Fulminant *Clostridioides difficile* colitis: evolution of surgery and outcomes in the modern era

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ABSTRACT

Introduction

Fulminant *Clostridioides difficile* colitis (FCDC) is a severe form of colitis secondary to C. difficile. FCDC often requires surgical intervention, with the standard of care being a total abdominal colectomy (TAC) with end ileostomy. It is associated with high postoperative mortality (approaching 50%), significant morbidity, and limited opportunities for restoration of gastrointestinal (GI) continuity. The creation of a diverting loop ileostomy (DLI) with colonic lavage has been advocated as a less invasive procedure with the potential for improved postoperative outcomes compared to TAC. Limited data exist on DLI especially with regards to post-discharge outcomes. In addition, there is a paucity of tools predicting postoperative mortality after surgery for FCDC that can help guide surgical decision making. Therefore, the objective of this thesis was to evaluate surgical outcomes of FCDC in the modern era.

Methodology

The first component of the work involved the development of a risk calculator to predict postoperative mortality after TAC. This was accomplished using a prospectively maintained validated surgical database (American College of Surgeons- National Surgical Quality Improvement Program, ACS-NSQIP). To evaluate generalizability, external validation was accomplished using a published cohort of patients who had a TAC for FCDC.

The second component of the work involved assessment of outcomes of DLI versus TAC. To describe the long-term trajectory of patients with FCDC undergoing DLI or TAC, a large American dataset with readmission information (Nationwide Readmission Database, NRD) was queried, and rates of readmission, in-hospital mortality including mortality during readmissions,

and rates of restoration of GI continuity were assessed. Finally, a multi-institutional retrospective cohort study (n=11 institutions) was conducted. Primary outcome was 30-day postoperative mortality, and secondary outcomes were 90-day postoperative mortality, major morbidity, GI restoration rates, and recurrences.

Results

In the first component, a risk calculator for postoperative mortality was developed in a cohort of 581 patients, and externally validated in 124 patients who underwent TAC for FCDC. The developed calculator demonstrated good internal and external predictive capability with an AUC between 68.4% and 74.7%. In the second component, I addressed post-discharge outcomes of patients undergoing surgery for FCDC using a review of the NRD that identified 1486 (71.8%) patients who underwent a TAC and 584(28.2%) patients who underwent a DLI. The 90-day unplanned readmission (TAC 26.1% vs. DLI 23.1%, *p* 0.26) and the 90-day post-discharge all-cause mortality (TAC 2.4% vs. DLI 2.1%, p = 0.85) rates were similar for both procedures. Restoration of GI continuity was higher for patients after DLI compared to TAC (26.4% vs. 8.3% $p<0.001$), with time to surgery being significantly shorter after DLI (7.5 (70.0–140.8) vs. 121.0 (90.8–154.0) days, $p = 0.028$). In the third component, in a multicentre cohort study, I observed that the overall 30 and 90-day post-operative mortality were 23.5% vs. 37.1% ($p=0.10$) and 29.4% vs. 46.2% ($p=0.10$) for DLI compared to TAC, respectively. Incidence of post-operative major morbidity was high in both groups (TAC 85.3% vs. DLI 67.6%, *p* 0.016). DLI was associated with a significantly lower rate of major morbidity ((OR [95%CI]; 0.33[0.11-0.97]) and recurrence rates after restoration of GI continuity were low.

Conclusion

In conclusion, morbidity, and mortality after surgery for FCDC remain high. DLI was associated with increased GI restoration rates and earlier time to surgery. DLI was also associated with decreased major morbidity, but comparable post-operative mortality. A risk prediction model for mortality after surgery for FCDC was developed and may help guide consent discussions with patients.

RÉSUMÉ

Introduction

La colite fulminante à *C. difficile* (CFCD) est une forme sévère de la colite à *C. difficile*. Le traitement chirurgical standard de la CFCD est une colectomie totale (CT) avec iléostomie terminale. Elle est associée avec un haut taux de mortalité (proche de 50%), morbidité, et un taux bas de rétablissement de la continuité intestinale. La création d'une iléostomie de dérivation (ID) avec lavage colique a été présenté comme une alternative pour la CT avec le potentiel d'améliorer les complications chirurgicales. Un nombre limité d'études ont évalué l'ID, surtout en ce qui concerne les données après le congé de l'hôpital. De plus, il existe un manque d'outils de prédiction pour la mortalité après la chirurgie pour la CFCD. Ainsi, l'objectif de cette thèse était d'évaluer les issues après la chirurgie pour la CFCD dans l'ère moderne.

Méthodologie

Dans un premier lieu, en utilisant une cohorte multicentrique prospectivement maintenue (American College of Surgeons- National Surgical Quality Improvement Program, ACS-NSQIP), un outil de prédiction pour la mortalité après la CT a été développé. Une validation externe a été accomplie en utilisant une cohorte publiée de patients ayant subis une CT pour CFCD.

La deuxième partie de ce travail inclut une comparaison des issues de l'ID versus la CT pour le traitement de la CFCD. Pour décrire les résultats post-opératoires à long terme, une banque de données administrative Américaine a été consultée (Nationwide Readmission Database, NRD). Les taux de réadmissions, mortalité hospitalière incluant mortalité durant les réadmissions, les

taux de restauration de la continuité intestinale ont été évalué. Finalement, une étude de dossiers multicentriques (n=11) a été faite avec objectif principal de comparer la mortalité à 30-jours. Les objectifs secondaires étaient de comparer la mortalité à 90 jours, la morbidité, la restauration de la continuité intestinale et les récidives.

Résultats

Un outil de prédiction de mortalité a été développé dans une cohorte de 581 patients et validé chez 124 patients qui ont eu une CT pour la CFCD. Après modélisation prédictive et validation interne, la calculatrice a été validée en externe et a montré une bonne capacité à prédire la mortalité (AUC entre 68.4% and 74.7% pour chacune des 5 séries de validation imputés). Utilisant la base de données NRD, 1486 patients 1486 (71.8%) patients qui ont subi une CT et 584(28.2%) une ID ont été revus. Le taux de réadmission non-planifié a 90-jours était similaire (CT 26.1% vs. ID 23.1%, *p* 0.26). La mortalité à 90-jours après le congé était aussi similaire (CT 2.4% vs. ID 2.1%, p = 0.85). Le rétablissement de la continuité intestinale était plus haut après une ID ((26.4% vs. 8.3% $p<0.001$), et ceci à un intervalle de temps plus courte (7.5 (70.0–140.8) vs. 121.0 (90.8–154.0) jours, $p = 0.028$). Dans notre revue de dossier multicentrique, la mortalité à 30 et 90 jours postopératoire était de 23.5% vs. 37.1% ($p=0.10$) et 29.4% vs. 46.2% ($p=0.10$) pour l'ID comparé à la CT, respectivement. L'incidence de morbidité majeure postopératoire était haute dans les deux groupes (CT 85.3% vs. ID 67.6%, *p* 0.016). L'ID était associé avec une diminution significative de la morbidité majeure ((OR [95%CI]; 0.33[0.11-0.97]) et les récidives après la restauration de la continuité intestinale étaient basses.

Conclusion

En conclusion, la morbidité et mortalité après chirurgie pour CFCD est élevée. L'ID est associée avec de plus haut taux de restauration de continuité intestinale et ceci en un délai plus court. L'ID est aussi associé avec une diminution de morbidité majeure, mais une mortalité postopératoire similaire à la CT. Une calculatrice qui prédit la mortalité après CT pour CFCD a été développée avec une performance acceptable. Cette dernière pourrait etre utilisée pour guider les discussions et le consentement éclairé avec les patients.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

The work presented in this thesis represents original contributions and adds to the body of knowledge on the operative management for fulminant *C. difficile* colitis.

In this dissertation I highlighted risk factors for morbidity and mortality following surgery for *C. difficile* colitis and developed a risk prediction model to predict post-operative mortality after surgery for this disease. I also describe the long-term trajectory of patients with *C. difficile* undergoing a total abdominal colectomy (standard of care) or a diverting loop ileostomy and colonic lavage, which has emerged as an alternative to a total colectomy in select patients.

While I have received the support of my supervisors and co-authors for each study presented, the data presented in the following chapters represents my original work.

FORMAT OF THE THESIS

This thesis is organized in a manuscript-based fashion as per the guidelines and specifications outlined by the thesis requirements of the Graduate and Postdoctoral Studies at McGill University. Each manuscript has its own reference list, figures, tables and appendices. A master reference list for the non-manuscript chapters appears at the end of the dissertation.

Chapter 1 is an introductory chapter with a comprehensive review of the literature.

Chapter 2 is based on the published article: Abou Khalil M, Bhatnagar SR, Feldman L, Longtin Y, Vasilevsky CA, Carignan A, Morin N, Boutros M. Development and validation of a clinical risk calculator for mortality after colectomy for fulminant Clostridium difficile colitis. Journal of Trauma and Acute Care Surgery. 2019 Oct 1;87(4):856-64. The peer-reviewed manuscript is the version that is used in this thesis, with permission from Wolters Kluwer.

Chapter 3 is a bridging chapter between Chapter 2 and Chapter 4.

Chapter 4 is based on the published article: Abou-Khalil M, Garfinkle R, Alqahtani M, Morin N, Vasilevsky CA, Boutros M. Diverting loop ileostomy versus total abdominal colectomy for Clostridioides difficile colitis: outcomes beyond the index admission. Surgical Endoscopy. 2021 Jun;35:3147-53. Reproduced with permission from Springer Nature.

Chapter 5 is a bridging chapter between **Chapter 4** and **Chapter 6.**

Chapter 6 is based on the article submitted to Annals of Surgery Open and is currently under review: Abou Khalil M, Demian M, Faris S, Longtin Y, Mukherjee K, Liberman S, Demyttenaere S, Sebajang H, Poirier M, Montpetit P, Vasilevsky CA, Boutros M. Morbidity and gastrointestinal restoration rates for diverting loop ileostomy with colonic lavage vs. total abdominal colectomy for fulminant Clostridioides difficile colitis: a multicenter retrospective cohort study.

Chapter 7 is the discussion.

Chapter 8 is the conclusion

AUTHOR CONTRIBUTIONS

I have made substantial contributions to each of the co-authored papers included within this thesis. Under the supervision of my supervisor Dr. Boutros the co-supervision of Dr. Feldman, I had an active role in the development of the research questions, study design, data acquisition, data analysis and interpretation, and drafting of the manuscripts. The contribution of co-authors of each manuscript in this thesis are described below:

1. Abou Khalil M, Bhatnagar SR, Feldman L, Longtin Y, Vasilevsky CA, Carignan A, Morin N, Boutros M. Development and validation of a clinical risk calculator for mortality after colectomy for fulminant Clostridium difficile colitis. Journal of Trauma and Acute Care Surgery. 2019 Oct 1;87(4):856-64.

   Study conception and design: Abou Khalil, Bhatnagar, Feldman, Longtin, Vasilevsky, Carignan, Morin, Boutros
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   Critical revision of manuscript: Abou Khalil, Bhatnagar, Feldman, Longtin, Vasilevsky, Carignan, Morin, Boutros

2. Abou-Khalil M*, Garfinkle R*, Alqahtani M, Morin N, Vasilevsky CA, Boutros M. Diverting loop ileostomy versus total abdominal colectomy for Clostridioides difficile colitis: outcomes beyond the index admission. Surgical Endoscopy. 2021 Jun;35:3147-53.

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3. Abou Khalil M, Demian M, Faris S, Longtin Y, Mukherjee K, Liberman S, Demyttenaere S, Sebajang H, Poirier M, Montpetit P, Vasilevsky CA, Boutros M. Morbidity and gastrointestinal restoration rates for diverting loop ileostomy with colonic lavage vs. total abdominal colectomy for fulminant Clostridioides difficile colitis: a multicenter retrospective cohort study. Submitted to Annals of Surgery Open.

   Study conception and design: Abou Khalil, Demian, Faris, Liberman, Demyttenaere, Sebajang, Poirier, Montpetit, Vasilevsky, Boutros
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ABBREVIATIONS

CDI- *Clostridioides difficile* infection
FCDC- Fulminant *Clostridioides difficile* colitis
DLI- Diverting loop ileostomy
RT-Ribotype
ICU-Intensive Care Unit
FMT- Fecal Microbiota Transplant

CHAPTER 1: INTRODUCTION

Background

Clostridioides (formerly Clostridium) difficile is an anaerobic gram-positive bacillus. First isolated in 1935 from healthy neonates, it gained recognition close to 40 years later as the most important cause of antibiotic associated diarrhea[1-4]. *C. difficile* can have a wide range of clinical presentations from mild colitis to fulminant disease with a severe infection and ensuing multi-system organ failure. While medical management with antibiotics and supportive care are the mainstay of treatment for the disease, severe colitis often requires surgical intervention.

Epidemiology and Pathogenesis

At the turn of the twenty first century, *C.* difficile infection (CDI) saw an unprecedented and widespread surge in its incidence[5]. *C. difficile* discharge diagnoses nearly doubled from 82,000 (95%CI 71,000-94,000) in 1996 to 178,000 (95%CI 151,000-205,000) in 2003 [6]. It became an important worldwide public health concern with estimates of nosocomial C. difficile reaching 3.54/10 000 patient-days/year[7]. This increased incidence was also accompanied by increased virulence, treatment resistance and recurrence resulting in a significantly higher associated morbidity and case fatality than previously reported[5,7-10]. As an example, in a review of a large American dataset, cases of severe colitis with toxic megacolon nearly tripled with an

increase from 3.61% in 2000 to 9.39% in 2010[11]. Mortality rates were high, reaching 30% for patients with toxic megacolon[11].

This led to the identification of new strains of *C. difficile* thought to be largely responsible for multiple outbreaks[1,12]. The province of Quebec, Canada witnessed an epidemic in large part attributed to a hypervirulent strain- ribotype 027 or RT027- associated with significantly increased morbidity and mortality[13-16]. Incidence in some parts of Quebec increased from 35.6/100,000 in 1991 to 156.3/100,000 in 2003 with an associated increase in mortality from 4.7% to 13.8%[15]. This strain also emerged as an important concern in other North American and European cities[17-20]. A similarly hypervirulent strain was prevalent in the Netherlands (RT078), and other strains are constantly being discovered with varying virulence [21-23].

The pathogenicity of *C. difficile* is thought to be the result of direct injury to colonocytes by two exotoxins (toxin A and toxin B), with ensuing profound secretory diarrhea and colitis resulting in CDI [24]. Hypervirulent strains are associated with mutations in the regulatory gene responsible for toxin production and results in higher amounts of toxins A and B[25]. They are also associated with the production of an additional toxin (binary toxin)[24,26]. The increased production of toxins A and B and the production of this additional toxin are thought to be behind the heightened virulence of these strains. This increased virulence is manifested by higher rates of recurrence, treatment resistance, intensive care unit (ICU) admission, sepsis and end-organ damage, need for surgical intervention, and mortality[11,14,27]. This also resulted in high transmission and outbreaks in healthcare institutions including hospitals and long-term care facilities[27].

As it is often the case, the epidemiology of infectious diseases is constantly evolving [10,28-32]. In the case of *C. difficile*, infection control measures and antibiotic stewardship programs have been

partly responsible for the dampening of CDI epidemic outbreaks seen in the early 2000s[33]. For example, from 2009 to 2015, a decrease in healthcare associated CDI was observed in Canada from 5.9 4.3 cases per 10 000 patient-days[33]. This has been associated with an increase in community acquired disease and a change in the predominant strain, as demonstrated by a 33% increase in annual incidence rate of community-associated CDI in Quebec, Canada from 0.51 (2008) to 0.68 cases/100,000 population [28,33,34].

Risk factors for CDI

Several risk factors for the development of CDI have been identified. Antibiotic use is the most widely recognized and common culprit[35]. While clindamycin was the first antibiotic to be associated with CDI, other antibiotic classes have since been implicated[36]. It is believed that the disruption of balanced normal colonic microbiota resulting from antibiotic use allows pathogenic *C. difficile* bacteria to multiply and cause the colitis associated with the disease. Increasing age is a very important risk factor consistently shown to be associated with CDI[35]. Other patient factors that have been associated with CDI include increasing comorbidity (thought to be in part related to greater healthcare contact), host immunity and immunosuppressed health states, inflammatory bowel disease, and gastrointestinal surgery[35,37]. Proton pump inhibitor use has inconsistently been reported to be a risk factor for CDI[38].

Patient factors and pathogen characteristics have been implicated in the severity of the clinical course. Increasing age, immunosuppression, and comorbidities are amongst the most

commonly reported predictors of severe disease presentation as highlighted by a recently published systematic review and meta-analysis[39]. The hypervirulent RT027 strain and the presence of binary toxin both had a significant effect, however this was not consistent across studies[39].

Recurrent disease

Recurrent CDI refers to the reappearance of symptoms up to 8 weeks after treatment for successful resolution of disease[40]. It has become an increasingly important problem, especially as certain disease strains increase the risk of relapse[41]. Recurrent CDI can have a mild course, or present with severe or fulminant disease. While recurrent symptoms are most commonly secondary to a relapse of the infection with the same strain, it can also result from infection with a new strain. Several predictors of recurrent disease have been identified. These include age, nosocomial acquired disease, previous recurrence, and the start of proton-pump inhibitor therapy during or after the diagnosis of CDI[39].

Clinical Presentation and Classification of Disease Severity

Although individuals can be asymptomatic carriers of *C. difficile*, colitis and diarrhea represent the hallmark of infection. Clinical presentation can resemble other causes of diarrhea including graft versus host disease, inflammatory bowel disease (IBD) flares or cytomegalovirus colitis. In these settings, in addition to testing for *C. difficile*, endoscopy can be helpful in ruling

out these other causes and may reveal the pathognomonic endoscopic appearance of CDI with pseudomembranes (raised white and yellow plaques consisting of toxin induced ulcers with inflammatory cells and mucous)[35]. With increasing disease severity, the colitis can progress and manifest with systemic signs of illness including fever, hypotension and tachycardia- an entity referred to as fulminant *C. difficile* colitis (FCDC)[38]. Of note, while diarrhea is typical for colitis, ileus and colonic atonicity may be present with advanced disease. Similar to severe presentations of IBD and other infectious colitis, patients with CDI can develop toxic megacolon, characterized by severe colonic dilation in the context of systemic toxicity[42-44].

Different CDI severity classification system exist, however there is no universally accepted system[38,45,46]. In general, the existing CDI severity classifications include a combination of factors associated with increased morbidity and mortality. These factors encompass physical examination findings, signs of shock, and laboratory data. A useful disease classification system was published in 2017 by the Infectious Disease Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA)[40]. In this classification, a non-severe episode is supported by leukocytosis with a white blood cell count of up to 15,000 cells/mL and a serum creatinine of <1.5mg/dL. A severe episode is characterized by a white blood cell count of more than 15,000 cells/mL or a serum creatinine >1.5 mg/dL. The hallmarks of a fulminant episode in this classification are the presence of hypotension or shock, ileus, or toxic megacolon. A comparison of definitions from two infectious disease societies is summarized in Table 1.

Medical treatment

Given the role of antibiotics in the development and recurrence of CDI, the offending antibiotic should be discontinued as soon as it is feasible to do so[47]. If CDI is suspected but not yet confirmed, early treatment is initiated while awaiting confirmatory tests to avoid unnecessary delays to treatment. This is especially important in patients with severe or fulminant disease, where early interventions may prevent worsening sepsis and its consequences. With regards to treatment, while enteral metronidazole was commonly used, vancomycin or fidaxomicin have both been found to be superior to metronidazole and have largely replaced it[38,46]. The recommended treatment regimen with these agents is based on disease severity, with dose escalation and combination therapy for increased disease severity (Table 1). Recurrences are managed with pulse-tapered vancomycin or fidaxomicin regimens[38]. For subsequent recurrences, fidaxomycin, vancomycin with or without rifaximin, and fecal microbiotia transplant (FMT) are used. As for recurrences presenting with fulminant disease, in addition to the antibiotic regimen administered, FMT can be added[41].

The medical management of patients with FCDC includes the administration of enteral vancomycin (500mg every 6 hours) and intravenous metronidazole (500mg every 8 hours). Vancomycin enemas (500mg in 100mL of normal saline or Ringer's lactate) can be added if ileus is present. FMT can be considered in patients with FCDC[41].

Patients with FCDC require special attention, and supportive care should be initiated[48]. Accurate measurements of intake and output should guide aggressive fluid resuscitation. Acute kidney injury is a common complication of the severe colitis and fluid losses, thus aggressive resuscitation is generally the initial approach. Patients should be kept fasting with complete

bowel rest until their symptoms improve. Serial examinations include vital sign monitoring, abdominal examination, and laboratory investigations as the clinical course can evolve rapidly[49,50]. This is usually done in a monitored setting like the intensive care unit, with multidisciplinary approach including the input of intensivists, gastroenterologists, infectious disease specialists and surgeons.

Surgical management

Surgery for antibiotic associated colitis predates the *C. difficile* epidemic[36,51]. It was estimated to be needed in about 20% of patients, but this rate precedes the introduction of aggressive medical treatments and supportive strategies[36]. Although rare, FCDC can present in 2-5% of cases, depending on the epidemic status [9,52-54]. Apart from clear operative indications such as abdominal compartment syndrome or colonic perforation, no strict clinical criteria have been agreed upon to trigger the decision for surgery. Nonetheless, surgery is reserved for patients whose fulminant disease fails to respond to medical management, worsens on aggressive medical treatment or in whom complications related to the colitis arise including hemodynamic compromise, abdominal compartment syndrome or the rare occurrence of colonic perforation[53].

Timing of surgical management

Despite the morbidity and mortality associated with emergency surgery in critically ill patients, evidence suggests that earlier time to surgical intervention in FCDC improves survival compared to continued medical management alone[55,56]. No clear guidelines exist on the optimal

timing of surgery for FCDC (the so-called "golden hour"); however, it is believed that early intervention before the progression of shock and end-organ damage improves post-operative outcomes[52]. With some patients with FCDC improving with medical management alone and in the face of operative morbidity and mortality, the decision to operate is not straightforward.

Total Abdominal Colectomy and end ileostomy: the standard of care

The standard surgical intervention for FCDC is a total abdominal colectomy with end ileostomy. This is usually performed with an open approach. Upon entry into the abdominal cavity, profuse ascites is encountered. With the exception of perforation, the serosa of the colon typically has a normal appearance as it is primarily a mucosal disease. The distal extent of the resection is at the rectosigmoid junction. If there is heightened concern for rectal stump blowout, a mucous fistula can be considered. Post-operatively, patients should remain in a monitored setting until their vital functions are stable without the supportive measures offered in the intensive care unit [47]. Post-operative length of stay is often prolonged by the comorbidities of the patient and the complications of the multisystem involvement of the disease.

Other surgical interventions for FCDC have been described with various uptake and success. Segmental colectomies have been largely abandoned due to the superiority of TAC in this setting[57]. Fecal stream diversion with diverting loop ileostomies, cecostomies and decompressive colostomies were historically performed, but had a prohibitively high rate of post-operative mortality approaching 60%[51]. It is possible that the failure of these diverting

ostomies and blowholes are a reflection of the medical management at the time, or the inability to clear the colon of the toxins themselves that are driving the colitis and systemic illness. It has also been hypothesized that these procedures failed because patients who were selected for these less-extensive surgical procedures were the most critically ill patients who were too sick to tolerate a TAC[51].

Diverting loop ileosotomy and colonic lavage

Most recently, the creation of a diverting loop ileostomy (DLI) with colonic lavage has been advocated as a less invasive alternative to TAC in this critically ill-patient population. In 2011, Neil et al described the creation of a diverting loop ileostomy with colonic lavage with warm polyethylene glycol solution and post-operative antegrade delivery of vancomycin through the ileostomy[58]. While similar to older descriptions of fecal diversion for the treatment of antibiotic associated pseudomembranous colitis mentioned above, the addition of mechanical lavage with polyethylene glycol and local delivery of vancomycin are thought to rid the colon of the bacteria and toxins driving the severe colitis and systemic inflammatory response[51]. In their single institution, single surgeon-series the authors compared 42 patients who underwent surgery for FCDC with 42 historical patients who had undergone TAC. A significantly decreased 30-day post-operative mortality was observed for patients who underwent a DLI compared to TAC (19% vs. 50%, *p* 0.006). Only three patients in the DLI group required conversion to a total abdominal colectomy either due to the development of abdominal compartment syndrome or for

failure of improvement. Since the first description of this novel procedure, few studies have compared it to TAC[59-62].

Restoration of gastrointestinal continuity

Both aforementioned operations require the creation of a stoma, whereby the terminal ileum is connected to the abdominal wall. After a TAC, the terminal ileum is brought to the abdominal wall as an end ileostomy. To restore gastrointestinal (GI) continuity, another surgery is performed to disconnect the ileum from the anterior abdominal wall and anastomose it to the remnant rectum through an abdominal approach (ileorectal anastomosis). For a diverting loop ileostomy, a loop of ileum is brought up and sutured to the abdominal wall. In this case, restoration of GI continuity is technically easier as it requires disconnecting the stoma from the abdominal wall, and anastomosing the two ends of the ileostomy together, obviating the need to go intra-abdominally. Not only is the closure of a loop ileostomy technically easier than the closure of a loop ileostomy, but it is also associated with less morbidity. Major complications after closure of DLI are estimated to be less than 5% compared to the 26% major morbidity reported after ileorectal anastomosis[63,64].

Low rates of GI restoration have been associated with TAC. In a study evaluating the long-term prognosis of patients undergoing surgery for FCDC, only 4 of the 29 patients (13.8%) who were discharged alive and had follow up had restoration of GI continuity[65]. Given the significant post-operative morbidity associated with a colectomy for severe CDI, many patients do not reach a level of fitness suitable to endure another extensive operation like ileorectal

anastomosis[9]. In their sentinel paper, Neal et al described a remarkably high rate of ileostomy closure after DLI compared to TAC (79% vs 19%)[58]. Similar ileostomy closure rates have been described by Fashandi et al (83% vs 43%), albeit described in a small number of patients (DLI= 10 patients, TAC=13 patients) [59].

Predictors of postoperative mortality

Despite the superiority of surgical intervention over continued medical management alone for patients with FCDC, mortality rates are high, approaching 50%[66]. This has prompted research focused on identifying predictors of mortality in this setting. Predictors of post-operative mortality include: 1) patient factors: older age, medical comorbidities including immunosuppression, and 2) clinical factors: increasing leukocytosis or leukopenia, acute kidney injury, hypoalbuminemia, increased lactate, preoperative ventilation and need for vasopressor support [52,54,55,67,68]. As many of these predictors are aggravated by worsening disease, earlier surgical intervention to decrease the high mortality associated with surgery in this setting has been advocated[52,53].

Clinical prediction tools are important and increasingly used adjuncts to guide medical and surgical decision-making. With a patient-centred and individualized approach to medicine, these tools can support clinicians in guiding consent discussions with patients and/or their next of kin.

In the setting of an emergent and life-threatening procedure, these prediction models are especially important to consult and act as a reference in pre-operative consent discussions. The development of these prediction models requires a large sample size, rigorous methodology to

assess internal validity, and external validation to demonstrate generalizability beyond the derivation cohort. In evaluating patients with FCDC for surgical intervention, it is helpful to predict the individual patient's risk of post-operative mortality. A few risk prediction models have been described for mortality in FCDC. Kulayat et al adapted various components of the C. difficile- associated risk of death score (CARDS), developed and validated to predict inpatient mortality for patients with CDI, to predict postoperative mortality after TAC[69]. The authors used the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database to develop an equation to predict the probability of postoperative mortality based both on patient's acute alterations in health state and their chronic comorbidities. Another example is a simple tool developed by Sailhamer *et al* which includes age, need for cardiopulmonary support, and severe leukocytosis [54]. This tool was developed in a cohort of patients with FCDC to predict mortality, but only 75/199 patients underwent surgical intervention making this applicability of this calculator somewhat limited to patients undergoing surgery. There is no universally accepted prediction model. This likely is the result of the limitations that these tools have, namely the difficulty of scoring systems to accurately predict the clinical course, be simple enough for bedside use, and allow for disease-specific variables to be adjusted as the patient's clinical course changes. In addition, many of these tools have been largely limited by their derivation from small cohorts or their lack of external validation[54,70].

Thesis Objectives

The first objective of this thesis was to develop a clinical risk calculator for postoperative mortality after total abdominal colectomy for *C. difficile* to be used as a guide for surgeons and decision-makers to guide management and be simple enough to allow widespread point-of-use. To accomplish this objective, I developed a risk calculator for postoperative mortality using a prospectively maintained and validated surgical database. I then externally validated this calculator using a published cohort of patients who underwent a total abdominal colectomy.

The second objective of this thesis was to describe and compare the post-discharge outcomes after TAC and DLI for *C. difficile* with regards to readmission, mortality beyond the index operation, and gastrointestinal restoration. To accomplish this objective, I queried a large American database with a nationally representative sample of the population and with readmission information.

The third objective of this thesis was to compare DLI and TAC for the treatment of FCDC. Outcomes of interest were 30 and 90-day postoperative mortality, morbidity, recurrence and gastrointestinal restoration. To accomplish this objective, I launched a multicenter trial recruiting patients with FCDC undergoing surgical management and ultimately conducted a retrospective cohort study at all participating institutions.

Table 1: Comparison of two infectious disease societies with regards to classification of disease severity and treatment

		IDSA/SHEA*[38]	ESCMID**[46]
Non-Severe	Definition	White blood cell count ≤15,000 cell/mL and serum creatinine level <1.5mg/dL	White blood cell count ≤15000 cells/mL and a serum creatinine level ≤50% above baseline, and core body temperature at presentation ≤38.5°C. No imaging features of severity.
	Treatment	Fidaxomicin (preferred) or vancomycin 125mg PO every 6 hours for 10 days Metronidazole 500mg PO every 8 hours for 10-14 days if neither available	Fidaxomicin (preferred) or vancomycin 125mg PO every hours for 10 days. Metronidazole 500 mg PO every 8 hours for 10 days. If high risk of recurrence especially elderly hospitalized, consider extended pulsed regimen of Fidaxomicin with 200mg PO BID for 5 days followed by 200mg PO every other day for 20 days or adjunctive bezlotoxumab if fidaxomicin is not unavailable
Severe	Definition	WBC count of >15000 cells/mL or a serum creatinine level ≥1.5 mg/dL.	WBC count of >15000 cells/mL or a rise in serum creatinine level >50% above baseline or core body temperature >38.5°C. Additional supporting factors, when available, are distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) on imaging.
	Treatment	Fidaxomicin STD or vancomycin 125mgPO every 6 hours for 10 days and adjunctive bezlotoxumab for primary CDI if other risk factors for recurrence (age above 65, immunocompromised host, recurrence in the past 6 months)	Fidaxomicin or vancomycin 125mg PO every 6 hours for 10 days
Severe-complicated or fulminant	Definition	Presence of hypotension or shock, ileus or megacolon.	Hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course of disease (i.e. rapid deterioration of the patient).
	Treatment	Vancomycin 500mg every 6 hours PO or by nasogastric tube and metronidazole 500mg IV every 8 hours and consider vancomycin per rectum if ileus is present	Fidaxomicin 200mg po bid for 10 days or vancomycin 125mgPO every 6 hours hours for 10 days and consider IV tigecycline 100mg load, then 50mg every 12 hours

*IDSA/SHEA: Infectious Diseases Society of America (IDSA) /Society for Healthcare Epidemiology of America (SHEA)
**ESCMID: European Society of Clinical Microbiology and Infectious Disease

CHAPTER 2. DEVELOPMENT AND VALIDATION OF A CLINICAL RISK CALCULATOR FOR MORTALITY AFTER COLECTOMY FOR FULMINANT CLOSTRIDIUM DIFFICILE COLITIS

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Abstract

Background: Clostridium difficile colitis is an increasingly important cause of morbidity and mortality. Fulminant C. difficile colitis (FCDC) is a severe form of the colitis driven by a significant systemic inflammatory response, and managed with a total abdominal colectomy. Despite surgery, postoperative mortality rates remain high. The aim of this study was to develop a bedside calculator to predict the risk of 30-day postoperative mortality for patients with FCDC.

Methods: After institutional review board approval, the American College of Surgeons National Surgical Quality Improvement Program database (2005–2015) was used to include adult patients who underwent emergency surgery for FCDC. A priori preoperative predictors of mortality were selected from the literature: age, immunosuppression, preoperative shock, intubation, and laboratory values. The predictive accuracy of different logistic regression models was measured by calculating the area under the receiver-operating char- acteristic curve. A cohort of 124 patients from Québec was used to validate the developed mortality calculator.

Results: A total of 557 patients met the inclusion criteria, and the overall mortality was 44%. After developing the calculator, no statistically significant differences were found in comparison with the American College of Surgeons National Surgical Quality Improvement Program probability of mortality available in the database (area under the receiver operating curve, 75.61 vs. 75.14; $p = 0.79$). External validation with the cohort of patients from Quebec showed an area under the curve of 74.0% (95% confidence interval, 65.0–82.9).

Conclusion: A clinically applicable calculator using preoperative variables to predict postoperative mortality for patients with FCDC was developed and externally validated. This calculator may help guide preoperative decision making

INTRODUCTION

Clostridium difficile infection (CDI) has evolved into an important worldwide concern, associated with a significant increase in morbidity and mortality taxing health care resources.[1-5] Although most patients respond well to medical management, a small proportion (3-10%) will develop a severe form of colitis and require surgery to overcome the toxin-driven systemic inflammatory response.[4] Although there are varying definitions for this severe form of the disease commonly referred to as fulminant *Clostridium difficile* colitis (FCDC), it is generally characterized by severe leukocytosis or leukopenia, hypoalbuminemia, and signs of systemic disease and end-organ damage including increased creatinine levels, fever, and the need for cardiopulmonary support.[6]

The standard surgical approach for FCDC is a total abdominal colectomy (TAC).[2,7] Despite this aggressive surgical procedure, postoperative mortality rates remain high (30-57%), prompting many authors to investigate predictors of this outcome.[7-9] The most frequently reported predictors of mortality include patient characteristics such as age or immunosuppression status, and clinical signs of end organ damage such as shock or kidney failure.[7,8,10,11] Since many of these factors may be indicative of prolonged shock or hypoperfusion, early surgical intervention has been advocated to improve outcomes.[9,12,13] However, in the absence of clear guidelines on the optimal timing of the procedure (the so-called "golden hour") and in the face of the high postoperative mortality of this invasive procedure and impact on quality of life for survivors, the decision to operate early is rarely straightforward. When discussing options with patients and families in this high-stakes decision, surgeons require information regarding the likelihood that an operation would be lifesaving and the optimal timing to intervene. Currently, no widely used

prediction tool exits to guide preoperative decision making for patients with FCDC who are being evaluated for surgery. Therefore, our objective was to develop and validate a clinical risk calculator that predicts 30-day postoperative mortality for patients with FCDC based on easily attainable preoperative parameters.

METHODS

Source of data and participants for development and validation cohorts

After Institutional Review Board approval, the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was used to develop the risk prediction model. This surgical database collects important 30-day postoperative outcomes including mortality and relevant preoperative patient demographic, clinical and operative variables from over 400 participating hospitals in North America. Adult patients with a postoperative diagnosis of *Clostridium difficile* colitis (defined by ICD 9 code 008.45) who underwent surgery between 2005-2015 were identified. Since colectomy for FCDC occurs on an emergency basis only, patients who had elective surgery were excluded. Furthermore, since FCDC implies severe systemic disease, patients who had an American Society of Anesthesiologist (ASA) score of 1 to 2 were excluded. Finally, patients who had evidence of concurrent procedures unrelated to a colectomy for FCDC as a primary surgery or who had segmental colonic resections were excluded. A breakdown of procedures performed is outlined in **Appendix 1.**

The validation cohort consisted of a previously published retrospective cohort of 124 patients with FCDC collected from four tertiary care hospitals in Québec, Canada from 1994-2007.[14]

Patients who underwent segmental colectomy were excluded from this dataset for comparison with the development cohort.

Outcome and predictors

The goal of the prediction model was to develop a calculator to evaluate the risk of 30-day postoperative mortality for patients with FCDC who are being considered for TAC. Predictors were considered for inclusion when they met all the following criteria: (1) significantly associated with postoperative mortality following TAC for FCDC in the literature; (2) were agreed upon by expert consensus at our institutions (colorectal surgeons, acute care general surgeons, and infectious disease specialists), and (3) were available in the derivation cohorts **(Table 1).**[4,7,8,10,15] As such, the seven chosen predictors of mortality were: patient age, immunosuppression status, preoperative ventilation, preoperative septic shock, and laboratory values including creatinine values and platelet and white blood cell (WBC) counts.

Immunosuppression was defined in the ACS-NSQIP database as administration of oral or parenteral corticosteroids or immunosuppressant medications within the 30 days prior to the principal operative procedure or at the time of evaluation for surgery. This variable was similarly defined in the validation cohort, but also included patients with hematological malignancies, organ transplantation, and human immunodeficiency virus infection. Preoperative shock was defined in the ACS-NSQIP database as the presence of systemic inflammatory response syndrome with an infectious source and evidence of end-organ damage. A composite outcome for shock was developed in the validation dataset to mirror the ACS-NSQIP definition and included evidence of end-organ damage with sepsis and/or hypovolemic shock and/or use of

vasopressors. Preoperative laboratory values were noted as the last available values before surgery in both the development and validation datasets, and thrombocytopenia was defined as platelet counts $<150 \times 10^9/L$.

Missing data

The missing data in both the development (17.4% preoperative WBC count, 0.3% preoperative platelet count) and validation (platelet count and preoperative ventilation) cohorts were handled via multiple imputations using Multivariate Imputation by Chained Equations (MICE) with default settings in R.[16-18] Five imputed datasets for each of the development and validation cohorts were analyzed.

Statistical Analysis Methods

In order to achieve the highest predictive accuracy, we assessed several functional forms (categorical, continuous or polynomial) for the seven *a priori* selected predictors in a logistic regression model. The model that led to the highest median Area Under the Receiver Operating Curve (AUC) from 200 bootstrapped samples of the development cohort was selected. We then trained this model on the five imputed development datasets and pooled the coefficients using the Barnard-Rubin adjusted degrees of freedom for small samples.[19]

This final chosen model from the development cohort was compared to the ACS-NSQIP probability score for mortality included in the database. This probability is based on a hierarchical logistic regression analysis using patient, surgery, and hospital-specific variables (21-30 variables), which can only be retrospectively attained by administrators and researchers,

thus limiting its use. Comparison between the developed prediction model and the ACS-NSQIP prediction of mortality was performed using DeLong's test for two correlated ROC curves to evaluate if there was a significant difference between the two models.

The developed prediction model was then assessed in each of the 5 imputed validation datasets for its ability to accurately predict the risk of postoperative mortality. The developed model's ability to predict mortality in this patient population was assessed using the AUC criterion. In the final step, the developed prediction model was converted to a clinically applicable bedside calculator and displayed in a web-based application. The risk calculator was developed and validated according to the TRIPOD checklist for prediction model development and validation.[20]

Proportions were compared using the chi-square or Fisher-exact tests, whenever appropriate, while continuous variables were compared using an unpaired *t* test or Wilcoxon rank sum test in the case of non-normality. The model was developed and validated with the help of an academic biostatistician to ensure a robust statistical methodology. All statistical analyses were performed using R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) and Stata (StataCorp.2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Development Cohort

After applying the inclusion and exclusion criteria, the development cohort included 581 patients **(Figure 1).** The 30-day postoperative mortality in this cohort was 40.6%. Compared to survivors, non-survivors were older, had a higher incidence of immunosuppression, thrombocytopenia, creatinine levels, as well as higher proportions of preoperative shock and ventilation **(Table 2).**

After internal validation with bootstrapping, the model with the highest AUC included both categorical variables (WBC, platelet counts, preoperative immunosuppression, preoperative ventilation) and second-degree polynomial variables (age, creatinine) in a predictive model with the following equation:

$$Probability\ of\ postoperative\ mortality = \frac{e^{lp}}{1 + e^{lp}}$$

with

$$\begin{aligned} &Linear\ predictor\ of\ postoperative\ mortality\ (lp) \\ &= 0.45 + 0.47\ Ventilation + 0.66 \times Shock \\ &+ 0.47 \times Immunosuppression - 0.98 \times No\ thrombocytopenia \\ &+ 0.44 \times WBC_{4-19.9\times\ ^{10^9}/_L} + 0.34\ \times\ WBC_{20-49.9\times\ ^{10^9}/_L} \\ &+ 3.41 \times\ WBC_{\geq 50\times\ ^{10^9}/_L} \times {}^{10^9}/_L + 0.72 \times Creatinine \\ &- 0.11 \times Creatinine^2 - 0.11 \times Age + 0.001 \times Age^2 \end{aligned}$$

Comparison of this model with the ACS-NSQIP mortality probability included in the database found no significant difference in the AUC for the two plotted ROC curves for each of the 5 imputed development cohorts as shown in **Figure 2A-E.**

Validation Cohort

Of the 130 patients included in the published validation cohort, 124 patients met the inclusion criteria. Postoperative mortality in the validation cohort was 37.9%. Although patients in the

development and validation cohorts were similar with regards to mean age, preoperative creatinine and 30-day postoperative mortality, there were several differences between available preoperative variables. Notably, the validation cohort had a higher proportion of patients with preoperative shock and immunosuppression **(Table 3).**

Using the mortality risk score developed from the ACS-NSQIP dataset to predict postoperative mortality in each of the 5 imputed validation datasets, the calculator had a good predictive capability with an AUC between 68.4 and 74.7% for the 5 imputed validation datasets **(Figure 3A-E).** Calibration and discrimination plots demonstrate moderate calibration and a good discriminative ability of the model (Appendix 2, 3).

Web-based calculator

To facilitate clinical point-of-care use of this risk prediction tool, a web-based calculator was developed and housed at the website: http://fcdcriskcalculator.com/. This website also has a visual representation of the probability of 30-day mortality and the confidence interval around the value. Furthermore, this web-based calculator provides graphical representation of mortality as a function of age, one of the strongest and most commonly available predictors of mortality for FCDC**. Table 4** presents 3 different clinical scenarios that highlight varying risks of mortality with different preoperative patient characteristics.

DISCUSSION

We developed a simple bedside prediction tool to predict postoperative mortality in patients with FCDC using a large prospectively maintained and validated surgical database. This tool was

externally validated using a published historical cohort. The developed calculator included 7 important patient and clinical factors (age, immunosuppression status, preoperative ventilation, preoperative shock, creatinine levels, and platelet and WBC counts), which accurately predicted the risk of 30-day postoperative mortality. The variables included in the calculator are readily available for all patients with CDI being evaluated for surgery facilitating its use at the time of surgical decision-making.

The important impact of CDI on outcomes of hospitalized patients has prompted several authors to publish scoring systems that risk-stratify patients by evaluating the risk of death or of a complicated course of CDI. However, these tools presented methodological limitations, lacked external validation, or were derived from small cohorts limiting their use in clinical practice. Sailhamer *et al.* described a bedside tool that predicts mortality based on three variables (age at least 70 years, need for cardiopulmonary support, and profound leukocytosis), which was developed from a retrospective review of 199 patients with FCDC, only 75 of whom underwent surgical intervention.[7] Another published tool, the Risk Scoring System (RSS), was developed to predict the development of FCDC (defined by the need for colectomy, ICU admission, or death due to CDI) for all patients with CDI from a prospective registry where only 48 (6.4%) developed FCDC.[21] The two latter scores are examples of simple clinical bedside calculators whose applicability for prediction of postoperative mortality was limited by lack of external validation, derivation from a small sample size of patients with FCDC, and with limited generalizability to postoperative mortality. The calculator that was developed in the present study, however, includes some of the predictors of mortality that were highlighted by these scoring systems and provides an individualized risk of post-operative mortality for varying

preoperative patient characteristics. Recently, Kulayat *et al*[22] applied various components of the *C difficile*-associated risk of death score (CARDS) to patients with FCDC from the ACS-NSQIP database to describe the sCARDS score, predicting postoperative mortality for patients with FCDC. The CARDS score was developed from the Nationwide Inpatient Sample but due to the lack of granular patient-level data, it relied on ICD-9 codes to define patient comorbidities and the need for intensive care/critical care admission. An important difference between our risk calculator and the sCARDS score is the presence of important laboratory values that were shown to be predictors of mortality in the literature.[7,8,10,14,15] The study by Kulyat *et al*[22] is based on categorical patient characteristics and co-morbidities, which are known static variables that impact outcomes of CDI.[23,24] Thus, despite the novelty of the work by Kulayat et al, a striking difference is that our calculator captures both important patient characteristics that are strong predictors of outcomes of colectomy for FCDC as well as key time-sensitive markers of worsened CDI severity that can help guide clinicians with decision-making as patients' clinical status changes. Furthermore, contrary to the sCARDS score that was adapted from a score developed in all patients with CDI and has not been externally validated, we developed and externally validated our score in patients with FCDC who underwent emergency surgery.

Timing of surgery is crucial in the management of patients with FCDC. Many authors have stressed the importance of early surgical intervention, before the development of multi-organ system failure, in an effort to decrease the high mortality associated with surgery in this setting.[8,9,12,13,25] As demonstrated by the literature pleading for early surgical intervention but the lack of guidelines to indicate exact timing of surgery, the decision of determining when to intervene remains a difficult consideration. In the absence of the rare but clear indications for

surgical intervention such as colonic perforation, ischemia, or abdominal compartment syndrome, surgeons may have different thresholds of when to operate. Currently no universally accepted clinical prediction tool exits to guide preoperative decision-making in the setting of FCDC, and as such surgeons may have different thresholds of when to operate. Thus, the developed calculator may be beneficial in the care-plan of patients with CDI in two important ways. First, it provides surgeons with a practical tool that can be used to assess individual risk of postoperative mortality at different stages in the progression of disease. Indeed, its ability to assess the change in risk of postoperative mortality with changing time-sensitive variables such as laboratory variables, worsening renal failure, shock, or the need for mechanical ventilation may be used as an adjunct to guide surgeons' recommendations to patients. Second, surgeons may use this tool to guide consent discussions with patients and their families regarding the likely outcome of surgical intervention. Given the heterogeneity of patients who undergo surgery for FCDC with their attendant high risk of postoperative mortality in this emergent setting, presenting patients with an individualized probability of postoperative mortality is important. This calculator will provide a framework on which to base discussions with patients and their families and help achieve a shared decision-making approach in these high stakes decisions.[26] For example, in certain cases this calculator may highlight the futility of a TAC in a more tangible and visual way, allowing patients and families to choose a more conservative treatment option. This calculator will place discussions of mortality at the center of the consent and decision-making process, emphasizing its importance in guiding patient-care.

The strengths of this calculator lie in its development from a large multi-institutional prospectively collected surgical database that has been validated and undergoes continuous

auditing and quality control. The calculator was developed from the largest available cohort of patients with FCDC who underwent surgical management from which important laboratory and clinical information was collected that was lacking in previously used administrative databases used to look at predictors of mortality.[4] The dichotomous endpoint of mortality has a low probability of observational bias, resulting in a hard measurable clinically important outcome for the calculator. Rigorous statistical methodology was used to derive the prediction tool from all participating ACS-NSQIP hospitals (not limited to community or specialized centers) and was validated in a cohort of patients who had a TAC during a time span that included an epidemic of the NAP-1 hypervirulent strain in Québec (which started in 2002), attesting to its generalizability.[14] The NAP-1 strain was associated with a significant increase in mortality and need for a colectomy due to the associated severity of disease evolution.[27,28] Work by Van Beurden *et al*[29] highlighted the important impact of *C. difficile* strain on the generalizability of prediction models in FCDC. The authors demonstrated that one of the three models they validated performed well when restricted to non-outbreak settings, however when they were not limited to an outbreak, the three models performed poorly. As the strain of *C. difficile* is not readily available in the clinical testing, nor used in day-to-day decision-making, its absence from the calculator is one of the strengths of this tool as it has proven to be predictive in both epidemic and non-epidemic settings, irrespective of strain.

An additional strength of this calculator lies is its ability to accurately predict postoperative mortality using easily collected clinical variables available at the bedside. Compared to the ACS-NSQIP probability of mortality included in the database that is derived from a hierarchical regression model with more than 20 preoperative variables only available retrospectively to

researchers and administrators, there was no difference in our model's ability to predict postoperative mortality with 7 simple and easily attained clinical variables. In order to facilitate point of care access to this information, we have created a web-based application of the calculator (http://fcdcriskcalculator.com/).

Despite its clinical relevance and importance, this calculator must be evaluated in view of some of its limitations. Although the ACS-NSQIP database is populated by trained clinical reviewers, it is at risk for miscoding and missing variables. Similarly, the validation cohort, not initially intended for validation purposes, was limited by its retrospective nature and by the absence of two variables (preoperative ventilation and platelet count). Multiple imputations were used to account for these missing variables, another limitation of the validation cohort. Although patients in the development and validation cohort were similar in terms of preoperative demographics and clinical factors, there were some differences between the two cohorts. Specifically, the validation cohort had a higher proportion of immunosuppressed patients, probably since the cohort was derived from three tertiary care centers with specialized expertise in cancer treatment and transplantation, and the definition for immunosuppression was wider in the validation cohort. Furthermore, the development cohort did not contain information on daily variation in laboratory values, granular information on patient's prior history with CDI, or information on timing from development of symptoms to FCDC. Thus, a potential association between these factors and the risk of postoperative mortality could not be evaluated. The most important limitation of the present study is its inability to define a threshold at which TAC offers a survival advantage despite the risk of postoperative mortality. The benefit of TAC compared to continued medical management alone in patients with FCDC was demonstrated in a systematic review on

this topic.[30] We were unable to define a threshold or show superiority of surgery compared to medical management alone since the database used to develop the cohort was surgical and information on patients with FCDC who did not undergo surgical intervention is not available. Furthermore, the exact threshold to operate cannot be developed with the dataset used to create our risk calculator, and this would best be determined by means of a multi-institutional prospective study. In addition, it is unclear whether this calculator has the same prediction capability for patients undergoing minimally invasive options for FCDC such as loop ileostomy and colonic lavage.[31] Validation of this calculator for prediction of postoperative mortality with different operative interventions may play an important role in determining the optimal type and timing of surgical intervention at different time points in the progression of the disease. The availability of time-sensitive parameters in the calculator will allow for future research to better define optimal operative thresholds.

CONCLUSION

In conclusion, a clinically applicable bedside calculator for prediction of 30-day postoperative mortality was developed and validated. This calculator may guide preoperative decision making for patients with FCDC and thus become an important adjunct in the management plan for these patients. Given the importance of patient and family involvement in this critical decision-making of these high-stakes surgeries, this calculator will be a useful tool to guide these discussions. Future validation of this calculator in different settings may better characterize operative thresholds and optimal type of surgical interventions.

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Legend of Figures and Tables

Figure 1: Patient flowchart for development cohort

Figure 2A-E: Comparison of AUC between the developed model and the ACS-NSQIP probability of mortality included in the ACS-NSQIP database for each of the 5 imputed datasets

Figure 3A-E: Receiver Operating Curve of the developed model for each of the 5 imputed validation datasets

Appendix 1: CPT codes

Appendix 2: Calibration plots for each of the five imputed validation sets

Appendix 3: Discrimination plots for each of the five imputed validation sets

Table 1- Predictors of mortality for fulminant *Clostridium difficile* colitis in the literature

Table 2- Comparison between survivors and non-survivors in the development cohort from the ACS-NSQIP database

Table 3 – Comparison between development and validation cohorts

Table 4- Probability of mortality using developed calculator in three different clinical settings

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Figure 1- Patient flowchart for the development cohort

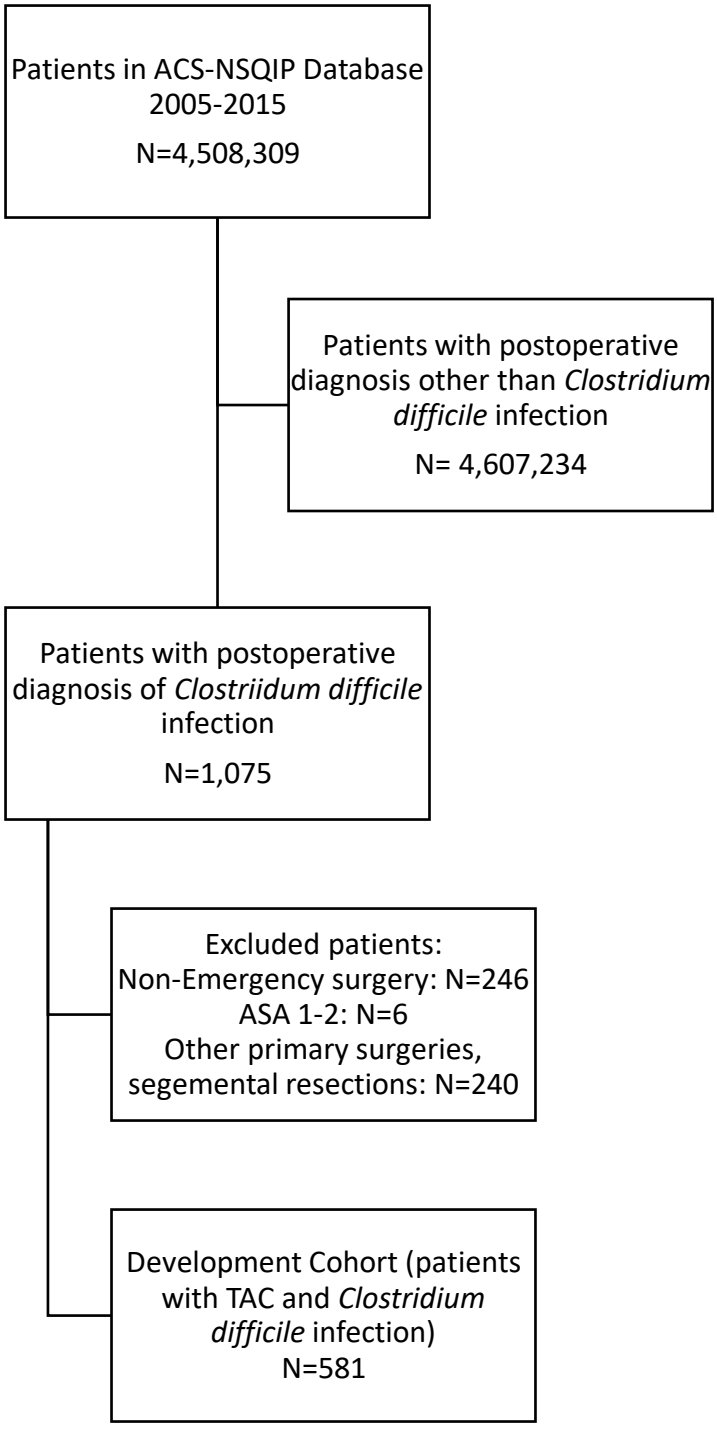

Figure 2. A-E, Comparison of AUC between the developed model and the ACS-NSQIP probability of mortality included in the ACS-NSQIP database for each of the five imputed data sets.

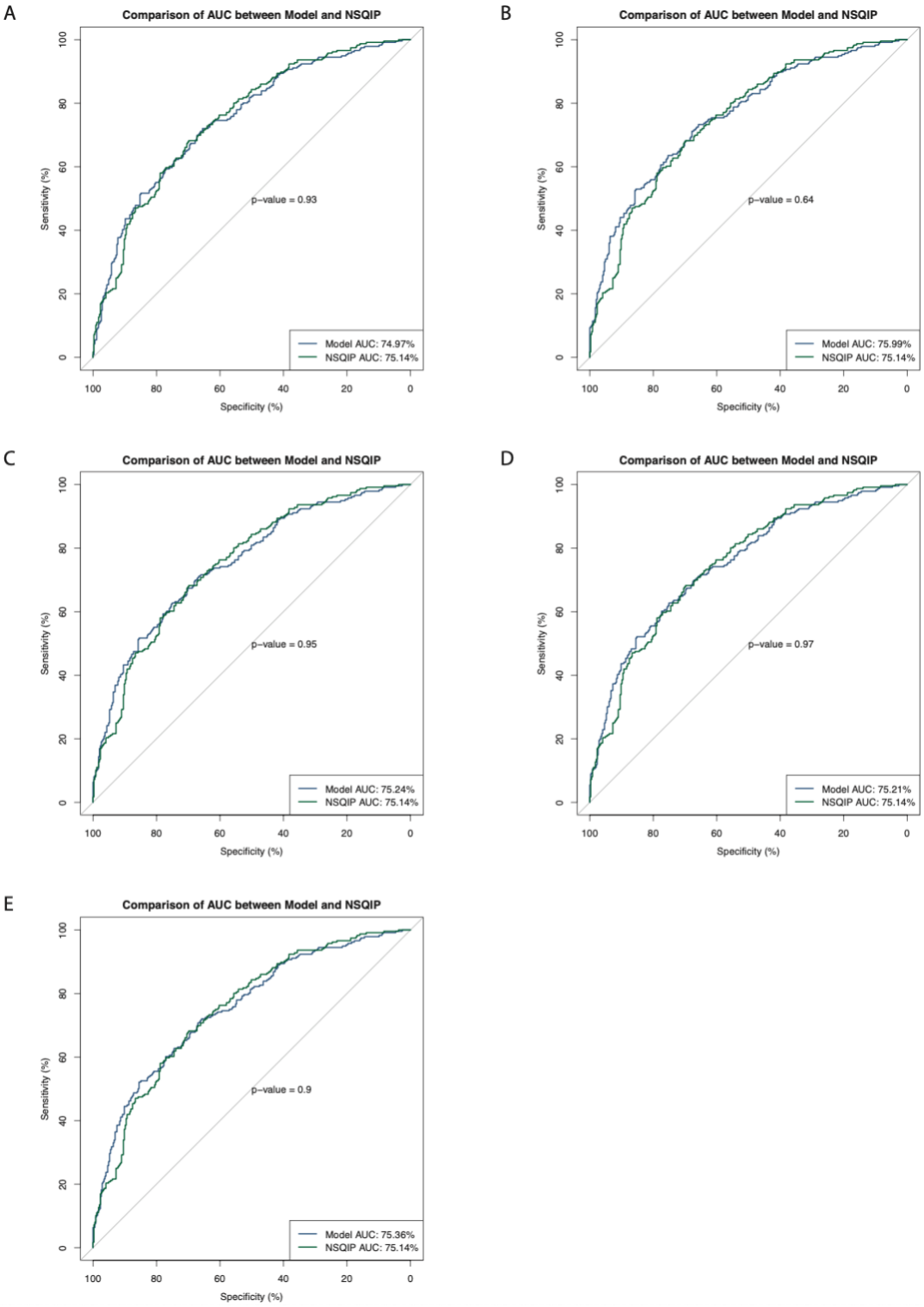

Figure 3. A-E, Receiver operating curve of the developed model for each of the five imputed validation data sets

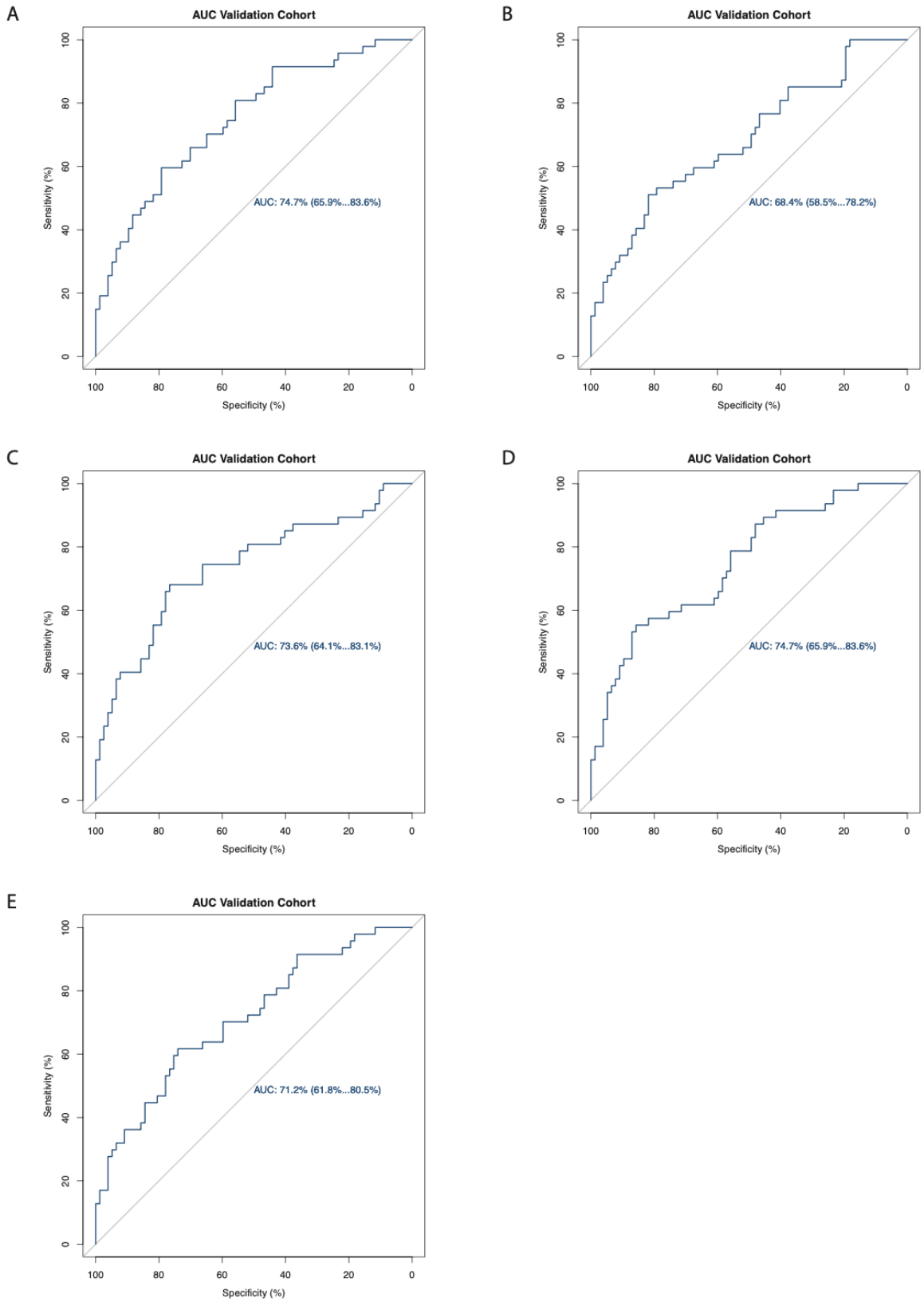

Table 1- Predictors of mortality for fulminant Clostridium difficile colitis in the literature

Study	**Design**	**Setting**	**Predictors**
Lee *et al*, 2014[10]	Retrospective review of prospectively maintained database (ACS-NSQIP)	Multicentric North-American surgical database N=335 surgical interventions for FCDC n=252 (total abdominal colectomies)	Age≥80, preoperative septic shock, preoperative severe COPD, preoperative dialysis dependence, preoperative cardiac arrest, wound classification (contaminated), preoperative thrombocytopenia, preoperative INR>2, preoperative BUN (mg/dL)>40
Halabi *et al.* 2013[4]	Retrospective review of prospectively maintained database (NIS)	Multicentric data, USA N=19,374 colectomies	Age>66, coagulopathy, ARF, respiratory failure, sepsis, peripheral vascular disease, congestive heart failure
Markelov *et al.*, 2011[15]	Retrospective chart review	Easton Hospital, Pennsylvania, USA N=13 (total abdominal colectomies)	WBC>34, Hypoalbuminemia, Septic Shock, Respiratory failure
Sailhamer *et al.*, 2009[7]	Retrospective chart review	Massachusetts General Hospital, USA N=199 (FCDC) n=69 (total abdominal colectomies)	Age≥70, WBC≥35,000, neutrophil bands ≥10%, WBC<4,000, preoperative vasopressors, preoperative intubation, absence of oral vancomycin
Lamontagne *et al.*, 2007[8]	Retrospective chart review	Hôpital Maisonneuve-Rosemont and Centre Hospitalier Universitaire de Sherbrooke, Québec, Canada N=165 (FCDC) N=38 (colectomies)	Age>75, immunosuppression, vasopressor use, lactate≥5, WBC≥50

FCDC= Fulminant *Clostridium difficile* colitis; COPD= Chronic Obstructive Pulmonary Disease; INR= International Normalized Ratio; BUN=Blood Urea Nitrogen; ARF= Acute renal failure; WBC=White Blood Cell

Table 2- Comparison between survivors and non-survivors in the development cohort from the ACS-NSQIP database

Preoperative patient characteristics		**Survivors (N=345)**	**Non-Survivors (N=236)**	***P* value**
Age, mean (SD)		66.4 (14.1)	71.2 (14.0)	**<0.001**
Male sex, n (%)		147 (42.6)	120 (50.8)	0.05
Hypertension, n (%)		227 (65.8)	159 (67.4)	0.69
Diabetes, n (%)		86 (24.9)	58 (24.6)	0.92
Immunosuppression, n (%)		46 (13.3)	49 (20.8)	**0.017**
Smoking, n (%)		63 (18.3)	45 (19.1)	0.81
Independent functional status, n (%)		175 (51.3)	130 (56.0)	0.27
BMI, mean (SD)		28.1 (8.2)	27.6 (7.0)	0.49
ASA	3-Severe Disturbance	83 (24.1)	22 (9.3)	**<0.001**
	4-Life Threatening	217 (63.1)	151 (64.0)	
	5-Moribund	44 (12.8)	63 (26.7)	
Preoperative white blood cell count (x10^3), mean (SD)		25.01 (15.67)	29.47 (20.40)	**0.003**
Thrombocytopenia (x10^3umol/L), n (%)		62 (18.0)	85 (36.2)	**<0.001**
Preoperative serum creatinine (mg/dL), median (IQR)		1.67 (0.9, 2.7)	2.1 (1.3, 3.1)	**<0.001**
Preoperative shock, n (%)		184 (53.3)	178 (75.4)	**<0.001**
Preoperative intubation, n (%)		102 (29.6)	108 (45.8)	**<0.001**

BMI: Body Mass Index
ASA: American Society of Anesthesiologists score

Table 3 – Comparison between development and validation cohorts

Variable	**Development Cohort (N=581)**	**Validation Cohort (N=124)**	***p*-value**
Age, mean (SD)	68.3 (14.2)	67.1 (15.1)	0.38
Immunosuppression, n (%)	95 (16.4)	45 (36.3)	**<0.001**
Preoperative white blood cell count, mean (SD)	26.76 (17.79)	28.44 (24.06)	0.82
Preoperative Creatinine, mean (SD)	2.2 (1.6)	2.0 (1.4)	0.15
Preoperative Shock, n (%)	362 (62.3)	98 (79.0)	**<0.001**
Preoperative intubation, n (%)	210 (36.1)	N/A	-
Preoperative thrombocytopenia, n (%)	147 (25.4)	N/A	-
30-day postoperative mortality, n (%)	236 (40.6)	47 (37.9)	0.58

Table 4- Probability of mortality using developed calculator in three different clinical settings

	Patient 1	**Patient 2**	**Patient 3**
Age	50	75	86
Immunosuppression	Yes	No	No
Preoperative intubation	No	No	Yes
Septic Shock	No	Yes	Yes
White blood cell count ($x10^9$/L)	30	19	40
Creatinine level (mg/dL)	1.5	3.5	2.5
Probability of mortality, % (95%CI)	15.5(9.8-29.2)	44.4 (31.9-57.8)	85.2 (75.8-91.4)

CHAPTER 3: LONG-TERM OUTCOMES AFTER SURGERY FOR FULMINANT CLOSTRIDIOIDES DIFFICILE COLITIS: A PREAMBLE

In the previous chapter, I developed a calculator that predicts postoperative mortality after total abdominal colectomy (TAC) for fulminant *C. difficile* colitis (FCDC). This calculator was developed in a prospectively maintained surgical database and externally validated using a published cohort of patients who underwent TAC. The simple prediction tool can be used at the bedside and includes seven important patient and clinical predictors which are readily obtained for patients with FCDC: age, immunosuppression status, preoperative ventilation, preoperative shock, creatinine levels, and platelet and white blood cell counts.

Other outcome measures are important to consider beyond 30-day postoperative mortality when considering outcomes after surgery. These include mortality beyond the index admission and markers of longer-term recovery. It is especially important to assess recovery in conditions like FCDC were there is the potential for multi-system organ failure and long-term disability.

In the setting of FCDC, diverting loop ileostomy with colonic lavage (DLI) has been advocated as an alternative to TAC. While contradictory data exists on its potential to decrease 30-day postoperative mortality, no study has looked at outcomes beyond the index admission[59,60]. Furthermore, limited data exist with regards to the rate of gastrointestinal restoration after surgery for *C difficile* using this novel approach. Thus, given the limited data available with regards to post-discharge outcomes, I sought to describe outcomes beyond the index admission.

I queried the Nationwide readmission database developed by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project. This is an American database with a nationally representative sample. A unique feature of this dataset is the ability to link readmissions during a calendar year within the state and using the same patient identifier, making it an ideal database to study post-discharge outcomes.

CHAPTER 4: DIVETING LOOP ILEOSTOMY VERSUS TOTAL ABDOMINAL COLECTOMY FOR CLOSTRIDIOIDES DIFFICILE COLITIS: OUTCOMES BEYOND THE INDEX ADMISSION

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Abstract

Introduction: Diverting loop ileostomy (DLI) and colonic lavage has emerged as a valid alternative to total abdominal colectomy (TAC) for the surgical management of Clostridium difficile colitis (CDC). However, little data is available on outcomes beyond the index admission. The objective of this study was to compare post-discharge outcomes between patients who underwent DLI and TAC for CDC.

Methods: Adult patients who underwent DLI or TAC for CDC between 2011-2016 were identified from the Nationwide Readmissions Database, and only discharges between January and September in each calendar year were included to allow for a 90-day follow-up period for all cases. Ninety-day overall in-hospital mortality (index admission mortality plus 90-day post-discharge mortality) and 90-day unplanned readmissions were compared. To assess 6-month ileostomy reversal rates, the cohort was then truncated to exclude discharges after July in each calendar year. Multivariate regression was used to adjust for patient demographics and disease severity.

Results: In total, 2,070 patients were discharged between January and September of each included year: 1,486 (71.8%) TAC compared to 584 (28.2%) DLI. Overall in-hospital mortality was higher among patients who underwent TAC (34.5% vs. 27.7%, p=0.004); however, this association did not remain on multivariate regression (OR: 1.14, 95% CI 0.91-1.43). Among the 1,434 patients who were discharged alive, the 90-day unplanned readmission rate was similar in both groups (TAC: 26.1% vs. DLI: 23.1%, p=0.26). After truncating the cohort to those patients discharged alive between January and June of each included year (n=1,016), patients who underwent DLI had a significantly greater 6-month ileostomy reversal rate (26.4% vs. 8.3%,

p<0.001). DLI was independently associated with higher odds of 6-month ileostomy reversal (OR: 2.68, 95% CI 1.80-4.00).

Conclusions: In the surgical management of CDC, DLI is associated with equivalent mortality and unplanned readmission, but greater likelihood of 6-month ileostomy reversal, compared to TAC.

Introduction:

Clostridioides difficile colitis is an important cause of nosocomial and community acquired infections (1). While the majority of patients have a mild disease course, a small subset of patients progress to fulminant disease characterized by severe colitis with end-organ damage and the need for operative intervention (2). Total abdominal colectomy (TAC) is the standard operation for patients with fulminant *C. difficile* colitis (FCDC) who fail medical management alone (3, 4). Despite its survival advantage compared to non-operative management, TAC is associated with a high postoperative mortality (5-7). Furthermore, patients often have a long path to recovery after colectomy, and the majority of patients do not become fit enough to be candidates for a second elective operation to restore intestinal continuity (6).

The description by Neal *et al* of a diverting loop ileostomy (DLI) and colonic lavage for FCDC in 2011 has gained interest in the surgical community (8). DLI was brought forth as a less invasive option with a potential survival advantage compared to TAC in the emergency setting (8). However, since its description, limited data are available comparing the two surgical interventions (9-12). Furthermore, the literature focuses almost exclusively on outcomes limited to the index admission, such as postoperative mortality and morbidity. No study has adequately described the course of patients who survived their index episode, especially with regards to post-discharge survival, hospital readmission and ileostomy closure. As patients with a DLI still have their diseased colon in situ, they may be at higher risk for treatment failure and post-discharge morbidity. Conversely, this heightened risk may be offset by a higher likelihood of gastrointestinal (GI) restoration, as DLI closure is a far less morbid operation than a takedown of an end ileostomy with an ileorectal anastomosis (13-16).

The objective of this study was to compare readmission rates, overall mortality beyond the index admission, and ileostomy closure rates between patients who underwent TAC or DLI for FCDC.

Methods:

Data source

After exemption from Institutional Review Board approval, we queried the American based Nationwide Readmissions Database (NRD), one of the largest discharge databases developed by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project (HCUP) in the United States. The NRD, similar to the National Inpatient Sample, is a nationally representative discharge database that includes information on diagnostic and procedure codes, demographic characteristics, hospital characteristics, and outcomes. It includes data from approximately 17 million discharges each year, for all payers and the uninsured. A unique feature of NRD is that it can link patient admissions, across a calendar year and within the same state, using unique patient identifiers. Thus, NRD is an ideal administrative database to study post-discharge outcomes.

Patient Population

This study included all adult (≥18 years-old) patients who underwent TAC or DLI for FCDC from 2011 to 2016. All admissions with a diagnosis of *C. difficile* colitis and a relevant procedure code for TAC or DLI were identified. Similar to previous work by Juo *et al,* patients were further included if: 1) the primary diagnostic code was *C. difficile* colitis; or 2) the secondary diagnostic code was *C. difficile* colitis, in the absence of any other colorectal diagnosis or procedure **(Figure 1) (11)**. This method ensured that cases of TAC or DLI performed for other

diagnoses, where *C. difficile* infection represented a benign postoperative complication rather than the indication for surgery, were excluded. Eligible admissions with a procedure code for both a TAC and DLI were considered to have undergone a TAC. All relevant ICD-9 and ICD-10 diagnostic and procedure codes used to generate the final cohort are listed in **Appendix 1**.

Outcomes

The primary outcomes of interest were the incidence of 90-day unplanned readmission, overall in-hospital mortality, and 6-month ileostomy closure. Ninety-day unplanned readmission was defined as a hospital readmission for any reason that occurred within 90 days of hospital discharge from the index admission. Overall in-hospital mortality was defined as all-cause mortality that occurred either on the index admission or during any readmission that occurred within 90 days of discharge. Ileostomy closure was defined as a procedure for GI restoration **(Appendix 1)**.

As admissions are only linked for a single calendar year, the data was truncated to allow for a similar follow-up length in each patient. For 90-day outcomes (readmission and overall in-hospital mortality), data was truncated to exclude discharges that occurred after September 30th of each calendar year. Similarly, when evaluating 6-month ileostomy closure, the data was further truncated to exclude discharges that occurred after June 30th of each calendar year.

Variable Definitions

Patient demographics, hospital characteristics, and disease severity were characterized using a variety of variables available in the NRD database. Insurance type was grouped as Medicare/Medicaid, private, or other. Hospital status was categorized as teaching or non-teaching. All Payer Refined Diagnostic Related Groups (APR DRG) risk of mortality was defined as the likelihood of dying during the admission, and APR DRG severity of illness as the

extent of physiologic decompensation or organ system loss of function; both were classified as minor, moderate, major, or extreme. These measures provide a validated and widely used substitute to physiologic scoring systems which are absent in administrative datasets (17-20). They have been demonstrated to be accurate measures of perioperative moratlity risk prediction amongst surgical patients(20). Chronic steroid use, septic shock, and acute renal failure were based on appropriate ICD-9 and ICD-10 codes **(Appendix 1)**.

Data Analysis

Data on patient demographics, hospital characteristics, and disease severity were presented as means with standard deviations, medians with interquartile ranges (Q1 – Q3), or frequencies with proportions, where appropriate. Baseline characteristics were compared between patients who underwent TAC and DLI. Multiple logistic regression models were performed for 90-day readmission, overall in-hospital mortality, and 6-month ileostomy closure, to evaluate for the association between each outcome and the procedure performed. Each model adjusted for the following covariates: age, sex, chronic steroid use, insurance status, hospital status, APR DRG risk of mortality, sepsis, and acute renal failure. In the models generated for overall in-hospital mortality and 6-month ileostomy closure, discharge disposition was also included as a covariate. An alpha=0.05 was set for statistical significance. All statistical analyses were performed with R v3.5.1 (R Development Core Team. 2017. *R: A Language and Environment for Statistical Computing*. Vienna, Austria).

Results:

Of 2,787 potentially eligible patients who underwent TAC or DLI for FCDC between 2011 and 2016, 2,070 were discharged or died between January 1st and September 30th of each

included calendar year. Patients who were excluded because of a discharge date in the months of October to December (n=717) were similar to included patients on all baseline characteristics, including the proportion of patients who underwent DLI **(Supplemental Table 1)**. Of those included, 1,486 (71.8%) underwent a TAC and 584 (28.2%) underwent a DLI. Patients who underwent TAC were similar to patients who underwent DLI with respect to median age (69.0 (59.0-78.0) vs. 69.0 (60.0-78.0) years, p=0.61) and sex (male: 42.7% vs. 43.8%, p=0.55). Patients who underwent TAC were more likely to have Medicare/Medicaid insurance (80.1% vs. 75.0%, p=0.0072). Patients who had a TAC had a higher proportion of patients with class 4 ("extreme") APR DRG risk of mortality (77.4% vs. 65.6%, p<0.001) and severity of illness (84.7% vs. 74.5%, p<0.001), however, chronic steroid use (2.2% vs. 2.2%, p=0.99), septic shock (72.5% vs. 73.4%, p=0.71), and acute renal failure (64.1% vs. 63.0%, p=0.67) were similar in both groups **(Table 1)**.

Among the 1,434 patients who were discharged alive, the 90-day unplanned readmission rate was similar in both groups (TAC: 26.1% vs. DLI: 23.1%, p=0.26). On multiple logistic regression, DLI was not associated with increased risk of readmission (OR: 0.85, 95% CI 0.65-1.12) **(Table 2)**. Younger age (OR: 0.98, 95% CI 0.97-0.99) and teaching hospital status (OR: 1.62, 95% 1.25-2.11) were the only factors independently associated with 90-day unplanned readmission.

Index admission postoperative mortality was lower for patients who underwent DLI compared to patients who underwent TAC (25.9% vs. 32.3%, p<0.001). The 90-day post-discharge all-cause mortality was similar by procedure (TAC 2.4% vs. DLI 2.1%, p=0.85). When combined with index admission mortality, overall in-hospital mortality was greater among patients who underwent TAC (34.5% vs. 27.7%, p=0.004). However, this association did not

remain on multiple logistic regression after adjusting for relevant confounders (OR: 1.14, 95% CI 0.91-1.43) **(Table 3)**. Older age (OR: 1.02, 95% CI 1.01-1.02) and class 4 ("extreme") APR DRG risk of mortality (OR: 7.25, 95% CI 5.25-10.28) were independently associated with increased odds of overall in-hospital mortality.

After further truncating the cohort to those patients discharged alive between January 1st and June 30th of each included calendar year (n=1,016), patients who underwent DLI had a higher 6-month ileostomy closure rate compared to those who underwent TAC (26.4% vs. 8.3%, $p<0.001$). Patients who underwent DLI also had a shorter median time-to-reversal (97.5 (70.0-140.8) vs. 121.0 (90.8-154.0) days, $p=0.028$). On multiple logistic regression, DLI was independently associated with higher odds of 6-month ileostomy reversal (OR: 2.68, 95% CI 1.80-4.00) **(Table 4)**. Private insurance status was also associated with increased odds of ileostomy closure (OR: 1.96, 95% CI 1.21-3.17).

Discussion:

In the largest cohort of patients with DLI for FCDC to date with longitudinal post-discharge information, DLI was associated with similar 90-day readmission rates and overall in-hospital mortality. Patients who had a DLI had significantly greater GI restoration rates 6 months postoperatively, and had earlier time to ileostomy closure compared patients who had a TAC.

Limited data exist on the role of DLI for the treatment of FCDC, especially with regards to outcomes beyond the initial hospitalization. A recent study exploring national trends for the surgical management of FCDC in the United States using NIS data (2011-2015) demonstrated increasing use of DLI, and equivalent postoperative mortality (11). However, NIS is limited to a single admission, and thus post-discharge outcomes were not reported. In their landmark

publication describing DLI as an alternative to TAC, Neal *et al* compared 42 patients with DLI performed at a single institution by a single surgeon to historical controls. The authors showed a decreased risk of 30-day postoperative mortality – with limited information on post-discharge morbidity or mortality. With regards to readmissions after DLI, Hall *et al* showed that 30-day readmissions were similar for both procedures (8.5% vs. 13.1%, p=0.489) (10). However, this study was again limited by the small sample size – with only 30 of 47 patients surviving discharge at 30 days – and the absence of readmission information beyond 30-days. Given it may take months for patients to recover fully after surgery for FCDC, outcomes beyond 30-days postoperatively are important in order to have a full picture of the true morbidity of DLI. As patients with DLI have the potential for recurrence with the diseased colon still in place, information on recurrence and readmissions after discharge is important when comparing the two procedures. For this reason, the finding of this study that 90-day readmission rates are similar between the two procedures is important, and adds significant knowledge to the post-discharge course of patients with FCDC. This study demonstrates that there is no added morbidity beyond the initial admission by performing this less invasive operation.

Along the same lines, the question of mortality beyond the initial admission with regards to this less invasive operation in patients with a life-threatening illness is important to address. To date, no data exist on mortality beyond the index procedure. A recent multi-institutional retrospective review of 21 patients with DLI compared to 77 patients with TAC demonstrated a decreased overall 30-day postoperative mortality on adjusted analysis for DLI (17.2% vs. 39.7%, p=0.002) (9). Although this was an adjusted analysis, it is not clear what confounders were included to risk-adjust this outcome. Findings of decreased 30-day postoperative mortality have not been replicated using large databases. In a review of a prospectively maintained surgical

database from the American College of Surgeons National Surgical Quality Improvement Program database, postoperative mortality was comparable for both procedures on unadjusted analysis (36% DLI vs. 31% TAC, p=0.45) (10). Similarly, evaluation of both procedures using the NIS database demonstrated comparable postoperative mortality after adjusting for potential confounders (OR 1.19; 95%CI [0.88 -1.61]) (11). This current paper demonstrates that there is no increase in the post-discharge in-hospital mortality after 90-days for patients undergoing DLI compared to TAC. This novel description of similar overall in-hospital mortality after DLI, despite the theoretical risk of complications arising from a diseased colon left in-situ, further validates DLI as an alternative option for the treatment of FCDC.

To date, the only information available on ileostomy closure after DLI come from a small series of 19 surviving patients, where the reported ileostomy closure rate was 79% (8). While takedown of an end ileostomy with an ileorectal anastomosis after TAC is a more challenging operation compared to closure of a loop ileostomy, there is no modern data on rates of GI restoration for patients post TAC (21). Even though the discussion often occurs in an emergency situation, information on ileostomy closure rates is an important aspect of the consent process with the patient. In the present study, rates of GI restoration in the first months after TAC were low (8.3%), and DLI was associated with over 2.5 fold increase in the odds of ileostomy reversal. Patients who underwent DLI also had a shorter median time-to-reversal compared to TAC (97.5 (70.0-140.8) vs. 121.0 (90.8-154.0) days, p=0.028). Based on this data, one might infer that patients who underwent DLI recovered quicker after their initial operation, allowing for an earlier ileostomy reversal. Nonetheless, it is clear from this data that DLI offers a significant advantage over TAC with regards to rates of GI restoration.

The major strength of this paper is the longitudinal follow-up of a large number of patients who underwent DLI for FCDC. Given the rarity of this surgical disease with a constantly changing epidemiology, a prospective trial on the use of DLI remains challenging (22, 23). Longitudinal data retrieved from linking patients across different databases is ideal for describing trends in ileostomy closure and other important outcomes post-discharge, such as morbidity, readmissions, and mortality. This makes the NRD an ideal dataset to explore these outcomes for a rare entity such as FCDC. Stringent inclusion and exclusion criteria were used to identify patients who underwent TAC or DLI for FCDC and avoid including patients who had these surgeries for reasons other than *C. difficile*. Although the outcome of overall in-hospital mortality is not described in other studies and is thus not comparable with other publications on FCDC, it is a clinically important outcome. Anecdotally, a non-trivial number of patients who survive the index admission of FCDC die in the short-term period after discharge, which can certainly be ascribed to the gravity of the initial insult from this severe disease. This post-discharge data can help guide consent discussions between physicians and patients in these high-risk procedures.

Despite its strengths, this study has several limitations which should be considered. One limitation of this work is the retrospective review of this administrative database with the absence of certain clinical and laboratory values. Large administrative databases such as this one rely on coding and are at risk for misclassification errors. Furthermore, the absence of specific ICD-9 or ICD-10 code to specifically indicate a DLI as well as missing procedural dates did not allow us to identify which patients failed DLI and required a subsequent TAC. Patients were counted as having a TAC if they had codes for both a TAC and any form of ileostomy. This grouping was made with the assumption that patients who had both a TAC and an ileostomy had

an *end* ileostomy. The cohort definitions used to define the two surgical groups are similar to those used by Juo et. al, and present a conservative methodology to define the two surgical groups (11). Another limitation is the potential for loss of follow up, as admissions can only be linked within the same state and within the same calendar year. However, patients are unlikely to be readmitted within 90-days to a hospital in another state, especially given the severity of their initial illness. To mitigate the issue of calendar year, the cohort was truncated for each outcome to allow for an equivalent follow-up length and an equal risk potential in each patient. While patients discharged in later months were excluded, they were not systematically different from those included. Furthermore, this work is limited by its inability to accurately investigate *C. difficile* recurrence rates among patients who underwent DLI, especially after ileostomy closure, as a secondary diagnostic code for *C. difficile* could be referencing the patient's personal history of disease rather than a true recurrent infection. This would be an important outcome to study because of the potential role of *C. difficile* prophylaxis in this subgroup of patients (24).

Conclusion:

This is the largest study to assess post-discharge outcomes after DLI or TAC for FCDC, including rates of GI restoration. This study adds significant new information to the limited data on this rare surgical indication, which can be used in the consent process with patients and their family members. DLI should be considered for select patients in the appropriate clinical setting, given its potential for increased gastrointestinal restoration without added post-discharge morbidity.

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Table 1: Comparison of patients who underwent total abdominal colectomy versus diverting loop ileostomy for *Clostridioides difficile* colitis, and who had a minimum follow-up of 90 days

Table 2: Multiple logistic regression model for 90-day unplanned readmission

Table 3: Multiple logistic regression model for overall in-hospital mortality

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Figure 1: Cohort inclusion criteria to identify patients who underwent diverting loop ileostomy or total abdominal colectomy for *Clostridioides difficile* colitis

Supplemental Table 1: Comparison of patients who were excluded for having a discharge date from October to December of each calendar year to those who were included

Appendix 1: List of ICD-9 and ICD-10 codes used to generate exposure, outcomes, and relevant covariates

Table 1 – Comparison of patients who underwent total abdominal colectomy versus diverting loop ileostomy for *Clostridioides difficile* colitis, and who had a minimum follow-up of 90 days

Characteristic	**Total Abdominal Colectomy n=1,486**	**Diverting Loop Ileostomy n=584**	***p***
Age, years, median, (Q1-Q3)	69.0 (59.0-78.0)	69.0 (60.0-78.0)	0.61
Male sex, n (%)	628 (42.7)	256 (43.8)	0.55
Chronic steroid use, n (%)	33 (2.2)	13 (2.2)	0.99
Insurance type, n (%)	-	-	0.0072
Medicare / Medicaid	1,190 (80.1)	438 (75.0)	-
Private	235 (15.8)	126 (21.6)	-
Other	61 (4.1)	20 (3.4)	-
Teaching hospital, n (%)	940 (63.3)	373 (63.9)	0.83
APR DRG risk of mortality, n (%)	-	-	<0.001
Extreme	1,150 (77.4)	383 (65.6)	-
Major	220 (14.8)	117 (20.0)	-
Moderate	82 (5.5)	57 (9.8)	-
Mild	34 (2.3)	27 (4.6)	-
APR DRG severity of illness, n (%)	-	-	<0.001
Extreme	1,259 (84.7)	435 (74.5)	-
Major	183 (12.3)	130 (22.3)	-
Moderate	37 (2.5)	16 (2.7)	-
Mild	7 (0.47)	3 (0.51)	-
Septic shock, n (%)	1,078 (72.5)	429 (73.4)	0.71
Acute renal failure, n (%)	953 (64.1)	368 (63.0)	0.67

APR = all patient refined

Table 2 – Multiple logistic regression model for 90-day unplanned readmission

Covariate	**OR**	**95% CI**
Diverting loop ileostomy	0.85	0.65-1.25
Age	0.99	0.98-0.99
Female	0.99	0.78-1.27
Chronic steroid use	1.41	0.62-3.01
Insurance (reference = Medicare/Medicaid)		
Private	0.78	0.55-1.09
Other	0.61	0.28-1.20
Teaching hospital	1.62	1.25-2.11
Extreme APR DRG risk of mortality	1.13	0.85-1.49
Sepsis	0.92	0.69-1.24
Acute renal failure	1.16	0.88-1.53
Disposition: home	0.77	0.57-1.03

APR = all patient refined

Table 3 – Multiple logistic regression model for overall in-hospital mortality

Covariate	**OR**	**95% CI**
Total abdominal colectomy	1.15	0.92-1.44
Age	1.02	1.01-1.02
Female	0.89	0.73-1.09
Chronic steroid use	1.12	0.56-2.17
Insurance (reference = Medicare/Medicaid)		
Private	0.80	0.59-1.09
Other	1.22	0.73-2.03
Teaching hospital	1.04	0.85-1.29
Extreme APR DRG risk of mortality	7.25	5.25-10.28
Sepsis	1.10	0.87-1.40
Acute Renal Failure	0.95	0.77-1.18

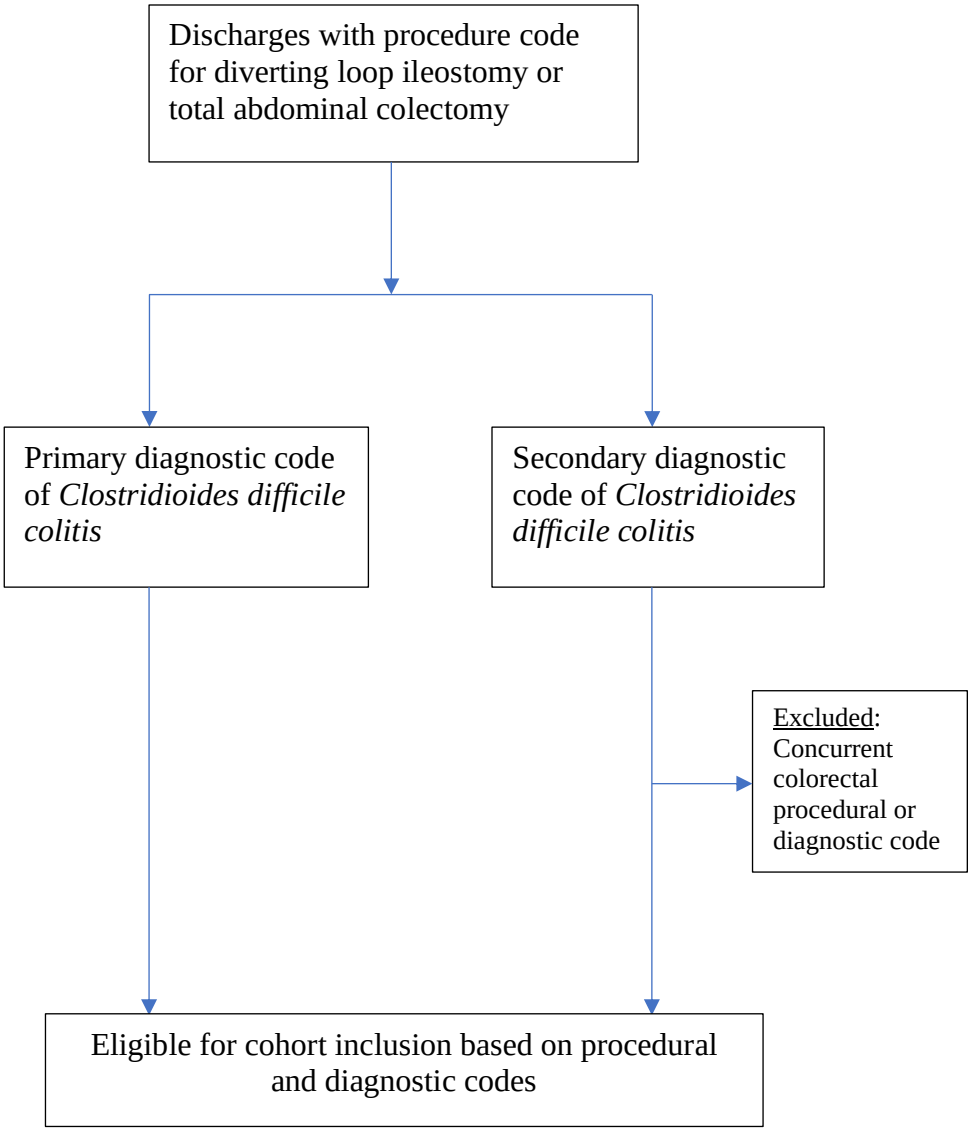
APR = all patient refined

Table 4 – Multiple logistic regression model for 6-month ileostomy closure

Covariate	**OR**	**95% CI**
Diverting loop ileostomy	2.68	1.80-4.00
Age	0.99	0.97-1.00
Female	0.94	0.63-1.40
Chronic steroid use	0.94	0.21-3.01
Insurance (reference = Medicare/Medicaid)		
Private	1.96	1.21-3.17
Other	1.46	0.52-3.53
Teaching hospital	1.03	0.68-1.56
Extreme APR DRG risk of mortality	0.78	0.51-1.21
Sepsis	1.12	0.70-1.82
Acute renal failure	0.83	0.54-1.30
Disposition: home	1.23	0.77-1.94

APR = all patient refined

Figure 1. Cohort inclusion criteria to identify patients who underwent diverting loop ileostomy or total abdominal colectomy for *Clostridioides difficile* colitis



Supplemental Table 1 – Comparison of patients who were excluded for having a discharge date from October to December of each calendar year to those who were included

Characteristic	**Included n=2,070**	**Excluded n=717**	***p***
Diverting loop ileostomy, n (%)	584 (28.2)	209 (29.1)	0.67
Age, years, median, (Q1-Q3)			0.61
Male sex, n (%)	884 (42.7)	335 (46.7)	0.068
Chronic steroid use, n (%)	46 (2.2)	18 (2.5)	0.76
Insurance type, n (%)	-	-	0.42
Medicare / Medicaid	1,628 (78.6)	575 (80.2)	-
Private	361 (17.4)	119 (16.6)	-
Other	81 (3.9)	23 (3.2)	-
Teaching hospital, n (%)	1,313 (63.4)	463 (64.6)	0.79
APR DRG risk of mortality, n (%)	-	-	0.68
Extreme	1,533 (74.1)	533 (74.3)	-
Major	337 (16.3)	109 (15.2)	-
Moderate	138 (6.7)	47 (6.6)	-
Mild	62 (3.0)	28 (3.9)	-
APR DRG severity of illness, n (%)	-	-	0.52
Extreme	1,694 (81.8)	590 (82.3)	-
Major	313 (15.1)	98 (13.7)	-
Moderate	52 (2.5)	23 (3.2)	-
Mild	11 (0.53)	6 (0.83)	-
Septic shock, n (%)	1,507 (72.8)	520 (72.5)	0.92
Acute renal failure, n (%)	1,321 (63.8)	441 (61.5)	0.29

APR = all patient refined

Appendix 1 – List of ICD-9 and ICD-10 codes used to generate cohort, outcomes, and relevant covariates

	ICD-9	ICD-10
Cohort Criteria		
Exposure		
Diverting loop ileostomy	4601, 4620, 4621	0D1B0Z4, 0D1B4Z4, 0D1B8Z4, 0D1B874, 0D1B8J4, 0D1B8K4
Total abdominal colectomy	458, 4581, 4582, 4583	0DTE0ZZ, 0DTE4ZZ, 0DTE7ZZ, 0DTE8ZZ, 0DBE0ZZ, 0DBE4ZZ
Clostridioides difficile colitis	008.45	A04.71, A04.72
Concurrent colorectal diagnosis		
Cancer	153.X, 154.0, 154.1	C18.X, C19, C20, C21.8
Benign neoplasm	211.3, 211.4	D12.X, K63.5
Diverticulitis	562.10, 562.12, 562.11, 562.13	K5720, K5721, K5732, K5733, K57.2, K57.4, K57.8
Crohn's disease	555.0, 555.1, 555.2, 555.9	K50.00, K50.011-4, K50.018-9, K50.10, K50.111-4, K50.118-9, K50.80, K50.811-4, K50.818-9, K50.90, K50.911-4, K50.918-9
Ulcerative colitis	556.0-9	K51.0, K51.00-1, K51.011-4, K51.018-9, K51.2, K52.20-1, K51.211-4, K51.218-9, K51.3, K51.30-1, K51.311-4, K51.318-9, K51.8, K51.80-1, K51.811-4, K51.818-9, K51.9, K51.90-1, K51.911-4, K51.918-9
Volvulus	560.2	K56.2
Obstruction	560.89, 560.9	K56.60, K56.69
Lower gastrointestinal bleeding	569.3	K62.5
Ischemic bowel	557.9, 557.1, 557.9, 557.0, 557.1	K55.9
Other colitis	558.9	K52.89, K52.9
Concurrent colorectal procedure		
Segmental colectomy	1731-6, 1739, 4571-6, 4579	0DTC(F,G,H,K,L,M,N)0ZZ, 0DTC(F,G,H,K,L,M,N)4ZZ, 0DTC(F,G,H,K,L,M,N)7ZZ, 0DTC(F,G,H,K,L,M,N)8ZZ,

		0DBE(F,G,H,K,L,M,N)0ZZ, 0DBE(F,G,H,K,L,M,N)4ZZ,
Proctectomy	485, 4850-2, 4859, 4861-6, 4869, 4840-3, 4849	0DTP0(4,7,8)ZZ, 0DBP0(4)ZZ
Appendectomy	470, 4701, 4709, 471, 4711, 4719	0DTJ0(4,7,8)ZZ, 0DBJ0(4)ZZ
Colostomy	4610-4	0D1H(K,L,M,N)0Z4, 0D1H(K,L,M,N)4Z4
Outcomes		
Gastrointestinal restoration		
Diverting loop ileostomy closure	4650, 4651, 465, 4590, 4602, 4674	0DBB0ZZ, 0DBB4ZZ, 0WQF0ZZ, 0WQF4ZZ, 0DQB0ZZ, 0DQB4ZZ, 0WQFX72, 0DTB0ZZ, 0DTB4ZZ
End ileostomy takedown	4590, 4592, 4593, 4602, 4604, 4676, 4674	0DTB0ZZ, 0DTB4ZZ, 0DQB0ZZ, 0DQB4ZZ, 0D1B0ZP, OD1B4ZP
Covariates		
Chronic steroid use	V58.65	Z79.5, Z79.52
Septic shock	785.52, 995.92, 038.9, 038.3	R65.20, R65.21, R65.11
Acute renal failure	584, 584.5, 584.9, 639.3, 586	N17, N17.0, N17.1, N17.2, N17.8, N17.9

CHAPTER 5: COMPARISON OF SURGICAL PROCEDURES FOR FULMINANT CLOSTRIDIOIDES DIFFICILE COLITIS: A PREAMBLE

In the previous chapter, I compared the post-discharge outcomes between patients who had a diverting loop ileostomy with colonic lavage (DLI) and those who had a total abdominal colectomy with end ileostomy (TAC). I observed similar readmission and in-hospital mortality for both procedures with a significantly increased odds of restoration of gastrointestinal continuity following DLI. However, despite the interest in this novel procedure, many hurdles prevented its universal adoption.

Being a surgical trainee in the province of Quebec, I witnessed first-hand the severity with which the hypervirulent RT027 strain affected our patients. Surgery for C. difficile colitis was a common occurrence, and despite expedient intervention in the form of TAC, patients had significant postoperative morbidity and mortality. After the publication by Neal *et al* who proposed DLI as an alternative surgical intervention to TAC, I became very interested the potential of this procedure to improve the outcomes of our patients[58]. While a diverting loop ileostomy is a common surgical intervention, there were many limitations to the widespread implementation of this procedure. First and foremost, was the lack of conclusive evidence supporting the safety of this procedure compared to TAC. This was especially true given the high associated mortality after TAC in the literature[52]. In addition, physicians were reluctant to offer patients in this life-threatening setting a procedure that was not standard of care) outside the confines of a clinical trial. As such, I set out to investigate the role of DLI in the treatment of FCDC and compare it to TAC. I launched a multi-centre (n=14) prospective cohort study in 2016 with a retrospective historical control arm[71].

The objective of this study was to determine if DLI decreases 30-day all-cause mortality compared to TAC for FCDC. Other outcomes of interest were 90-day all-cause mortality, morbidity, quality of life and gastrointestinal restoration rates. Patient reported outcome measures had not been reported in any of the studies, and while it is presumed that patients would prefer a procedure with a higher chance of gastrointestinal restoration, the trade-off with potentially increased mortality needed to be evaluated.

A non-randomized trial design was selected due to the overall rarity of the procedure and expected difficulty in recruiting and randomizing patients in the emergency room setting, bearing in mind the reluctance of surgeons and patients to leave decision making up to random chance. After gaining experience with the procedure, I developed an instructional video and highlighted tips and tricks for the success of the DLI and lavage (presented at the Society of American Gastrointestinal and Endoscopic Surgeon's annual conference in 2017, available online at https://www.youtube.com/watch?v=1VMQrEI6jro). This video was shared with all sites and investigators. Institutional Board Reviewal was obtained at each recruited institution (14 in Quebec, Canada). We were proactive in continuing to recruit sites across Canada. We promoted this study by presenting it at multiple conferences including the Canadian Association of General Surgeon's annual conference (2016-2017), the Association Quebecoise de chirurgie and by presenting grand surgical rounds at multiple hospitals across Quebec. We used promotional flyers to assist in site recruitment (Appendix 1). Given that patients were few and far between, we made every effort to ensure no patient was missed. We created flyers that we put up in the clinic spaces and on surgical floors of the participating institutions (Appendix 2). We also created staff cards that residents and staff could attach to their lanyards with key procedural steps and our contact information (Appendix 3). A pocket-sized flyer with important procedural steps

was also distributed (Appendix 4). Soon after we launched at 14 institutions and after a year of open accrual, we did not meet the expected number of patients estimated to be enrolled at each institution (estimated at 3 patients per year per institution). Having noticed the decrease in *C. difficile* requiring surgery at our own institutions, a review of the Quebec provincial surveillance program confirmed that rates of fulminant *C. difficile* colitis requiring surgical intervention had paralleled a decrease in overall CDI rates in the province[72]. Our sample size calculation (for an absolute mortality risk reduction of 22%, Type I error of 0.05, power of 80% and 1:1 control to intervention ratio) had estimated a sample size of 63 patients in each of the DLI and TAC arms. Given the poor accrual, it became evident that we would not be able to sustain the study, and we unfortunately had to end the prospective arm trial.

With such few studies evaluating the role of DLI for the treatment of *C. difficile*, I felt it was important to continue the study with a retrospective design in order to capture all the DLI cases performed at the participating institutions within recent years. Eleven North American institutions were recruited for the retrospective cohort study. With robust granular data collection sheet, I captured a plethora of information with regards to the procedure itself, patient's disease severity of disease, and post-discharge outcomes. One of the most important but very rarely reported outcomess is the risk of recurrent *C. difficile* for patients who have their diseased colon left in-situ after a DLI, which we were able to evaluate in this study.

The results of this multicentre cohort study will be presented in Chapter 6.

Appendix 1: Promotional Flyer

LESS MAY BE MORE

Loop Ileostomy with Colonic Lavage for Fulminant *C. Difficile* Colitis
A Prospective Multi-Center Cohort Study

Basic study design:

This is a multi-center prospective cohort study to evaluate loop ileostomy and colonic lavage to the standard of care, total abdominal colectomy with end ileostomy. This study will consist of a prospective registry (from 2015 to 2018) with 2 prospective arms: the loop ileostomy group and the control (TAC) group. We require 63 patients per arm. In addition, we will concurrently perform a retrospective chart review at all participating sites from (from 2010 to 2014) to serve as a third group of historical controls.

Included Sites:

We already have 14 sites included and are looking to recruit more sites.

If you are interested in joining this study, please contact:
Principal investigator: **Marylise Boutros**, MD, FRCSC, FASCRS at: [redacted]
Research associate: **Marie Demian**, MSc at: [redacted]

Specific Aim and Hypothesis:

The objective of this study is to determine if loop ileostomy and colonic lavage reduces 30-day all-cause mortality compared to the current standard of care for fulminant *C. difficile colitis* (FCDC), total abdominal colectomy with end ileostomy.

We hypothesize that loop ileostomy and colonic lavage will:

1. ↓ 30-day all-cause mortality
2. ↓ 30-day morbidity
3. ↓ 90-day all-cause mortality
4. ↑ gastrointestinal restoration rates

Inclusion criteria:

1. Adult patients >18 years old
2. Able to provide informed consent, or presence of a legally authorized representative
3. Meets criteria for operative management as below

Criteria A, B and C all need to be met:

A. A diagnosis of FCDC as determined by a history consistent with *C. difficile* infection and one of the following:

1. A positive toxin assay
2. Endoscopic finding of pseudomembranes
3. CT scan findings of pancolitis or segmental colitis with ascites

B. At least 2 of the following:

1. Worsening abdominal distention or abdominal pain
2. Cessation of diarrhea with worsening abdominal distention
3. Sepsis: 2 of the following (HR>100bpm, MAP<60mmHg, temperature>38.5C or<36.5C, and fluid requirement >2L/24hours)
4. New onset ventilatory requirement
5. Vasopressor requirement
6. Mental status changes
7. Unexplained clinical deterioration
8. Stable elevated leukocytosis or leukopenia, or worsening leukocytosis, defined as >20,000 or <3,000x10^9/L
9. Worsening renal function (with creatinine 1.5x baseline or above 150 µmol/L)
10. Worsening CT scan findings (progression to pancolitis with ascites)

C. Attending physician of record (ICU, ER or medicine/surgery) is in agreement with an operative approach.

Appendix 2: Flyer to assist with patient recruitment

LESS MAY BE MORE

Loop Ileostomy with Colonic Lavage for Fulminant *C. Difficile* Colitis
A Prospective National Multi-Center Cohort Study

Specific Aim and Hypothesis:

The objective of this study is to determine if loop ileostomy and colonic lavage reduces 30-day all-cause mortality compared to the current standard of care for fulminant *C. difficile* colitis (FCDC), total abdominal colectomy with end ileostomy.

We hypothesize that loop ileostomy and colonic lavage will:

1. ↓ 30-day all-cause mortality
2. ↓ 30-day morbidity
3. ↓ 90-day all-cause mortality
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Inclusion criteria:

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Criteria A, B and C all need to be met:

A. A diagnosis of FCDC as determined by a history consistent with *C. difficile* infection and one of the following:

1. A positive toxin assay
2. Endoscopic finding of pseudomembranes
3. CT scan findings of pancolitis or segmental colitis with ascites

B. At least 2 of the following:

1. Worsening abdominal distention or abdominal pain
2. Cessation of diarrhea with worsening abdominal distention
3. Sepsis: 2 of the following (HR>100bpm, MAP<60mmHg, temperature>38.5C or<36.5C, and fluid requirement >2L/24hours)
4. New onset ventilatory requirement
5. Vasopressor requirement
6. Mental status changes
7. Unexplained clinical deterioration
8. Stable elevated leukocytosis or leukopenia, or worsening leukocytosis, defined as >20,000 or <3,000x10^9/L
9. Worsening renal function (with creatinine 1.5x baseline or above 150 µmol/L)
10. Worsening CT scan findings (progression to pancolitis with ascites)

C. Attending physician of record (ICU, ER or medicine/surgery) is in agreement with an operative approach.

Contact:

If you have a patient that may meet the inclusion criteria, please page the research team at your site or any of the following:

Research Associate: **Marie Demian,** [redacted]

Co-Investigator: **Maria Abou Khalil,** [redacted]

Principal Investigator: **Marylise Boutros,** [redacted]

Appendix 3: Staff Lanyard Card

LESS MAY BE MORE

Loop Ileostomy with Colonic Lavage for Fulminant *C. Difficile* Colitis
A Prospective National Multi-Center Cohort Study

The objective of this study is to determine if loop ileostomy and colonic lavage reduces 30-day all-cause mortality compared to the current standard of care for fulminant *C. difficile* colitis (FCDC), total abdominal colectomy with end ileostomy.

If you have a patient that may meet the inclusion criteria, please page the research team at your site or any of the following:

Research Associate:
Marie Demian, [redacted]

Co-Investigator:
Maria Abou Khalil, [redacted]

Principal Investigator:
Marylise Boutros, [redacted]

Site-investigators:
MGH: **Sender Liberman,** [redacted]
RVH: **Francine Tremblay** [redacted]
St. Mary's: **Sebastian Demyttenaere,** [redacted]

Inclusion criteria:

1. Adult patients >18 years old
2. Able to provide informed consent, or presence of a legally authorized representative
3. Meets criteria for operative management as below

Criteria A, B and C all need to be met:

A. A diagnosis of FCDC as determined by a history consistent with *C. difficile* infection and one of the following:

1. A positive toxin assay
2. Endoscopic finding of pseudomembranes
3. CT scan findings of pancolitis or segmental colitis with ascites

B. At least 2 of the following:

1. Worsening abdominal distention or abdominal pain
2. Cessation of diarrhea with worsening abdominal distention
3. Sepsis: 2 of the following (HR>100bpm, MAP<60mmHg, temperature>38.5C or<36.5C, and fluid requirement >2L/24hours)
4. New onset ventilatory requirement
5. Vasopressor requirement
6. Mental status changes
7. Unexplained clinical deterioration
8. Stable elevated leukocytosis or leukopenia, or worsening leukocytosis, defined as >20,000 or <3,000x10^9/L
9. Worsening renal function (with creatinine 1.5x baseline or above 150 µmol/L)
10. Worsening CT scan findings (progression to pancolitis with ascites)

C. Attending physician of record (ICU, ER or medicine/surgery) is in agreement with an operative approach.

Appendix 4: Pocket information flyer

Technical Tips for Loop Ileostomy and Colonic Irrigation

Step 1 : Loop Ileostomy

- Laparoscopy or laparotomy can be used at the discretion of the surgeon (laparoscopy is preferable if pt is a good candidate and surgeon is comfortable)
- Creation of loop ileostomy (use of rod up to discretion of surgeon)
- 18Fr foley catheter inserted

Step 2 : Irrigation

- Irrigation of 8L of warmed (37degrees) PEG solution
- Use tap water enema bag with connector to foley
- A rectal tube should be inserted into the rectum and attached to a large drainage bag and kept in place until 8L irrigation is complete
  - Malicot drain • Endotracheal tube • Flexi-seal tube
- Irrigate 1L at a time and ensure that effluent has reached rectal drainage tube
- If laparoscopic, you may choose to maintain pneumoperitoneum at 7-15mm of Hg during irrigation and to use laparoscopic bowel graspers to aid in pushing the fluid along colon during irrigation
- If open, maintain the abdomen opened and manually aid the fluid irrigation through colon
- If trouble getting fluid through colon, you may choose to use trendelberg and reverse trendelberg positions, as well as left side up/down right side up/down to move fluid along the colon or you may choose to mobilize the hepatic and or splenic flexures mobilize flexure(s)
- If the irrigation is not complete, and the patient needs to leave the OR for any reason:
  - Complete 1L of irrigation in OR before leaving, making sure the effluent reache the rectal drainage tube
  - Continue irrigation at 1L/hour fast flushes in the ICU/step-down/ward

Step 3 : Avoiding / managing Abdominal Compartment Syndrome (ACS)

- Due to fluid sequestration and the distended colon, abdominal compartment syndrome may occur during or after the operation
- ACS should be suspected if any of these signs occur with increased abdominal distention :
  - Bladder pressure ≥25mmHg
  - ↑ Difficulty ventilating
  - Worsening hypotension
  - ↑ Tachycardia
  - ↑ Central venous pressure
  - Worsening oliguria
  - Worsening lactic acidosis
- You may choose to leave a 19Fr round Jackson Pratt drain in the abdomen to drain excessive ascites. You may remove this drain at any time in the post-operative course once the patient is well.

Step 4 : Fixation of foley catheter

- After intra-operative irrigation is complete, secure the 18Fr Foley to the ileostomy with an O silk suture. Alternatively, one can fix the 18Fr Foley to the ileostomy via an O silk tied to the Foley, left long and held in place with the stoma appliance cap.

Step 5 : Post-operative medication administration

1. Antegrade vancomycin flushes (500mg in 500ml of Lactated Ringers ; q8 hours) for a duration of 10 days via a foley catheter (18 Fr) left in the efferent limb of the ileostomy
2. IV metronidazole (500mg q8 hours) for 10 days

- If patient's clinical status not back to baseline (normal vital signs, stoma functioning and normal WBC), continue vancomycin flushes and IV metronidazole until back to baseline or until FCDC not deemed the reason for these abnormalities.

LESS MAY BE MORE

Loop Ileostomy with Colonic Lavage for Fulminant *C. Difficile* Colitis A Prospective National Multi-Center Cohort Study

If you have a patient that may meet the inclusion criteria, please page the research team at your site or any of the following :

Research Associate : Marie Demian, [redacted]
Co-Investigator : Maria Abou Khalil, [redacted]
Principal Investigator : Marylise Boutros, [redacted]
Site-investigators : MGH : Sender Liberman, [redacted]
RVH : Francine Tremblay, [redacted]
St. Mary's : Sebastian Demyttenaere, [redacted]

Project Description to guide discussion with Patient

Clostridium difficile (*C.difficile*) is a bacterial infection that can cause an inflammation of the colon, (*C.difficile* colitis). This sometimes progresses to a sudden and severe illness. The present treatment for fulminant colitis is a total abdominal colectomy with end ileostomy. This means, a surgery is performed which removes the entire diseased colon. The end of the small intestine is then brought out to the front of the abdomen as a stoma, and the patient wears a bag. Despite this invasive treatment, there remains a significant rate of death (38-55%). In addition, patients have a long recovery after this long operation and many (67%) will not be fit for a second big operation to remove the stoma (that is to reconnect the intestine).

The purpose of our study is to determine if a loop ileostomy with colonic lavage will result in better outcomes. A loop ileostomy is when a loop of small intestine is brought out to the abdomen and the colon remains in the abdomen. The diseased colon, which is preserved, is washed with a warm solution (like the solution used in a colonoscopy preparation) and then treated with an antibiotic via this ileostomy. So far, one study has been done using a loop ileostomy with colonic lavage. 42 patients who underwent this treatment were compared to 42 patients that underwent the standard of care (complete removal of the colon with end ileostomy). The 42 patients who underwent a loop ileostomy showed a significant decrease in rate of death compared to the standard of care. Also, in the study, patients who underwent a loop ileostomy had a much higher rate of reconnection of the intestine (closing the stoma). The purpose of this study is to see if a loop ileostomy with colonic lavage can treat patients with fulminant colitis with less risk of death than the standard of care.

The decision to undergo loop ileostomy or TAC will be left up to the discretion of the surgeon and the patient.

Inclusion criteria :

1. Adult patients >18 years old
2. Able to provide informed consent, or presence of a legally authorized representative
3. Meets criteria for operative management as below

Criteria A, B and C all need to be met :

A. A diagnosis of FCDC as determined by a history consistent with C. difficile infection and one of the following :

1 A positive toxin assay
2. Endoscopic finding of pseudomembranes
3. CT scan findings of pancolitis or segmental colitis with ascites

B. At least 2 of the following :

1. Worsening abdominal distention or abdominal pain
2. Cessation of diarrhea with worsening abdominal distention
3. Sepsis : 2 of the following (HR>100bpm, MAP<60mmHg, temperature>38.5C or<36.5C, and fluid requirement >2L/24hours)
4. New onset ventilatory requirement
5. Vasopressor requirement
6. Mental status changes
7. Unexplained clinical deterioration
8. Stable elevated leukocytosis or leukopenia, or worsening leukocytosis, defined as >20,000 or <3,000x10^9/L
9. Worsening renal function (with creatinine 1.5x baseline or above 150 µmol/L)
10. Worsening CT scan findings (progression to pancolitis with ascites)

C. Attending physician of record (ICU, ER or medicine/surgery) is in agreement with an operative approach.

Exclusion criteria :

1. Children (<18 years old)
2. Allergy to vancomycin or polyethyleneglycol (PEG)
3. Colonic perforation, necrosis or other
4. Pregnancy

NOTE : Points 2, 3 and 4 are exclusion criteria for admitting patients to the loop ileostomy arm. These patients will have to undergo a TAC with end ileostomy.

CHAPTER 6: MORBIDITY AND GASTROINTESTINAL RESTORATION RATES FOR DIVERTING LOOP ILEOSTOMY WITH COLONIC LAVAGE VS. TOTAL ABDOMINAL COLECTOMY FOR FULMINANT CLOSTRIDIOIDES DIFFICILE COLITIS: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Abstract

Background: Limited data exist on the role of diverting loop ileostomy and colonic lavage for fulminant *Clostridioides difficile* colitis compared to total abdominal colectomy with end ileostomy. The objective of this work was to compare outcomes of both procedures.

Methods: After institutional review board approval, a multicenter retrospective chart review was conducted at eleven North American hospitals identifying patients who underwent a total abdominal colectomy or a diverting loop ileostomy for fulminant *C. difficile* colitis (2010-2018). Primary outcome was 30-day post-operative mortality. Secondary outcomes were 90-day post-operative mortality, post-operative major morbidity, gastrointestinal restoration rates and recurrence rates.

Results: Of 177 patients, 143(80.9%) had total abdominal colectomy and 34(19.1%) had diverting loop ileostomy. Patients in both groups were similar with regards to demographic and pre-operative markers of disease severity. Overall 30 and 90-day post-operative mortality were 23.5% vs. 37.1% (p=0.10) and 29.4% vs. 46.2% (p=0.10) for diverting loop ileostomy compared to total abdominal colectomy, respectively. Multivariate logistic regression identified age (1.07[1.03-1.12]), pre-operative vasopressor use (5.39[1.96-14.83]), and creatinine levels (1.34[1.07-1.69]) as independent predictors of 30-day post-operative mortality. Incidence of post-operative major morbidity was high in both groups, however diverting loop ileostomy was associated with a significantly decreased odds of major morbidity (0.33[0.11-0.97]). Gastrointestinal continuity was established more often and earlier in patients after diverting loop ileostomy, and recurrence of *C. difficile* infection after gastrointestinal restoration was low.

Conclusions: Diverting loop ileostomy was associated with similar postoperative mortality, decreased postoperative morbidity, and increased gastrointestinal restoration rates compared to total abdominal colectomy.

Introduction

Clostridioides difficile infection (CDI) is an important cause of nosocomial and community acquired colitis[1,2]. The infection generally resolves with medical management with antibiotics alone without any end-organ damage or mortality [3]. Surgical management is reserved for the treatment of the rare but severe form of infection characterized by multi-organ system failure, termed fulminant *Clostridioides difficile* colitis (FCDC)[4,5]. The standard surgical approach for FCDC is an open total abdominal colectomy and end ileostomy (TAC)[6-8].

In 2011, a single-surgeon, single-institution case-series proposed the creation of a diverting loop ileostomy with colonic lavage (DLI) as a surgical option for FCDC[9]. Although the primary outcome of the study was resolution of CDI, the significantly decreased mortality after DLI compared to TAC highlighted it as a potentially superior alternative to TAC. The authors described the creation of a diverting loop ileostomy with lavage of the diseased colon with 8L of a warmed polyethylene glycol solution, followed by vancomycin flushes continued for 10 days post-operatively. This was similar to older descriptions of blow-holes and diverting stomas that were used as an effective bridge to semi-elective surgery for patients with inflammatory bowel disease presenting with severe toxic colitis [10]. These temporizing procedures were used to avoid emergency colectomy with its associated morbidity and mortality for critically ill patients.

Since 2011, limited studies have evaluated DLI for FCDC[11-15]. Importantly, beyond the absolute contra-indications for DLI (frank perforation, transmural necrosis, etc.) equipoise exists with regards to the role of DLI as an alternative for TAC. Furthermore, the optimal patient population that may benefit from this procedure is unclear and information regarding CDI

recurrence rates after DLI is also lacking. Given that the colon remains in situ following the operation, there is the potential for a higher risk for recurrent CDI after DLI. We hypothesized that DLI would be associated with decreased post-operative morbidity and mortality but increased gastrointestinal (GI) restoration rates. As such, the objective of this study was to compare post-operative morbidity and mortality, GI restoration rates and CDI recurrences for patients with FCDC undergoing TAC or DLI.

Materials and Methods

Study population

After multi-institutional ethics review board approval, a retrospective chart review was conducted at eleven North American hospitals evaluating adult patients who underwent a TAC or a DLI for *C. difficile* from January 1, 2010 to December 31, 2018. The Infectious Disease Society of America refers to FCDC as an entity defined by hypotension/shock, ileus or megacolon[16]. It is based on this definition that patients with severe *C. difficile* who underwent operative management (TAC or DLI) for the treatment of this condition were selected. As such, all charts were reviewed to ensure that included patients had surgery for severe fulminant disease, and did not have surgery for other indications or indolent, benign, or recalcitrant disease. To identify these patients, hospital databases were searched by discharge code for CDI and procedure codes for TAC or DLI. Patient lists were supplied by the ethics department or the archives department, depending on hospital policy. Patients who had surgery for diagnoses other than FCDC, and patients who had segmental colonic resections for CDI were excluded.

Participating centers were in Quebec, Canada and Los Angeles, USA and included academic and community hospitals. Study data were collected and managed on REDCap, a secure web-based platform specifically designed to support data capture for research studies[17,18].

Outcomes and definitions

The primary outcome was 30-day all-cause mortality. Other outcomes evaluated included 30-day major morbidity (a composite binary outcome to include all Clavien-Dindo grade II-V complications), 90-day all-cause mortality, restoration of GI continuity by ileostomy closure after DLI or takedown of end ileostomy and ileorectal anastomosis after TAC, length of hospital and intensive care unit (ICU) stay, and recurrence of CDI after surgery[19,20]. A patient was noted to have a recurrence if there was documentation of a recurrent episode of CDI after surgery which required medical treatment.

The data collected included patient demographics, baseline medical history, markers of disease severity (including Acute Physiologic Assessment and Chronic Health Evaluation (APACHE)II scores, pre-operative intubation and vasopressor use), operative details, and post-operative and post-discharge outcomes. The APACHE II scoring system is a validated tool used to grade the severity of illness in critically ill patients[21]. Immunosuppression was defined as the regular administration of oral or parenteral corticosteroids, or other immunosuppressant medications or health states 30-days prior to the operation.

Statistical analyses

Descriptive and quantitative analyses were performed. Data were summarized as mean (± standard deviation), median (interquartile range), or percentage (%), for normally distributed and non-normally distributed continuous variables, and categorical variables, respectively. On crude analysis, normally, non-normally distributed and categorical variables were compared using a two-tailed student's *t* tests, Wilcoxon rank sum tests and Pearson's chi-square tests, respectively. Multiple logistic regression analysis to investigate risk factors for mortality and major morbidity with complete patient data were used to adjust for patient demographics and markers of disease severity, chosen a priori based on subject knowledge for being associated with outcomes after surgery for FCDC[22-27]. These factors were age, sex, use of pre-operative vasopressors, pre-operative respiratory dysfunction requiring intubation, immunosuppression, pre-operative white blood cell count, creatinine levels, and thrombocytopenia. Patients who underwent a TAC after failed DLI were counted in the DLI group. A two-tailed p value< 0.05 indicated statistical significance. All statistical analyses were performed using Stata software version 17.0 (StataCorp LLC, College Station, TX).

Results

Of 177 patients with FCDC, 143 (80.9%) underwent a TAC while 34 (19.1%) underwent a DLI (Figure 1). Median follow-up was 39.5 (IQR, 11.3 to 84.0) months. Overall, the absolute number of patients with FCDC undergoing surgery progressively decreased throughout the study period, while DLI was noted to be used more frequently after 2011 (Table 1).

Patient demographics in both groups were similar with respect to pre-operative factors such as patient age (71.5 vs. 70.0 p=0.54), female sex (53.8% vs. 61.8%, p=0.40) and immunosuppression status (28.2% vs. 34.5%, p=0.51) (Table 2). Fifty-eight percent of patients were in the ICU prior to being transferred to the operating room. There were no differences in markers of disease severity including APACHE II scores, pre-operative vasopressor use, pre-operative intubation, and in pre-operative laboratory markers such as, white blood cell count, lactate and creatinine level between the two groups (Table 2). Thrombocytopenia was more common in patients who underwent a DLI (23.2% vs. 41.2%, p=0.034). Patients undergoing TAC had a history of prior CDI in 8% of cases, compared to 20% for patients undergoing DLI (p=0.071). All patients were treated pre-operatively with intravenous metronidazole and enteric vancomycin.

Laparoscopy was utilized in 17 (50%) patients for the creation of a DLI. Drains were used in a minority of cases (TAC 34.5% vs. DLI 7.6%, p 0.057). Use of vasopressors intra-operatively was similar in both groups (TAC 78.6% vs. DLI 73.5%, p= 0.53). In patients who underwent TAC compared to DLI, estimated operative blood loss was greater (528.7 mL (±628.7) vs. 54.4mL (184.3), p <0.001) and median operative time was significantly longer (160 (120,203) vs.118 (100,160) min, p=0.003). In most patients who underwent DLI, the colonic lavage was performed intraoperatively (n=32 (94.1%)), with a warmed polyethylene glycol (27 (79.41%)). The median length of surgery for DLI was longer than what is expected only for the creation of a diverting ileostomy, as a majority of surgeons completed the colonic washout with

8L of PEG intraoperatively, ensuring the effluent was collected through the stool management system and was not building up in an atonic colon.

Post-operative and post-discharge outcomes are summarized in Table 3. Median post-operative length of stay (23.0 (13.0,43.0) vs. 29.5 (16.0,66.0) days, p= 0.20) and intensive care unit stay (7.0 (3.0,13.0) vs. 7.5 (2.0,17.0) days, p=0.90) were similar for TAC and DLI, respectively. There was no difference in volume of crystalloids and colloids administered 24 hours post-operatively, or in the mean number of post-operative ventilator days in both groups.

Overall 30 and 90-day post-operative mortality were 23.5% vs. 37.1% (p=0.10) and 29.4% vs. 46.2% (p=0.10) for DLI compared to TAC, respectively. Multivariate logistic regression identified age (adjusted OR[95%CI]; 1.07[1.03-1.12]), preoperative vasopressor use (aOR, 5.39[1.96-14.83]), and creatinine levels (aOR, 1.34[1.07-1.69]) as independent predictors of 30-day mortality (Table 4).

Incidence of post-operative major morbidity was high in both groups (TAC 85.3% vs. DLI 67.6%, p 0.016). After adjustment of potential confounders, DLI was associated with significantly decreased odds of major morbidity (OR [95%CI]; 0.33[0.11-0.97]) (Table 5). While the incidence of post-operative infectious complications was similar in both groups, patients with DLI had a significantly lower risk of post-operative 30-day surgical site infections (13.3% vs. 33.1%, p =0.033).

Of the 34 patients who underwent a DLI, 3 patients required reoperation and a TAC for failure to improve after DLI with a median time to re-operation of 2(1,2) days. Indications for TAC after

DLI were abdominal compartment syndrome (one patient) and worsening sepsis after a period of improvement. Of the 3 patients who required a TAC after DLI, 2 patients failed to improve despite TAC and passed away during the same hospitalization. All of the patients who underwent DLI had post-operative vancomycin flushes in an antegrade fashion instilled to the diseased colon.

Amongst patients who underwent a TAC, seventeen (11.9%) required an unplanned reoperation. Indications for reoperation included bleeding (5 (29.4%)), abdominal compartment syndrome (3 (17.7%)), fascial dehiscence (3 (17.7%)), ischemic small bowel/stoma necrosis (3 (17.7%)), and infectious complications (2 (11.8%)). Rectal stump dehiscence occurred in one patient (5.9%).

Patients who underwent a DLI were discharged home directly 38.2% of the time compared to 17.5% for those who underwent a TAC ($p = 0.054$). Unplanned readmissions up to 90-days after discharge occurred in 27.0% of patients who had TAC compared to 12.0% of patients who underwent DLI ($p=0.15$) (Table 3). Readmissions were related to gastrointestinal reasons including stoma related issues and abdominal pain in the majority of cases (15 (62.5%)).

GI restoration occurred more often after DLI (75.0% vs. 19.7%, $p<0.001$) (Table 3). Median time to restoration was shorter for patients undergoing closure of a loop ileostomy compared to a takedown of end ileostomy with ileorectal anastomosis (379 [260,444] vs. 163 [78,249] days, $p = 0.001$). CDI recurrence after restoration was rare and occurred in 2 (11.0%) patients following closure of ileostomy for DLI and in 3 patients (10.0%) after ileorectal anastomosis ($p = 0.93$). Preoperative prophylaxis with oral vancomycin prior to GI restoration was described in 4 patients (2 post DLI and 2 post TAC), all of whom had a history of recurrent CDI. Only one patient with a DLI underwent preoperative vancomycin flushes through the

ileostomy prior to ileostomy closure. Six patients were given post-operative prophylaxis with oral vancomycin after DLI closure while fecal microbiotia transplant was performed in one patient prior to diverting loop ileostomy closure because of recurrent disease after surgery.

Discussion:

The surgical management of FCDC, traditionally with a TAC, has recently been challenged by the emergence of DLI as an alternative option. However, the lack of high quality and longitudinal data post DLI has dampened its widespread adoption, especially given the high morbidity and mortality already associated with FCDC and concerns regarding the safety of DLI in this emergency setting. In this study, we present the largest retrospective multi-institutional cohort of patients with FCDC with detailed clinical and post-discharge outcomes. Compared to TAC, DLI was associated with a significant decrease in overall major morbidity, and increased rates of gastrointestinal continuity without a concomitant increase in mortality, recurrence rates, or readmissions.

In their original paper, Neal *et al* described a significant decrease in 30-day post-operative mortality associated with DLI[9]. This impact on post-operative mortality was again observed in a multicenter review of 21 patients with DLI compared to TAC (17.2% vs. 39.7%, p=0.002), although it is not evident that the two groups were similar in terms of severity of illness as well as which factors were used to adjust for confounders in the multivariate analysis [9,11]. These findings have not been replicated in other studies, which used the American College

of Surgeons National Surgical Quality Improvement Program database as well as the Nationwide inpatient sample, which showed similar 30-day post-operative mortality for DLI and TAC [12,13]. Absent from all of these studies is information regarding 90-day post-operative mortality. As patients with FCDC may have a long and complicated hospitalization, capturing mortality beyond 30-days is an important marker of recovery. Our findings of similar 30 and 90-day post-operative mortality in both groups supports that DLI, without increased mortality, may be an option in select patients with FCDC. It is possible that our study did not find DLI to be associated with a decrease in post-operative mortality given that patients may have failed DLI secondary to advanced systemic disease, leading to mortality or TAC. Timing of surgery for FCDC is important, and earlier time to definitive operative intervention in critically-ill patients has been associated with improved survival.[6,9,23,27]

FCDC is associated with high post-operative morbidity, with the majority of patients suffering from post-operative complications (75%)[11]. In our study, we observed that the less invasive nature of DLI compared to TAC was associated with a significant decrease in post-operative major morbidity. This improvement which occurred without an increase in post-operative mortality, suggests DLI as an alternative to be considered in select patients with FCDC. In this study, 3 patients in the DLI group ultimately underwent TAC and 2 of them died. Although the cause of these deaths is likely multifactorial, one risk that surgeons must consider in the decision-making for FCDC, is the lack of definitive immediate source control in patients that undergo DLI.

To guide decision making and appropriate patient selection, surgeons require a complete overview of the outcomes of this novel and rare procedure, especially with respect to the post-discharge course. A recent study by our group that utilized the Nationwide Readmission Database (NRD) comprised of 2070 patients with FCDC who underwent surgery attempted to clarify these concerns, and demonstrated no increase in unplanned readmissions for patients after DLI compared to TAC, with significantly increased rates of GI restoration after DLI [28]. Increased rates of GI restoration 6 months after DLI were also reported in the study by Neal *et al* (79% vs. 19%)[9] and are similar to the findings of our current study, demonstrating rates of GI restoration to be significantly higher after DLI compared to TAC (75.0% vs. 19.7%, $p<0.001$). In the present study, half of the DLI were performed laparoscopically. This procedure can be done either laparoscopically or open, and is a testament to its potential application in all settings. Part of the morbidity benefits of DLI may be in part contributed by laparoscopy and the less invasive nature of the procedure. Moreover, it has been hypothesized that part of the morbidity benefit may also be conferred by the mechanical colonic washout with polyethylene glycol. A study is underway to evaluate the benefit of colonic washout through less invasive ways such as nasojejunal administration[29].

Additionally, we observed an earlier time to ileostomy closure after DLI similar to the NRD study which can be used as a surrogate marker for positive post-operative recovery. This is likely a reflection of the burden of the second operation - a diverting loop ileostomy being a smaller, less difficult operation to recover from than an ileorectal anastomosis[28].

With limited data available in the literature, questions remain concerning post-discharge CDI monitoring and prophylaxis recommendations prior to GI restoration. Due to limitations of the

dataset, the aforementioned NRD study was not able to investigate CDI recurrence amongst patients who underwent DLI, especially after GI restoration. Neal *et al*. described one patient with recurrence of CDI after discharge from the hospital for DLI, treated with vancomycin flushes through the ileostomy, but did not report on the peri-operative management of patients prior to GI restoration or the rates of recurrence after this procedure. Given that the colon, the primary site of CDI infection, is still in situ after a DLI, and the patient is exposed to risk factors for recurrent CDI, recurrences and their management are important to consider. In 2016, Fashandi *et al* reported a single case of fatal recurrence of FCDC subsequent to closure of DLI, and raised concerns regarding the lack of information with regards to recurrence rates and their management[15]. This current study adds to our knowledge on the treatment of FCDC by being the first study to find low recurrence rates of CDI following GI restoration in both groups across different institutions. There was no universal protocol used for ileostomy closures after DLI, and only several patients received prophylaxis with oral vancomycin or vancomycin flushes. An individualized approach to each patient was proposed as an important principle in the risk stratification of patients and subsequent recommendations for perioperative prophylaxis prior to ileostomy closure.

The strengths of this paper arise from its multicenter design, robust collection of clinical data and the longitudinal follow-up of patients. The multi-institutional nature of this study draws a real-life representation of the management of FCDC. The IDEAL framework recommends study designs for each stage of development for a novel procedure.[30] The use of DLI for FCDC is in the exploration phase of a novel procedure whereby a technique has been described and replicated, but emphasis needs to be made on the adverse outcomes or advantages of the

procedure using muticenter "real-life" data collection, prior to conducting a randomized trial.[30] With the difficulties that arise with the investigation of a new surgical technique, a study design such as this one is the most feasible to ensure monitoring of this rare operative intervention[30-32]. Furthermore, the large sample size of these rare surgical interventions allowed us to account for important confounding factors in the multivariate logistic regression analysis. Moreover, unlike large administrative databases, a chart review allows for more accurate inclusion and exclusion of patients, as well as for more descriptive analyses. While this is the largest retrospective cohort of patients with detailed clinical information, the small sample size limits the number of covariates that could be included in the multivariate analysis without causing over-adjustment. In addition, the primary outcome is a hard outcome measure with no risk for misclassification. Since the publication of the first study describing its use for FCDC, this is the only comparative study to report on long term outcomes including CDI recurrence.

However, this study is not without its limitations, most importantly its retrospective design which inherently introduces selection bias. This is especially important when comparing two different operative strategies. Ideally, a randomized control trial is required to address the equipoise between these two procedures. However, prospective trials involving a rare disease entity with a changing epidemiology are difficult to conduct. Furthermore, trials in critically-ill patients have the added obstacle of the life-threatening situation that besets many of these patients. These challenges resulted in the early termination of two prospective trials, including our own, due to slow recruitment [33,34]. This highlights the fact that, a multi-institutional retrospective study design is the most pragmatic way to ensure data capture and dissemination of

results in the setting of a surgical procedure that is still under investigation with few yearly cases per institution.

Although a potential limitation of this study is loss of follow up, patients with FCDC are critically-ill and thus unlikely to move in the post-operative period. The absence of information on the strain of *C. difficile* is yet another limitation. The emergence of the hypervirulent NAP1 strain in Québec in 2002 resulted in a significant increase in the severity of CDI, with an increase in colectomies performed during that time-period[6,26,27]. We began our data collection in 2010, in a post-epidemic era, without information on strain as it was not readily available in clinical practice. While all patients were treated preoperatively with IV metronidazole and PO/PR vancomycin, the use of other agents such as IVIG and the duration of treatment prior to surgery was not collected. Moreover, we were unable to identify patients who would benefit more from DLI compared to TAC as well as to define the "golden hour" for surgical intervention-in which the benefit of surgical intervention would be superior to continued medical management alone. In addition, given the retrospective nature of this study, we were unable to determine the reason why surgeons selected one procedure over the other, for example foregoing a DLI because of colonic atonicity. Furthermore, although we noted the presence or absence of vasopressors, we were unable to accurately report the dosages of vasopressors given.

Conclusion:

Compared to TAC, DLI is associated with decreased major morbidity and increased gastrointestinal restoration rates without a significant increase in 30 and 90-day post-operative mortality, readmission or CDI recurrence rates. Despite the limitations of the retrospective

design of this study, DLI can be considered as an alternative to TAC in select patients. Future research should elucidate the ideal patient population who would benefit from one operation compared to the other.

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Legend:
Figure 1: Study population flow diagram
Table 1: Distribution of cases throughout the study period
Table 2: Patient Baseline Characteristics
Table 3: Post-operative and post-discharge outcomes, univariate analysis
Table 4: Multivariate regression for 30 and 90-day post-operative mortality
Table 5: Multivariate logistic regression for major morbidity

Figure 1: Study population flow diagram

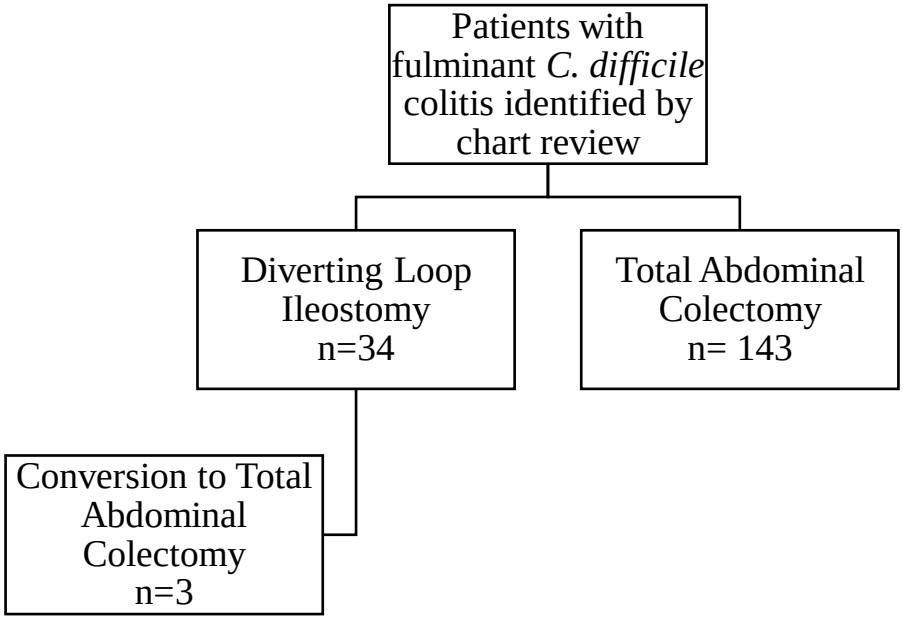

Table 1. Distribution of cases throughout the study period

	Total Abdominal Colectomy [n (%)]	Diverting loop ileostomy [n (%)]
Year		
2010	24 (100)	0 (0)
2011	30 (100)	0 (0)
2012	30 (90.9)	3 (9.1)
2013	26 (81.3)	6 (18.8)
2014	12 (54.6)	11(45.5)
2015	6 (50.0)	6 (50.0)
2016	8 (61.5)	5 (38.5)
2017	2 (50.0)	2 (50.0)
2018	5 (83.3)	1 (16.7)

Table 2. Patient Baseline Characteristics

	Total abdominal colectomy (TAC) [n (%), mean (±SD)]	Diverting loop ileostomy (DLI) [n (%), mean (±SD)]	*p*-value
N	143	34	
Age	71.52 (±12.87)	70 (±13.7)	0.54
Male sex	77 (53.8)	21 (61.8)	0.40
Immunosuppression	35 (28.2)	10 (34.5)	0.51
ICU* or ER** Location prior to transfer to OR, n(%)	104 (72.7)	26 (76.5)	0.66
Location of patient prior to transfer to the operating room, n(%)			
ICU*	82 (58.2)	21 (61.8)	0.39
ER**	22 (15.6)	5 (14.7)	
Medical Floor	26 (18.4)	3 (8.8)	
Surgical Floor	11 (7.8)	5 (14.7)	
Preoperative vasopressors, n(%)	66 (46.8)	14 (43.8)	0.75
Preoperative intubation, n(%)	49 (39.2)	7 (25.0)	0.16
Preoperative lactate (mmol/L)	3.58 (±3.6)	2.39 (±1.5)	0.082
Serum Creatinine (mg/dl),	2.24 (±1.7)	2.09 (±1.5)	0.64
White Blood Cell Count (x10^9/L)	34.98 (±21.4)	28.86 (±18.7)	0.13
Categorical White Blood Cell Count, x10^9/L			
<4	5 (3.5)	4 (11.8)	0.23
≥4 &<20	30 (21.1)	8 (23.5)	
≥20 & <50	78 (54.9)	17 (50.0)	
≥50	29 (20.4)	5 (14.7)	
Hematocrit	30.77 (±10.4)	29.29 (±9.6)	0.45
Thrombocytopenia ***	33 (23.2)	14 (41.2)	0.034
Platelet count (x10^9/L)	256.6 (±140.78)	223.35 (±149.32)	0.22
APACHE II Score	34.36 (±7.89)	34.4 (±9.81)	0.98

*ICU= Intensive care unit,**ER= Emergency Room, ***Thrombocytopenia= Platelet counts <150,000

Table 3. Post-operative and post-discharge outcomes, univariate analysis

	Total abdominal colectomy (TAC) [n (%), mean (±SD), or median (25th, 75th quartiles)]	D [n (%), mean (±SD), or median (25th, 75th quartiles)]	p-value
Post-operative outcomes			
Crystalloids administered 24 hours post-operatively (mL)	3,547.32 (±1,951.6)	3,051.36 (±2,068.8)	0.20
Colloids administered 24 hours post-operatively (mL)	333.37 (±562.9)	328.78 (±521.7)	0.97
Post-operative length of stay(days)	23.0 (13.0, 43.0)	29.5 (16.0, 66.0)	0.20
Post-operative ICU* stay (days)	7.0 (3.0, 13.0)	7.5 (2.0, 17.0)	0.90
Time to post-operative mortality (days)	18.0 (5.0, 29.0)	24.0 (1.5, 35.5)	0.69
30-day post-operative infectious complications	74 (51.7)	13 (38.2)	0.16
90-day post-operative mortality, n(%)	66 (46.2)	10 (29.4)	0.076
30-day post-operative mortality	53 (37.1)	8 (23.5)	0.14
Post-operative surgical site infection - 30 days	40 (33.1)	4 (13.3)	0.033
Ventilator days	6.10 (±7.4)	6.37 (±9.2)	0.86
Readmission to ICU*	20 (17.4%)	2 (6.7)	0.14
Post-operative recurrence of C difficile infection	8 (7.4)	2 (7.7)	0.96
Major Morbidity	122 (85.3)	23(67.6)	0.016
Reoperation	17 (11.9)	5 (14.7)	0.65
Post-discharge outcomes			
Restoration of gastrointestinal continuity	15 (19.7)	18 (75.0)	<0.001
Time to restoration of gastrointestinal continuity (days)	379 (260, 444)	163 (78, 249)	0.001
Destination of patient after discharge form hospital			
Home	24 (17.5)	13 (38.2)	0.054
Rehabilitation center	40 (29.2)	9 (26.5)	
Other hospital	7 (5.1)	2 (5.9)	
N/A (mortality)	66 (48.2)	10 (29.4)	
Readmitted to hospital within 90 days	21 (27.0)	3(12.0)	0.15
Recurrence after Restoration of gastrointestinal continuity	3(10.0)	2(11.0)	0.93

Table 4. Multivariate regression for 30 and 90-day post-operative mortality

	30-day post-operative mortality			90-day post-operative mortality		
	OR	*p* value	95%CI	OR	*p* value	95%CI
Diverting loop ileostomy	0.47	0.17	0.16-1.38	0.40	0.09	0.14-1.14
Age	1.07	0.001	1.03-1.12	1.08	0.00	1.04-1.12
Male sex	1.49	0.32	0.68-3.30	1.53	0.28	0.71-3.30
Pre-operative vasopressors	5.39	0.001	1.96-14.83	4.76	0.00	1.79-12.65
Pre-operative intubation	1.16	0.77	0.44-3.05	1.21	0.70	0.46-3.17
Immunosuppression	1.85	0.20	0.73-4.69	2.34	0.07	0.94-5.85
White blood cell count (x10^9/L)						
<4	0.58	0.57	0.09-3.73	2.09	0.44	0.33-13.44
Reference						
≥20 & <50	0.88	0.82	0.32-2.48	2.43	0.35	0.38-15.42
≥50	0.39	0.15	0.11-1.39	1.83	0.55	0.26-12.90
Creatinine	1.34	0.012	1.07-1.69	1.25	0.05	1.00-1.57
Thrombocytopenia	2.15	0.10	0.86-5.36	2.36	0.07	0.92-6.04

Table 5. Multivariate logistic regression for major morbidity

	OR	*p* value	95%CI
Diverting loop ileostomy	0.33	0.045	0.11-0.97
Age	1.05	0.013	1.01-1.09
Male sex	1.47	0.45	0.55-3.93
Pre-operative vasopressors	1.47	0.51	0.46-4.69
Pre-operative intubation	2.95	0.13	0.7-12
Immunosuppression	1.43	0.52	0.48-4.31
White blood cell count (x10^9/L)			
<4	0.21	0.13	0.03-1.61
Reference			
≥20 & <50	0.51	0.28	0.15-1.73
≥50	0.94	0.94	0.18-4.95
Creatinine	1.10	0.59	0.79-1.52
Thrombocytopenia	2.93	0.12	0.76-11.22

CHAPTER 7: DISCUSSION

Clostridioides difficile colitis is an important cause of nosocomial diarrhea and an increasingly recognized cause of community acquired infection. While the overwhelming majority of patients have an uncomplicated course of the disease, a small proportion (2-3%) can develop a severe form of the disease characterised by severe colitis and shock, termed fulminant *C. difficile* colitis (FCDC) [73]. Despite improvements in the medical management, some patients will require surgery, traditionally in the form of a total abdominal colectomy (TAC) to resolve the sepsis. This operation in this setting is associated with a high postoperative mortality (30-57%) and morbidity with prolonged intensive care unit (ICU) admission and prolonged hospitalization[52,54]. Furthermore, even if patients survive the operation, rates of gastrointestinal (GI) restoration are low and most patients will end up with a permanent stoma[65]. In a single centre, single surgeon series, diverting loop ileostomy (DLI) in combination with colonic lavage was proposed as an alternative option to TAC and showed promise in improving postoperative outcomes[58]. There is however a paucity of data surrounding the use of this procedure for FCDC, its long-term sequelae and how it compares to TAC. The central goal of this thesis was to evaluate postoperative outcomes after FCDC and to elucidate the role of DLI in this disease.

First, using the American College of Surgeons National Surgical Improvement Program (ACS-NSQIP) database, I developed and externally validated a clinical risk calculator to predict postoperative mortality after surgery for FCDC (Chapter 1). With the potential poor outcomes associated with CDI, many scoring systems have been described predicting the risk of

complicated disease or mortality[74]. Tools predicting post-operative mortality for patients with FCDC are largely limited by lack of methodological rigor or external validation. The strength of our prediction model arises from its development using a large derivation cohort with granular patient-level clinical data which was then externally validated using rigorous statistical methodology.

Although the ACS-NSQIP database participant use data files (PUFs) contain a predicted probability of mortality calculated for each patient based on a hierarchical regression model altered yearly, this individual patient probability is only available to administrators and individuals who have access to the database, thus limiting its generalizability and use. The ACS-NSQIP risk calculator which is available online for clinicians and utilises around 20 variables was not compared to this calculator, and its ability to predict postoperative mortality for FCDC specifically was not verified. The ability of the calculator presented in this thesis to predict a probability of postoperative mortality for patients with FCDC undergoing surgery with a good predictive capability using only 7 predictors of mortality compared to 20-30 variables for the ACS-NSQIP database is an advantage.

Our calculator adds to the breadth of knowledge on mortality after surgery for FCDC by providing physicians with the ability to input their individual patient data at time-sensitive points in their care. Although the predictors identified in the model are familiar clinical risk factors for increased complications after surgery, already appreciated by surgeons, the novelty of this calculator and its applicability will be in aiding physicians to evaluate individualized risks of postoperative mortality. Indeed, one of the advantages of this calculator is that it uses clinically relevant variables that capture disease evolution. For example where a surgeon is evaluating an elderly patient 70 year old male, who is immunosuppressed, with severe sepsis requiring

intubation and vasopressors, the calculator can differentiate the risk of post-operative mortality based on important variables that may change along the acute clinical course of the disease such as a change in white blood cell count from 7,500 to 30,000 (increased post-operative mortality from 38% to 46%) or a rise in creatinine from 1 to 2.2 (increased post-operative mortality from 38% to 48%), or finally both these changes (increased post-operative mortality from 38% to 57%). Thus, though it is clear that the patient described is critically ill, his risk of mortality may still vary from 38% to 57% based on fine details that the calculator can detect and take into account. Thus, by having an interactive calculator with adjustable patient factors the physician is capable of assessing the risk of postoperative mortality at different stages in the disease progression, and this may be used to guide surgical decision.

This calculator may be used to guide consent discussions and act as the foundation for shared decision-making between physicians and the patients or their families. In shared decision making, clinicians and patients come together and make an informed decision on the best course of action using the best available data[75].This is especially important in situations with high stake outcomes like mortality. This calculator was developed with this in mind: to be used as an adjunct during a clinical encounter in the emergency setting and guide the operative risk discussion for a particular patient at the time of surgical decision-making. The calculator may for example show the futility of surgery, or the need to operate quickly before the onset of renal failure. While this calculator was not validated for use in patients with DLI, future research efforts should assess the applicability of this novel calculator in this setting. As FCDC evolves, and as newer treatment modalities are introduced in the algorithm for treatment of this surgical disease, recalibration of these tools is important to reflect the changing era.

Surgeons have often resorted to less invasive operations to temporize and potentially treat critically ill patients who would otherwise not survive the standard major operation that is indicated. For example, trauma surgeons often apply the concept of "damage control surgery": expedient control of contamination and life-threatening bleeding followed by termination of the operation and correction of physiologic abnormalities in the intensive care unit prior to returning to the operating room at a later date for definitive surgical management[76]. In the 1970s, Turnbull et al described the use of decompressing blowhole colostomies and diverting ileostomy for patients with toxic megacolon associated with ulcerative colitis [44]. This operation, an alternative to a TAC in the setting of fulminant colitis, would decrease the high risk of poor outcomes associated with a TAC in these patients and act as a temporizing measure, until a TAC can be performed under better physiologic conditions. Similar to this concept, Neal et al presented a case series of patients who had a DLI and colonic lavage for FCDC, as a less invasive operation in this critically ill patient population[58]. The authors demonstrated a significant reduction in post-operative mortality compared to historical controls who had undergone a TAC (19% vs 50%, *p* 0.006). While these results from a single institution and a single surgeon were met with enthusiasm, there was some apprehension from the surgical community with regards to its generalizability outside this case series[49,77]. Prior to the CDI epidemic, descriptions of fecal diversions for toxic pseudomembranous antibiotic associated colitis resulted in very high postoperative mortality (around 60%)[51]. One hypothesis is that patient selection was the driver for this historically high postoperative mortality: perhaps patients were selected for this less invasive operation because of their inability to tolerate a more radical operation. Another hypothesis is that the new operation including the addition of the mechanical colonic lavage with

polyethylene glycol and the administration of anti-*C. difficile* antibiotic (vancomycin) directly to the diseased colon was superior to historical diversions alone as it effectively rid the colon of the bacterial toxins and bacterial load driving the systemic inflammatory response. Since Neal et al's report, two retrospective cohort studies and two database studies have been published on the topic[59-62]. Fashandi et al presented their retrospective single center outcomes of 23 patients with FCDC, 10 of whom underwent a DLI. Postoperative 30 day mortality was not different between both groups (TAC 23% vs. DLI 30%, p=1.00)[59]. Ferrada et al published the results of a multicentre retrospective cohort study including 98 patients, 21 of whom had a DLI[60]. They found DLI to be significantly associated with decreased mortality compared to TAC (17.2% vs. 39.7%, *p* 0.002). Hall et al and Juo et al compared DLI and TAC for FCDC using the ACS-NSQIP and the NIS databases, respectively, and found no difference in 30-day post-operative mortality between both groups[61,62]. Recent systematic reviews and meta-analyses found no difference with regards to 30-day postoperative mortality between TAC and DLI[78-81].

Despite the growing number of studies evaluating post-operative mortality for FCDC using DLI, there remains a paucity of longitudinal post-discharge information. This does not allow clinicians to understand the full clinical picture and postoperative trajectory of patients who undergo surgery for FCDC. We sought to evaluate this knowledge gap using the American Nationwide Readmissions Database (NRD), part of the Healthcare Cost and Utilization Project (HCUP). The NRD has the unique ability to link patient readmissions within the same state in a calendar year, allowing a longitudinal outcome assessment. Long-term outcomes investigated included readmission, overall in-hospital mortality and gastrointestinal restoration rates. Overall in-hospital mortality was defined as all-cause mortality occurring either on the index admission

or a subsequent readmission that occurred within 90 days of discharge. Amongst 2070 patients identified, 1486 (71.8%) underwent a TAC compared to 584 (28.2%) who underwent a DLI. We found no difference in readmissions (TAC: 26.1% vs. DLI: 23.1%, *p* 0.26) or post-discharge in-hospital mortality (25.9% vs. 32.3%, *p* <0.001) based on type of operation. However, gastrointestinal restoration rates at 6 months were significantly higher after DLI on adjusted multivariate analysis (aOR 2.68 1.80-4.00). Closure of a diverting ileostomy being a technically easier operation and less morbid than takedown of an end-ileostomy with an ileorectal anastomosis, it was not surprising that the results of Neal *et al.* (DLI 42 patients, 73% closure) and Fashandi et al. (19 patients, 82% closure) were reproduced in our study (26.4% vs. 8.3%, p < 0.001). However, our study was the first study to demonstrate this higher rate of closure and the similarities of in-hospital mortality using a large database, further adding to the body of data on DLI. In addition, this is the first study to describe earlier time to ileostomy closure for patients who underwent DLI (median time-to-reversal 97.5(70.0-140.8) vs. 121(90.8-154) days). These outcomes are important in order to elucidate the longer-term trajectory of patients with FCDC undergoing surgery, especially after introducing a new procedure like DLI and colonic lavage.

National trends evaluating the surgical management of FCDC identified DLI as an increasingly accepted procedure[62]. Despite the growing body of evidence for DLI and its inclusion as a surgical option, a knowledge gap still remained with regards to DLI[49,77]. While administrative databases allowed me to evaluate long term outcomes (Chapter 4), they lacked the granular information reflecting the nuanced decision-making for FCDC. This is especially true with regards to detailed surgical management and post-discharge outcomes including recurrence

and antibiotic management around restoration of gastrointestinal continuity. I present the largest institutional cohort study of patients with FCDC undergoing operative management in the literature (Chapter 6). The charts of 177 patients from 11 North-American institutions were reviewed, 34 of whom underwent DLI. We did not find a difference in 30 (23.5% vs. 37.1%, *p* 0.10) or 90-day postoperative mortality (29.4% vs. 46.2%, *p* 0.10) for DLI vs. TAC. Multivariate logistic regression identified age (adjusted OR[95%CI]; 1.07[1.03-1.12]), preoperative vasopressor use (aOR, 5.39[1.96-14.83]), and creatinine levels (aOR, 1.34[1.07-1.69]) as independent predictors of 30-day mortality. Halabi et al identified similar predictors of mortality (age >60 OR 1.97, acute renal failure OR 1.67 and preoperative sepsis OR 1.40)[73].While no difference in post-operative mortality was found, we did find a decrease in postoperative major morbidity (defined by Clavien-Dindo Classification II-V) for patients undergoing DLI (aOR 0.33[0.11-0.97])[82]. This is similar to the findings of Neal et al of decreased morbidity associated with DLI including embolic complications, surgical site infections and pneumonia[58]. In addition, a decreased risk of surgical site infections was also detected (DLI 13.3% vs. TAC 33.1%, *p* 0.033), as it was in the study by Neal et al (DLI 7.1% vs. 21%)[58]. This was in part driven by the increased use of laparoscopy in DLI (n=17(50%)). Interestingly, Neal et al describe the creation of a DLI laparoscopically in the majority of patients (n=35(83%)). The difference in laparoscopic use may be the result of surgeon preference or patient factors prohibiting laparoscopic use.

With regards to reoperation for failure of DLI, only a small number of patients required conversion to TAC (n=3), due to abdominal compartment syndrome or persistent sepsis. Despite conversion to TAC, 2 of these patients passed away during the same hospitalization. These numbers are also similar to conversion to TAC described by Neal et al (3 of 42 patients)[58].

With the colon- primary site of disease- still in situ, the potential for increased risk of recurrence has been raised. In their institutional experience with DLI, Fashandi et al described a very high recurrence after DLI (TAC 30% vs. DLI 57%, *p* 0.35)[59]. This is much higher than the recurrence rate we found, which was also similar in both groups (TAC 7.4 % vs. DLI 7.7%, *p* 0.96). This was also partially evaluated by assessing readmissions using the NRD database (Chapter 4), which would capture recurrences severe enough to require hospitalization.

With regards to recurrence of CDI after ileostomy closure, one of the concerns was also that the recurrence would manifest in complicated disease, as described by the case report of a patient who had overwhelming CDI following gastrointestinal restoration[83]. Our study adds to the knowledge on the treatment of FCDC by being the first multicentre study to find low recurrence rates following gastrointestinal restoration for DLI or TAC (11% DLI vs. 10% TAC), and describe perioperative antibiotic management in these patients.

Increased rates and earlier time to restore gastrointestinal continuity for DLI vs. TAC was seen in our retrospective cohort study (Chapter 6) and in the NRD study (Chapter 4). Beyond the fact that diverting ileostomy closure is a technically easier operation than closure of an end ileostomy with an ileorectal anastomosis, this observation could also be a surrogate marker for recovery after the index FCDC episode. The morbidity of an ileorectal anastomosis (around 26%) being higher than that of a closure of a diverting loop ileostomy (estimated to be <5%), it is natural that this elective operation only be offered to patients who have fully recovered and have a good functional status[63,64].

In this dissertation, I described surgical outcomes of FCDC in the modern era. Nowadays, new surgical procedures like DLI for FCDC are constantly emerging, and are quickly and internationally disseminated. Prior to the implementation of a new technique like DLI for FCDC, rigorous research should test its outcomes and feasibility. The first identified challenge of research on surgical *C. difficile* is the challenge related to study design. While randomized controlled trials (RCT) are the gold standard study design to compare interventions because of their intrinsic low risk of bias, their application in surgical research is often limited. The quality of surgical research was criticized in a controversial commentary published in the Lancet in 1996 because of the low number of surgical publications that used a RCT design[84]. Despite the success in improving surgical research, it remains true that RCTs in surgery are rare[85]. This is multifactorial, in part due to difficulties in conducting RCTs in surgery with regards to recruitment (surgeon or patient preference), lack of blinding and difficulty with timing of the randomisation[86]. Authors have brought forth that basing the quality of surgical research solely on the use of RCTs is inadequate in view of the particular challenges that accompany surgical research[87].

This led to the development of frameworks like the IDEAL framework (Idea, Development, Exploration, Assessment, and Long-term study), whereby each step of the surgical development process is evaluated using various study designs[88]. The development phase focuses on the early experience of surgical innovation. In the case of DLI, an example would be the publication by Neal et al, of their single-center case series[58]. The exploration phase implies the replication by other clinicians, usually in the form of multicenter cohort studies. The application of this stage of the framework in the assessment of the role of DLI for FCDC is through multicentric prospective trial. After successfully securing grants to assess this important question, I launched this

prospective trial at 14 hospital centers in Canada. The trial design was a prospective non-randomized cohort study, due to expected difficulty of enrolling patients in an emergency situation and the equipoise that made surgeons uneasy about leaving treatment allocation to chance. This trial design was also selected as a randomized trial assessing the same question closed due to poor accrual[89]. This highlights the second identified challenge with regards to research on FCDC: difficulties in patient accrual in an acute life-threatening situation. This is not an uncommon situation: Chapman et al found that one in five surgical randomised controlled trials are discontinued early, and that in 44% of cases, this was due to poor recruitment[90]. Unfortunately, a further challenge that I faced was a change in the disease epidemiology with a decrease in cases of FCDC that prompted early termination of our prospective study as well. This highlights the third challenge in research on the surgical management of *C. difficile*: factors outside the investigator's control that impact recruitment, such as a changing disease epidemiology and decreased cases. The last stage of the framework is the long-term stage. Large cohort observational studies have a particularly important role in the assessment of this stage of a surgical innovation. They can evaluate safety in practice, assess rare events and long-term outcomes and evaluate treatment effects beyond those that were initially studied[86]. The inability to conduct prospective cohort or randomized studies has led me to resort to large cohort observational studies: I performed a multicentric retrospective cohort study (Chapter 6) and looked at both population-based studies using clinical registries (ACS-NSQIP, Chapter 2) and administrative data (NRD, Chapter 4). When evaluating this work, the inherent risks of selection bias conferred by the retrospective and cohort study design of included papers is an important limitation to consider. Despite the limitations associated with these study designs, attempts to decrease bias and improve the validity of these studies were made. First, our studies were

protocol-driven to allow for appropriate planning. Second, wherever possible, efforts to decrease missing data or handle missing data appropriately were made (for example the use of imputation in Chapter 2). Third, in each study, the outcomes evaluated were specific and measurable, minimizing information bias (for example mortality is a hard non-competing outcome). Finally, whenever feasible, regression analyses adjusting for confounding were performed.

CHAPTER 8: CONCLUSION

In this thesis, I developed a calculator to predict postoperative mortality after surgery for FCDC, evaluated long-term post-discharge outcomes, and described the surgical experience at 11 North American institutions with FCDC over the course of 8 years. A prospective study to evaluate the role of DLI for FCDC was developed, but a changing disease epidemiology led to the premature closure of the study. With difficulties in conducting prospective randomized trials, research evaluating rare surgical diseases in the acute setting require innovative solutions to identify the problem and generate evidence. Infectious diseases have an everchanging epidemiology, and clinical knowledge is additive, constantly building on prior discoveries. While the virulence of CDI is currently at bay, there is the constant threat that new virulent strains will emerge, or that colonic diseases with similar pathophysiology will require us to use the knowledge that we gained from this work [91].

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