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## **Postoperative diarrhea in Crohn's disease: Pathogenesis, diagnosis, and therapy**

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### **Abstract**

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Diarrhea is a frequent symptom in postoperative patients with Crohn's diseases (CD) patients, and several different mechanisms likely account for postoperative diarrhea in CD. A targeted strategy based on a comprehensive understanding of postoperative diarrhea is helpful for better postoperative recovery.

### **INTRODUCTION**

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Crohn's disease (CD) is an unexplained intestinal inflammatory disease that affects the entire digestive tract. It involves chronic inflammation of the intestine, damage and distortion of tissue architecture, and loss of digestive functions. This can lead to intestinal stenosis; intestinal fistula; abdominal abscess; and other complications such as malnutrition, perianal lesions, and diarrhea. Statistically, > 50% of the patients with CD require surgical intervention for unmanageable disease, and many require repeated surgery for recurrent disease. Although biological agents reduce the risks associated with CD surgery, surgery is still one of the main treatments for CD. Diarrhea is a prevalent symptom of CD. Approximately 82% of the patients with CD present with diarrhea during the course of the disease [1]. Diarrhea is one of the important factors that affect the postoperative quality of life in patients with CD. Previous studies reported that the incidence of postoperative diarrhea was 24% in patients with colon cancer and 79% in patients with ileum resection of over 10 cm [2-4]. Postoperative diarrhea can be

divided into inflammatory and noninflammatory diarrhea. Because of the characteristics of CD, postoperative diarrhea is clinically very common; however, not much attention is paid to it. In this article, we review the causes, diagnoses, and treatments of postoperative diarrhea in CD.

## Causes of postoperative diarrhea in CD

### 1.1 Gut microbiota disorders

The gut microbiota is considered an additional organ of the human body and is populated by a complex and dynamic microbial ensemble<sup>[5]</sup>. According to previous studies, the number of bacterial species in gut microbiota range from 1,000–1,150 and each human has at least 160 species<sup>[5]</sup>. It is different in various parts of the intestine<sup>[6]</sup>. The homeostasis of gut microbiota is the basis of digestive functions. <sup>10</sup> The gut microbiota of patients with inflammatory bowel disease (IBD) is characterized by low microbial diversity, for instance, a reduction in *Bifidobacterium* and *Lactobacillus* sp. and an increase in adherent/invasive *Escherichia coli* or *Clostridium difficile* compared with healthy controls<sup>[7–10]</sup>. As the diversity of gut microbiota is changed, its ability to respond to external environment changes <sup>[11, 12]</sup>.

The ileocecal valve can be considered a “fence” that isolates the contents of the colon and small intestine. The ileocecum is also the most commonly involved location in CD. Dysfunction of ileocecum may lead to the loss of this “fence” and alters the number and variety of microbiota species in the small intestine. Disturbance in the small intestinal microbiota would cause small bowel bacterial overgrowth (SIBO) <sup>[13]</sup>. A retrospective observational cohort research a substantial increase in the prevalence of SIBO in patients with CD compared with healthy individuals, and was independently linked to clinical relapse in quiescent patients<sup>[14]</sup>. CD patients were supposed to be at higher risk of SIBO after loss of ileocecum caused by resection. Overall, surgery will alter the intestinal histology, physiology, or microbiota and further aggravate dysbiosis. This would lead to the occurrence of SIBO and increased possibility of postoperative diarrhea<sup>[14, 15]</sup>.

In addition, some specific bacteria in the gut can cause diarrhea<sup>[16, 17]</sup>, such as adherent/invasive *E. coli*, *C. difficile*. An increase in the incidence and severity of *C. difficile*-associated diarrhea (CDAD) is observed in patients with CD<sup>[18-20]</sup>. Abdominal surgery is thought to be a risk factor for CDAD. The reported rates of postoperative CDAD range from 0.2%–8.4%<sup>[21-23]</sup>. Moreover, the use of antibiotics, glucocorticoid, and biological agents, would increase the risk of postoperative CDAD<sup>[10, 24-28]</sup>. Therefore, we should pay attention to the specific bacteria related to postoperative diarrhea.

### 1.2 Bile Acid (BA) Diarrhea (BAD)

BA is the end-product of cholesterol catabolism and is synthesized in the liver, excreted into the duodenum in bile, reabsorbed in the ileum, and then recirculated back to the liver<sup>[29-32]</sup>.

The effects of BA on the intestine include: (1) induce high amplitude propagated contractions in colonic, (2) increased intestinal mucosal permeability, (3) induced secretion of water and electrolytes, and (4) expedited colonic transit. Therefore, ileal dysfunction, impaired reabsorption, or disorders of BA metabolism would lead to diarrhea. (Figure 1)

The types of BAD are based on the original classification of BA malabsorption<sup>[33]</sup>:

- (1) Type 1: BAD caused by ileal dysfunction and impaired reabsorption, as related to CD in the ileum and/or ileal resection<sup>[34, 35]</sup>.
- (2) Type 2: Primary or idiopathic BAD producing high levels of fecal BA, watery diarrhea, and response to BA sequestrants in the absence of ileal or other obvious gastrointestinal diseases. This type may be related to FGF-19<sup>[36]</sup>.
- (3) Type 3: BAD due to other gastrointestinal disorders that affect absorption, such as SIBO, celiac disease, or chronic pancreatitis<sup>[37]</sup>.

Recent studies suggested that BA levels are significantly reduced in patients with IBD. Significant reductions of the pool size of chenodeoxycholic acid, and the total bile acid in patients with CD compared with those in normal subjects were observed<sup>[38]</sup>. Patients with active disease are more likely to have BA absorption disorders than those with



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causing diarrhea. Patients with CD usually have intestinal edema due to malnutrition or hypoproteinemia, resulting in osmotic diarrhea due to poor intestinal absorption. About 65-75% of patients with Crohn's disease have undernutrition<sup>[50]</sup>. 2). Intolerance to enteral nutrition components. Lipase deficiency can occur postoperatively in patients. About 1.6% of patients with Crohn's disease were diagnosed with celiac disease<sup>[51]</sup>. Infections or malnutrition can cause lactase deficiency. If the components of enteral nutrition contain substances that cannot be digested and absorbed, such as those with higher lipid content, it will lead to diarrhea. (3). If the enteral nutrition infusion speed is too fast, it will lead to diarrhea. Enteral nutrition contains a large number of nutrients. It is a good "bacterial culture medium." The bacterial infection leads to disorders of intestinal flora, causing diarrhea. In recent years, strategy to enhance recovery after surgery is getting increasing attention. Early enteral nutrition support speeds up the postoperative recovery of patients. However, ignoring the influence of the above related factors may lead to postoperative diarrhea and affect postoperative recovery.

#### 1.4 *Diversion colitis*

Diversion colitis is considered a nonspecific inflammation in the diverted colon. Glotzer named this inflammation "diversion colitis" in 1981. Since then, the disease has been reported in both retrospective and prospective studies<sup>[52-54]</sup>. The term diversion colitis (DC) is usually used in cases of resection of descending and/or sigmoid colon, in which the remaining rectum is either buried in the abdomen or externalized as a mucinous fistula. As a consequence of the absence of feces, SCFAs (which are the source of the left colon mucosa cells) are absent in the rectal or rectosigmoid energy stump, resulting in the appearance of an inflammatory process which may not substantially differ from the inflammation appearing in ulcerative colitis<sup>[55-57]</sup>. In CD, due to preoperative intestinal obstruction, intestinal fistula, or abdominal infection, the one-stage anastomosis may not be performed; diversion colitis may occur in these patients. The reason for diversion colitis may be a shortage of short-chain fatty acids<sup>[58]</sup>. Butyrate is a type of short-chain fatty acid and has been proven to reduce inflammation<sup>[59, 60]</sup>.

Studies have reported that patients with IBD have relatively low levels of short-chain fatty acids in the gut compared with healthy individuals <sup>[61]</sup>. Short-chain fatty acids are the main end-product of carbohydrate metabolism by bacteria in the gastrointestinal tract and constitute approximately 10% of the daily calories required by the human body<sup>[62]</sup>. Reduced levels of short-chain fatty acids can lead to reduced absorption of NaCl and water, resulting in diarrhea<sup>[63]</sup>. Patients with CD in the perioperative period may use antibiotics to control the infection, which will undoubtedly reduce the synthesis of short-chain fatty acids. Therefore, postoperatively, patients with CD may exhibit a higher probability of occurrence of diarrhea due to a lack of short-chain fatty acids than patients with other diseases.

#### *1.5 Early postoperative inflammatory activity*

Although surgery is able to alleviate the symptoms and resolve the related complications it can not cure CD. Most patients suffer postoperative recurrence. Studies have reported that the risk of post-operative endoscopic recurrence in CD was 90% by one year<sup>[64]</sup>, and within 1 year after the surgery, nearly 30% of the CD patients developed clinical recurrence, and 5%–10% of them required surgical treatment<sup>[64, 65]</sup>. The shortest recorded relapse time is within 1 wk after the surgery <sup>[66]</sup>. Histological disease activity in an endoscopically normal neoterminal ileum may occur as early as one week after surgery <sup>[67]</sup>. The most common clinical symptom of early intestinal inflammatory activity is diarrhea. Therefore, diarrhea is more likely to occur after surgery in patients with CD than in patients with other diseases.

#### *1.6 Short bowel syndrome*

Some patients with CD may have an increased area of intestinal lesions as they may have had more intestinal mass removed by emergency surgery due to perforation. It is generally believed that to meet the body's nutritional needs, the small intestine should be at least 100-cm long and have a complete colon, and the small intestine that remains after colectomy should be more. The intestine has a strong compensatory



capacity. The removal of 50% of the intestinal absorption area may not severely affect digestion and absorption; however, if > 75% of the intestinal absorption area is removed, the patients may exhibit short bowel syndrome after surgical treatment. The removal of a big mass of the small intestine leads to increased secretion of gastric acid, increased secretion by the small intestine and colon, and peristaltic acceleration, resulting in postoperative diarrhea. Patients with Crohn's disease are at high risk for recurrent disease and often undergo multiple operations. A recent review suggests the incidence of SBS is 0.8% at 5 years, 3.6% at 10 years, and 8.5% at 20 years after surgery in CD<sup>[68]</sup>. IBD-related SBS remains a challenging issue.

### 1.7 Irritable Bowel Syndrome (IBS)

Infection at the incision site may cause pain and the slow recovery of intestinal functions. Additionally, it may cause abdominal pain, diarrhea, and postoperative emotional anxiety. This type of diarrhea may be due to IBS. This clinical manifestation of diarrhea and abdominal pain is difficult to distinguish from IBD <sup>[69]</sup>. Marie systematically reviewed 12 studies and reported that postoperatively, patients with IBD had a higher risk of depression than other patients<sup>[70]</sup>. Symptoms of anxiety and depression are more common in Asian patients with IBD <sup>[71]</sup>. Due to the disease itself and the postoperative recurrence of CD, patients with CD may have a higher probability of acquiring IBS after surgery. IBS can affect gastrointestinal motility and change the gut microbiota, leading to diarrhea <sup>[72]</sup>. Patients with CD and IBS may have a higher risk of postoperative diarrhea than other patients.

### Evaluation Of Postoperative Diarrhea in Crohn's disease

Diarrhea should be assessed based on history and clinical features. Additionally, some specific clinical features can help us to investigate the cause of diarrhea <sup>[73]</sup>. For instance, in diarrhea caused by bacteria, feces can have specific odors, *e.g.*, fishy. Considering the possibility of bacterial infection, diarrhea caused by *C. difficile* often exhibits "egg patterns," and with a severe *C. difficile* infection, exfoliated intestinal



mucosa can be observed in feces. In diarrhea caused by BAD, the color of feces is often "dark green." In osmotic diarrhea, undigested enteral nutrition may be observed in the feces. Intestinal mucus is often observed in the feces of patients with diversion colitis. In diarrhea due to short bowel syndrome, feces are bulky and contain undigested food. Patients with IBS after surgery for CD may simply present with an increased frequency of defecation; however, the volume of feces is not large. Medical history should include the patient's past physical condition, recent drug history, eating habits, and other related problems. <sup>2</sup> Characteristics of the feces, including the presence of visible blood, pus, mucus, fat, and undigested food particles, may suggest a potential pathophysiological mechanism and guide further evaluation. <sup>3</sup> Moreover, it is important to review the diet and medication history. Abdominal examination should be done in order to confirm or exclude acute abdominal processes. Rectal examination is mandatory to assess the presence of blood in stool and stool consistency.

Laboratory tests should include routine blood, electrolytes, liver function, and renal function tests. If a patient has malabsorption, the status of trace elements should be clarified. The relevant examination results can indicate whether a patient has metabolic disorders and help the doctor in assessing the patient's current physical condition. Analysis of feces can provide important information, particularly for patients with CD. <sup>1</sup> Fecal calprotectin is a very sensitive marker for inflammation in the gastrointestinal tract and is useful for differentiating IBD from IBS. Fecal calprotectin is used in the diagnosis of IBD, monitoring disease activity, treatment guidance, and prediction of disease relapse and postoperative recurrence [74-76]. Besides, endoscopy or radiologic imaging should be consider if the diagnosis is unclear.

Diarrhea is usually caused by a single factor; however, for patients with CD, diarrhea should be assessed in detail. First, CD is a type of intestinal inflammation with unknown causes, and intestinal inflammation can cause diarrhea. Second, intestinal function is correlated with the intestinal environment and gut microbiota. These factors may interact with each other. Surgical treatment is a strategy to relieve the symptoms of the disease but not to cure the disease. Moreover, postoperative lesions can cause

diarrhea. After surgical treatment, the cause of preoperative diarrhea may change, and the strategy to treat postoperative diarrhea should be changed according to the course of the disease. Therefore, postoperative diarrhea in patients with CD needs to be evaluated from multiple perspectives.

## Treatment

Diarrhea can be acute, persistent, or chronic. The majority of cases of acute diarrhea are self-limiting. Patients with signs of dehydration, such as dry mouth, swollen tongue, and change in mental status, should be noticed. Therapeutic options in acute diarrhea patients include oral rehydration, early refeeding, antidiarrheal medications, antibiotics, probiotics. However, for patients with CD, the treatment strategy for diarrhea needs to be designed after considering patients' medical history, medication, surgical methods to make a comprehensive judgment. Some patients may require comprehensive treatment because of two or more factors. The treatment method is flexible for patients with diarrhea due to the same cause.

Diarrhea due to inflammatory disease, controlling inflammation is extremely important. Medications, such as cortisol hormones, immunosuppressants, and biological agents, are used to induce and maintain clinical remission. The choice of drugs should be based on the patient's previous treatment<sup>[77-79]</sup>. In cases of enteric infection, appropriate antimicrobial therapy should be provided. CDAD is initially treated with metronidazole. Early use of vancomycin is recommended for patients with symptoms of severe CDAD or if a patient's condition fails to improve or deteriorates after metronidazole administration. If there is evidence of SIBO, antibiotics such as tetracyclines, ciprofloxacin, metronidazole, or rifaximin can be considered. In patients with ileal disease or resection, cholestyramine can ameliorate or abolish diarrhea by binding to bile salts in the lumen of the intestine. Cholestyramine is given in divided doses before meals and separated from other medications. Many patients with diarrhea-predominant IBD benefit from nonspecific antidiarrheal therapy. Opiate drugs, such as loperamide and diphenoxylate, primarily slow intestinal transit and allow more contact

time for absorption. Probiotics may be also useful. Recently, A meta-analysis showed a moderate protective effect of probiotics for preventing antibiotic-associated diarrhea<sup>[80]</sup>.

For patients with enterostomy, distal intestinal perfusion with liquid containing short-chain fatty acids can be used to prevent postoperative diarrhea <sup>[81, 82]</sup>. In addition, chyme reinfusion is a method to prevent postoperative diarrhea<sup>[83]</sup>. Some studies have reported that patients with CD can benefit from the use of enteral nutrition preparations <sup>[84]</sup>. The selection of appropriate enteral nutrition preparation, combined with parenteral nutrition, can ensure a balance of homeostasis. Diarrhea can be controlled by adjusting the amount and drip rate of enteral nutrition and the appropriate use of antidiarrheal agents and dietary fiber. The treatment strategy can be gradually changed according to the patient's condition<sup>[85]</sup>. Clinically, the maintenance and treatment of patient's mental health is an important part of their postoperative clinical recovery <sup>[71]</sup>. It should be noted that the causes of postoperative diarrhea in patients with CD may change with the treatment and postoperative recovery. Due to the characteristics of CD, we should pay attention to whether the adverse reactions of the drugs will have adverse effects on the disease during the treatment. (Table 1)

## **CONCLUSION**

Postoperative diarrhea is very common in CD. Severe diarrhea can lead to disturbed homeostasis of the internal environment, insufficient fluid in body, and aggravation of systemic reactions that seriously affect postoperative recovery. Diarrhea is caused by various factors, which may be related and interact with each other. For patients undergoing surgical treatment for CD, the most obvious change is the change in intestinal histology, physiology, or microbiota, and this change may lead to a difference in preoperative and postoperative diarrhea. A targeted strategy based on a comprehensive understanding of postoperative diarrhea is helpful for better postoperative recovery.

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