

# An Update on the Medical Management of Inflammatory Pouch Complications

Kevin P. Quinn, MD<sup>1</sup> and Laura E. Raffals, MD<sup>1</sup>

**Total proctocolectomy with ileal pouch-anal anastomosis is the surgical procedure of choice for patients with medically-refractory ulcerative colitis or ulcerative colitis with associated dysplasia. Although most patients after ileal pouch-anal anastomosis experience good functional outcomes, a number of complications may develop. Of the long-term complications, pouchitis is most common. Although most respond to antibiotic treatment, some patients develop chronic pouchitis, leading to substantial morbidity and occasionally pouch failure. In patients with pouchitis who are not responsive to conventional antimicrobial therapy, secondary causes of chronic pouchitis need to be considered, including Crohn's disease of the pouch. In recent years, more literature has become available regarding the medical management of chronic pouchitis and Crohn's disease of the pouch, including the use of newer biologic agents. We herein provide a concise review on inflammatory complications involving the ileal pouch, including a focused approach to diagnosis and medical management.**

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## INTRODUCTION

Up to 20%–30% of patients with ulcerative colitis (UC) will require colectomy at some point during their disease course, although this number may be declining in the era of biologic therapy (1,2). For patients who require surgery for medically-refractory UC or associated colonic dysplasia, total proctocolectomy with ileal pouch-anal anastomosis (IPAA) remains the surgical procedure of choice (3). After IPAA, most patients experience good functional outcomes and quality of life (QoL) (4,5). However, several early and late complications may occur, with pouchitis being most common (6,7). Although most pouchitis is idiopathic, it is important to recognize that this is a heterogeneous disorder with several secondary causes that need to be considered, including Crohn's disease (CD) of the pouch (8,9). Distinguishing between pouchitis and other pouch inflammatory disorders can be challenging but is essential to provide appropriate therapy. In this review, we aim to identify the various causes of IPAA-associated inflammation, discuss an approach to diagnosis, and provide an update on the management of pouchitis and other pouch inflammatory disorders.

## NORMAL POUCH ANATOMY AND FUNCTION

### Pouch anatomy

Before managing pouch-related complications, it is important to have a clear understanding of pouch anatomy and expected functional outcomes. Total proctocolectomy with IPAA was first made popular by Parks and Nicholls in 1978, offering improved QoL compared with the use of a Kock pouch (i.e., K pouch or continent ileostomy) or Brooke ileostomy by avoiding an abdominal stoma and reducing incontinence (10,11). Various IPAA configurations have been used over the years, with 2 (J-pouch), 3 (S-pouch), and 4 (W-pouch) limbs of small intestine used to form the ileal reservoir (Figure 1) (10,12). Although perioperative complications seem similar between IPAA configurations, W-pouches have largely

fallen out of favor because of their bulkier design and longer surgical time (13). Compared with J-pouches, S-pouches more often require intubation because of inefficient emptying, limiting their utility (14). Thus, J-pouches are typically preferred because of the overall reliable function and ease of construction (15).

Formation of a J-pouch, or other pouch configuration, typically occurs over a multistage procedure. A 3-stage IPAA involves subtotal proctocolectomy with end ileostomy, then completion proctectomy with IPAA and diverting ileostomy, followed by ileostomy closure. In a 2-stage procedure, the first step includes total proctocolectomy with IPAA and diverting ileostomy, which is then followed by ileostomy closure (Figure 2). More recently, a modified 2-stage procedure has gained popularity, consisting of subtotal colectomy with end ileostomy, then completion proctectomy and IPAA formation, thereby avoiding a diverting ileostomy. Controversy exists regarding which approach is preferred. Although a 3-stage IPAA has traditionally been favored over 2 stages for patients who are acutely ill and at higher risk for complications, more recent data suggest comparable outcomes (16).

### Normal pouch function

Patients with IPAA generally experience good long-term functional outcomes and improved QoL. In fact, patients with UC experience health-related QoL that is indistinguishable from a normal healthy population 12 months after ileostomy closure (17). However, most undergo an adaptation phase during the initial postoperative period because the pouch expands and adapts to holding larger stool volumes. During this period, patients can expect increased stool frequency, urgency, and more difficulty differentiating gas and stool. Over several months, the pouch accommodates to hold more stool, whereas the small bowel increases water absorption (18), leading to gradual improvement in stool frequency and consistency. Beginning 6–12 months after

<sup>1</sup>Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA. **Correspondence:** Laura E. Raffals, MD. E-mail: [Raffals.Laura@mayo.edu](mailto:Raffals.Laura@mayo.edu). Received October 18, 2019; accepted April 1, 2020; published online May 25, 2020

ileostomy closure, patients can expect 4–8 bowel movements per day with up to 1–2 nocturnal bowel movements (19). Stools tend to be semiliquid or liquid consistency in most patients after IPAA.

### Diet and pharmacotherapy for maintaining pouch function

In IPAA patients with bothersome symptoms, certain dietary modifications and medications can be used to help improve stool consistency and reduce stool frequency, urgency, and incontinence. This may be especially helpful in the early adaptation period after ileostomy closure. Although there is a paucity of literature to guide dietary recommendations, patients should generally be advised to avoid foods that loosen stool consistency or increase gas production while favoring foods that tend to thicken stool (Table 1). Caffeine-containing products may be particularly bothersome in some patients (20). In addition, timing and volume of meals may also affect the pouch function. Specifically, if nocturnal bowel movements are an issue, eating a smaller, earlier dinner should be advised. Dietitians can serve as a great resource to help patients individualize their diet because they acclimate to life after IPAA.

To thicken stool and decrease frequency, a bulk-forming agent, such as psyllium or methylcellulose, may be helpful in some, although supportive evidence is lacking. We recommend either agent be taken as a slurry, starting with 1 tablespoon mixed with 4 ounces of water or yogurt. For those who respond, the dose can be gradually increased as tolerated. In those who do not respond or symptoms persist despite fiber supplementation, antidiarrheal agents, including loperamide or diphenoxylate/atropine, can be considered. In general, these should be started at the lowest recommended dose, then gradually increased based on response.

### SPECTRUM OF POUCH INFLAMMATORY DISORDERS

Despite the overall favorable outcomes and improved QoL for most patients, a number of complications can develop after IPAA that result in pouch dysfunction. These include inflammatory, infectious, postoperative, structural, functional, and dysplastic or neoplastic complications of the pouch. Of these, inflammation of the pouch, or pouchitis, is most common. Pouchitis is a nonspecific term that refers to inflammation within the ileal pouch reservoir (8). However, inflammation can involve any part of the pouch apparatus, including the body of the pouch, ileum immediately proximal to the pouch (i.e., prepouch ileum), and/or the rectal cuff (Figure 3). Although most pouchitis is idiopathic and likely driven by dysbiosis, secondary causes of pouchitis are important to consider because treatment may differ based on the underlying etiology. This is especially true in patients with chronic pouchitis because up to 20%–30% patients may have an identifiable secondary cause (21). Secondary causes of pouchitis include CD of the pouch, infections caused by *Clostridioides difficile*, cytomegalovirus (CMV), and other enteric pathogens, ischemic pouchitis, nonsteroidal anti-inflammatory drugs, and pouch outflow obstruction because of an anastomotic stricture or pouch evacuation disorder. Surgical complications involving the pouch, including leaks, abscesses, fistulas, and strictures may also mimic pouchitis or CD of the pouch but characteristically occur early in the postoperative period.

When evaluating symptomatic patients with an ileal pouch, 1 must also consider functional diseases of the pouch, including irritable pouch syndrome because symptoms may overlap with pouchitis and other inflammatory pouch disorders. Irritable pouch syndrome is a diagnosis of exclusion characterized by an increase in bowel movement frequency with abdominal pain,

cramping, change in stool consistency, and/or perianal or pelvic discomfort in the absence of an inflammatory or structural pouch disorder (22). Analogous to irritable bowel syndrome in patients with an intact colon, management is empiric and focused on improving symptoms, including those related to underlying visceral hypersensitivity while also addressing any underlying psychological comorbidities (23). Thus, pharmacotherapy may include antidiarrheal agents (e.g., loperamide, diphenoxylate/atropine, or cholestyramine), antispasmodics (e.g., hyoscyamine or dicyclomine), and low-dose tricyclic antidepressants (e.g., amitriptyline or nortriptyline) (22,24).

For this review, we will focus on the diagnosis and management of the most commonly encountered inflammatory disorders of the pouch, including cuffitis, primary pouchitis, and CD of the pouch.

### CUFFITIS

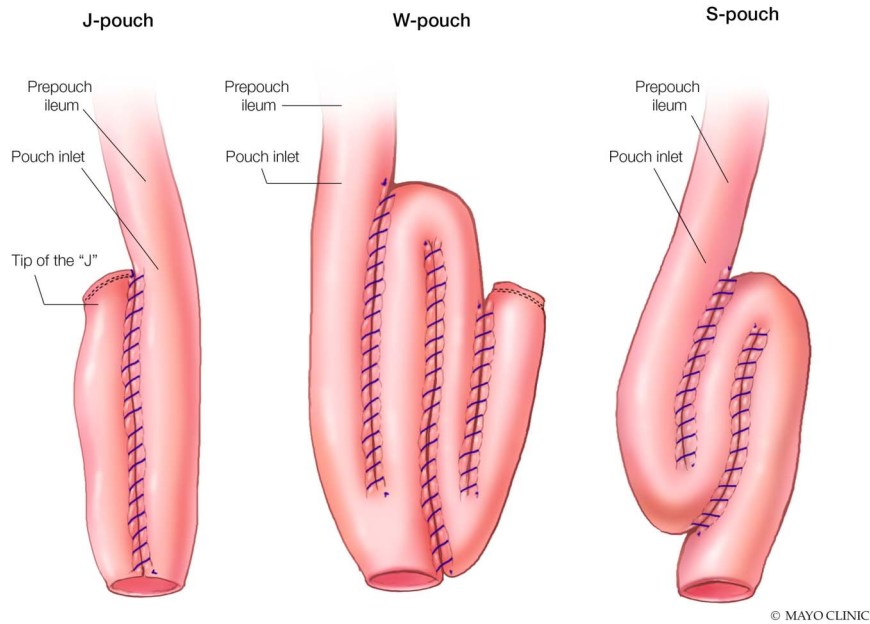
During IPAA formation, 2 different surgical techniques have been used to form the pouch-to-anal anastomosis. The first approach involves mucosectomy of the anal transition zone (ATZ), followed by a hand-sewn anastomosis. The second approach involves a stapled anastomosis with preservation of the ATZ (22). The ATZ, which extends over a variable distance proximally from the dentate line, has been loosely defined as the tissue interposed between the squamous epithelium of the anoderm and dentate line below and the rectal columnar epithelium above (25). Leaving this area intact with a stapled anastomosis is generally preferred because of shorter operative times and improved outcomes (26). Meanwhile, a hand-sewn anastomosis with mucosectomy makes for a longer procedure and is more prone to functional complications, including incontinence (27). The downside to the stapled technique is that to allow transanal passage of the stapler head, a 1–2 cm segment of rectal columnar mucosa (i.e., rectal cuff) is left in place (27). This short segment of rectal mucosa is then at risk for the development of inflammation (i.e., cuffitis) or dysplasia.

### Diagnosis

Cuffitis refers to inflammation involving the residual rectal mucosa. This is most often attributed to recurrence of UC within the rectal cuff and occurs in up to 13% of patients after IPAA (28,29). Symptoms tend to overlap with those of pouchitis and include increased stool frequency, tenesmus, and urgency. However, 1 notable difference is bleeding, which occurs more frequently with cuffitis (30). Nonetheless, it is important to keep in mind that cuffitis and pouchitis may often coexist. Thus, to reliably establish a diagnosis in a symptomatic patient, pouchoscopy with biopsies of the rectal cuff is necessary. Endoscopically, the presence of erythema, friability, nodularity, and/or ulcerations of the rectal cuff with or without inflammation of the pouch body establishes the diagnosis in a symptomatic patient.

### Management

Importantly, antibiotics are generally not effective in treating cuffitis. This fact underscores the importance of distinguishing cuffitis from pouchitis via a careful endoscopic examination. Most cuffitis responds to either mesalamine suppositories or topical corticosteroids, which are considered first-line therapies (27,31). Although systemic therapy is seldom necessary, refractory cuffitis can occur. In such cases, topical injection of a long-acting corticosteroid can be considered (31). Refractory cuffitis should raise concern for an alternative etiology, such as



**Figure 1.** Pouch configurations. Various ileo-anal pouch configurations, including J-pouch (left), W-pouch (middle), and S-pouch (right).

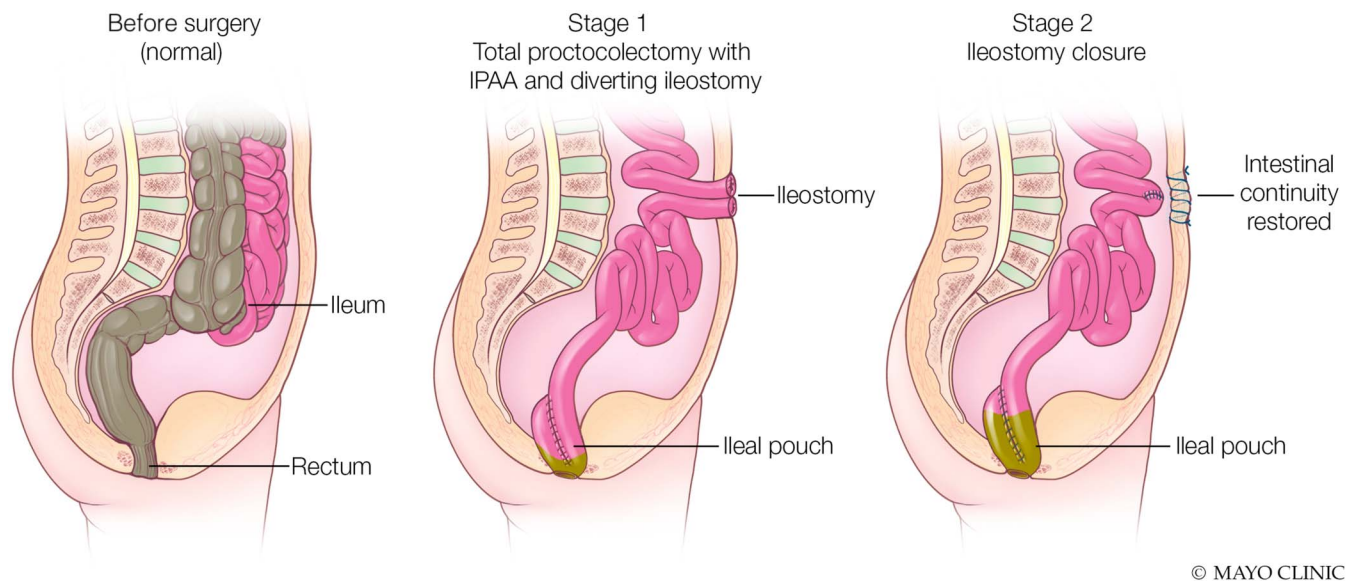
CD of the pouch. Overall, pouch failure due to refractory cuffitis is rare, occurring in <1% of all patients with IPAA (29).

## POUCHITIS

### Incidence and etiology

Pouchitis is the most frequent complication after IPAA, with an incidence up to 50% at 10 years and 80% at 30 years (19,32–34). Most pouchitis is idiopathic, lacking an identifiable cause. In these cases, the pathophysiology remains somewhat unclear, although it is believed to involve an abnormal immune response to alterations in the pouch microbiota (i.e., dysbiosis) (6,35,36). The role

of dysbiosis in the pathogenesis of pouchitis is supported by the fact that most episodes respond to antibiotic therapy. Furthermore, pouchitis is only observed after restoration of the fecal stream through the pouch (37). Fecal stasis resulting from surgically-altered intestinal anatomy, an anastomotic stricture, or pouch evacuation disorder may further promote dysbiosis (38). Several risk factors for pouchitis have been identified, including genetic susceptibility (polymorphisms of interleukin-1 receptor antagonist and NOD2/CARD15, noncarrier status of TNF allele 2), extensive UC before IPAA, the presence of extraintestinal manifestations, particularly primary sclerosing cholangitis (PSC),



**Figure 2.** Stages of ileal pouch-anal anastomosis (IPAA). Surgical steps involved in a 2-stage IPAA: stage 1 involves a total proctocolectomy with IPAA formation and diverting ileostomy, which is followed by ileostomy closure (stage 2) to restore gastrointestinal continuity. A 3-stage procedure (not pictured) involves subtotal proctocolectomy with end ileostomy (stage 1), then completion proctectomy with IPAA and diverting ileostomy (stage 2), followed by ileostomy closure (stage 3).

**Table 1. Dietary considerations in patients with IPAA**

Thicken stool	Thin stool	Increase gas
Applesauce	Alcohol drinks	Beans
Bananas	Caffeine-containing products	Beer
Breads	Fruit juice (i.e., apple, grape, etc.)	Broccoli
Cheeses	Other juice beverages	Brussel sprouts
Pasta and rice	Soda	Cabbage
Peanut butter		Carbonated beverages
Tapioca		Cauliflower
		Onions

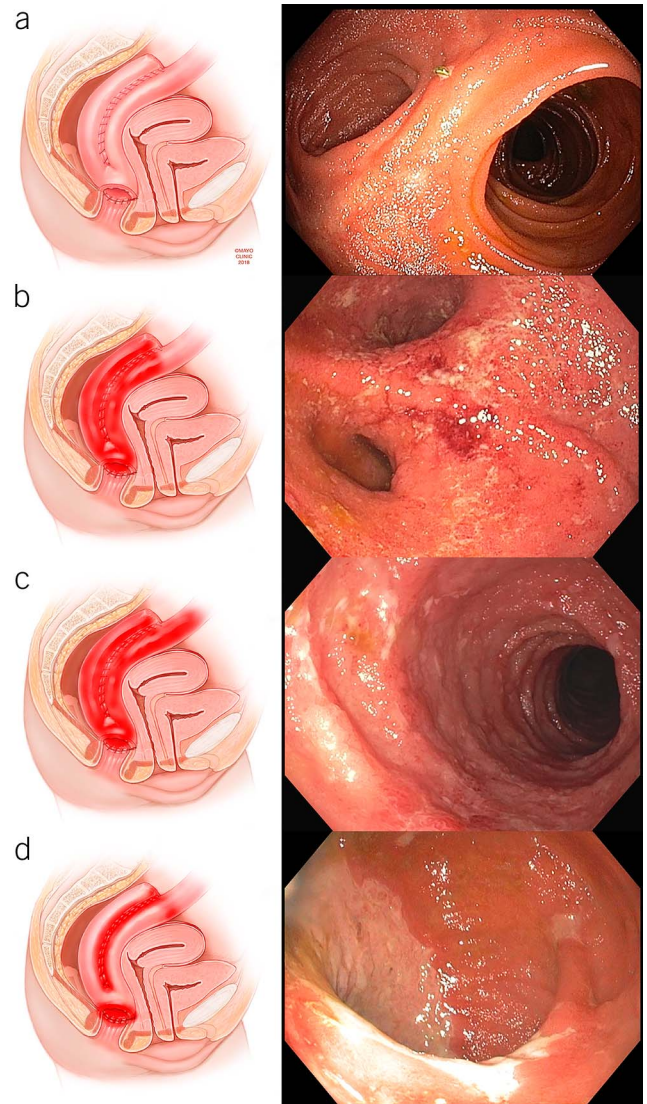
IPAA, ileal pouch-anal anastomosis.

backwash ileitis, concomitant autoimmune disorders, preoperative thrombocytosis or corticosteroid use, the presence of perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), nonsmoking status, and use of nonsteroidal anti-inflammatory drugs (8,39).

### Classification and diagnosis

There are multiple ways to classify pouchitis (Table 2) (40). Of the commonly used classifications schemes, duration of symptoms and response to antibiotics are most clinically useful. Pouchitis commonly presents with increased stool frequency, urgency, incontinence, and abdominal/pelvic cramping or pain. Fevers and other systemic symptoms may also be present (9,39). However, symptoms alone are insufficient to diagnosis pouchitis because they are nonspecific and overlap with other pouch inflammatory and non-inflammatory conditions. As such, when pouchitis is suspected, endoscopic and histologic assessment should be performed to confirm the diagnosis and exclude other etiologies (38). Endoscopically, idiopathic or primary pouchitis is classically characterized by diffuse inflammation throughout the body of the pouch with sparing of the prepouch ileum proximal to the pouch inlet (Figure 3b) (22). Although nonspecific, prepouch ileitis tends to occur more frequently in PSC-associated pouchitis than idiopathic pouchitis, analogous to backwash ileitis in patients with UC and concurrent PSC (Figure 3c) (41). Although no standard definition exists, we consider extensive prepouch ileitis to include inflammation extending >10 cm proximal to the pouch. Extensive prepouch ileitis, especially in the presence of other features, such as deep ulcerations, fistulas, and nonanastomotic strictures, should raise concern for CD. Meanwhile asymmetric, sharply demarcated inflammation may suggest ischemic pouchitis (Figure 3d) (7).

Biopsies are often obtained during pouchoscopy, although histology by itself is insufficient to make a diagnosis of pouchitis. Histology correlates poorly with the degree of inflammation (39,42). Moreover, biopsies obtained from the pouch often demonstrate chronic inflammatory changes, regardless of the presence of endoscopic inflammation, likely representing adaptive changes to fecal stasis within the ileal pouch (43). Histology can be useful, however, in identifying secondary causes of pouchitis when specific histologic features are present, including viral inclusions in CMV pouchitis or granulomas, which are present in



**Figure 3.** Normal pouch anatomy and patterns of pouchitis. (a) Normal J-pouch anatomy with pouchoscopy demonstrating healthy-appearing mucosa and classic “owls eye” configuration. (b) Idiopathic or primary pouchitis demonstrating diffuse inflammation throughout the ileal pouch with sparing of the prepouch ileum. (c) Primary sclerosing cholangitis-associated pouchitis demonstrating diffuse inflammation throughout the ileal pouch with extension into the prepouch ileum. (d) Ischemic pouchitis is characterized by sharply demarcated and segmental inflammation adjacent to normal-appearing mucosa.

up to 10%–12% of those with CD of the pouch (44). Thus, although histology can be supportive of the diagnosis and help to rule out alternative etiologies, pouchitis should be diagnosed and treated only in the presence of symptoms plus endoscopic inflammation. Various scoring systems have also been developed to aid in the diagnosis. The 18-point Pouchitis Disease Activity Index (PDAI) has been commonly used for research purposes and consists of symptom, endoscopy, and histology subscores (45). This has been further simplified for clinical use with the modified PDAI which omits histologic subscores and uses a score cutoff of  $\geq 5$  to define pouchitis (46).

In patients with chronic pouchitis that is refractory to conventional therapy, further diagnostic testing is necessary to exclude

**Table 2. Clinical classification of pouchitis**

Classification	Description
Etiology	
Primary	Idiopathic
Secondary	Identifiable cause, including CD of the pouch, infections ( <i>C. difficile</i> , <i>Candida</i> , or CMV), NSAID use, ischemia, radiation injury, or pouch outflow obstruction (anastomotic stricture or pouch evacuation disorder)
Symptom duration	
Acute	<4 wk
Chronic	≥4 wk
Clinical pattern	
Infrequent	<4 episodes per year
Relapsing	≥4 episodes per year
Continuous	Symptoms that persist without periods of resolution
Response to antibiotics	
Antibiotic-responsive pouchitis	Infrequent episodes (<4 per year) of pouchitis which respond to a 2–4-week course of antibiotic therapy
Chronic antibiotic-dependent pouchitis (CADP)	Frequent episodes (≥4 per year) of pouchitis or persistent symptoms that require long-term, continuous antibiotic or probiotic therapy to maintain remission
Chronic antibiotic-refractory pouchitis (CARP)	Failure to respond to a 4-week course of antibiotic therapy, requiring prolonged treatment (≥4 wk) with an oral or topical 5-aminosalicylate or corticosteroid, immunomodulator, anti-TNF, or other biologic agent
Distribution of inflammation	
Diffuse pouchitis	
Segmental or patchy pouchitis	
Pouchitis with prepouch ileitis	
Pouchitis with concurrent cuffitis	
CD, Crohn's disease; CMV, cytomegalovirus; NSAID, nonsteroidal anti-inflammatory drugs.	

alternative etiologies (Table 3). Infectious workup should include stool testing for *C. difficile* and histology to rule out CMV pouchitis. Computed tomography or magnetic resonance (MR) enterography should be considered to assess for strictures or inflammation involving small bowel proximal to the pouch, whereas an MR pelvis or examination under anesthesia can help to evaluate for leaks, abscesses, or fistulas involving the pouch (47,48). Anorectal manometry and/or MR defecography are useful when there is suspicion of a pouch evacuation disorder (49).

### MANAGEMENT OF ACUTE POUCHITIS

Most episodes of pouchitis are acute and respond readily to antibiotics, which remain the mainstay of treatment. However, treatment with antibiotics is largely empiric because few clinical trials have been conducted (50). Despite this, vast clinical experience has

established the efficacy of antimicrobial therapy in most cases, which has helped to perpetuate the theory of dysbiosis and/or bacterial overgrowth as key components in the pathogenesis of pouchitis.

Patients who intermittently develop acute pouchitis generally feel well in between pouchitis episodes. Thus, clinical remission is typically the goal when treating acute pouchitis. A return to baseline pouch function should be expected after successful treatment.

Traditionally, metronidazole was the most commonly used antibiotic for acute pouchitis (51–53). Metronidazole was compared with placebo in a double-blind crossover trial of 11 patients with active pouchitis, with 73% experiencing improvement in bowel movement frequency while on metronidazole compared with 9% while on placebo ( $P < 0.05$ ) (54). Notably, there was no change in the degree of endoscopic inflammation with metronidazole compared with placebo, although treatment duration was

**Table 3. Secondary causes of symptoms in the pouch apparatus**

Diagnosis	Clinical features	Diagnostic evaluation
CD of the pouch	Diagnosis based on presence of pouch fistulas, nonanastomotic strictures, extensive prepouch ileitis, and/or granulomas on histology Timing: >6–12 months after IPAA completion	Pouchoscopy + biopsies of pouch and prepouch ileum CT or MR enterography ± MRI pelvis ± EUA
Postsurgical complications	Includes postoperative leaks, abscesses, sinus tracts, fistulas, and/or strictures Timing: <6–12 months from IPAA completion	Pouchoscopy + biopsies of pouch and prepouch ileum CT or MR enterography ± MRI pelvis ± EUA
Infections <i>C. difficile</i> CMV Other enteric organisms	Pseudomembranes present in minority of patients with <i>C. difficile</i> pouchitis Suspect CMV in immune-compromised patients with deep pouch ulcers	Stool tests for <i>C. difficile</i> toxin Pouchoscopy + biopsies for histology, immunohistochemistry, and tissue PCR for CMV
Ischemia	Asymmetric, sharply demarcated inflammation within pouch body and/or prepouch ileum	Pouchoscopy + biopsies of inflamed and non-inflamed segments
Pouch outflow obstruction Anastomotic stricture Pouch evacuation disorder	Suspect whether patients complain of straining, incomplete evacuation, constipation, bloating, or require use of laxatives	Digital examination Pouchoscopy HR-ARM with balloon expulsion test ± MR or barium defecography
Cuffitis	Symptoms overlap with pouchitis but more likely to present with rectal bleeding and small volume bowel movements	Pouchoscopy + biopsies demonstrating inflammation of the rectal cuff
Irritable pouch syndrome	Characterized by increase in bowel frequency with abdominal pain, cramping, change in stool consistency, and/or perianal or pelvic discomfort in the absence of an inflammatory or structural pouch disorder	Pouchoscopy Exclude other causes of diarrhea, including celiac disease and dietary factors ± HR-ARM with balloon expulsion test

CD, Crohn's disease; CMV, cytomegalovirus; CT, computed tomography; EUA, examination under anesthesia; HR-ARM, high-resolution anorectal manometry; IPAA, ileal pouch-anal anastomosis; MR, magnetic resonance; PCR, polymerase chain reaction.

only 7 days (54). Although metronidazole is clinically effective for acute pouchitis, its use may be limited by poor tolerability due to metallic taste, nausea, and diarrhea. Neurotoxicity, particularly peripheral neuropathy, may be a concern with more long-term use (>4 weeks) but seems to resolve in most cases on discontinuation of the medication (55). Owing to poor tolerability with metronidazole, the use of other antibiotics, particularly ciprofloxacin, has increased (56). Shen et al. (57) compared the effectiveness and tolerability of ciprofloxacin (1,000 mg/d) vs metronidazole (20 mg·kg<sup>-1</sup>·d<sup>-1</sup>) for 2 weeks in a randomized controlled trial (RCT) of 16 patients with acute pouchitis. Although both ciprofloxacin and metronidazole improved total PDAI, reduction in the total PDAI score was significantly greater in the ciprofloxacin group (6.9 ± 1.2 vs 3.8 ± 1.7; *P* = 0.002), which also experienced greater reductions in symptom and endoscopic subscores (57). Furthermore, there were no adverse events in the ciprofloxacin group, whereas 3 patients on metronidazole developed nausea, dysgeusia, and transient peripheral neuropathy (57). Ciprofloxacin is now generally considered the first-line therapy for treating acute pouchitis (56). However, when using this medication and other fluoroquinolones, it is important to recognize tendinitis and tendon rupture as uncommon but potentially disabling side effects (58).

Although ciprofloxacin and metronidazole remain the most commonly used antibiotics for acute pouchitis, several alternatives have been used successfully in open-label studies and in clinical practice, including rifaximin, amoxicillin-clavulanate, tinidazole, and topical metronidazole (58–62). Rifaximin, a poorly absorbed broad-spectrum antibiotic, demonstrated promise as a monotherapy for active pouchitis in an open-label study (62). In a subsequent placebo-controlled trial that included patients with both acute and chronic pouchitis, 25% (2/8) of those treated with rifaximin achieved clinical remission at 4 weeks compared with 0% (0/9) on placebo, although this did not reach statistical significance (63). A number of nonantibiotic agents have also shown promise in the management of acute pouchitis. In a small RCT, Sambuelli et al. (64) demonstrated similar efficacy of budesonide enemas to oral metronidazole for acute pouchitis, with budesonide enemas being somewhat better tolerated. High-dose De Simone Formulation (formerly VSL#3), a *Lactobacillus*-containing proprietary probiotic, and oral and topical 5-aminosalicylate have also demonstrated efficacy in acute pouchitis via small open-label or observational studies (65–67).

Antibiotics remain the preferred treatment for acute pouchitis, with ciprofloxacin (500 mg twice daily) or metronidazole (500 mg 2–3 times daily) for 2–4 weeks as recommended first-line

**Table 4. Antibiotic regimens for acute pouchitis**

Medication	Dose	Duration
First line		2–4 wk <sup>a</sup>
Ciprofloxacin	500 mg BID (55)	
Metronidazole	20 mg·kg <sup>-1</sup> ·d <sup>-1</sup> (55) OR 500 mg BID or TID <sup>b</sup>	
Second line		
Rifaximin	400 mg TID (61) OR 550 mg BID <sup>b</sup>	
Amoxicillin-clavulanate	875–125 mg BID <sup>b</sup>	
Tinidazole	500 mg daily (59)	

BID, two times daily; TID, three times daily.

<sup>a</sup>Based on clinical response at 2 weeks. If only partial response, it may extend to 4 weeks.

<sup>b</sup>Expert opinion.

options (Table 4). If there is reason to avoid both ciprofloxacin and metronidazole (e.g., previous intolerance or adverse event), then an alternative antibiotic should be used. If patients develop acute pouchitis <3 months after completion of antibiotic therapy, a 2-week course of antibiotics can be repeated, followed by a 2-week course at half the dose. In patients with partial or inadequate response to ciprofloxacin or metronidazole monotherapy, there is some evidence to suggest that combination therapy with both agents for 4 weeks can help to induce clinical remission (68). Other antibiotic combinations that have shown efficacy after initial nonresponse to antibiotic monotherapy include ciprofloxacin-rifaximin and ciprofloxacin-tinidazole (69–71). We do not routinely use nonantibiotic agents for acute pouchitis, although they may have a role in patients with intolerance to multiple antibiotics.

### MANAGEMENT OF CHRONIC POUCHITIS

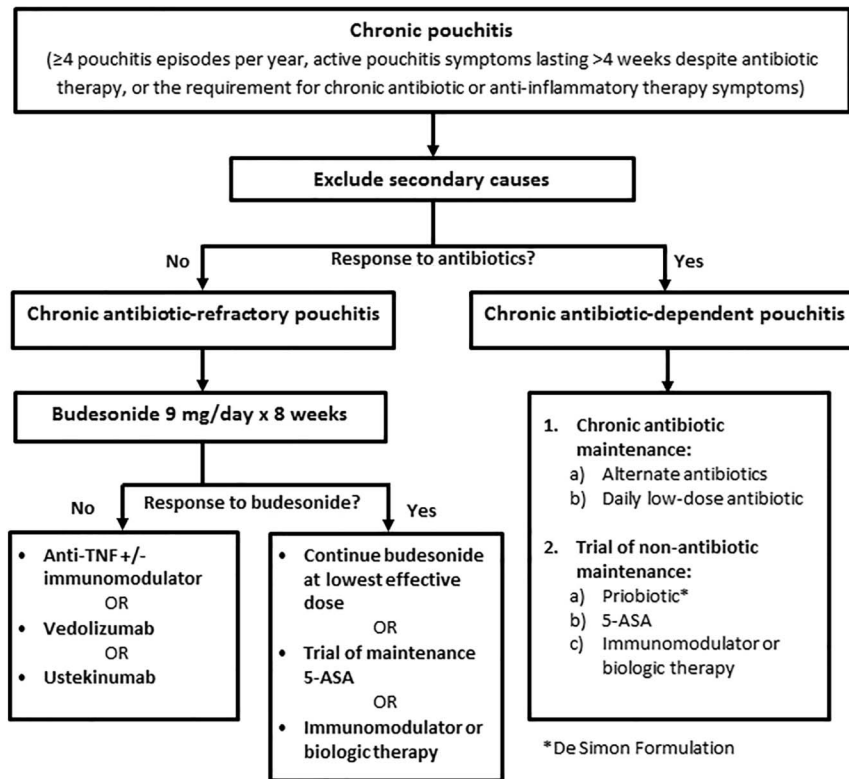
Although most patients respond to antimicrobial therapy, 10%–20% will develop chronic pouchitis that requires long-term treatment or is refractory to conventional therapy (56,72,73). The management of chronic pouchitis remains challenging and is largely empiric because of the lack of controlled trials. Importantly, the initial approach to managing patients with chronic pouchitis should include a thorough investigation for secondary causes (Table 3) (38,74). Once alternative etiologies have been excluded, it is important to distinguish between chronic antibiotic-dependent pouchitis (CADP) vs chronic antibiotic-refractory pouchitis (CARP), as defined in Table 2. Antibiotics remain an important treatment option for those patients who respond but have frequent relapses or continuous symptoms when antibiotics are discontinued (38). In this group of antibiotic-dependent patients, multiple antibiotic regimens have been used in practice and in the literature.

Unlike acute pouchitis in which the aim is clinical improvement or remission, treatment goals in chronic pouchitis are less clear. Although mucosal healing has emerged as the major treatment objective in UC, there are no data to define the role of mucosal healing as a treatment target in chronic pouchitis. Complicating this picture is the fact that histologic changes of chronic pouchitis are seen even in biopsies of asymptomatic patients with endoscopically normal pouches. In general when treating patients with chronic pouchitis, we aim for both clinical and endoscopic remission. However, further studies are necessary to better define treatment endpoints in this subset of patients.

### Chronic antibiotic-dependent pouchitis

In patients with response to antibiotic monotherapy or combination therapy but frequent relapses ( $\geq 4$  per year) when treatment is withdrawn (i.e., CADP), maintenance therapy should be considered in an attempt to prevent or reduce the frequency of subsequent relapses. Maintenance therapy can be in the form of antibiotic or nonantibiotic therapy. Several studies have evaluated various probiotics in secondary prevention of pouchitis, with De Simone Formulation being the most robustly studied (65,75–79). Two trials have demonstrated benefit of De Simone Formulation in preventing relapse after achieving clinical and endoscopic remission with a 4-week course of ciprofloxacin-rifaximin or ciprofloxacin-metronidazole (75,76). In the first study by Gionchetti et al., (75) 85% of patients treated with the proprietary probiotic remained in remission at 9 months compared with none in the placebo group ( $P < 0.001$ ). Similarly, in a subsequent study, 85% of those maintained on De Simone Formulation were in remission at 12 months vs 6% in the placebo group ( $P < 0.0001$ ) (76). The results of other probiotic formulations in secondary prevention have been mixed (80). Despite limited evidence to support the use of probiotics, especially De Simone Formulation, poor adherence because of cost and side effects has limited probiotic use in real-world experience (78). No studies exist on the efficacy of 5-aminosalicylate therapy for maintenance in chronic pouchitis. However, in our anecdotal experience, mesalamine (time released oral or topical) have shown promise as maintenance therapy, particularly in PSC-associated pouchitis, and can be considered in patients hoping to avoid long-term antibiotics or immunosuppressive therapy.

For patients who respond to antibiotics but have rapid recurrence of symptoms when withdrawn or do not respond to nonantibiotic maintenance, chronic antibiotic therapy is often used. In this subset of antibiotic-dependent patients, there is a paucity of literature to guide management. Studies of antibiotic maintenance therapy are limited to rifaximin. In an open-label study of rifaximin in 53 patients with antibiotic-dependent pouchitis, 65% of patients remained in remission at 3 months, of which 58% were in remission at 12 months (81). In clinical practice, daily ciprofloxacin and/or metronidazole at the lowest effective dose are often used. However, the effects of prolonged antibiotic use in this setting have not been rigorously studied and concern remains for long-term sequelae, including the promotion of antibiotic resistance (36,82). A recent study found that even 1 course of antibiotics for pouchitis resulted in point mutations for fluoroquinolone resistance and mobile antibiotic resistance genes.



**Figure 4.** Approach to medical management of chronic pouchitis.

Fortunately, in this study, the resistant organisms were reduced within 1 month of antibiotic completion (36). Little data exist to help guide the optimal antibiotic approach in patients with CADP. In clinical practice, rotating antibiotics on an as needed or scheduled basis may help to mitigate the risk of resistance, although dedicated studies are necessary to determine the best practice in this subset of patients. When antibiotics prove ineffective at achieving clinical and endoscopic response, or in those patients who wish to avoid long-term antibiotics (i.e., antibiotic-sparing therapy), escalating therapy to include a biologic or immunosuppressive agent may be warranted.

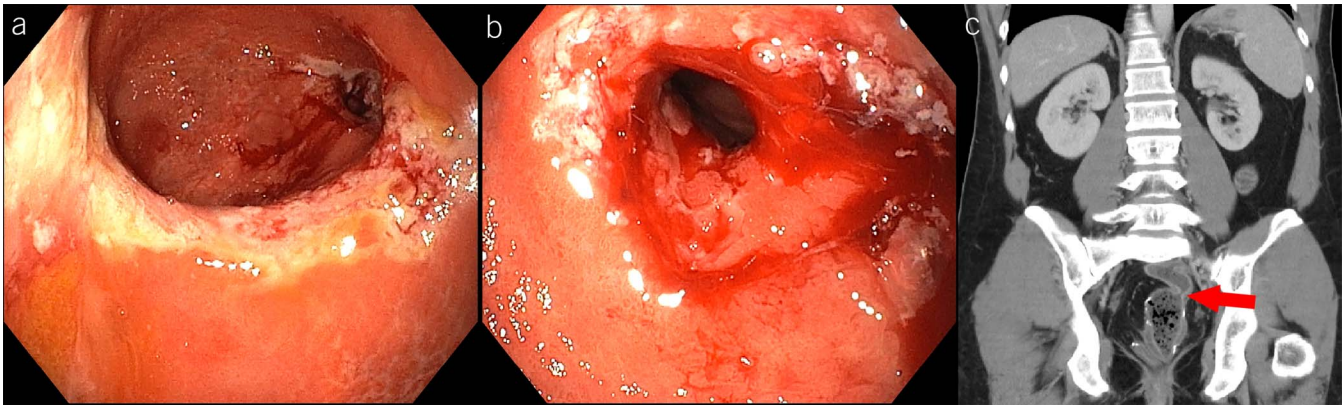
#### Chronic antibiotic-refractory pouchitis

Patients who fail to respond to prolonged and/or combination antibiotic therapy are considered to have CARP. Treatment of CARP is largely based on observational studies and expert opinion, with corticosteroids, immunomodulators, and biologics often used. When antibiotics have proven ineffective, it is important to consider the secondary causes of pouchitis, including CD of the pouch and postsurgical complications (e.g., leaks, sinus tracts, and fistulas). When secondary causes are confidently excluded, treatment with oral budesonide can be considered to see whether the inflammatory process is responsive to a non-antibiotic approach, which can then lead to the exploration of more long-term maintenance strategies. Budesonide, a synthetic steroid with low systemic bioavailability, has demonstrated efficacy in small, uncontrolled studies of patients with CARP (83,84). In 1 observational study, budesonide (9 mg/d) for 8 weeks achieved remission in 75% of patients with CARP (84). As such, a trial of budesonide 9 mg/d for 8 weeks is recommended for those

without contraindications to corticosteroids (74). For those who respond to budesonide therapy, there are no data to guide subsequent treatment. Depending on the severity of inflammation, a trial of maintenance therapy with oral or topical mesalamine or continued budesonide at the lowest effective dose can be considered. Alternatively, biologics are a therapeutic option to maintain remission while avoiding long-term steroid exposure (Figure 4) (56).

If no response to budesonide, rescue therapy with a biologic ( $\pm$  combination immunomodulator) should be considered. There is growing evidence to support the use of biologic agents in this subset of patients who are refractory to all other treatment options. Several case reports and retrospective studies have shown benefit of the tumor necrosis factor inhibitors (anti-TNFs), infliximab (IFX), and adalimumab (ADA) (85–94). A recent meta-analysis included 313 patients treated with IFX (n = 194) or ADA (n = 119) for CARP and CD of the pouch (95). Considering only patients with CARP, clinical remission at 8 weeks and 12 months was achieved in 10% and 37%, respectively (95). There was no significant difference between IFX and ADA (95). In the only placebo-controlled RCT for anti-TNFs in chronic pouchitis, ADA (n = 6) did not differ compared with placebo (n = 7) regarding clinical or endoscopic improvement at 12 weeks, although this study was limited by its small sample size and short duration of follow-up (96).

The role of newer biologics, vedolizumab and ustekinumab, in treating patients with chronic pouchitis has been the focus of recent observational studies. Several case reports and retrospective studies have demonstrated efficacy of vedolizumab, a gut-specific monoclonal antibody directed against  $\alpha 4\beta 7$  integrin, in the treatment of chronic pouchitis (97–101). In a retrospective study by Bär et al.,



**Figure 5.** Crohn's disease of the pouch. Representative findings in a patient with Crohn's disease of the pouch: (a) pouchoscopy demonstrating deep, stellate ulcerations involving the pouch with surrounding of mucosal erythema, (b) ulceration and stenosis at the level of the pouch inlet, which is also seen on (c) Computed tomography abdomen/pelvis with red arrow corresponding to the proximal pouch stricture.

(99) 20 patients with chronic pouchitis (CADP or CARP) were treated with vedolizumab. Clinical and endoscopic response rates at 14 weeks were 65% and 64%, respectively (99). In another retrospective, multicenter study, 83 patients with chronic pouchitis ( $n = 29$ ) or CD of the pouch ( $n = 53$ ) were treated with vedolizumab, with most having previous anti-TNF exposure (102). In a subgroup analysis of those with chronic pouchitis, 51.9% and 58.3% achieved clinical response and endoscopic response at 6 months, respectively (102). Case reports of ustekinumab, a human monoclonal antibody directed against interleukin-12 and interleukin-23, have also demonstrated efficacy in patients with chronic pouchitis (103,104). Moreover, in a recent retrospective, multicenter study examining role of ustekinumab in the treatment of CD of the pouch, 5 of the 6 patients included with chronic pouchitis demonstrated clinical response at 6 months (105).

In summary, the treatment of patients with chronic pouchitis depends on the responsiveness to antibiotics (Figure 4). In those with antibiotic-dependence, we recommend alternating between antibiotics on an as needed or scheduled basis to minimize risk of adverse events and resistance. In those refractory to antibiotics, induction with budesonide 9 mg/d for 8 weeks can be attempted, followed by a taper off of the budesonide or maintenance with the lowest effective dose. Biologic therapy can also be considered a steroid-sparing treatment in this group of patients. If there is no response to budesonide, biologic therapy should be initiated, with or without concomitant immunomodulator. There is not enough evidence to suggest 1 biologic agent as superior, so the decision between an anti-TNF, vedolizumab, or ustekinumab should be individualized based on individual characteristics, previous biologic exposure, and history of intolerance or adverse events.

## CROHN'S DISEASE OF THE POUCH

### Incidence and diagnosis

CD of the pouch develops de novo in up to 13% of those who undergo IPAA for UC (106,107). Although uniform diagnostic criteria are lacking, CD of the pouch is often diagnosed based on the presence of pouch-related fistulas, nonanastomotic strictures, and/or prepouch ileitis (Figure 5) (108). In some cases, the distinction between CD of the pouch and chronic pouchitis is blurred. One such example includes the presence of deep pouch ulcers in the absence of other Crohn-defining features. In this circumstance, the term "Crohn's-like disease of the pouch" is sometimes favored. To

help determine chronic pouchitis vs Crohn's-like disease of the pouch, isolated pouch ulcers should be initially treated with a trial of antibiotics before escalating therapy in those who do not respond.

Creating further diagnostic uncertainty is the fact that clinical features of CD of the pouch may substantially overlap with postoperative complications, which can also present with fistulas or strictures. In this case, timing is critical to differentiate between the 2 entities because CD of the pouch typically develops more than 6–12 months after IPAA completion, with postsurgical complications occurring earlier in the postoperative period (107). Making this distinction is important because it has major implications on management.

### Management

Similar to chronic pouchitis, data are lacking to define treatment goals for CD of the pouch. Specifically, the role of complete mucosal healing in this population remains unclear. In general, we approach these patients similarly to chronic pouchitis with a goal of clinical and endoscopic remission.

The mainstay of treatment for CD of the pouch remains immunosuppressive therapy. Treatment approach is largely driven by several observational studies and expert opinion (92,109–112). Anti-TNF therapy, particularly IFX or ADA, with or without an immunomodulator, is often used as the first-line treatment once CD of the pouch has been diagnosed. As suggested by a recent meta-analysis, anti-TNF agents seem effective in CD of the pouch (95). Patients with CD of the pouch had a higher rate of clinical remission at 8 weeks compared with chronic pouchitis (64% vs 10%,  $P = 0.06$ ) (95). Meanwhile, the rate of clinical remission at 12 months for CD of the pouch was 57% compared with 37% in patients with chronic pouchitis ( $P = 0.57$ ) (95). There was no statistically significant difference between IFX and ADA (95).

Newer data exist to support the use of vedolizumab and ustekinumab in CD of the pouch as well. In the aforementioned retrospective, multicenter study of vedolizumab, 65.4% and 53.6% of patients with CD of the pouch demonstrated clinical and endoscopic response at 6 months, respectively (102). Most patients had previous exposure to anti-TNF therapy, although those without seemed more likely to achieve clinical and endoscopic response (102). Similarly, in the previously mentioned multicenter study of ustekinumab, 83% of those with CD of the pouch had clinical response at 6 months (11% clinical remission)

(105). There was no significant difference in response rates based on previous anti-TNF exposure (105).

### POUCH FAILURE

Pouch failure, defined as requiring pouch excision or permanent diversion, occurs in 5%–10% of patients after IPAA (19,73,113–115). Pouch failure can occur early (<12 months after ileostomy closure) or late (>12 months after ileostomy closure), with most early-onset pouch failure due to surgery-related complications, such as pelvic sepsis or an anastomotic leak (116). Late-onset pouch failure is generally secondary to chronic pouchitis or CD of the pouch. In 1 single center experience of patients with late-onset pouch failure, 39% and 24% were due to CD of the pouch and chronic pouchitis, respectively (116).

### FUTURE DIRECTIONS

There remain many gaps in the diagnosis and management of pouch inflammatory disorders, especially regarding chronic pouchitis and CD of the pouch. The diagnosis of CD of the pouch remains imprecise and variable across providers and institutions. Features may often overlap with other inflammatory pouch conditions, including chronic pouchitis, leading some to favor the term Crohn's-like disease of the pouch. Diagnostic criteria for CD of the pouch must be better defined to more uniformly approach diagnosis and treatment in these patients. Regarding management, optimal endpoints remain unknown. Further work is necessary to clarify goals of treatment, including the role of mucosal healing in patients with chronic pouchitis and CD of the pouch. Finally, although many patients with chronic pouchitis are antibiotic-dependent, the risk of long-term antibiotic use on overall health has not been rigorously studied in this patient population. It may be time to place a greater emphasis on antibiotic-sparing approaches in these patients, especially given the efficacy and safety profile of newer biologic agents. In addition, there may be opportunity to manipulate the pouch microbiome without the use of antibiotics using dietary therapies or more targeted probiotics. However, all of these approaches warrant further study.

### SUMMARY

Although most patients with pouchitis respond quickly to a course of antibiotics, up to 20% develop chronic pouchitis, often leading to antibiotic-dependence or the need for long-term immunosuppressive therapy. In this subset of patients, it is important to carefully assess for other causes of inflammation of the pouch to help guide appropriate therapy. Chronic pouchitis and other chronic inflammatory conditions of the pouch lead to significant morbidity and carry increased risk of pouch failure. A multidisciplinary approach to managing these patients is often necessary, with pharmacotherapy playing an imperative role in reducing inflammation and improving clinical outcomes. As such, it is important to be familiar with available treatment options and rationale for their use.

### CONFLICTS OF INTEREST

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