Pouchitis

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INTRODUCTION — For the surgical treatment of ulcerative colitis (UC) and familial adenomatous polyposis (FAP), proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the favored alternative to proctocolectomy with permanent ileostomy since it preserves intestinal continuity and sphincter function and removes the entire colorectal mucosa. This procedure consists of total abdominal colectomy, stripping of the rectal mucosa with preservation of the anal sphincter, and the construction of an ileal pouch that is anastomosed to the anus.

The most frequently observed long-term complication of IPAA is acute and/or chronic inflammation of the ileal reservoir, called pouchitis. This is not a well-defined entity, and much uncertainty remains regarding its true prevalence, etiology, and natural history. However, the condition continues to overshadow the overall good functional results of this sphincter-saving operation.

EPIDEMIOLOGY — Patients who undergo ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC) have a higher incidence of pouchitis compared to those who undergo the procedure for FAP [1,2]. In patients who undergo IPAA for UC, the reported prevalence of pouchitis varies widely from less than 7 percent [1,3-8] to as high as 44 percent [9]. The large variations that have been reported reflect differences in diagnostic criteria and follow-up and are responsible for much of the confusion surrounding pouchitis. As an example, in one series of 149 patients, the incidence of mild pouchitis (diagnosed by symptoms and endoscopy) was 21, 26, and 39 percent at 6, 12, and 48 months; the respective values for severe pouchitis were 9, 11, and 14 percent [9].

PATHOGENESIS — The etiology of pouchitis remains uncertain although preoperative and postoperative factors may contribute.

Preoperative — Factors associated with acute pouchitis include use of steroids before colectomy, and a history of extensive colitis [10,11]. Extraintestinal manifestations of colitis and primary sclerosing cholangitis are associated with an increased risk of chronic pouchitis [1,10,12], while smoking appears to protect against the development of acute and chronic pouchitis [1,10].

Patients with mutations in the gene that encodes the protein NOD2/CARD15 appear to be at increased risk of pouchitis following proctocolectomy with ileal pouch-anal anastomosis (IPAA). In a case-control study of 107 patients with an IPAA and 269 controls, NOD2/CARD15 mutations were noted in 67 percent of patients with severe pouchitis, compared with 9 percent of healthy controls, 5 percent of patients who were asymptomatic following IPAA, and 14 percent of patients with an IPAA and Crohn's disease-like complications (eg, perianal fistula, pouch inlet stricture, proximal small bowel disease) [13].

Postoperative — A number of factors developing after surgery have also been proposed as contributors to pouchitis [14-25]:

- Overgrowth of bacterial flora that become more anaerobic may occur because of stasis. Pouchitis has been described in patients with excessively large pouches that empty poorly and in those with anastomotic strictures which are often associated with bacterial overgrowth. However, no close relationship between

reduced reservoir emptying and the incidence of pouchitis has been established [14,24,26].

Bacterial overgrowth might cause pouchitis indirectly by either changing the pouch contents or by altering mucosal defense mechanisms. One theory proposes that colonic metaplasia in the pouch predisposes to growth of sulfate-reducing bacteria that produce hydrogen sulfide, which (in high concentrations) is toxic to colonocytes [27]. A small cross-sectional study of 32 patients with IPAA for ulcerative colitis (UC) demonstrated a direct correlation between pouch granulocyte and monocyte mucosal infiltration, colony counts of Bacteroides spp. and Clostridiaceae spp., mucosal ulceration, and the number of daily stools. Conversely, in patients with pouchitis, Enterococcaceae spp. counts were lower than in healthy subjects. Enterobacteriaceae spp., Streptococcaceae spp. and Enterococcaceae spp. counts correlated inversely with immune cell infiltration [28].

The response of pouchitis to treatment with metronidazole and other antibiotics (see 'Prognosis and treatment' below) suggests a bacterial etiology for reservoir inflammation; however, no intestinal pathogen has been consistently incriminated [15,16].

- The presence of perinuclear cytoplasmic antibodies (pANCA) is associated with the development of chronic pouchitis in 60 to 80 percent of patients. In a group of 60 pouch patients who were pANCA positive, pouchitis occurred in 56 percent of those with a high titer of pANCA (>100 ELISA units) while the risk in patients with a lower titer was no greater than in pANCA negative individuals [23].
- The role of the fecal stream and its bacterial and biochemical composition on the reservoir has also been the subject of controversy. Serial biopsies of pouches showed that significant acute and/or chronic inflammation, villous atrophy, and crypt hyperplasia developed only after ileostomy closure in the majority of patients, suggesting that the fecal stream plays an important role [25].
- Nonsteroidal antiinflammatory drug consumption
- Lack of mucosal trophic factors (such as short-chain fatty acids)
- Decreased resistance of the mucosal immune system due to reduced number of intraepithelial T-lymphocytes
- Increased cytotoxicity due to bile acids
- Raised levels of platelet activating factor or oxygen-derived free radicals, caused by transient mucosal ischemia.

CLINICAL MANIFESTATIONS — The diagnosis is based upon the presence of compatible clinical, endoscopic, and pathological features and exclusion of disorders that can produce similar features.

Symptoms of pouchitis include [1]:

- Increased stool frequency
- Urgency
- Hematochezia
- Abdominal pain
- Fever

A small proportion of patients have pre-pouch ileitis accompanying pouchitis. The disabling symptoms associated with pre-pouch ileitis are similar to pouchitis and include increased stool frequency and urgency. Pre-pouch ileitis is not a sign of Crohn's disease [29].

DIFFERENTIAL DIAGNOSIS — Other conditions produce similar symptoms, such as outlet obstruction, specific bacterial or parasitic infections, cytomegalovirus (CMV) infection, recurrent or misdiagnosed Crohn's disease, anal

stenosis, a peripouch abscess, and functional bowel syndromes such as irritable pouch syndrome (IPS).

IPS is a functional disorder in patients with ileal pouch-anal anastomosis (IPAA), which presents with symptoms in the absence of structural abnormalities of the pouch [30]. Thus, it resembles functional disorders such as irritable bowel syndrome. IPS is characterized by visceral hypersensitivity in the presence of normal rectal biomechanics. Patients with IPS have severe diarrhea, abdominal pain, urgency, and pelvic pain with a normal pouchoscopy and pelvic magnetic resonance imaging (MRI). The management approach to IPS is similar to that for IBS in patients with IBD. (See "Irritable bowel syndrome in patients with inflammatory bowel disease", section on 'Treatment'.)

In patients who have undergone a stapled ileal pouch-anal anastomosis, cuffitis can cause symptoms mimicking pouchitis.

DIAGNOSIS — Symptoms alone, however, are not sufficient to define pouchitis [31]. The following tests may help confirm the diagnosis of pouchitis and exclude other disorders that can produce similar features.

Stool markers — Measurement of fecal lactoferrin concentration (a marker of neutrophil activation) has been proposed as a noninvasive initial screening test for distinguishing pouchitis from other causes of symptoms but its accuracy is unclear [32].

Endoscopy — Pouchitis is accompanied by endoscopic stigmata of mucosal inflammation, ie, diffuse erythema, swelling, and friability of the mucosa, and sometimes hemorrhages, erosions and/or ulcerations [24,31].

Macroscopic inflammation correlates significantly with stool frequency and with extensive histologic inflammation. In most patients with lesser degrees of inflammation, mucosal lesions on endoscopy are absent and alteration in stool frequency is quite variable [24].

Pathology — Histologic evaluation can help confirm the diagnosis and help exclude cytomegalovirus (CMV) infection (which can masquerade as or complicate pouchitis) [33-35]. Histologic features of chronic inflammation in the reservoir are much more prevalent than are acute changes (picture 1). In an illustrative series [24]:

- Less than 4 percent of patients were completely free of pouch inflammation, whereas acute and chronic inflammation was noted in 30 and 87 percent, respectively.
- Intense acute inflammation was uncommon (11 percent of patients) and found only in patients operated on for UC. There was no difference between ulcerative colitis (UC) and FAP with regard to chronic inflammation.
- Chronic inflammation of the reservoir was usually associated with villous atrophy, and was always accompanied by crypt hyperplasia.

The prevalences of both acute and chronic inflammation of the reservoir mucosa vary with the duration of follow-up, and the number and sites of biopsies. This emphasizes the need for multiple biopsies. In a series of 78 patients with UC and an IPAA, with a mean follow-up of 95 months, and a mean number of biopsies per patient of 5.4 (range 1 to 13), histopathologic changes were noted in 95 percent of the specimens [36]. Mild and severe chronic inflammation was seen in 56 and 39 percent of the biopsy specimens, respectively. Normal mucosa was found in only 24 biopsies (5.4 percent) in 18 patients. However, previous or subsequent biopsies from the same patient always showed pathologic changes. A heterogeneous distribution of pathologic changes in the pouch was found: maximal lesions usually occur in the lower and posterior regions.

Another common pathologic finding is partial colonic metaplasia, seen in 35 to 96 percent of patients with IPAA [36,37].

PROGNOSIS AND TREATMENT — In the large experience of the Mayo Clinic, one-half of the affected patients experienced recurrent episodes of pouchitis requiring repeated treatment [1]. Approximately 10 to 20 percent of patients with pouchitis develop chronic pouchitis, defined as symptoms lasting greater than four weeks.

Acute pouchitis is easily treated, while chronic pouchitis remains difficult to treat. Chronic pouchitis can be either

responsive or refractory to treatment (see Figure 1, "Treatment algorithm for pouchitis").

Antibiotics — Antibiotics have been shown to be effective in treating pouchitis [38].

- Metronidazole – Oral metronidazole, at a dose of 1 to 2 g daily for seven days [4,8] has been used to treat pouchitis. Treatment may be most effective with acute episodes, and may be less effective with chronic disease. One double-blind cross-over trial randomly assigned patients with chronic unremitting pouchitis to metronidazole (400 mg three times daily for seven days) or placebo [39]. Metronidazole was associated with a significant reduction in stool frequency by three movements per day (versus an increase of one per day with placebo) but there was no change in the endoscopic or histologic grade of inflammation.

- Ciprofloxacin – Oral ciprofloxacin at a dose of 1 g daily is an effective treatment for pouchitis, including those patients who failed metronidazole [40,41]. In one study, 16 patients who were randomly assigned to either ciprofloxacin 1 g/day or metronidazole 20 mg/kg per day showed a response to both drugs, but had significantly better improvement and fewer side effects (0 versus 33 percent) with ciprofloxacin [40].

  Because of its better tolerance, we choose ciprofloxacin at 1 g daily as the initial treatment for acute pouchitis reserving metronidazole for those failing ciprofloxacin.

  For patients who have relapsing symptoms, we use chronic, low dose ciprofloxacin.

- Rifaximin – The nonabsorbed antibiotic rifaximin has also been used in pouchitis but was not more effective than placebo in a small controlled trial [42]. However, rifaximin maintenance therapy was effective in preventing relapse in 65 percent of patients with antibiotic-dependent pouchitis after induction of remission with a variety of antibiotics [43].

- Combination antibiotic approaches, including ciprofloxacin and rifaximin [44,45], metronidazole and ciprofloxacin [46], and ciprofloxacin and tinidazole [47] have also been reported to be efficacious in the treatment of chronic refractory pouchitis [48].

Fecal coliform sensitivity testing has shown to be helpful in guiding choice of effective antibiotics in patients with antibiotic-resistant pouchitis [49]. In this study, 80 percent of patients achieved a clinical remission with individualized therapy based on sensitivity results.

Budesonide — For patients who fail antibiotics, budesonide may be a treatment option. Oral budesonide (9 mg/day for eight weeks) was effective in a series of patients with acute pouchitis refractory to antibiotics [50].

Budesonide suppositories for four weeks showed endoscopic improvement or remission at the end of the treatment in all patients with acute pouchitis [51]. However, 6 of 10 patients relapsed eight weeks later.

In a controlled trial, 26 patients were randomly assigned to budesonide enemas (2 mg per 100 mL at bedtime) plus placebo tablets or oral metronidazole (500 mg twice daily) plus placebo enemas [52]. Both regimens were associated with similar clinical improvement but adverse effects were more common in those receiving metronidazole.

Probiotics — Changes in the microflora have been demonstrated in patients with pouchitis providing a rationale for treatments aimed at altering the flora [53]. In a study of 40 patients, the probiotic preparation, VSL#3 was more effective in maintaining remission than placebo (85 versus 15 percent) [54]. When VSL#3 was discontinued, all patients relapsed. In another placebo-controlled trial, more patients receiving VSL#3 remained in remission at one year compared to those receiving placebo (85 versus 6 percent) [55]. (See "Probiotics for gastrointestinal diseases".)

Other approaches

- Glucocorticoid and/or mesalamine enemas followed by a short course of oral steroids if enemas cannot be retained can be used as a therapeutic trial [56].

- Infliximab was effective long-term (20 months) in IPAA patients with refractory luminal inflammation and in three of seven patients with pouch fistulas [57]. However, risks and benefits need to be considered; and this treatment is likely reserved for patients with the most severe symptoms. (See "Anti-tumor necrosis factor therapy in ulcerative colitis".) 6-mercaptopurine or azathioprine can also be considered in these patients.

SURVEILLANCE FOR CANCER — The major long-term concern in patients with ileal pouch-anal anastomosis (IPAA) is the possibility that chronic inflammation of the reservoir may carry the same risk of mucosal dysplasia and cancer as does ileorectal anastomosis. (See "Surgical management of inflammatory bowel disease", section on 'Postoperative monitoring'.)

Adenocarcinoma has been observed in patients with familial adenomatous polyposis (FAP) and long-established ileostomies [58,59]. The ileal mucosa transforms into a colonic-like mucosa in most patients after IPAA [36,37], and increased cell proliferation has been observed in reservoirs whether or not the patients had pouchitis [60]. Chronic inflammation of the reservoir mucosa is almost universally noted when the mucosa is carefully sampled [24].

Only a few studies have followed patients for more than 10 years. A report with one of the longest follow-up periods (15 to 20 years) found that the development of dysplasia was rare [61]. Nevertheless, severe mucosal atrophy together with dysplastic epithelial changes and DNA aneuploidy have been described [62,63]. However, very few cases of cancer in the pouch of patients operated for ulcerative colitis (UC) have been described. The presence of a rectal cuff is a risk factor for cancer and the incidence of dysplasia or cancer after IPAA is strongly associated with the presence of dysplasia or cancer in the proctocolectomy specimen. Based in part upon these observations, it has been suggested that endoscopic and histopathologic surveillance of the reservoir mucosa should be undertaken in patients with IPAA [36,64]. Since mucosal abnormalities might be focal, multiple biopsies would be needed.

We support endoscopic surveillance of the pouch beginning three years after pouch construction and every three years thereafter. If severe mucosal atrophy is found, then yearly surveillance is suggested.

SUMMARY AND RECOMMENDATIONS

- Pouchitis is characterized by the development of chronic inflammation associated with symptoms (urgency, tenesmus, bleeding, incontinence and increased stool frequency) in the pouch following ileal pouch-anal anastomosis (IPAA). (See 'Clinical manifestations' above.)

- The diagnosis is based upon the presence of compatible clinical, endoscopic and pathological features and exclusion of disorders that can produce similar features. The differential diagnosis includes outlet obstruction, specific bacterial or parasitic infections, cytomegalovirus (CMV) infection, ulcerative colitis (UC) of the pouch, recurrent or misdiagnosed Crohn's disease, anal stenosis, a peripouch abscess, and functional bowel syndromes including irritable pouch syndrome (IPS). (See 'Differential diagnosis' above.)

- Many patients with pouchitis have acute episodes that respond well to a single course of antibiotics. We suggest patients be treated initially with oral metronidazole at a dose of 1 to 2 g daily (in divided doses) for seven days or ciprofloxacin 1 g daily for seven days (**Grade 2B**). (See 'Prognosis and treatment' above.)

- For patients who respond to initial treatment but have relapsing symptoms, we suggest using the probiotic VSL#3 (3 to 6 g/day) or chronic low dose antibiotics (**Grade 2C**). (See "Probiotics for gastrointestinal diseases".)

- For patients who do not respond to initial antibiotic treatment with metronidazole or ciprofloxacin, treatment options include other antibiotic or antibiotic combinations, budesonide, other antiinflammatory drugs, infliximab, or 6-mercaptopurine or azathioprine. (See 'Antibiotics' above and 'Budesonide' above and 'Other

approaches' above.)

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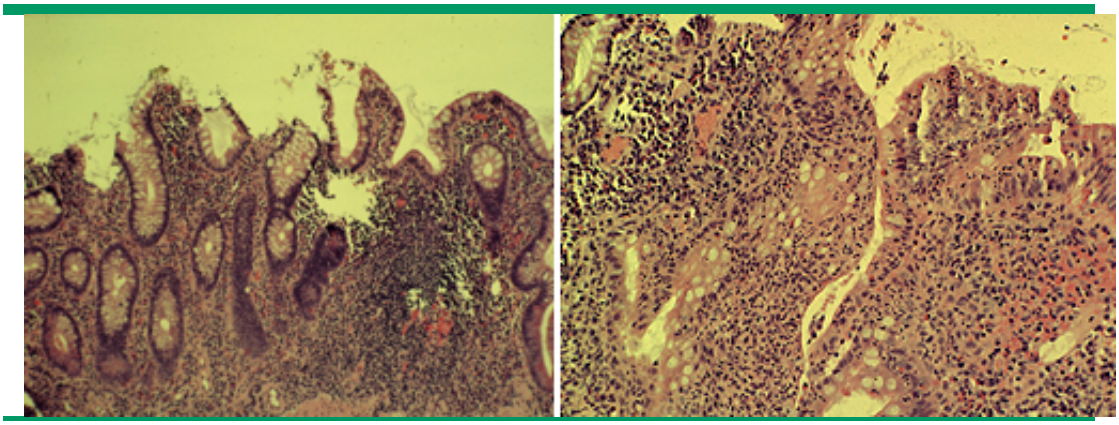
GRAPHICS

Pouchitis



Low (left panel) and high (right panel) power view of a biopsy specimen from a patient with pouchitis. There is a moderately severe acute inflammatory infiltrate with superficial ulceration. *Courtesy of Sydney Phillips, MD.*