REVIEW

Pouchitis: a practical guide

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ABSTRACT

Up to 30% of patients with ulcerative colitis (UC) will require surgical management. The established surgical procedure of choice is colectomy with ileal pouch–anal anastomosis (IPAA) for most patients. Patients with UC who have undergone IPAA are prone to develop inflammatory and non-inflammatory complications. Up to 50% of patients can be expected to experience at least one episode of pouchitis, and most of these patients will experience at least one additional acute episode within 2 years. In other cases, pouchitis might follow a relapsing–remitting course or a chronically active course. The specific aetiology of pouchitis is unknown and the optimal means of diagnosis and classification of pouchitis is not completely agreed upon. Diagnosis of pouchitis based on symptoms alone has been shown to be non-specific due to the fact that symptoms can originate from a myriad of aetiologies, not necessarily inflammatory in nature. As a result, the diagnosis of pouchitis should generally be based on the appropriate constellation of symptoms, combined with endoscopic and histological assessment. Due to the frequently relapsing course of pouchitis, and the fact that the aetiology and pathogenesis are not entirely clear, the long-term management can sometimes be challenging. This review outlines the features suggestive of deviation from ‘normal’ pouch function and provides an approach to the optimal use of diagnostic modalities and medical therapies to treat pouchitis in its various forms.

INTRODUCTION

Up to 30% of patients with ulcerative colitis (UC), will require surgical management of their disease because of medically intractable disease, fulminant course, dysplasia or cancer and even due to patient preference not to take medication on an indefinite timeline. Before the 1980s surgical management typically involved a total proctocolectomy and permanent ileostomy. However, advances in surgical techniques led to the establishment of colectomy with ileal pouch–anal

anastomosis (IPAA) as the standard operation of choice for most patients (see figure 1).

Patients with UC who have undergone IPAA are prone to develop inflammatory and non-inflammatory complications, which include early or late surgical complications (such as an anastomotic stricture or leaks, fistulae and pelvic abscess), cuffitis, irritable pouch syndrome and pouchitis. According to some series approximately 50% of patients can be expected to experience at least one episode of pouchitis (see figure 2). In a study of complications and long-term outcomes in 1310 patients who underwent IPAA for chronic UC, 559 patients had at least one episode of pouchitis.¹ The cumulative risk of having at least one episode was 18% at 1 year after surgery and 48% at 10 years. Approximately 394 of the 559 patients who had at least one attack of pouchitis had a second episode. The cumulative probability of having a second episode after an initial attack within 2 years of IPAA was 64%.

Patients with IPAA for UC tend to experience a variety of symptoms, ranging from mild pelvic or perianal discomfort to a debilitating complex of symptoms that may eventually lead to pouch excision thereby necessitating the construction of a permanent ileostomy. The most common complication of the ileal pouch, among patients with UC, is pouchitis, affecting up to 50% of patients. The specific aetiology of pouchitis is unknown and the method for diagnosis and classification of pouchitis is not completely agreed upon. Clinicians typically base their suspicion of pouchitis on a constellation of clinical symptoms such as: an increase in stool frequency, tenesmus, change in stool consistency, abdominal cramps and rectal bleeding. Treatment is often prescribed based on these clinical symptoms alone. However, diagnosis of pouchitis based on symptoms alone has been shown to be

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Figure 1 Ileal pouch–anal anastomosis, schematic description courtesy of: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

non-specific due to the fact that symptoms can originate from a myriad of aetiologies, not necessarily inflammatory in nature.

Due to the relapsing nature of pouchitis, and the fact that the aetiology and pathogenesis are not entirely clear, the long-term management is quite a challenging one.

In this review we will try to outline the features suggestive of deviation from ‘normal’ pouch function, and present to the practising gastroenterologist diagnostic tools and therapeutic approaches to treat pouchitis in its various forms.

WHAT IS ‘NORMAL’ POUCH FUNCTION?

Despite the fact that patients with IPAA report frequent and various symptoms, large series have reported a generally good quality of life.

There is no single absolute number or variable that indicates ‘normal’ pouch function. Stool frequency is the symptom that is most commonly used to describe the function of the pouch, with aspects of urgency and continence also being commonly used. Unfortunately, there is a wide range of stool frequency, urgency and leakage that is considered to be consistent with ‘normal’ pouch function. However, previous series have reported median stool frequency of six bowel motions per day with a range of one to 20.

In the series presented by Fazio *et al.*,² seepage was reported in 17–29% of patients, many of whom (6%) were subject to dietary restrictions in order to minimise symptoms.¹ Up to 47% of patients reported occasional usage of antidiarrhoeal agents.

It is commonly believed that the pouch function stabilises 1 year after the ileostomy is closed. From that point onwards acute and persistent changes in

Figure 2 A typical endoscopic appearance of pouchitis.

symptoms should be addressed by either a diagnostic work-up to determine the underlying aetiology of the changes or empirically treated based on the presumed diagnosis.

DIAGNOSING POUCHITIS

It is generally accepted that a diagnosis of pouchitis should be based, not simply on the presence of symptoms described above, but on the combination of clinical, endoscopic and histological findings.³

Two composite scores are used to diagnose pouchitis and to assess disease severity. These are the pouchitis disease activity index (PDAI)⁴ and the pouchitis activity score (PAS)⁵ (see tables 1 and 2). In the PDAI, an overall score is calculated from three separate six-point scales comprising clinical symptoms, endoscopic findings and histological changes. The PDAI incorporates histological features of acute inflammation, and establishes a cut-off of seven for differentiation between ‘pouchitis’ (≥ 7 points) and ‘no pouchitis’ (< 7 points). The PAS incorporates elements similar to those of the PDAI but also includes the histological features of chronic inflammation. The resulting total score distinguishes between three grades of pouch inflammation: mild adaptive, moderate pouchitis and severe pouchitis. Only individuals with scores greater than 13 are considered to have pouchitis, as a degree of mild inflammation is an almost universal finding.

Despite the fact that the PDAI and PAS have become commonly used in clinical trials evaluating different therapies of pouchitis, it has been suggested that the clinical components of the scores correlate poorly with endoscopic and histological findings, presumably due to the fact that conditions other than pouchitis can result in pouch dysfunction.^{5 6} Due to the variety of aetiologies that can result in pouch dysfunction, it is important that endoscopy is performed

Table 1 Summary of the PDAI

	Range
I. Clinical	
1. Stool frequency	(0, 1, 2)
2. Fecal urgency/Abdominal cramps	(0, 1, 2)
3. Rectal bleeding	(0, 1)
4. Fever > 37.8°C	(0, 1)
Maximal clinical subscore: 6	
II. Endoscopic finding	
1. Oedema	(0, 1)
2. Granularity	(0, 1)
3. Friability	(0, 1)
4. Loss of vascular pattern	(0, 1)
5. Mucous exudates	(0, 1)
6. Ulcerations	(0, 1)
Maximal endoscopic subscore: 6	
III. Histology—acute histological inflammation	
1. Polymorphonuclear infiltration	(0, 1, 2, 3)
2. Ulceration per low power field (mean)	(0, 1, 2, 3)
Maximal histological subscore: 6	
Maximal total PDAI: 18	
PDAI, pouchitis disease activity index.	

and it is a general consensus among many inflammatory bowel disease centres that pouch endoscopy and histological evaluation should be performed in order to diagnose pouchitis accurately.

Based on aetiology, disease duration and response to treatment, pouchitis may be classified into four categories: (1) idiopathic versus secondary; (2) acute (<4 weeks) versus chronic (≥4 weeks); (3) infrequent episodes (less than two acute episodes) versus relapsing (three or more acute episodes) or continuous; (4) antibiotic responsive versus refractory.⁷

The diagnostic work-up

At the initial occurrence of symptoms that might suggest ‘pouchitis’ infectious aetiologies should be excluded by sending stool for culture and *Clostridium difficile* toxin assay and, in the appropriate setting, by ruling out cytomegalovirus infection.

Once infectious aetiologies and other possible contributors have been ruled out, pouch endoscopy should be performed if feasible. If not, a trial of antibiotics may be administered as being both therapeutic and diagnostic of ‘pouchitis’. However, the use of an empiric course of antibiotics as a means of diagnosis of pouchitis should be practised with caution because, as discussed later, it is our impression and that of others that patients with pouch symptoms may respond quite rapidly to the administration of antibiotics without having evidence of the endoscopic or histological inflammation that is required to make a diagnosis of pouchitis.

On endoscopy, it is important to examine the pouch, the pre-pouch ileum and the rectal cuff.

Table 2 Summary of the PAS

	Range
I. Clinical	
1. Stool frequency	(0, 2, 4, 6)
2. Fecal urgency	(0, 3)
3. Rectal bleeding	(0, 3)
Maximal clinical subscore: 12	
II. Endoscopic findings	
1. Oedema	(0, 1)
2. Granularity	(0, 1)
3. Friability	(0, 1, 2)
4. Erythema	(0, 2, 3)
5. Mucosal flattening	(0, 2)
6. Ulcerations/erosions	(0, 2, 3)
Maximal endoscopic subscore: 12	
III. Histological	
Acute inflammation	
1. Polymorphonuclear infiltration	(0, 1, 2, 3)
2. Ulcerations/erosions	(0, 1, 2, 3)
Chronic inflammation	
1. Mononuclear infiltration	(0, 1, 2, 3)
2. Villous atrophy	(0, 1, 2, 3)
Maximal (total) histological subscore: 12	
Maximal total PAS: 36	
PAS, pouchitis activity score.	

Biopsies from the pouch may be helpful even from normally appearing pouch mucosa, as findings of acute inflammation may still be present. Conversely, the yield of sampling an apparently normal pre-pouch ileum seems to be low.

The endoscopic features of pouchitis may range from anywhere between minimal changes, including erythema, friability and mucus exudate to frank ulcers and bleeding. Histological assessment will focus on acute inflammatory infiltrates and also dysplastic changes to rule out the rare case of progression to malignant transformation.

More complicated cases, presenting with systemic symptoms and signs of inflammation, fistulas, leaks or abscesses, may warrant additional modalities, such as abdominal and pelvic CT scan, pelvic MRI, perineal or transanal ultrasound, pouchography or examination under anaesthesia.

TREATMENT OF POUCHITIS

It has been observed that the usual anti-inflammatory therapies are not as effective for pouchitis as for other forms of inflammatory bowel disease, whereas antibiotics seem to be more effective^{8–9} and have therefore become the mainstay of treatment for pouchitis. Many patients with IPAA can experience rapid and significant clinical improvement following the commencement of antibiotic treatment for acute onset of symptoms, even before endoscopy has been

performed.^{10 11} For a first attack of typical pouchitis a course of empiric antibiotic therapy without endoscopy and biopsy is reasonable, but if there is easy access to endoscopic evaluation and biopsy, it is still preferable to visualise and biopsy the pouch mucosa before starting therapy.

Recurrent episodes, with similar features to the initial presentation, may be treated in the same manner as initially and the likelihood of diagnosing them accurately without endoscopy is high.

Antibiotics

Metronidazole has been evaluated in several randomised controlled trials, and an overall response rate of 73% has been demonstrated compared with a 10% response rate in patients receiving placebo.^{10 12}

Ciprofloxacin at a dose of 1000 mg/day was compared with metronidazole 20 mg/kg per day, given for 2 weeks, and both agents significantly reduced the PDAI, with all subscores showing improvement. However, patients who were given ciprofloxacin had greater reductions in mean total PDAI than those in the metronidazole group.¹³

These findings, together with the frequent intolerance and potential occurrence of peripheral neuropathy caused by metronidazole, have placed ciprofloxacin as a first-line treatment for pouchitis, notwithstanding the rare occurrence of tendon rupture reported in patients receiving ciprofloxacin.

Rifaximin has been used as an alternative treatment for active pouchitis and has also been studied for its ability to maintain remission. In one study rifaximin was shown to maintain remission up to 3 months in 65% of patients who had remission induced with other antibiotics given for 2 weeks.¹⁴

Combination antibiotic therapy has also been studied and has been found to be effective for treating pouchitis. In one study of combination therapy with ciprofloxacin and tinidazole, the antibiotic therapy was shown to be superior, in terms of PDAI reduction, over the administration of oral, enema or suppository of mesalamine.¹⁵

Response to antibiotics has been used to classify patients with pouchitis. Patients are considered to be antibiotic responsive when they have an episode of pouchitis that responds to a 2-week course of antibiotics, and are considered to be antibiotic dependent when the disease requires long-term, continuous antibiotic therapy to maintain remission. Those with antibiotic-resistant pouchitis fail to respond to antibiotics and may require oral or topical 5-aminosalicylates, corticosteroid therapy, or oral immunomodulator therapy,¹⁶ as outlined below.

'Second-line' approach and treatment of chronic pouchitis

As 10–20% of patients with pouchitis may progress to chronic pouchitis, which may be antibiotic dependent or antibiotic resistant, other therapeutic options are

necessary in order to prevent pouch failure and the need for pouch excision or diversion.

Mesalamine-containing preparations

Several uncontrolled reports have suggested that mesalamine, given either in an oral delayed release formulation or in an enema formulation, may be of benefit in treating pouchitis. Given the small size of these reports or series, further properly controlled studies are needed. In cuffitis, when the residual cuff of rectal mucosa is inflamed, mesalamine suppositories appear to relieve symptoms (as well as improving endoscopic and histological findings) of cuffitis.¹⁷

Corticosteroids

There are anecdotal reports regarding the usage of budesonide enemas in the treatment of pouchitis. However, there are not sufficient high quality data to recommend corticosteroids as a standard therapy for pouchitis routinely. These agents are currently reserved as second-line therapy, when antibiotics fail.

Combination of antibiotics

For patients who are antibiotic resistant, the following combinations have been tried in different studies:

1. Rifaximin 2 g/day plus ciprofloxacin 1 g/day, for 15 days, with 89% of the patients achieving either improvement or remission.¹⁸
2. Metronidazole 1 g/day plus ciprofloxacin 1 g/day, for 28 days, with 82% of the patients achieving remission.¹⁹
3. Ciprofloxacin 1 g/day plus tinidazole 15 mg/kg per day, for 4 weeks, with 88% of the patients achieving remission.¹⁵

'Dependent' patients

After achieving remission, many patients become dependent on either antibiotics or, in some cases, on budesonide enemas. This brings up the therapeutic concept of treatment dependence, which may be managed with treatment with either azathioprine or 6-mercaptopurine.

Biological agents

Infliximab has been shown to be effective in a small group of patients with chronic active pouchitis who do not respond to either antibiotics or oral budesonide.²⁰

In a difficult-to-treat subset of patients with pelvic pouches and Crohn's-like complications (namely, pouch fistulae and small bowel stricturing disease, unrelated to surgery), Haveran *et al*²¹ have shown encouraging results with treating pouch fistulising disease with infliximab and stricturing disease or antibiotic-resistant pouchitis with only an immunomodulator (either azathioprine or 6-mercaptopurine).

Figure 3 Diagnostic and treatment algorithm for new onset pouchitis symptoms.

Probiotics

Response to antibiotic therapy supports the hypothesis that bacterial flora are, in some way, contributing to mucosal inflammation. This may be related to the fact that the pouch flora are distinct from normal small intestinal flora, and that the functional nature of the pouch predisposes to altered motility and stasis with resulting bacterial overgrowth. However, the importance of bacterial flora has also led researchers to test probiotics as a ‘forced’ means of altering the pouch bacterial flora. Using VSL #3, a probiotic preparation containing eight different probiotic bacteria strains, has been shown to prevent initial episodes of pouchitis, with only 10% of the patients receiving VSL #3 experiencing pouchitis compared with 40% of patients in the placebo group.²² This treatment was also shown to be effective in maintaining remission

that was achieved with antibiotic therapy, with 15% of patients in the probiotic group relapsing compared with 100% of patients relapsing in the placebo group, up to 9 months.²³

Other treatments

Several other approaches have been tried, including butyrate suppositories²⁴ (based on its nature as being a major colonic mucosal nutrient and contributing to its mucosal barrier) as well as bismuth carbomer enemas,²⁵ but these have yielded insufficient evidence on which to base therapeutic decisions.

Removal of white blood cells from circulation by means of leucocytapheresis has been reported as a potential therapy for patients with active pouchitis.²⁶ Eight patients were treated in an open-label treatment

protocol, six of whom achieved remission with no adverse reactions observed.

All of the above-mentioned treatment modalities were tried in small series and, as a result, drawing conclusions about their potential efficacy is difficult. However, the therapeutic approach should initially involve antibiotics, and should this fail or should the patient become antibiotic dependent, other options may be tried with clearly defined treatment endpoints and careful evaluation of these endpoints in the individual patient.

CONCLUSIONS

Patients with UC who have undergone IPAA very commonly experience a wide variety of symptoms, which may range anywhere from being very mild to very debilitating symptoms necessitating pouch excision and the construction of a permanent ileostomy. The most common complication of the ileal pouch among patients with UC is pouchitis, affecting up to 50% of patients. Notwithstanding its high incidence, the symptoms attributed to pouchitis are rather non-specific and may be attributed to a myriad of diagnoses: surgical, inflammatory as well as functional in nature.

Due to the variety of aetiologies that can result in pouch dysfunction, it is important that endoscopy be performed in order to differentiate between the possible causes of pouch symptoms. Nevertheless, due to the frequently observed rapid response to antibiotics, we would support the approach of empirically treating patients with a change in stool frequency, fecal urgency or abdominal cramps with antibiotics as a first-line approach, in the absence of 'alarm symptoms'. Should more concerning symptoms be present (eg, fever, severe bleeding, pain or weight loss) or should there be no response to treatment with antibiotics within 7–14 days, the patients should undergo a pouch endoscopy and perhaps other imaging studies to rule out other complications such as fistula, abscess, proximal small bowel disease or neoplasia.

Using an algorithm for the classification and management of suspected pouchitis takes into account the severity of inflammation (graded by the activity scores), the cause (primary or secondary) and the course of disease (acute or chronic). Finally, the response to therapy can help direct the physician to resume or change the therapeutic and diagnostic approach to the individual patient. Therefore we propose an evaluation and treatment algorithm (see figure 3).

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