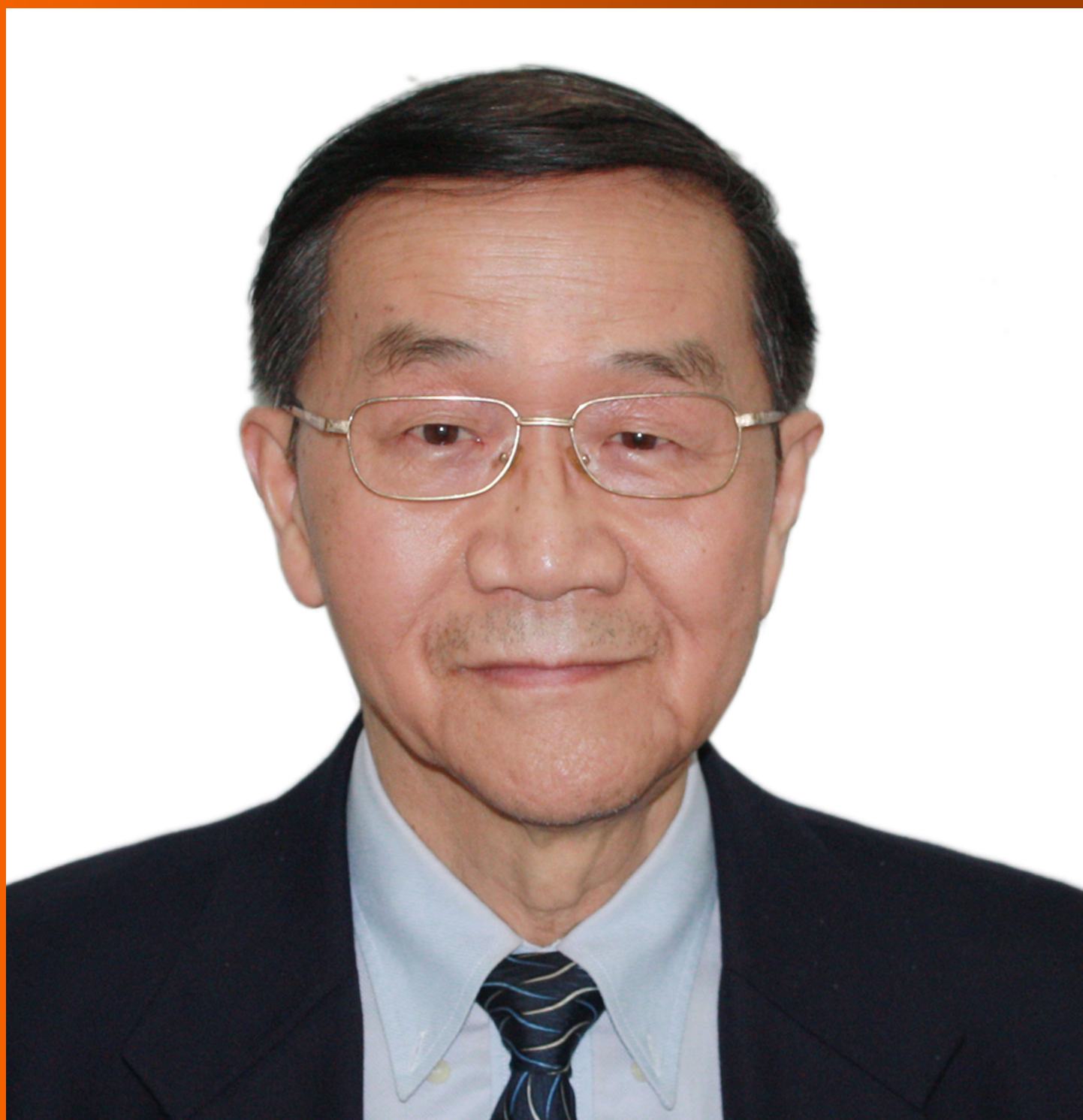


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World J Gastroenterol 2018 April 28; 24(16): 1679-1824



**REVIEW**

- 1679 Beneficial effects of naringenin in liver diseases: Molecular mechanisms
Hernández-Aquino E, Muriel P
- 1708 Naturally occurring hepatitis B virus reverse transcriptase mutations related to potential antiviral drug resistance and liver disease progression
Choi YM, Lee SY, Kim BJ

MINIREVIEWS

- 1725 Nucleotide-binding oligomerization domain 1 and *Helicobacter pylori* infection: A review
Minaga K, Watanabe T, Kamata K, Asano N, Kudo M
- 1734 Diversion colitis and pouchitis: A mini-review
Tominaga K, Kamimura K, Takahashi K, Yokoyama J, Yamagiwa S, Terai S

ORIGINAL ARTICLE**Basic Study**

- 1748 Nonalcoholic steatohepatitis severity is defined by a failure in compensatory antioxidant capacity in the setting of mitochondrial dysfunction
Boland ML, Oldham S, Boland BB, Will S, Lapointe JM, Guionaud S, Rhodes CJ, Trevaskis JL
- 1766 Mucosa repair mechanisms of Tong-Xie-Yao-Fang mediated by CRH-R2 in murine, dextran sulfate sodium-induced colitis
Gong SS, Fan YH, Wang SY, Han QQ, Lv B, Xu Y, Chen X, He YE
- 1779 Sodium chloride exacerbates dextran sulfate sodium-induced colitis by tuning proinflammatory and antiinflammatory lamina propria mononuclear cells through p38/MAPK pathway in mice
Guo HX, Ye N, Yan P, Qiu MY, Zhang J, Shen ZG, He HY, Tian ZQ, Li HL, Li JT

Retrospective Cohort Study

- 1795 High tacrolimus intra-patient variability is associated with graft rejection, and *de novo* donor-specific antibodies occurrence after liver transplantation
Del Bello A, Congy-Jolivet N, Danjoux M, Muscari F, Lavayssière L, Esposito L, Hebral AL, Bellière J, Kamar N

Randomized Clinical Trial

- 1803 Papillary fistulotomy *vs* conventional cannulation for endoscopic biliary access: A prospective randomized trial
Furuya CK, Sakai P, Marinho FR, Otoch JP, Cheng S, Prudencio LL, de Moura EG, Artifon EL

META-ANALYSIS

- 1812 Compared efficacy of preservation solutions on the outcome of liver transplantation: Meta-analysis
Szilágyi ÁL, Mátrai P, Hegyi P, Tuboly E, Pécz D, Garami A, Solymár M, Pétervári E, Balaskó M, Veres G, Czopf L, Wobbe B, Szabó D, Wagner J, Hartmann P

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Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
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Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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7901 Stoneridge Drive, Suite 501,
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Diversion colitis and pouchitis: A mini-review

Kentaro Tominaga, Kenya Kamimura, Kazuya Takahashi, Junji Yokoyama, Satoshi Yamagiwa, Shuji Terai

Kentaro Tominaga, Kenya Kamimura, Kazuya Takahashi, Junji Yokoyama, Satoshi Yamagiwa, Shuji Terai, Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata 951-8510, Japan

ORCID number: Kentaro Tominaga (0000-0001-6792-1005); Kenya Kamimura (0000-0001-7182-4400); Kazuya Takahashi (0000-0002-3097-9841); Junji Yokoyama (0000-0002-1810-7709); Satoshi Yamagiwa (0000-0003-4791-6107); Shuji Terai (0000-0002-5439-635X).

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Correspondence to: Kenya Kamimura, MD, PhD, Lecturer, Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. kenya-k@med.niigata-u.ac.jp
Telephone: +81-25-2272207
Fax: +81-25-2270776

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Abstract

Diversion colitis is characterized by inflammation of the mucosa in the defunctioned segment of the colon after colostomy or ileostomy. Similar to diversion colitis, diversion pouchitis is an inflammatory disorder occurring in the ileal pouch, resulting from the exclusion of the fecal stream and a subsequent lack of nutrients from luminal bacteria. Although the vast majority of patients with surgically-diverted gastrointestinal tracts remain asymptomatic, it has been reported that diversion colitis and pouchitis might occur in almost all patients with diversion. Surgical closure of the stoma, with reestablishment of gut continuity, is the only curative intervention available for patients with diversion disease. Pharmacologic treatments using short-chain fatty acids, mesalamine, or corticosteroids are reportedly effective for those who are not candidates for surgical reestablishment; however, there are no established assessment criteria for determining the severity of diversion colitis, and no management strategies to date. Therefore, in this mini-review, we summarize and review various recently-reported treatments for diversion disease. We are hopeful that the information summarized here will assist physicians who treat patients with diversion colitis and pouchitis, leading to better case management.

Key words: Diversion colitis; Diversion pouchitis; Ileitis; Inflammatory bowel disease

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Core tip: Diversion colitis is characterized by inflammation of the mucosa in the defunctioned segment of the colon after colostomy or ileostomy. The vast majority of diverted patients remain asymptomatic,

however diversion colitis occurs in almost all diverted patients. Pharmacologic treatment using short-chain fatty acids, mesalamine, or corticosteroids are reportedly effective for those who are not candidates for surgical reestablishment; however, there are no established assessment criteria for determining the severity of diversion colitis, and no management strategies to date. In this mini-review, we summarize and review various recently-reported diversion disease treatments. We hope this review will be useful for future treatment.

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INTRODUCTION

Diversion colitis was first described by Morson *et al*^[1] in 1974 as a non-specific inflammation in the diverted colon. Glotzer *et al*^[2] labeled this inflammation "diversion colitis" in 1981. Since then, the disease has been reported in both retrospective^[3-20] and prospective studies^[21-27] which have described the characteristic clinical, endoscopic, and pathological findings. Surprisingly, the prospective study reported that almost all cases exhibit colitis, evidenced by endoscopic analyses, 3 to 36 mo after the colostomy^[21]. Symptomatic cases make up only around 30% of all cases diagnosed *via* endoscopic studies, and the precise pathogenesis of this condition remains unclarified. Although a wide range of symptoms are reportedly associated with the disease, including abdominal discomfort, tenesmus, anorectal pain, mucous discharge, and rectal bleeding^[3,4], there are no established diagnostic criteria for assessing disease severity. Diversion pouchitis is similar to diversion colitis, featuring inflammation of the ileal pouch that results from fecal stream exclusion and the subsequent lack of nutrients from luminal bacteria. Therefore, the difference between the pouchitis and diversion pouchitis is whether the lesion is exposed to the fecal stream or not. Patients generally present with varying symptoms such as tenesmus, bloody or mucus-like discharge, and abdominal pain^[28]. The incidence of diversion pouchitis is unknown; however, it appears more commonly in patients with underlying inflammatory bowel disease (IBD). Nonsurgical approaches for the treatment of diversion pouchitis include the use of short chain fatty acids (SCFA), topical 5-aminosalicylic acids, and topical glucocorticoids. Unfortunately, efficacy study outcomes are conflicting, and the only curative approach is surgical re-anastomosis with the reestablishment of gut continuity^[28-30].

In their 1989 examination of non-surgical treatment options procedure, Harig *et al*^[5] reported the efficacy of short-chain fatty acids. The usefulness of the 5-ASA enema in patients with diversion colitis was reported for

the first time by Triantafyllidis *et al*^[31] in 1991; Glotzer *et al*^[2] reported the efficacy of steroid enemas in patients with diversion colitis in 1984, and similar results were subsequently reported by Lim *et al*^[32] and Jowett *et al*^[33]. Nonsurgical treatments include short-chain fatty acids, 5-aminosalicylic acids, glucocorticoids, antibiotics, and so on. However, due to the lack established assessment methods, the efficacy of these treatments has not been clearly confirmed. Consequently, surgical re-anastomosis remains the most reliable and effective treatment option. There is an unmet need for a summary of these therapeutic options and information regarding the disease assessment, and this need informed the present literature review. We believe that the information summarized in this mini-review will help physicians treat cases and, by increasing the number of treated cases, we will support the establishment of novel criteria for disease assessments and therapeutic decision trees.

LITERATURE ANALYSIS

A literature search was conducted using PubMed and Ovid, with the terms "diversion colitis" or "diversion proctitis" and "diversion pouchitis" used to extract studies published over the preceding 45 years. All appropriate English-language publications from relevant journals were selected. We summarized the available information on demographics, clinical symptoms, endoscopic and histological findings, treatment, and the clinical course.

CLINICAL CHARACTERS

Epidemiology

A total of 69 articles, including 25 case reports, were matched to our definition of diversion colitis and pouchitis assessment; this information is summarized in Tables 1 and 2. Based on our review, the prevalence estimates of these conditions appear extremely high, reaching almost the entire population of interest if the phenomenon is followed prospectively, beginning at 3 to 36 mo after colostomy^[21]. In a recent study, Szczepkowski *et al*^[3] described more than 90% incidence of diversion colitis on endoscopy in a series of 145 patients. The study further reported that there were no significant associations between diversion colitis and age, sex, type of stoma, or mode of surgery performed. The frequency of disease occurrence ranged from 70%-74% in patients without pre-existing IBD^[22] and 91% in patients with pre-existing IBD^[6,21]. In patients with histories of Crohn's disease chronic severe inflammation, often with transmural disease, has been described after defunctioning colostomies^[34]. It has also been hypothesized that diversion colitis may be a risk factor for ulcerative colitis in predisposed individuals, and that ulcerative colitis can be triggered by anatomically discontinuous inflammation in the large bowel^[35]. Among the 46 reported cases of diversion colitis and

Table 1 Clinical characteristics of case report

Case (No)	Reference	Reporting yr	Country	Age (yr)	Gender (male/female)	Primary illness (reason for diversion)	Type of diversion (surgical procedure)	Period of up to diagnosis from operation	Symptoms	Endoscopy findings	Pathological findings	Diagnosis
1	Glutzer <i>et al</i> ^[2]	1981	United States	49	M	Free perforation sigmoid diverticulum	Loop sigmoid colostomy	2.5 mo	No symptoms	Erythema, friability, petechiae, atrophy	Crypt abscess, surface epithelial cell degeneration, acute inflammation, chronic inflammation, regeneration	Diversion colitis
				56	F	Adenocarcinoma. Protect low anastomosis	Loop transverse colostomy	3 mo	No symptoms	Erythema, friability, petechiae	Normal	Diversion colitis
				78	M	Sigmoid diverticulitis with perforation	Loop sigmoid colostomy	6 mo	No symptoms	Erythema, friability, granularity	No biopsy	Diversion colitis
				70	F	Sigmoid diverticulitis found at pelvic operation	Loop sigmoid colostomy	3 mo	No symptoms	Erythema, friability, nodularity	Regeneration	Diversion colitis
				43	F	Sigmoid diverticulitis with perforation	Loop sigmoid colostomy	8 mo	No symptoms	Erythema, friability	Crypt abscess, acute inflammation.	Diversion colitis
				41	F	Fecal incontinence secondary to cordotomy for pain	Loop sigmoid colostomy	18 mo	No symptoms	Erythema, friability, petechiae	No biopsy	Diversion colitis
				65	M	Sigmoid diverticulitis with perforation	Loop transverse colostomy	3 yr	No symptoms	Erythema, friability, granularity, petechiae, inflammatory polyp	Crypt abscess, surface epithelial cell degeneration, chronic inflammation, regeneration.	Diversion colitis
				83	M	Sigmoid diverticulitis with perforation	Loop transverse colostomy	6 mo	No symptoms	Erythema, friability, granularity	Crypt abscess	Diversion colitis
				26	M	Fecal incontinence after T9-10 cord transection	Loop transverse colostomy	7 yr	Rectal discharge	Erythema, friability, petechiae	Surface epithelial cell degeneration, chronic inflammation.	Diversion colitis
				70	M	Colonic ileus secondary to anticholinergics for Parkinson's disease	Loop transverse colostomy	4 mo	No symptoms	Erythema, friability, petechiae, inflammatory polyp	Crypt abscess	Diversion colitis
2	Lusk <i>et al</i> ^[39]	1984	United States	28	M	Perforated sigmoid colon for gunshot	Loop sigmoid colostomy	6 wk	No symptoms	Red granular rectum with aphthous ulcers	Moderate loss of goblet cells with focal edema and lymphocytosis of the lamina propria.	Diversion colitis
3	Scott <i>et al</i> ^[46]	1984	United States	68	M	Sigmoid carcinoma	Loop transverse colostomy	6 wk	No symptoms	Multiple aphthae	Not obtained	Diversion colitis
				21	M	Gunshot	Loop transverse colostomy	2 mo	No symptoms	Multiple, small, polypoid lesions in the rectum and sigmoid colon up to the cutaneous part of the mucous fistula.	Mucosal biopsies of the rectal lesions were interpreted as "chronic nonspecific colitis with pseudopolyps, probably from diversion colitis".	Diversion colitis
4	Korelitz <i>et al</i> ^[42]	1984	United States	22	F	Crohn's Disease	Ileostomy and subtotal colectomy	2 yr	No symptoms	Friable, nodular	Not obtained	Diversion colitis

34	F	Crohn's ileitis	Ileocolic anastomosis and Loop ileostomy	2 yr	No symptoms	Exudate	Focal chronic inflammation, edema, erosions, and an increased number of lymphoid follicles.	Diversion colitis
31	M	Crohn's ileitis	Ileocolic anastomosis and Loop ileostomy	1 yr	No symptoms	Aphthous lesions	Chronic inflammation	Diversion colitis
32	M	Crohn's ileitis	Ileocolic anastomosis and Loop ileostomy	1 yr	No symptoms	Friable, exudate	Not obtained	Perforation due to complication of barium enema and diversion colitis
5	F	Perforated sigmoid diverticulum	Loop sigmoid colostomy	22 yr	Rectal bleeding	N/A	Diffuse multiple superficial ulcerations and intense inflammatory infiltrates composed mainly of plasma cells, lymphocytes, and some eosinophils.	Diversion colitis
6	M	Perineal laceration as result of a motor vehicle accident	End sigmoid colostomy	1 yr	Rectal bleeding	Diffuse nodularity and ulceration	Moderate to severe nonspecific inflammation.	Diversion colitis
63	F	Irradiation of rectum	Mucus fistula	13 mo	Bloody discharge	Endoscopic index of 10	Inflammatory infiltrate of both acute and chronic cells in the lamina propria and the crypt abscess. Lining epithelial cells show decreased mucin secretion.	Diversion colitis
54	M	Perianal fistulas	Rectosigmoid pouch	35 mo	Bloody discharge	Endoscopic index of 9	Erosions, surface exudate, crypt abscesses, edema.	Diversion colitis
56	M	Diverticulitis	Mucus fistula	N/A	N/A	Endoscopic index of 8	Lymph follicles	Diversion colitis
64	F	Diverticula with perforation	Hartman's type of operation laparotomy	16 mo	Bloody rectal discharge	Endoscopic index of 9 (quite inflamed with friability and erythema)	N/A	Diversion colitis
85	F	Small bowel perforation with a ruptured chronic pelvic abscess secondary to diverticular disease	End transverse colostomy	10 wk	Bloody rectal discharge	Erythematous and friable, with diffuse exudation, petechiae, and ulceration	Severe inflammatory infiltration, formation of lymph follicles, surface erosions, edema, and crypt abnormalities.	Diversion colitis
45	F	Chronic constipation	Loop transverse colostomy	25 yr	Sepsis(no symptoms such as rectal bleeding)	Large ulcers with overlying pseudomembrane	Acute and chronic inflammation with cryptitis.	Diversion colitis
10	F	Chronic constipation	Loop transverse colostomy	25 yr	Sepsis(no symptoms such as rectal bleeding)	Large ulcers with overlying pseudomembrane	Infiltration primarily with plasma cells and lymphocytes was noted, as well as a moderate numbers of polymorphonuclear cells, large lymphoid aggregates were seen in the lamina propria	Diversion colitis

11	Lai <i>et al</i> ^[47]	1997	United States	49	M	Intractable ileus, C6 ASIAB tetraplegic	Colostomy	10 yr	Rectal pain and bleeding.	Partial stricture 70 cm proximally to the rectum. The colonic mucosa appeared granular and friable with evidence of linear ulceration.	Extravasation of erythrocytes, lymphocytic and neutrophilic cells infiltrates, and edema were present within the lamina propria. No evidence of malignancy and glandular dysplasia was found. Pathologic report was consistent with chronic colitis.	Diversion colitis
12	Lim <i>et al</i> ^[32]	1999	United Kingdom	60	F	Faecal incontinence for DM	End sigmoid colostomy	6 mo	Blood and mucus per rectum	Edematous mucosa with bloodstained mucopurulent exudate	Active chronic colitis with focal cryptitis and crypt abscesses.	Diversion colitis → UC
				16	M	Imperforate anus	Ileostomy and colostomy	6 mo	Blood and mucus per rectum	Granular, erythematous mucosa with contact bleeding	Active inflammation with polymorphs infiltrating crypts and a diffuse increase in lymphocytes and plasma cells in the lamina propria.	Diversion colitis → UC
13	Jowett <i>et al</i> ^[33]	2000	United Kingdom	75	F	Faecal incontinence	End colostomy	8 mo	Blood and mucus per rectum	Granular, congested, and oedematous mucosa with contact bleeding	Mixed inflammatory cell infiltrate with distortion of the crypt architecture and cryptitis.	Diversion colitis (→ UC)
14	Lim <i>et al</i> ^[35]	2000	United Kingdom	66	M	Sigmoid carcinoma	Hartmann's procedure with colostomy.	18 mo	No symptoms	Mildly inflamed	Active colitis	Diversion colitis (→ UC)
15	Kiely <i>et al</i> ^[36]	2001	United Kingdom	6	M	Ulcerative colitis	Total colectomy and ileostomy	9 mo	Rectal bleeding	Endoscopic index of 8	Lymphoid hyperplasia, lymphoplasmacytosis, crypt abscesses and moderate mucosal architectural disruption.	Diversion proctocolitis
				3	M	Perforated typhoid disease	Subtotal colectomy and ileostomy	5 mo	Rectal bleeding and abdominal pains	Endoscopic index of 8	Lymphoplasmacytic infiltration of lamina propria, and architectural disruption.	Diversion proctocolitis
				8	F	Aplastic anemia, a large solitary rectal ulcer	Loop sigmoid colostomy	4 mo	Rectal discharge	Endoscopic index of 9	Lymphoplasmacytic and neutrophilic infiltrate in the lamina propria, mucin depletion, and Paneth cell metaplasia.	Diversion proctocolitis
				3	M	Hirschsprung's disease	ileostomy	N/A	Rectal bleeding	Florid colitis	Lymphoid hyperplasia, lymphoplasmacytosis and mucin depletion,	Diversion proctocolitis
				10	M	Rectovesical fistula	Loop sigmoid colostomy	N/A	Rectal discharge	Florid colitis	Lymphoid hyperplasia, lymphoplasmacytosis.	Diversion proctocolitis
16	Komuro <i>et al</i> ^[41]	2003	Japan	46	M	Ascending colon diverticular perforation (systemic lupus erythematosus and chronic renal failure)	Loop transverse colostomy	N/A (On surveillance colonoscopy)	No symptoms	Mild colitis with a decreased vascular pattern, oedema and mucosal tear	N/A	Diversion colitis

17	Tsironi <i>et al</i> ^[48]	2006	United Kingdom	40	M	UC pancolitis-type	Rectal stump and ileostomy, subtotal colectomy and ileostomy	5 mo	Blood and mucus per rectum	Severe chronic inflammation with ulceration and numerous inflammatory polyps	Diffuse chronic inflammation with patchy cryptitis	Diversion colitis with clostridium difficile infection.
18	Boyce <i>et al</i> ^[47]	2008	United Kingdom	29	M	Life-long constipation	Subtotal colectomy	15 yr	Rectal bleeding and anal pain	The mucosa of the rectal stump was found to be chronically inflamed and ulcerated.	Inflammatory change	Diversion pouchitis
19	Haugen <i>et al</i> ^[49]	2008	United States	36	F	Faecal incontinence due to spina bifida	Laparoscopic sigmoid colectomy and creation of a Hartmann's pouch	N/A	Rectal discharge	N/A	N/A	Diversion colitis
20	Talisetti <i>et al</i> ^[50]	2009	United States	19	F	Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)	Gastrostomy and ileostomy	4 yr	Abdominal pain and rectal bleeding	Friable mucosa with areas of pinpoint hemorrhage from the anal verge to 30 cm proximally	Acute cryptitis and scattered crypt abscesses, consistent with diversion colitis.	Diversion colitis
21	Kominami <i>et al</i> ^[51]	2013	Japan	84	M	Angiodysplasia S/O	Subtotal colectomy and ileostomy	5 yr	Blood in the stool	Granular, edematous mucosa with contact bleeding	Lymphoplasmacytic and neutrophilic infiltrate in the lamina propria.	Diversion colitis
22	Watanabe <i>et al</i> ^[44]	2014	Japan	76	F	UC	3-stage pancolectomy with construction of an IPAA	13 yr	Bloody purulent rectal discharge	Severely active pouchitis with large erosions	N/A	Diversion pouchitis
23	Gundling <i>et al</i> ^[45]	2015	Germany	75	F	Chronic constipation	Permanent end-colectomy	N/A	Tenesmus and severe rectal pain	Severe DC was seen on colonoscopy	Confirmed histologically	Diversion colitis
24	Matsumoto <i>et al</i> ^[52]	2016	Japan	65	M	UC pancolitis-type	Subtotal colectomy and ileostomy	4 mo	Rectal bleeding	Moderate mucosal inflammation	Ulcer, granulation tissue and epithelial defect	Diversion colitis or exacerbation of UC was suspected.
25	Custon <i>et al</i> ^[29]	2017	United States	44	M	UC complicated by colitis-associated low-grade dysplasia	Total proctocolectomy with 2-stage IPAA	7 yr	Blood in the stool	Edematous and coated with old and fresh blood	N/A	Severe diversion pouchitis

pouchitis, there was a slight male predominance (28 males, 18 females), and the age of the patients ranged from 3 to 85 years old^[2,5,13,29,31,33,35-52]. The period from diagnosis to surgical treatment was a median of 8 mo, ranging from 2 wk to 25 years (Table 1). The types of diversions included: 9 cases of loop sigmoid colectomy; 3 cases of end sigmoid colectomy; 9 cases of loop transverse colectomy; 4 cases of loop ileostomy; 7 cases of proctocolectomy; 3 cases of proctocolectomy; 2 cases of Hartmann's type with colectomy; and only one case of other operations (Table 1).

Pathogenesis

The basic mechanisms underlying diversion colitis are still unclear. Giotzer hypothesized that it might be the result of bacterial overgrowth, the presence of harmful bacteria,

Table 2 Clinical course of case reports

Case (No)	Ref.	Age (yr)	Gender (male/female)	Ineffective treatment	Effective treatment	Prognosis
1	Glotzer <i>et al</i> ^[2]	49	M	N/A	Closure 4 mo post-diversion	Asymptomatic. Proctoscopy and biopsy normal 2.5 and 30 mo postclosure.
		56	F	N/A	Closure 3 mo post-diversion	Recurrent Ca. Mucosa not inflamed grossly or microscopically 18 mo post closure.
		78	M	N/A	Closure 6 mo post-diversion	Asymptomatic 1 yr postclosure.
		70	F	N/A	Closure 5 mo post-diversion	Asymptomatic. Normal sigmoidoscopy 2 mo postclosure.
		43	F	N/A	Closure 2 yr post-diversion	Asymptomatic. Normal sigmoidoscopy 3 yr postclosure.
		41	F	N/A	None	Asymptomatic 2 yr after ileostomy.
		65	M	N/A	None	Abdominal cramps purulent rectal discharge. Continued inflammation 8 yr after colostomy.
		83	M	N/A	None	Asymptomatic. Continued mild inflammation 4.5 yr after colostomy.
		26	M	N/A	Steroid enemas	Improved. Continued 8 yr after colostomy.
2	Lusk <i>et al</i> ^[39]	28	M	-	Colostomy closure	Tenesmus, discharge and fever 4 yr after colostomy. Resolved with steroid enemas.
		68	M	-	Colostomy closure	Continued inflammation at 8 yr. Normal at 16 mo follow-up.
3	Scott <i>et al</i> ^[46]	21	M	-	Colostomy closure	Normal at 7 wk after closure. One month later, the patient was examined by flexible sigmoidoscopy, which demonstrated normal mucosa throughout with no sign of pseudopolyps.
4	Korelitz <i>et al</i> ^[42]	22	F	Steroid enemas	Ileocolic reanastomosis (ileostomy closure)	3 mo (interval from reanastomosis to normal sigmoidoscopy), 7 yr (duration normal).
		34	F	-	Ileostomy closure	1 mo (interval from reanastomosis to normal sigmoidoscopy), 2 yr (duration normal).
		31	M	-	Ileostomy closure	3 mo (interval from reanastomosis to normal sigmoidoscopy), 18 mo (duration normal).
		32	M	-	Ileostomy closure	2 mo (interval from reanastomosis to normal sigmoidoscopy), 14 mo (duration normal).
5	Fernand <i>et al</i> ^[40]	67	F	-	Left hemicolectomy and left salpingo-oophorectomy	She recovered well and discharged 9 d later.
6	Frank <i>et al</i> ^[13]	38	M	Oral and topical steroids	Abdominoperineal resection of the diverted loop and permanent colostomy	No evidence of inflammatory bowel disease has developed. Barium study of the small bowel was normal 1 yr after surgery.
7	Harig <i>et al</i> ^[5]	63	M	N/A	Short-chain-fatty acid irrigation	N/A
		63	F	N/A	Short-chain-fatty acid irrigation	N/A
		54	M	N/A	Short-chain-fatty acid irrigation	N/A
		56	M	N/A	Short-chain-fatty acid irrigation	N/A
8	Triantafillidis <i>et al</i> ^[31]	64	F	-	5-aminosalicylic acid enemas comparison with Betamethasone enemas	There were no differences in the degree of clinical improvement, or in the endoscopic and histologic scores seen at the end of the trials, between betamethasone and 5-ASA.
9	Tripodi <i>et al</i> ^[43]	85	F	-	5-aminosalicylic acid enemas	Clinically asymptomatic at a 6-mo follow-up.
10	Lu <i>et al</i> ^[38]	45	F	Intravenous metronidazole	Colectomy of the diverted segment	Without complications and has been doing well postoperatively.
11	Lai <i>et al</i> ^[47]	49	M	-	Daily 5-ASA suppository and total parenteral nutrition	6 wk of treatment with 5-ASA, the patient had decreased rectal pain and bleeding.
12	Lim <i>et al</i> ^[32]	60	F	-	Oral prednisolone, oral mesalazine, and mesalazine enemas	PSL was tapered off over four months and she remained well.
		0	M	Closure of the loop ileostomy→oral prednisolone, oral olsalazine and oral metronidazole→sigmoid loop colostomy	The defunctioned rectosigmoid was partially removed, leaving the lower rectum and anal canal; the loop colostomy was refashioned into an end colostomy→colectomy and removal of residual rectal stump and anal canal was performed and an end ileostomy fashioned	He subsequently made a good recovery and steroid therapy was discontinued.
13	Jowett <i>et al</i> ^[33]	75	F	-	Topical steroid enemas.	UC
14	Lim <i>et al</i> ^[35]	66	M	-	Steroid enemas	6 mo later he developed ulcerative colitis.

						Oral PSL was continued at the reduced rate of 5mg on alternate days until he underwent an uneventful rectal excision and J-pouch anal anastomosis 1 mo later. Two months after this, his ileostomy was closed.
15	Kiely <i>et al</i> ^[36]	6	M	PSL and AZA	SCFA	His ileostomy was closed 3 mo later, and he was remained symptom free.
		3	M	Salazopyrine	SCFA	Her ulceration was virtually healed and showed a reduction in endoscopic index from 9 to 3. Treatment was maintained until her colostomy was reversed a month later. After stoma closure, SCFAs were discontinued with no further recurrence of symptoms.
		8	F	-	SCFA	For redo pull-through
		3	M	N/A	SCFA	Rectal excision
		10	M	N/A	SCFA	
16	Komuro <i>et al</i> ^[41]	46	M	-	-	The post endoscopic course was uneventful without any treatment.
17	Tsironi <i>et al</i> ^[48]	40	M	Mesalazine suppository and steroid enemas	Metronidazole suppository	Improved quickly and remains well and asymptomatic 12 wk after treatment.
18	Boyce <i>et al</i> ^[37]	29	M	-	Completion proctectomy	Completion proctectomy was uneventful and from which the patient made an unremarkable recovery.
19	Haugen <i>et al</i> ^[49]	36	F	The water and vinegar solution enema, steroid enema, bismuth subsalicylate (standard treatment SCFA enmas was not option due to insurance and spina bifida)	Antegrade irrigations of her distal bowel with tap water	Weekly to twice weekly irrigations completely stopped the malodorous and troublesome discharge.
20	Talisetti <i>et al</i> ^[50]	19	F	SCFA enema, steroids, metronidazole	Colectomy(entire colon was ultimately resected, Since only 15 cm of jejunum appeared healthy, her mid and distal small bowel was also resected up to 15 cm from the ligament of Treitz)	N/A
21	Kominami <i>et al</i> ^[51]	84	M	Short-chain fatty acid enema	5-aminosalicylic acid enemas	Undergoing 5-aminosalicylic acid enemas maintenance therapy.
22	Watanabe <i>et al</i> ^[44]	76	F	Oral mesalazine, corticosteroid, metronidazole, and ciprofloxacin	Leukocytapheresis, following low dose of metronidazole and ciprofloxacin	After 18 mo, her condition remains stable without the need for medication.
23	Gundling <i>et al</i> ^[45]	75	F	Enemas containing 5-aminosalicylic acid and steroids and antibiotic therapy	Autologous fecal transplantation	All symptoms improved dramatically within 5 d after the first treatment. Colonoscopy 28 d after the first treatment showed no major signs of inflammation in the colonic stump.
24	Matsumoto <i>et al</i> ^[52]	65	M	Corticosteroid and mesalazine enemas, prednisolone injections.	A combined mesalazine plus corticosteroid enema	Finally proctectomy and ileal pouch-anal anastomosis were successfully performed.
25	Custon <i>et al</i> ^[29]	44	M	-	Dextrose(hypertonic glucose) spray endoscopically	The patient did not experience further episodes of recurrent bleeding during the 6-mo follow-up. No prescribed medicines were given after the endoscopic therapy.

nutritional deficiencies, toxins, or disturbance in the symbiotic relationship between luminal bacteria and the mucosal layer^[2]. Reportedly, concentrations of carbohydrate-fermenting anaerobic bacteria and pathogenic bacteria are reduced in de-functioned colons^[5,23,53] and these reports indicate that the overgrowth of anaerobic bacteria or a pathogenic bacterium is unlikely to be an important etiological factor. On the

other hand, there is an increase of nitrate-reducing bacteria in patients with diversion colitis^[7] and nitrate-reducing bacteria produce nitric oxide (NO) which plays a protective role in low concentrations, but at higher levels it becomes toxic to the colonic tissue^[54]. Thus, it has been suggested that increases in nitrate-reducing bacteria may result in toxic levels of NO, leading to the diversion colitis.

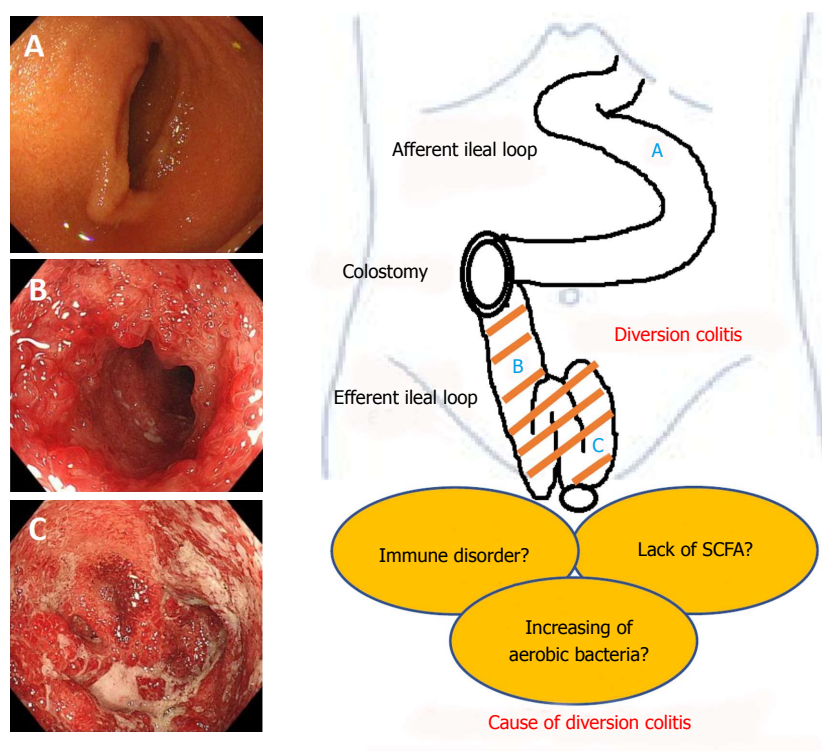


Figure 1 Schematic presentation of diversion colitis and pouchitis.

Recently, ischemia has been proposed as a cause of diversion colitis^[8]. The explanation surely lies in changes to the luminal flora consequent to fecal stream interruption. Normal luminal bacteria produce SCFA, such as butyric acid. Butyrate is the principal oxidative substrate for colonocytes^[55] and patients with diversion colitis may improve following topical treatment with SCFA, especially with butyrate enemas^[5,36]. This hypothesis is based on evidence that suggests SCFA relax vascular smooth muscle and that butyrate deficiencies may induce increased tone in the pelvic arteries, therefore leading to relative ischemia of the colorectal mucosa and intestinal wall^[5]. It is obvious that additional, basic research is necessary in order to discern disease mechanisms. We have summarized the pathogenesis of this disease entity in Figure 1.

Symptoms

Most patients are asymptomatic^[22], however about one third of patients may exhibit symptoms of diversion colitis^[2,3,6,9]. Patients generally present with varying symptoms such as abdominal discomfort, tenesmus, anorectal pain, mucous discharge, and rectal bleeding. The most common symptoms include bloody, serous, or mucous discharge in 40% of the population, and abdominal pain and tenesmus in 15% of the population^[3]. There have been several reports of severe rectal bleeding^[24,29,56]. There is a report of massive rectal distension causing bilateral ureteric obstruction^[37] and a case report of diversion colitis causing severe sepsis requiring a colectomy^[38]. These symptoms can start within 1 mo to 3 years after surgery^[22,24]. Our

review also showed that clinical symptoms of rectal bleeding were seen in 25 cases, abdominal pain in 3 cases, anal pain in 3 cases, and sepsis in 1 case^[38]. On the other hand, 21 of 46 cases had no symptoms (Table 1), as previously reported^[24]. Additionally, in the presence of Crohn's disease and ulcerative colitis, the number of symptomatic patients rises to 33% and 87% respectively^[53]. Our review showed cases with primary illness of diverticula with perforation ($n = 11$), fecal incontinence ($n = 6$), chronic constipation or ileus ($n = 5$), ulcerative colitis ($n = 5$), Crohn's disease ($n = 4$), carcinoma ($n = 3$), and various other diseases (Table 1).

Macroscopic findings

Macroscopically, diversion colitis may involve the whole de-functioned colon or isolated segments. These findings include erythema, diffuse granularity, and blurring of vascular pattern in about 90% of the population. It is also associated with mucosal friability (80%) edema (60%), aphthous ulceration, and bleeding, to varying degrees^[2,3,8-12,39,40]. There is a case report of diversion colitis causing mucosal tears within the defunctioned colon^[41]. Recently, Hundorfean *et al.*^[57] reported a first description and *in vivo* diagnosis of diversion colitis after surgery, by virtual chromoendoscopy and fluorescein-guided confocal laser endomicroscopy. Our literature review showed that endoscopic findings were evidenced in 44 out of 46 cases, and severe inflammation with ulceration (endoscopic index ≥ 8) in 17 cases.

Microscopic findings

The pathological finding of diversion colitis and pouchitis

usually vary with degree of severity, therefore, no specific microscopic findings have been noted. The histological features of diversion colitis can mimic those of IBD, even when a pre-existing IBD has not been documented^[10,11,13-15]. The most notable feature often seen in diversion colitis is lymphoid follicular hyperplasia^[9,14,58]. Atrophy, crypt branching, mucin depletion, crypt distortion, regenerative hyperplasia, paneth cell metaplasia, thickening of muscularis mucosa, diffuse active mucosal inflammation with crypt abscesses, ulceration, and vacuolar and epithelial degeneration along with features of chronic inflammation (usually confined to the mucosa) are seen with varying degrees of severity^[9-12,14,16,17,59]. More recently, features of ischemia, such as superficial coagulative necrosis and fibrosis, have been described^[8]. Our review showed that 37 out of 46 cases exhibited pathological findings including 15 cases of crypt abscess or cryptitis^[2], and 14 cases of lymphoid follicular hyperplasia (which was not previously identified as a feature of diversion colitis). These features are non-specific and, to date, no characteristic feature or features of diversion colitis have been identified.

Treatment

Because of the small number of patients and the unknown etiology, there is no established standard therapy for diversion colitis and pouchitis. Szczepkowski *et al.*^[4] proposed a management strategy for patients with de-functioned distal stomas. He divided patients with diversion colitis into three groups based on a study of 145 patients. These groups consisted of Group 1 (no clinical, morphological or endoscopic evidence of diversion colitis), Group 2, (mild or moderate signs of diversion colitis), and Group 3 (severe diversion colitis). Group 1 can be treated conservatively, Group 2 can be treated using conservative management prior to restoration of colonic continuity and Group 3 should ideally undergo restoration of colonic continuity. If a surgical option is not feasible, pharmacologic treatment options should be tried to resolve the inflammation. A summary of the clinical courses of case reports is shown in Table 2.

Surgery

Treatment of diversion colitis should be primarily directed at restoring bowel continuity to restore the luminal flow. This will resolve the symptoms and assist the bowel to return to normal. Re-anastomosis has proven to be consistently effective in halting the symptoms of diversion colitis in a number of studies^[2,10,25,39,42]. Re-anastomosis of diverted segments in patients with preexisting inflammatory bowel disease is a more difficult decision because inflammation in the diverted segment could represent inflammatory bowel disease or diversion colitis, each of which dictate different courses of action^[3,21,42]. Resection is not typically required. Indications for resection include uncontrolled perianal

sepsis, perianal fistulous disease, anal incontinence, and uncontrolled symptoms related to diversion colitis.

Diet and lifestyle

Nutritional imbalance in the excluded colon is likely responsible for the pathologic changes and symptoms of diversion colitis. However, current evidence does not support the effectiveness of lifestyle modifications or nutritional imbalance^[60].

Pharmacologic treatment is generally indicated for the temporary control of symptoms in preparation for surgery. It is used occasionally for patients who are not considered surgical candidates because of severe medical comorbidities, poor sphincter function, or reasons of technical difficulty.

Short-chain-fatty acid

Short-chain fatty acids, mainly butyrate, are the major fuel source for the epithelium. Their absence in the diverted tract may produce mucosal atrophy and inflammation. Bacteria produce SCFAs as byproducts of carbohydrate fermentation in the colonic lumen, and SCFAs provide the primary energy source for colonic mucosal cells^[13]. In human neutrophils, SCFAs reduce the production of reactive oxygen species, which are the agents of oxidative tissue damage^[61]. Treatment of diversion colitis with SCFA or butyrate has shown inconsistent results. Harig successfully improved symptoms and endoscopic inflammatory change by SCFA^[5]. Komorowski *et al.*^[10] reported similar results in four patients with diversion colitis with SCFA irrigation. However, Guillmot *et al.*^[16,28] failed to demonstrate either histological or endoscopic improvement. The differences in response may be partially accounted for by disease groupings. In recent years, several studies on the usefulness of SCFA, including of butyrate, are reported^[19,62]. Cristina *et al.*^[27] proposed that butyrate enemas may prevent the atrophy of the diverted colon/rectum, thus improving the recovery of tissue integrity.

5-aminosalicylic acid

Usefulness of 5-aminosalicylic acid (5-ASA) enemas in diversion colitis was reported for the first time by Triantafillidis *et al.*^[31] in 1991. Tripodi *et al.*^[43] has also reported similar results in 1992. Caltabiano *et al.*^[63] reported that 5-ASA enema reduces oxidative DNA damage in colonic mucosa and reduces mucosal damage using rats in a diversion colitis model. It is considered that the mucosal disorder may be improved by protective action against oxidative DNA damage and the anti-inflammatory action of 5ASA^[64].

Corticosteroids

Glutzer reported on several patients with diversion colitis treated by steroid enemas in 1984^[2]. Lim and Jowett also reported the efficacy of the steroid enemas in 2000^[32,33]. Corticosteroids are first-line agents for symptomatic diversion colitis, with varying effectiveness.

Table 3 Summary of pharmacologic treatments

Treatment	Ref.	Procedure/standard dosage	Efficacy	Complications/main side effects
Surgical anastomosis	[2,3,10,21,25,39,42]	Mobilization of both ends of the bowel with either sutured or stapled anastomosis.	The most effective method of eliminating the signs and symptoms	Bleeding, infection, anastomotic leak, anastomotic stricture, anesthetic risks
Corticosteroids	[2,32,33]	Hydrocortisone (100 mg per 60 mL bottle) enema is administered once daily for up to 3 wk. Occasional treatment may be given for 2 to 3 mo depending on clinical response.	Response to treatment is generally seen in 3 to 5 d.	Local pain and burning, occasionally rectal bleeding. Prolonged treatment may result in systemic absorption, causing systemic side effects.
5-aminosalicylic acid (5-ASA) enemas	[31,43,63,64]	4 g of mesalazine in 60 mL suspensions, administered rectally once-daily dose for 4 to 5 wk.	Varying effect	Occasionally produces acute intolerance manifested by cramping, acute abdominal pain, bloody diarrhea, fever, headache, and rash.
Short-chain-fatty acid (SCFA)	[5,10,13,18,19,26,27,61,62]	SCFA enema rectally twice a day for 2 wk, and then tapered according to response over 2 to 4 wk.	Varying effect	None
Irrigation with Fibers	[65,66]	Solution containing 5% fibers (10 g/d) for 7 d.	The endoscopic score which is used to quantify the intensity of the inflammation at the mucosa at the diverted colon diminished after treatment.	Probably none
Leukocytapheresis	[44]	Leukocytapheresis, at flow rate of 40 mL/min for 60 min, once weekly for 5 wk, following low dose of metronidazole and ciprofloxacin, another set of weekly leukocytapheresis was added.	Significant improvement in her pouchitis disease activity index (PDAI) from 14 to 1.	The common side effects were nausea, vomiting, fever, chills, and nasal obstruction.
Autologous fecal transplantation	[45]	Feces were collected from the colostomy bag, diluted with 600 mL of sterile saline (0.9 %), stirred and filtered three times using an ordinary coffee filter, irrigation endoscopically. This procedure was repeated 3 times within 4 wk (on day 0, day 10 and day 28).	All symptoms improved dramatically within 5 d after the first treatment. Colonoscopy 28 d after the first treatment showed no major signs of inflammation in the colonic stump	None, patient's tolerance required.
Dextrose spray (hypertonic glucose)	[29]	Endoscopically sprayed with 150 mL 50% dextrose via a catheter.	Follow-up pouchoscopy 2 wk after the dextrose spray showed normal pouch mucosa with no evidence of bleeding or mucosal friability.	It has a very low chance of causing transient hyperglycemia because there is no direct injection of the hypertonic solution into blood vessels.

SCFA: Short chain fatty acids; 5-ASA: 5-aminosalicylic acid.

Irrigation with fibers

Resolution of diversion colitis, based on endoscopic and histologic examination, has been reported following irrigation of the diverted segment of the colon with fibers^[65,66]. Joaquim *et al.*^[66] investigated the effect of irrigating the colorectal mucosa of patients with a colostomy using a solution of fibers. In 11 patients with loop colostomies, the diverted colorectal segment was irrigated with a solution containing 5% fibers (10 g/d) for 7 d. Irrigation with fibers improves inflammation within the defunctionalized colon, so this therapy may play a role in the preoperative management of colostomies, potentially decreasing the high incidence of diarrhea after reestablishment of the intestinal transit.

Leukocytapheresis

Watanabe *et al.*^[44] reported successful treatment of

leukocytapheresis in a patient with chronic antibiotic-refractory diversion pouchitis following IPAA for UC with diverting ileostomy. The mucosa of the diverted pouch is less exposed to the fecal stream and pathogens. Therefore, altered immunity likely plays a major role in the maintenance of diversion pouchitis. Leukocytapheresis to address the altered immunity would seem a reasonable approach for antibiotic-refractory pouchitis following IPAA for UC with diverting ileostomy, and its effectiveness in the case suggests that altered immunity may be a key contributing factor compared with dysbiosis, bacterial pathogens, and ischemia.

Autologous fecal microbiota transplantation

Fecal microbiota transplantation (FMT), which consists of transferring stool from a healthy donor to the patient's colon, is an effective treatment for some diseases of the

colon such as Crohn's disease and recurrent *Clostridium difficile* infections^[67]. Gundling *et al*^[45] presented that autologous FMT might be an effective and safe option for relapsing DC after standard therapies have failed. Since the interruption of the fecal stream is central to the development of DC, FMT seems to be a hopeful treatment.

Dextrose spray

Custon *et al*^[29] presented a patient with ulcerative colitis with severe hematochezia and diffuse mucosal bleeding in a diverted ileal pouch, which was successfully treated with endoscopic spray of hypertonic glucose (50% dextrose). Hypertonic glucose may work thorough osmotic dehydration and sclerosant effects, inducing long-term mural necrosis and fibrotic obliteration of mucosal vessels^[68,69]. Glucose spray is safe and inexpensive, and it carries a very low risk of complications. The approach has the potential to reduce recurrent bleeding and need for surgical interventions.

SUMMARY OF PHARMACOLOGIC TREATMENTS

The goal of treatment is the reduction or elimination of symptoms. Patients who desire stoma closure and have acceptable risks should undergo surgery to re-establish intestinal continuity. In their prospective study, Son *et al*^[20] reported that the severity of DC is related to diarrhea after an ileostomy reversal and may adversely affect quality of life. Pharmacologic treatments are needed for symptomatic patients with permanent stomas and patients who are unable to undergo stoma closure for reasons of technical difficulty, poor anal sphincter function, or persistent perianal sepsis. In our review, SCFA^[5,10,18,19,26,27,36,62], 5-ASA enemas^[31,43,47,51], steroid enemas^[21,32,33], and irrigation with fibers^[65,66] have been tried with various efficacies for mucosal inflammation. Only case reports of therapy involving leukocytapheresis^[44], autologous fecal microbiota transplantation (FMT)^[45] and dextrose (hypertonic glucose) spray^[29] have been tried with some effect. We have summarized the method, advantages and disadvantages of each pharmacologic treatment in Table 3.

CONCLUSION

The vast majority of diverted patients remain asymptomatic, however diversion colitis occurs in almost all diverted patients. It generally resolves following colostomy closure. However, those patients with significant symptoms or histories of colitis or diarrhea should undergo a complete proximal and distal colonic evaluation prior to stoma closure, and some treatments need not be delayed in these patients. Patients with permanent diversions should undergo periodic pharmacologic treatment. This review of various treatments for diversion colitis will hopefully be useful for determining future treatments.

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