Diagnosis and Management of Postoperative Ileal Pouch Disorders

Bo Shen, M.D.[1]

ABSTRACT

Although restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the surgical treatment of choice for patients with refractory ulcerative colitis (UC) or UC with dysplasia, surgical, inflammatory, and noninflammatory adverse sequelae are common. Pouchitis, representing a spectrum of disease phenotypes, is the most common long-term complication of IPAA. De novo Crohn disease (CD) of the pouch can occur in patients with a preoperative diagnosis of UC. Differential diagnosis between fibrostenotic or fistulizing CD and surgery-associated strictures, sinuses, and fistulas often requires a combined assessment of symptom, endoscopy, histology, radiography, and examination under anesthesia. There is a role for endoscopic therapy for stricturing complications of IPAA. Chronic antibiotic-refractory pouchitis, refractory cuffitis, as well as fibrostenotic or fistulizing CD of the pouch are the leading late-onset causes for pouch failure.

KEYWORDS: Complication, ileal pouch, inflammatory bowel disease, restorative proctocolectomy

Objectives: On completion of this article, the reader should be able to summarize the diagnosis, differential diagnosis, and management of complex ileal pouch disorders.

Even if the era for biological therapy for inflammation bowel disease (IBD) has arrived, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is still the surgical treatment of choice for the majority of patients with ulcerative colitis (UC) who fail medical therapy or develop dysplasia or neoplasia as well as for patients with familial adenomatous polyposis (FAP). Although this bowel-anatomy-altering procedure improves patients' health-related quality of life and substantially reduces the risk for UC-associated neoplasia, mechanical/surgical, inflammatory, and functional complications are common. Some of these complications can lead to pouch failure with pouch excision or permanent diversion. In a meta-analysis of 43 studies of 9,317 patients from mostly tertiary-care settings, the frequency of pouch failure was estimated to be 7% with a median follow-up of 37 months; the frequency increased to 9% after more than 60 months.[1] The most common causes for early-onset pouch failure are pouch leaks, abscess, and pelvic sepsis.[2,3] Whereas the leading causes for late-onset pouch failure are chronic pouchitis, Crohn disease (CD) of the pouch,[4] refractory cuffitis,[5] and chronic deep, complex pouch sinus.[6] Recognition and appropriate diagnosis of these pouch-related conditions are imperative for proper management and prognosis.

[1]Department of Gastroenterology/Hepatology, Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio.

Address for correspondence and reprint requests: Bo Shen, M.D., Digestive Disease Institute, Desk A31, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195 (e-mail: shenb@ccf.org).

SURGERY-ASSOCIATED COMPLICATIONS

Pouch leak can occur after IPAA and the most common locations are the pouch-anal anastomosis and the tip of the "J."[7] Patients with immediate postoperative leak usually present with symptoms related to pelvic sepsis.[2] Soluble contrast pouchogram, pelvic magnetic resonance imaging (MRI), and examination under anesthesia can help detect the location, feature, and depth of the leak.[8] Immediate postoperative pelvic sepsis and pelvic abscess occurs in 5 to 20% of patients undergoing restorative proctocolectomy with IPAA, and ~30% of these patients will eventually have pouch failure.[1,2,4,9] Pelvic sepsis was associated with anastomotic leak in 34%, fistulas in 25%, and even mortality in 3% of patients.[2] Pelvic sepsis often requires surgical intervention. There is a limited role for practicing gastroenterologists in the diagnosis and management of acute anastomotic leaks.

Pouch sinus is typically a later presentation of an initial anastomotic leak. The most common location of a pouch sinus is the pouch-anal anastomotic site, which is frequently located at the presacral space (Fig. 1). Some patients can present with symptoms suggestive of pelvic sepsis, pouchitis, CD of the pouch, or refractory cuffitis; others may be asymptomatic. Common symptoms in patients with pouch sinus are perianal pain, pelvic pressure and discomfort, and tailbone pain. Severe and complex sinus may result in intermittent fever, weight loss, and anemia. In extreme cases, chronic deep pouch sinus can lead to osteomyelitis of tailbone posteriorly and pouch-vaginal or pouch-vesicular fistulas anteriorly. For patients with clinical presentations suspected of pouch sinus, a careful pouchoscopy should be performed with attention to the anastomosis and the tip of the "J." However, abdominal imaging with water-soluble con-

trasted pouchogram and/or MRI of the pelvis is often needed to delineate the complexity, depth, and possible complicating abscess. Sinus opening and sinus tract can be detected by a combined assessment of pouchoscopy, contrasted pouchogram, examination under anesthesia and pelvic MRI.[10] Treatment usually includes periodic incision and drainage of the chronically infected superficial sinuses to promote secondary healing and closure. It may take up to 9 to 12 months before these sinuses heal. Fibrin glue injection of the sinus may be attempted.[11] Patients with a long sinus track who do not have complete healing following ileostomy closure, are usually candidates for a redo pouch procedure.[11,12] Our group started using endoscopic needle knife therapy for the treatment of simple, shallow (<5 cm in depth) presacral sinus (Fig. 2). The procedure has been performed in patients with or without protecting diverting ileostomy.[13] Our anecdotal experience suggests that ~50% of patients with a simple, short sinus can be treated with endoscopy.

Surgery-associated fistulas can originate at any levels of the pouch with the most common location being at the anastomosis, and they can extend into any adjacent organs or to the skin. The distinction between surgery-induced fistulas and CD-associated fistulas can be challenging. Pouch-vaginal fistula (PVF) is a unique and yet common condition with IPAA and a major source of morbidity and a common cause for pouch failure.[14] Although diagnosis of PVF is mainly based on symptoms, endoscopic and radiographic documentation is often needed for the differential diagnosis and direction of treatment. Our recent study found that examination under anesthesia is more accurate than pouch endoscopy, MRI, computed tomography (CT), and water-contrasted pouchogram.[15] A diagnosis of CD
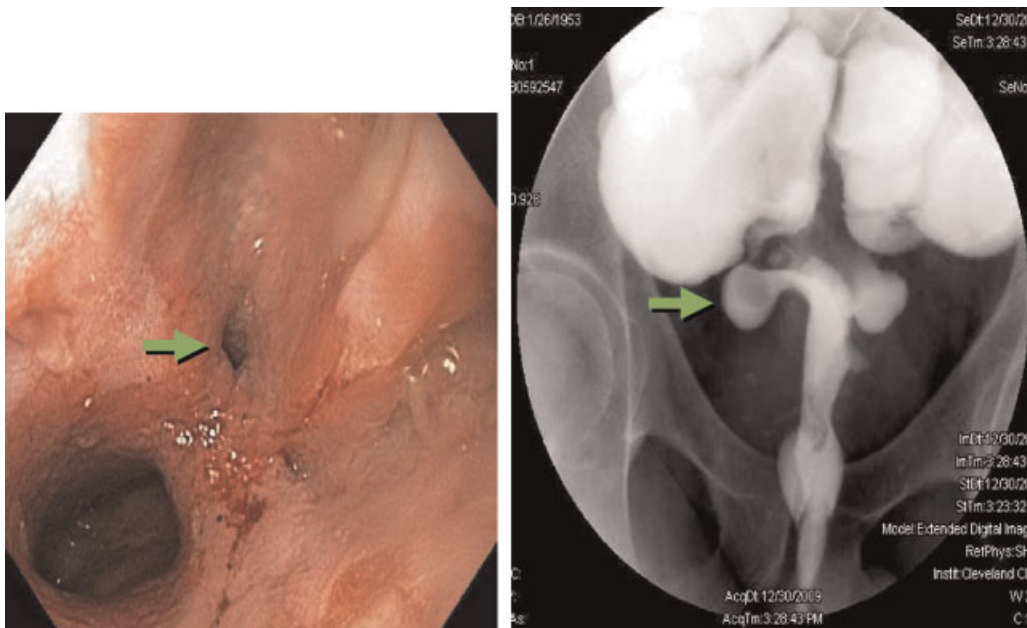
Figure 1 Pouch sinus on pouch endoscopy and contrasted pouchogram (arrows).
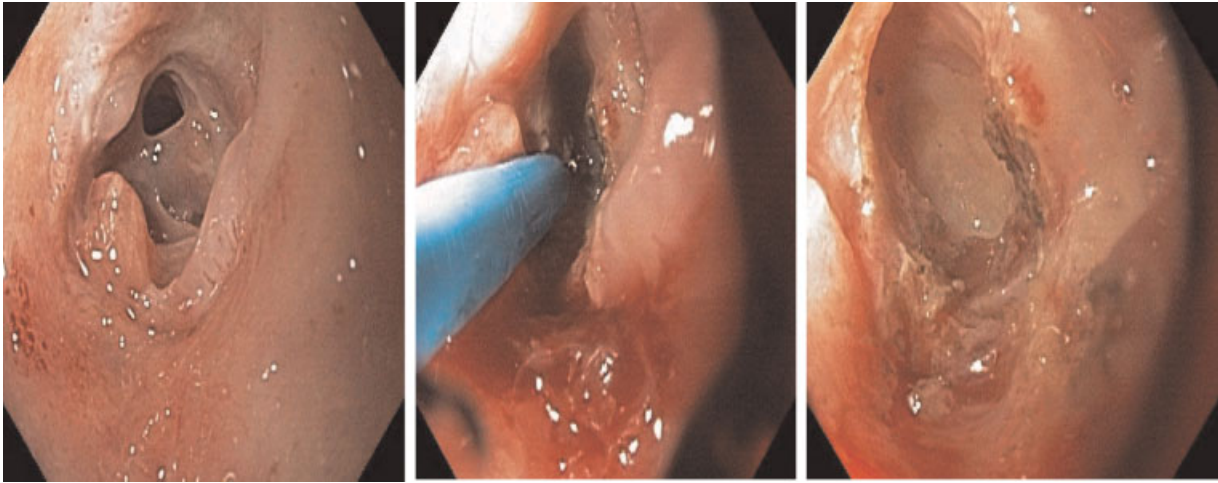
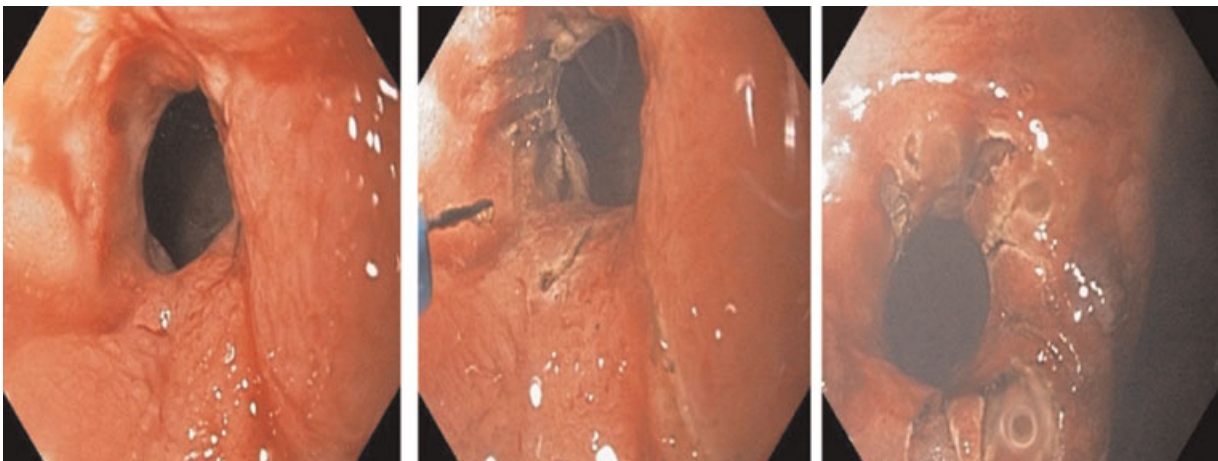**Figure 2** Endoscopic needle knife therapy for a distal pouch sinus.

should be suspected in patients with PVF, if the patients have a preoperative diagnosis of CD before IPAA, the presence of a fistula 6 to 12 months after IPAA in the absence of immediate postoperative leaks, pelvic abscess or pelvis sepsis, a complex fistula outside the anastomosis or dentate line, concurrent ulcers in the proximal small bowel or afferent limb, or repeated failure for fistula repair or fibrin glue therapy. However, surgical intervention is often required for PVF, despite the etiology of PVF.[16]

Strictures after IPAA are common. In a series of 1,884 cases with IPAA, pouch strictures occurred in 213 patients (11%).[17] However, most of those strictures are self-limiting web-type strictures that are recognized and dilated at the time of stoma closure. Common locations are at the anastomosis, pouch inlet, and site of prior ileostomy. Contributing etiological factors include surgery-associated ischemia, use of nonsteroidal antiinflammatory drugs (NSAIDs), and CD. Strictures can be treated with medical therapy (including cessation of NSAIDs and pharmaceutical treatment for CD) as

well as endoscopic[18] or bougie dilations, endoscopic needle knife therapy (Fig. 3), surgical stricturoplasty, bowel resection and anastomosis, or pouch diversion or excision.[19]

POUCHITIS

Pouchitis, a nonspecific inflammation of the ileal reservoir, is the most common long-term complication in patients with IPAA. It significantly affects patients' health-related quality of life.[20] Reported cumulative frequency rates of pouchitis 10 to 11 years after IPAA surgery range from 23 to 46%,[21,22] with an incidence of 40% within the first 12 months after ileostomy closure.[23] Pouchitis almost exclusively occurs in patients with underlying UC and is rarely seen in patients with FAP.[24,25] Although its etiology and pathogenesis are not entirely clear, multiple lines of evidence suggest that an abnormal mucosal immune response to altered commensal bacterial flora (dysbiosis) leads to acute or chronic inflammation of the pouch reservoir in a genetically

Figure 3 Endoscopic needle knife therapy for a pouch inlet stricture.

susceptible host.[26–28] Reported risk factors for pouchitis include genetic polymorphisms of IL-1 receptor antagonist[29–31] and NOD2/CARD15;[32] noncarrier status of tumor-necrosis factor allele 2;[31] extensive UC[22,33,34] backwash ileitis;[33] precolectomy thrombocytosis;[35,36] preoperative corticosteroid use;[36] extraintestinal manifestations, especially PSC and arthropathy;[21,34,36–39] the presence of perinuclear antineutrophil cytoplasmic antibodies;[40–42] being a nonsmoker;[36,43,44] and regular use of NSAIDs.[34,44] Some of these risk factors are therapeutically modifiable.

Pouchitis is not a homogenous disease entity. Rather, it represents a disease spectrum with a wide range of clinical presentations, endoscopic and histologic features, disease courses, and prognoses. Increased stool frequency, urgency, incontinence, nocturnal seepage, abdominal cramping, pelvic discomfort, and arthralgia are the most common presenting symptoms.[17] The severity of symptoms does not necessarily correlate with the degree of endoscopic or histologic inflammation of the pouch.[45,46] In addition, these symptoms are not specific for pouchitis, as they can be presented in patients with other inflammatory or functional disorders of the pouch, such as CD, cuffitis, pouch sinus, and irritable pouch syndrome (IPS). Endoscopy is the most reliable tool for diagnosis and differential diagnosis of pouchitis.[45] Ideally, a combined assessment of symptoms and endoscopic and histologic features should be performed to diagnose pouchitis.

It is imperative to classify the phenotype of pouchitis before initiating therapy. Although there is no validated and universally accepted classification system, pouchitis, from different clinical perspectives, may be categorized into (1) idiopathic versus secondary, (2) remission versus active, (3) acute versus chronic with a cutoff duration of 4 weeks, (4) infrequent episodes (e.g., <4 episodes a year) versus relapsing (≥4 episodes a year) versus continuous course, and (5) antibiotic-responsive, antibiotic-dependent versus antibiotic-refractory refractory.[47–49] Chronic antibiotic-refractory pouchitis is one of the leading causes for pouch failure, resulting in permanent diversion or pouch excision. In a study of 100 consecutive UC with IPAA, 5 developed chronic pouchitis, of whom 2 had pouch failure.[47] One would expect that there will be an increasing number of patients with chronic antibiotic-refractory pouchitis in clinical practice, as a cumulative number of patients with IPAA are expanding. For patients with a disease course refractory to conventional antibiotic therapy, secondary etiologies should be evaluated. These secondary etiologic factors include infection from intestinal pathogens (e.g., *Clostridium difficile*,[50] *Candida*,[51] cytomegalovirus,[52,53] and *Campylobacter* species,[54] NSAID use,[55] concurrent autoimmune disorders (e.g., celiac disease),[56] and pouch ischemia.[57]

Treatment strategies vary in different types of pouchitis.[58] A common scenario is that a patient with active endoscopic inflammation of the pouch may be asymptomatic. However, it is advisable to still treat the patient, as chronic smoldering inflammation may lead to a "stiff" pouch. For antibiotic-responsive pouchitis, the first-line therapy generally includes a 14-day course of metronidazole (15–20 mg/kg/day) or ciprofloxacin (1000 mg/day).[59,60] Other agents were reported in open-label trials including tetracycline, doxycycline, clarithromycin, amoxicillin/clavulanic acid, oral or topical budesonide, alicaforsen enemas (an antisense inhibitor of intercellular adhesion molecule-1), leukocytapheresis,[61] probiotics,[62] and a carbon microsphere adsorbent agent.[63]

Patients with antibiotic-dependent pouchitis often require long-term maintenance therapy to keep disease in remission. Maintenance agents include probiotics (such as VSL#3[®], VSL Pharmaceuticals, Gaithersburg, MD[64,65]) and a low dose of antibiotics (such as rifaximin).[66] Although the probiotic agents have been shown to be highly effective in primary and secondary prophylaxis of pouchitis in randomized controlled trials, the results of postmarket routine clinical use have been disappointing.[67]

Treatment of antibiotic-refractory pouchitis is often challenging. It is important to investigate contributing factors related to failure of antibiotic therapy, such as *Clostridium difficile* and cytomegalovirus infection, NSAID use, and current autoimmune disorders. Recently, we also found that some patients with pouchitis had ischemic features on endoscopy and abdominal imaging. A classic endoscopic feature of ischemic pouchitis is the presence of inflammation in the half of the pouch body sparing the rest half of the pouch with a sharp demarcation between inflamed and noninflamed parts along the suture line (Fig. 4).[57] After exclusion of infection of the specific bacterial or viral pathogens, patients with antibiotic-refractory pouchitis can be treated with a prolonged course of combined antibiotic agents. Options could be combined ciprofloxacin (1000 mg/d) with rifaximin (2000 mg/d),[68,69] metronidazole (1000 mg/d),[70] or tinidazole (1000–1500 mg/d) for 4 weeks.[71] However, maintenance of remission in this group of patients after the induction therapy with dual antibiotics remains challenging.[72] These agents include bismuth carbomer enemas,[73] short-chain fatty acid enemas,[74] glutamine enemas, oral budesonide,[75] mesalamine enemas, 6-mercaptopurine or azathioprine, and infliximab.[76]

Cuffitis

Cuffitis, considered to be a variant form of UC in the rectal cuff, is common in patients with IPAA, particularly in those with stapled anastomosis without
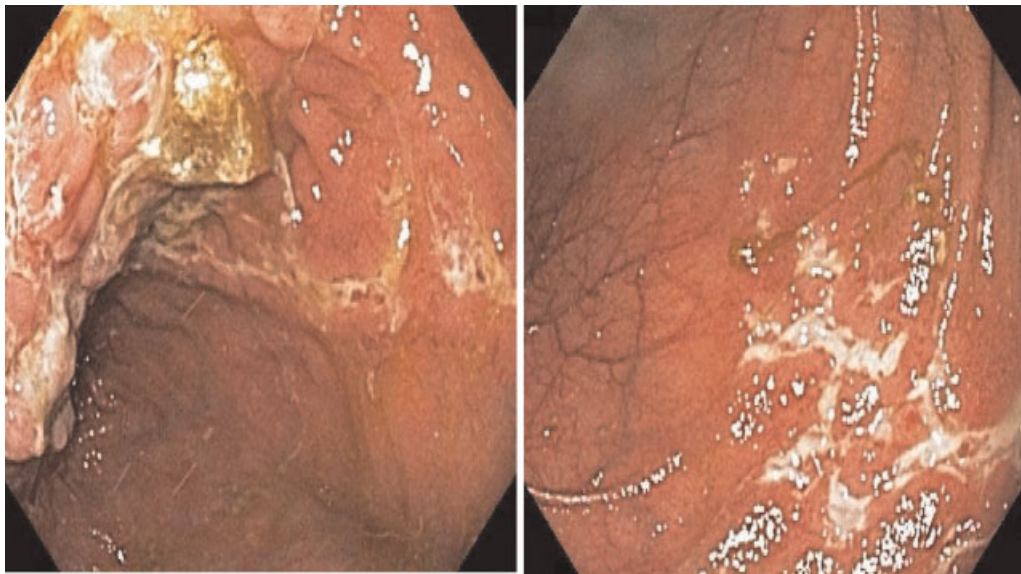
Figure 4 Ischemic pouchitis on endoscopy with sharp demarcation of inflamed and noninflamed parts of pouch along the suture line (left) and triangular-shaped disease distribution (right).

mucosectomy. Clinical symptoms of cuffitis are similar to those in pouchitis. In addition, patients with cuffitis often present with small-quantity bloody bowel movements. Cuffitis can be treated with mesalamine suppositories,[77] or topical lidocaine/corticosteroid agents. In our clinical practice, we occasionally treat refractory cuffitis with endoscopic injection of long-acting corticosteroids. Systemic agents are rarely needed. Of note, cuffitis may not be a simple residual ulcerative colitis, as surgery-associated ischemia may contribute inflammation at the anal transitional zone. Patients with cuffitis refractory to topical mesalamine and/or corticosteroid therapy should be evaluated for other disease processes at or around the cuff, such as fistula and chronic anastomotic leaks. Refractory cuffitis can also be a sign of CD of the pouch. Chronic cuffitis can be a contributing factor for anastomotic stricture. Refractory cuffitis associated with CD or surgery-complications can lead to pouch failure.[78]

Crohn Disease of the Pouch

Reported cumulative frequencies of CD of the pouch ranged from 2.7 to 13%.[48] CD of the pouch can occur after IPAA, which is intentionally performed in a selected group of patients with Crohn colitis with no previous small intestinal or perianal disease[79]; CD is also inadvertently found in colectomy specimens of patients with a preoperative diagnosis of UC. CD of the pouch diagnosed in these two settings may be classified into early-onset CD of the pouch.[80] De novo CD of the pouch may develop weeks to years after IPAA for UC and a reassessment of the proctocolectomy specimens may show no evidence of CD. De novo CD developed

months to years after IPAA may be considered as late-onset CD.[80]Patients with late-onset CD of the pouch typically appear to have a poorer prognosis with a higher risk for pouch failure than those with early onset CD.[80]

The etiology and pathogenesis of CD of the pouch are not clear. It has been postulated that IPAA with components of procedure-associated ischemia, anastomosis, and fecal stasis may create a CD-friendly environment.[81] Therefore, extensive preoperative endoscopic, serological, histologic, and radiographic evaluation, which would have excluded CD, does not guarantee nondevelopment of CD after IPAA. On the other hand, patients with Crohn colitis, a relative contraindication for IPAA, who had the procedure intentionally performed, may not necessarily have developed CD of the pouch.[82] Therefore, the natural history of CD of the pouch is poorly defined.

Assessment of risk factors for the development of CD of the pouch may help the decision of whether, when, and which surgical procedure is performed. Reported risk factors for CD of the pouch include family history of CD and smoking.[83,84] Intraoperative or immediate postsurgical histopathological evaluation of colectomy specimen for neural hypertrophy may be predictive of the development of CD of the pouch.[85] The role of IBD serology in predicting postoperative development of CD of the pouch warrants further evaluation with confirmation studies.[83]

CD of the pouch can be classified into *inflammatory*, *fibrostenotic*, or *fistulizing* phenotypes.[48] The clinical phenotypes of CD of the pouch are associated with different risk factors and clinical presentations.[86] Presentation of CD of the pouch, however, often overlap with that from other inflammatory disorders of the

pouch (e.g., pouchitis and cuffitis) and surgery-associated strictures, sinuses, and fistulas. Therefore, the diagnosis of CD of the pouch should be based on a combined assessment of symptom, endoscopy, histology, abdominal imaging, and sometimes examination under anesthesia. Endoscopic and/or histologic documentation of upper GI disease with esophagogastroduodenoscopy may be helpful for the diagnosis of CD. The role of serology in the diagnosis and differential diagnosis of CD of the pouch needs further investigation.

Although symptoms from various disease conditions of the pouch often overlap, there are symptoms and signs that may suggest a diagnosis of CD, particularly fibrostenotic and fistulizing CD. Clinical presentations of CD of the pouch can be persistent abdominal pain, nausea, anemia, weight loss, failure to thrive, fever, and fistular drainage. It is critical to differentiate NSAID-induced ileitis/pouchitis from CD ileitis and backwash ileitis with diffuse pouchitis. It is also important to distinguish surgical ischemia-associated stricture and fistulizing complications from fibrostenotic or fistulizing CD. However, these distinctions can be difficult to make. In clinical practice, CD of the pouch should be suspected if a patient develops de novo fistula more than 6 to 12 months after ileostomy take-down in the absence of postoperative leak, abscess, and sepsis.

There are scant data on the treatment of CD of the pouch. Patients should be strongly encouraged to avoid cigarette smoking and NSAID use. The majority of CD patients require life-long medical therapy to avoid permanent ileostomy. Stratification of patients based on clinical phenotypes is important for treatment. CD can be treated with a combined medical,[87] endoscopic (e.g., balloon dilation of stricture),[88] and surgical (e.g., stricturoplasty)[89] therapies. Inflammatory CD of the pouch may be treated with topical and oral 5-aminosalicylate agents, oral or topical corticosteroids, antibiotics, immunomodulators, and biologics. Commonly used agents include oral mesalamines and budesonide. Break-capsule mesalamines or budesonide mixed with applesauce may provide better coverage for patients with proximal small bowel disease. In patients whose disease is refractory to these agents, particularly when they have concurrent extraintestinal symptoms, biological agents such as infliximab and adalimumab may be used.

For fibrostenotic CD of the pouch, endoscopic therapy together along with medical therapy is often needed. Although medical therapy alone has a minimum therapeutic impact on mechanical strictures, it may help reduce mucosal inflammation in between the strictures. Endoscopic balloon dilation can be attempted for CD-associated stricture. Endoscopic balloon dilation with or without guidewire can be safely performed without fluoroscopic guidance.[18] For patients with long and high-grade strictures, endoscopic needle knife "stricturoplasty" treatment, particularly with Doppler ultrasound guidance may be attempted in experienced hands. Refractory, multiple, and angulated strictures may be treated with surgical stricturoplasty, resection and anastomosis, or proximal diversion.

The management of fistulizing CD of the pouch has been difficult. Antibiotics, immunomodulators, and biologics may be tried. Biologics such as infliximab and adalimumab appeared to be effective in short-term induction, with decreased fistular drainage.[87,90] However, whether the biological therapy could maintain the disease in remission in the long term or have a positive impact on the natural history of CD of the pouch remains to be seen. Medical therapy for PVF and pouch-bladder fistula has been disappointing. Surgical intervention is usually required.

IRRITABLE POUCH SYNDROME

Irritable pouch syndrome is a functional disorder in patients with IPAA.[91] The disease entity has a significant negative impact on health-related quality of life.[20] Its etiology and pathophysiology are not clear. It may be attributed to psychosocial factors,[20] visceral hypersensitivity as measured by electronic barostat,[92] and enterochromaffin cell hyperplasia of the pouch mucosa.[93] Currently, IPS is a diagnosis of exclusion. Treatment is empiric, and therapeutic agents include antidiarrheals, antispasmodics, tricyclic antidepressants, and oral or topical narcotic agents.

POUCH NEOPLASIA

Although proctocolectomy with IPAA substantially reduces the risk for dysplasia and cancer in UC patients, dysplasia or adenocarcinoma can still occur in the rectal cuff (anal transitional zone) or pouch body, presenting as flat or polypoid lesions.[94–97] Reported risk factors for dysplasia or cancer in the ileal pouch or cuff include a longer duration of UC (irrespective of duration of IPAA),[98] a preoperative or intraoperative diagnosis of dysplasia or cancer from underlying UC,[99] the presence of pancolitis with backwash ileitis,[100,101] villous atrophy of the pouch mucosa or histologic type C mucosa (pouch mucosa with persistent severe atrophy),[94,98,100,102] chronic pouchitis,[98] and primary sclerosing cholangitis.[98] Our recent study of 3203 pouch patients with underlying IBD showed the cumulative incidences for pouch neoplasia at 5, 10, 15, 20, and 25 years were 0.9%, 1.3%, 1.9%, 4.2%, and 5.1%, respectively. In multivariable analysis, the risk factors associated with pouch neoplasia was a preoperative diagnosis of UC-associated cancer or dysplasia, with adjusted hazard ratios of 13.43 (95% confidence interval [CI] = 3.96–45.53, $p < 0.001$) and 3.62 (95% CI = 1.59–8.23, $p = 0.002$), respectively.

Pouch endoscopy with biopsy, the current gold standard for surveillance, may still miss the detection of neoplasia at the dysplasia stage.[103]

In summary, restorative proctocolectomy IPAA is a technically challenging procedure that requires appropriate skills and expertise to minimize surgery-associated complications. Adverse sequelae of IPAA are common. Accurate diagnosis, classification, and differential diagnosis of pouch disorders and associated complications are important for proper management and prognosis and for improving long-term surgical outcome. De novo CD of the pouch can occur. The risk for neoplasia in patients with UC and IPAA is small, but it not eliminated by colectomy or mucosectomy. A preoperative diagnosis of dysplasia or cancer of colon or rectum is a risk factor for pouch dysplasia or adenocarcinoma.

REFERENCES

1. Hueting WE, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. Dig Surg 2005;22(1-2):69–79

2. Sagap I, Remzi FH, Hammel JP, Fazio VW. Factors associated with failure in managing pelvic sepsis after ileal pouch-anal anastomosis (IPAA)—a multivariate analysis. Surgery 2006;140(4):691–703; discussion 703–704

3. Prudhomme M, Dehni N, Dozois RR, Tiret E, Parc R. Causes and outcomes of pouch excision after restorative proctocolectomy. Br J Surg 2006;93(1):82–86

4. Nicholls RJ. Review article: ulcerative colitis—surgical indications and treatment. Aliment Pharmacol Ther 2002;16(Suppl 4):25–28

5. Shen B, Lian L, Remzi FH, et al. Natural history of cuffitis in ulcerative colitis patients with restorative proctocolectomy and ileal pouch-anal anastomosis. Poster presented at: Digestive Disease Week; May 1–10, 2010; New Orleans, LA

6. Garrett KA, Remzi FH, Kirat HT, Fazio VW, Shen B, Kiran RP. Outcome of salvage surgery for ileal pouches referred with a diagnosis of Crohn's disease. Dis Colon Rectum 2009;52(12):1967–1974

7. Paye F, Penna C, Chiche L, Tiret E, Frileux P, Parc R. Pouch-related fistula following restorative proctocolectomy. Br J Surg 1996;83(11):1574–1577

8. Hedrick TL, Sawyer RG, Foley EF, Friel CM. Anastomotic leak and the loop ileostomy: friend or foe? Dis Colon Rectum 2006;49(8):1167–1176

9. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998;85(6):800–803

10. Tang L, Cai H, Moore L, Shen B. Evaluation of endoscopic and imaging modalities in the diagnosis of structural disorders of the ileal pouch. Inflamm Bowel Dis 2010;16(9):1526–1531

11. Swain BT, Ellis CN. Fibrin glue treatment of low rectal and pouch-anal anastomotic sinuses. Dis Colon Rectum 2004;47(2):253–255

12. Whitlow CB, Opelka FG, Gathright JB Jr, Beck DE. Treatment of colorectal and ileoanal anastomotic sinuses. Dis Colon Rectum 1997;40(7):760–763

13. Lian L, Geisler D, Shen B. Endoscopic needle knife treatment of chronic presacral sinus at the anastomosis at an ileal pouch-anal anastomosis. Endoscopy 2010;42(Suppl 2):E14

14. Shah NS, Remzi F, Massmann A, Baixauli J, Fazio VW. Management and treatment outcome of pouch-vaginal fistulas following restorative proctocolectomy. Dis Colon Rectum 2003;46(7):911–917

15. Rochey H, Navaneethan U, Kiran R, Shen B. Evaluation of diagnostic modalities for pouch vaginal fistula in patients with inflammatory bowel disease and restorative proctocolectomy. Paper presented at: American College of Gastroenterology Annual Meeting; October 18–20, 2010; San Antonio, TX

16. Burke D, van Laarhoven CJ, Herbst F, Nicholls RJ. Transvaginal repair of pouch-vaginal fistula. Br J Surg 2001;88(2):241–245

17. Prudhomme M, Dozois RR, Godlewski G, Mathison S, Fabbro-Peray P. Anal canal strictures after ileal pouch-anal anastomosis. Dis Colon Rectum 2003;46(1):20–23

18. Shen B, Fazio VW, Remzi FH, et al. Endoscopic balloon dilation of ileal pouch strictures. Am J Gastroenterol 2004;99(12):2340–2347

19. Lucha PA Jr, Fticsar JE, Francis MJ. The strictured anastomosis: successful treatment by corticosteroid injections—report of three cases and review of the literature. Dis Colon Rectum 2005;48(4):862–865

20. Shen B, Fazio VW, Remzi FH, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol 2005;100(1):93–101

21. Penna C, Dozois R, Tremaine W, et al. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996;38(2):234–239

22. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg 1995;222(2):120–127

23. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology 2003;124(5):1202–1209

24. Penna C, Tiret E, Kartheuser A, Hannoun L, Nordlinger B, Parc R. Function of ileal J pouch-anal anastomosis in patients with familial adenomatous polyposis. Br J Surg 1993;80(6):765–767

25. Tjandra JJ, Fazio VW, Church JM, Oakley JR, Milsom JW, Lavery IC. Similar functional results after restorative proctocolectomy in patients with familial adenomatous polyposis and mucosal ulcerative colitis. Am J Surg 1993;165(3):322–325

26. Gosselink MP, Schouten WR, van Lieshout LMC, Hop WC, Laman JD, Ruseler-van Embden JG. Delay of the first onset of pouchitis by oral intake of the probiotic strain Lactobacillus rhamnosus GG. Dis Colon Rectum 2004;47(6):876–884

27. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119(2):305–309

28. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut 2004;53(1):108–114

29. Carter MJ, Di Giovine FS, Cox A, et al. The interleukin 1 receptor antagonist gene allele 2 as a predictor of pouchitis following colectomy and IPAA in ulcerative colitis. Gastroenterology 2001;121(4):805–811

30. Brett PM, Yasuda N, Yiannakou JY, et al. Genetic and immunological markers in pouchitis. Eur J Gastroenterol Hepatol 1996;8(10):951–955

31. Aisenberg J, Legnani PE, Nilubol N, et al. Are pANCA, ASCA, or cytokine gene polymorphisms associated with pouchitis? Long-term follow-up in 102 ulcerative colitis patients. Am J Gastroenterol 2004;99(3):432–441

32. Meier CB, Hegazi RA, Aisenberg J, et al. Innate immune receptor genetic polymorphisms in pouchitis: is CARD15 a susceptibility factor? Inflamm Bowel Dis 2005;11(11):965–971

33. Schmidt CM, Lazenby AJ, Hendrickson RJ, Sitzmann JV. Preoperative terminal ileal and colonic resection histopathology predicts risk of pouchitis in patients after ileoanal pull-through procedure. Ann Surg 1998;227(5):654–662; discussion 663–665

34. Achkar JP, Al-Haddad M, Lashner B, et al. Differentiating risk factors for acute and chronic pouchitis. Clin Gastroenterol Hepatol 2005;3(1):60–66

35. Okon A, Dubinsky M, Vasiliauskas EA, et al. Elevated platelet count before ileal pouch-anal anastomosis for ulcerative colitis is associated with the development of chronic pouchitis. Am Surg 2005;71(10):821–826

36. Fleshner P, Ippoliti A, Dubinsky M, et al. A prospective multivariate analysis of clinical factors associated with pouchitis after ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol 2007;5(8):952–958, quiz 887

37. Shepherd NA, Hultén L, Tytgat GNJ, et al. Pouchitis. Int J Colorectal Dis 1989;4(4):205–229

38. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg 1990;211(5):622–627; discussion 627–629

39. Hata K, Watanabe T, Shinozaki M, Nagawa H. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. Scand J Gastroenterol 2003;38(10):1055–1058

40. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. Gut 2001;49(5):671–677

41. Kuisma J, Järvinen H, Kahri A, Färkkilä M. Factors associated with disease activity of pouchitis after surgery for ulcerative colitis. Scand J Gastroenterol 2004;39(6):544–548

42. Hui T, Landers C, Vasiliauskas E, et al. Serologic responses in indeterminate colitis patients before ileal pouch-anal anastomosis may determine those at risk for continuous pouch inflammation. Dis Colon Rectum 2005;48(6):1254–1262

43. Merrett MN, Mortensen N, Kettlewell M, Jewell DO. Smoking may prevent pouchitis in patients with restorative proctocolectomy for ulcerative colitis. Gut 1996;38(3):362–364

44. Shen B, Fazio VW, Remzi FH, et al. Risk factors for diseases of ileal pouch-anal anastomosis in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2006;4:81–89

45. Shen B, Achkar J-P, Lashner BA, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. Gastroenterology 2001;121(2):261–267

46. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. Int J Colorectal Dis 1986;1(3):167–174

47. Sandborn WJ. Pouchitis: risk factors, frequency, natural history, classification and public health prospective. In: Me Leod RS, Martin F, Sutherland LR, Wallace JL, Williams CN, eds. Trends in Inflammatory Bowel Disease 1996. Lancaster, UK: Kluwer Academic Publishers; 1997:51–63

48. Shen B, Remzi FH, Lavery IC, Lashner BA, Fazio VW. A proposed classification of ileal pouch disorders and associated complications after restorative proctocolectomy. Clin Gastroenterol Hepatol 2008;6(2):145–158; quiz 124

49. Shen B. Diagnosis and treatment of patients with pouchitis. Drugs 2003;63(5):453–461

50. Shen BO, Jiang Z-D, Fazio VW, et al. Clostridium difficile infection in patients with ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol 2008;6(7):782–788

51. Kühbacher T, Ott SJ, Helwig U, et al. Bacterial and fungal microbiota in relation to probiotic therapy (VSL#3) in pouchitis. Gut 2006;55(6):833–841

52. Muñoz-Juarez M, Pemberton JH, Sandborn WJ, Tremaine WJ, Dozois RR. Misdiagnosis of specific cytomegalovirus infection of the ileoanal pouch as refractory idiopathic chronic pouchitis: report of two cases. Dis Colon Rectum 1999;42(1):117–120

53. Moonka D, Furth EE, MacDermott RP, Lichtenstein GR. Pouchitis associated with primary cytomegalovirus infection. Am J Gastroenterol 1998;93(2):264–266

54. Shen B. Campylobacter infection in patients with ileal pouches. Am J Gastroenterol 2010;105(2):472–473

55. Shen B, Fazio VW, Bennett AE, et al. Effect of withdrawal of non-steroidal anti-inflammatory drug use in patients with the ileal pouch. Dig Dis Sci 2007;52:3321–3328

56. Shen B, Remzi FH, Nutter B, et al. Association between immune-associated disorders and adverse outcomes of ileal pouch-anal anastomosis. Am J Gastroenterol 2009;104(3):655–664

57. Shen B, Plesec TP, Remer E, et al. Asymmetric endoscopic inflammation of the ileal pouch: a sign of ischemic pouchitis? Inflamm Bowel Dis 2010;16(5):836–846

58. Nicholls RJ. Review article: ulcerative colitis—surgical indications and treatment. Aliment Pharmacol Ther 2002;16(Suppl 4):25–28

59. Madden MV, McIntyre AS, Nicholls RJ. Double-blind crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. Dig Dis Sci 1994;39(6):1193–1196

60. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. Inflamm Bowel Dis 2001;7(4):301–305

61. Araki Y, Mitsuyama K, Nagae T, et al. Leukocytapheresis for the treatment of active pouchitis: a pilot study. J Gastroenterol 2008;43(7):571–575

62. Gionchetti P, Rizzello F, Morselli C, et al. High-dose probiotics for the treatment of active pouchitis. Dis Colon Rectum 2007;50(12):2075–2082, discussion 2082–2084

63. Shen B, Pardi DS, Bennett AE, et al. The efficacy and tolerability of AST-120 (spherical carbon adsorbent) in active pouchitis. Am J Gastroenterol 2009;104(6):1468–1474

64. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119(2):305–309

65. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut 2004;53(1):108–114

66. Shen B, Remzi FH, Lopez AR, Queener E. Rifaximin for maintenance therapy in antibiotic-dependent pouchitis. BMC Gastroenterol 2008;8:26 [electronic journal]

67. Shen B, Brzezinski A, Fazio VW, et al. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. Aliment Pharmacol Ther 2005;22(8):721–728

68. Gionchetti P, Rizzello F, Venturi A, et al. Antibiotic combination therapy in patients with chronic, treatment-resistant pouchitis. Aliment Pharmacol Ther 1999;13(6):713–718

69. Abdelrazeq AS, Kelly SM, Lund JN, Leveson SH. Rifaximin-ciprofloxacin combination therapy is effective in chronic active refractory pouchitis. Colorectal Dis 2005;7(2):182–186

70. Mimura T, Rizzello F, Helwig U, et al. Four-week open-label trial of metronidazole and ciprofloxacin for the treatment of recurrent or refractory pouchitis. Aliment Pharmacol Ther 2002;16(5):909–917

71. Shen B, Fazio VW, Remzi FH, et al. Combined ciprofloxacin and tinidazole therapy in the treatment of chronic refractory pouchitis. Dis Colon Rectum 2007;50(4):498–508

72. Viscido A, Kohn A, Papi C, Caprilli R. Management of refractory fistulizing pouchitis with infliximab. Eur Rev Med Pharmacol Sci 2004;8(5):239–246

73. Tremaine WJ, Sandborn WJ, Wolff BG, Carpenter HA, Zinsmeister AR, Metzger PP. Bismuth carbomer foam enemas for active chronic pouchitis: a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 1997;11(6):1041–1046

74. Wischmeyer P, Pemberton JH, Phillips SF. Chronic pouchitis after ileal pouch-anal anastomosis: responses to butyrate and glutamine suppositories in a pilot study. Mayo Clin Proc 1993;68(10):978–981

75. Gionchetti P, Rizzello F, Poggioli G, et al. Oral budesonide in the treatment of chronic refractory pouchitis. Aliment Pharmacol Ther 2007;25(10):1231–1236

76. Calabrese C, Gionchetti P, Rizzello F, et al. Short-term treatment with infliximab in chronic refractory pouchitis and ileitis. Aliment Pharmacol Ther 2008;27(9):759–764

77. Shen B, Lashner BA, Bennett AE, et al. Treatment of rectal cuff inflammation (cuffitis) in patients with ulcerative colitis following restorative proctocolectomy and ileal pouch-anal anastomosis. Am J Gastroenterol 2004;99(8):1527–1531

78. Shen B, Lian L, Remzi FH, et al. Natural history of cuffitis in ulcerative colitis patients with restorative proctocolectomy and ileal pouch-anal anastomosis. Poster presented at: Digestive Diseases Week; May 1–5, 2010; New Orleans, LA

79. Panis Y, Poupard B, Nemeth J, Lavergne A, Hautefeuille P, Valleur P. Ileal pouch/anal anastomosis for Crohn's disease. Lancet 1996;347(9005):854–857

80. Melton GB, Fazio VW, Kiran RP, et al. Long-term outcomes with ileal pouch-anal anastomosis and Crohn's disease: pouch retention and implications of delayed diagnosis. Ann Surg 2008;248(4):608–616

81. Shen B. Crohn's disease of the ileal pouch: reality, diagnosis, and management. Inflamm Bowel Dis 2009;15(2):284–294

82. Shen B, Patel S, Lian L. Natural history of Crohn's disease in patients who underwent intentional restorative proctocolectomy with ileal pouch-anal anastomosis. Aliment Pharmacol Ther 2010;31(7):745–753

83. Melmed GY, Fleshner PR, Bardakcioglu O, et al. Family history and serology predict Crohn's disease after ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum 2008;51(1):100–108

84. Shen B, Remzi FH, Hammel JP, et al. Family history of Crohn's disease is associated with an increased risk for Crohn's disease of ileal pouch-anal anastomosis. Inflamm Bowel Dis 2009;15:163–170

85. Nasseri Y, Melmed G, Wang HL, Targan S, Fleshner P. Rigorous histopathological assessment of the colectomy specimen in patients with inflammatory bowel disease unclassified does not predict outcome after ileal pouch-anal anastomosis. Am J Gastroenterol 2010;105(1):155–161

86. Shen B, Fazio VW, Remzi FH, et al. Risk factors for clinical phenotypes of Crohn's disease of the ileal pouch. Am J Gastroenterol 2006;101(12):2760–2768

87. Colombel J-F, Ricart E, Loftus EV Jr, , et al. Management of Crohn's disease of the ileoanal pouch with infliximab. Am J Gastroenterol 2003;98(10):2239–2244

88. Shen B, Fazio VW, Remzi FH, et al. Endoscopic balloon dilation of ileal pouch strictures. Am J Gastroenterol 2004;99(12):2340–2347

89. Matzke GM, Kang AS, Dozois EJ, Sandborn WJ. Mid pouch strictureplasty for Crohn's disease after ileal pouch-anal anastomosis: an alternative to pouch excision. Dis Colon Rectum 2004;47(5):782–786

90. Shen B, Remzi FH, Lavery IC, et al. Administration of adalimumab in the treatment of Crohn's disease of the ileal pouch. Aliment Pharmacol Ther 2009;29(5):519–526

91. Shen B, Achkar J-P, Lashner BA, et al. Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. Am J Gastroenterol 2002;97(4):972–977

92. Shen B, Sanmiguel C, Bennett AE, et al. Irritable pouch syndrome is characterized by visceral hypersensitivity. Inflamm Bowel Dis 2010 Aug 3;[Epub ahead of print]

93. Shen B, Liu W, Remzi FH, et al. Enterochromaffin cell hyperplasia in irritable pouch syndrome. Am J Gastroenterol 2008;103(9):2293–2300

94. Freeman H. Dysplasia-associated polypoid mucosal lesion in a pelvic pouch after restorative proctocolectomy for ulcerative colitis. Can J Gastroenterol 2001;15(7):485–488

95. Negi SS, Chaudhary A, Gondal R. Carcinoma of pelvic pouch following restorative proctocolectomy: report of a case and review of the literature. Dig Surg 2003;20(1):63–65

96. Laureti S, Ugolini F, D'Errico A, Rago S, Poggioli G. Adenocarcinoma below ileoanal anastomosis for ulcerative

colitis: report of a case and review of the literature. Dis Colon Rectum 2002;45(3):418–421

97. Hyman N. Rectal cancer as a complication of stapled IPAA. Inflamm Bowel Dis 2002;8(1):43–45

98. Das P, Johnson MW, Tekkis PP, Nicholls RJ. Risk of dysplasia and adenocarcinoma following restorative procto-colectomy for ulcerative colitis. Colorectal Dis 2007;9(1): 15–27

99. Sarigol S, Wyllie R, Gramlich T, et al. Incidence of dysplasia in pelvic pouches in pediatric patients after ileal pouch-anal anastomosis for ulcerative colitis. J Pediatr Gastroenterol Nutr 1999;28(4):429–434

100. Veress B, Reinholt FP, Lindquist K, Löfberg R, Liljeqvist L. Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. Gastroenterology 1995;109(4):1090–1097

101. Heuschen UA, Hinz U, Allemeyer EH, et al. Backwash ileitis is strongly associated with colorectal carcinoma in ulcerative colitis. Gastroenterology 2001;120(4): 841–847

102. Gullberg K, Ståhlberg D, Liljeqvist L, et al. Neoplastic transformation of the pelvic pouch mucosa in patients with ulcerative colitis. Gastroenterology 1997;112(5): 1487–1492

103. Kariv R, Remzi FH, Lian L, et al. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. Gastroenterology 2010;139(3): 806–812; 812, e1–e2