

## Clostridium Difficile Infection in Rectal Cancer Patients after Diverted Loop Ileostomy Closure

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**Abbreviations:**

CDI: Clostridium Difficile Infection;  
Gy: Grey;  
BMI: body mass index.

### Rezumat

#### *Infecția cu Clostridium difficile la pacienții cu cancer de rect după închiderea de ileostomie*

**Scopul:** Infecția cu *Clostridium difficile* reprezintă o cauză de morbiditate și mortalitate crescută în mediul spitalicesc, în special la pacienții cu patologie oncologică. Există mai mulți factori favorizanți de dezvoltare a infecției cu *Clostridium difficile* în rândul pacienților oncologici, dintre care enumerăm vârsta, expunerea la antibioterapie și inhibitori de pompă de proton, cât și chimioterapia. Acest studiu a fost efectuat pentru a observa prevalența infecției cu *Clostridium difficile* în momentul închiderii ileostomiei protective din chirurgia cancerului de rect, efectuată atât pe cale clasică, cât și prin abord laparoscopic.

**Metodă:** Un studiu retrospectiv al pacienților operați într-o singură echipă chirurgicală pentru cancer de rect ce au beneficiat de ileostomie derivativă, pe o perioadă de 4 ani.

**Rezultate:** 23 pacienți au prezentat infecție cu *Clostridium difficile*, dintr-un total de 63. Toți cei 23 pacienți au beneficiat de închiderea de ileostomie la peste 3 luni de la intervenția primară, iar post-operator precoce li s-a administrat antibioticoterapie asociată cu inhibitori de pompă de protoni.

**Concluzii:** Închiderea de ileostomie la mai mult de 3 luni de la intervenția principală, asociată cu chimioterapia, antibioticoterapia și inhibitori de pompă de protoni, crește riscul de a dezvolta infecție cu *Clostridium difficile*.

**Cuvinte cheie:** *Clostridium difficile*, ileostomie derivativă, închidere

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**Abstract**

**Aim:** *Clostridium difficile* infection is a cause of increased morbidity and mortality in hospitals, particularly in patients with cancer pathology. There are several factors favouring the development of *Clostridium difficile* infection among cancer patients, including age, exposure to antibiotic and proton pump inhibitors therapy, and chemotherapy. This study was conducted to observe the prevalence of *Clostridium difficile* infection after the reversal of ileostomy loop for rectal cancer surgery, which were initially operated either open or laparoscopic.

**Method:** A retrospective study was performed on patients who were operated in a single surgical team for rectal cancer who benefited of a diverted loop ileostomy over a 4-year period.

**Results:** 23 patients were documented with *Clostridium difficile* infection out of a total of 63. All 23 patients underwent ileostomy closure later than 3 months after primary surgery, and post-operatively received antibiotic therapy associated with proton pump inhibitors in the first 24 hours.

**Conclusions:** Closure of ileostomy later than 3 months after primary surgery, combined with chemotherapy, antibiotic therapy and proton pump inhibitors, increases the risk of developing *Clostridium difficile* infection.

**Key words:** *Clostridium difficile*, loop ileostomy, closure

**Introduction**

*Clostridium difficile* (CD) is a gram-positive, anaerobic, spore-forming bacterium found in approximately 3% of the healthy population associated with significant morbidity and mortality in the hospital environment, being the leading cause of antibiotic-associated diarrhea, colitis, toxic megacolon and pseudomembranous colitis (1-4).

*Clostridium difficile* mainly colonizes the large bowel as a part of normal intestinal flora, having toxigenic and non-toxigenic strains. Releasing of exotoxins as TcdA and TcdB results in colitis and other diseases (5-7).

Toxin A, an enterotoxin, causes excretion of inflammatory fluid from the colonic epithelium. In contrast, toxin B, a cytotoxin, causes loss of polarity and cell death by disrupting the actin cytoskeletal components of the colonocyte (8).

Disease development is strongly associated with antibiotic use in over 96% of patients. However, other risk factors of *Clostridium difficile* infection are: advanced age, renal insufficiency, immunosuppression; presence of nasogastric tube; recent gastrointestinal procedures; acid secretory therapy and exposure to health-care services (8,9).

Moreover, older adults are more likely to develop severe CDI, as well as other fatal complications, due to age-related changes in the intestinal microbiota and their immune response to infection (10,11).

The spectrum of CDI can range from mild to life-threatening fulminant colitis.

In the 2017 Infectious Diseases Society of America (IDSA) guidelines, definition of severe CDI is based on expert opinion and comprised markers: leukocytosis >15.000 cells/ $\mu$ l or a serum creatinine level > 1.5 mg/ dL (6).

An increase in *Clostridium difficile* infection (CDI) has been noted amongst patients underwent colorectal surgery (2,12), furthermore postoperative CDI has been reported in multiple cases following ileostomy closure (1).

Proximal faecal diversion by forming defunctioning ileostomy is widely used to protect distal anastomosis in patients having low anterior resection for rectal cancer, which are at higher danger of anastomotic leakage (13,14).

Although being perceived as a relatively minor procedure, reversal of ileostomy is associated with significant morbidity (1). A systematic review of 48 studies including 6.107 cases was made and found the overall morbidity to be 17.3%, with a mortality of 0.4% (15).

**Table 1.** Localisation of the tumour, the operative approach (either open or laparoscopic) and number of patients who benefited of diverted ileostomy

Localisation		Open		Laparoscopic		Loop ileostomy	
		No of cases	N %	No of cases	N %	No of cases	N %
Low rectum		15	21%	18	35%	11	16%
Medium rectum		33	45%	19	37%	44	66%
Superior rectum		25	34%	14	28%	12	18%
Total		73	100.0%	51	100.0%	67	100.0%

Although the exact mechanism by which the reversal of ileostomy increases the risk of developing CDI is unknown, postoperative CDI following ileostomy closure has been reported in multiple case series (1).

Despite the unclear association between the reversal of ileostomy and the development of CDI, Wilson et al in a large series of 13245 United States patients undergoing ileostomy closure, reported an incidence of 1.6% of pseudo-membranous colitis, which makes it an important factor to be considered, especially if an earlier closure can, in fact, reduce the risk (16).

## Materials and Methods

A retrospective study of rectal cancer patients who underwent oncological surgery, in elective conditions, followed by reversal of loop ileostomy, in a single surgical center, was conducted between 01.01.2017 until 31.12.2020, which postoperatively developed diarrhoea, with or without the *Clostridium difficile* positive tests.

In a four-year period, 124 patients underwent surgery for rectal cancer. The exclusion criteria in this study was first the patients who did not benefit of loop ileostomy, complicated forms of rectal cancer with metastatic or locally advanced tumours, and also patients that were surgically approached in emergency conditions, due to tumoral complications, such as perforation, bleeding or intestinal obstruction.

All statistical reports were obtained by using IBM SPSS Statistics Version 27.

Summary data for categorical variables is presented as counts and percentages, while for continuous data central tendency indicators

(mean or median) and dispersion indicators (standard deviation or range) as appropriate, based on the evaluation of the normality of the distribution were used. The normality was assessed through visual inspection of the histogram and Shapiro-Wilk test. For comparing continuous data between two groups we used T test (for normally distributed data) or Mann-Whitney U (for data with a distribution different from normal), based on the evaluation of the distribution of the data.

The level for statistical significance was consider  $p < 0.05$ .

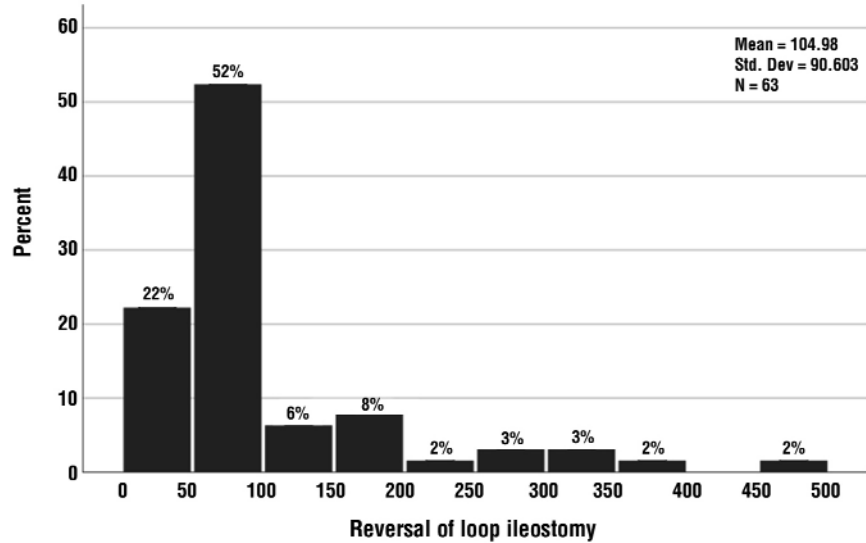
## Results

In a four-year period, 124 patients underwent surgery for rectal cancer, either laparoscopic or open procedure, out of which 67 benefited of a diverted loop ileostomy (Table 1). We can observe that 59% of the patients underwent surgery in an open approach, and 41% underwent laparoscopic approach (Table 2). Out of 124 patients, 50.4% of the patients benefited of a loop ileostomy. Closure of the loop ileostomy was performed in 63 patients, in a period between 33 days to 491 days, with a mean of 104 days (Fig. 1).

Out of all 124 patients with rectal cancer, 88 benefited of neoadjuvant radiotherapy, representing 71% of the total, while in 36

**Table 2.** Number of surgeries and percentages for the rectal cancer, in terms of technique

	No of cases	Percent
Laparoscopic	51	41%
Open	73	59%

**Figure 1.** Reversal of loop ileostomy**Table 3.** Comorbidities of the rectal cancer patients who benefited of diverted loop ileostomy, gender classification

	Male		Female		Total	
	No of cases	N %	No of cases	N %	No of cases	N %
Obesity	11	69%	5	31%	16	100.0%
Type 2 Diabetes	12	75%	4	25%	16	100.0%
Hypertension	23	58%	17	42%	40	100.0%

patients, primary rectal surgery was performed, representing 29%. All 88 patients underwent neoadjuvant radiotherapy, either VMAT or IMRT technique, with the maximum dose of 50.4 Gy.

After the primary surgery for rectal cancer, 88.7% of the patients underwent adjuvant chemotherapy, most of the patients being histologically diagnosed with G2 adenocarcinoma.

From those 67 patients, who were initially operated for rectal cancer and benefited of diverted loop ileostomy, had a mean age of 67.09 years old, with a minimum of age of 40 and a maximum of 89, and, in terms of comorbidities we can observe that 40 patients had arterial hypertension (23 males, and 17 females), 16 patients presented type 2 diabetes mellitus and obesity (Table 3) with a mean BMI of 26.59 kg/m<sup>2</sup>, with a maximum of BMI of 41 kg/m<sup>2</sup>.

Out of 63 patients who underwent reversal

loop ileostomy, 89% of the patients needed adjuvant chemotherapy, while 11% did not (Table 4).

Reversal of ileostomy had a range between 33 days to a maximum of 491 days after the primary surgery, with a median of 67 days, most of the reversal being performed under 100 days after the primary surgery. The distribution of the data differed in a statistically significant way from a normal distribution (skewed histogram and significant Shapiro-Wilk test p<0.001). The patients who underwent reversal of the loop ileostomy under 100

**Table 4.** Patients who underwent reversal of loop ileostomy, who needed adjuvant chemotherapy, and developed diarrheic syndrome or Clostridium Difficile infection after the reversal

Reversal of loop ileostomy	N	% of Total N
Adjuvant chemotherapy	56	89%
Diarrheic syndrome	46	73%
Clostridium Difficile	23	37%

days, either did not require postoperative chemotherapy or they had the second surgery before starting the oncological treatment. In this matter, most of the patients in the current study, were initially diagnosed in 35 cases with T2 tumours, representing 52% of cases, followed by T3 tumours, in 24 cases, representing 36%.

73% of the patients developed diarrhetic syndrome (Table 4) after the reversal of loop ileostomy, while 37% of the patients, were tested positive for *Clostridium difficile* infection (Table 4). From those 23 patients with CDI infection, 16 were tested positive for both toxin A and B, while, 7 were tested positive either for toxin A or toxin B. Onset symptomatology had a range between 1 to 4 days, with mean of 1.68 days, and a remission of symptomatology between 2 and 8 days, with a mean of 3.37 days (Table 5).

Patients who developed diarrhetic syndrome, without the presence of *Clostridium difficile*, were treated by adding to their medication probiotics, which lead to a favourable evolution, with normalization of the stool consistency in 2 to 3 days.

All patients who developed *Clostridium difficile* infection, benefited of reversal of loop ileostomy after 90 days (Table 6), and were treated first day postoperatively, prior to the onset symptomatology, with inhibitor pump proton and antibiotics. The observed difference between the two groups (patients with or without C. difficile infection) was statistically significant ( $z=6.19$ ,  $p<0.001$ ).

As it is studied in literature, association of inhibitor pump protons and antibiotics have higher risk to develop CDI. Also, all patients

who had reversal of loop ileostomy later than 100 days, developed CDI.

For all patients who were tested positive for CDI, Mentronizadole 0.5 g every 8 hours intravenous for 5 days, continuing for next 10 days orally, and Vancomicine 125 mg every 6 hours orally was added to their medication (17). All patients were isolated in a hospital room with private bathroom. Out of 23 patients, 7 of them developed mild to severe form of CDI, with biological impact, with decreased levels of natrium (up to 125 mmol/l) and kalium (2.9 mmol/l), and a moderate increase of creatinine and urea, up to 2.1 mg/dL for creatinine, 110 mg/dL for urea. 2 patients had a recurrence in the first 15 days after the initial remission.

In terms of postoperative complications, none of the patients developed anastomotic leakage or bleeding, nor intestinal bowel obstructions. However 3 patients (4.76% of cases) developed wound infections, that required prolonged antibiotic therapy after the bacterial wound culture study.

## Discussions

We observed as well as in the literature, a high incidence of developing CDI after loop ileostomy closure, the incidence in our team being 37%. After studying the literature, we observed that worldwide the ileostomy loop closure was performed 6 to 8 months after the primary surgical intervention, while in our team the closure was performed at approximately 3.5 months later.

Reviewing the literature, and also in our current practice, we observed a higher incidence of developing a CDI in patients

**Table 5.** Statistics

	Onset symptomatology		Remission	
	Valid	Missing		
N	63	0	63	0
Mean	1.68		3.37	
Std. deviation	1.216		2.743	
Median	2.00		3.00	
Minimum	0		0	
Maximum	4		8	

**Table 6.** Reversal of loop ileostomy

	<i>Clostridium difficile</i>		
	No	Yes	Total
N	40	23	63
Mean	60.00	183.22	104.98
Std. Deviation	23.206	110.007	90.603
Median	63.00	144.00	67.00
Minimum	33	66	33
Maximum	182	491	491

which had an association of antibiotics with proton pump inhibitors (16,18). Also, an important fact that has to be kept in mind, is that all the patients who undergo loop ileostomy closure, have been at least once admitted in hospital in the last year for the primary surgery, and they already have been exposed to perioperative antibiotics and proton pump inhibitors, which can also increase the risk of developing CDI.

In our study, the initial hospitalization was between 2 and 16 days, with a mean of 8.73 days (Table 7). In this period, to all patients were administrated cephalosporin and Metronidazol antibiotics for 5 days, associated with proton pump inhibitors for 2 to 3 days.

In our current study, we observed a higher rate of reversal of loop ileostomy under 100 days (with a mean of 84.33 days) for patients who were initially operated by laparoscopic approach. In comparison, most of the patients who underwent primary surgery in an open approach, had the reversal of loop ileostomy after 100 days, with a mean of 123.76 days.

The observed differences (Table 8) are statistically significant ( $z=1.99$ ,  $p=0.047$ ), indicating a higher number of days to reversal of loop ileostomy in patients with open intervention.

Although, we can't say that the laparoscopic approach can decrease the incidence of *Clostridium difficile* infections, we can assume that, an early closure of loop ileostomy, may reduce the risks of developing CDI.

The patients who developed CDI had a longer hospitalization, with an average of 8 days, comparing to those who had diarrheic syndrome or had a favourable postoperative outcome, which is also suggested by other authors (19-21).

Another risk factor for developing a CDI observed in our patients was the administration of adjuvant chemotherapy. As it is showed above (Table 9, 10), most of the patients needed postoperative chemotherapy, and association of it with delayed diverted ileostomy closure increased the risks of developing CDI.

**Table 7.** Initial hospitalization days

Mean	8.73
Median	8.00
Std. Deviation	2.847
Range	14
Minimum	2
Maximum	16

**Table 8.** Reversal of loop ileostomy

	Intervention Type		
	Open	Laparoscopic	Total
N	33	30	63
Mean	123.76	84.33	104.98
Std. Deviation	103.616	69.719	90.603
Median	69.00	64.00	67.00
Minimum	33	37	33
Maximum	491	352	491

**Table 9.** Reversal of loop ileostomy

	<i>Clostridium difficile</i>		
	No	Yes	Total
N	40	23	63
Mean	60.00	183.22	104.98
Std. Deviation	23.206	110.007	90.603
Median	63.00	144.00	67.00
Minimum	33	66	33
Maximum	182	491	491

Significant statistic value ( $z=6.194$ ,  $p<0.001$ )

**Table 10.** Reversal of loop ileostomy

	Diarrheic syndrome		
	No	Yes	Total
N	17	46	63
Mean	45.24	127.07	104.98
Std. Deviation	9.641	97.107	90.603
Median	44.00	82.00	67.00
Minimum	33	62	33
Maximum	67	491	491

Significant statistic value ( $z=5.773$ ,  $p<0.001$ )

## Conclusions

CDI represents an important morbidity factor in patients with surgically removed rectal cancer who benefited of loop ileostomy closure,

but with low incidence mortality. We consider that sooner closure of the loop ileostomy in patients with low risks in developing anastomotic leakage, before starting the adjuvant chemotherapy may reduce the incidence of CDI. Supplementary studies should be conducted in order to develop a guideline considering the best period for loop ileostomy closure, in order to prevent the development of CDI.

### Author's Contributions

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All authors have read and agreed to the published version of the manuscript.

### Conflict of Interest

The authors declare no conflict of interest.

### Ethical Statement

The current study has an ethical approval waived by the local Ethics Committee of Emergency County Hospital Constanta, Romania, no. 16/05.12.2018.

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