Management of acute and chronic pouchitis

AUTHOR: Bo Shen, MD, AGAF, FACG, FASGE
SECTION EDITOR: Sunanda V Kane, MD, MSPH
DEPUTY EDITOR: Kristen M Robson, MD, MBA, FACG

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INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is performed for treating patients with ulcerative colitis (UC) or familial adenomatous polyposis (FAP). However, patients with IPAA are at risk for pouchitis, an inflammatory disorder that typically presents with increased stool frequency and urgency and is a common complication of IPAA or a continent ileostomy (eg, Kock pouch).

The focus of this topic is management of acute pouchitis and chronic pouchitis. The epidemiology, pathogenesis, clinical manifestations, and diagnosis of pouchitis are discussed in detail, separately. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis".)

Surgical management of UC is discussed separately. (See "Surgical management of ulcerative colitis".)

Management of FAP is discussed separately. (See "Familial adenomatous polyposis: Screening and management of patients and families".)

Surgical complications and outcomes associated with proctocolectomy and IPAA are discussed separately. (See "Restorative proctocolectomy with ileal pouch-anal anastomosis: Laparoscopic approach".)

SPECTRUM OF DISEASE

Pouchitis and other ileal pouch disorders (eg, cuffitis) have been classified based on disease characteristics (eg, duration of symptoms, response to antibiotics, pattern of activity, etiology). Classification of pouch disorders is supported by consensus guidelines from the International Ileal Pouch Consortium and is discussed in more detail separately [1]. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Spectrum of disease'.)

Many patients with ileal pouches have some degree of endoscopic inflammation of the ileal pouch reservoir, and pouchitis likely represents a disease spectrum with a range of presentations that may evolve over time. As an example, acute antibiotic-responsive pouchitis may evolve into chronic antibiotic-refractory pouchitis.

TREATMENT GOALS

The goal of therapy is to alleviate symptoms and achieve clinical and endoscopic remission by demonstrating mucosal healing. Histologic improvement (ie, resolution of acute inflammatory cell infiltrate) is emerging as an additional component of disease remission [2,3].

Assessing treatment response for patients with pouchitis includes recognizing that the normal stool pattern for patients with an ileal pouch is four to seven formed stools daily without seepage, and typically without nocturnal bowel movements.

Endoscopic healing is an important goal of therapy because symptoms alone may not reflect the inflammatory status of the pouch [2,4-6]. However, the definition of mucosal healing varies among clinical studies. For example, endoscopic mucosal healing has been defined as completely normal mucosa [7], the absence of erosions or ulcers [8], or Pouchitis Disease Activity Index (PDAI) endoscopy subscores of 0 or 1 as well as no ulcers [9]. The PDAI and other scoring systems are described separately. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Scoring systems for assessing disease activity'.)

PRIMARY PREVENTION

For primary prevention of pouchitis and to promote optimal pouch function, patients with an ileal pouch are advised to:

- Avoid nonsteroidal antiinflammatory drugs (NSAIDs) because NSAIDs are associated with an increased risk for chronic pouchitis [10].

- Maintain ideal body weight, because weight gain is a risk factor for pouch failure, and this is discussed separately. (See "Restorative proctocolectomy with ileal pouch-anal anastomosis: Laparoscopic approach", section on 'Risk factors for pouch failure'.)

We do not routinely use probiotics or other pharmacologic agents for primary prevention of acute pouchitis. Studies on probiotics for primary prevention of acute pouchitis after pouch construction are uncertain and are limited by small trials [11]. Probiotics are organisms belonging to the gut flora that may have health benefits. (See "Probiotics for gastrointestinal diseases".)

However, probiotics are used for secondary prevention of active pouchitis. (See 'Maintenance therapy' below.)

ACUTE IDIOPATHIC POUCHITIS

General measures — Accurate and timely diagnosis and classification of pouchitis are key for successful treatment. Patients with acute idiopathic pouchitis have endoscopic evidence of active pouch inflammation without a clear cause based on histology, stool studies, and blood tests, and the following measures apply to such patients (algorithm 1) (see "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Evaluation'):

- Avoid nonsteroidal antiinflammatory drugs (NSAIDs) – We advise patients with pouchitis to avoid NSAIDs because NSAIDs are associated with increased risk for chronic pouchitis [10].

- Dietary adjustments – The author advises patients with normal pouches or active pouchitis to adhere to a diet that is low in poorly digested carbohydrates and low in fiber, as fermentation of dietary carbohydrates or fiber by small intestinal bacterial overgrowth in the pouch can cause increased stool frequency and bloating. Of note, dietary modification is used for symptomatic relief, rather than healing of pouch inflammation. The dietary approach is similar to the low fermentable oligo-, di-, monosaccharides and polyols diet. (See "Treatment of irritable bowel syndrome in adults", section on 'Dietary modification'.)

  Preliminary data suggest that a Crohn Disease Exclusion Diet was associated with improvement in symptoms and endoscopic healing [12]. In addition, fruit consumption may be associated with a lower risk of pouchitis [13].

- Specialty consultation – We suggest that patients with pouchitis are referred to an inflammatory bowel disease center or pouch clinic for long-term management.

For patients who progress to antibiotic-dependent pouchitis or chronic antibiotic-refractory pouchitis (CARP), management includes medical therapy and modification of risk factors [14]. (See 'Managing nonresponders' below and 'Managing relapse' below.)

Initial therapy — First-line therapy for acute pouchitis consists of an oral antibiotic for two weeks (ciprofloxacin 500 mg every 12 hours). Alternatives to ciprofloxacin for initial therapy include metronidazole 500 mg every 12 hours or tinidazole 500 mg every 12 hours.

Selecting initial therapy for acute idiopathic pouchitis has been guided by clinical experience and few small trials [11,15,16]. In a systematic review that included one trial of 16 patients with acute pouchitis, ciprofloxacin resulted in higher rates of remission after two weeks compared with metronidazole (100 versus 33 percent, risk ratio 2.68 [95% CI 1.13 to 6.35]) [11,15]. In addition, patients treated with ciprofloxacin had lower rates of adverse events (eg, vomiting, dysgeusia, peripheral neuropathy) (0 versus 33 percent). We consider tinidazole to be a reasonable alternative to ciprofloxacin based on the author's experience and limited indirect data [16].

The use of antibiotic therapy has been supported by studies that have linked intestinal microbiota to the development of pouchitis. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Intestinal microbiota'.)

Most patients with acute pouchitis have symptomatic improvement (eg, improved stool frequency, no urgency) within three days after initiating antibiotic therapy [15,17].

Patients who respond to initial treatment but have frequent relapses (≥3 episodes per year) are described as having antibiotic-dependent chronic pouchitis. For such patients, we suggest maintenance therapy with a probiotic or a nonabsorbable antibiotic. (See 'Managing relapse' below.)

However, we do not routinely use probiotics for patients with uncomplicated acute pouchitis, and this approach is supported by consensus guidelines [14].

Subsequent management — For patients with acute pouchitis who do not respond to initial antibiotic treatment, we perform stool culture and susceptibility testing of bacterial flora and select a single active antibiotic based on those results for a four-week course [18,19]. If such testing is not available, we give a prolonged course (eg, four weeks) of dual oral antibiotic therapy consisting of ciprofloxacin (500 mg every 12 hours) combined with metronidazole (500 mg every 12 hours) or tinidazole (500 mg every 12 hours) or rifaximin (550 mg every 12 hours) [14].

For patients who respond to ≥4 weeks of antibiotic therapy (based on susceptibility testing of bacterial flora or empiric treatment), we give maintenance therapy to prevent relapse, similar to the approach for patients with antibiotic-dependent chronic pouchitis. (See 'Managing relapse' below.)

For patients with persistent symptoms despite ≥4 weeks of antibiotic therapy, we reassess the patient before proceeding with additional treatment options. (See 'Managing nonresponders' below.)

Dual antibiotic therapy has been associated with symptomatic and endoscopic improvement in patients with pouchitis. In four observational studies including a total of 86 patients with active pouchitis, dual antibiotic therapy (ciprofloxacin plus tinidazole or rifaximin or metronidazole) was associated with clinical response or remission in 73 patients (85 percent) [18,20-22].

For patients with long-term antibiotic use, the reported rates of infection or colonization with antibiotic-resistant bacterial strains are low [23-25]. However, the risk of long-term use of absorbable antibiotics remains a concern. Long-term antimicrobial therapy for antibiotic-responsive pouchitis may result in colonization of ciprofloxacin-resistant nonpathogenetic intestinal microbiota [24]. As an example, in one study that examined stool samples from 43 patients with an ileal pouch, ciprofloxacin use was associated with increased risk of having bacteria with quinolone-resistant mutations in the *gyrA* and *parC* genes [25].

Assessing response — For patients with acute idiopathic pouchitis, response to antibiotic therapy is typically assessed clinically (symptomatic improvement) and endoscopically (pouchoscopy with biopsy) after completing therapy, and this approach is supported by consensus guidelines [14]. While endoscopic mucosal healing may lag behind symptomatic improvement, mucosal healing is a treatment target for patients with pouchitis [7].

Correlation between symptom, endoscopic, and histologic scores is limited in studies on treatment outcomes for patients with pouchitis [4,26]. Ideally, a combined score consisting of symptoms, endoscopy, and histology should be used to measure treatment response [14]. Some studies have used disease activity instruments to measure response to treatment. As an example, in a study using a modified RAND/University of California Los Angeles appropriateness process, items that appropriately evaluated pouchitis included stool frequency and fecal urgency; severity of endoscopic findings (ie, extent of pouch body inflammation and ulceration); and histologic findings (ie, lamina propria chronic inflammation, epithelial and lamina propria neutrophils, epithelial damage, erosions and ulcers) [27].

MANAGING RELAPSE

Patients with infrequent relapse — For patients with acute pouchitis who have a clinical relapse of pouchitis after achieving remission with <4 weeks of antibiotic therapy, we begin another course of antibiotic monotherapy for two weeks. When treating relapse, the single antibiotic agent that was effective initially may be used again. (See 'Initial therapy' above.)

For patients who have infrequent relapses (ie, <3 episodes of acute pouchitis per year), we do not use maintenance therapy.

Patients with frequent relapse — Patients with acute pouchitis who respond initially to antibiotic therapy (ie, <4 weeks) but who relapse ≥3 times per year are given long-term maintenance therapy, typically with a probiotic or an alternative agent [14]. (See 'Maintenance therapy' below.)

Patients who develop symptoms of active pouchitis while on maintenance therapy are reassessed before proceeding with additional treatment options. (See 'Managing nonresponders' below.)

Maintenance therapy — For patients with pouchitis who respond initially to antibiotic therapy but who relapse ≥3 times per year or who required ≥4 weeks of antibiotic therapy (dual or monotherapy) initially (ie, chronic antibiotic-dependent pouchitis), we typically use maintenance therapy with a probiotic. Initial maintenance therapy consists of the probiotic VSL#3 (*Bifidobacterium breve, B. longum, B. infantis,* Lactobacillus acidophilus, L. plantarum, L. paracasei, L. bulgaricus, Streptococcus thermophilus, 6 to 9 g daily) with the rationale that changes in the microflora have been demonstrated in patients with pouchitis [28,29]. [Note: Studies before 2015 were performed with the original Italian (DeSimone) preparation. In the United States, VSL#3 formulation is somewhat different and has different functional properties [30,31]. General issues of regulation and safety of dietary supplements are discussed separately. (See "Overview of herbal medicine and dietary supplements".)]

Data supporting the use of VSL#3 for maintaining remission are mixed [32-35]. In a trial including 40 patients with chronic pouchitis, maintenance therapy with VSL#3 (6 g daily) resulted in lower relapse rates after nine months compared with placebo (15 versus 100 percent) [32]. However, in open-label studies, the response rate to VSL#3 was lower than that reported in randomized trials and the discontinuation rate was high [33,35]. In a study of 31 patients with antibiotic-dependent pouchitis who received VSL#3 as maintenance therapy, 25 patients (81 percent) discontinued the probiotic at eight months due to lack of efficacy or the development of adverse effects [33]. It is unclear if these conflicting results are due to

differences in study population characteristics, inclusion criteria, induction therapy with antibiotics, and/or the composition and dosage of the probiotic agents.

An alternative to chronic probiotic therapy for maintenance is a nonabsorbable antibiotic or low-dose systemic antibiotic; however, risk of adverse effects, antibiotic resistance, and cost are limitations of this strategy. We do not routinely use antibiotic therapy for long-term maintenance therapy (ie, >3 months). Options for maintenance therapy include rifaximin (in doses ranging from 200 mg once daily to 600 mg every eight hours) and low-dose ciprofloxacin (250 to 500 mg daily) [33]. Rifaximin, a nonabsorbable antibiotic, has the advantage of a favorable safety profile; however, its long-term use may be limited by cost. Adverse effects of ciprofloxacin and other fluoroquinolones (eg, risk of tendinopathy, *Clostridioides difficile* infection, aortic dissection) are discussed separately. (See "Fluoroquinolones", section on 'Adverse effects'.)

Data on efficacy of antibiotic maintenance therapy for chronic pouchitis are limited to small observational studies [33,36,37]. As an example, in a case series including 39 patients with chronic antibiotic-dependent pouchitis who had been maintained on antibiotics for at least one year, symptomatic remission was achieved by eight patients (21 percent) over a mean duration of six years [37]. Adverse effects from long-term antibiotic use (ie, ciprofloxacin, metronidazole) developed in 11 patients (28 percent).

Some patients continue to have frequent episodes of acute pouchitis despite maintenance therapy with probiotics or antibiotics, and such patients have developed chronic antibiotic-refractory pouchitis. (See 'Managing nonresponders' below.)

MANAGING NONRESPONDERS

Pretreatment evaluation — Patients with pouchitis who do not have symptomatic improvement despite at least four weeks of antibiotic therapy are regarded as having chronic antibiotic-refractory pouchitis (CARP). Therapy for CARP is guided by pretreatment evaluation that includes (see "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis" and 'Special populations' below):

- Pouchoscopy with biopsy to reassess mucosal healing of the pouch following antibiotic therapy and to exclude infection (eg, cytomegalovirus).
- Laboratory testing to confirm that secondary causes and coexisting conditions have been excluded (eg, infection, primary sclerosing cholangitis [PSC]). Blood tests include aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, celiac

disease serology, antinuclear antibody, and immunoglobulin G4 (IgG4) level, and stool specimen for *Clostridioides difficile* is also obtained. (See "Diagnosis of celiac disease in adults", section on 'Serologic evaluation'.)

Patients with elevated liver biochemical tests in a cholestatic pattern (predominantly elevated alkaline phosphatase) are evaluated for PSC with liver ultrasound or magnetic resonance cholangiopancreatography, and the diagnosis of PSC is discussed separately. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis".)

- Patients with CARP who report frequent bowel movements, straining, and/or a sense of incomplete evacuation should be evaluated for pouch outlet obstruction related to structural (eg, anastomotic stricture and distal pouch prolapse) or functional (eg, dyssynergic defecation) causes.

Immune-mediated chronic pouchitis — Patients with CARP who do not have PSC, IgG4 disease, or a secondary cause for inflammatory changes of the pouch (eg, infection, ischemia, Crohn disease) are managed as immune-mediated CARP. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Differential diagnosis'.)

The management approach for patients with CARP is generally similar to the management of ulcerative colitis (ie, induction and maintenance therapy) [14]. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)

Initial therapy — Initial therapy for immune-mediated CARP is topical (rectal/pouch) mesalamine for four weeks [38,39]. Mesalamine is widely available in two forms: suppository or enema (table 1). We typically use mesalamine suppository 1 g once daily or mesalamine enema 4 g once daily, and the dosing is similar to that used for patients with ulcerative proctitis. For patients without symptomatic relief (ie, decreased stool frequency) after two weeks of topical (rectal) mesalamine, we add oral mesalamine and continue topical mesalamine daily. We typically use oral mesalamine (ie, 2.4 to 4.8 g daily) for two to four weeks.

The use of mesalamine for chronic pouchitis has been supported by limited direct data and the author's experience. In an observational cohort of 10 patients with refractory pouchitis, oral or topical mesalamine was associated with clinical remission rates of 50 percent [18].

For patients with chronic pouchitis and coexisting arthritis, an alternative to oral mesalamine is sulfasalazine (2 to 4 g daily) and folic acid (1 mg daily) [40,41]. Adverse effects of mesalamine and sulfasalazine and treatment of arthritis associated with inflammatory bowel disease are discussed separately. (See "Treatment of arthritis associated with inflammatory bowel disease" and "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease".)

Subsequent therapy — For patients who do not have symptomatic improvement after four weeks of topical (rectal) and oral mesalamine therapy, subsequent options include (table 1):

- Begin topical (rectal) hydrocortisone (suppository, foam, enema) once daily for two weeks.
- Begin topical (rectal) budesonide (eg, foam, 2 mg per application) once daily for two weeks [42,43].
- Begin oral budesonide (9 mg daily for eight weeks). Oral budesonide is typically used for patients who have not improved with topical mesalamine, oral mesalamine, and topical glucocorticoids. The dosing and pharmacology of budesonide is discussed separately. (See "Overview of budesonide therapy for adults with inflammatory bowel disease".)

  An alternative to oral budesonide is oral beclomethasone dipropionate (10 mg daily for eight weeks), but oral beclomethasone dipropionate is not widely available [44,45].

For example, for patients on mesalamine therapy who have some symptomatic improvement but without symptom resolution, we typically add a topical glucocorticoid or oral budesonide while continuing mesalamine.

For patients who do not improve with mesalamine or glucocorticoids or who develop recurrent symptoms upon drug discontinuation, other options include biologic therapy. (See 'Other options' below.)

The use of topical and oral glucocorticoids for patients with CARP is based on limited published data and the author's experience [42-44,46]. In an observational study of 20 patients with antibiotic-refractory pouchitis who were treated with oral budesonide, 15 patients (75 percent) achieved clinical remission based on Pouchitis Disease Activity Index (PDAI) score after eight weeks [46].

Other options — For patients with immune-mediated chronic pouchitis who fail mesalamine and glucocorticoid therapy, we begin biologic therapy and typically use vedolizumab as first-line therapy, followed by ustekinumab as the second choice, and this approach is supported by guidelines [14,47-49].

We reserve anti-tumor necrosis factor (TNF) agents (eg, infliximab, adalimumab) as induction therapy for patients who fail vedolizumab and possibly ustekinumab [14]. The pretreatment evaluation, dosing, and administration of these agents for patients with chronic pouchitis are similar to the approach for patients with ulcerative colitis (UC), and this is discussed in more detail separately. (See "Overview of dosing and monitoring of biologic agents and small

molecules for treating ulcerative colitis in adults" and "Management of moderate to severe ulcerative colitis in adults", section on 'Ustekinumab'.)

Most data on biologic agents for chronic pouchitis are based on few clinical trials and observational studies [48,50,51].

- Vedolizumab – Vedolizumab, a gut-selective anti-integrin agent, has been associated with symptom and endoscopic improvement in chronic pouchitis [7,48,51,52]. In a systematic review of seven studies including 44 patients with chronic pouchitis who were treated with vedolizumab, 33 patients (75 percent) had symptomatic improvement at 12 weeks, and 28 of 38 patients (74 percent) had endoscopic improvement at six months [48]. In a randomized trial including 102 patients with active chronic pouchitis, vedolizumab resulted in higher rates of combined clinical and endoscopic remission as measured by the modified PDAI compared with placebo after 14 weeks (31 versus 10 percent) [51]. Vedolizumab also resulted in higher rates of sustained remission after 34 weeks (35 versus 18 percent). Rates of serious adverse events were numerically similar between groups. (See 'Treatment goals' above and "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Scoring systems for assessing disease activity'.)

- Ustekinumab – The use of ustekinumab, an anti-interleukin 12/23 antibody, for chronic pouchitis is supported mainly by case series [8,47,50,53,54]. In a study including 24 patients with CARP with a median follow-up time of 13 months, 12 patients (50 percent) had symptomatic response and four of nine patients (44 percent) had endoscopic improvement [47].

- Anti-TNF agents – The use of anti-TNF agents for chronic pouchitis may be limited by precolectomy exposure to the drug [52,55-59]. In a study including 23 patients with chronic pouchitis who were treated with infliximab, 10 patients (44 percent) achieved clinical remission at 14 weeks of therapy [52]. Adverse events associated with infliximab (eg, infusion reactions, hypersensitivity) led to discontinuation of the drug in nine patients (39 percent), possibly due to immunogenicity in patients with prior exposure to anti-TNF agents. In a cohort of 13 patients with chronic pouchitis who were treated with adalimumab, five patients (39 percent) achieved clinical remission at 14 weeks [52]. In a small trial comparing adalimumab with placebo in 13 patients with refractory pouchitis, there were no statistically significant differences in rates of improved PDAI scores between groups [59].

Although patients with pouchitis who were nonresponders to a specific biologic agent prior to colectomy can be treated with the same biologic agent after surgery, use of the prior biologic

agent has been associated with an increased risk for treatment failure [14,60].

Patients with chronic pouchitis who fail medical therapy and whose quality of life is significantly compromised may be referred to a colorectal surgeon for consideration of surgical intervention (eg, fecal diversion with ileostomy). Risk of pouch failure is discussed separately. (See "Restorative proctocolectomy with ileal pouch-anal anastomosis: Laparoscopic approach" and "Surgical management of ulcerative colitis", section on 'Surgical complications'.)

Investigational therapies — Therapies that have been studied for treating CARP but remain investigational include:

- Tofacitinib – Several case reports have shown that the small molecule tofacitinib was effective for treating patients with CARP who have failed anti-TNF agents, anti-interleukin agents, or anti-integrin agents [61,62]. Tofacitinib therapy for patients with UC is discussed separately. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Janus kinase (JAK) inhibitors'.)

- Intravenous immunoglobulin – In a small case series of 16 patients with refractory pouchitis, intravenous immunoglobulin infusion was associated with clinical and endoscopic improvement as measured by the modified PDAI [63].

- Hyperbaric oxygen therapy (HBOT) – Data from case series suggested that HBOT was beneficial for some patients with chronic inflammatory disorders of the pouch [64-67]. In a systemic review of 19 studies including 60 patients with pouch disorders, HBOT was associated with clinical remission rates of 31 percent [67].

- Vancomycin – Oral vancomycin is a standard therapy for *Clostridioides difficile* infection in pouch patients [68]. In addition, case reports suggested that oral vancomycin had therapeutic effects for PSC-associated pouchitis and enteritis [69-71]. In a case series of 41 patients with pouch disorders, oral vancomycin was associated clinical response in 21 patients (51 percent) after four weeks of therapy and sustained clinical response at three and six months in 16 of 21 responders (76 percent) [72].

- Topical alicaforsen – Data on topical application of alicaforsen for treating CARP are mixed [73,74]. In an observational study including 12 patients with CARP, treatment with alicaforsen enema for six weeks was associated with clinical improvement as measured by reduction in PDAI score [74]. However, in a subsequent trial, there was no statistically significant improvement with alicaforsen enema in patients with pouchitis [75]. Alicaforsen is an antisense inhibitor of intercellular adhesion molecule-1 oligonucleotide.

- Topical tacrolimus – In an observational study of 10 patients with antibiotic-refractory pouchitis, topical tacrolimus for eight weeks was shown to reduce symptom, endoscopy, and histology scores [76].

- Therapies of no or uncertain benefit – Fecal microbiota transplantation (FMT) has been studied for treating non-*Clostridioides difficile* infection; however efficacy has not been established [77-85]. The use of FMT for treating *Clostridioides difficile* infection is discussed separately. (See "Fecal microbiota transplantation for treatment of *Clostridioides difficile* infection".)

  Butyrate and glutamine suppositories [86] and bismuth carbomer foam [87] have been studied for treating chronic pouchitis, but their efficacy has not been established.

SPECIAL POPULATIONS

Inflammatory pouch disorders are not limited to acute pouchitis. Consensus guidelines from the International Ileal Pouch Consortium on the classification of ileal pouch disorders will help standardize terminology and classification of disease phenotypes, predict prognosis, and guide medical, endoscopic, and surgical therapies [14].

Pregnant patients — The incidence of acute pouchitis in pregnant patients is uncertain, although pregnancy does not appear to be a risk factor for developing pouchitis [88]. In a systematic review of 283 pregnancies, postpartum pouchitis was reported in approximately 2 percent of patients [89]. Management of pouchitis during pregnancy includes an assessment of possible risks associated with abdominal and pelvic imaging, pouchoscopy, and medication use. Input from a multidisciplinary team is required for some patients. (See "Diagnostic imaging in pregnant and lactating patients".)

Therapeutic options for pregnant patients include penicillin-based antibiotics (eg, amoxicillin/clavulanic acid) or vancomycin. We avoid the use of quinolones and nitroimidazoles during pregnancy, especially during the first trimester [14]. The use of glucocorticoids, immunomodulators, and biologic agents in pregnant patients with pouchitis is similar to their use in pregnant patients with inflammatory bowel disease, and this is discussed separately [90-92]. (See "Fertility, pregnancy, and nursing in inflammatory bowel disease".)

PSC-associated chronic pouchitis — Patients with an ileal pouch and underlying primary sclerosing cholangitis (PSC) are at higher risk for chronic antibiotic-refractory pouchitis (CARP), and patients with PSC-associated chronic pouchitis are generally managed with therapies that target mucosal inflammation in the pouch body and afferent limb. PSC-associated pouchitis and

enteritis are considered a distinct phenotype with unique clinical, endoscopic, and histologic features, treatment response, and risk of neoplasia [1,93-95]. The diagnosis of PSC is discussed in more detail separately. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Patients with ileal pouch and coexisting PSC commonly have endoscopic and/or histologic inflammation of the pouch body, afferent limb, and cuff [93]. The author has also observed that patients often have mild symptoms in the presence of marked pouch inflammation and a long segment of enteritis (>10 cm). On endoscopy, the pouch inlet shows a patulous appearance. Patients with PSC-associated pouchitis are typically given antibiotic therapy initially while oral mesalamine is an alternative option. (See 'Acute idiopathic pouchitis' above and 'Immune-mediated chronic pouchitis' above.).

For patients with PSC who do not respond to initial therapy, we typically use an eight-week course of oral budesonide (9 mg daily) or budesonide enema or foam daily [42,96]. Because symptomatic and endoscopic relapse is common, patients who respond to oral budesonide may require maintenance therapy with the same agent at a lower dose (eg, oral budesonide 3 mg daily). Dosing and adverse effects of budesonide are discussed separately. (See "Overview of budesonide therapy for adults with inflammatory bowel disease", section on 'Dosing'.)

For some patients who fail budesonide, the author has observed that oral vancomycin (500 to 1000 mg daily) may be beneficial for treating both pouchitis and enteritis [69-71].

For patients who achieved clinical remission with glucocorticoids, an alternative approach for maintenance therapy is to use an immunomodulator (eg, oral 6-mercaptopurine [6-MP] 25 to 50 mg daily or methotrexate 7.5 to 12.5 mg subcutaneously weekly). Pretreatment evaluation, dosing, and monitoring for immunomodulators are discussed separately. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease" and "Major side effects of low-dose methotrexate".)

Data on managing PSC-associated pouchitis and enteritis with biologic agents are limited. Vedolizumab is an option for patients with PSC-associated pouchitis and enteritis [97]. In studies on the use of other biologic agents (eg, ustekinumab, infliximab, adalimumab) for CARP and other inflammatory disorders of the pouch, some of the study participants had concurrent PSC, but subgroup analyses were not reported. (See 'Other options' above.)

IgG4-associated chronic pouchitis — Patients with immunoglobulin G4 (IgG4)-related pouchitis are at higher risk for antibiotic-refractory pouchitis, and such patients are primarily managed with therapies that target mucosal inflammation [98,99]. (See "Treatment and prognosis of IgG4-related disease".)

Initial therapy is typically oral budesonide (9 mg daily) for eight weeks [100]. (See "Overview of budesonide therapy for adults with inflammatory bowel disease".)

For patients who fail budesonide or who relapse with discontinuation, other options include low dose immunomodulator (eg, 6-MP 50 mg daily). Pretreatment evaluation, dosing, and monitoring for immunomodulators are discussed separately. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease".)

Patients with prepouch enteritis or ileitis — Prepouch ileitis represents a spectrum of inflammatory disorders ranging from nonsteroidal antiinflammatory drug (NSAID)-induced enteritis to immune-mediated pouchitis to Crohn disease of the pouch [101]. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Differential diagnosis'.)

Patients with pouchitis and coexisting prepouch ileitis (≥10 cm) may be initially treated with antibiotics or oral budesonide, 9 mg daily for eight weeks, followed by 3 mg daily for maintenance therapy. Pharmacology and safety of budesonide for patients with inflammatory bowel disease is discussed separately. (See "Overview of budesonide therapy for adults with inflammatory bowel disease".)

An alternative to oral budesonide is oral mesalamine (2 to 4 g daily) or mesalamine enemas daily (table 1). Biologic agents have been studied, but failed to achieve remission in most patients [102].

Prepouch ileitis associated with Crohn disease is treated similarly to the inflammatory Crohn disease of the pouch [14]. (See 'Crohn disease of the pouch' below.)

Crohn disease of the pouch — Crohn disease of the pouch can be classified into inflammatory, fibrostenotic, or fistulizing phenotype [14]. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Differential diagnosis'.)

Studies on therapy for Crohn disease of the pouch are limited [8,9,55,57]. Principles for treating Crohn disease of the pouch that were endorsed by the International Ileal Pouch Consortium include [14]:

- Antibiotics may be an adjunct to induction therapy for Crohn disease.
- Oral or topical budesonide is an option for induction therapy.
- Biologics (eg, anti-tumor necrosis factor (TNF) agents, vedolizumab, ustekinumab) and small molecules (eg, tofacitinib) are options for treating inflammatory or penetrating

Crohn disease of the pouch [103]. Immunomodulators can be used as monotherapy or in combination with anti-TNF agents for maintenance therapy in inflammatory or penetrating Crohn disease of the pouch.

- Loss of response to biologic therapy before colectomy in patients with inflammatory bowel disease does not prohibit using the same agent for treating Crohn disease of the pouch, provided that the patient did not develop anti-drug antibodies.

- While endoscopic (eg, balloon dilation, endoscopic stricturotomy) and/or surgical (eg, stricturoplasty, resection and anastomosis) interventions are often used for fibrotic Crohn disease of the pouch, medical therapy (eg, glucocorticoids, biologics) is an alternative, especially for inflammatory strictures.

- The following therapies are not routinely used: mesalamine (oral or topical) or, for patients with indeterminate colitis, prophylaxis against the developing Crohn disease.

Cuffitis — Classic cuffitis is a recurrence of ulcerative colitis in the residual cuff of rectal mucosa following proctocolectomy with ileal pouch-anal anastomosis. (See "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Differential diagnosis'.)

Cuffitis is treated with topical (rectal) mesalamine (suppository or enema) or topical (rectal) glucocorticosteroid (eg, hydrocortisone suppository or budesonide foam 2 mg once a day) (table 1) [39,104]. Some patients with cuffitis may benefit from maintenance therapy with the topical agents, whereas others may have a limited response to topical therapy. Thus, cuffitis is classified into (topical) mesalamine or glucocorticoid-responsive, glucocorticoid-dependent, or glucocorticoid-refractory [1]. Classic cuffitis usually responds to topical therapy, whereas non-classic cuffitis can result from other etiologies (eg, Crohn disease) that may respond to targeted therapy [1,14].

Ischemia-associated pouchitis — Among nonsurgical therapies for ischemic pouchitis, hyperbaric oxygen therapy may be beneficial [14,64-66]. However, ischemic pouchitis responds poorly to antibiotic therapy [105].

Fecal stasis-associated pouchitis — Fecal stasis-associated pouchitis may be more common in patients with underlying familial adenomatous polyposis [106]. Based on clinical experience, therapy for structural (eg, endoscopic balloon dilation of anastomotic stricture) or functional (eg, biofeedback) pouch outlet disorders often results in improvement of pouch inflammation. (See "Management of chronic constipation in adults", section on 'Biofeedback'.)

Diversion pouchitis — Medical therapy for diversion pouchitis is similar to therapy for diversion colitis, and this is discussed separately.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pouchitis".)

SUMMARY AND RECOMMENDATIONS

- **Spectrum of disease** – Pouchitis is an inflammatory condition of the ileal pouch reservoir of an ileal pouch-anal anastomosis. Pouchitis has been classified based on disease characteristics such as the duration of symptoms, response to antibiotics, frequency of flares, etiology, and disease activity. Most patients with an ileal pouch have some degree of endoscopic or histologic inflammation, and pouchitis likely represents a disease spectrum with a range of presentations that may evolve over time. (See 'Spectrum of disease' above.)

- **Treatment goals** – Goals of therapy for patients with acute pouchitis are to alleviate symptoms and to achieve clinical and endoscopic remission by demonstrating mucosal healing. Histologic improvement (ie, resolution of acute inflammatory cell infiltrate) is emerging as an additional component of disease remission. Assessing treatment response for patients with pouchitis includes recognizing that the normal stool pattern is typically four to seven formed stools daily without seepage. (See 'Treatment goals' above.)

- **Initial therapy** – For patients with acute idiopathic pouchitis, we suggest initial therapy with ciprofloxacin rather than other antibiotics or observation (**Grade 2C**). We typically use ciprofloxacin 500 mg every 12 hours for two weeks, while alternatives to ciprofloxacin include metronidazole or tinidazole since these agents have also been associated with symptomatic improvement (algorithm 1). (See 'Initial therapy' above.)

- **Subsequent management** – For patients with acute idiopathic pouchitis who do not respond to initial antibiotic treatment, we perform stool culture and susceptibility testing of bacterial flora and select a single active antibiotic based on those results for a four-week course. If such testing is not available, we suggest empiric, dual antibiotic therapy rather than antibiotic monotherapy (**Grade 2C**). We typically use ciprofloxacin combined with metronidazole or tinidazole or rifaximin for four weeks. (See 'Subsequent management' above.)

- **Maintenance therapy** – For patients with pouchitis who respond to antibiotic therapy but who relapse ≥3 times per year or who required ≥4 weeks of antibiotic therapy to achieve remission, we suggest maintenance probiotic therapy rather than no maintenance or chronic antibiotic therapy (**Grade 2C**). We typically use the probiotic VSL#3; however, chronic antibiotic therapy (eg, rifaximin daily) is an alternative option. (See 'Managing relapse' above and "Probiotics for gastrointestinal diseases".)

- **Managing nonresponders** – Patients with pouchitis who do not have symptomatic improvement despite at least four weeks of antibiotic therapy are regarded as having chronic antibiotic-refractory pouchitis. After confirming that secondary causes of pouchitis have been excluded, we suggest initial management with topical (rectal) mesalamine rather than further antibiotics (**Grade 2C**). If there is no symptomatic improvement in two weeks, we add oral mesalamine. For patients who do not respond after four weeks of topical and oral mesalamine, subsequent options include topical or oral glucocorticoids (eg, budesonide) or a biologic agent (eg, vedolizumab). (See 'Managing nonresponders' above.)

- **Surveillance** – The approach to surveillance for patients with inflammatory bowel disease including those with an ileal pouch is discussed separately. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

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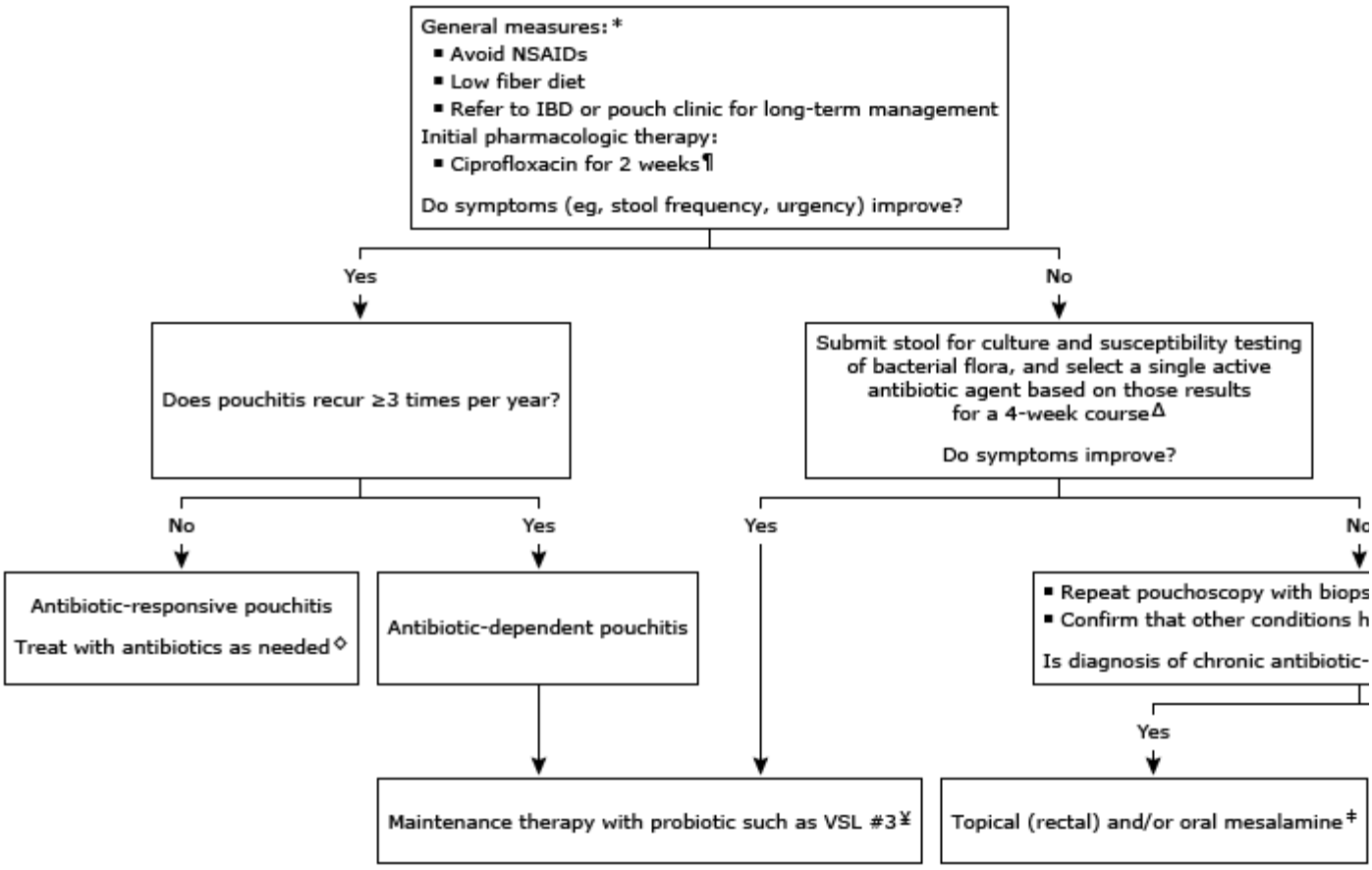
Topic 93857 Version 22.0

GRAPHICS

Medical management of acute idiopathic pouchitis



Refer to UpToDate content on management of pouchitis.

NSAIDs: nonsteroidal anti-inflammatory drugs; IBD: inflammatory bowel disease.

* Patients with acute idiopathic pouchitis have endoscopic evidence of active pouch inflammation without a histology, stool studies, or blood tests. Refer to UpToDate content on the diagnosis of acute pouchitis.

¶ Ciprofloxacin is typically used for initial therapy, while metronidazole or tinidazole are reasonable alternat

Δ If susceptibility testing is not available, an alternative approach is an empiric dual antibiotic regimen (eg, c metronidazole) for 4 weeks.

◇ Patients with <3 episodes of pouchitis per year are treated with a single antibiotic agent as needed. The a effective initially may be used again.

§ Laboratory testing including stool specimen for Clostridioides (formerly Clostridium) difficile is performed causes and coexisting conditions have been excluded.

¥ An alternative option for maintenance therapy is an antibiotic (eg, rifaximin).

‡ For patients who do not respond to topical and/or oral mesalamine, subsequent options include topical ar or a biologic agent.

Graphic 129598 Version 1.0

Medical therapy for mild to moderate ulcerative colitis

Role	Medication	Brand name (United States or as noted)	Usual dose
Induction of remission	**Topical (rectal) mesalamine***		
	Suppository	Canasa, Mezera¶, Pentasa¶, Salofalk¶	1 gram (one suppository) once daily at bedtime
	Retention enema	Pentasa¶, Rowasa, Salofalk¶	4 grams once daily at bedtime or twice daily$^{\Delta}$
	Rectal foam (United States: Not available)	Mezera¶	2 grams (two actuations) once daily at bedtime
	Topical (rectal) glucocorticoids		
	Hydrocortisone suppository	Anucort-HC, Anusol-HC, Hemmorex-HC, Proctocort	One suppository (25 or 30 mg) once or twice daily
	Hydrocortisone aerosol foam 10%	Cortifoam	90 mg (one applicatorful) once or twice daily
	Hydrocortisone enema	Cortenema, Colocort	100 mg (one 60 mL unit) once or twice daily
	Budesonide aerosol foam	Uceris	2 mg (one metered dose) once or twice daily
	Budesonide enema (reconstituted dispersible tablets)	Entocort¶	2 mg (one enema) once daily prior to bedtime
	Oral 5-aminosalycylic acid (5-ASA) derivatives		
	Sulfasalazine tablet	Azulfidine, Salazopyrin¶	4 grams per day in four divided doses
	Mesalamine*◇		
	▪ Delayed release enteric coated tablet	Asacol¶, Asacol HD	2.4 to 4.8 grams daily in three divided doses
		Mezera¶	3 grams daily in three divided doses
		Octasa¶	4.8 grams daily or in divided doses
		Salofalk¶	3 to 4 grams daily in three to four divided doses

	▪ Capsule containing delayed release enteric coated tablet	Delzicol	2.4 grams daily in three divided doses
	▪ Delayed and extended release tablet, multimatrix (MMX)	Lialda, Mezavant[¶]	2.4 to 4.8 grams daily once daily
	▪ Capsule containing delayed release enteric coated granules	Apriso	1.5 to 4.5 grams once each morning
	▪ Controlled release capsule	Pentasa	4 grams daily in four divided doses
	▪ Mesalamine granules (United States and Canada: Not available)	Salofalk sachet[¶]	1.5 to 3 grams daily in one to three divided doses
		Pentasa sachet[¶]	2 to 4 grams daily in two to four divided doses
	Olsalazine capsule	Dipentum	2 to 3 grams daily in two to four divided doses
	Balsalazide capsule	Colazal	6.75 grams daily in three divided doses
	Oral glucocorticoids		
	Budesonide delayed and extended release tablet, multimatrix (MMX)	Uceris	9 mg once daily in the morning for eight weeks
	Prednisone or prednisolone		40 to 60 mg once daily in the morning or in two divided doses
Maintenance of remission	**Topical (rectal) mesalamine***		
	Suppository	Canasa, Mezera[¶], Pentasa[¶], Salofalk[¶]	1 gram (one suppository) once daily at bedtime
	Enema	Pentasa[¶], Rowasa, Salofalk[¶]	1 to 4 grams once daily at bedtime[Δ]

Oral 5-aminosalycylic acid (5-ASA) derivatives		
Sulfasalazine tablet	Azulfidine, Salazopyrin[¶]	2 to 4 grams daily in three or four divided doses
Mesalamine*[◇]		
▪ Delayed release enteric coated tablet	Asacol[¶], Asacol HD	1.6 to 2.4 grams daily in one to three divided doses
▪ Capsule containing delayed release enteric coated tablet	Delzicol	1.6 to 2.4 grams daily in one to three divided doses
▪ Delayed and extended release tablet, multimatrix (MMX)	Lialda, Mezavant[¶]	2.4 to 3.6 grams once daily
▪ Capsule containing delayed release enteric coated granules	Apriso	1.5 to 3 grams once each morning
▪ Controlled release capsule	Pentasa	1.5 to 4 grams daily in three to four divided doses
▪ Mesalamine granules (United States and Canada: Not available)	Salofalk sachet[¶]	1.5 to 4 grams daily in one to three divided doses
	Pentasa sachet[¶]	2 to 4 grams once daily
Olsalazine capsule	Dipentum	1 gram daily in two divided doses
Balsalazide capsule	Colazal	2.25 to 6.75 grams daily in three divided doses

Choice of medication is based on factors including disease location, patient preference and tolerance, and medication availability; refer to UpToDate topic. Approved uses vary by drug, formulation, and country. Refer to product-specific labeling for more detail. Generic (nonproprietary) products may also be available.

5-ASA: 5-aminosalicylate.

* Mesalamine is a United States generic name. Mesalazine is an international generic (nonproprietary) name.

¶ Not available in the United States; however, is available in other areas (eg, Canada, United Kingdom, Europe).

Δ In the United States, mesalamine enema is available as 4 g/60 mL. Other concentrations and dosages are available elsewhere. Refer to product-specific information.

◇ Oral mesalamine may be dosed once daily instead of multiple times daily; there is no significant difference in efficacy and safety.[1,2]

Data courtesy of authors with additional data from:

1. *Ko CW, Singh S, Feuerstein JD, et al. American Gastroenterological Association Institute Clinical Guidelines Committee. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. Gastroenterology 2019; 156:748.*
2. *Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: Ulcerative colitis in adults. Am J Gastroenterol 2019; 114:384.*
3. *Lexicomp Online. Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.*

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Contributor Disclosures

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