,004	$84,717 ± $63,529	< **0.001**

*Mean ± standard deviation depicted for all outcomes of interest.

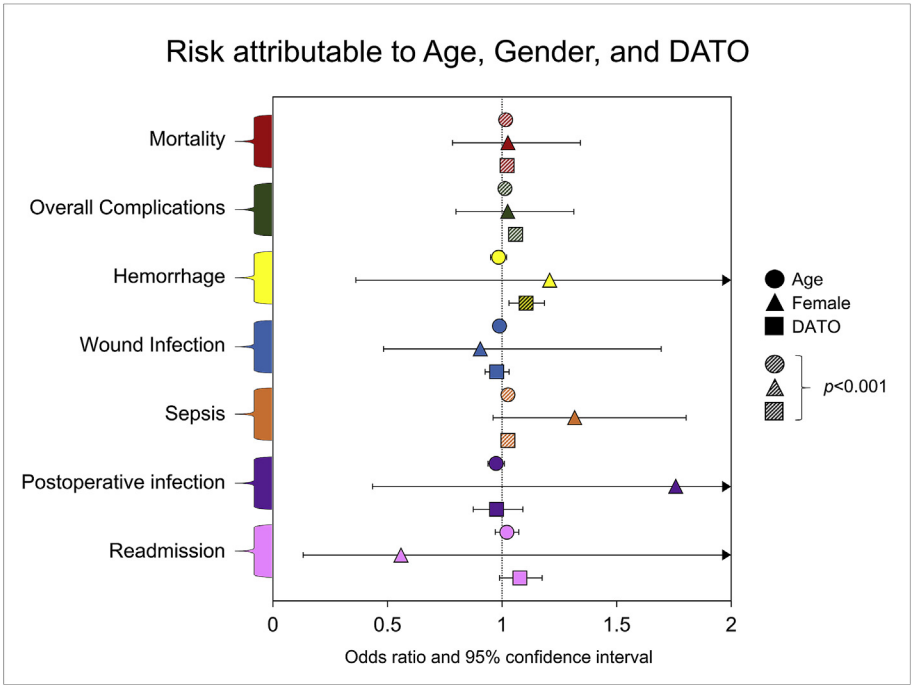

Fig. 1. Forest plot of odds ratios for patient age (squares) and DATO (triangles) with respect to outcomes including infectious complications (blue), any complication (red), 30-day readmission (green) and 30-day mortality (yellow). Patient race and gender were included in the multivariable logistic regression analysis; however, neither was significantly associated with any outcomes of interest and are not depicted. Here, we see that DATO is higher risk than patient age for infectious complications (OR 1.040, 95% CI 1.018–1.062, p = 0.001 vs. OR 1.015, 95% CI 1.005–1.024, p = 0.002), any complication (OR 1.034, 95% CI 1.014–1.054, p = 0.001 vs. OR 1.013, 95% CI 1.005–1.021, p = 0.002), and 30-day mortality (OR 1.022 95% CI 1.001–1.044, p = 0.040 vs. OR 1.016, 95% CI 1.007–1.025, p = 0.001), respectively. Age was seen to be associated with lower risk for 30-day readmission (OR 0.984, 95% CI 0.974–0.993, p = 0.001). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

such, TAC remains the standard of care for patients with CDI and is the recommended surgical approach by several medical and surgical organizations including the Infectious Diseases Society of America (IDSA), American College of Gastroenterology (ACG), Eastern Association for the Surgery of Trauma (EAST), and the American Society of Colon and Rectal Surgeons (ASCRS).[7,14–16]

Medical and surgical clinical practice guidelines differ regarding indications for and timing of surgical consultation. The 2018 IDSA guidelines recommend medical therapy for fulminant colitis with surgery reserved for only "severely ill" patients; however this is not further delineated.[15] Both the 2013 ACG and 2015 ASCRS guidelines recommend that surgical consultation be obtained in the setting of complicated disease (i.e. peritonitis, perforation, vasopressor requirements etc.); however the 2014 EAST guidelines recommend that surgical consultation be obtained before such events occur.[7,14–16] Discrepancies such as these may contribute to delayed surgical consultation and subsequent intervention, which in turn, may contribute to high operative mortality as evidenced from our analysis.

It should be noted that this database study is limited by its retrospective nature and is subject to selection bias as mentioned above; however it is reflective of current practice patterns. In this study, older patients tended to undergo early operative intervention, which may represent the perception that older patients are less able to recover from an extended physiologic insult. Similarly, we found that patients who underwent surgery at later dates had higher rates of stroke. This could be indicative of the selection bias within the patient population. In order to reduce this potential selection bias we only included "high risk" patients with SOI scores of 3–4. Additionally, our logistic regression analysis accounts for some of this potential bias. This is evidenced by the fact that 30-day mortality did not differ between DATO groups on univariate analysis; however, once age and other factors were accounted for, DATO was noted to be significantly associated with 30-day mortality. It should be noted that the odds ratios associated for DATO were relatively small; however, it should also be emphasized that this risk is cumulative, and increases with every unit increase in DATO. We elected to exclude patients operated on the day of admission to best capture patients who underwent a meaningful attempt at non-operative management. This resulted in exclusion of 14% of our sample and demonstrates that the vast majority of patients who were admitted with severe CDI are initially treated non-operatively. By only including patients with a primary admission diagnosis of CDI, these results may not be generalizable to patients who develop CDI while in the hospital, which is a limitation to this study. Similarly, this study is limited in that we only report outcomes for patients who required operative intervention which represents a minority of patients diagnosed with CDI. Another limitation to this study is the inability to differentiate between pre- and postoperative ICU and hospital length of stay. This should be considered when interpreting the length of stay data. Finally, we chose not to investigate outcomes of loop ileostomy for antegrade colonic lavage. These data may not be representative of patients undergoing that surgical approach.

Patient who undergo TAC for CDI often experienced progressively worsening disease over days to weeks. This period represents a "window of opportunity" to surgically intervene and distinguishes CDI from other indications for emergent TAC (i.e. trauma) for which no such period exists. In consideration of this, it is reasonable to believe that certain treatment strategies, including earlier surgical intervention, may reduce surgical mortality in CDI. In summary, our data suggest that patients who are expected to undergo prolonged non-operative management, and would be amenable to living with a stoma, may benefit from surgical

intervention prior to physiologic decompensation, including use of vasopressor medications, end organ dysfunction, altered mental status and admission to an intensive care unit. In order to accomplish the above, we believe it will be necessary for surgeons to work closely with medical doctors to expedite appropriate surgical consultation.

Conclusions

We have demonstrated that patients with severe CDI at admission who received prolonged non-operative therapy followed by TAC experienced higher mortality and complications rates, as well as increased cost. Surgical consultation should be considered prior to physiologic decompensation, and earlier surgical intervention should be considered in patients who are expected to have a prolonged course of inpatient therapy and would be willing and able to care for a potentially permanent ileostomy.

Conflicts of interest

All authors have nothing to disclose.

Summary

The Vizient database was queried for high-risk patients admitted with severe colonic clostridium difficile infection who underwent open total abdominal colectomy and end ileostomy. Prolonged non-operative management was associated with increased risk of mortality, infectious complications, and overall complications.

Disclosures

The authors have no financial interests to disclose.

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