

Pouchitis and Disorders of Ileal Pouches

by Bo Shen

INTRODUCTION

Approximately 30% of patients with ulcerative colitis (UC) eventually require surgery, despite medical therapy (1). Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the surgical treatment of choice for patients with UC who fail medical therapy or develop dysplasia and for patients with familial adenomatous polyposis (FAP). While the surgical modality significantly improves patients' functional status and health-related quality of life (QOL), short-term and long-term complications can occur. Disorders of the ileal pouch can be classified into: 1) inflammatory complications, such as pouchitis, Crohn's disease (CD) of the pouch, cuffitis; 2) surgical or mechanical complications, including anastomotic leak, sinuses, abscess, strictures; 3) functional disorders, such as irritable pouch syndrome (IPS), paradoxical contractions, and megapouch; 4) dysplasia or neoplasia; and 5) systemic or metabolic disorders, such as osteoporosis, anemia, and

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vitamin B₁₂ deficiency. With a high prevalence of UC in the developed countries and IPAA as a standard surgical therapy, patients with pouchitis or other pouch disorders are increasingly encountered in the clinical practice of gastroenterology.

POUCHITIS AND INFLAMMATORY DISORDERS OF THE ILEAL POUCHES

Pouchitis is the most common long-term complication in patients with IPAA which significantly affects patients' QOL (2). Reported cumulative frequency of pouchitis in 10 years after surgery ranged from 23% to 46% (3,4), and incidence within 12 months after ileostomy take-down was 40% (5). Pouchitis almost exclusively occurs in patients with underlying UC and is rarely seen in patients with FAP (6,7). The etiology and pathogenesis of pouchitis are not entirely clear. Strong evidence suggests that abnormal mucosal immune response to dysbiosis of microflora in the pouch leads to acute or chronic inflammation (5,8–11).

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Table 1
Classification and Treatment of Pouchitis

<i>Classification Based on Disease Course</i>	<i>Classification Based on Response to Antibiotic Therapy</i>	<i>Therapeutic Options</i>
Acute pouchitis	Antibiotic-responsive pouchitis	<ul style="list-style-type: none"> • 2-week metronidazole or ciprofloxacin
Acute relapsing Pouchitis	Antibiotic-dependent pouchitis	<ul style="list-style-type: none"> • 2–4 week antibiotic therapy (ciprofloxacin ± metronidazole or rifaximin) for induction followed by probiotic or low-dose antibiotic agents for maintenance
Chronic pouchitis	Antibiotic-refractory pouchitis	<ul style="list-style-type: none"> • 4-week ciprofloxacin + metronidazole or rifaximin or tinidazole • Oral or topical mesalamine agents? • Immunomodulators? • Oral or topical corticosteroids? • Anti-TNFα agents?

The disease course of pouchitis is heterogeneous, ranging from acute antibiotic-responsive entity to chronic antibiotic-refractory disorder. Increased stool frequency, urgency, seepage abdominal cramping, and pelvic discomfort are the most common presenting symptoms. Fever and bloody bowel movements are rare. Patients may predominantly present with extraintestinal symptoms, such as arthralgia. These symptoms, however, are not specific and can be present in other disorders of IPAA, such as CD, cuffitis, and IPS. The severity of symptoms does not necessarily correlate with the degree of endoscopic or histologic inflammation of the pouch (8,12,13). Endoscopic evaluation together with symptom assessment and histology evaluation is the key to an accurate diagnosis and differential diagnosis. There are no universally accepted diagnostic criteria for pouchitis. Pouchitis disease activity index is the most commonly used instrument in published clinical trials, and it applies quantitative scores to clinical symptoms as well as to endoscopic and histologic acute inflammation (14).

It is important to accurately classify the disease before initiating appropriate therapy, although there are no validated and universally accepted classification systems (Table 1). From various perspectives, pouchitis may be categorized into: 1) idiopathic versus secondary; 2) remission versus active; 3) acute versus chronic; 4)

infrequent episodes versus relapsing versus continuous course; and 5) responsive versus refractory (15). Another useful classification can be based on the response to antibiotic therapy (16). Analogous to the classification of UC according to the response or dependency to corticosteroids, pouchitis can be classified based on the manner of the patient's response to antibiotics: antibiotic-responsive pouchitis, antibiotic-dependent pouchitis, and antibiotic-refractory pouchitis (15).

The management and prognosis vary in different types of pouchitis (Table 1). For antibiotic-responsive pouchitis, the first-line therapy includes a 2-week course of metronidazole or ciprofloxacin (8,17,18). A relapsing course of pouchitis is common. Of the patients with acute pouchitis, 61% would develop at least one recurrence (19). Approximately 5% to 19% of patients with acute pouchitis develop refractory or rapidly relapsing symptoms that require frequent and/or protracted therapy (10). Typically, patients' symptoms and endoscopic and histologic inflammation respond favorably to antibiotic therapy, but symptoms quickly recur when antibiotics are discontinued. This group of patients is classified as having antibiotic-dependent pouchitis and often requires long-term antibiotic or probiotic therapy to keep disease in remission. Antibiotic-refractory pouchitis is often difficult to treat and this type of pouchitis is a common cause of

pouch failure(15). The patients typically do not respond to full-dose, single-agent antibiotic therapy. It is important to investigate why patients do not respond to antibiotic therapy. Possible causes of refractory disease include use of NSAIDs, concurrent *Clostridium difficile* or cytomegalovirus infection, celiac disease, cuffitis, and CD. For patients without obvious causes, treatment options include a prolonged course of combined antibiotic therapy, 5-aminosalicylates, corticosteroids, immunosuppressive agents or even biological therapy. Safe and effective regimens reported in open-labeled trials including combined ciprofloxacin (1 gm/d) with rifaximin (2 gm/d) or metronidazole (1 gm/d) or tinidazole (1–1.5 gm/d) for 4 weeks.

Probiotics have been used for primary and secondary prophylaxis of pouchitis, although therapeutic mechanisms in pouchitis are not entirely clear. Randomized, placebo-controlled trials showed that VSL#3[®] was safe and very effective in the prevention of pouchitis (5,10,11,20). However, an open-labeled post-marketing trial showed discrepant results (19). Other agents reported in non-controlled trials include tetracycline, clarithromycin, amoxicillin/clavulanic acid, doxycycline, rifaximin, budesonide enema, enema formulation of alicaforsen (an antisense inhibitor of intercellular adhesion molecules-1), bismuth carbomer enemas, short-chain fatty acid enemas, and glutamine enemas, 6-mercaptopurine, and infliximab.

Cuffitis is a common inflammatory disorder in patients with IPAA. One of two anastomotic techniques is used to construct IPAA: a hand-sewn IPAA with mucosectomy of the anal transitional zone (ATZ) mucosa (also named rectal columnar cuff mucosa) or a stapled IPAA at the level of the anorectal ring without mucosectomy of the anal transitional zone. Stapled IPAA without mucosectomy has been routinely advocated at our institution for patients with medically refractory UC who require surgery, unless there is synchronous colorectal cancer or rectal dysplasia. The preservation of the ATZ is meant to optimize anal canal sensation, eliminate sphincter stretching, and preserve normal post-operative resting and squeeze pressures. However, in order to allow transanal insertion of the stapler head, it is normally necessary to leave a 1-cm to 2-cm strip of the rectal columnar cuff which is at risk for developing symptomatic inflam-

mation (cuffitis) or dysplasia. Clinical symptoms of cuffitis are similar to that in pouchitis. In addition, patients with cuffitis often present with bloody bowel movement. Cuffitis can be treated with topical 5-aminosalicylate or corticosteroid agents. Topical mesalamine (1 gm/day) appears to be well tolerated and effective in treating patients with cuffitis (21).

Crohn's disease of the pouch can occur in patients with a preoperative diagnosis of UC, with cumulative frequencies of 2.7% to 13% (22–29). The development of CD of the pouch in patients with a pre-operative diagnosis of UC is a cause of concern for patients and clinicians. Clinically CD of the pouch can be classified into inflammatory, fibrostenotic, to fistulizing phenotypes, which are associated with different risk factors and clinical presentations (30). There is limited data on the treatment of CD of the pouch. Fibrostenotic CD can be treated with combined medical, endoscopic (e.g. endoscopic balloon dilations of strictures)(31), and surgical (e.g. stricturoplasty) (32) therapy. Patients who are diagnosed with CD of the pouch often require long-term maintenance therapy. In a case series of 26 patients with CD of the pouch, 62% had a complete response to infliximab infusion and 23% had a partial response. After a median follow-up of 22 months, 33% had pouch resection, while the pouch was functional in the remaining 67% of patients (33).

SURGICAL OR MECHANICAL COMPLICATION OF ILEAL POUCH SURGERY

Performance of IPAA requires high technical skills and expertise. Surgery-related complications are common. These complications include anastomotic leak and stricture, abscess or fistula formation, sepsis, and small bowel obstruction. There are two unique forms of surgical complications, “afferent and efferent limb syndromes.” Afferent limb syndrome is characterized by a long, redundant pre-pouch neo-terminal ileum, leading to a sharp angulation between the afferent limb and the pouch. During the pouch endoscopy, the endoscopist may find it difficult to intubate the afferent limb. Efferent limb syndrome is seen in patients with S pouch with long, redundant efferent limb, causing kink and obstruction. Patients with afferent limb syndrome or efferent limb syndrome often present with dyschezia,

pelvic discomfort, and bloating. Surgical correction is often required.

FUNCTIONAL DISORDER OF THE ILEAL POUCH

Irritable pouch syndrome is a newly described functional disorder in patients with IPAA (34). Patients with IPS have significantly poorer QoL scores than patients with healthy pouches (2). The etiology and pathophysiology are not clear. A recent study showed that patients using antidepressants or anti-anxiety agents have a higher risk of having IPS, suggesting that psychological factors may play a role in the pathogenesis (35). Our recent study demonstrated that the pouch compliance and tone in IPS patients were similar to that in patients with healthy pouches. However, there was a decreased threshold for perception of gas, urge to defecate, and pain in patients with IPS, indicating visceral hypersensitivity of the ileal pouch (36). These pathophysiologic features resemble those seen in irritable bowel syndrome. Cellular or molecular mechanisms of IPS warrant exploration. Enterochromaffin cell hyperplasia with increased numbers of serotonin-expressing cells in the pouch mucosa has been demonstrated in patients with IPS, indicating a possible role of over-activation of the neuroenteric system (37).

Currently, IPS is a diagnosis of exclusion based on the presence of symptoms of increased frequency of bowel movement with change in stool consistency, abdominal pain or cramping, and perianal or pelvic discomfort in the absence of endoscopic and histologic inflammation. Treatment of IPS is empiric. There are no published trials or established algorithms for the management of IPS. The common clinical features shared by patients with IPS and irritable pouch syndrome suggest that the pathophysiology of the two diseases may overlap. Therefore, it is reasonable to speculate that the treatment modalities effective in irritable bowel syndrome may also be successful in IPS. We found that dietary fibers are often not helpful in patients with IPS. However, dietary modifications such as low-fat and low-carbohydrate diet and avoidance of dairy products, excessive caffeine or alcohol sometimes help to relieve symptoms. Occasionally, patients may report improvement in symptoms with

antibiotic therapy. This may be explained by the fact that some of patients with IPS may in fact have proximal small bowel bacterial overgrowth. Pharmaceutical therapy includes antispasmodic agents and tricyclic antidepressants.

Patients presenting with constipation or dyschezia symptoms in the absence of mechanical obstruction should be suspected as having anismus or pelvic floor dysfunction. Pouch manometric evaluation may reveal paradoxical contractions, asymmetric sphincter pressures, poor pouch sensation or mega-pouch. Management of these conditions can be challenging. Biofeedback has been empirically used.

DYSPLASIA IN THE ILEAL POUCH

Proctocolectomy and IPAA reduce the risk for dysplasia or cancer in UC patients. However, dysplasia and cancer can still occur in the rectal cuff or ileal pouch mucosa. The risk of development of dysplasia is significantly associated with a pre-operative or intra-operative diagnosis of dysplasia or cancer (38). Patients with hand-sewn IPAA with mucosectomy are not immune to dysplasia, since islands of the rectal columnar mucosa can regrow or may have been preserved due to incomplete mucosectomy (39). Residual islets of rectal mucosa can be found in 20% of patients who underwent hand-sewn IPAA with mucosectomy (39). The true incidence of *dysplasia in the rectal cuff* is unknown, and it may depend on the duration and intensity of endoscopy surveillance. In a study of 135 patients with stapled IPAA without mucosectomy with a median follow-up of 56 months, no dysplasia or cancer were found in the cuff (40). In another study of 178 patients who underwent IPAA and had serial endoscopic surveillance biopsy of the cuff with a minimum follow-up of 10 years, dysplasia was detected in 4.5% of patients (2 high-grade dysplasia and 6 low-grade dysplasia) (38). In another study of cuff specimens from patients with IPAA, Gilchrist, et al (41) reported that 15 patients (16%) had low-grade dysplasia, of whom 73% had histologic cuffitis. In patients with persistent dysplasia, mucosectomy, and perianal pouch advancement and neo-ileal pouch-anal anastomosis are recommended (42). There are only several case

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reports on adenocarcinoma in the ATZ (43–46). Typically IPAA was performed for dysplasia or cancer in these patients (44–46). It can occur even with hand-sewn and mucosectomy (45,47). Dysplasia may accompany or precede the development of cancer at the cuff. Pouch excision is often required (46).

Dysplasia in the ileal pouch is rare (48–52). Herline, et al (53) surveyed 160 UC patients with IPAA with a total of 222 times, only one patient had a focal low-grade dysplasia. Thompson-Fawcett, et al (50) studied 106 “high-risk” patients out of a 1,221 patient cohort, including these with chronic pouchitis, severe villous atrophy, neoplasia on colectomy specimens, a long duration of IPAA and only found one patient with multifocal low-grade dysplasia and two patients with DNA aneuploidy. Dysplasia of ileal pouch mucosa can be present as flat (53) or polypoid (54) lesions. Patients with severe villous atrophy of pouch mucosa may have an increased risk for dysplasia (52,55). Adenocarcinoma arising from ileal pouch mucosa is extremely rare (48). Patients with pancolitis and backwash ileitis before IPAA have an increased risk for colorectal dysplasia (56) and if these patients have chronic pouchitis after IPAA they may have a particular risk for dysplasia or cancer of the ileal pouch (48). There is a case report that large cell lymphoma developed in pouch mucosa with underlying UC (49). Therefore biopsy in surveillance endoscopy should not only include the cuff mucosa but also the pouch mucosa. The cost effective approaches for surveillance have not been evaluated. ■

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