Pouchitis: What Every Gastroenterologist Needs to Know

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Pouchitis is the most common complication among patients with ulcerative colitis who have undergone restorative proctocolectomy with ileal pouch–anal anastomosis. Pouchitis is actually a spectrum of diseases that vary in etiology, pathogenesis, phenotype, and clinical course. Although initial acute episodes typically respond to antibiotic therapy, patients can become dependent on antibiotics or develop refractory disease. Many factors contribute to the course of refractory pouchitis, such as the use of nonsteroidal anti-inflammatory drugs, infection with *Clostridium difficile*, pouch ischemia, or concurrent immune-mediated disorders. Identification of these secondary factors can help direct therapy.

Keywords: Ileal Pouch; Pouchitis; Restorative Proctocolectomy; Ulcerative Colitis.

The past decade has witnessed a rapid process in the medical treatment for ulcerative colitis (UC), particularly the availability and a wide use of anti–tumor necrosis factor (TNF) biological agents. Although the medical community has anticipated that the advance in pharmaceutical therapy may have an impact on the disease course of UC, by reducing the need for colectomy, the long-term efficacy of the biological agents is still unclear. On the other hand, restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) has become the surgical treatment of choice for the majority of patients with UC or familial adenomatous polyposis (FAP) who require colectomy.

Over the years, various forms of the ileal pouch configuration have been developed, ranging from Kock pouch (also known as K or continent ileostomy), S pouch, to W or J pouches (Figure 1). One pouch configuration may offer technical advantages over the other. For example, UC patients with a poor anal sphincter function may elect to have a K pouch after colectomy. Obese UC patients with a short mesentery may be chosen to have an S pouch after colectomy because this particular pouch configuration offers an additional 2 to 2.5 cm of small bowel, as an efferent limb, to reach the anal canal. The W pouch, which was designed in the 1980s, largely has been abandoned because of its frequent complications. The choice between the various forms of ileal pouches depends on the following: (1) indication for colectomy (colitis-associated neoplasia vs refractory UC); (2) mucosectomy vs no mucosectomy; and (3) technical feasibility (body mass index, length of mesentery, and pathology of the anal canal or rectal stump). Currently, the most commonly performed ones are J and S pouches.

The pouch procedure has been shown to improve patients’ health-related quality of life significantly and to reduce the risk for colitis-associated neoplasia. On the other hand, various complications from the pouch surgery have been reported, ranging from procedure-associated leaks, strictures, sinus, or fistulae, to pouchitis, cuffitis, and de novo Crohn’s disease (CD)-like conditions of the pouch and irritable pouch syndrome (IPS).

Pouchitis is the most common complication in UC patients with IPAA, with a reported cumulative prevalence ranging from 23% to 46%, and an annual incidence up to 40%. Oral antibiotic therapy has been the mainstay treatment for patients with pouchitis based on the current theory that the inflammation at the ileal pouch reservoir results from or is triggered by the alteration in the composition of microbiota. However, we have encountered an increasing number of patients with pouchitis who initially responded to antibiotic therapy and developed refractory disease later on. The management of chronic antibiotic-refractory pouchitis (CARP) has been challenging and, in fact, chronic pouchitis is one of the most common causes for pouch failure, defined as permanent diversion, pouch excision, or complete pouch revision.

Etiology and Pathogenesis

Mounting evidence suggests that gut microbiota play a key role in the initiation and disease progression of pouchitis. The contribution of gut microbiota to the pathogenesis of pouchitis may be 2-fold: the alteration in commensal bacteria (ie, dysbiosis) and the emergence of pathogenic bacteria, fungi, or viruses (such as *Clostridium difficile*). The role of bacterial diversity or dysbiosis in the pathogenesis of pouchitis is not entirely clear, as it is in the field of inflammatory bowel disease (IBD). The construction of the ileal reservoir leads to an altered bowel anatomy that can promote fecal stasis and colonic metaplasia in the pouch body from the original ileal mucosa, creating an environment favorable to the development of inflammation. It is intriguing that certain bacterial species, such as *Bacteroidaceae* species and *Clostridaceae* species, were shown to be associated with inflammation of the pouch mucosa, whereas others, such as *Enterococccaceae* species, may have an active role in maintaining immunologic homeostasis in the pouch body.

Abbreviations used in this paper: CARD15, caspase recruitment domain family, member 15; CARP, chronic antibiotic-refractory pouchitis; CD, Crohn’s disease; CDI, *Clostridium difficile* infection; CMV, cytomegalovirus; FAP, familial adenomatous polyposis; IBD, inflammatory bowel disease; IL, interleukin; IPAA, ileal pouch-anal anastomosis; IPS, irritable pouch syndrome; NOD2, nucleotide-binding oligomerization domain containing 2; NSAID, nonsteroidal anti-inflammatory drug; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UC, ulcerative colitis.
pouch mucosa.15 Unfortunately, even with the state-of-the-art molecular microbiology technology, no individual species or phylotypes have been shown consistently to be related specifically to pouchitis.12,16 Potential candidate bacterial species related to pouchitis may include Lachnospiraceae, Incertae Sedis XIV, and Clostridial cluster IV.17

Pathogen-associated pouchitis can occur in a subset of patients. C difficile infection (CDI) is common in symptomatic patients with IPAA, with either enzyme immunoassay (EIA)13 or polymerase chain reaction (PCR)18-based assays. Patients who were positive for C difficile after IPAA had a wide spectrum of clinical presentations, ranging from being asymptomatic carriers (with colonization) to those with fatal outcomes.19 Other pathogens have been reported to be associated with episodes of active pouchitis, including C perfringens,2 group D streptococci (Enterococcus species),21 hemolytic strains of E coli,22 and cytomegalovirus (CMV)23,24 infection. These pathogenic microbes detected in pouchitis patients with systemic symptoms may contribute to disease episodes or be responsible for a refractory course to conventional antibiotic therapy.

The alteration in both innate and adaptive mucosal immunity in the noninflamed pouch and pouchitis has been studied extensively.25–30 Different bacterial species may exert different impacts on innate and adaptive mucosal immune function.15,31 Fecal stasis, the increased microbial load, and constant exposure to lumen contents might collectively cause adaptive morphologic alterations in the pouch mucosa that mimic colonic metaplasia.32 Colonic metaplasia seems to be associated with dysbiosis, particularly the presence of sulfate-reducing bacteria.33 Alterations in mucin glycoproteins, similar to those seen in UC, also occur in pouchitis.34 Altered glycoproteins are more susceptible than the native molecules to enzymatic degradation by microbiota with the breach of mucosal barrier function.35 An increased permeability of the gastrointestinal mucosa to microbiota was observed in the ileal pouch.35 Aberrant expression of Toll-like receptors have been found in the ileal pouches of patients with and without pouchitis.31,36,37 Antimicrobial peptides produced by intestinal Paneth cells and other gut epithelial cells are important components of innate immunity in the gastrointestinal tract.38–40 The expression of Paneth-cell-specific human defensin-5 is increased in both inflamed and noninflamed pouches compared with that in the normal terminal ileum.41,42 The findings suggest that innate mucosal immunity actively is involved in both normal adaptation to fecal stasis/bacterial overload and the development of pouchitis.

Adaptive mucosal immunity also has been studied in pouchitis for the past 2 decades. There was an increased proliferation of immature plasma cells in pouchitis.29,30,43 There was also an increased production of proinflammatory mediators/cytokines, such as TNF,44–47 cell adhesion molecules,48 platelet-activating factor,49 lipoxigenase products of arachidonic acids,50,51 vascular endothelial growth factor,51 and proinflammatory neuropeptides.45,52–54 UC pouches were shown to have higher levels of proinflammatory cytokines than that of FAP pouches.55 Imbalance between proinflammatory (such as interleukin [IL]-8) and immunoregulatory (such as IL-10) cytokines may contribute to the inflammatory process of pouchitis.56 However, the abnormalities in adaptive mucosal immunity probably reflect activation of a nonspecific inflammatory cascade or pathway.57 Nonetheless, the up-regulation of the proinflammatory mediators may provide therapeutic targets, particularly in CARP.

**Risk Factors**

In addition to gut microbiota and mucosal immunity, genetic, vascular, and luminal factors (such as nonsteroidal anti-inflammatory drugs [NSAIDs]) are likely to contribute to the initiation, exacerbation, and progression of pouchitis. Pouchitis almost exclusively occurs in patients with restorative proctocolectomy with underlying IBD and rarely in those with FAP, suggesting the contribution of genetic and/systemic factors to its pathogenesis. Immunogenetic studies showed that genetic polymorphisms such as those of IL-1–receptor antagonist,56 nucleotide-binding oligomerization domain containing 2/caspase recruitment domain family, member 15 (NOD2/CARD15),57,58 or a combined carriership of Toll-like receptor 9-1237C and CD14-260T alleles,59 were associated with the risk for chronic pouchitis. Mutations of NOD2/CARD15 and TNFSF15 also were shown to be related to severe pouchitis.60
Gastrointestinal, systemic, or environmental risk factors reported to be associated with pouchitis include extensive UC,61,62 the presence of backwash ileitis,61,63 preectectomy thrombocytosis,64 the presence of concurrent primary sclerosing cholangitis (PSC)63,65,66 or other immune-mediated disorders,67 being a nonsmoker,62,68 the regular use of NSAIDs,62,66 and ischemia.69 Systemic immune reactions to bacterial antigens as well as host’s self-tissue also have been studied in pouchitis. Reported pouchitis-related serology markers include perinuclear antineutrophil cytoplasmic antibodies,6,63,70,71 anti-CBir1 flagellin,6 IgG4,72 and microsomal antibodies.73 It should be pointed out that pouchitis represents a disease spectrum from an acute antibiotic-responsive form to a chronic antibiotic-refractory phenotype. Different phenotypes of pouchitis may reflect the same disease process at different stages or different disease processes with various etiopathogenetic pathways. As such, acute and chronic pouchitis may be associated with different risk factors.62 For example, smoking was associated with acute pouchitis,6 whereas extraintestinal manifestations,6 preoperative thrombocytosis, a long duration of IPAA,6 and postoperative surgery-related complications,74 were reported to be associated with chronic pouchitis. Smoking appears to be a protective factor against the development of chronic pouchitis.75 Patients with CARP, not acute pouchitis, were reported to be associated with concurrent autoimmune disorders.67

**Diagnosis and Differential Diagnosis**

The diagnosis of pouchitis is not always straightforward because of the lack of specific symptoms and signs. Patients with healthy pouches are expected to have 4 to 7 soft bowel movements a day, with continence. Patients with pouchitis can have a wide range of clinical presentations, ranging from increased stool frequency, urgency, abdominal cramps, night time seepage, to incontinence. These symptoms, however, are not specific and they can be present in other inflammatory and noninflammatory disorders of the pouch. Furthermore, the severity of subjective symptoms does not correlate with the objective degree of objective inflammation on endoscopy or on histology.76,77 Therefore, the diagnosis of pouchitis should not be dependent solely on the symptom assessment. To complicate the matter further, the diagnosis of pouchitis may resemble hitting a moving target because the disease process of pouchitis and other pouch disorders may not be static. For example, a patient who has typical acute antibiotic-responsive pouchitis as an initial presentation may later develop CD of the pouch. Therefore, a combined assessment of symptoms, endoscopic features, and histologic features is advocated for the diagnosis and differential diagnosis of pouchitis.76,78 Several diagnostic instruments have been proposed for the diagnosis of pouchitis and grading of severity. Among them is the 18-point Pouchitis Disease Activity Index consisting of symptom, endoscopy, and histology subscores,78 which has been the most commonly used, mainly as a research tool. The endoscopy is the most accurate to grade the degree of inflammation.

**Differential diagnosis.** Various inflammatory and functional disorders of the pouch share similar clinical presentations with pouchitis. Among them are IPS, cuffitis, CD of the pouch, and fecal incontinence from anal sphincter damage. IPS, by definition, is featured with clinical symptoms of diarrhea, cramps, and urgency, in the absence of endoscopic or histologic inflammation of the pouch. Currently, IPS is a diagnosis of exclusion, although evaluation with a barostat examination yields evidence of visceral hypersensitivity in patients.79 Cuffitis, which is considered a variant of ulcerative proctitis, typically causes urgency and blood in stools. De novo CD of the pouch can occur in patients with a preoperative diagnosis of UC. It has 3 phenotypes: inflammatory, fibrostenotic, and fistulizing. Pouch body inflammation can be a part of CD.

**Endoscopic evaluation.** It is important to correctly identify the landmarks of J, S, and K pouches during endoscopic and radiographic evaluation. The characteristic landmarks include the afferent limb, pouch inlet, the tip of J (in J pouch), efferent limb (which are different between J and S pouches), and the pouch outlet (the anal transitional zone or rectal cuff for J and S pouches or the nipple valve for a K pouch) (Figure 1).

Pouchoscopy is the most valuable tool for the diagnosis and differential diagnosis of pouchitis. A careful pouchoscopy should include the evaluation of the earlier-described landmarks, including the afferent limb, pouch inlet, the tip of the J pouch body, anastomosis, and anal transitional zone or cuff (Figure 2A). Sedated or nonsedated pouchoscopy provides the most valuable information on the configuration and distensibility of the pouch body, severity, extent, or distribution of mucosal inflammation (Figures 2 and 3), and the presence of concurrent backwash ileitis, cuffitis, or inflammatory polyps. The presence of a mucosal ridge, inflammatory polyps (Figure 2D), poorly distensible or pouch body (Figure 2B), or the loss of the “owls’ eye” configuration of a J pouch (Figure 2A), suggests chronic inflammation. Immune-mediated pouchitis, such as those associated with PSC or autoimmune disorders, and IgG4-associated pouchitis, often has concurrent long segment inflammation at the afferent limb in addition to diffuse pouchitis (Figure 3B and C). Asymmetric distribution of inflammation in the pouch body may be a sign of ischemic pouchitis. Typically, inflammation in ischemic pouchitis is present only at the distal half to quarter of the pouch body or at one limb of the pouch body, sparing the rest of the pouch, with a sharp demarcation of inflamed and noninflamed parts of pouch body (Figure 2C).80

Pouchoscopy is also a major modality for the diagnosis of CD of the pouch and surgery-related complications (such as stricture, fistula, sinus [Figure 3D], and prolapse).81 Patients with CD of the pouch typically have segmental inflammation of the pouch body and/or afferent limb, strictures at the pouch inlet or afferent limb, the presence of complex perianal fistulas or pouch-vaginal fistulas with an internal fistular orifice at the anal canal (rather than at the dentate line for cryptoglandular fistula or at the anastomosis for surgical leak).

**Abdominal/pelvic imaging.** Abdominal imaging is an important part of the evaluation for the diagnosis and differential diagnosis of ileal pouch disorders. Pouchitis can be present alone or with other concurrent inflammatory or mechanical/structural complications (such as stricture, sinus, or fistula). In fact, pouch inflammation can be a part of CD. A water-soluble contrast pouchogram often is used to delineate the pouch shape and anatomy and the presence of luminal angulation, stricture, sinus, or fistula. Computed tomography enterography or magnetic resonance imaging enterography is useful for the evaluation of the location, number, and degree of strictures, the presence of an abscess, or the presence of inflam-
mation of the pouch as well as the proximal small bowel. Contrast pelvic magnetic resonance imaging with fistula protocol is valuable for the evaluation of the anatomy and abnormalities around the pouch body and anal transitional zone, such as fistula, sinus, abscess, and presacral sinus-associated osteomyelitis. Anorectal ultrasound often is useful in the detection of anal sphincter injury, sinus, or fistula. In addition, examination under anesthesia in the operating room may be needed in complex pouch disorders (Figure 4). Histologic evaluation. Histology may have a limited role in grading acute or chronic inflammation of the pouch because it does not correlate with the more robust endoscopy scoring system. However, histologic evaluation provides valuable information on special features, such as granulomas, viral inclusion bodies (for CMV infection), pyloric gland metaplasia (a sign of chronic mucosal inflammation), and dysplasia, and the presence of excessive crypt apoptosis (a sign of autoimmune enteritis) or IgG4-expressing plasma cells in the lamina propria.

Laboratory evaluation. Laboratory testing is often necessary as a part of the evaluation for patients with pouch disorders, particularly in those with chronic pouchitis. Patients with healthy or diseased pouches often have iron-deficiency anemia and/or a low vitamin D level. Pouch patients with a cholestatic picture on the liver function panel, such as an increase of alkaline phosphatase, should be investigated for the presence of PSC. In patients with persistent symptoms, a stool test for CDI should be performed. For the majority of patients with a repeated or chronic exposure to antibiotics, CDI has been a growing problem. For patients with systemic symptoms, such as chills, fever, and night sweats, a fecal assay for other intestinal pathogens (such as Campylobacter species) and a blood or tissue assay for CMV or Epstein–Barr virus infection may be needed.

In patients with chronic pouchitis, fecal coliform culture and sensitivity testing could help to identify effective antibiotic agents. For patients with CARP, other etiologies need to be evaluated; in particular, one must look for the components of autoimmunity. The serology panel may include celiac tests, antinuclear antigens, serum IgG4 level, and antimicrosomal antibodies. Fecal assays of lactoferrin and calprotectin have been investigated for the diagnosis and differential diagnosis of pouchitis. They may have some value in the assessment of treatment outcome (eg, mucosal healing). Genetic testing and IBD serology have been shown to provide useful information on the pathogenesis and prognosis of pouch disorders and IBD. However, the role of current available genetic and serologic profiles in the diagnosis and differential diagnosis of pouchitis is limited.

Classification and Disease Course

Pouchitis represents a disease spectrum, with ranging pathogenetic pathways, clinical presentations, and disease courses. Clinically, the treatment for different phenotypes of
pouchitis is not the same. Initial episodes of pouchitis in the majority of patients respond favorably to therapy with oral broad-spectrum antibiotics such as metronidazole, ciprofloxacin, and tinidazole. According to the duration of pouch-related symptoms, pouchitis can be classified into acute (<4 wk) and chronic (&ge;4 wk) forms. Based on the response to and frequency of antibiotic therapy, pouchitis can be categorized into antibiotic-responsive, antibiotic-resistant, or refractory forms. Figure 3 shows various etiologies of pouchitis on endoscopy. Figure 4 is a diagnostic algorithm for recurrent pouchitis. ANA, antinuclear antibody; LFT, liver function test.
### Table 1. Controlled Trials in Pouchitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>N</th>
<th>Indication</th>
<th>Agent</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madden et al,105 1994</td>
<td>RCT</td>
<td>13</td>
<td>Treatment of chronic pouchitis</td>
<td>Metronidazole 1.4 g/d vs placebo</td>
<td>1 wk</td>
<td>↓ in stool frequency, more in study group than in placebo</td>
</tr>
<tr>
<td>Gionchetti et al,111 2000</td>
<td>RCT, placebo-controlled</td>
<td>40</td>
<td>Secondary prophylaxis of relapsing pouchitis</td>
<td>Probiotics a 6 g/d vs placebo</td>
<td>9 mo</td>
<td>Relapse in 15% of study group; 100% in placebo (P &lt; .001) ↓ in PDAI score; ciprofloxacin — 6.7; metronidazole — 5.9</td>
</tr>
<tr>
<td>Shen et al, 2001106</td>
<td>RCT</td>
<td>16</td>
<td>Treatment of acute antibiotic responsive pouchitis</td>
<td>Ciprofloxacin 1 g/d vs metronidazole 20 mg/kg/d</td>
<td>2 wk</td>
<td>Pouchitis in 10% of the study group; 40% in placebo (P &lt; .05)</td>
</tr>
<tr>
<td>Gionchetti et al,7 2003</td>
<td>RCT, placebo-controlled</td>
<td>40</td>
<td>Primary prophylaxis of pouchitis</td>
<td>Probiotics a 3 g/d vs placebo</td>
<td>12 mo</td>
<td>Relapse in 15% of the study group; 94% in placebo (P &lt; .0001)</td>
</tr>
<tr>
<td>Mimura et al,112 2004</td>
<td>RCT, placebo-controlled</td>
<td>36</td>
<td>Secondary prophylaxis of relapsing pouchitis</td>
<td>Probiotics a 6 g/d vs placebo</td>
<td>Up to 1 y</td>
<td>Remission in 25% of the study group; 0% in control (P = .206)</td>
</tr>
<tr>
<td>Isaacs et al,104 2007</td>
<td>RCT, placebo-controlled</td>
<td>18</td>
<td>Treatment of active pouchitis</td>
<td>Rifaximin 1.2 g/d vs placebo</td>
<td>4 wk</td>
<td></td>
</tr>
</tbody>
</table>

PDAI: Pouchitis Disease Activity Index (range, 0–18 points); RCT, randomized, controlled trial.

aVSL#3 contains 4 strains of *Lactobacillus (L casei, L plantarum, L acidophilus, and L delbrueckii subspecies bulgaricus)*, 3 strains of *Bifidobacterium (B longum, B breve, and B infantis)*, and 1 strain of *Streptococcus salivarius* subspecies *thermophilus*.

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dependent, and antibiotic-refractory phenotypes. Based on the etiology, pouchitis also can be divided into idiopathic and secondary (such as NSAID-induced, ischemia-related, and CMV-associated) entities. Sometimes, the terminology combining the earlier-described features is used to characterize certain types of pouchitis, such as chronic antibiotic-refractory pouchitis (CARP).

The timing of the initial onset of pouchitis may suggest its etiology. In our anecdotal experience, pouchitis, which occurs immediately after ileostomy closure, may result from procedure-associated complications, such as ischemia or anastomotic leaks. On the other hand, the late initial onset of pouchitis (ie, onset occurring years after ileostomy construction), can be related to systemic or local factors, such as excessive weight gain.95

The natural history of pouchitis may follow the disease course of IBD, progressing from an acute disease of bacterial etiology to a chronic disease with persistent inflammation from dysregulated immunity. For example, acute, antibiotic-responsive pouchitis may evolve into CARP. The disease course varies between affected individuals. Approximately 40% of patients with acute pouchitis who have a single episode responding to antibiotic therapy may never have recurrence.96 However, relapse of pouchitis or recurrent pouchitis is common; however, in this study, the remaining 60% had at least one subsequent relapse. It is estimated that 5% to 19% of patients with acute pouchitis develop refractory pouchitis or a frequently relapsing form of the disease.97-99 CARP is one of the common causes for pouch failure, resulting in permanent diversion or pouch excision.

### Management

Pouchitis patients often benefit from low-carbohydrate and/or low-fiber diets. Its rationale is the presence of small-bowel bacterial overgrowth from the lack of valve function at the junction between the afferent limb and pouch body. An elemental diet has been shown to help relieve symptoms of chronic pouchitis.100 Antidiarrheal agents can be used for the treatment of frequent and/or loose/watery bowel movements.

**Primary prophylaxis of initial episodes of pouchitis.** Primary prophylaxis of the initial episodes of pouchitis after ileostomy closure, using probiotic or antibiotic agents, has been investigated. In a randomized trial of a probiotic agent, called VSL#3 (containing *Lactobacillus species, Bifidobacterium species, Streptococcus salivarius species*, and *Thermophilus species*) (Sigma-Tau Pharmaceuticals, Inc, Gaithersburg, MD), 2 of 20 patients (10%) in the study group and 8 of 20 (40%) in the placebo group developed pouchitis within 12 months of ileostomy closure.7 The administration of *Lactobacillus rhamnosus* GG also was shown to be effective in the primary prophylaxis.101,102 A small, randomized, placebo-controlled trial of oral tinidazole also showed some efficacy in preventing initial episodes of pouchitis.103

**Treatment of acute pouchitis.** Patients with initial episodes of acute pouchitis typically respond to antibiotic therapy. In patients who experience pouchitis symptoms immediately after pouch construction and ileostomy closure and do not respond to the antibiotic therapy, surgery-associated complications, such as pouch anastomotic leaks or sinus, should be suspected. There are few published randomized placebo-controlled trials on the treatment of or on the secondary prevention of pouchitis (Table 1). Metronidazole, ciprofloxacin, tinidazole, and rifaximin104 commonly have been used in the treatment of acute pouchitis in clinical practice. The first-line therapy includes a 14-day course of metronidazole (15-20 mg/kg/d) or ciprofloxacin (1 g/d).94,105,106 An open-label trial of combination therapy using ciprofloxacin and metronidazole for 4 weeks was shown to be effective in treating pouchitis and backwash ileitis in patients with or without concomitant PSC.107 Other antibiotic or nonantibiotic agents also have been investigated and shown to be effective in some patients in small case studies, including amoxicillin-clavulanic acid and a carbon...
microsphere agent. Diffuse pouchitis can be associated with backwash ileitis, particularly in patients with concurrent PSC, which can be treated with oral budesonide. High-dose VSL#3 was reported to be effective for treating mild pouchitis.

Secondary prophylaxis of subsequent episodes of pouchitis. Relapse of pouchitis or recurrent pouchitis is common after the treatment and resolution of the initial treatment. An estimated 5% to 19% of patients with acute pouchitis develop treatment-refractory or a frequently relapsing form of the disease. Randomized placebo-controlled trials have shown that VSL#3 was effective for maintaining antibiotic-induced remission in patients with relapsing pouchitis. In the first randomized controlled trial from Bologna, Italy, VSL#3 was given at a dose of 6 g/d as maintenance therapy after remission had been induced by oral ciprofloxacin (1 g/d) and rifaximin (2 g/d). During this 9-month trial conducted in 40 patients, 15% of patients in the probiotic group relapsed, compared with 100% of patients in the placebo group. Similar results were reported in another randomized controlled trial of VSL#3 from St Mark’s Hospital in London, in which 29 of 36 participants also were from Bologna, Italy. In postmarketing, open-label studies, the response rate to VSL#3 was not as high as in the randomized controlled trials. In a study of 31 patients with antibiotic-dependent pouchitis, who received VSL#3 as maintenance therapy after induction of remission using 2 weeks of treatment with ciprofloxacin, 25 patients (81%) had stopped taking the probiotic at 8 months because of the lack of efficacy or the development of adverse effects. Similar results with 13% efficacy were reported in a separate open-label trial of this agent. The discrepancy in the reported efficacy among the published or presented studies may be owing to the dietary structure of the study populations, inclusion criteria, and dosage of the probiotic agents. Other options for maintenance therapy for antibiotic-dependent pouchitis could be rifaximin, and oral or topical mesalazine.

Treatment of chronic antibiotic-refractory pouchitis. Patients with CARP, by definition, do not respond to conventional antibiotic therapy. The treatment of CARP has been challenging. The commonly used broad-spectrum antibiotics, such as ciprofloxacin and metronidazole, do not target any specific bacterial agents. Therefore, fecal bacterial culture and sensitive assay have been recommended to identify suitable antibiotics. Secondary factors that are associated with an antibiotic-refractory course should be identified and managed. These factors include NSAID use, concurrent pouch surgery-related mechanical complications (such as ischemia, stricture, fistula, and sinus), CDI, CMV infection, and the presence of immunemediated disorders (eg, PSC and celiac disease).

Treatment options for CARP include a prolonged course of combined antibiotic therapy, such as 4 weeks of a combination of ciprofloxacin (1 g/d) with rifaximin (2 g/d), metronidazole (1 g/d), or tinidazole (1–1.5 g/d). In small case series, corticosteroids (including topical or oral budesonide), immunosuppressive agents, or even infliximab or adalimumab have been studied for the treatment of CARP with some efficacy. The efficacy of these agents suggests the role of immune-mediated processes in the disease initiation, relapse, and progression of CARP. Newly described autoimmune pouchitis and IgG4-associated pouchitis also may be evaluated. The treatment for immune-mediated pouchitis is empiric at this point and treatment options include corticosteroids, immunomodulators, or anti-TNF biologics. It should be pointed out that there is a great overlap in pharmaceutical therapy between the treatment of CARP and CD of the pouch. For example, a long-term single or dual antibiotic therapy or topically active corticosteroid (budesonide) has been used for both CARP and CD of the pouch. Although immunomodulator or anti-TNF biological therapy commonly is used in treating the fistulizing form of CD of the pouch, those agents are not applied routinely in CARP. For fibrostenotic CD of the pouch, medical therapy often is combined with endoscopic treatment.

Chronic pouchitis may be associated with concurrent mechanical or structural disorders of the pouch, such as strictures and anastomotic sinus. For example, pouch outlet obstruction (such as anastomotic stricture), can be associated with pouchitis, presumably owing to bacteria overload from prolonged stasis. The release of the obstruction, often along with concurrent antibiotic therapy, may promote the resolution of pouchitis.

Treatment of *C difficile* pouchitis. CDI poses a unique problem for patients with ileal pouches. Fecal *C difficile* toxins should be tested routinely in patients with antibiotic-dependent or antibiotic-refractory pouchitis. Pouch patients with a positive stool test for *C difficile* toxins may have a different clinical presentation, ranging from being an asymptomatic carrier to having fulminant pouchitis/enteritis. With an emerging prevalence and severity of CDI in patients with or without IBD (including those with ileal pouches), it has been recommended that oral vancomycin be considered as the first-line therapy in severe infection requiring hospitalization. Oral or intravenous metronidazole traditionally has been considered the first-line therapy for CDI. However, its efficacy specifically in the IBD or pouch population with CDI is unknown. Failure rates of metronidazole before the emergence of the epidemic BI/NAP1/027 strain were 16%, but more recently reported failure rates have been alarmingly high at 35%. In pouch patients with or without CDI, a vast majority were exposed to, and were on, oral metronidazole therapy. Therefore, I recommend that for patients with CARP or severe pouchitis and CDI, which can be fulminant and lethal, oral vancomycin may be considered as the first-line therapy. The recommended dose of oral vancomycin is 125 to 250 mg four times daily for 4 weeks. For patients with mild acute pouchitis, without prior or concurrent exposure to metronidazole, oral metronidazole may be used as the first-line therapy. Oral fidoxicam 200 mg twice a day for 10 to 14 days or fecal microbiota transplantation (personal unpublished data) may be an alternative for refractory or recurrent CDI.

Prospective View and Recommendations

It is obvious that microbiota play a critical role in the pathogenesis of pouchitis. In fact, all currently published randomized controlled trials in pouchitis are regarding the efficacy of antibiotics or probiotics (Table). On the other hand, the investigation of the role of gut microbiota in the etiopathogenesis of pouchitis has been difficult because 90% of gut bacteria are not culturable. Molecular microbiology techniques for the qualitative and quantitative measurement of microbiota are expensive and labor-intensive, particularly for the identification of the individual responsible bacteria. There are great variations in the composition of gut microbiota among healthy individuals, not mentioning the difference among healthy and dis-
 eased individuals. Therefore, the interpretation of the microbiota profile in cross-sectional studies comparing healthy and diseased pouches can be difficult. Furthermore, the commonly used broad-spectrum antibiotic agents are not targeted for any specific bacteria species. We hope that those agents can help restore the normal balance between good and bad bacteria in the pouch. It is common that patients with antibiotic-responsive pouchitis later develop antibiotic dependency or resistance.

We speculate that the persistent alteration of gut microbiota or dysbiosis, despite intermittent or chronic antibiotic therapy or probiotic therapy, consistently induces an abnormal mucosal immune response, leading to chronic pouchitis or CARP. Patients with genetic susceptibility (such as those with a NOD2/CARD15 mutation) and/or systemic immune-mediated disorders (such as PSC, IgG4-associated systemic disorders) may be particularly vulnerable to the development of CARP. A molecular classification of pouchitis, with a combined assay of immunogenetic, serologic, and clinical markers, would be invaluable for the identification of etiopathogenesis, diagnosis, treatment stratification, and prognosis prediction.

It has become clear that we should take a 3-dimensional view of pouchitis. Pouchitis represents a disease spectrum with various pathogenetic pathways, clinical presentations, and disease courses ranging from acute antibiotic-response types to chronic antibiotic-refractory phenotypes. For each individual patient, on the other hand, the diagnosis of pouchitis or other pouch disorders can be a moving target. Therefore, patients with IPAA should be monitored closely. Pouchoscopy is the best way to monitor the disease status of the pouch, to grade the degree of inflammation, and to identify structural abnormalities. Patients with minimal symptoms but with endoscopic inflammation still should be treated to minimize smoldering inflammation causing chronic “stiff” pouch with transmural inflammation, which can result in pouch failure. More importantly, different treatment strategies should be applied to treat different phenotypes of pouchitis at different stages.

Diagnosis (Figure 4) and treatment (Figure 5) algorithms are proposed based on published studies as well as my own experience in the subspecialty Pouch Center at the Cleveland Clinic. If a patient has symptoms of increased bowel frequency, watery stools, or urgency, antidiarrheal agents can be used first. If the symptoms do not get better in 1 to 2 days, the patient should be evaluated and in some cases treated empirically with antibiotics. Pouchoscopy, the diagnostic test of choice, needs to be performed, along with laboratory evaluation. In most cases, the combined evaluation of endoscopy, histology, and laboratory testing often provides clues for triggering, or etiologic factors for, the flare-up. For patients with diffuse pouchitis and diffuse enteritis of the afferent limb, immune-mediated pouchitis/enteritis may be considered. For patients with pouch inflammation that is distributed asymmetrically and has a sharp demarcation of inflamed and noninflamed parts of the pouch body, ischemic pouchitis is a possibility (Figure 4). Often, pouchoscopy may show clues of structural abnormalities, such as strictures, fistulas, and sinuses. If CD of the pouch is suspected, abdominal and pelvic imaging or examination under anesthesia often is needed.

The treatment of antibiotic-responsive pouchitis is straightforward. The prognosis of pouchitis is determined by the frequency of the need for antibiotic therapy (antibiotic-dependent pouchitis) and the development of the refractory disease course (CARP). A prolonged course of dual antibiotic therapy may help induce remission in patients with CARP. Oral or topical mesalamine agents and a topically active corticosteroid agent (budesonide) are the preferred first-line drugs for immune-mediated pouchitis/enteritis. Back-up agents may include 6-mercaptopurine/azathioprine, methotrexate, tacrolimus, or anti-TNF agents (Figure 5).

In summary, the diagnosis and management of pouchitis and the identification of its etiologic or triggering factors can be challenging. Pouchitis represents a disease spectrum, ranging from an acute antibiotic-responsive form to a chronic antibiotic-refractory phenotype, with different disease mechanisms and prognoses. A combined evaluation of pouchoscopy, histology, and laboratory testing may help classify disease phenotypes and stratify their management.

Figure 5. Treatment algorithm for pouchitis.
References


Reprint requests
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Conflicts of interest
The author discloses the following: Bo Shen has received honoraria from Aptalis, Abbott, and Prometheus Lab.

1. Treatment strategies for pouchitis include
   a. vancomycin 125mg tid
   b. metronidazole 15-20 mg/kg; 14 days
   c. ciprofloxacin 500mg bid; 14 days
   d. rifaximin 1.2g/day, 4 weeks
   e. budesonide for PSC related backwash ileitis

2. Laboratory evaluation of patients with CARP should include
   a. IgG4 levels
   b. ANA
   c. IgM levels
   d. CMV DNA PCR
   e. Liver enzymes
   f. TTG antibodies

**True or False**

3. Patients with a pouch complaining of diarrhea, cramps, urgency and having a normal endoscopic exam of the pouch have mild pouchitis

4. After an initial episode of pouchitis that responds to antibiotics, recurrence occurs in up to 60% of patients.

5. The presence of fistulae or perianal disease suggests recurrent Crohn’s disease

6. Pouchitis is as likely to develop in patients undergoing IPAA for UC as those undergoing IPAA for familial adenomatous polyposis coli.

7. VSL#3 may be effective in secondary prophylaxis of pouchitis

8. Asymmetric distribution of inflammation in the pouch may indicate ischemia

9. Patients with healthy pouches should have no more than 2 stools a day

10. Histology will provide an accurate assessment of the severity of the pouchitis

11. Vancomycin 125mg qid is recommended for the treatment of c. difficile pouchitis

12. Pouchitis presenting very soon after pouch creation is more likely secondary to procedure-associated complications such as ischemia

13. All patients with an ileal pouch are at risk for cuffitis