Diagnosis and Treatment of Pouchitis

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Abstract: Ileal pouch-anal anastomosis following total proctocolectomy has become part of the standard surgical treatment for patients with ulcerative colitis or familial adenomatous polyposis who require colectomy. Although this surgery has improved patient quality of life and significantly reduced the risk of dysplasia or neoplasia in ulcerative colitis patients, complications are common. Pouchitis is the most common long-term complication of ileal pouch surgery and has a significant adverse impact on patient quality of life. The diagnosis and differential diagnosis of pouchitis are not straightforward, and the management of pouchitis, particularly chronic antibiotic-refractory pouchitis, which is one of the leading causes of pouch failures, can be challenging.

The last decade has witnessed major advances in medical treatment of ulcerative colitis (UC). The options for medical therapy of moderate-to-severe UC have extended to anti-tumor necrosis factor (TNF)-α biologic regimens. However, it is not clear whether these new agents will ultimately alter the natural history of UC. Approximately 30% of patients with UC eventually require colectomy.[1] Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the surgical treatment of choice for the majority of patients with UC who fail medical therapy or develop dysplasia and the majority of patients with familial adenomatous polyposis (FAP). The advantages of the surgical procedure include re-establishment of gastrointestinal continuity; improvement in health-related quality of life; positive impact on body image; avoidance of long-term use of UC-related medications in the majority of patients; and a substantial reduction in the risk of dysplasia or cancer. However, after the surgery, adverse outcomes or complications often occur, of which pouchitis is the most common long-term inflammatory complication.

Prevalence

Pouchitis is generally considered a nonspecific inflammatory condition in the ileal pouch reservoir.[2] Reported cumulative frequency rates of pouchitis 10 years after IPAA surgery range from 23% to 46%.[3,4] It is estimated that approximately 50% of patients who undergo IPAA surgery for UC will develop at least 1 episode of

pouchitis.[5] The estimated incidence of pouchitis within 12 months of ileostomy take-down has been reported to be as high as 40% in one drug trial.[6] The discrepancy in the reported cumulative frequencies from different institutions likely results from the variance in diagnostic criteria, the intensity of follow-up with or without pouch endoscopy, and the inclusion or exclusion of other inflammatory or functional disorders of the pouch and related surgical conditions.

Pathophysiology

Pouchitis almost exclusively occurs in patients with underlying UC or indeterminate colitis and is rarely seen in patients with FAP.[7,8] Although the etiology and pathogenesis of pouchitis are not entirely clear, the alteration in bowel anatomy from the surgery may create an "inflammation-prone" environment. The normal function of the distal ileum, which involves the absorption of nutrients, is artificially converted to that of a storage reservoir. Qualitative and quantitative changes in the ileal pouch may constitute a triggering factor for the development of pouchitis.[9-12] Evidence suggests that an abnormal mucosal immune response to altered microflora in the pouch leads to acute and/or chronic inflammation.[6,12-15] Immune mechanisms of pouchitis have been extensively studied in a fashion similar to those of inflammatory bowel disease. An ex-vivo study has demonstrated that an ileal pouch of long duration has increased bacterial permeability.[16-21] Proinflammatory cytokines such as TNF-α are released mainly in inflamed mucosa by macrophages and monocytes, leading to tissue injury, and are considered a secondary pathophysiologic mechanism in pouchitis.[21] As in UC, the production of other inflammatory mediators, including cytokines,[22-25] cell adhesion molecules,[26] platelet-activating factor,[27] lipoxygenase products of arachidonic acids,[28] and proinflammatory neuropeptides[23,29-31] is also increased. Abnormalities of immunoregulatory cytokines such as interleukin (IL)-2, interferon-gamma,[19,32] IL-4,[32] and IL-10 are also seen in pouchitis. Imbalance between proinflammatory and immunoregulatory cytokines has been described in patients with pouchitis.[25] However, it is likely that those abnormalities in mucosal immunity are nonspecific and secondary in nature.

Risk Factors

The risk factors associated with pouchitis have been extensively studied. Genetic polymorphisms such as those associated with the IL-1 receptor antagonist[33-35] and *NOD2/CARD15*[36] may increase the risk of pouchitis. The reported risk factors of pouchitis also include noncarrier status of TNF allele 2,[35] extensive UC,[4,37,38] backwash ileitis,[37] proctocolectomy thrombocytosis,[39] concurrent primary sclerosing cholangitis,[3,40,41] seropositive perinuclear antineutrophil cytoplasmic antibodies (pANCA),[42,43] being a nonsmoker,[38,44] and use of nonsteroidal anti-inflammatory drugs (NSAID).[38,44] In addition to pANCA, the presence of the serologic markers *anti-Saccharomyces cerevisiae* antibodies (ASCA), the Crohn's disease (CD)-related antigen from *Pseudomonas fluorescens,* and the outer membrane porin C of *Escherichia coli* in patients with pre-operative indeterminate colitis appears to be associated with persistent inflammation of the pouch after restorative proctocolectomy.[45] Acute and chronic pouchitis may be associated with different risk factors.[38,46]

Presentation

Patients with pouchitis can develop a wide range of clinical presentations, including increased stool frequency, urgency, tenesmus, incontinence, nocturnal seepage, abdominal cramping, and pelvic discomfort. Although bloody bowel movements are uncommon in typical pouchitis, patients with IPAA with or without pouchitis can have iron-deficiency anemia.[47,48] Patients with severe pouchitis occasionally present with fever, dehydration, and malnutrition, which may require hospitalization. Patients may chiefly complain of predominantly extraintestinal symptoms such as arthralgia. These symptoms, however, can be present in other disorders of the pouch, including cuffitis, CD of the pouch, proximal small-bowel bacterial overgrowth, and irritable pouch syndrome.

Diagnosis

The diagnosis of pouchitis should not depend solely upon the presenting symptoms of a patient. The severity of symptoms does not necessarily correlate with the degree of endoscopic or histologic inflammation of the pouch.[49,50] A combined assessment of symptoms and endoscopic and histologic features is ideal for the diagnosis and differential diagnosis of pouchitis. There are no universally accepted diagnostic criteria for pouchitis. The 18-point Pouchitis Disease Activity Index (PDAI), although the most commonly used index in clinical trials, is seldom utilized in routine clinical practice.[51]

Pouch endoscopy yields valuable information on the severity and extent of mucosal inflammation (Figure 1), the presence or absence of concurrent backwash ileitis, CD of the pouch (Figure 2) or cuffitis (Figure 3), and the presence or absence of structural abnormalities such as strictures, sinus openings, and fistula openings. In addition, pouch endoscopy with segmental biopsy is the main surveillance procedure for dysplasia and can deliver

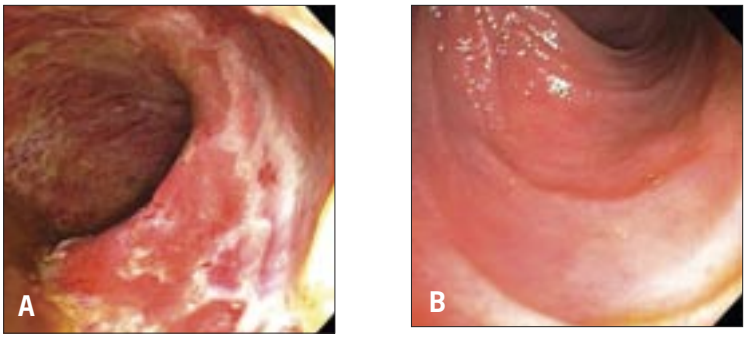

Figure 1. Active pouchitis: Diffuse endoscopic inflammation of the pouch (A) with normal afferent limb mucosa (B).

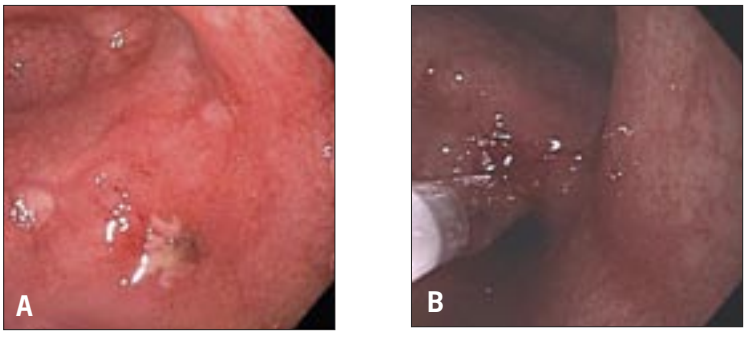

Figure 2. Crohn's disease of the pouch: Pouch inlet stricture (A) with balloon dilation therapy (B).

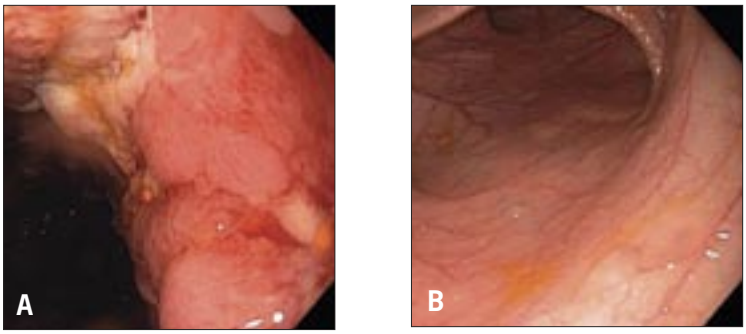

Figure 3. Cuffitis: Inflammation at the anal transitional zone or cuff (A) with normal pouch mucosa (B).

effective therapy, including balloon stricture dilations and polypectomy. Histopathology is invaluable for the detection of dysplasia or neoplasia, viral inclusion bodies of cytomegalovirus infection, granulomas, pyloric gland metaplasia, mucosal prolapse, and ischemic changes. It should be noted that villous blunting and an increase in the number of mononuclear cells in the lamina propria can be part of the "normal" adaptive changes of the pouch mucosa to fecal stasis in the pouch and do not necessarily indicate pouchitis or CD of the pouch.

In cases of suspected complicated pouchitis, CD of the pouch and complications related to surgical procedures should be excluded. Imaging studies such as contrast pouchography, computed tomography, and particularly magnetic resonance imaging of the pelvis are typically utilized to assess the presence of mucosal and transmural disease activity within and around the pouch.[52] Wireless capsule endoscopy appears to be safe for use in patients with chronic pouchitis[53] or anemia[54] for assessment of small-bowel diseases.

Disease Variance

The disease course of pouchitis varies. Pouchitis likely represents a disease spectrum from acute, antibiotic-responsive to chronic, antibiotic-refractory. Based upon

various criteria, pouchitis can be classified into the following categories: idiopathic versus secondary (based upon etiology); remission versus active (based upon disease status); acute versus chronic (based upon disease duration); infrequent episodes versus relapsing disease versus continuous disease (based upon disease pattern); and responsive versus refractory (based upon response to antibiotic therapy).[55] Although the majority of patients with pouchitis respond favorably to antibiotic therapy, particularly in the initial stages of disease, some patients develop pouchitis refractory to routine antibiotic treatment. This leads to an additional useful clinical classification based upon the response to antibiotic therapy.[56] Analogous to the classification of UC according to response to or dependency on corticosteroids, pouchitis can be classified based upon the manner of the patient's response to antibiotics: antibiotic-responsive, antibiotic-dependent, or antibiotic-refractory pouchitis.[44] A subpopulation of patients experience pouchitis associated with identifiable and modifiable causes (namely secondary pouchitis), such as *Clostridium difficile*[57,58] and cytomegalovirus[59,60] infections as well as regular NSAID use.[61] A recent study using immunohistochemistry and polymerase chain reaction found that viral genes and proteins were detected in samples from 12 of 34 patients (35.2%) with pouches, more frequently in patients with pouchitis than those without pouchitis. Cytomegalovirus infection may contribute to the disease course of pouchitis in some patients,[62] though whether antiviral therapy is beneficial is not clear.

Disease Management

As the majority of patients who develop acute pouchitis do so within the first year post-IPAA,[63] the probiotic VSL#3, which contains viable lyophilized bacteria with 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium* species, and *Streptococcus salivarius* subsp. *Thermophilus,* was evaluated for the primary prophylaxis of the initial pouchitis episode. Two of 20 patients (10%) treated with VSL#3 developed pouchitis within 12 months after IPAA, whereas 8 of 20 patients (40%) experienced pouchitis in the placebo group during the same period of time.[6]

Management and prognosis vary among the different types of pouchitis. For antibiotic-responsive pouchitis, first-line therapy includes a 14-day course of metronidazole (15–20 mg/kg/day) or ciprofloxacin (1,000 mg/day).[64,65] A randomized trial of ciprofloxacin and metronidazole showed that patients treated with ciprofloxacin experienced significantly greater reductions in PDAI scores and fewer adverse effects than those treated with metronidazole.[65] A small randomized trial of oral rifaximin 1,200 mg daily versus placebo (N=18) showed a marginal therapeutic benefit for active pouchitis.[66] Other agents used in open-label trials include tetracycline, clarithromycin, amoxicillin/clavulanic acid, doxycycline, rifaximin, budesonide enemas,[67] alicaforsen enemas, an antisense inhibitor of intercellular adhesion molecule-1,[68] and AST-120, a highly adsorptive, porous, carbon microsphere.[69]

Patients with antibiotic-dependent pouchitis often require long-term maintenance therapy with either antibiotics or probiotics for maintenance of disease remission. A randomized trial of VSL#3 at a dose of 6 g daily was conducted for the maintenance and secondary prophylaxis of pouchitis relapse after remission was induced by oral ciprofloxacin (1,000 mg/d) and rifaximin (2,000 mg/d). During the 9-month trial in 40 patients with relapsing pouchitis, only 15% of the probiotic group relapsed as opposed to 100% of the placebo group.[14] A separate randomized trial of VSL#3 in patients with antibiotic-dependent pouchitis showed that 17 of 20 patients (85%) in the VSL#3 group maintained clinical remission compared to 1 of 16 patients (6%) in the placebo group.[15] However, in a recent postmarket, open-label trial of VSL#3 in 31 patients with antibiotic-dependent pouchitis, patients received 2 weeks of treatment with ciprofloxacin followed by VSL#3.[70] After 8 months, 6 of the 31 patients (19%) were still taking VSL#3 and the remaining 25 patients (81%) had stopped mainly due to the lack of efficacy, low compliance, or the development of adverse effects.[70] A small open-label trial of high-dose VSL#3 showed that treatment with the agent resulted in remission in 16 of 23 patients (69%) with active pouchitis.[71] However, the role of probiotics in induction therapy warrants further study.

Antibiotic-refractory pouchitis is often difficult to treat and a common cause of pouch failure. Patients typically do not respond to full-dose, single-agent antibiotic therapy. It is important to investigate contributing causes (in secondary pouchitis) related to failure of antibiotic therapy. Secondary causes of refractory disease include the use of NSAIDs, concurrent *C. difficile* or cytomegalovirus infection, celiac disease and other autoimmune disorders, cuffitis, CD of the pouch, pouch ischemia, and inflammatory polyps of the pouch.[72] There have been no randomized trials in the literature for this category of pouchitis. For patients without obvious causes of pouchitis, treatment options include a prolonged course of combined antibiotic therapy, 5-aminosalicylates, corticosteroids, immunosuppressive agents, or even biologic therapy. Regimens reported to be safe and effective in open-label trials include ciprofloxacin (1,000 mg/d) combined with one of the following: rifaximin (2,000 mg/d),[73,74] metronidazole (1,000 mg/d),[75] or tinidazole (1,000–1,500 mg/d)[76] for 4 weeks. However, maintenance of remission in this group of patients after induction therapy with dual antibiotics remains a challenge.[77] In addition, overuse of

antibiotics may explain the possibility that the microflora responsible for pouchitis may shift from conventional to nonconventional forms, such as *C. difficile*,[58] fungi,[78] or even parasites (the authors' nonpublished data). Anti-inflammatory agents, immunomodulators, and biologic therapy have been used to treat pouchitis; these agents include bismuth carbomer enemas, short-chain fatty acid enemas, glutamine enemas, mesalamine enemas, oral budesonide,[79] 6-mercaptopurine, and infliximab.

Natural History and Prognosis

The natural history of pouchitis is poorly defined. In a study of 100 consecutive UC patients who underwent restorative proctocolectomy with IPAA, 32 patients developed pouchitis episodes and 5 patients had chronic refractory pouchitis, 2 of whom had pouch.[55] Few studies have been conducted to identify the natural history of pouch and pouchitis. Patients with initial episodes of pouchitis almost uniformly respond to antibiotic therapy. However, pouchitis relapse is common. Of the patients with acute pouchitis, 39% have a single acute episode that responds to antibiotic therapy whereas the remaining 61% of patients develop at least 1 recurrence.[80] Approximately 5–19% of patients with acute pouchitis develop refractory or rapidly relapsing forms of the disease.[81-83] The disease course of antibiotic-responsive pouchitis may evolve into antibiotic-dependent pouchitis and then antibiotic-refractory pouchitis. The latter is one of the leading causes for pouch failure, resulting in pouch excision or permanent diversion. Although concurrent primary sclerosing cholangitis appears to be a risk factor for pouchitis,[3,40,41] liver transplantation with posttransplant use of immunosuppressive agents does not appear to have an adverse impact on the disease course of pouchitis.[84,85] In addition, chronic inflammation of the pouch and cuff may convey an increased risk for the development of dysplasia or cancer.[86,87]

Summary

Pouchitis is the most common long-term complication of restorative proctocolectomy. Its natural history, however, has not yet been defined. Patients with pouchitis can have a wide range of clinical presentations, disease courses, and prognoses. As medical therapy for pouchitis is largely antibiotic-based, management of antibiotic-dependent and antibiotic-refractory pouchitis remains a challenge.

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