

Diagnosis and Management of Pouchitis

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The disease pouchitis was first reported by Kock¹ in 1977 as an inflammatory condition of the continent ileal reservoir (Kock pouch) in patients who had undergone proctocolectomy. The Kock pouch was later replaced by the ileal pouch anal anastomosis (IPAA, also known as the ileoanal pouch) which was independently described by Parks and Utsunomiya^{2,3} in 1980. The ileoanal pouch is now the surgical option of choice in patients with familial adenomatous polyposis (FAP) and ulcerative colitis (UC) with either dysplasia or disease refractory to medical therapy. Pouchitis is the most common long-term complication of IPAA in UC.⁴ This review discusses the diagnostic criteria, cause, and management of acute and chronic pouchitis.

Definition

The variation in the reported frequency of pouchitis at different centers and at the same center at different points in time is a reflection of the lack of uniform classification and diagnostic criteria. The definition of pouchitis has evolved to encompass clinical, endoscopic, and histologic criteria. A sensitive but non-specific designation developed by the Mayo Clinic in 1987 defined pouchitis as a clinical syndrome of watery, frequent, at times bloody stool accompanied by urgency, incontinence, abdominal cramps, malaise, and fever. The symptoms must be present for at least 2 days and should be relieved within 48 hours by metronidazole therapy.⁴ A more specific diagnostic criteria proposed by the St. Marks Hospital defined pouchitis as a triad of diarrhea (≥ 6 stools/day), endoscopic findings (≥ 4 findings of edema, granularity, friability, loss of vascular pattern, mucosal hemorrhage, or ulceration), and a minimum grade of 4 in a 6-point histopathologic index (polymorphonuclear leukocyte infiltration and percent ulceration per low-power field).⁵

The Pouchitis Disease Activity Index (PDAI) was developed in 1994, incorporating the Mayo Clinic definition and the St. Marks pouchitis triad and histopathologic index.⁶ The PDAI attempted to provide a standardized definition of pouchitis based on clinical, endoscopic, and histologic markers (Table 1), with pouchitis defined

as a score greater than or equal to 7 points. The specificity and sensitivity of diagnosis was increased by defining the disease as a continuum from mild to severe pouchitis with symptoms individualized to the norms of each patient. The operational use of the PDAI has evolved such that active pouchitis is defined as a PDAI score greater than or equal to 7 points in a patient with a definite diagnosis of pouchitis, whereas a PDAI score greater than or equal to 7 points in a patient with a history of a definite diagnosis of pouchitis indicates that the pouchitis is in remission.

In 2001, Heuschen described the Heidelberg Pouchitis Activity Score (PAS),⁷ which again attempted to provide a common definition of pouchitis (Table 2). The PAS and PDAI are very similar with the major exception of the inclusion within the former of chronic inflammation as a variable in the histopathology category, the exclusion of fever among the clinical symptoms, and minor variations in the endoscopic score. Heuschen then applied both the PAS and PDAI to 41 patients over 103 outpatient visits and compared them with the gold standard of a physician and surgeon's independent diagnosis of pouchitis.⁸ The clinicians diagnosed pouchitis in 24.3% of patients, the PAS in 35.9%, and the PDAI in 17.5%. When compared to the clinician, the PAS had a sensitivity and specificity of 84% and 79.5%, respectively, while the PDAI had a sensitivity and specificity of 60% and 96.2%, respectively. In patients with and without pouchitis, there was no significant difference in the clinical symptoms score in the PAS or the PDAI, but there was a difference in the total endoscopic score and the total histologic score. In addition, although the endoscopic and histologic examinations correlated in both the PAS and the PDAI, there was no correlation

Abbreviations used in this paper: EIM, extraintestinal manifestations; FAP, familial adenomatous polyposis; IL, interleukin; IPAA, ileal pouch anal anastomosis; pANCA, serum antineutrophil cytoplasmic antibody-perinuclear staining pattern; PAS, Pouchitis Activity Score; PDAI, Pouchitis Disease Activity Index; PSC, primary sclerosing cholangitis; QOL, quality of life; SCFA, small chain fatty acids.

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between clinical and endoscopic or clinical and histologic findings in either scoring system.

Overall, the PAS seems to overestimate pouchitis by 11% and the PDAI seems to underestimate pouchitis by 18% when compared with the gold standard of the clinician's assessment. Both the PDAI and the Heidelberg PAS need to be revalidated to determine the scores required to define symptomatic remission and global remission, and to determine the minimum clinically significant difference in the scores needed to define symptomatic improvement and global improvement.

Once a diagnosis of pouchitis is made, it can be further classified.⁹ The activity of pouchitis is stratified as remission (no active pouchitis), mild to moderately active (increased stool frequency, urgency, infrequent incontinence), or severely active (hospitalization for dehydration, frequent incontinence). The duration of pouchitis is defined as acute (≤ 4 weeks) or chronic (> 4 weeks) and the pattern of pouchitis is classified as infrequent (1 or 2 acute episodes), relapsing (≥ 3 acute episodes), or con-

Table 1. The Pouchitis Disease Activity Index

Clinical criteria	Score
Stool frequency	
Usual postoperative stool frequency	0
1–2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency/abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature > 100⁵ Fahrenheit)	
Absent	0
Present	1
Endoscopic criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucus exudates	1
Ulceration	1
Acute histologic criteria	
Polymorph infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (average)	
<25%	1
$\geq 25\% \leq 50\%$	2
>50%	3

Pouchitis is defined as a total PDAI score ≥ 7 points. Adapted with permission from: Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis following ileal pouch-anal anastomosis: a pouchitis disease activity index. *Mayo Clin Proc* 1994;69:409–415.

Table 2. The Heidelberg Pouchitis Activity Score: Maximum 36 Points

Clinic	Score	Score	
1. Stool frequency/24 hours		2. Fecal urgency	
< 8	0	absent	0
8–10	2	present	3
11–13	4		
>13	6		
3. Rectal bleeding			
absent	0		
present	3		
			Max. 12
Endoscopy	Score	Score	
1. Edema		2. Granularity	
absent	0	absent	0
present	1	present	1
3. Friability		4. Erythema	
absent	0	absent	0
mild	1	mild	2
severe	2	severe	3
5. Flattening of mucosal surface		6. Ulcerations/erosions	
absent	0	absent	0
present	2	mild	2
		severe	3
			Max. 12
Histology	Score	Score	
1. Acute histologic inflammation		2. Chronic histologic inflammation	
Polymorphonuclear leukocyte infiltration		Mononuclear leukocyte infiltration	
absent	0	absent	0
discrete and patchy (largely confined to surface epithelium)	1	mild and patchy	1
moderate with (\pm) crypt abscesses or cryptitis	2	moderate	2
extensive with (\pm) crypt abscesses or cryptitis	3	extensive	3
Ulcerations/erosions		Villous atrophy	
absent	0	absent	0
mild and superficial	1	minimal	1
moderate	2	partial	2
extensive	3	subtotal/total	3
			Max. 12

Reprinted with permission from Heuschen et al. *Dis Colon Rectum* 2001;44:487–499.

tinuous. Finally, the response to medical therapy is labeled as treatment-responsive or treatment-refractory with the medications for either case specified.

Diagnostic Tests

The key point of both the PDAI and the PAS is that endoscopic and histopathologic evaluation is required to make the diagnosis of pouchitis. This finding was corroborated by Shen¹⁰ in a study applying the PDAI to the evaluation of 46 patients who had ileal pouches.

Forty-eight percent of patients were given a diagnosis of pouchitis based on a PDAI score of ≥ 7 . No correlation was found between the symptom, endoscopy, and histology scores. Patients who had low clinical scores, but a PDAI of ≥ 7 decreased their PDAI by ≥ 3 points after 2 weeks of antibiotic therapy. The mean reductions in the total PDAI score, symptom, endoscopy, and histology scores were all significantly lower than before treatment. Conversely, 25% of patients who had clinical symptoms of pouchitis who did not meet the PDAI criteria for pouchitis did not respond symptomatically to empiric antibiotic therapy in the past. This latter group of patients can be classified as having irritable pouch syndrome.¹¹

On endoscopy, the neoterminal ileum above the pouch should be normal; inflammation and ulceration here indicates Crohn's disease. Inflammation of the pouch mucosa with granularity, edema, mucosal hemorrhage, contact bleeding, and superficial ulcers can be present with varying degrees of severity.¹² Inflammation can be uniform throughout the pouch or more severe in the distal pouch.¹³ Histopathologic findings in pouchitis include acute and chronic inflammatory cell infiltration, ulceration, and villous atrophy with crypt abscesses and hyperplasia.¹⁴

If pouchitis is refractory to medical therapy or has atypical components, further diagnostic tests should be performed to exclude alternate diagnoses. Infectious etiologies should be ruled out by stool sampling and pouch biopsy. Multiple cases in the literature document cytomegalovirus of the pouch in patients who had refractory pouchitis. Treatment with ganciclovir led to resolution of symptoms.^{15,16}

Pouchography (luminal contrast study) can show ileoanal anastomotic separations, pouch fistulas, and anastomotic strictures. If Crohn's disease is suspected, a small bowel follow-through x-ray will rule out disease above the pouch. A computerized axial tomography (CAT) of the pelvis or magnetic resonance imaging will detect peripouch abscesses or inflammatory phlegmons. Endoluminal transpouch ultrasonography has also been used in pouch dysfunction with reported higher rates of fistula and abscess detection than both CAT scan and pouchography.¹⁷ Anorectal manometry assesses for pelvic floor dysfunction and is another useful tool in evaluating poor pouch function. Finally, scintigraphic pelvic pouch emptying scans can be used to evaluate patients who have inefficient or inadequate pouch evacuation.¹⁸ If a diagnosis of pouchitis is not made on endoscopic and histologic criteria and other disease states are ruled out, it is possible that the patient may have irritable pouch syn-

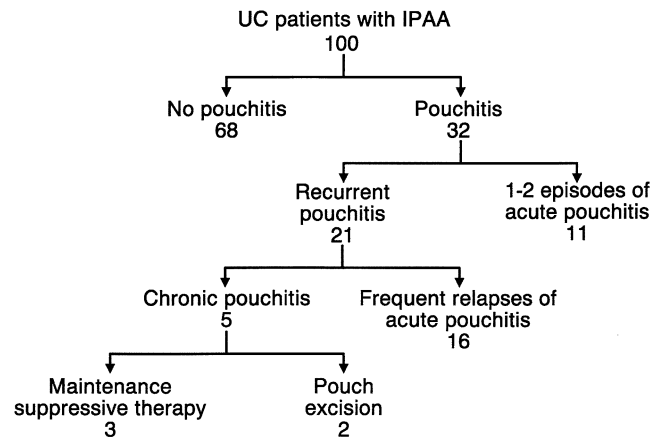


Figure 1. The clinical outcome of 100 patients at the Mayo Clinic who underwent ileal pouch anal anastomosis for ulcerative colitis. Reprinted with permission from Sandborn WJ. Pouchitis: Definition, risk factors, frequency, natural history, classification, and public health perspective. In: McLeod RS, Martin F, Sutherland LR, et al., eds. Trends in inflammatory bowel disease 1996. Lancaster, UK: Kluwer Academic, 1997:51–63.

drome.¹¹ In these clinically symptomatic patients, treatment strategies similar to those used in irritable bowel syndrome (antidiarrheals, anticholinergics, antidepressants) may be used with some benefit.

Epidemiology, Risk Factors, and Natural History

Frequency

The cumulative risk of having one or more episodes of pouchitis varies from 15% to 53% in patients who have UC.^{19–26} This wide range reflects the varied methods of defining and diagnosing pouchitis in the different studies. The rate of occurrence of a new diagnosis of pouchitis appears to be highest in the first 6 months after closure of the loop ileostomy, and then decreases significantly after 12 months.²⁴ The overall frequency of pouchitis is much lower in patients with FAP (3%–14%).^{19,21,27} The frequency of refractory pouchitis ranges from 4.5% to 5.5%, with severe intractable pouchitis leading to excision of the pouch in 0.3% to 1.3% of patients. Figure 1 shows the clinical outcome of 100 UC patients at the Mayo Clinic who underwent IPAA.⁹

Predictive Factors

Pouchitis does not appear to have a predilection for age or race, although one small study did note a decreased incidence in African Americans when compared with Caucasians.²⁸ Males may have higher rates of chronic pouchitis.²⁹ Surgical technique does not seem to affect the frequency of pouchitis, although indication for

surgery (FAP vs. UC) does. Pouchitis rates are similar in J vs. K reservoirs,³⁰ S vs. W reservoirs,³¹ one- vs. two-stage restorative proctocolectomy,³² and in laparoscopic IPAA.³³

Penna et al. found a cumulative risk of pouchitis in UC patients to be 15.5%, 22.5%, 36%, and 45.5% at 1, 2, 5, and 10 years after IPAA, respectively. This risk was much higher in patients who had primary sclerosing cholangitis (PSC), whose risk at 1, 2, 5, and 10 years was 22%, 43%, 61%, and 79%, respectively.²³ Stahlberg et al. found similar results with a cumulative risk of 51% at 4 years. All 6 patients (100%) who had PSC developed pouchitis, and extraintestinal manifestations (EIM) as a whole were a predictive factor for pouchitis.²⁴

Many other studies report an increased frequency of pouchitis in patients who have EIM.^{28,34–36} Seronegative arthritis responsive to steroids and associated only with active pouchitis has been reported.³⁷ Lohmuller et al. studied 734 patients who underwent IPAA. Patients with preoperative EIMs had a 39% incidence of pouchitis vs. 26% in those who did not. Patients who developed EIM after colectomy with IPAA had a 53% frequency of pouchitis vs. 25% in those who did not. Similar to UC, smoking may be protective against the development of pouchitis. Merrett reported a 33% frequency of pouchitis in former smokers, 25% in patients who never smoked, and 6% in current smokers.³⁸ These findings have been confirmed by other investigators.^{24,28}

The importance of the extent of preoperative UC as a risk factor for the development of pouchitis is more controversial. Samarasekera found no relationship between distal colitis or more extensive disease and the frequency of pouchitis in 177 patients.³⁹ In contrast, Schmidt reported that colonic extent of disease had a significant association with the subsequent development of pouchitis after IPAA. However, the severity of the UC preoperatively was not found to be predictive.⁴⁰

Backwash ileitis or inflammation in the terminal ileum as a risk factor for pouchitis is also controversial. One study found no correlation with development of pouchitis,⁴¹ whereas another study found that the eosinophils and villous blunting in the terminal ileum were predictive of the degree of pouch inflammation.⁴⁰ The potential role of eosinophils is further supported by the finding of a 3-fold increase in the eosinophil concentration in preoperative colonic mucosa in patients who subsequently developed pouchitis versus those who did not.⁴²

A genetic marker shown to predict the development of pouchitis is the interleukin-1 receptor antagonist gene (IL-1ra) allele 2. IL-1 is a major proinflammatory cyto-

kine. IL-1ra competitively binds to IL-1 receptors without inducing signal transduction. However, IL-1ra allele 2 is associated with decreased levels of IL-1ra,⁴³ leading to an imbalance of IL-1ra/IL-1 which has been implicated in the pathogenesis of UC.⁴⁴ In a study by Carter,⁴⁵ patients who had pouchitis were found to have higher allele 2 carriage versus patients without pouchitis (72% vs. 45%). IL-1ra is not only a possible marker predicting pouchitis, but also a potential target for biologic therapy.

The predictive value of serum antineutrophil cytoplasmic antibody-perinuclear staining pattern (pANCA) is more controversial. The prevalence of pANCA in UC patients is 60%.⁴⁶ Whether this number is decreased after proctocolectomy^{47,48} or unchanged^{49–52} is uncertain. The literature is also divided as to whether there is a correlation between pANCA and the development of pouchitis. Four studies have found that the prevalence of pANCA is higher than expected in IPAA patients who have pouchitis (89% to 100%) and lower than expected in patients who do not have pouchitis (18% to 74%).^{46,50,51,53} However, 7 more recent studies have shown that there is no correlation between pANCA and the occurrence of pouchitis.^{34,48,52,54–57} Whether the failure of these later studies to show an association is based on the definitions of pouchitis used, the ANCA assay methodology, disease heterogeneity, or a true absence of association remains to be determined.

A provocative but small study by Fleshner⁵⁸ measured the quantitative levels of pANCA before colectomy for UC and divided them into high level (>100 EU/mL), moderate (40 to 100 EU/mL), and low level (<40 EU/mL). Sixty of 95 patients were pANCA-positive before colectomy, of which 9 were high-level, 32 moderate, and 19 low-level. pANCA (+) and pANCA (–) patients did not differ in the overall frequency of pouchitis (acute or chronic), and pANCA levels were not predictive of acute pouchitis. However, pANCA levels were predictive of chronic pouchitis: the cumulative risk of developing chronic pouchitis was significantly higher in patients with high-level pANCA (56%) than in moderate (22%), low-level (16%), or pANCA (–) patients (20%).⁵⁸

PANCA levels are also increased in patients who have PSC.⁵⁹ PSC, in turn, is a risk factor for pouchitis.^{23,47,60} Patients who have PSC and who undergo IPAA have a 63% chance of developing pouchitis versus only 32% for those who do not have PSC. The cumulative risk of developing pouchitis in patients who have PSC is also higher at 1, 2, 5, and 10 years than that in patients who have UC and do not have PSC.²³ The increased incidence of pouchitis in patients who have PSC and other EIM suggests that there may be a particular genotype of UC

Table 3. Predictive Factors for the Development of Pouchitis

1. Male gender (chronic pouchitis)
2. Primary sclerosing cholangitis
3. Extraintestinal manifestations
4. Nonsmoker
5. Extent of colitis^a
6. Backwash ileitis^a
7. Preoperative quantitative pANCA level (chronic pouchitis)^a
8. IL-1ra gene allele 2

^aDenotes that the data is mixed.

that has a stronger predisposition to develop pouchitis. PANCA may or may not be a serological marker for that genotype. These correlations also support the theory that pouchitis may be either a recurrence of UC in the pouch or a third, new form of inflammable bowel disease (IBD). Table 3 summarizes the potential predictive factors for the development of pouchitis.

Quality of Life

Aside from pouchitis, outcome after IPAA is variable and is dependent on surgical expertise. Most studies report an average of six bowel movements a day and some fecal incontinence in approximately 50% of patients.^{61,62} Despite these numbers, the health-related quality of life (QOL) after IPAA has consistently been comparable to normal populations and is better than in active UC.^{63–66} However, poor functional status, increased number of bowel movements, and chronic pouchitis do decrease health-related QOL.⁶⁶ Improved QOL overall after surgery but a worse QOL with pouchitis⁶⁷ has been confirmed by use of the Cleveland Global Quality of Life score, a tool specifically developed to assess patients with a restorative proctocolectomy.⁶⁸ The IBD questionnaire,⁶⁹ a QOL tool validated in UC and Crohn's disease, appears to correlate with PDAI and is another tool that can be used to measure QOL in patients who have pouchitis.⁷⁰

Complications

The effect of acute pouchitis on long-term functional results is not clear. Whereas one prospective study of 137 patients found that even one episode of acute pouchitis can result in poorer long-term functional results,²⁰ Keranen et al. found that only chronic pouchitis affects functional outcomes.²² Chronic pouchitis is rarely a cause for pouch excision.^{62,71} Women who have IPAA have significantly lower fertility rates than those who have UC,⁷² and while pregnant have poorer QOL scores⁶⁷ with transient worsening of pouch function.⁷³ The contribution of pouchitis to this is unknown.

Metabolic sequelae after IPAA have been found to be associated with pouchitis and include decreased levels of

albumin, calcium, total cholesterol, triglycerides, and vitamin E. Vitamin A, B₁₂, and D deficiency have also been found.⁷⁴ Osteopenia has been found using bone densitometry testing in patients who have villous atrophy of the ileal reservoir, a hallmark of pouchitis.⁷⁵

Etiology

The etiology of pouchitis is unknown. Speculation has centered on the role of genetic susceptibility, fecal stasis, and/or bacterial overgrowth, an altered balance of luminal bacteria (dysbiosis), nutritional deficiencies, ischemic complications of surgery, a novel third form of IBD, a recurrence of UC in the pouch, or a missed diagnosis of Crohn's disease. The significantly higher occurrence of pouchitis in patients who have UC versus FAP suggests that the mechanism is not related to surgical changes common to both diseases (i.e., ischemia and fecal stasis). However, the efficacy of antibiotics and probiotics in treating pouchitis suggests that the latter mechanism may play a role. The ileal pouch undergoes adaptive changes once it is exposed to the fecal stream. Functionally, it changes from a primarily absorptive organ to an organ of storage. The histopathologic changes that follow reflect this transition. Ileal pouches acquire certain colonic characteristics such as goblet cells, villous atrophy, and crypt hyperplasia; however, complete colonic metaplasia does not seem to occur.^{76,77} The UC host may be genetically more susceptible to having an inflammatory response to insults in their adapted pouch mucosa, much as they are thought to be susceptible to such insults in their now resected colon. Table 4 summarizes the potential etiologies of pouchitis.

Treatment

The treatment of pouchitis is predominantly empiric given the few controlled trials available. To date, there have been at least 9 published controlled trials on the treatment of pouchitis.^{78–86} Antibiotics are the mainstay of acute and chronic treatment, but probiotics may play a role in the maintenance of remission in chronic pouchitis. Table 5 lists the treatment options currently available.

Antibiotics

Metronidazole and ciprofloxacin are the first-line therapy for pouchitis. Evidence that metronidazole is effective comes from an "N-of-1" randomized trial⁷⁸ and a randomized controlled crossover trial which showed a 73% response (defined as a decrease in stool frequency) in 13 patients with chronic pouchitis. The placebo response was 9%.⁷⁹ Hurst et al. found that 41 of 52 patients

Table 4. Potential Etiologies in the Development of Pouchitis

Cause	Supportive evidence	Negative evidence	Reference nos.
Altered immunoregulation	+/- pANCA IL-1ra gene allele 2 ↑ Lymphocyte densities ↑ Inflammatory cytokines Extraintestinal manifestations		45, 58, 135, 136
Crohn's disease	Ileal inflammation Fistulas	Disease in pouch only	92
Fecal stasis Bacterial overgrowth Dysbiosis	Antibiotics Probiotics	Same bacterial count w/ or w/o pouchitis	137-140
Fecal bile acids		Same total bile acid concentration in pouchitis vs. healthy	92, 140, 141
Short chain fatty acids		No correlation between SCFA, pouchitis, fecal bacterial concentrations	140
Ischemia	↓ Mucosal blood flow	Same surgery as FAP Allopurinol ineffective	83, 142

(79%) with acute pouchitis responded to a 7-day course of metronidazole at 250 mg orally 3 times a day with complete relief.²⁷ Two small series found metronidazole to have a response rate of 100% when given as a topical solution instilled at 75 to 150 mg daily⁸⁷ or 40 to 160 mg daily.⁸⁸

Hurst reported that 11 of 52 patients did not respond to metronidazole. These patients were then given ciprofloxacin 500 mg twice a day, of whom 8 (73%) responded. Thus, the overall antibiotic response rate was 96%.²⁰ A randomized trial by Shen⁸⁵ compared 2 weeks of treatment with metronidazole 20 mg · kg⁻¹ · day⁻¹ to ciprofloxacin 1000 mg/day in patients who had acute pouchitis. Both drugs significantly reduced the PDAI score, but ciprofloxacin had a greater reduction in overall PDAI score (6.9 ± 1.2 vs. 3.8 ± 1.7, *P* = .002), symptom score (2.4 ± 0.9 vs. 1.3 ± 0.9, *P* = .03), and endoscopic score (3.6 ± 1.3 vs. 1.9 ± 1.5, *P* = .03) vs. metronidazole. None of the patients who were administered ciprofloxacin experienced side effects whereas 33% of the patients who were administered metronidazole had adverse events. The side effect profile of metronidazole includes dysgeusia, dyspepsia, nausea, and peripheral neuropathy. For many practitioners, these undesirable sequelae of therapy have made ciprofloxacin the drug of choice for pouchitis therapy. Other antibiotics used with anecdotal success include amoxicillin/clavulanic acid, erythromycin, and tetracycline.⁸⁹

In patients who have chronic recurrent or refractory pouchitis, antibiotic combination therapy may be effective. Gionchetti used rifaximin 1 g twice daily in combination with ciprofloxacin 500 mg twice daily for 15 days in 18 patients who had chronic treatment resistant

pouchitis.⁹⁰ Six of 18 (33%) had complete remission defined as a PDAI of 0. Ten of 18 (55.6%) had clinical improvement with a decrease of 3 points on their PDAI score, for a total response rate of 88.8%. An open-label trial of metronidazole 400 to 500 mg twice daily, plus ciprofloxacin 500 mg twice daily for 28 days in patients who had recurrent or treatment refractory pouchitis noted an 82% remission rate. The median PDAI scores before and after therapy were 12 (range, 8 to 17 points) and 3 (range, 1 to 10 points), respectively.⁷⁰

An initial episode of pouchitis should be treated with ciprofloxacin 500 mg twice daily or metronidazole 250 mg 3 times a day for 7 to 10 days. Response should be seen within 2 to 3 days. Responding patients who experience recurrent episodes and are able to tolerate the medication should be retreated with the same regimen. Some patients who have chronic pouchitis will require anywhere from 500 mg of ciprofloxacin or 250 mg of metronidazole every third day to 500 mg ciprofloxacin twice daily or 250 mg metronidazole 3 times daily to maintain their response. Others may develop resistance and require combination antibiotic therapy or a rotating schedule of 3 or more antibiotics. If antibiotics fail, other therapeutic options should be considered. Patients who have chronic pouchitis should be considered for probiotic therapy as described below (Figure 2).⁹¹

Mesalamine

Anecdotal reports suggest a benefit from topical mesalamine.^{12,92,93} Miglioli et al. describe three patients who had pouchitis after IPAA for UC. They were administered mesalamine as a suppository or enema at 1.2

Table 5. Treatment Options

Class	Efficacy	Example
1. Antibiotics	+ Acute pouchitis	A. Metronidazole ^a
	+ Chronic pouchitis	B. Ciprofloxacin ^a
		C. Amoxicillin/clavulanic acid
		D. Erythromycin
		E. Tetracycline
		F. Rifaximin + ciprofloxacin
		G. Metronidazole + ciprofloxacin ^a
2. Probiotics	+ Prophylaxis	A. VSL #3 ^a
	+ Maintenance	B. <i>E. coli</i> Nissle 1917
3. Mesalamine	+/-	A. Mesalamine enemas
		B. Sulfasalazine
		C. Oral mesalamine agents
4. Corticosteroids	+/-	A. Corticosteroid enemas
		B. Budesonide suppositories
		C. Budesonide enemas ^a
		D. Oral corticosteroids
5. Nutritional agents	+/-	A. SCFA enemas/suppositories ^b
		B. Glutamine suppositories ^b
		C. Inulin ^a
6. Immune modifier agents/biologics	+/-	A. Cyclosporine enemas
		B. Azathioprine/6-mercaptopurine
		C. Infliximab
7. Oxygen free radical inhibitor	- prophylaxis	A. Allopurinol ^b
8. Smoking/nicotine	+	A. Smoking
		B. Transdermal nicotine (?)
9. Antidiarrheal/antimicrobial	+/-	A. Bismuth subsalicylate
		B. Bismuth carbomer enemas ^b
10. Surgical options		A. Ileal pouch exclusion
		B. Ileal pouch excision

^aDenotes positive randomized controlled trial.

^bDenotes negative randomized controlled trial.

to 4 g daily. After 20 to 30 days, clinical and endoscopic improvement was noted with partial histological recovery.⁹⁴

The bacteria required to split the azo-bond in sulfasalazine and release the mesalamine moiety is present in the reservoir of patients after IPAA,⁹⁵ suggesting that sulfasalazine is a rational treatment modality. Pentasa may also achieve some release of mesalamine into the ileal pouch. However, there are no randomized controlled trials of any oral mesalamine agents for the treatment of pouchitis.

Corticosteroids

When antibiotics fail, oral and topical corticosteroids have been tried with limited anecdotal success.^{92,93}

A small open trial of budesonide suppositories was conducted in 10 patients who had active pouchitis. After budesonide 1.5 mg per day for 4 weeks, all patients had clinical and endoscopic improvement or remission, but 6 (60%) relapsed within 8 weeks.⁹⁶ A randomized, placebo-controlled trial of 2-mg budesonide enemas versus metronidazole also showed efficacy.⁸⁴ Twenty-six patients who had acute pouchitis by PDAI score ≥ 7 were randomized to either budesonide enemas or oral metronidazole 500 mg twice daily for 6 weeks. Fifty-eight percent of budesonide patients and 50% of metronidazole patients improved. Fifty-seven percent of metronidazole patients had adverse events versus only 25% of budesonide patients. Oral-controlled release budesonide has not been reported for the treatment of pouchitis, but anecdotal experience suggests that it may be effective (W. J. Sandborn, unpublished data, December 2002).

Immunosuppressive Therapy

MacMillan reported a small retrospective series of 4 patients who had chronic pouchitis that were treated with azathioprine or 6-mercaptopurine.⁹⁷ Patients were able to discontinue steroids and maintain a sustained response for up to 3 years. Immunosuppressive therapy is not protective against the development of pouchitis in the posttransplant setting. Zins reported 7 patients who had IPAA who underwent orthotopic liver transplanta-

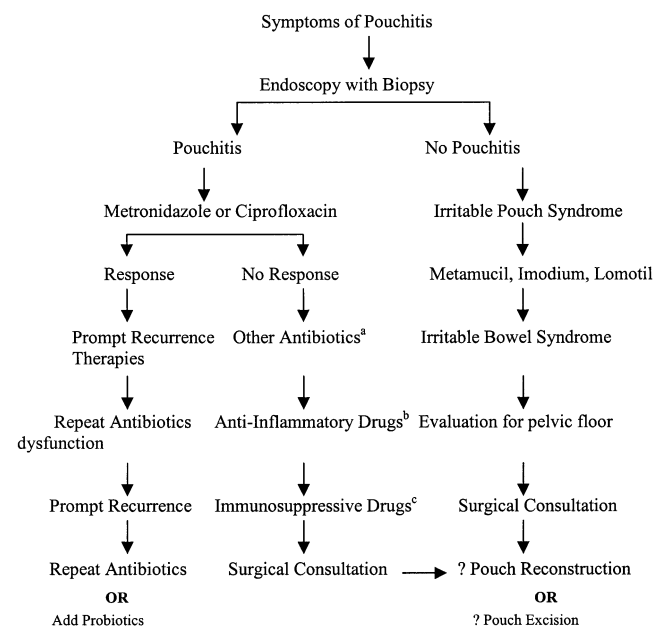


Figure 2. Treatment algorithm for pouchitis. ^aOther antibiotics indicates: rifaximin; amoxicillin/clavulanate; erythromycin; tetracycline; and cycling of multiple antibiotics. ^bAnti-inflammatory drugs indicates: bismuth subsalicylate, mesalamine enemas, sulfasalazine, and oral mesalamine. ^cImmunosuppressive drugs indicates: budesonide, steroid enemas, oral steroids, azathioprine.

tion for PSC.⁹⁸ Five of 7 had chronic or recurrent pouchitis before transplant, of whom 4 continued to have chronic pouchitis after transplant despite a triple immunosuppressive regimen of prednisone, azathioprine, and either cyclosporine or FK 506. One patient who had been free of pouchitis before transplant developed a single acute episode posttransplant. Similarly, Rowley reported that 1 of 4 patients with an orthotopic liver transplant for PSC who underwent colectomy with IPAA for UC developed chronic pouchitis despite immunosuppression with cyclosporine.⁹⁹

Infliximab has been reported to be of benefit for treating Crohn's disease in the ileal pouch.¹⁰⁰ More recently, Arnott¹⁰¹ reported that 2 patients who had refractory pouchitis responded to a single infusion of infliximab (response defined as a decrease in the number of bowel movements and less urgency) with benefit sustained to 12 weeks. No long-term follow-up information was provided.

Bismuth

Bismuth-containing carbomer foam enemas showed promising results in an open label trial.¹⁰² Twelve patients who had treatment refractory chronic pouchitis were treated with 230 mg elemental bismuth-containing carbomer foam enemas. The enemas were given nightly for 45 days. Ten of 12 (83%) patients had a clinical response with a decrease in their PDAI scores by 2 points or more. Of these 10, 6 (60%) maintained their response over 12 months while receiving an enema every third night. No side effects were reported. Unfortunately, a randomized double-blind placebo control trial in 40 patients did not show a difference between placebo and bismuth carbomer foam enema in the treatment of chronic pouchitis.⁸¹ Twenty patients received a placebo enema containing a gum resin and 20 patients received 270 mg of elemental bismuth complexed with carbomer delivered as foam enemas for 3 weeks. No patients achieved remission (PDAI of 0) but 9 patients (45%) in each group achieved a clinical response with a 3-point decrease in their PDAI. The investigators cite low concentrations of bismuth in the enemas, short duration of treatment, therapeutic efficacy of gum resin (given the high placebo rate of 45%), or a true treatment failure to explain the lack of efficacy of bismuth.

A retrospective series of 13 patients who had chronic pouchitis studied the effect of oral bismuth subsalicylate tablets (Pepto-Bismol, Proctor and Gamble, Cincinnati, OH) on disease course. All patients were receiving antibiotics (metronidazole or ciprofloxacin) but remained symptomatic. All patients received an initial dose of eight 262-mg chewable bismuth subsalicylate tablets per

day for 4 weeks. Eleven of 13 had a clinical response with a decrease in stool frequency, fecal incontinence, and/or abdominal cramping. One patient reduced their dose secondary to bloating, while the 7 others reduced their dose because of similar benefit at the lower dose. Five of 11 responders were able to discontinue antibiotic use after 4 weeks.¹⁰³ These inconsistent results with bismuth indicate that an additional controlled trial of oral bismuth may be warranted.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor. The theoretical basis for its use in pouchitis is to inhibit the production of free radicals and thus inhibit mucosal injury. A small trial by Levin et al. showed a 50% response rate in acute and chronic pouchitis.¹⁰⁴ Eight patients who had acute pouchitis received 300 mg twice daily of allopurinol. Four had resolution of symptoms. Fourteen patients who had chronic pouchitis were treated with the same dose for 28 days; 7 of 14 had a clinical response. However, a randomized controlled trial of allopurinol for the prophylaxis of pouchitis was negative.⁸³ In this study, 184 patients who had UC who were undergoing IPAA were randomized to receive postoperative allopurinol 100 mg twice daily or placebo. The cumulative risk of pouchitis was 31% in the allopurinol group and 28% in the placebo group, which was not significant. Additionally, there was no difference in overall pouch function between these 2 groups. These findings do not lend credence to the theory of ischemic damage and free radical injury contributing to the pathogenesis of pouchitis.

Nutritional Agents

Fiber. Thirlby et al. showed that oral fiber supplementation with either pectin, a soluble fermentable fiber supplement, or Citrucel (Glaxo Smith Kline, Research Triangle Park, NC), a methyl cellulose-based, nonfermentable fiber, has no benefit on stool frequency, pouch function, bloating, and stool consistency in patients after IPAA.¹⁰⁵ Inulin, a dietary fiber that is fermented to short-chain fatty acids (SCFA), was studied in a randomized placebo-controlled trial of 3 weeks duration.⁸⁶ Pouch patients receiving 24 g/day of inulin had increased butyrate concentrations (18.9 vs. 11.7, $P = 0.01$), decreased fecal pH (5.33 vs. 5.62, $P = 0.02$), decreased concentrations of *Bacteroides fragilis* (6.77 vs. 7.68, $P = 0.02$), and lower levels of some secondary bile acids in the feces compared with patients on placebo. The overall PDAI score was lower in inulin-treated patients (4.05 vs. 5.39, $P = 0.01$) than in placebo, with significantly lower endoscopic (0.95 vs. 1.47, $P = 0.04$) and

histologic scores (2.11 vs. 2.61, $P = 0.04$), but no difference in the clinical score (1.00 vs. 1.26, $P = 0.17$). However, because all of these patients did not meet the definition of pouchitis by PDAI score and there was no significant improvement in clinical symptom scores, the actual benefit to the patient of receiving inulin therapy is unclear.

Short chain fatty acids/glutamine. SCFA (acetate, propionate, butyrate) are produced by anaerobic bacterial fermentation. They are the major source of energy for the colonic mucosa.¹⁰⁶ Glutamine is the analogous energy source for the small intestinal mucosa. Studies reporting the use of SCFA as a treatment for pouchitis are limited, and the results are mostly negative. Two small series used the same SCFA enema formulation of 60 mmol/L sodium acetate, 30 mmol/L sodium propionate, and 40 mmol/L sodium *n*-butyrate in a combined total of 10 patients who had chronic pouchitis.^{107,108} Only 3 patients had a clinical response whereas 2 patients actually had worsening of their clinical symptoms. Den Hoed described a single patient who had refractory pouchitis who completely responded to treatment with a similar SCFA enema.¹⁰⁹ Another study randomized patients with chronic pouchitis to either butyrate or glutamine suppositories for 10 days. Three of nine (33%) patients whose symptoms were treated with butyrate and 6 of 10 (60%) patients whose symptoms were treated with glutamine responded.⁸² Given the lack of a placebo control, it is unclear whether these two therapies are similarly effective or similarly ineffective.

Smoking/Nicotine

Current smoking has been reported to be protective against pouchitis.^{24,28,38} To date, there have been no trials of nicotine enemas or transdermal nicotine patch for the treatment of pouchitis.

Probiotics

Probiotics are live organisms, typically bacteria, found as commensals in the human gastrointestinal tract. Based on the hypothesis that an imbalance in the usual fecal flora (dysbiosis) may result in inflammatory conditions such as pouchitis, Gionchetti conducted a randomized double-blind placebo controlled trial of the probiotic formulation VSL-3 (Sitia-Yomo, Milano, Italy).¹¹⁰ Forty patients who had chronic pouchitis in remission after treatment with antibiotics (PDAI = 0) received either placebo or a 6 g daily oral dose of VSL-3 for 9 months. VSL-3 contains 5×10^{11} /g of viable lyophilized bacteria consisting of 4 strains of lactobacilli (*L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *L. plantarum*, *L. casei*), three strains of bifidobacteria (*B. infantis*, *B. longum*, *B.*

breve) and one strain of *Streptococcus salivarius* subsp. *thermophilus*. Seventeen of 20 patients (85%) who were treated with VSL-3 maintained remission (relapse was defined as an increase in the PDAI ≥ 2 points) compared to none of 20 patients who were treated with placebo. No adverse events were reported. The VSL-3–treated group was found to have an increase in fecal concentrations of lactobacilli, bifidobacteria, and *S. thermophilus* by day 15. A second controlled trial of VSL-3 for the treatment of chronic pouchitis was conducted in 36 patients with similar results.¹¹¹ VSL-3 is also more effective than placebo as a prophylaxis against the development of pouchitis in the first year after surgery.¹¹² A case report of 2 patients suggested that another probiotic, *Escherichia coli* strain Nissle 1917, may be of benefit for the treatment of active pouchitis and the maintenance of remission as well.¹¹³

The mechanism of action of probiotics in pouchitis is unclear. Patients who have pouchitis and who received probiotic therapy with VSL-3 were found to have increased concentrations of the anti-inflammatory cytokine IL-10 and a reduction of the proinflammatory cytokines IL-1 α , interferon- γ , and tumor necrosis factor- α , as well as inducible nitric oxide synthase and matrix metalloproteinase activity to concentrations similar to those found in noninflamed pouches.¹¹⁴ *E. coli* Nissle 1917 was able to induce IL-8 while VSL-3 was not, suggesting that these 2 probiotic formulations may have different modes of action.¹¹⁵

Crohn's Disease

When Crohn's disease is diagnosed in the pouch (based on pre-pouch ileitis or fistula involving the pouch), treatment is similar to the treatment of Crohn's disease elsewhere in the gastrointestinal tract. Berrebi reported on 2 patients who had IPAA and were diagnosed with Crohn's disease in the reservoir. Both responded to corticosteroid and azathioprine therapy, with eventual maintenance on azathioprine alone.¹¹⁶ Ricart reported a series of 7 patients who had IPAA for UC who were subsequently diagnosed with Crohn's disease and who were refractory to conventional therapy. These patients were treated with infliximab. Six patients had a complete response with closure of all fistulous tracts, and one had a partial response.¹⁰⁰

Pouch Excision

Pouch excision is rare and occurs more commonly for pouch dysfunction than for true chronic pouchitis. However, Penna et al. estimate that approximately 1.3% of patients who undergo IPAA for UC will need a pouch excision for chronic treatment refractory pouchitis.²³

Dysplasia

There have been at least 17 cases of adenocarcinoma arising in the permanent (Brooke) ileostomy of patients who had UC. The case described by Reissman notes diffuse colonic metaplasia in the ileostomy around the adenocarcinoma with sulfomucin production.¹¹⁷ In 1997, the first case of an adenocarcinoma arising in a continent ileostomy (Kock pouch) was described in a patient who had UC. The pouch mucosa showed chronic inflammation with villous atrophy and mild to moderate dysplasia.¹¹⁸ It was not clear if this patient suffered from recurrent pouchitis. Also in 1997, a case of large cell lymphoma arising in the pouch of a patient who had UC was described. This patient suffered from chronic refractory pouchitis, which may in retrospect have been due to the invasive lymphoma, undetected until surgical resection of the pouch for pouch dysfunction.¹¹⁹

Rectal cancer has developed after IPAA in the residual columnar epithelium or rectal cuff.^{120–122} Although this makes intuitive sense, the risk of dysplasia and adenocarcinoma developing in the ileal reservoir has been mostly a theoretical concern. However, dysplasia has now been noted by 3 groups in the ileal reservoir including the development of adenocarcinoma of the pouch in one patient who had chronic pouchitis.^{123–126}

In 1991, Lofberg et al.¹²⁷ reported the first case of pelvic pouch dysplasia. The patient was a 36-year-old man who underwent a colectomy, mucosal proctectomy, and IPAA with a S-type pelvic pouch. No dysplasia was noted in the colectomy specimen. The patient suffered from chronic pouchitis and was on long-term metronidazole therapy. Four years after pouch creation, he was noted to have low-grade dysplasia on biopsy and DNA aneuploidy by flow cytometry. The patient then underwent periodic surveillance pouchoscopy with biopsy, and in 1996 high-grade dysplasia was detected.¹²⁶ In 1997, the patient was diagnosed with primary cholangiocarcinoma, with likely underlying subclinical PSC.¹²⁸

In 1995, the same group reported the results of 87 patients who had IPAA for UC whose cases were followed for a mean of 6.3 years. Three types of mucosal adaptation were noted in the reservoir. Type A (51% of patients) was characterized by normal mucosa or a mild villous atrophy and no or mild inflammation. Type B (40% of patients) showed transient atrophy with temporary moderate or severe villous atrophy followed by normalization. Finally, Type C (9%) showed constant atrophy with permanent total or subtotal villous atrophy accompanied by severe pouchitis. It was in this last group that low-grade dysplasia was found in 3 of 8

patients. This group also had the highest level of sulfomucin-producing goblet cells in the pouch.¹²⁴ A prospective follow-up study of 7 patients who had Type C mucosa and 14 who had Type A patterns was performed. Dysplasia was noted in 5 of 7 Type C pouches (71%) (4 low-grade dysplasia and 1 high-grade dysplasia). There was no correlation with dysplasia in the colectomy specimen, but there was an association with an early onset of UC. The investigators believed that patients who were identified as having a Type C response 4 years after ileostomy closure should have at least annual pouchoscopy with surveillance for dysplasia.¹²⁶

Other investigators have not found dysplasia on surveillance of the pouch,^{129–132} but have found similar rates of Type A, B, and C mucosa in adults¹³¹ and children¹³² who have an IPAA for UC. Setti Carraro confirmed the finding that only patients who had Type C mucosa developed chronic pouchitis. He also noted that the categorization of response type could be made at 6 months after ileostomy closure.¹³¹ In a study of six patients who had chronic severe pouchitis, one had a genetic alteration associated with colorectal carcinoma, a loss of heterozygosity at 5q15-22.¹³³

In 2001, Thompson-Fawcett¹²³ surveyed the pelvic pouches of 106 patients who had potential risk factors for dysplasia—chronic pouchitis, pelvic pouch for 12 years or more, Kock pouch for 14 years or more, and neoplasia in the colectomy specimen. One patient who had a long-standing pouch had multifocal low-grade dysplasia. She had never had an episode of pouchitis and opted for pouch excision.

In 2000, Iwama reported a case of adenocarcinoma in a J-pouch that had been outside of the fecal stream for 18 years.¹³⁴ In 2001, Heuschen et al. reported the first adenocarcinoma of a functioning pelvic pouch that clearly developed from the ileal mucosa.¹²⁵ This was a patient who had pancolitis and backwash ileitis who underwent IPAA for multifocal dysplasia. The patient developed chronic pouchitis and was noted to have a tubulovillous neoplasia on pouch biopsy 3 years after surgery. Pouch excision was performed and a flat carcinoma in the proximal pouch was found.

Overall, pouch dysplasia is very rare. No screening program is currently advocated for patients with IPAA after colectomy for UC. Further studies are needed to delineate which patients need screening, when, where within the pouch, and how often. Potential risk factors for pouch dysplasia may be dysplasia in the original colectomy specimen, chronic pouchitis, and the age of the pouch. It is reasonable, based on the available data, to perform random mucosal sampling in the reservoir of all

patients who have a history of UC and a pouch 1 year after closure of the ileostomy. Those found to have Type C mucosal changes and/or chronic pouchitis should undergo annual surveillance pouchoscopy, as is done for patients who have UC. Patients who have dysplasia on colectomy may need to be surveyed regardless of evidence for chronic pouchitis.

Summary

Pouchitis is an idiopathic inflammatory disease of the ileal reservoir in patients who have undergone IPAA. Approximately half of all UC patients who undergo this procedure will have at least 1 episode of pouchitis with approximately 15% experiencing a chronic course. PSC and other EIM increase the likelihood of developing pouchitis, whereas smoking is protective. Similar genetic and autoimmune mechanisms to UC appear to occur in an ileal reservoir that shows increasingly colon-like adaptations with respect to bacterial content and mucosal characteristics. Although most patients have a good response to antibiotic therapy, increasing evidence supports a role for probiotics in prevention and maintenance. Finally, dysplasia is a rare but real concern, and pouch surveillance guidelines must be developed.

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