

NEERAJ NARULA

MD, MPH, FRCPC



Neeraj Narula is currently an Associate Professor of Medicine at McMaster University and Staff Gastroenterologist at Hamilton Health Sciences, with a clinical and research focus in Inflammatory Bowel Diseases (IBD). He also serves as Director of the IBD clinic at Hamilton Health Sciences and Director of the IBD fellowship for McMaster University. During the course of his career, he has published over 120 peer-reviewed articles and 4 book chapters and he has received over \$3 million in research funding and grants. His advanced training includes Present-Levison Advanced Inflammatory Bowel Diseases Fellowship at Mount Sinai Hospital (New York, NY) and Masters of Public Health at Harvard TH Chan School of Public Health (Boston, MA). He has been an invited speaker at several international congresses including Digestive Diseases Week (American Gastroenterology Association), European Crohn's and Colitis Organization Conference, United European Gastroenterology Week, and Ontario Association of Gastroenterology Annual Meetings.

Affiliations:

Department of Medicine, Division of Gastroenterology, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON

Management of Pouchitis: **Clinical Pearls for the Gastroenterologist**

Introduction

Ileal pouch anal anastomosis (IPAA) is a surgical procedure conducted in patients with ulcerative colitis (UC) with medically refractory disease; in patients with the autosomal dominant inherited disease familial adenomatous polyposis (FAP); or in patients who have experienced dysplasia/colon cancer. The procedure aids in the management of these diseases, improves patients' quality of life, prevents the need for a permanent stoma, and reduces the risk of colorectal cancer. A common complication from IPAA is pouchitis, which is characterized as an idiopathic non-specific inflammation within the created pouch resulting in symptoms including increased frequency of bowel movements and abdominal pain. Pouchitis is much more common in patients treated for UC (up to 60%) than in those receiving treatment for other indications (0-10%).¹ This might be due to immune activation or dysbiosis in these patients.

Normal anatomy and function of a J pouch

The IPAA consists of an ileal-anal anastomosis and the creation of an ileal reservoir, the pouch, which is situated near the original space of the rectum.² The reservoir pouch is created by connecting the ileum to the anus to bypass the removed colon. Three types of pouches (J, S or W) can be created; they vary in shape. The most commonly used ileal pouch is the J pouch. This structure has improved storage and emptying function compared to the S and W pouch structures. The J pouch is created by folding two 15-20 cm loops of the ileum and stapling or sewing these together, after which the internal walls are removed to create a shape resembling the letter J. Most patients will have an average of five-six bowel movements per day after the IPAA, and one-two nocturnal bowel movements, and for patients who previously had medical refractory UC, this often is an improvement from their prior symptoms resulting in

enhanced quality of life. Pouch function has generally been reported as stable over the long term; however, complications may arise.

Pouchitis

Pouchitis is the most common long-term complication of the IPAA procedure. There are various presentations of pouchitis, and risk factors and characteristics vary. Therefore, treatment may depend on the type of pouchitis present in the patient.

Acute pouchitis lasts less than or equal to four weeks, while chronic pouchitis is characterized as pouchitis with a duration of more than four weeks. Chronic pouchitis can be classified as antibiotic-dependent or antibiotic-refractory based on the response to antibiotics treatment. Patients with chronic antibiotic-dependent pouchitis generally have continued relapses despite using antibiotics multiple times per year (at least three courses). Patients who continue to experience symptoms and have inflammation characteristics of the pouch, despite multiple courses of antibiotics and other treatments, are categorized as having chronic antibiotic-refractory pouchitis (CARP), which is the most challenging form to manage.

Diagnosis

Patients with increased urgency and stool frequency, blood in the stool, abdominal pain, extra-intestinal manifestations involving joints, eyes, skin, and liver, and/or fever, may have pouchitis. As these symptoms may also indicate other diagnoses, diagnostic procedures should include a pouchoscopy evaluation with biopsy. An activity score can be determined based on subjective information on symptoms obtained from patients and the objective data obtained from the pouchoscopy and histopathology determined from biopsies. The most used and validated scoring system for pouchitis is the Pouchitis Disease Activity Score (PDAI).³ Pouchitis is defined as a PDAI score of seven or higher. Although used within clinical trials, it has not been routinely adapted in clinical practice due to subjectivity in pouchoscopy interpretation and nuances in histology reporting. More recently, the Atlantic pouchitis index (API) has been suggested as a new way to assess endoscopic and histologic disease activity, which includes the simple endoscopic score for Crohn's disease and the Robarts histopathology index. The API has been shown to be reliable but needs to be validated in other datasets.⁴

Differential diagnosis

The differential diagnosis for symptoms that may indicate pouchitis are:

Inflammatory

- Cuffitis, which is defined as residual inflammation of the rectal cuff
- Infectious diarrhea, e.g., as caused by cytomegalovirus (CMV) or *Clostridium difficile*
- Crohn's-like phenomenon of the pouch

Mechanical/Structural

- Afferent and efferent limb syndromes
- Irritable pouch syndrome
- Pouch ischemia
- Pouch stenosis
- Pelvic floor dysfunction
- Adhesions
- Neoplastic complications (often in the cuff)

Dysmotility

- Impaired pouch emptying
- Bile salt malabsorption
- Pouch stricture

Treatment

Acute pouchitis

Clinical studies assessing the optimal treatment strategies for acute pouchitis have been limited in number and generally consist of small cohorts, resulting in low quality of evidence. The majority of treatments focus on treating the potential underlying bacterial dysbiosis. The most common antibiotics prescribed are ciprofloxacin, rifaximin, and metronidazole. While all three medications can be effective, ciprofloxacin generally has better outcomes as it is better tolerated by the majority of patients.^{1,5} Biopsies have shown that antibiotics reduce the number of bacteria in the pouch that may be responsible for the inflammation. For example, ciprofloxacin has been shown to reduce *Clostridium perfringens* and *Escherichia coli*, while metronidazole reduced *C. perfringens* but not *E. coli*.² The majority of patients experience improvements in symptoms after one or two days of antibiotic treatment. Therefore, first-line therapy should consist of a two-week antibiotics treatment protocol for the first episode. In patients with multiple episodes or symptoms returning quickly after completion of an antibiotics course, a longer course (≥ 4 weeks) or an alternative antibiotic class could be

considered. Approaches may include to first assess the efficacy of ciprofloxacin 500 mg twice/day and if not tolerated, consider metronidazole 500 mg twice/day. Some case studies have also shown responses to tinidazole, doxycycline, erythromycin, tetracycline, rifaximin, and the combination of amoxicillin and clavulanic acid (clavulin), but the quality of evidence around these antibiotics is low.⁶

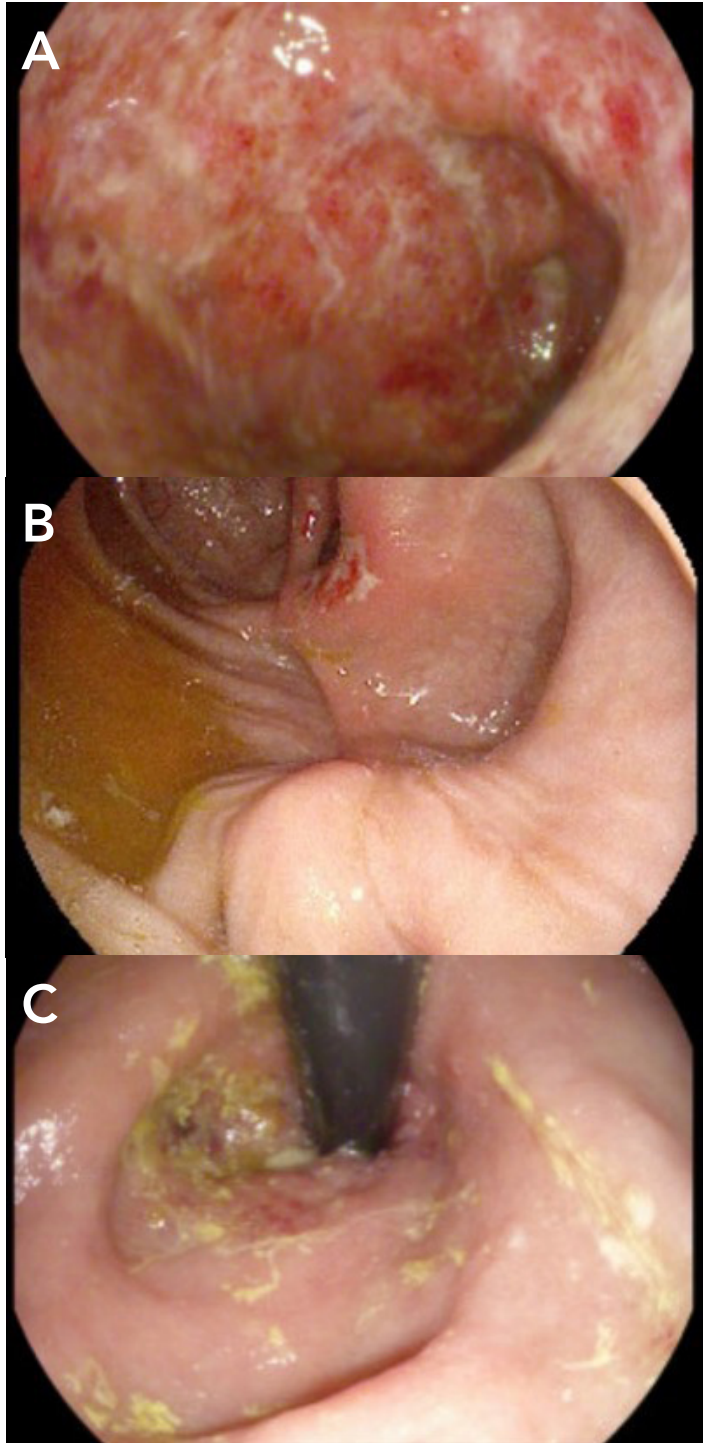


Figure 1. Pouchoscopy examples of A) Classic pouchitis; B) Ischemic pouchitis; and C) Cuffitis; courtesy of Neeraj Narula, MD

The use of probiotics has been shown to have potential as a prophylaxis to prevent pouchitis or to maintain remission following antibiotics. This is due to their alteration of the pouch flora. The most studied and most commonly-used probiotic treatment is VSL #3[®] (Alfasigma, Covington, LA), which has been shown to induce a remission rate of 85% over a median follow-up of one year.⁷ The mechanism of action of this treatment is a restoration of the bacterial and fungal balance in the pouch, as treatment results in an increase in bacterial and fungal diversity. Biopsy samples of patients treated with VSL #3 contain higher concentrations of *Lactobacilli spp*, *Bifidobacterium spp* and *E. coli*. Currently, the data does not support the use of probiotics as first-line therapy.

Treatment with 5-aminosalicylic acid (5-ASA) has been suggested for pouchitis;⁸ however, patients with cuffitis might benefit from this strategy to the greatest extent with the use of topical 5-ASA suppositories.⁹ The use of steroids can be considered in patients who are unable to tolerate antibiotics. Two clinical studies with small cohorts have demonstrated beneficial effects with budesonide (oral or enema), resulting in remissions, lower PDAI scores and endoscopic improvements.^{10,11}

Chronic pouchitis

Whether chronic pouchitis is antibiotic-dependent or refractory, escalation of therapy should be considered.

For patients who do not respond to initial antibiotics, a prolonged course (e.g. 4 weeks) or dual combined antibiotics can be provided. Dual antibiotics may consist of ciprofloxacin (500 mg twice/day) combined with metronidazole (500 mg twice/day) or rifaximin (550 mg twice/day).¹² Trials of antibiotics in other classes (some examples provided above) should be considered at least once or twice as well before exploration of other agents, such as biologics (discussed below).

Chronic antibiotic-dependent pouchitis

Patients who have continuing relapses despite antibiotics multiple times per year, are considered to have chronic antibiotic-dependent pouchitis and require long-term maintenance therapy. Those on maintenance treatment who lose response may benefit from rotating antibiotics in 1-3 week intervals (e.g. switching between metronidazole, ciprofloxacin, and rifaximin). These patients may also benefit from probiotics as a maintenance approach.

Chronic antibiotic-refractory pouchitis

Patients who do not respond to induction antibiotics

treatment and probiotics are considered as having CARP, which requires long-term maintenance therapy. This condition is difficult to manage. Secondary causes of pouchitis should be reconsidered (**see Differential Diagnosis**). Steroids could be considered for this group of patients and patients should be monitored for steroid-associated adverse events.¹² Budesonide has been assessed in small studies that showed 75% of patients had remission in response to this therapy, and could be considered in highly selected patients, such as those with primary sclerosing cholangitis-associated pouchitis and enteritis.^{12,13} Betamethasone has also been assessed in a small study, resulting in an 80% remission rate.¹⁴ Therefore, this strategy could be attempted for eight weeks in patients with antibiotic-refractory pouchitis.

Limited data is available regarding biologics for treatment in these patients, but those who respond to induction therapy with biological agents should receive those as maintenance treatment.¹² Vedolizumab is a monoclonal antibody directed at integrin $\alpha4\beta7$ which has undergone testing in patients with chronic antibiotic-refractory pouchitis. A meta-analysis assessing 15 clinical studies with a total of 311 patients demonstrated that vedolizumab treatment achieved endoscopic improvement in 61.2% of patients.¹⁵ A recent randomized, controlled, Phase 4 clinical trial assessed vedolizumab in 102 patients (51 of these received treatment). Sustained remission was achieved in 27.5% of patients, and endoscopic results revealed that treatment with vedolizumab resulted in reductions in the occurrence of ulcers. The treatment was well-tolerated.¹⁶ In the meta-analysis cited above, the anti-TNF α antibody infliximab reported endoscopic remission in 70.3% of patients.¹⁵ Adalimumab, also a TNF α inhibitor, was studied in a randomized, controlled trial in 13 patients (6 patients received treatment). Total PDAI improved in 100% of patients on treatment.¹⁷ Ustekinumab is an antibody directed at IL-12 and IL-23, which has been used in smaller clinical studies. A retrospective study of 24 patients revealed clinical responses in 50% of patients, and endoscopic data showed a reduction in ulcers in the majority of assessable patients.¹⁸ Larger randomized controlled trials are necessary to determine the optimal biologic for this patient cohort.

Other agents that have been used for maintenance therapy in CARP are immunomodulators, such as mercaptopurine and azathioprine. Limited published evidence for this treatment is available, but these strategies may benefit patients with immune-mediated pouchitis.¹² Furthermore, some case reports and case studies have suggested the use of topical ciclosporin or tacrolimus as treatment options for CARP.¹²

Future directions include FMT and diet

Given the implied importance of the microbiome in pouchitis, other strategies to alter the microbiome composition are being investigated. Fecal microbiota transplantation (FMT) is gaining attention for various conditions, having shown efficacy for *Clostridium difficile* infections. Few studies have assessed the use of FMT in chronic pouchitis. A meta-analysis revealed a lack of effectiveness, but the studies included were heterogeneous in their study design, had differences in the delivery of the fecal transplant, included few patients, and diagnostic criteria for pouchitis also varied, making the interpretation of studies challenging.¹⁹ A current Phase II randomized controlled trial investigates FMT once a week for six weeks in patients with active pouchitis (NCT03545386). Other options to improve the microbiome composition focus on diet. It has been shown that patients who consume more fruit in the first year after IPAA surgery have a reduced chance of pouchitis and have increased microbial diversity.²⁰ A small study assessing the elemental diet suggested that it may improve pouchitis symptoms in some patients but has limited effect at inducing remission.²¹ Therefore, further studies into the effect of diet on the microbiome in pouchitis are warranted.

Clinical Pearls

- All pouch problems are not necessarily pouchitis, think of other inflammatory/infectious/ischemic causes, structural causes, and dysmotility
- Proper evaluation of pouch problems requires proper endoscopic evaluation (often with sedation) as well as imaging (pouch-gram, MRE) to rule out alternative problems.
- Ischemia of the pouch can mimic pouchitis in its appearance but it usually manifests in the distal pouch and has a clear margin of demarcation or ulceration
- Cuffitis is best managed with suppositories targeting the site of inflammation. Suppository treatments to be considered are 5-aminosalicylic acid, hydrocortisone, and the immunosuppressant tacrolimus (calcineurin inhibitor).
- Inflammation in the afferent limb is not always an indication of Crohn's disease. A section of 10 cm of mild disease/aphthous ulcers in the afferent limb manifests in some instances of pouchitis. In these cases, antibiotics should be attempted before escalating to therapies used to manage Crohn's disease.
- Inflammation and ulceration along the staple line may not resolve and typically are asymptomatic. Familiarity with the anatomy of a pouch can allow the identification of patients with staple line/ischemic ulcers who are frequently asymptomatic and do not require management with therapy.

Conclusions

Use of colectomy with ileal-anal pouch anastomosis and J-pouch formation remains necessary for the management of certain patients, including those with medically refractory UC. Pouchitis is a common complication for patients with a pouch, and antibiotic therapy remains a mainstay of treatment in acute pouchitis. Response to manipulation of the microbiome with antibiotics provides clues into the pathogenesis of pouchitis, and further studies are needed to understand the role of other strategies of microbial manipulation (e.g. FMT, diet). Patients with chronic antibiotic-dependent or refractory pouchitis are candidates for advanced therapy including biologics, although the overall quality of evidence remains low.

Correspondence:

Neeraj Narula

Email: neeraj.narula@medportal.ca

Financial Disclosures:

Speaking/advising fees: Janssen, Abbvie, Takeda, Pfizer, Merck, Sandoz, Fresenius Kabi, Innomar, Iterative Scopes, Bristol Myers Squibb, Viatrix and Ferring

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