Drugs 2003; 63 (5): 453-461
0012-6667/03/0005-0453/$33.00/0

Diagnosis and Treatment of Patients with Pouchitis

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Contents

Abstract

Pouchitis is the most common long-term complication of ileal pouch-anal anastomosis in patients with underlying ulcerative colitis. Clinical symptoms of pouchitis are not specific, and they can be caused by other conditions such as rectal cuff inflammation and irritable pouch syndrome. Therefore, to make an accurate diagnosis, endoscopic evaluation together with symptom assessment is necessary. Among five available treat-first and test-first strategies, the initial approach with pouch endoscopy without histology was the most cost-effective strategy for the diagnosis of pouchitis. On the basis of clinical course, pouchitis can be classified into acute, relapsing and chronic forms. Pouchitis can also be classified into three categories based on the response to antibacterial therapy: (i) antibacterial-responsive; (ii) antibacterial-dependent; and (iii) antibacterial-resistant. Metronidazole and ciprofloxacin are both effective in treating acute pouchitis. Although antibacterial therapy can induce and maintain remission, probiotics such as VSL#3 can also be used as to maintain clinical remission and prevent relapse in patients with relapsing or chronic pouchitis. For patients with chronic pouchitis that is resistant to antibacterials, therapy with anti-inflammatory agents and immunomodulators is often required.

Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for patients with refractory ulcerative colitis (UC) or UC with dysplasia. The same procedure is also routinely performed in patients with familial adenomatous polyposis (FAP). Although the surgery generally cures UC, complications can occur after IPAA. The most common long-term complication is pouchitis, an inflammatory process of the ileal reservoir (pouch).[1-3] Studies have shown that as many as 24–46% of patients with UC develop at least one episode of pouchitis within 10–11 years after surgery.[3,4] In contrast, the prevalence of pouchitis in patients with underlying FAP ranges from 0 to 10%,[5-9] suggesting that some aspect of the underlying UC predisposes patients to this complication. Risk factors associated with pouchitis include severe underlying UC,[3] backwash il-

eitis,[10] a previous episode of pouchitis,[11] the presence of extra-intestinal manifestations of UC, especially primary sclerosing cholangitis,[4,6] the presence of perinuclear neutrophil cytoplasmic antibodies,[12-14] and evidence of Crohn's colitis.[2,3]

The aetiology and pathophysiology of pouchitis are not entirely clear. The fact that pouchitis almost exclusively occurs in patients with underlying UC, and that it generally responds to antibacterial therapy, suggests an infectious aetiology with a genetic predisposition. Other factors may play a role as well, such as direct and indirect effects of increased microbial load, alterations of innate and acquired immunity, interactions between microbial and host defence factors, and inflammatory bowel disease component of the disease.

Diagnosing and treating patients with pouchitis can be challenging. This paper discusses the approaches associated with each of these aspects of clinical management.

1. Diagnosis

The most frequently reported symptoms of pouchitis are increased stool frequency, faecal urgency, abdominal cramping and pelvic discomfort. Occasionally, patients also develop fever, malaise, bloating, bleeding and extra-intestinal manifestations. However, these symptoms are not specific and can also develop in patients with pouch ischaemia, rectal cuff inflammation, anastomotic stricture, Crohn's disease, proximal jejunal bacterial overgrowth, celiac disease and irritable pouch syndrome (IPS). Moreover, we[15] and others[1,16-19] have noted that these symptoms do not necessarily correlate with objective endoscopic and histologic findings of pouchitis. The lack of correlation between symptoms, endoscopy and histology is difficult to explain. Patients with pouchitis are not a homogenous group and, thus, may manifest different endoscopic and histologic features of their disease. In addition to organic aspect, symptoms in some patients may have a functional component.

There are two ways to approach the symptomatic patients with IPAA, the treat-first strategy and the test-first strategy. In clinical practice, pouchitis is often diagnosed by starting the patient on a diagnostic therapeutic trial of antibacterials (metronidazole or ciprofloxacin). If a patient responds to the trial of antibacterials, a diagnosis of pouchitis is assumed. If not, further evaluation with pouch endoscopy is warranted. Although this treat-first approach has some merits, our previous study has suggested that up to 25% of symptomatic patients are unnecessarily exposed to antibacterials.[15] Moreover, nearly 50% of patients in a series of 61 consecutive symptomatic patients with IPAA did not meet the diagnostic criteria for pouchitis[20] but yet they would have received antibacterials. These results suggest that a relatively large number of patients who are treated empirically based on symptoms alone do not have pouchitis.

The potential problems of empirical antibacterial therapy are well known: (i) increased costs (especially for ciprofloxacin); (ii) adverse effects (peripheral neuropathy, dysgeusia, nausea and vomiting from metronidazole); and (iii) overuse that might contribute to microbial resistance. Furthermore, there may be a placebo effect with antibacterial therapy, especially in patients with IPS. Patients with symptoms caused by proximal jejunal bacterial overgrowth with no pouch inflammation could respond to antibacterial therapy also. In these two latter situations, the response to antibacterials may be erroneously interpreted as confirming the clinical suspicion of pouchitis. Therefore, the diagnosis ideally should be confirmed by pouch endoscopy with or without biopsy.[1,15]

It is reasonable to propose the test-first strategy as an initial approach to the diagnosis of pouchitis. However, there were no universally accepted diagnostic criteria in terms of endoscopy and histology. Attempts have been made to standardise diagnostic criteria. Semi-objective assessments to diagnose pouchitis in patients with IPAA have been proposed using composite scores such as the Pouchitis Triad,[17] Heidelberg Pouchitis Activity Score[21] and Pouchitis Disease Activity Index (PDAI).[22] Each of these diagnostic instruments consists of three components - clinical symptom, endoscopy and histology. Although it has not been statistically

Table I. The 18-point pouchitis disease activity index (PDAI)[22]a

Criteria	Score
Clinical	
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
Faecal urgency or abdominal cramps	
none	0
occasional	1
usual	2
Fever (temperature >37.8°C)	
absent	0
present	1
Endoscopic inflammation	
Oedema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucoid exudate	1
Ulceration	1
Acute histological inflammation	
Polymorphic nuclear leucocyte infiltration	
mild	1
moderate + crypt abscess	2
severe + crypt abscess	3
Ulceration per low-power field (mean)	
<25%	1
25–50%	2
>50%	3

a Pouchitis was defined as a total PDAI score ≥7.

validated, the PDAI is the most commonly used diagnostic instrument.[15,17,23-29] An overall PDAI score is calculated from three separate six-point scales for clinical symptoms, endoscopic findings and histological changes (table I). Patients with a total PDAI score of seven or higher are diagnosed with pouchitis.[22] The PDAI includes multiple clinical symptoms of pouchitis, and measures endoscopic and acute histological inflammation scores continuously. These changes allow a diagnosis of pouchitis to be made in patients with symptoms of mild or moderate disease severity.[17,30,31] Despite its merits, the PDAI has been mainly used as a research tool. It has not yet been incorporated into routine clinical practice because of the cost for the pouch endoscopy with histological evaluation, the complexity in calculating PDAI scores and the time delay in determining histology score.

We and others[14] have noted that a combination of symptom and endoscopic evidence of mucosal inflammation may obviate the need for biopsy and histological evaluation in most symptomatic patients. This prompted us to determine how much the histology score in the PDAI contributes to the sensitivity and specificity of the diagnostic instrument. We found that omitting endoscopic biopsy and histological evaluation was justifiable, and that it did not compromise the diagnostic sensitivity or specificity, with an area under the receiver-operating characteristic curve of 0.995, compared with the standard PDAI.[32] We therefore proposed a 12-point modified PDAI (mPDAI) consisting of symptom and endoscopy scores without biopsy and histology. Of symptom (from 0 to 6) and endoscopy (from 0 to 6) scores, a total mPDAI score of greater than or equal to 5 meets the criteria for the diagnosis of pouchitis. Avoiding the need for biopsy and histological evaluation shortens the procedure time, reduces costs and provides immediate, on-site calculation of mPDAI scores. Thus, the patient is able to receive appropriate therapy without delay.[32] The mPDAI was further validated by application to our previous randomised, clinical trial. In a study of 16 patients with acute pouchitis diagnosed by the 18-point PDAI with a cut-point of 7, all patients (n = 7) in the ciprofloxacin group and six patients (67%) in the metronidazole group responded to the antibacterial therapy, with response defined as a reduction of PDAI score of 3 or more. When we applied the 12-point mPDAI and defined response as a reduction of mPDAI score of 2 or more, to the same study pop-

ulation, the response rates in both groups was the same.

Ideally, pouchitis should be diagnosed on the basis of combined assessment of symptoms, endoscopic and histological evaluation. However, this approach ($US352) may not be cost-effective compared with the treat-first approach. Omission of histological evaluation (cost of histological evaluation = $US85) from the PDAI in the mPDAI instrument would reduce the cost of the test-first approach by 40%. Our data suggest that the mPDAI works just as well as the traditional PDAI in terms of diagnostic accuracy, however, we wanted to ensure that the latter was cost effective. Thus, we conducted a cost-effectiveness analysis to compare five available diagnostic strategies: (i) a diagnostic trial of metronidazole; (ii) a diagnostic trial of ciprofloxacin; (iii) a diagnostic trial of metronidazole and ciprofloxacin; (iv) pouch endoscopy with biopsy using the PDAI; and (v) pouch endoscopy without biopsy using the mPDAI.[32] The pouch endoscopy without biopsy strategy was the most cost-effective approach.[33] The merit of this strategy is that it avoids diagnostic delays and promotes timely initiation of appropriate medical therapy. In the future, there may be new, non-invasive and more cost-effective ways, such as biomarkers, to diagnose pouchitis. On the other hand, in patients with chronic refractory pouchitis, the pouch endoscopy with biopsy together with stool and serological studies is recommended to exclude rare causes such as *Clostridium difficile* or cytomegalovirus infection, Crohn's disease and celiac disease.

2. Classification

Once a patient is diagnosed with pouchitis, it is important to accurately classify the disease because the classification will affect the treatment strategy. For example, treatment regimens for acute and chronic pouchitis are different. Most patients with acute pouchitis respond quickly to antibacterial therapy, whereas patients with chronic pouchitis frequently have less favourable responses.

Evolution of thought on the diagnosis as well as pathogenesis of pouchitis has parallels with that in inflammatory bowel disease in general. With improved understanding of the natural history of pouchitis, pouchitis can be categorised using a classification system that is used with other forms of inflammatory bowel disease: (i) idiopathic versus secondary, based on aetiology; (ii) remission versus mildly, moderately or severely active, based on disease activity; (iii) acute (≤4 weeks of symptoms) versus chronic (>4 weeks of symptoms), based on symptom duration; (iv) infrequent episodes versus relapsing versus continuous course, based on disease patterns; and (v) responsive versus refractory, based on the response to treatment.[30]

Patients with symptoms can be classified as having either structural disease or functional disease. Of the structural diseases, celiac disease, Crohn's disease, cytomegalovirus infection, and proximal jejunal bacterial overgrowth should be excluded. Not all patients with symptoms have pouchitis. Symptomatic patients with IPAA may have structural disease (such as pouchitis) or functional disease, a condition resembling irritable bowel syndrome. In our previous study of 61 consecutive symptomatic patients with IPAA,[20] patients could be classified into three large categories: pouchitis (50.8%), rectal cuff inflammation or cuffitis (6.6%), and IPS (42.6%), based on combined evaluation of symptom, endoscopy and histology.[20] There was an overlap of symptoms among patients with pouchitis, cuffitis and IPS. Endoscopic evaluation could differentiate the three groups. Typically patients with IPS had no endoscopic and histological inflammation of the ileal pouch or rectal cuff, despite having symptoms suggestive of pouchitis. The aetiology, pathogenesis, and clinical features and outcomes of this newly defined syndrome warrant further study.

On the basis of the clinical course, pouchitis can be divided into acute, relapsing and chronic forms. We can also classify patients with pouchitis into three categories according to their response to antibacterial therapy: (i) antibacterial-responsive;

(ii) antibacterial-dependent; and (iii) antibacterial-resistant. Patients with antibacterial responsive pouchitis normally have an acute course with infrequent flare-ups of symptoms, which quickly (within 2 weeks) respond to antibacterial therapy. Patients with antibacterial-dependent pouchitis typically have frequent flare-ups of symptoms (e.g. >4 flare-ups per year), especially when they try to taper their use of antibacterials. However, their symptoms also quickly responded to a short-course (e.g. 2 weeks) of full-dose antibacterial therapy. These patients often require long-term, low-dose antibacterial therapy as maintenance therapy or frequent pulse administration of a course of full-dose antibacterials. Patients with antibacterial-resistant pouchitis typically have a chronic course and frequently do not respond to the routine, single-agent, short-course (e.g. 2 weeks) antibacterial therapy. Their disease course sometimes mimics ulcerative proctitis or Crohn's disease. Topical or oral mesalazine (mesalamine; 5-aminosalicylate) or corticosteroid agents have been used. Some of the patients may require immunomodulators, such as 6-mercaptopurine (mercaptopurine) and azathioprine or infliximab.[34]

3. Treatment

The treatment of pouchitis is largely empirical. Uncontrolled trials have reported that many treatments are beneficial, including amoxicillin/clavulanic acid, erythromycin, tetracycline, mesalazine enemas, corticosteroid enemas, and oral sulfasalazine and mesalazine, oral corticosteroids, allopurinol, azathioprine and bismuth salicylate. However, there is a paucity of randomised, clinical trials for pouchitis. In addition, definition, disease pattern, disease course and measurement of the outcomes of treatment vary in the published trials.

For acute pouchitis, metronidazole and ciprofloxacin are the two most commonly used antibacterials. Metronidazole is the first antibacterial to have been studied in one of a few randomised clinical trials. Madden et al.[35] performed a crossover trial in which 11 patients with active pouchitis received a 1-week course of oral metronidazole 1200 mg/day and then a 1-week course of placebo. The overall response rate was 73% for metronidazole compared with 9% for placebo ($p < 0.05$). On the basis of such results, and the low cost of metronidazole, this agent at a dose of 15–20 mg/kg/day has generally been used as first-line therapy for pouchitis.[1-3,9]

However, some patients develop adverse effects from metronidazole such as nausea, vomiting, metallic taste, dysgeusia, peripheral neuropathy or seizure. In addition, metronidazole is contraindicated in patients who use alcohol because of its antabuse effect.[1,36]

If patients do not respond to or cannot tolerate metronidazole, second-line therapy should be considered. Second-line therapy generally consists of broad-spectrum antibacterials, such as ciprofloxacin, tetracycline, clarithromycin, amoxicillin/clavulanic acid, doxycycline or rifaximin.[4,26,37] In clinical practice, ciprofloxacin with a dose of 500–1500 mg/day is the most commonly used therapy. Sequential therapy with metronidazole then ciprofloxacin (if the patient does not respond to metronidazole) has been shown to be effective in a non-controlled trial.[38] In a small, non-controlled study, 8 of 11 patients (94%) with pouchitis who did not respond to or could not tolerate a 7-day course metronidazole 750 mg/day responded to a 7-day course of ciprofloxacin 1000 mg/day.[38] Ciprofloxacin has been shown to be efficacious in treating chronic pouchitis when combined with rifaximin (the latter is not available in the US).[23] It also has a favourable adverse effect profile.

In our randomised, clinical trial of 16 patients with acute pouchitis (defined as disease duration ≤4 weeks), both ciprofloxacin 1000 mg/day for 2 weeks and metronidazole 20 mg/kg/day for 2 weeks significantly lowered total symptom, endoscopic and histological PDAI scores. However, when compared with the metronidazole group, patients in the ciprofloxacin group experienced significantly larger reductions in mean total PDAI scores, symptom subscores and endoscopy subscores. The difference in reduction of pre- to post-treatment total PDAI scores between the two

groups was 3.2. None of the patients in the ciprofloxacin group experienced adverse effects, whereas three patients in the metronidazole group (33%) developed nausea, vomiting, dysgeusia or transient peripheral neuropathy.[26] These results suggest that: (i) both ciprofloxacin and metronidazole are efficacious in treating acute pouchitis in that they significantly reduced the total PDAI scores, and significantly improved clinical symptoms and endoscopic and histological scores; and (ii) ciprofloxacin is more efficacious and less toxic. Therefore, despite a higher cost, ciprofloxacin should also be considered as first-line therapy.

Acute pouchitis can also be treated with budesonide enema. In a 6-week, double-blind, controlled trial of budesonide enema 2mg/100ml at bedtime and oral metronidazole 1000 mg/day in 26 patients with acute pouchitis, both groups significantly improved as measured by reductions in their PDAI scores. Fifty-eight percent of patients in the budesonide group and 50% of patients in the metronidazole group experienced a reduction in their PDAI scores by three or more points ($p > 0.05$). However, adverse effects were frequently observed, 25% in the budesonide group and 57% in the metronidazole group.[29] Because of its cost and similar efficacy to metronidazole, budesonide enema may be used as an alternative therapy for metronidazole and ciprofloxacin for patients with acute pouchitis.

Patients who respond to a 2-week course of antibacterials can be considered as having antibacterial-responsive pouchitis if they do not have frequent flare-ups (e.g. interval between flare-ups >3 months). Most patients with acute pouchitis respond promptly to antibacterial therapy, but 5–19% develop refractory or rapidly relapsing symptoms that require protracted therapy.[39-41] Of the patients with acute pouchitis, 39% have a single acute episode that responds to treatment with antibacterials, whereas the remaining 61% of patients go on to develop at least one recurrence.[6] Treatment and prevention of relapsing pouchitis and chronic pouchitis are often challenging. Those patients often require frequent antibacterial treatment to keep the disease in remission, either with a low-dose maintenance therapy or with a full-dose pulse therapy.

Several topical agents have been tried in patients with relapsing and chronic pouchitis. In a randomised clinical trial of 40 patients with relapsing pouchitis, the overall response rate in the bismuth carbomer enema group after 3 weeks of treatment was the same as the placebo group: 45%. The odds ratio for response to bismuth carbomer enemas was 1.00 (95% CI 0.29–3.42).[25] Therefore, bismuth carbomer foam enemas are not effective therapy for chronic active pouchitis. Short-chain fatty acids and glutamine are essential nutrients for the enterocytes. A randomised clinical trial evaluated 19 patients with chronic pouchitis and found that relapse rates after a 3 weeks of treatment were 67% (6/9) in patients receiving glutamine suppositories compared with 40% (4/10) in those receiving butyrate suppositories ($p > 0.05$).[42] There is no difference between glutamine and butyrate suppositories for maintaining remission in patients with chronic pouchitis. Unfortunately, the trial was not placebo-controlled.

It is interesting to note that probiotics appear to be effective in preventing flare-ups of pouchitis. A randomised, double-blind, placebo-controlled trial evaluated the use of a probiotic named VSL#3®**1** (Yovis, Sigma-Tau, Pomezia, Italy) at a dose of 6 g/day containing 5×10^{11}/g of viable lyophilised bacteria of four strains of *Lactobacillus*, three *Bifidobacterium* spp. and *Streptococcus salivarius thermophilus* for the maintenance of relapsing pouchitis after remission was induced using ciprofloxacin and rifaximin.[24] During the 9-month trial of 40 patients with relapsing pouchitis (defined as ≥3 relapses per year), only 3 of 20 patients (15%) in the probiotic group relapsed within the 9-month follow-up, whereas all 20 patients (100%) in the placebo group relapsed.[24] During probiotic treatment, faecal concentrations of *Lactobacillus*, *Bifidobacterium* and *Streptococcus salivarius* increased by 10^2–10^6 colony-forming units/g stool

1 Use of tradenames is for identification purposes only and does not imply endorsement.

dry weight, with no change in other commensal bacteria. Probiotics may help maintain remission in patients with pouchitis by: (i) suppressing resident pathogenic bacteria; (ii) stimulating mucin glycoprotein production by intestinal epithelial cells; (iii) preventing adhesion of pathogenic strains to epithelial cells; and (iv) inducing host immune responses.[37] Preventing relapse of pouchitis using non-toxic, physiological bacteria is a significant clinical advance. However, the efficacy and potential adverse effects should be validated in a large, randomised clinical trial. According to author's experience, the dosage of VSL#3® should be individualised because some patients may experience adverse effects such as constipation, bloating and gas.

For patients with chronic pouchitis, especially those with features of Crohn's disease, management is even more challenging. These patients usually do not respond to routine, 2-week course, full-dose, single-agent antibacterial therapy. In a non-randomised study of 18 patients with chronic antibacterial-resistant (defined as symptom duration >4 weeks despite a single-agent 4-week course antibacterial), combination therapy with ciprofloxacin 1000 mg/day and rifaximin 2000 mg/day was used. Sixteen patients (89%) experienced improved symptoms (n = 10) or went into remission (n = 6).[43] In a recent open label trial,[44] 82% (36/44) of patients with relapsing pouchitis or chronic pouchitis, who received a combination therapy of ciprofloxacin 500mg twice daily and metronidazole 500mg twice daily for 4 weeks, were able to achieve remission.

Topical and oral mesalazine (e.g. Rowasa® enema 4g twice daily, Canasa® suppository 500mg twice daily, oral Asacol® 3.6–4.8 g/day) and corticosteroid (e.g. Cortiform® 1 application twice daily, budesonide enema 2mg/100ml at bedtime) therapy to induce the remission can also be tried. To maintain remission, long-term maintenance therapy with topical or oral mesalazine, oral 6-mercaptopurine or azathioprine is a reasonable approach. For patients with evidence of Crohn's disease involving the ileal pouch, such as pouch-vaginal fistula, treatment with infliximab (a chimeric monoclonal antibody to human tumour necrosis factor α) can be useful. In a retrospective study, seven patients with Crohn's disease of the pouch received up to four infliximab infusions at a dose of 5 mg/kg and clinically improved. Six patients achieved complete response defined as cessation of fistula drainage and total closure of all fistula(s) or cessation of diarrhoea, incontinence and abdominal pain. One patient achieved partial response. The median time interval from start of inliximab therapy to complete symptomatic clinical response was 5 weeks. After a median observation period of 13.4 weeks, no relapses had occurred among the six patients with initial complete response. Of note, all patients received immunosuppressive therapy with methotrexate, 6-mercaptopurine or azathioprine to maintain the remission.[34]

6-Mercaptopurine and azathioprine are the two most commonly used immunosuppressive agents in maintenance therapy in patients with inflammatory bowel disease. Although 6-mercaptopurine and azathioprine have not been studied in patients with pouchitis, they can be used in patients with chronic, antibacterial-resistant pouchitis according to our anecdotal experience. The starting dose for both medicines is 50mg/day, with a similar target dose to that in Crohn's disease and UC, i.e. 1.5mg/kg/day for 6-mercaptopurine and 2.5mg/kg/day for azathioprine. Close monitoring of blood counts and liver function tests is required. Long-term therapy is often needed. The clinical value of periodic monitoring of 6-mercaptopurine metabolites and estimating thiopurine methyltransferase activity in patients with pouchitis has not been established.

Because of the paucity of data from randomised controlled trials, clinicians should start patients with a diagnosis of acute pouchitis on antibacterials. If patients respond to the antibacterial therapy and have infrequent relapses (for example, ≤4 flare-ups in a 12 month period), they can be treated with the same antibacterial. If patients initially respond to the antibacterial therapy but have fre-

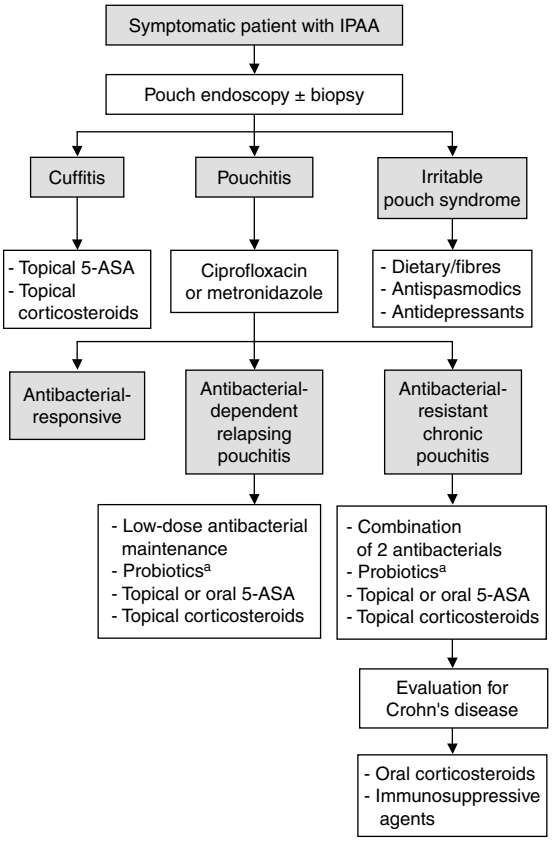

Fig. 1. Algorithm for the diagnosis and treatment of pouchitis. **a** VSL#3®. **5-ASA** = mesalazine or 5-aminosalicylate; **IPAA** = ileal pouch-anal anastomosis.

quent flare-ups, which require frequent courses of antibacterial therapy or a low-dose antibacterial as a maintenance therapy, a trial of probiotics, such as VSL#3®, with individualised dosage is a reasonable alternative. Of note, a variety of probiotics are available. All probiotics are not equivalent in quality and quantity of bacteria. Only VSL#3® has been studied in patients with pouchitis. If patients have chronic pouchitis that is resistant to routine single-agent antibacterial therapy, a combination of two antibacterials can be tried. If remission can be achieved with the combination therapy, probiotics may be used to maintain the remission. If patients with chronic pouchitis show evidence of Crohn's disease, immunomodulatory therapy, such as infliximab and azathioprine, may be beneficial. An algorithm for the diagnosis and treatment of pouchitis has been developed (figure 1).

4. Conclusions

Diagnosis and medical therapy of pouchitis can be challenging. Endoscopy together symptom assessment is required to make accurate diagnosis of pouchitis. Ciprofloxacin and metronidazole are effective in treating patients with acute pouchitis. To maintain remission after successful antibacterial therapy for patients with relapsing pouchitis, probiotics may be helpful. Immunomodulators may be required for patients with chronic pouchitis, especially those with features of Crohn's disease.

Acknowledgements

This manuscript in supported by an American College of Gastroenterology Clinical Research Grant.

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