Pouchitis in inflammatory bowel disease: a review of diagnosis, prognosis, and treatment

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Patients with inflammatory bowel disease (IBD) occasionally need a restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) because of medically refractory colitis or dysplasia/cancer. However, pouchitis may develop in up to 70% of patients after this procedure and significantly impair quality of life, more so if the inflammation becomes a chronic condition. About 10% of patients with IBD who develop pouchitis require pouch excision, and several risk factors of the failure have been reported. A phenotype that has features similar to Crohn’s disease may develop in a subset of ulcerative colitis patients following proctocolectomy with IPAA and is the most frequent reason for pouch failure. In this review, we discuss the diagnosis and prognosis of pouchitis, risk factors for pouchitis development, and treatment options for pouchitis, including the newer biological agents. (Intest Res 2021;19:1-11)

Key Words: Pouchitis; Pouch failure; Inflammatory bowel disease; Crohn disease; Colitis, ulcerative

INTRODUCTION

In patients with inflammatory bowel disease (IBD), surgical intervention is sometimes required due to medically refractory colitis or development of dysplasia/cancer. A restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is a standard procedure for those with severe and refractory colitis. The 10-year colectomy rate of patients with ulcerative colitis (UC) was reported as approximately 10% to 30% in the Western world and less than 10% in Asia, and the incidence of colectomy has declined after the introduction of biological treatments. However, inflammation of this reservoir (“pouchitis”) can develop in up to 70% of patients after the surgery, and the incidence of pouch failure requiring diversion ileostomy or pouch excision was reported in up to 10%. Furthermore, even in patients originally diagnosed with UC, 10% of patients can be diagnosed with Crohn’s disease (CD) of the pouch.

In this review, we discuss the diagnosis and prognosis of pouchitis, risk factors for pouchitis development, and treatment options for pouchitis, including the newer biological agents.

CLINICAL COURSE AND DIAGNOSIS OF POUCHITIS

Pouchitis is classified as acute or chronic pouchitis. Acute pouchitis is defined as symptoms lasting less than 4 weeks and responding to 2-week courses of antibiotics. Chronic pouchitis is defined as having symptoms lasting longer than 4 weeks despite standard antibiotic courses and requiring chronic antibiotics or anti-inflammatory therapy. Approximately 10% to 15% of patients with acute pouchitis develop chronic pouchitis which has subgroups such as antibiotic-dependent and antibiotic-refractory pouchitis.

The diagnosis of pouchitis is based on the combined assessment of symptoms, endoscopic, and histologic findings.
Sandborn et al.\textsuperscript{9} proposed the pouchitis disease activity index (PDAI), consisting of not only the score of clinical symptoms, but also endoscopic and histological scores. A later study suggested that the omission of histological scores from PDAI (modified PDAI) can offer similar diagnostic accuracy when compared with the PDAI for patients with acute pouchitis.\textsuperscript{10} The most frequently reported symptoms of pouchitis are increased bowel movement frequency, urgency, abdominal cramping, and pelvic discomfort.\textsuperscript{10} However, these symptoms are not specific for pouchitis, as following conditions could share these symptoms:\textsuperscript{11} infections including cytomegalovirus (CMV) and\textit{Clostridioides difficile}, pouch-outlet obstruction, anal sphincter or pelvic floor dysfunction, decreased pouch compliance or emptying, pouch or anastomotic stricture, CD of the pouch,\textsuperscript{12} immune-mediated pouchitis,\textsuperscript{13} cuffitis,\textsuperscript{14} irritable pouch syndrome,\textsuperscript{15} and small intestinal bacterial overgrowth.\textsuperscript{14,16,17} To rule out other differential diagnoses as described above, serum or stool tests, imaging studies, and functional tests should be considered. Serum or tissue CMV polymerase chain reaction and stool tests including \textit{C. difficile} toxins assay are helpful to exclude infections. Contrast X-ray of the pouch (“pouchogram”) are useful to assess pouch compliance, emptying, strictures, and fistulas. Pelvic magnetic resonance imaging should be performed if fistulas would be suspected. When fecal incontinence is the primary symptom, especially in the absence of pouch inflammation, anorectal manometry and/or anal ultrasound are indicated to diagnose anal sphincter or pelvic floor dysfunction.\textsuperscript{12} A subgroup of patients with pouchitis has concurrent immune-mediated conditions including primary sclerosing cholangitis (PSC), seropositivity for immunoglobulin G4 (IgG4) or perinuclear antineutrophil cytoplasmic antibody (pANCA), and infiltration of IgG4-expressing plasma cells in the pouch mucosa.\textsuperscript{13} Hence, serum markers of autoimmune diseases including IgG4 or pANCA might be beneficial to identify underlying autoimmune in patients with pouchitis. If all these tests including pouchoscopy are negative, irritable pouch syndrome or small intestinal bacterial overgrowth would be considered.

Diagnostic strategy for pouchitis is described in Fig. 1. If patients with proctocolectomy and IPAA have symptoms suggestive of pouchitis, pouchoscopy should be recommended. Although there are no standard strategies of proactive monitoring for asymptomatic patients with IBD, postoperative pouchoscopy is suggested based on findings from a study showing that approximately 50% of asymptomatic UC patients have abnormal endoscopic pouch findings.\textsuperscript{17} A recent study also showed that mucosal breaks including ulcers and/or erosions were observed in about 20% of asymptomatic patients and were associated with an increased risk of acute pouchitis.\textsuperscript{18} Hence, pouchoscopy is an essential procedure to confirm the diagnosis of pouchitis.

During pouchoscopy, it is important for providers to define the endoscopic phenotype of the J pouch based on the observation of different anatomic areas of the J pouch: the afferent

\textbf{Fig. 1.} Diagnostic strategy for pouchitis. *Pouchitis disease activity index (PDAI) includes these variables. IPAA, ileal pouch-anal anastomosis; CMV, cytomegalovirus; \textit{C. difficile, Clostridioides difficile}; PCR, polymerase chain reaction; MRI, magnetic resonance imaging; IgG4, immunoglobulin G4, pANCA, perinuclear antineutrophil cytoplasmic antibody.
limb, inlet, tip of the J, proximal and distal pouch, anastomosis, rectal cuff, anal canal, and perianal area (Fig. 2). For instance, in patients with CD of the pouch, the afferent limb would have endoscopic inflammation including stricture or the perianal area might have fistula. Such phenotype would have a high risk of pouch removal and intensive treatment with careful monitoring are required to improve its prognosis. Persistent inflammation in a strip of rectal cuff is also a major complication in IBD patients treated by proctocolectomy with IPAA and cuff biopsies are helpful to diagnose cuffitis.

Furthermore, pouchoscopy with biopsy focusing on the rectal cuff should be recommended in patients with preoperative neoplasia of the colon and/or rectum. Although there are no consensus guidelines for endoscopic surveillance for pouch neoplasia, patients undergo surveillance pouchoscopy every 1–3 years at the discretion of the IBD specialists in some institutions. There is an unmet need to investigate whether endoscopic activity of pouchitis may be a “target to treat” even in asymptomatic patients and which endoscopic phenotypes of the J pouch can affect the prognosis. The standard proactive monitoring of pouch inflammation and surveillance of pouch neoplasia must be established for IBD patients after proctocolectomy with IPAA.

The rate of pouch failure requiring diversion ileostomy or pouch excision has been reported to be as high as 10% and several risk factors contributing to the failure have been reported (Table 1). Manllich et al. identified 4 factors that contributed to pouch failure at the Cleveland Clinic (Cleveland, OH, USA): (1) completion proctocolectomy, (2) handsewn anastomosis, (3) CD diagnosis on postoperative histopathology, and (4) diabetes. However, a multicenter cohort analysis of these factors did not show the suitable performance for clinical practice. This validation study showed that only handsewn anastomosis contributed to pouch survival and found ileo-anal anastomotic leakage and CD of the pouch, which were not included in the Cleveland Clinic study, were strongly associated with pouch failure.

Pelvic sepsis including anastomotic leakage, abscess, and fistula can be developed in up to 20% of UC patients treated by proctocolectomy with IPAA. Fazio et al. described pelvic sepsis as an independent risk factor of pouch failure. Previous studies demonstrated that the rate of anastomotic leak or abscess in patients with handsewn anastomoses was significantly higher than those with stapled anastomosis. However, a meta-analysis did not show any significant difference in the rate of pelvic sepsis, anastomotic leak, and pouch-related fistula between the 2 groups.

CD of the pouch can develop in a subset of UC patients treated by proctocolectomy with IPAA and is the most frequent reason for pouch failure and excision. A recent meta-analysis showed that, among 4,843 patients with an IPAA for UC or indeterminate colitis, 10.3% of patients were diagnosed with CD of the pouch. Although a uniform definition of CD of the pouch is still lacking, the most commonly reported diagnostic criteria were (1) presence of fistula/fistulae, (2) stricture

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**Table 1. Predictive Factors of Pouch Failure**

| Factor                                                      | Reference |
|--------------------------------------------------------------|-----------|
| Handsewn anastomosis                                         | Handsewn anastomosis |
| Pelvic sepsis                                                | Pelvic sepsis |
| CD of the pouch                                               | CD of the pouch |
| Preoperative CD diagnosis (intentional IPAA creation)         | Preoperative CD diagnosis (intentional IPAA creation) |
| Postoperative CD diagnosis based on the pathological findings of colectomy samples (incidental IPAA creation) | Postoperative CD diagnosis based on the pathological findings of colectomy samples (incidental IPAA creation) |
| Preoperative *Clostridiodes difficile* infection              | Preoperative *Clostridiodes difficile* infection |

CD, Crohn’s disease; IPAA, ileal pouch-anal anastomosis.
involving the pouch or pre-pouch ileum, and (3) presence of pre-pouch ileitis. Shen et al. demonstrated that 16% of patients with CD of the pouch developed pouch failure in a median of 6 years after ileostomy takedown. Patients diagnosed with CD before colectomy (intentional IPAA) and those with UC or indeterminate colitis whose diagnosis was revised to CD based on the pathological findings of colectomy specimens (incidental IPAA) have a risk of pouch failure. A recent meta-analysis showed that the pouch failure rate in CD patients with intentional and incidental IPAA was significantly higher compared to UC (odds ratio [OR], 2.48; 95% confidence interval [CI], 1.25–4.92 and OR, 8.53; 95% CI, 3.21–22.66, respectively). 

C. difficile infection is the most common nosocomial pathogen responsible for severe colitis and frequently complicated with IBD. Previous studies found that C. difficile infection before colectomy does not increase the risk of the development of pouchitis but can be associated with poor pouch outcomes. Lightner et al. showed that the rate of pouchitis was not significantly different between UC patients with pre-operative C. difficile infection and those without. However, patients with pouchitis who had been exposed to C. difficile infection prior to colectomy were more likely to require anti-tumor necrosis factor (TNF) drugs and diverting ileostomy, and pouch excision.

**RISK FACTORS FOR THE DEVELOPMENT OF POUCHITIS**

Previous studies have reported factors contributing to the development of pouchitis (Table 2). Extraintestinal manifestations of IBD are associated with increased likelihood of the development of chronic pouchitis. About 2% to 7.5% of patients with UC may have co-existent PSC, a chronic cholestatic syndrome of unknown cause characterized by fibrosing obliteration of the bile ducts. The presence of PSC increases the risk of acute and chronic pouchitis and is an independent risk factor for the development of pouchitis. The cumulative risk of pouchitis at 10 years after IPAA was 79% for UC patients with PSC and 46% for those without. Backwash ileitis, which is frequently observed in UC patients with PSC, is reported as a considerable risk of developing chronic pouchitis. A later prospective study showed the incidence of acute or chronic pouchitis did not differ significantly between patients with backwash ileitis and those without. The relationship between backwash ileitis and the development of pou-

**Table 2. Factors Related to the Development of Pouchitis**

| Factors                                                                 | Comments                                                                 |
|------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Primary sclerosing cholangitis (PSC)                                   | PSC increases the risk of acute and chronic pouchitis.                   |
| Backwash ileitis                                                       | Backwash ileitis was reported as a considerable risk of developing chronic pouchitis. A later prospective study showed the incidence of acute or chronic pouchitis did not differ significantly between patients with backwash ileitis and those without. |
| Smoking                                                                | A retrospective study showed that smoking cessation may increase the risk of pouchitis. A prospective study has demonstrated that current or prior history of smoking can increase the risk of acute pouchitis but be protective against the development of chronic pouchitis. A meta-analysis showed the odds of pouchitis development was not significantly lower in smokers compared with non-smokers. |
| Extensive colitis                                                      | Pancolitis was reported to be directly related to the development of chronic pouchitis. Case-control studies showed extensive colonic disease was associated with increased risk for both acute and chronic pouchitis. |
| Male sex                                                               | Male patients were found to have an increased risk for chronic pouchitis. |
| Antineutrophil cytoplasmic antibody (ANCA)                             | A meta-analysis showed the risk of chronic pouchitis was higher in ANCA-positive patients, but the risk of acute pouchitis was unaffected by ANCA status. |
| Histologic findings of colectomy samples                              | The combination of the degree of mononuclear cell infiltration (MNCI), segmental distribution of MNCI, and eosinophil infiltration in the resected total colon had a utility to predict the development of chronic pouchitis. |
| 3-Stage ileal pouch-anal anastomosis (IPAA)                            | A multicenter, retrospective cohort study of pouchitis in pediatric ulcerative colitis showed that 3-stage IPAA may increase the risk of pouchitis. |
| Nonsteroidal anti-inflammatory drugs (NSAIDs)                          | NSAIDs was reported to increase the risk of pouchitis. Case-control studies showed postoperative use of NSAIDs was a risk factor for chronic pouchitis and possibly for acute pouchitis. |
TREATMENT OF POUCHITIS

1. Acute Pouchitis
The mainstay of the treatment for acute pouchitis was antibiotics, including ciprofloxacin, metronidazole, or rifaximin. A small randomized controlled study found that ciprofloxacin achieved a greater reduction in the PDAI and was better tolerated than metronidazole. Hence, ciprofloxacin is recommended as first-line treatment. The concentrated probiotic mixture VSL#3 was also reported to prevent acute pouchitis developed within the first year after surgery. A double-blind, placebo-controlled study showed that patients treated with VSL#3 had a significantly lower incidence of acute pouchitis (10%) compared with those with placebo (40%).

2. Chronic Pouchitis
To treat chronic pouchitis, a combination of oral antibiotics, budesonide, topical tacrolimus, or beclomethasone dipropionate are available. Once in remission from chronic pouchitis, VSL#3 can help to maintain remission. Two double-blind, placebo-controlled studies have demonstrated that VSL#3 is effective to maintain remission after induction with combination antibiotic therapies. If a combination of oral antibiotics fail to induce or maintain remission, oral or topical mesalamine, corticosteroids, anti-TNF drugs including infliximab and adalimumab are shown to be effective for chronic pouchitis. According to a recent meta-analysis regarding the efficacy of anti-TNF therapy on chronic refractory pouchitis, the rates of short-term (8 weeks) and long-term (12 months) clinical remission were 0.10 (95% CI, 0.00–0.35) and 0.37 (95% CI, 0.14–0.62), respectively. Vedolizumab, a novel humanized IgG1 monoclonal antibody against α4β7 integrin, can be safe and effective in the management of chronic pouchitis. Vedolizumab acts by suppressing intestinal inflammation through inhibition of leukocyte trafficking to the digestive tract. A recent meta-analysis evaluated the efficacy of anti-TNF therapy in distinguishing patients with chronic antibiotic-refractory pouchitis from those with CD of the pouch. In this study, CD of the pouch was defined as the presence of non-anastomotic fistula and/or stenosis and/or significant pre-pouch ileitis. Anti-TNF therapy had higher and faster efficacy in patients with CD of the pouch.

Vedolizumab and ustekinumab can be effective therapy for CD of the pouch.
zumab demonstrated that the proportion of patients with CD of the pouch who achieved a clinical response was 48.9% at 12 months after starting vedolizumab. The proportion of endoscopic response at 6 months was 53.6% in CD of the pouch. For ustekinumab, a retrospective multicenter study found that the rate of clinical and endoscopic response 6 months after ustekinumab induction was 83% and 60%, respectively (Table 3, Fig. 3).

**SUMMARY AND FUTURE DIRECTIONS**

Pouchitis can frequently develop in patients with IBD after creation of an IP AA and significantly impair quality of life. In this article, we reviewed the diagnosis, prognosis, and treatment of pouchitis in IBD patients.

However, much remains uncertain in our clinical intervention of pouchitis in patients with IBD. Studies to improve
Pouch outcomes are essential and, as presented in this review, could begin with investigating a proactive monitoring protocol. Since the pouch inflammation can be identified by pouchoscopy even in asymptomatic patients, we need to investigate endoscopic activity as a proactive target to treat pouchitis. Furthermore, though previous studies demonstrated that CD of the pouch is a poor prognostic factor in IBD patients, the definition of CD of the pouch is still controversial and further studies should be warranted to characterize this phenotype. The detailed assessment of endoscopic findings in each anatomical area of the J pouch would be helpful to understand which endoscopic phenotypes may be associated with the J pouch prognosis. Such an analysis may provide meaningful information to clarify which endoscopic findings should be a target to improve outcomes. Endoscopic phenotyping of the J pouch might also be useful for future research to understand the pathogenesis of heterogeneous types of pouchitis in IBD patients, which in turn may improve therapeutic options.💋

Overall, our experiences with pouchitis—its diagnosis, prognosis, and treatment—are growing and so should our efforts to standardize screening protocols, classification, and treatment of this type of IBD.

ADDITIONAL INFORMATION

Funding Source
The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest
Rubin DT has received grant support from Takeda, and has served as a consultant for Abbvie, Abgenomics, Allergan Inc., Boehringer Ingelheim Ltd., Bristol-Myers Squibb, Celgene Corp/Syneos, Check-cap, Dizal Pharmaceuticals, GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, Ichnos Sciences S.A., GlaxoSmithKline Services, Janssen Pharmaceuticals, Lilly, Narrow River Mgmt, Pfizer, Prometheus Laboratories, Reistone, Shire, Takeda, and Techlab Inc. Akiyama S and Rai V report no conflicts of interest.

Rubin DT is an editorial board member of the journal but did not involve in the peer reviewer selection, evaluation, or

Fig. 3. Treatment strategy for pouchitis. PO, per os; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor.
decision process of this article. No other potential conflicts of interest relevant to this article were reported.

**Author Contribution**

Conceptualization: Akiyama S, Rubin DT. Investigation: Akiyama S, Rai V. Supervision: Rubin DT. Writing - original draft: Akiyama S. Writing - review & editing: Akiyama S, Rai V, Rubin DT. Approval of final manuscript: all authors.

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