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Clostridium difficile Infection and Colorectal Surgeries: A Narrative Review

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ABSTRACT

Clostridium difficile infection (CDI) is a significant health-related infection rarely seen in colorectal patients after surgery. However, over the past two decades, there has been an increase in the incidence and severity of CDI. In addition, the healthcare system is impacted significantly by the morbidity, mortality, and costs associated with CDI. While antibiotic use was initially thought to be the only cause, CDI has now been associated with hospitalization and residence in long-term care facilities. The risk of developing CDI is higher for patients who undergo gastrointestinal procedures, including colectomy. Hence, targeting preventive measures and reducing the burden associated with CDI can be achieved by identifying colorectal surgery patients at high risk for this increasingly prevalent disease. In the present article, we aim to review the current evidence of pre-and postoperative CDI in patients with underlying colorectal surgeries due to benign or malignant conditions, pointing to risk factors for infection, clinical impact, and outcomes.

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1. Introduction

Clostridium difficile infection (CDI) is the most common cause of healthcare-associated diarrhea. Over the past two decades, there has been an increase in the incidence and severity of CDI and it was found in approximately 20% to 30% of patients with antibiotic-associated diarrhea (1).

About 3% of healthy individuals are affected by *Clostridium difficile*, an anaerobic, gram-positive, spore-forming, and toxin-producer bacteria (2). However, the risk of developing CDI is higher for patients who undergo gastrointestinal procedures, such as colectomy (3, 4, 5).

The gastrointestinal microbiota protects the intestines, which prevents colonization and infection by pathogens (6). The suppression of commensal gut flora can cause *C. difficile* overgrowth, which may lead to colonic inflammation by producing toxins (7). The presence of two large exotoxins (TcdA and TcdB) in *C. difficile* results in colitis symptoms, including diarrhea, fever, and abdominal pain (8). In addition, fulminant colitis, toxic megacolon, and death may occur as a result of CDI in rare cases (2). CDI is characterized by risk factors such as old age (>65 years), antibiotic exposure, medical co-morbidity, malnutrition, long-term hospitalizations, immune deficiency, and PPI (proton pump inhibitors) (2, 9).

Watery diarrhea, a positive stool test for *C. difficile* toxins, or endoscopic/histological findings that demonstrate pseudomembranous colitis are necessary for CDI diagnosis (10). However, CDI can be transmitted to others by asymptomatic individuals with no clinical signs who are colonized without symptoms. The likelihood of asymptomatic colonization among healthy adults with no prior risk factors for CDI is from 0% to 15% (2, 11).

In this article, we review the current evidence on pre- and postoperative CDI in colorectal surgeries and highlight the epidemiological data, risk factors, and clinical outcomes.

2. C. difficile Infection After Colorectal Surgery

The incidence rate for postoperative CDI can vary from just over 1% to almost 20%, making it a potentially devastating complication after surgery (12, 13). In addition, the prevalence of patients who underwent colon surgery and stoma reversal is even higher (4%) than other procedures (14). The normal enteric flora is altered by preoperative mechanical bowel preparation and antibiotics, which increases the risk of *C. difficile* colonization and colitis (15). Many studies have reported colorectal surgery as a key risk factor for *C. difficile*-associated colitis. For instance, the incidence of *C. difficile*-associated colitis was 5.6%, as reported by Kent et al. after examining 374 surgery patients (12). In a study by Yeom et al., the rate of postoperative *C. difficile*-associated colitis was 6.8% (13). However, Damle et al. showed that 1.5% of patients experienced CDI after colorectal resection (16). In this section, the risk factors of CDI in various surgeries have been discussed.

2.1. C. difficile Infection in Malignant Conditions

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CDI is more likely to develop in patients with malignancy and its incidence in some cancer populations has been estimated to be roughly twofold higher than that in general hospital patients (17). The antibiotic-like activity of several chemotherapy drugs and neutropenia caused by chemotherapy are responsible for this (18). On the other hand, the gut microbiota barrier prevents *C. difficile* colonization in the large intestine, and cancer is a major risky condition since it can weaken this resistance and result in infection In addition, gut microbiota protection could be compromised by a relatively prolonged disease course and more aggressive treatment in patients with stage T4 and LN metastasis, which may facilitate *C. difficile* colonization (19, 20).

Several studies have explored the significance, risk factors, and outcomes of CDI in patients who have undergone colorectal surgeries due to colorectal cancer (5). To illustrate, in a study on 695,010 patients from the Nationwide Inpatient Sample from 2004 to 2006, Lesperance et al, found that 1.4% of individuals undergoing elective colonic resections had postoperative CDI. Compared to non-CDI cases, the risk of mortality and length of hospital stay were both significantly increased, along with significant increases in pulmonary and gastrointestinal complications (8). Yasunaga et al. also showed that in patients who undergo digestive cancer surgery, postsurgical CDI was associated with high mortality, long hospital stays, and high costs (21).

Rubin et al. reported tumors, chronic obstructive pulmonary disease, impairment of immune function, anti-peristaltic drugs, and renal impairment as potent risk factors for severe colitis in cancer patients with postoperative CDI (18). Yeom et al. also studied the risk factors for *C. difficile*-associated colitis after colorectal cancer surgery and declared that preoperative metallic stent insertion and age sixty and older were the potent risk factors (13). In another study, Hebbard et al. reported that in cancer patients undergoing gastro-intestinal/abdominal surgery, the cases who received chemotherapy, PPI therapy, or antibiotics 30 days before surgery, were significantly at higher risk for developing CDI (22). Gaertner et al. also revealed that in cancer patients who undergo elective colon and rectal operations, risk factors for postoperative CDI included a history of CDI, chronic PPI use, and mechanical bowel preparation (23). In 2017, Zheng et al. reported that CRC patients with more advanced disease (T4 or LN metastasis) who require adjuvant chemotherapy after surgery are more likely to have *C. difficile* colonization (24). Therefore, to avoid discontinuing chemotherapy due to severe diarrhea and postoperative complications, it is crucial to screen and monitor for *C. difficile* before surgery in these patients.

2.2. C. difficile *Infection in Benign Conditions*

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred option for patients with chronic ulcerative colitis (CUC) (25). The occurrence of inflammatory complications after IPAA, such as pouchitis, cuffitis, and Crohn's disease of the pouch, is frequent among individuals with underlying inflammatory bowel disease (IBD) (26, 27). On the other hand, IBD patients were identified as a risk category for CDI (27). Between 10.7 and 18.3% of IBD patients with an IPAA experience CDI (28, 29). The relationship between IBD and CDI has been assessed by several studies, with evidence showing higher rates of CDI and worse outcomes for those with IBD compared to controls (30). Damle et al. examined 84,648 patients undergoing colorectal surgery and demonstrated that IBD, emergent procedure, and higher severity of illness were significant risk factors for postoperative CDI. Moreover, they compared outcomes in CDI patients with non-CDI cases. They found that CDI could lead to a higher rate of complications, intensive care unit (ICU) admission, longer preoperative inpatient stay, 30-day readmission rate, and death within 30 days (16).

CDI has the potential to cause a refractory course of pouchitis, and the CDI of the pouch can be lethal (29, 31). According to Shen et al., CDI was found in 18.3% of symptomatic patients with ileal pouches and CDI in the pouch was more likely to occur among patients who were male or had preoperative left-sided colitis (29). The report by Li et al. also suggests that CDI in ileal pouch patients may be associated with recent hospitalization or constitutional symptoms, such as weight loss (28). In another study, sun et al. reported a postoperative CDI prevalence of 20.6% and established that the risk of postoperative CDI in the pouch was not affected by preoperative CDI. In addition, male patients were found to have an increased likelihood of having CDI of the pouch compared to their female counterparts. Their findings also indicated that postoperative CDI can be a result of preoperative comorbidities or antibiotic use for other indications. (32). Similarly, Lightner et al. observed no correlation between preoperative CDI and pouchitis risk in patients with CUC (25). In contrast to the mentioned studies, Skowron et al. showed that a pouch failure after reconstruction was related to a history of preoperative *C. difficile* colitis. Their study revealed that individuals with a history of CDI were more than twice as likely to develop CD of the pouch (33). In 2023, Shore et al. studied patients with chronic antibiotic-dependent pouchitis or Crohn 's-like disease of the pouch and revealed that 9.1% of the patients developed CDI. It was also observed that preoperative CDI seems to be the most significant risk factor for postoperative CDI (34), which was in line with the Skowron study (33). In addition, Ugarte et al. similar to Sun et al. found a strong association between CDI of the pouch and preoperative taking of antibiotics, PPIs, and immunosuppressive medications (35).

Razik et al. demonstrated through a retrospective analysis that IBD patients have a 33% higher likelihood of having recurrent CDI than the general population (36). Furthermore, it is common for patients with an ileal pouch with CDI, to experience refractory or recurrent disease. Seril et al. revealed that postsurgical mechanical intestinal complications or low serum immunoglobulin levels may lead to refractory or recurrent CDI (37).

Diverticular disease of the colon is a common problem that affects a substantial amount of the population, particularly elderly people, with an estimated incidence of 50-66% in individuals over the age of 80 (38). Diverticulitis is associated with worse CDI outcomes and a higher risk of recurrent CDI, as suggested by several studies. A large retrospective study conducted by Buchner et al. on the Veterans Administration population revealed that patients with diverticulitis were at an increased risk of CDI (39). In another study by Messick et al, on 24,700 operations over 10 years, diverticular disease along with older age and greater body mass index were the risk factors of postoperative CDI (40). However, in 2019, Abdalla et al. demonstrated that CDI in patients with diverticulosis and diverticulitis resulted in a significant decrease in mortality, shorter length of in-hospital stay, and lower hospitalization costs in comparison with those without diverticular disease (41). Their results were different from prior studies. On the other hand, Feuerstadt et al. compared "CDI and diverticulosis" patients with "CDI and no diverticulosis" cases, and the 30-day outcomes, which included intensive care unit requirement, hospitalization stay, and mortality, were found to have no significant differences. Their findings indicated that diverticulosis in the ascending colon is associated with an increased rate of CDI recurrence and a decrease in relapse in diverticular disease of the descending and sigmoid colon (42).

2.3. Stoma Reversal and the Risk of C. difficile *Infection*

Ileostomy reversal might lead to complications such as surgical site infection, which can be mitigated by the use of prophylactic antibiotics. Furthermore, the reversal of ileostomy is associated with an increased risk of CDI and its incidence is reported to be up to 4 percent in patients who undergo ileostomy closure, which can be associated with significant morbidity (14, 43). Patients who are undergoing ileostomy closure have undergone a previous surgical procedure that caused a hospital stay and usage of antibiotics. Moreover, animal model studies have demonstrated that the defunctioned colon undergoes both mucosal and muscular atrophy. When the colon is brought back into the circuit after stoma closure, infective diarrhea may occur due to parallel physiological and microbiological modifications in the small bowel and defunctioned colon (11).

CDI diagnosis is contingent upon watery diarrhea presence, a positive stool test for CDI toxins, or endoscopic/histological findings (10). On the other hand, diarrhea occurs frequently following stoma reversal, which could also be associated with diversion colitis. Hence, in patients who had stoma surgery, the diagnosis of this infection could be misleading and challenging (11).

In a retrospective colectomy database review of 2015, 2235 patients who underwent elective stoma reversal were compared with 10403 patients who underwent elective colon resection, and it was revealed that the patients undergoing stoma reversal were significantly at higher risk of CDI incidence in the 30-day

postoperative period. They also found that besides stoma reversal, smoking, steroids, and disseminated cancer were associated with postoperative CDI (44). Randall et al. also found that after ileostomy closure, CDI incidence increased by 4.2%, twice what was seen in right hemicolectomy and four times that observed for anterior resection (43). In a systematic review by Harries et al, they demonstrated that CDI following reversal of ileostomy occurs relatively uncommonly, and 1.8% of cases experienced CDI (14). Zacharioudakis et al also performed a meta-analysis of risk factors for CDI and found that patients who had been hospitalized within the previous three months were 63% more likely to develop CDI compared to those who had not (45). Recently, Kim et al. reported a 3.6% CDI incidence in patients who received ileostomy closure for rectal cancer. Furthermore, they revealed that adjuvant chemotherapy and anastomosis leakage (which leads to prolonged exposure to antibiotics) are the only risk factors for CDI (46).

The timing of ileostomy reversal should be carefully considered. In Harries et al. systematic review, all the included studies reported a mean defunctioning time over 6 months (14). In addition, Rubio-Perez et al. discovered a significant correlation between the incidence of pseudomembranous colitis and ileostomy reversal that is delayed for longer than 6 months; while 9 to 15 months was the range of reported defunctioning time for those affected (47). In 2023, Tirelli et al. documented that CDI after stoma reversal following Transanal Total Mesorectal Excision (TaTME) for rectal cancer is mainly influenced by delayed stoma closure (11).

Based on the mentioned studies, preoperative counseling is necessary to adequately inform patients about the risk of CDI before surgery. Furthermore, colonization detection before proceeding to surgery may be recommended for individuals who have been hospitalized within the past 3 months before the reversal of ileostomy. Minimizing the time delay for reversal beyond 6 months is also suggested.

3. Preoperative Oral Antibiotics in Colorectal Surgery

In colorectal surgery, it is common to use bowel preparation and prophylactic antibiotics to reduce complications, such as infection. Given the strong association between antibiotic usage and CDI, it is probable that pre-operative prophylactic antibiotics will lead to higher rates of post-operative diarrhea and CDI (48). The risk of CDI is highest when using antibiotics such as clindamycin, cephalosporins, fluoroquinolones, and also proton pump inhibitors (49).

The treatment of choice for CDI is oral therapy with metronidazole or vancomycin (2). The effectiveness of oral metronidazole and oral vancomycin in treating CDI is comparable, with both options significantly more efficient than intravenous metronidazole alone (50). In proven cases of mild to moderate CDI, current guidelines consistently recommend metronidazole as the first-line treatment due to its low cost and the emergence of vancomycin-resistant enterococcus (2).

There are no current guidelines for antibiotic prophylaxis in surgical patients to prevent CDI, and there is still limited literature available. Although the use of metronidazole as part of pre-operative bowel preparation has been suggested to play a role in reducing intestinal *C. difficile* colonization, this has not been shown to have any significance in previous studies (51). Most of the work has focused on controlling infection, minimizing antibiotic use, and reducing risk factors (52).

In the context of using pre-operative prophylactic antibiotics, Wren et al. showed that in elective colon surgery patients, oral antibiotic-treated cases had a higher rate of CDI than patients who did not receive oral antibiotics (48). In 2017, Fernandes et al. evaluated the rates of post-operative diarrhea and CDI in elective ileostomy reversal surgery patients given pre-operative single-shot metronidazole, compared with multiple doses of cefuroxime plus metronidazole. They found that patients who received single-dose metronidazole had a significantly lower rate of post-operative diarrhea and CDI (51). In 2017, Hebbard et al. showed that each day of cumulative antibiotic therapy leads to approximately a 4% increase in the risk of CDI development, and this effect may be multiplied if several antibiotics are administered (22). Earlier studies also suggested that factors such as an increase in cumulative dose, number of antibiotics, and days of antibiotic exposure are associated with an increase in CDI development (53). However, Yeom et al. observed no significant differences in the development of colitis when compared to patients with preoperative oral antibiotics and no oral antibiotics group (13). Recently, a systematic review was conducted by Khorasani et al. to determine the correlation between preoperative oral antibiotic use and the incidence of postoperative CDI in patients undergoing colorectal surgery. They found that in adult patients undergoing colorectal surgery, the odds of developing CDI were not significantly increased by the inclusion of prophylactic oral antibiotics in preoperative bowel preparation. Moreover, they suggested that considering the beneficial role of oral antibiotics in the reduction of surgical site infections, the fear of CDI is not sufficient to avoid oral antibiotics in this setting (54).

Therefore, it is necessary to plan prophylactic antibiotics carefully and conduct further trials to examine the ideal prophylactic antibiotic choice.

4. Conclusion

C. difficile-associated colitis has the potential to extend the length of hospitalization required after surgery, raise expenses, and impact both morbidity and mortality. Thus, it is important to evaluate the risk factors for CDI at admission, early diagnosis, and treatment of *C. difficile*-associated colitis with care and thoroughness. CDI occurs at high rates after colorectal surgery, especially stoma reversal. In addition, CRC patients and cases with IBD are at greater risk of postoperative CDI. Therefore, strategies to prevent CDI are necessary in these cases, particularly for elderly patients over 60 years old. More investigation is required to verify the risk factors and effects of CDI in colorectal surgeries. A multicentric registry would be also helpful in assessing the impact of CDI in colorectal surgery. A comprehensive analysis of a large number of cases would provide insight into the role of this hospital-acquired or healthcare-associated infection in the postoperative course of colorectal surgical patients.

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