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Early Emergency General Surgery Is Associated with a Higher Incidence of *Clostridium difficile* Infection

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Abstract

Background: *Clostridium difficile* infection (CDI) is an important surgical complication. Emergency general surgery (EGS) is a developing area of the acute care surgical practice. Few studies evaluating the incidence and risk factors of CDI in this patient population are available.
Patients and Methods: A prospectively maintained Acute and Critical Care Surgery registry spanning from 2008 to 2015 was queried for cases of operative EGS with clinical suspicion of CDI post-operatively. Diagnosis of CDI was made using toxin A/B assay in stools. Demographics, co-morbidities, surgical procedures, length of stay (LOS), intensive care unit LOS, antibiotic use, and death were obtained. The patients positive and negative for CDI were compared using chi-squared and Student's t-test. Multi-variable logistic regression was used to determine risk factors for CDI.
Results: A total of 550 patients were identified. The total incidence of CDI was 12.7%. There was no significant difference in demographics between CDI positive and negative patients. Average time to CDI diagnosis was 10.1 ± 8.5 days post-operatively. Patients who received three or more antibiotic classes were at higher risk of CDI developing post-operatively (83% vs. 75%, $p = 0.04$). The CDI positive patients underwent an EGS significantly earlier than CDI negative patients (0.9 ± 2.3 vs. 3.2 ± 9.2 days, $p < 0.001$). The most common procedures were partial colectomies (21.4%); small bowel resections/repairs (12.9%); gastric repair for perforated peptic ulcer (10%); skin and soft tissue procedure (7.1%), and laparotomies (5.7%). There was no difference in outcomes between the groups. On linear regression, an EGS performed later after admission was an independent risk factor for lower CDI (OR 0.87; CI 95% [0.79–0.96], $p < 0.01$).
Conclusion: Patients undergoing an early EGS have a high incidence of CDI. The number of antibiotic classes administered post-operatively affects CDI status. Bowel resections appear to be at increased risk for CDI. Clinicians should have a high index of suspicion and low threshold for testing *C. difficile* in high-risk EGS patients.

Keywords: *Clostridium difficile;* emergency general surgery; general surgery; health-care–associated infection

CLOSTRIDIUM DIFFICILE is an anaerobic, toxigenic, spore-forming bacterium that was described initially by Hall and O'Toole in 1935 as normal flora in the gut of newborn infants [1–3]. The incidence of *C. difficile* infection (CDI) has doubled in the last 15 years, and currently CDI represents one of the most common causes of health-care–associated infection (HAI) in the United States [3–5]. A number of outbreaks have been described worldwide, and more toxigenic strains causing associated complications continue to be on the rise [1,6]. Not only does CDI carry high morbidity and death, but it also places an important financial burden on healthcare facilities with associated costs ranging from $1 billion to $4.9 billion annually [7,8].

Surgical patients are at increased risk for CDI, and this condition represents a severe post-operative complication [9]. In previous studies including most surgical specialties, the total incidence of CDI has been reported at approximately 0.5% [10,11]. In those that included a more specific surgical population such as trauma, colorectal, or transplant patients, the incidence of CDI has been even higher, ranging between 3% and 7% [12–16].

Emergency General Surgery (EGS) is a developing area of the acute care surgical practice. It has been defined by the American Association for the Surgery of Trauma (AAST) as ''any patient requiring an emergency surgical evaluation (operative or nonoperative) for diseases within the realm of

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general surgery as defined by the American Board of Surgery'' [17]. Patients undergoing EGS carry an overall higher in-hospital morbidity and death compared with non-EGS patients [18].

Although previous studies have shown that patients undergoing emergency operations are at elevated risk for CDI development [10, 19], to our knowledge, there are no studies evaluating CDI specifically in EGS patients. The aim of our study was to determine the incidence of CDI in patients undergoing EGS and to identify the risk factors that are associated with the rate of infection in this surgical patient population.

Patients and Methods

We performed a retrospective review of a prospectively maintained Acute and Critical Care Surgery registry containing more than 8000 patients at our institution from 2008–2015. We queried for individuals who had at least one of the 35 most common EGS procedures, as described by Scott et al. [20] and defined by AAST based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes [17] (Supplementary Table 1; see online supplementary material at http://www.liebertpub.com). We then identified patients with a clinical suspicion for infection by *C. difficile* post-operatively, defined as the presence of a toxin assay in a stool test in the same hospitalization. Patients who were admitted with CDI or in whom CDI developed before the EGS procedure were excluded. The toxin assay is performed at our institution using an immunoassay for *C. difficile* toxins A and B; Toxin A/B Quick Check (TECHLAB® Inc, Blacksburg, VA), which has a reported sensitivity of 90.2% and specificity of 99.7%.

We obtained demographics, body mass index, Charlson Comorbidity Index, American Society of Anesthesiologists (ASA) score, antibiotic use, length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, and death for all the patients included in our study. The days from admission to the EGS procedure and from EGS procedure to the CDI diagnosis were calculated. We determined antibiotic exposure and categorized the individuals as having received none, one, two, or three or more antibiotic classes.

After identifying CDI positive and negative patients, we used chi-square for categoric variables and the Student's t-test for continuous variables to compare demographics, outcomes, time from admission to EGS procedure, and antibiotic exposure. Multi-variable logistic regression adjusting for demographics, LOS, ICU LOS, Charlson Comorbidity Index, and time from admission to EGS procedure was performed to determine risk factors for CDI. A p value of <0.05 was considered significant. The SPSS version 23 was used for statistical analysis.

Table 1. Demographics of Emergency General Surgery Patients by *Clostridium difficile* Infection Status

Demographics	*Total group*	*CDI positive*	*CDI negative*	*p*
Total	550 (100%)	70 (12.7%)	480 (87.3%)	
Age	57.7 (± 16.2)	59.56 (± 15.3)	57.43 (± 16.3)	0.31
Gender				
- Female	279 (50.6%)	36 (51.4%)	243 (50.6%)	0.99
- Male	272 (49.4%)	34 (48.6%)	237 (49.4%)	
Race				
- Caucasian	376 (68.2%)	45 (64.3%)	330 (68.8%)	
- AA	152 (27.6%)	23 (32.9%)	129 (26.9%)	0.64
- Asian	3 (0.5%)	0	3 (0.6%)	
- Other	20 (3.7%)	2 (2.9%)	18 (3.8%)	
Comorbidities				
Myocardial infarction	81 (14.7%)	10 (14.3%)	71 (14.8%)	0.91
Peripheral vascular disease	116 (21.1%)	16 (22.9%)	100 (20.8%)	0.71
CHF	112 (20.4%)	13 (18.6%)	99 (20.6%)	0.69
Cerebrovascular disease	51 (9.3%)	7 (10%)	44 (9.2%)	0.82
Paralysis or hemiplegia	24 (4.4%)	3 (4.3%)	21 (4.4%)	0.97
Dementia	11 (2%)	3 (4.3%)	8 (1.7%)	0.14
COPD	160 (29.1%)	25 (35.7%)	135 (28.1%)	0.19
Mild liver disease	64 (11.6%)	4 (5.7%)	60 (12.5%)	0.12
Moderate to severe liver disease	19 (3.5%)	1 (1.4%)	18 (3.8%)	0.32
Peptic ulcer disease	64 (11.6%)	7 (10%)	57 (11.9%)	0.65
Diabetes mellitus without complications	139 (25.3%)	18 (25.7%)	121 (25.2%)	0.93
Diabetes mellitus with complications	44 (8%)	4 (5.7%)	40 (8.3%)	0.45
Renal disease	135 (24.5%)	21 (30%)	114 (23.8%)	0.26
Connective tissue disease	24 (4.4%)	4 (5.7%)	20 (4.2%)	0.55
Solid organ tumor	54 (9.8%)	11 (15.7%)	43 (9%)	0.08
Metastatic solid organ tumor	30 (5.5%)	5 (7.1%)	25 (5.2%)	0.51
Human immunodeficiency virus	6 (1.1%)	1 (1.4%)	5 (1%)	0.77
Charlson Index	4.46 (± 3.2)	4.9 (± 3.4)	4.4 (± 3.22)	0.27
American Association of Anesthesiologists score	3.25 (± 0.7)	3.24 (± 0.7)	3.26 (± 0.7)	0.88
Body mass index	30.26 (± 10.55)	29.6 (± 10.21)	30.36 (± 10.6)	0.58

CDI = *Clostridium difficile* infection; AA = African American; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

Results

A total of 550 patients were identified for our study. The average age for the entire group was 57.7 ± 16.2 years, and there was a similar distribution of female and male patients (50.6% vs. 49.4%). The incidence of CDI in our study was 12.7%, with 70 patients having a positive result for CDI and 480 patients a negative result. There were no significant differences in demographics, comorbidities, Charlson Comorbidity Index, and ASA score of patients with a positive CDI and those with a negative CDI result (Table 1).

The average number of days for CDI diagnosis from admission was 11.6 ± 8.7 and 10.1 ± 8.5 days post-operatively. Patients with a positive CDI result underwent an EGS significantly earlier than those with a negative result (0.93 ± 2.3 vs. 3.23 ± 9.2, p < 0.01). There was no difference in: LOS, ICU LOS, and ventilator days (Table 2). Mortality rate was similar between CDI positive and negative patients (11.3% vs. 12.7%, p = 0.76). None of the 70 patients who tested positive for *C. difficile* required a total colectomy because of their CDI status.

Of all the 35 EGS procedures that were used for the selection of our study group, small bowel resections (ICD9-CM 45.6x) and partial colectomies (IC9-CM 45.7x) were the most common surgical procedures performed with 109 and 92 cases, respectively. This was followed by repair of perforated peptic ulcer (ICD9-CM 44.4x), 34 cases (6.2%). Infection with *C. difficile* was most commonly seen in patients undergoing a partial colectomy, 15 (21.4%), followed by small bowel resections, 9 (12.9%), and repair of perforated peptic ulcer, 7 (10%). In patients with a negative CDI result, small bowel resections were the most common procedure, 100 (20.8%), followed by partial colectomies, 77 (16%), and laparotomies (ICD9-CM 54.1x), 28 (5.83%). There was no significant difference among the EGS procedure performed between CDI positive and CDI negative patients (p = 0.85). A complete list of procedures by CDI status is shown in Table 3.

All of the 70 persons with a positive CDI result and 451 with a negative result received antibiotic agents before their diagnosis. Overall, the average number of days receiving antibiotic agents previous to being tested for CDI in the study group was 10.3 ± 10.3 days. When the two cohorts were compared, patients with CDI positive and negative result were receiving antibiotic agents for a similar number of days (10.52 ± 9.1 vs. 10.3 ± 10.5, p = 0.85). We categorized the patients based on the numbers of antibiotic classes received before their *C. difficile* test was performed. The number of antibiotic classes given post-operatively significantly impacted CDI status. A positive result was more common among patients who received two and three or more antibiotic classes (12.9% vs. 9.2% and 82.9% vs. 75.4%, p = 0.04), whereas a negative result was more common among those who received none or one antibiotic agent post-operatively (1.4% vs. 6% and 2.9% vs. 9.4%, p = 0.04).

On multi-variable logistic regression adjusting for demographics, Charlson Comorbidity Index, time to procedure, and LOS, time to procedure remained significant. Our regression model showed that an EGS procedure performed later after admission is an independent predictor for lower CDI post-operatively (OR 0.87; confidence interval [CI] 95% [0.79 – 0.96], p > 0.01). The LOS became significant and showed to be an independent risk factor for development of CDI (1.013; CI 95% [1.003–1.024], p = 0.02) (Table 4).

Discussion

To our knowledge, this is the first study reporting the incidence and risk factors associated with post-operative CDI in EGS patients. The total incidence of CDI in our study group was approximately 13%, and although not much data exist regarding EGS patients, this is a considerably higher number when compared with that of trauma patients who are also part of the acute care practice. A previous study by Lumpkins et al. [12] found an incidence of 3.3% of CDI in trauma patients who were admitted to the ICU and who were tested based on a clinical suspicion in a two- year period.

Emergency general surgery is a developing area in the acute care practice. The AAST defined this group of patients, and several other authors have used this definition to determine their demographic characteristics and overall morbidity and death. Havens et al. [18], using five years of data from the American College of Surgeons National Surgical Quality Improvement Program, found that EGS patients were significantly older and that their burden of morbidity and death was higher compared with non-EGS patients; also, they found that having an EGS procedure was an independent risk factor for death and post-operative complications.

Our data show that patients undergoing EGS are usually older, have a similar gender distribution, and higher index of comorbidities on admission with an average Charlson Comorbidity Index of 4.46 and ASA of 3.25. We also found that EGS patients have a long hospital LOS with almost three weeks total and ICU LOS of close to two weeks, which shows how complicated this surgical population can be.

Interestingly, we did not find any significant difference in demographics or outcomes between patients with a positive *C. difficile* result and those with a negative result. As mentioned before, persons undergoing EGS represent a sicker

Table 2. Outcomes of Emergency General Surgery Patients by *Clostridium difficile* Infection Status

Outcomes	*Total*	*CDI positive*	*CDI negative*	*p*
Length of stay*	24.3 (± 21.5)	27.9 (± 29)	23.7 (± 20.2)	0.13
ICU Length of stay*	11.5 (± 16.1)	13.2 (± 15.9)	11.3 (± 16.1)	0.35
Ventilator days	3.4 (± 8.5)	2.2 (± 6.5)	3.6 (± 8.8)	0.2
Death	69 (12.5%)	8 (11.4%)	61 (12.7%)	0.76
Time from admission to EGS procedure*	2.9 (± 8.6)	**0.9 (± 2.3)**	**3.2 (± 9.2)**	**<0.01**

CDI = *Clostridium difficile* infection; ICU = intensive care unit; EGS = Emergency General Surgery.
*Days.
Statistically significant results are bolded.

Table 3. Emergency General Surgery Procedures by *Clostridium difficile* Infection Status

ICD-9 procedure code	*Procedure*	*CDI positive*	*CDI negative*	*p*
45.7x	Open and other partial resection of large intestine	15 (21.4%)	77 (16%)	0.85
45.6x	Other excision of small intestine	9 (12.9%)	100 (20.8%)	
44.4x	Control of hemorrhage and suture of ulcer of stomach or duodenum	7 (10%)	27 (5.6%)	
86.2x	Excision or destruction of lesion or tissue of skin and subcutaneous tissue	5 (7.1%)	25 (5.2%)	
54.1x	Laparotomy	4 (5.7%)	28 (5.8%)	
84.1x	Amputation of lower limb	3 (4.3%)	10 (2.1%)	
44.6x	Other repair of the stomach	3 (4.3%)	10 (2.1%)	
46.7x	Other repair of intestine	3 (4.3%)	11 (2.3%)	
53.6x	Repair of other hernia of anterior abdominal wall with mesh	3 (4.3%)	22 (4.6%)	
47.0x	Appendectomy	2 (2.9%)	20 (4.2%)	
51.2x	Cholecystectomy	2 (2.9%)	21 (4.4%)	
53.0x	Other unilateral repair of inguinal hernia	2 (2.9%)	7 (1.5%)	
54.2x	Diagnostic procedures of abdominal region	2 (2.9%)	8 (1.7%)	
83.4x	Other excision of muscle, tendon, and fascia	2 (2.9%)	27 (5.6%)	
46.8x	Dilation and manipulation of intestine	1 (1.4%)	7 (1.5%)	
53.7x	Repair of diaphragmatic hernia, abdominal approach	1 (1.4%)	4 (0.8%)	
83.0x	Incision of muscle, tendon, fascia, and bursa	1 (1.4%)	7 (1.5%)	
83.3x	Excision of lesion of muscle, tendon, fascia, and bursa	1 (1.4%)	17 (3.5%)	
53.4x	Repair of umbilical hernia	1 (1.4%)	3 (0.6%)	
46.0x	Exteriorization of intestine	1 (1.4%)	2 (0.4%)	
54.0x	Incision of abdominal wall	1 (1.4%)	4 (0.8%)	
46.1x	Colostomy	1 (1.4%)	4 (0.8%)	
54.5x	Lysis of peritoneal adhesions	0 (0%)	21 (4.4%)	
46.5x	Closure of intestinal stoma	0 (0%)	6 (1.3%)	
45.8x	Total intra-abdominal colectomy	0 (0%)	5 (1%)	
34.5x	Pleurectomy	0 (0%)	3 (0.6%)	
53.5x	Repair of other hernia of anterior abdominal wall (with or without mesh)	0 (0%)	2 (0.4%)	
48.8x	Incision or excision of perirectal tissue or lesion	0 (0%)	1 (0.2%)	
49.4x	Procedures on hemorrhoids	0 (0%)	1 (0.2%)	

ICD-9 = International Classification of Diseases, Ninth Revision, Clinical Modification; CDI = *Clostridium difficile* infection.

patient population, and this could potentially explain why having an associated post-operative CDI would not incur worse hospital outcomes. Nonetheless, this adds another risk factor to an already complicated patient and an associated economic burden to the healthcare system.

Infection with *C. difficile* has been included in the list of conditions for which the Centers for Medicare and Medicaid Services require public reporting, and that may carry financial penalties for hospitals that underperform in the prevention of this complication [4,21]. Abbett et al. [22] developed an observational study in which a prevention bundle was introduced targeting CDI among hospitalized patients and found a reduction in their incidence of CDI from 1.10 to 0.66 per 1000 patients. This shows how developing pathogen-directed preventive strategies could potentially lower the elevated incidence of CDI among EGS patients, reducing the high costs and penalties associated with this infection.

Table 4. Multi-Variable Logistic Regression for Risk Factors Associated with *Clostridium difficile* Infection

Variables	*Odds ratio*	*95% CI*		*p*
Time to procedure	**0.87**	**0.786**	**0.963**	**<0.01**
Length of stay	**1.013**	**1.003**	**1.024**	**0.02**
Charlson Comorbidity Index	1.036	0.943	1.139	0.46
Age	1.005	0.986	1.024	0.64
Female	0.982	0.587	1.641	0.94
Race				0.47
White	1.815	0.393	8.387	0.45
Non-white	1.325	0.296	5.930	0.71
Constant	0.06			**<0.01**

CI = confidence interval.

We found that patients undergoing an EGS on their first day of admission were at significantly higher risk for development of CDI than those who had an operation later. After adjusting for potential confounders, time to operation remained significant and showed a reduction in the odds of development of CDI post-operatively of 13% per each day passed after admission that the EGS was performed. There is no real explanation for these findings; we believe that this might be because of a more complicated disease process on admission. There were also similarities among the EGS procedures performed on CDI positive and negative patients, however; partial colectomies, small bowel resections, and gastric repairs for perforated peptic ulcers represented almost half of all the patients with a positive *C.*

difficile result, which coincides with the previous data published [10].

Li et al. [19] performed a retrospective review of the Veterans Affairs Surgical Quality Improvement Program and found that the incidence of CDI was higher in emergency operations (1.4% vs. 0.34%, $p < 0.001$) and in surgical procedures performed early in the admission; patients with a CDI also received a significantly higher number of antibiotic classes (three or more) compared with those without CDI. Zerey et al. [10] used five years of the Agency for Healthcare Research and Quality—National Inpatient Sample to estimate the burden of *C. difficile;* their results showed that patients undergoing emergency operations were at higher risk of development of CDI compared with elective patients (0.8% vs. 0.3%, $p < 0.01$), and that certain surgical procedures, such as colectomies, small bowel resections, and gastric resections, carried a higher risk of CDI.

Abdelsattar et al. [11] had similar findings of a higher incidence of CDI in patients undergoing emergency operation, and that colon and small bowel resections, along with gastric or esophageal procedures, were among those with the highest rate of post-operative CDI. A study in the United Kingdom performed by Rodriguez et al. [23] found that gastrointestinal procedures (upper and lower gastrointestinal) were most commonly performed on CDI positive patients compared with CDI negative patients.

It is well known that antibiotic use is linked to the development of CDI. Although both groups in our study received antibiotic agents for a similar number of days (10.5 days vs. 10.3 days), the number of antibiotic classes administered post-operatively was significantly associated with increased risk of CDI. The rate of *C. difficile* cases was significantly higher in the patients who received two and three or more antibiotic classes (12.9% vs. 9.2% and 82.9% vs. 75.4%, $p = 0.04$) than that of those with none or only one antibiotic class prescribed post-operatively (1.4% vs. 6% and 2.9% vs. 9.4%, $p = 0.04$), which is in accordance with the data previously described [19].

Limitations to our study are: First, that this is a retrospective review of a single center, prospectively collected database. We used the presence of toxin A/B assay in stools as a surrogate for clinical suspicion of CDI, understanding that a group of patients may be colonized and test positive but never have symptoms and another group may have presented symptoms, received treatment, but were never tested for CDI. Unlike other studies that use administrative discharge data, however, all of our patients tested for CDI, negative or positive, had their results confirmed by chart review, which provides higher accuracy in the number of cases reported.

Conclusion

Infection with *C. difficile* continues to represent a challenging post-operative complication. Patients undergoing EGS seem to be at higher risk of this infection developing. Time to operation predicts the risk of development of CDI post-operatively, with a late EGS associated with a reduction in the odds of becoming infected with *C. difficile* post-operatively. At any point with our findings, we would suggest to delay patient care; instead, these data should be seen as an observational and descriptive study to give clinicians a high index of suspicion in EGS patients who might be at elevated risk for CDI and to help develop strategies to reduce the high incidence of CDI in EGS patients.

Author Disclosure Statement

No competing financial interests exist.

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