A Prospective Program to Reduce the Clinical Incidence of *Clostridium Difficile* Colitis Infection after Cystectomy

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Abstract:

Purpose: The development of Clostridium difficile infection after cystectomy is associated with significant morbidity and mortality. We implemented a prospective screening program to identify asymptomatic carriers of Clostridium difficile and assessed its impact on clinical Clostridium difficile infection rates compared to historical matched controls.

Materials and Methods: Prospective Clostridium Difficile screening prior to cystectomy began in March 2015. The 380 consecutive patients undergoing cystectomy prior to initiation of screening (control cohort) were matched based on 5 clinical factors with the 386 patients who underwent cystectomy from March 2015 to December 2017 (trial cohort). Screened positive patients were placed in contact isolation and treated prophylactically with Metronidazole. Multivariable models were built on an intention-to-screen and an effectiveness of screening basis to determine if screening reduced the rates of symptomatic Clostridium Difficile infections postoperatively.

Results: With the implementation of the screening protocol, Clostridium difficile infections rates declined from 9.4 to 5.5% (OR 0.52, p=0.0268) on an intention-to-screen protocol and from 9.2 to 4.9% on an effectiveness of screening protocol (OR 0.46, p=0.0174).

Conclusions: Clostridium difficile screening prior to cystectomy is associated with a significant decrease in rates of clinically symptomatic infections postoperatively. These results should be confirmed in a randomized controlled trial.

Introduction:

Clostridium difficile infectious colitis (CDI) prolongs hospital stays and increases complication rates, hospital costs and mortality worldwide [1-6]. Unfortunately, the incidence of CDI has increased [5,7,8]. A new strain of Clostridium difficile (CD) was discovered in North America in 2005 which exhibited greater toxicity and was associated with poor outcomes [4,9]. Twelve and a half percent of these infected patients experienced a severe outcome defined as an ICU admission, colectomy, or death with older patients more likely to experience a severe outcome. Mortality with these toxic strains range from 5.4% for patients age 61-70 and rises with each decade of life to 14.7% for patients age >90 [9]. Recent studies also suggest that asymptomatic carriers of CD can transmit to others and therefore contribute to increased rates of CDI in a hospital setting particularly when patient rooms are not easily isolated [10-15].

Cystectomy patients are at higher risk of CDI than the general patient population due to their increased age, underlying comorbidities, and recent antibiotic exposure with published rates of CDI in cystectomy patients ranging from 1.4-14% [16-21]. It has been demonstrated that the development of CDI after cystectomy is associated with a 2.5-fold increase in mortality and adds approximately $22,634 in cost per hospitalization per patient [17]. Our institution's CDI incidence from 2010 to 2013 was closer to the high end of this range as reported in 2015 [19]. The incidence of asymptomatic CD carriage is unfortunately unknown in cystectomy patients.

Screening of asymptomatic patients for CD is discouraged by the Infectious Disease Society of America (IDSA) and the Center for Disease Control (CDC), but recent studies suggest a benefit in high-risk populations [22-25]. We implemented a prospective screening program prior to cystectomy to address our high incidence of CDI despite the adoption of the IDSA and CDC recommendations for the isolation and management of symptomatic CDI patients. We

hypothesized that preoperative screening in cystectomy patients would decrease our institutions incidence of CDI by allowing us to isolate and treat CD carriers prior to transmission or development of CDI.

Methods:

Study Cohorts:

A total of 765 consecutive patients underwent cystectomy (simple or radical) at our institution between June 2012 and December 2017. This sample included a cohort of 379 patients who underwent cystectomy between June 2012 – February 2015 prior to the initiation of the screening trial (control cohort) and 386 patients who underwent cystectomy March 2015 – December 2017 after the initiation of the prospective screening for CD trial (trial cohort). The trial and control cohorts were then matched based on five demographical and clinical factors: age within 5 years, cancer, preoperative antacid use (use of a proton pump inhibitor or a histamine2 channel antagonist), prolonged antibiotic use (>24 hours perioperative), and receipt of neoadjuvant chemotherapy. Each patient in the trial cohort had at least one matched patient in the control cohort based on the matching criteria, and vice versa for each patient in the control cohort.

The matched sample consisted of 720 patients, including 358 patients in the trial cohort and 362 patients in the control cohort. Among the patients in the trial cohort, 283 patients had screening results for CD (trial screened) and 75 patients had insufficient screening results (trial unscreened) for CD due to lab errors or refusal.

We defined the intention-to-screen cohort as patients within the trial (n=358) and patients in the control cohort (n=362). The effectiveness of screening cohort was defined as patients

within the trial who were screened (n=258) and patients who were unscreened (n=437, including 362 controls and 75 trial patients without screening results). All our subsequent analysis were based on those two cohorts.

Screening:

Preoperative screening for CD in cystectomy patients began in March of 2015. Screening consisted of rectal examination immediately prior to cystectomy while under general anesthesia. Stool samples were collected and sent to the lab where a CD PCR assay was run. Our laboratory PCR assay tests for the gene responsible for toxin B of CD. If stool was not obtained during the digital rectal examination, a swab of rectal mucous was used for analysis. Carriers of CD (screened positive individuals) were placed into isolation rooms with appropriate contact precautions. Carriers were also treated with intravenous metronidazole (500mg three times daily) until the return of bowel function. Return of bowel function was defined as passage of flatus. Carrier negative patients were otherwise treated on a standardized clinical pathway that has been in existence since 2012 with little change (Figure 1).

Primary Outcomes:

The primary outcome was the incidence of post-operative CDI defined as 3 or more diarrhea episodes per day associated with a positive CD assay within 30 days of the operation. Patients' demographical and clinical factors were collected prospectively on all patients as part of quality improvement measures into an IRB approved departmental database.

Statistical Analysis:

Patients' demographic and clinical characteristics were reported and compared between the screened trial cohort (n=283), the unscreened trial cohort (n=75) and the control cohort

(n=362). Analysis of Variance (ANOVA) and the Kruskal-Wallis Test were used to compare normally and non-normally distributed continuous variables, respectively. Categorical variables were compared using the Chi-Square Test. Logistic regression models were fit to examine the cohort difference in post-surgery CDI using the intention-to-screen and the effectiveness of screening cohorts. All models included known risk factors for CDI, i.e., age, cancer, antibiotic use, antacid use, and chemotherapy as covariates. All analysis was completed at a two-tailed significance level of 0.05 using SAS 9.4 (SAS Institute, Cary, NC).

Results:

Baseline Demographics and Clinical Characteristics:

A flowchart is presented in Figure 2 that defines the patient population as well as the rate of CDI in each cohort. Patient demographic and clinical characteristics by cohort are summarized in Table 1. Overall, the groups were well matched. There was a significant difference in antacid use prior to cystectomy between cohorts. Compared with the control cohort, patients in the trial cohort were more likely to be taking antacids prior to cystectomy (30.1% vs 19.1%, p=<0.0001). The method of urinary reconstruction was different between the three groups (p=0.00**2**6) The trial unscreened population was more likely to receive a non-continent diversion than the other cohorts (63.6**%** trial screened vs 74.7**%** trial unscreened vs 63.4% control).

Intention-to-Screen Analysis of CDI:

The rate of post-operative CDI was 9.4% for the control cohort and 5.5% for the trial cohort. Absolute risk reduction was 3.9% with a number needed to screen of 26 patients to prevent one postoperative CDI. After adjusting for patient's age, cancer status, use of prolonged antibiotics, use of antacid, and status of receiving neoadjuvant chemotherapy, the intention-to-

screen led to a 48% reduction in the odds of CDI (OR 0.52, 95%CI 0.29-0.93, p=0.0268) (Table 2).

Effect of Screening Analysis of CDI:

About 21% of patients in the trial cohort did not have screening results (trial unscreened) due to the inadequate laboratory stool specimen. The rate of CDI was similar in the control cohort and the trial unscreened cohort (9.4 vs 8.0%, p=0.7870). The rate of CDI was 4.9% in the trial screened cohort and 9.2% in the unscreened cohort (the control cohort and the trial unscreened cohort combined). Absolute risk reduction was 4.3% with a number needed to screen of 24 patients to prevent one postoperative CDI. After adjusting for patient's age, cancer status, use of prolonged antibiotics, use of antacid, and status of receiving neoadjuvant chemotherapy, the protective effect of screening demonstrated a 54% reduction in the odds (OR 0.46, 95%CI 0.24-0.87, p=0.0174) on post-operative CDI (Table 3).

Adverse events:

No adverse events were identified from screening or treating screened positive patients with a short course of antibiotics. No patients experienced an acute reaction or allergy to metronidazole. Specifically, only 1 patient had an ileus and 1 patient required readmission who received metronidazole.

Postoperative complications did not differ between groups as shown in Table 1. However, three unscreened patients died who were diagnosed with CDI postoperatively (2 control, 1 trial unscreened). No patients diagnosed with CDI in the trial cohort died postoperatively. Two of the deaths in the control cohort were clearly attributable to CDI.

Discussion:

After screening for CD was implemented, our institution's incidence of CDI decreased substantially in patients undergoing cystectomy. When controlling for demographical and clinical factors, screening as well as the "intention to screen" had a protective effect on developing CDI. None of the other clinical covariates were predictors of developing CDI. Fifty-two (18.4%) patients screened positive for CD (asymptomatic carriers). Screened positive patients received a short course of metronidazole post-operatively (mean length of 3 days). The overall use of antibiotics was low given the short duration of use and the low percentage of asymptomatic carriers. The incidence of CDI at our institution prior to implementation of the screening trial was 9.4%. Thus, we would have anticipated that 34 patients would have developed CDI during the subsequent two years if screening had not been initiated. Instead, only 20 patients developed CDI. We treated 52 patients with a short course of metronidazole in order to prevent the treatment of 14 patients with a protracted course of metronidazole and/or vancomycin and the associated potential morbidity and mortality of post-operative CDI. The limitation of morbidity and mortality secondary to post-operative CDI must be stressed. Three of the fifty-four patients who developed CDI died postoperatively with two of these events clearly attributable to CDI. All deaths occurred in unscreened patients.

We hypothesized that the lower incidence of CDI in the trial cohort is due to two main interventions. First, asymptomatic carriers of CD were placed in single-occupancy rooms under contact isolation with stricter hand washing policies. The separation of carriers likely reduced the transmission of CD from carrier to non-carriers. This hypothesis is supported by the 4.6% reduction in CDI incidence between the control cohort and the trial cohort members who screened negative. Results of recent studies support our hypothesis. Genome sequencing was performed in 1,223 patients diagnosed with CDI in the United Kingdom. Forty-five percent of

cases had significant genetic diversity to indicate that the infection originated from another source other than symptomatic cases [26]. Authors concluded that transmission likely occurred from asymptomatic carriers of CD. Another group evaluated 3,006 patients were screened for CD over a 5-month period. Molecular subtyping determined that 29% of active CDI cases were genetically associated with asymptomatic carriers in the same hospital [11]. A smaller study of 634 patients reported that 84% of nosocomial CDI were preceded by documented admission of the strain to the ward by an asymptomatic carrier [16]. Plausible mechanisms of transmission include contamination of the environment and caregivers' hands [13,27]. These studies support the hypothesis that asymptomatic carriers of CD can transmit CD to others and contribute to increased CDI rates in hospitals. Our data suggests that isolation of asymptomatic carriers of CD may decrease symptomatic CDI within hospital units presumably by reduced transmission.

Second, precautionary treatment with metronidazole likely reduced the rates of symptomatic infection in carriers of CD. Colonization with CD was found to be an independent risk factor for developing symptomatic infections in patients admitted to the Intensive Care Unit [25]. By prophylactically treating colonized patients, we demonstrated a 3.6% reduction in CDI incidence between the control cohort and the trial cohort members who screened positive. Antibiotic administration in carriers of CD is controversial and not supported by the American College of Gastroenterology (ACG). This recommendation is based off of an older study which focused on eliminating asymptomatic carriage of CD [28]. This was not our intent as we sought to reduce symptomatic CDI in a high-risk cohort. A recent quasi-experimental study evaluated the role of isolation without prophylactic antibiotic treatment of asymptomatic carriers on incidence of CDI. Carriers of CD in this trial were placed in contact isolation precautions until discharge. Compared to the pre-intervention control period, the incidence of CDI was drastically reduced

after screening (3.9 per 10,000 patient days versus 6.0 per 10,000 patient days). This group concluded that screening and isolating carriers of CD was associated with lower rates of hospital acquired CDI [24]. Our results would appear to corroborate these findings. Future studies will need to assess the impact of isolation and prophylactic treatment to determine the optimal intervention strategy.

The results of our study should be considered in the context of several limitations. First, our trial represents an observational quality improvement project where rates of CDI in a screened population were compared with a control population. Further multi-institutional and randomized investigations are needed to confirm our findings. However, our results give sufficient proof of concept to justify the design and conduction of these more laborious and costly evaluations. We fully acknowledge that we are presenting an observation of a clinical change in practice at our institution. The quasi-experimental pre-post design is limited in the ability to assess changes in CDI rates over time that may have been due to global institutional interventions. However, no other obvious changes in practice aside from the screening protocol explain the lower rates of CDI. All patients were treated by the same urologists and admitted to the same floor of the hospital throughout the period of analysis. To support this, the rate of CDI during the study period on the urology ward declined by 38% when compared to the control period which exceeded the CDI rate reduction of the entire hospital (32%). CDI rates on other floors, including medical and colorectal surgical wards, demonstrated a less pronounced rate of CDI reduction ranging from 5 to 33%. The generalizability of our results may be limited due to the higher incidence rate of CDI compared to other institutions [16-19]. However, CDI rates are rising and recent reports suggest that CDI rates in cystectomy patients may be even higher at other institutions [5,20]. Moreover, multiple agencies (ACG, IDSA, CDC) have produced

guidelines against screening for CD in the general population [22,23]. Our results directly contradict these statements and suggest that screening in high-risk patients requires further attention. Lastly, recent reports suggest that isolation of asymptomatic carriers alone substantially lowers CDI rates [24]. Further evaluation on the necessity of prophylactic antibiotic administration and isolation versus isolation only of asymptomatic carriers is needed.

These limitations notwithstanding, we believe that our data is compelling enough to warrant future formal study of this subject. To our knowledge, this is the first report investigating the role of screening for CD in patients undergoing cystectomy. This patient population is at high-risk for CDI due to a multitude of patient and disease-related risk factors. , Screening reduced the risk of CDI by 46-54%. Our prospective, low-risk screening program demonstrated significant promise in reducing morbidity and mortality secondary to CDI in patients undergoing cystectomy.

Conclusion:

Implementing a screening protocol in cystectomy patients was associated with significantly decreased incidence of CDI. Although this data is observational, we believe it is compelling. Further study in the form of randomized trials is warranted to confirm our findings.

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Table 1: Patient Demographics and Clinical Characteristics by Cohort

	Control Cohort (n=362)	Trial Unscreened Cohort (n=75)	Trial Screened Cohort (n=283)	p value
Age (IQR)	67 (60-76)	69 (58-75)	67 (57-75)	0.4522[1]
Gender, male (%)	266 (73.5)	56 (74.7)	210 (74.2)	0.9659[2]
Pre-op Antacid Use, yes (%)	69 (19.1)	20 (26.7)	88 (31.1)	0.0018[2]
Pre-op Chemotherapy, yes (%)	98 (27.1)	17 (22.7)	95 (33.6)	0.0839[2]
Prolonged Antibiotics (%)	95 (26.2)	26 (34.7)	72 (25.4)	0.2607[2]
Cancer, yes (%)	302 (83.4)	59 (78.7)	249 (88)	0.0853[2]
Diversion Type (%)				0.0026[2]
Ileal Conduit	229 (63.4)	56 (77.7)	180 (63.6)	
Indiana Pouch	82 (22.7)	10 (13.3)	48 (17)	
Neobladder	50 (13.9)	8 (10.7)	54 (19.1)	
Other	0	1 (1.3)	1 (0.4)	
CDI*	34 (9.4)	6 (8)	14 (4.9)	0.1026[2]
C. diff Carrier Status (%)				--
Positive	0	0	52 (18.4)	
Negative	0	0	231 (81.6)	
Unknown	362 (100)	75 (100)	0 (0)	
Hospital Days (IQR)	8 (6-10)	7 (6-12)	7 (6-10)	0.1263[3]
Clavien (IQR)	1 (0-2)	1 (0-2)	0 (0-2)	0.0949[3]

* Clostridium Difficile Infection
[1] ANOVA
[2]Chi-Square
[3]Kruskal-Wallis

Table 2: Logistic Regression Model: Effect of Trial on CDI

Effect (ref)	Odds Ratio	95% CI	p value
Age	1.02	1.00-1.05	0.0855
Cancer (no)	1.37	0.48-3.92	0.5558
Prolonged antibiotics (no)	1.15	0.61-2.17	0.6627
Antacid use (no)	1.64	0.88-3.05	0.1224
Neoadjuvant chemotherapy (no)	1.42	0.75-2.69	0.2763
Intention to Screen (Control)	**0.52**	**0.29-0.93**	**0.0268**

Table 3: Logistic Regression Model: Effect of Screening on CDI

Effect (ref)	Odds Ratio	95% CI	p value
Age	1.02	1.00-1.05	0.0874
Cancer (no)	1.41	0.49-4.04	0.5188
Prolonged antibiotics (no)	1.14	0.60-2.15	0.6862
Antacid use (no)	1.65	0.88-3.07	0.1169
Neoadjuvant chemotherapy (no)	1.45	0.77-2.75	0.2523
Intention to Screen (Control + Trial Unscreened)	**0.46**	**0.24-0.87**	**0.0174**

Figure 1: Perioperative Cystectomy Pathway at Indiana University

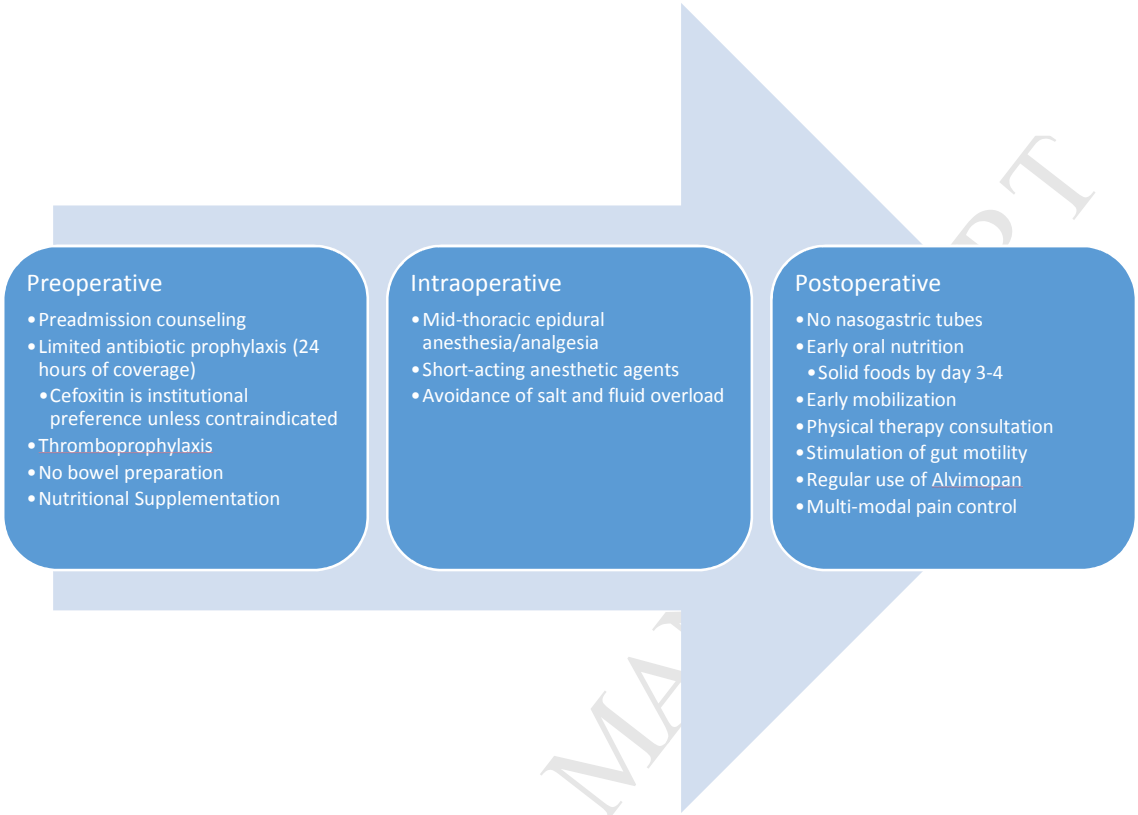

Figure 2: Flow Chart of the Study Population