

Pouchitis: Treatment dilemmas at different stages of the disease

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Abstract

Pouchitis is a frequent complication in ulcerative colitis patients after proctocolectomy with ileal pouch–anal anastomosis. It is an unspecific inflammation of the pouch with unknown aetiology. First-line treatment for acute and chronic pouchitis is antibiotics. Some cases of severe chronic refractory pouchitis may benefit from biological treatment. Anti-tumour necrosis factor should be recommended as the first option, leaving the new biologicals for multirefractory patients. Permanent ileostomy may be an option in severe cases, after failure of medical treatment. Prophylaxis therapy with a probiotic mixture is recommended after the first episode of pouchitis, whereas it is not clear whether probiotics are useful for all patients after surgery. Here, we present a case report and review the treatment options in different forms of pouchitis.

Keywords

Ulcerative colitis, pouchitis, probiotics, antibiotics, anti-TNF

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Case report

A 40-year-old man underwent proctocolectomy with ileal pouch–anal anastomosis (IPAA) for refractory ulcerative colitis (UC), maintaining remission for 3 years after surgery. At this point, he developed abdominal pain and around 15 loose bloody stools per day. Pouch endoscopy and histopathological analysis were consistent with pouchitis (Figure 1). Antibiotics, probiotics, budesonide and infliximab were given with no response; adalimumab was then started and symptoms were controlled with this drug for 3 years. After that, clinical relapse motivated adalimumab intensification, without response; therefore, the patient swapped to vedolizumab. Since the patient has always refused permanent ileostomy, he has recently started ustekinumab therapy, being aware of the lack of strong evidence regarding its efficacy.

Diagnosis

Despite advances in medical treatment for UC, between 6 and 15% of patients eventually require surgery due to refractory disease, dysplasia or colorectal cancer (CRC).¹ Proctocolectomy with IPAA has been considered the first-line surgical treatment since 1989²

and pouchitis is the most frequent complication, affecting almost one-half of patients within 5 years after surgery.³ Pouchitis is an unspecific inflammation of the ileal reservoir whose pathogenesis is still unknown. In order to diagnose pouchitis, clinical manifestations, as well as compatible endoscopic and histological findings, are required.⁴ After proctocolectomy with IPAA, patients usually have four to eight bowel movements, and about 700 cc of soft or liquid stool every day, compared with lower rates in healthy subjects. The most typically reported symptoms of pouchitis are watery diarrhoea, abdominal pain or cramps, tenesmus, urgency, faecal incontinence, fever and, less frequently, extraintestinal manifestations.⁵ Patients can also report rectal bleeding, but this is more often related to cuffitis than to pouchitis. Nevertheless, this clinical setting is not specific to pouchitis, and this is why the diagnosis

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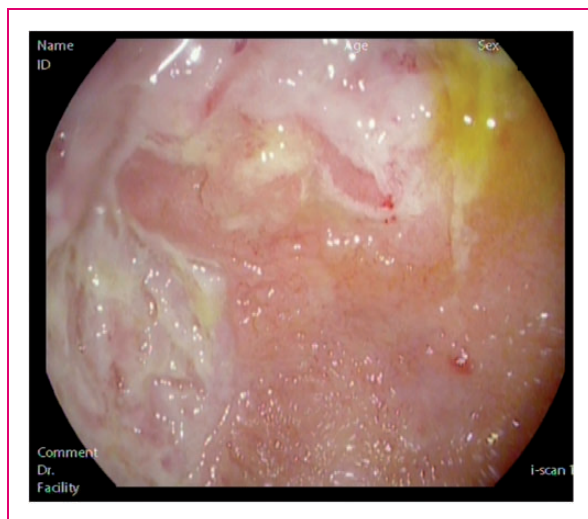


Figure 1. Endoscopic image of pouchitis.

has to be confirmed by endoscopic and histological abnormalities, allowing us to rule out other entities such as irritable pouch syndrome or concurrent surgery-related mechanical conditions. Pouch endoscopy should include not only the careful examination of the pouch, but also the afferent ileal limb, the anastomosis and the rectal cuff (if present). Taking into account the fact that some patients develop a stenosis of the pouch–anal anastomosis, doctors usually choose a gastroscope to perform the endoscopy, due to its flexibility and reduced diameter.⁶ The main endoscopic features of pouchitis include erythema, oedema, friability, haemorrhage, absent vascular pattern, erosions and ulcerations. Small ulcers confined to the anastomosis are frequent, but they do not necessarily establish the diagnosis of pouchitis or Crohn's disease.⁷ Thus, this area should be avoided when taking biopsies as its foreign-body granulomas can be misunderstood as Crohn's disease of the pouch. In spite of the normal appearance of the mucosa and according to some experts, we recommend that biopsies are taken from the pouch and the afferent limb, in order to distinguish between pouchitis and Crohn's disease, Citomegalovirus (CMV) infection, ischaemia and dysplasia.

Microscopic findings of pouchitis include chronic and acute inflammation changes such as villous atrophy, crypt distortion and chronic inflammatory infiltrates, together with crypt abscesses, mucosal ulceration and neutrophilic infiltrates.⁸

There are different diagnostic criteria for pouchitis, but the most widely used index is the Pouchitis Disease Activity Index (PDAI) (Table 1), which includes clinical, endoscopic and histological parameters. A modified index without histological criteria has been developed (mPDAI) due to the PDAI's

Table 1. Pouchitis Disease Activity Index.

Variable	Score
1. Clinical criteria	
Postoperative stool frequency	
Usual stool frequency	0
One to two stools/day more than is postoperatively usual	1
Three or more stools/day than is postoperatively usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Faecal urgency or abdominal cramping	
None	0
Occasional	1
Usual	2
Fever (temperature $\geq 38^{\circ}\text{C}$)	
No	0
Yes	1
2. Endoscopic criteria	
Oedema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucosal exudate	1
Ulcerations	1
3. Histological criteria	
Polymorphonuclear infiltration	
Mild	1
Moderate and crypt abscess	2
Severe and crypt abscess	3
Ulceration due to a field with low increase	
<25%	1
25–50%	2
>50%	3

Pouchitis is defined as Pouchitis Disease Activity Index ≥ 7 .

complexity in clinical practice. Both indices have high correlations with each another, and both PDAI ≥ 7 and mPDAI ≥ 5 establish a diagnosis of pouchitis.^{9,10}

Natural history of pouchitis

Multiple studies suggest that the first episode of pouchitis most probably occurs in the first year following surgery. The course of pouchitis may be similar to that of UC, since it can appear as a chronic condition characterized by continuous inflammation that displays episodic symptomatic exacerbations. In some patients, it can also be limited to one isolated episode or very infrequent flares.

Table 2. Risk factors associated with pouchitis.

Extraintestinal manifestations
Thrombocytosis
Long duration of ileal pouch–anal anastomosis
Non-smoker
Primary sclerosing cholangitis
Anti-neutrophil cytoplasmic antibodies
Postoperative non-steroidal anti-inflammatory drug usage

The condition may be classified into distinct entities depending on its evolution. Regarding the duration of symptoms, it is classified as acute (<4 weeks) or chronic (>4 weeks), and regarding its course, pouchitis can be infrequent (less than three episodes per year), recurrent (more than three episodes per year) or continuous. After a single episode of acute pouchitis, 39% of patients will respond to antibiotic treatment without recurrence while 61% will have at least one recurrent episode.¹¹

Several studies have identified different risk factors for pouchitis. Thus, smoking has been pointed out as a risk factor for acute pouchitis, while it seems to protect against chronic pouchitis. Some clinical factors related to chronic pouchitis are extraintestinal manifestations,^{12,13} an elevated platelet count and a long duration of IPAA¹⁴ (Table 2).

According to the response to antibiotics, patients are divided into responsive (good response), dependent (need for maintenance therapy) or refractory (no response) groups. Previous studies have shown that refractory or frequently relapsing pouchitis appears in 5–19% of patients with acute pouchitis.

Considering the aetiology, pouchitis is classified as idiopathic or secondary to infections (e.g. CMV or *Clostridium difficile*), surgical complications, non-steroidal anti-inflammatory drug intake or other autoimmune conditions (e.g. primary sclerosing cholangitis or Crohn's disease of the pouch).

The cumulative probability of pouch failure, and consequently the need for definitive ileostomy and excision of the pouch, ranges from 3–15% in large series. This often occurs due to refractory pouchitis.¹⁵

Pouchitis may be complicated by fistulae, abscesses and stricture of the pouch–anal anastomosis. Another important complication is the development of a pouch neoplasia, which is defined by the appearance of low- or high-grade dysplasia, or CRC at the anal transitional zone, cuff, pouch body or afferent limb.^{4,16} In the Cleveland Clinic, a study of 3203 patients with IPAA revealed cumulative incidences of pouch neoplasia of 1.3 and 5.1% at 10 and 25 years after surgery, respectively.¹⁷

The presence of pre-colectomy dysplasia or CRC has been shown to increase the risk of getting pouch

Table 3. Patients who need regular surveillance.

Pre-colectomy colon dysplasia or colorectal cancer
Primary sclerosing cholangitis
Family history of colorectal cancer
Chronic pouchitis
Chronic cuffitis
Crohn's disease of the pouch

neoplasia by 4- and 25-fold, respectively. This hazard is also raised in patients with concomitant primary sclerosing cholangitis, a family history of CRC and chronic pouch inflammation secondary to different entities (e.g. chronic pouchitis). The best management and surveillance strategies in these patients remain uncertain, but the performance of regular surveillance biopsies of the pouch may be recommended⁶ (Table 3). This strategy is recommended even in patients with mucosectomy, since it does not avoid the risk of pouch neoplasia.¹⁸ The efficacy of surveillance is not clear in cases of low-grade dysplasia. Wu et al. have reported that it may be recommended to take biopsies in these patients at 3–6-month intervals. If dysplasia disappears, it could be reasonable to lengthen this periodicity from several months to 1 year, but if the patient has risk factors for progression, surgical intervention may be needed.¹⁹

Treatment dilemmas

Should a first pouchitis episode be prevented after surgery?

Due to the high risk of developing pouchitis after IPAA, a great dilemma for gastroenterologists is to decide whether prophylaxis treatment will be necessary in all patients after surgery. In a well-designed trial of probiotics for primary prevention of pouchitis, 40 patients were randomized to a specific probiotic mixture with eight bacterial strains that included Lactobacilli (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii ssp. bulgaricus*), Bifidobacteria (*Bifidobacterium longum*, *B. breve* and *B. infantis*), and *Streptococcus thermophilus* or placebo. Of the patients treated with this probiotic mixture (currently called De Simone formulation), 10% developed pouchitis after 12 months, compared with 40% of the placebo-treated group (risk ratio (RR) 1.5, 95% confidence interval (CI) 1.02–2.1), and their quality of life was also better.²⁰

The same probiotic mixture was evaluated in an open-label randomized study in 31 pouchitis patients, comparing it with a group of patients without any treatment. Despite no new case of pouchitis appearing in the patients undergoing treatment, there was no

statistically significant difference (RR 1.10, 95% CI 0.89–1.36) because the rate of pouchitis in the control group was very low (8%).²¹

Regarding conventional drugs, an uncontrolled retrospective study with sulfasalazine 2g showed efficacy. After 68 months, pouchitis developed in 15% of patients on sulfasalazine in comparison with 64.5% not taking any drug.²²

With these results, and as figures from the probiotic mixture trial have not been replied and other drug studies are not of high quality, prophylaxis in all patients cannot be recommended. A recommendation could be to treat only patients with a high risk of pouchitis after surgery with a probiotic mixture.

How to treat acute pouchitis?

Antibiotics are the first-line treatment for acute pouchitis, with response rates near to 80%. Both metronidazole and ciprofloxacin are effective in pouchitis patients. However, randomized trials are scarce. Only one head-to-head study has compared these two antibiotics. Over 14 days, 16 patients were randomized for ciprofloxacin 1g/day ($n=7$) or metronidazole 20mg/kg/day ($n=9$). PDAI scores improved with both antibiotics, but were more significant in those that had been treated with ciprofloxacin ($p=0.002$). Regarding specific items like symptom and endoscopic scores, again the benefits were higher with ciprofloxacin ($p=0.03$). Another important finding of the study was observed regarding adverse events, because while no patients in the ciprofloxacin group were referred, those one in three metronidazole-treated patients reported adverse events.²³ Other antibiotic agents, including amoxicillin-clavulanic acid and rifaximin, have been also investigated and showed some effect in case series with a limited number of patients. Despite some positive results with probiotic mixtures and budesonide, in our opinion, these treatments are only recommended in cases of intolerance or non-response to antibiotics.⁴

Is prophylaxis treatment necessary after a first pouchitis episode?

Between 7 and 20% of patients who suffer a first pouchitis episode will relapse and develop chronic pouchitis. This is the reason why prophylaxis treatment with a probiotic mixture that includes *Lactobacilli* (*L. casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii* ssp. *bulgaricus*), *Bifidobacteria* (*B. longum*, *B. breve* and *B. infantis*) and *Streptococcus thermophilus* is indicated. Robust data have come from a randomized controlled trial performed in 40 patients who achieved remission with antibiotics, and were randomized to a probiotic mixture (dose of 6g/day) or placebo for 9 months for

the prevention of new episodes. All patients treated with placebo presented a new episode, while only 15% of those treated with the probiotic mixture developed chronic pouchitis.²⁴ Compatible results were reported in a very similar trial performed with the same probiotic mixture.²⁵ A joint analysis of both studies that included 76 patients showed that 85% of patients who received the probiotic mixture maintained remission compared with only 3% treated with placebo (RR 20.24, 95% CI 4.28–95.81).²⁶ In open-label studies, the response rates to probiotic mixtures were not as high as in the randomized controlled trials. In a study of 31 patients with antibiotic-dependent pouchitis, who received a probiotic mixture as maintenance therapy after the induction of remission with ciprofloxacin, 81% had stopped the probiotic at 8 months because of a lack of efficacy or adverse effects.²⁷ Different options like rifaximin or mesalamine did not show similar efficacy, so in all patients we recommend the use of a probiotic mixture after a first episode of pouchitis in order to prevent new episodes.

What is the treatment for chronic pouchitis?

Treatment with a combination of antibiotics for ≥ 4 weeks is the chosen next step in patients who do not responded to 2-week treatment with an antibiotic. Ciprofloxacin with metronidazole or rifaximin is the most recommended combination, based on well-designed studies that showed high rates of response (around 80%), but also increased risk of adverse effects due to prolonged use of antibiotics. Another problem is that a percentage of patients who respond initially can them lose their ability to respond and become antibiotic-dependent. In such cases, other therapies should be evaluated.²⁸

In cases with an absence of response to antibiotic combination, the next step is to change this treatment to locally active steroids. An open study of 20 patients showed remission in 75% of patients treated with a high dose of budesonide (9mg) for 8 weeks, together with improved quality of life. Beclomethasone dipropionate, at a higher dose than is usual (10mg daily) for 8 weeks, was also effective in another open-label study in antibiotic-refractory patients.²⁹

Do immunosuppressive or biological drugs play a role in chronic refractory pouchitis?

Due to an absence of data about the use of thiopurines or methotrexate for the treatment of chronic refractory pouchitis, we cannot recommend these drugs in such patients. Regarding cyclosporine, despite some cases having being treated with enemas, evidence is too scarce to recommend its use in clinical practice.

Regarding biological therapy, anti-tumour necrosis factor (TNF) drugs have been more frequently evaluated. In the absence of clinical trials, as with other drugs regarding chronic refractory pouchitis, open series have shown their potential utility in these patients. First reports of data from a small case series with infliximab were optimistic, with high short-term remission rates, but two larger series published from Ferrante et al. and Barreiro-de Acosta et al. have shown that after 1 year, response rates were around 50%.^{30,31} Data with adalimumab have been limited to

patients who have failed infliximab, and after 1 year of treatment with this drug, 50% had avoided permanent ileostomy.³² In cases of pouchitis with anti-TNF treatment failure, vedolizumab and ustekinumab have shown efficacy in recent case series and, in our opinion, are alternative options in order to avoid permanent ileostomy.^{33,34}

In Figure 2, we propose an algorithm for the treatment of pouchitis. Despite all these treatment options, around 25% of patients will still require permanent ileostomy.³⁵

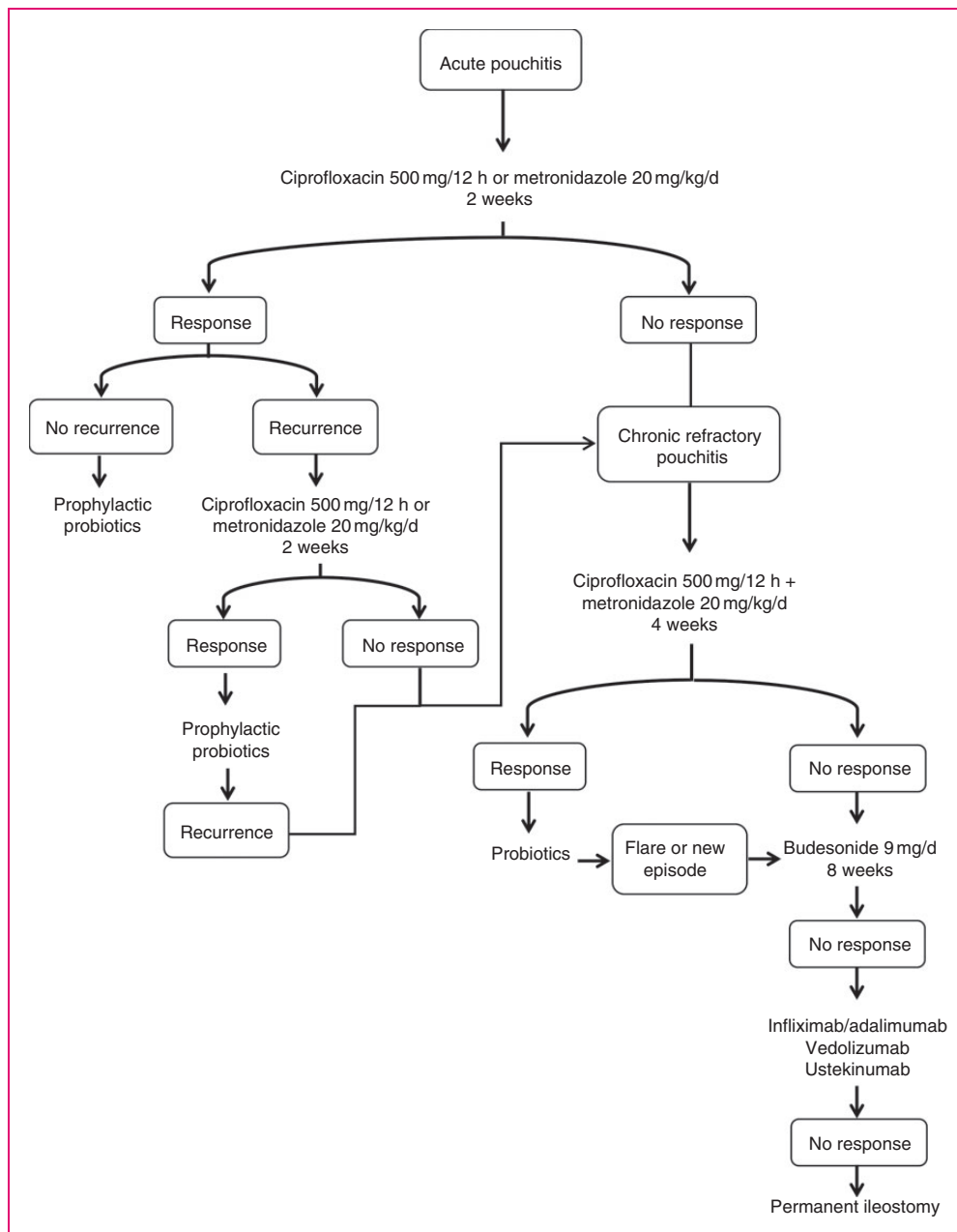


Figure 2. Treatment algorithm for pouchitis.

Conclusions

In our opinion, pouchitis treatment represents one of the biggest gaps of knowledge in inflammatory bowel disease treatment, fundamentally due to a lack of well-designed studies because of the heterogeneity of patients and their limited numbers per centre. More specific studies are needed; until they become available the following of expert opinion recommendations from physicians with significant expertise remains a good option.

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Declaration of conflicting interests

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