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CLINICAL REVIEW

Clinical Approach to Diseases of Ileal Pouch-Anal Anastomosis

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Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for ulcerative colitis (UC) patients with medically refractory disease or dysplasia. IPAA significantly improves quality of life in UC patients who require surgery. However, certain inflammatory and noninflammatory diseases can develop after the surgery, including pouchitis, Crohn's disease of the pouch, cuffitis, and irritable pouch syndrome. The etiology and pathogenesis of these disease conditions of IPAA are largely unknown. Accurate diagnosis and classification are important for appropriate management. Endoscopic evaluation is the most important tool for the diagnosis and differential diagnosis.

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INTRODUCTION

Ulcerative colitis (UC) is common in the United States, affecting at least half million Americans. The incidence of UC and Crohn's disease (CD) appears to be increasing. Approximately 25–33% of patients with UC eventually require total proctocolectomy. Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for UC patients with medically-refractory disease, dysplasia or cancer, and for the majority of patients with familial adenomatous polyposis (FAP) (1, 2). Most UC patients with proctocolectomy are candidates for IPAA. The main contraindications for IPAA include a preoperative diagnosis of CD, absent or decreased anal sphincter muscle tone, and pelvic floor dysfunction.

Diseases of the ileal pouch may be classified into: surgery-related/mechanical complications; inflammatory or infectious disorders; functional disorders; dysplasia or neoplasia; and systemic or metabolic disorders (Fig. 1). Pouchitis, CD of the pouch, cuffitis, and irritable pouch syndrome (IPS) may develop after IPAA, which adversely affect outcomes and patients' health-related quality of life (3). Occasionally, patients may present with a combination of these diseases. In other cases, the disease status changes over the time. For example, a patient with pouchitis may later develop CD of the pouch or IPS. Diagnosis and management of these diseases can be challenging.

POUCHITIS

Pouchitis is the most common long-term adverse sequela after IPAA (1, 2, 4–7). Purported risk factors for pouchitis include extensive UC (1, 8), backwash ileitis (8), extra-intestinal manifestations, especially primary sclerosing cholangitis (6, 9–11), the presence of perinuclear antineutrophil cytoplasmic antibodies (12, 13), interleukin-1 receptor antagonist gene polymorphisms (14, 15), being a nonsmoker (16, 17), and nonsteroidal anti-inflammatory drug (NSAID) use (17, 18). However, there is little agreement in the literature as to which factors definitely increase a patient's risk for pouchitis. This discrepancy could be due to duration and intensity of follow-up after IPAA (7); diagnostic criteria of pouchitis used; stratification of pouchitis—acute *versus* chronic pouchitis or a combination of both (19); inclusion or exclusion of CD of the pouch (3) or cuffitis (20); and the number of patients studied.

The etiology and pathophysiology of pouchitis are not clear. The fact that pouchitis almost exclusively occurs in patients with underlying UC, is rarely seen in patients with FAP, and generally responds to antibiotic therapy suggests an infectious etiology in genetically susceptible inflammatory bowel disease (IBD) patients. Prevailing theory holds that pouchitis results from an overgrowth of commensal bacteria (2, 21). Moreover, whether a UC patient has genetic predisposition to pouchitis seems to affect the bacterial composition in the ileal pouch. While levels of anaerobes (*Lactobacilli*, *Bifidobacterium*, *Bacteroides*, and *C. perfrigens*), *Enterococci* and *Coliform* in pouches in UC patients are similar to that of FAP patients, sulfate-producing bacteria are almost exclusively detected in pouches of UC patients (21). In UC patients, levels of *Lactobacilli*, *Bifidobacterium*, *Bacteroides*, *C. perfrigens*, *Enterococci*, and *Coliform* in the pouch are markedly higher than that in ileostomy effluent (21, 22). During episodes of pouchitis, the total anaerobes, *C. perfringens* and hemolytic strains of *E. coli* are increased, while total aerobes are decreased (23). Antibiotic therapy decreases total anaerobic and

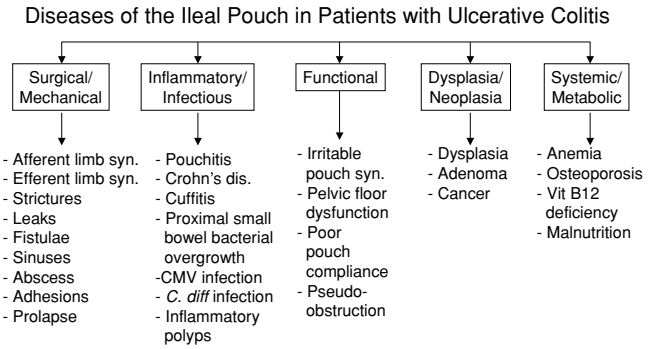

Figure 1. Classification of diseases of ileal pouch-anal anastomosis in patients with ulcerative colitis.

aerobic bacterial concentrations and selectively inhibits *Bacteroides*, *Enterococci*, *Bactobacillus*, and *Bifidobacterium*, which corresponds to the resolution of pouch inflammation (24). For example, metronidazole therapy reduces anaerobic flora whereas ciprofloxacin therapy causes *C. perfringens* and all *Coliforms*, including hemolytic strains of *E. coli*, to disappear (23).

While the majority of patients with pouchitis respond to a 2-wk treatment course with a single antibiotic, some may have refractory disease, requiring long-term anti-inflammatory agents or immunomodulators. Pouchitis is not a homogenous disease. Rather, it likely represents a disease spectrum ranging from an acute, antibiotic-responsive entity to a chronic, antibiotic-refractory disorder. While acute antibiotic-responsive pouchitis likely stems from an infectious etiology, chronic antibiotic-refractory pouchitis shares similar clinical features with chronic IBD with possible common pathogenesis pathways.

Diagnosis and Classification

The most common symptoms of pouchitis are increased stool frequency, urgency, abdominal cramping, and pelvic discomfort. Fever and bleeding are rare. These symptoms, however, are not specific, and may be seen in diseases of IPAA other than pouchitis. In addition, symptoms do not necessarily correlate with endoscopic and histologic inflammation of the pouch mucosa (2, 25, 26). On endoscopy, inflammation of the pouch can be patchy or diffuse with edema, ulceration, nodularity, friability, or exudates (Fig. 2). Endoscopic evaluation together with symptom assessment and histology evaluation is the key to an accurate diagnosis of pouchitis. Specifically, endoscopic and histologic evaluation can distinguish pouchitis from other inflammatory diseases or functional disorders of the pouch (25).

There are no universally accepted diagnostic criteria for pouchitis. Semi-objective assessments to diagnose pouchitis in patients with IPAA have been proposed using composite scores such as the Pouchitis Triad (26), Heidelberg Pouchitis Activity Score (27), and Pouchitis Disease Activity Index (PDAI) (28). The PDAI is the most commonly used diagnostic instrument; it applies quantitative scores to

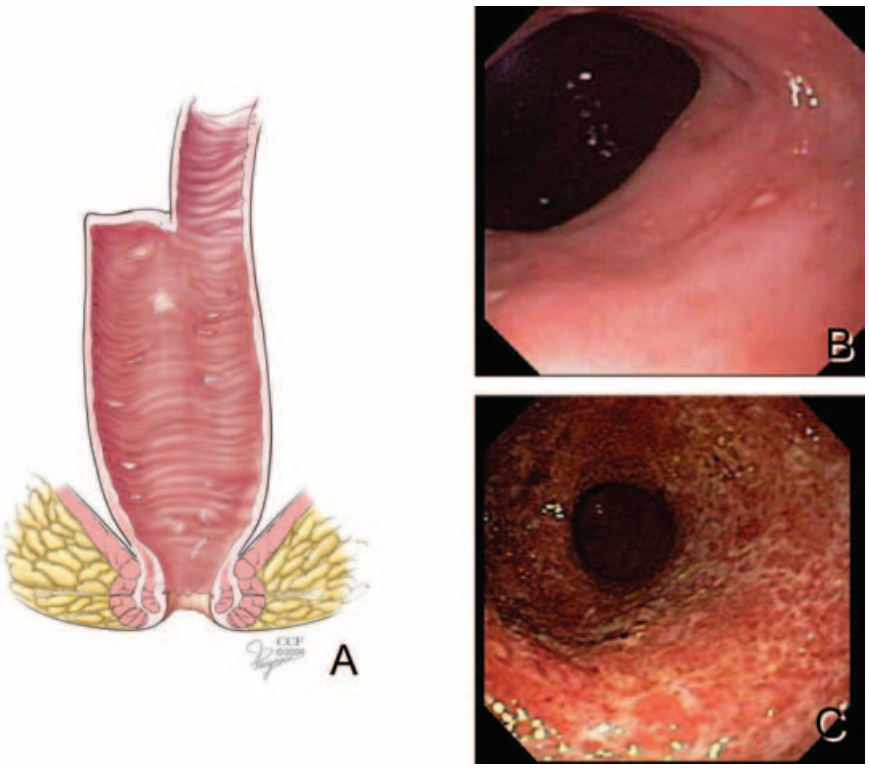

Figure 2. Pouchitis. (*A*) Despite diffuse inflammation of the ileal pouch, the afferent limb of the pouch is typically not involved. (*B*) Mild pouchitis with discrete small ulcers and (*C*) severe pouchitis with hemorrhage, friability, nodularity, ulceration, and loss of vascular pattern.

clinical symptoms and endoscopic and histologic acute inflammation. Pouchitis was defined as a total of PDAI score $\geq$7 points (28). While histologic evaluation is of limited value in the quantification of mucosal inflammation, it is useful for the assessment of characteristic features of certain diseases of the pouch, such as granulomas in CD of the pouch, cytomegalovirus (CMV) infection and pyloric gland metaplasia in chronic pouchitis, ischemic changes, and mucosal prolapse.

Clinicians frequently have options in selecting the most cost-effective way to diagnose pouchitis. There are two practical approaches to patients with symptoms suggestive of pouchitis: a diagnostic–therapeutic trial with antibiotics and pouch endoscopy with or without biopsy. A cost-effectiveness analysis comparing six competing strategies of treat-first and test (endoscopy)-first approaches showed that pouch endoscopy without biopsy is cost-effective (29). The measurement of fecal lactoferrin was shown to have a high sensitivity and specificity for the diagnosis of pouch inflammation, and it may be promising for future routine clinical use (30).

It is important to accurately classify the disease before initiating appropriate therapy. Although there are no prospectively validated and universally accepted classification systems. Pouchitis can be categorized into: idiopathic *versus* secondary, based on the etiology; remission *versus* active, based on disease activity; acute *versus* chronic, based on symptom duration with a cut-off of 4 wks; infrequent episodes *versus* relapsing *versus* continuous course, based on disease course; and responsive *versus* refractory, based on response to medical therapy (31). Another useful classification may be based specifically on the response to antibiotic therapy (3, 32). We propose that antibiotic-responsive pouchitis is a condition in which patients have infrequent episodes (<4 episodes per yr) responding to a 2-wk course of a single antibiotic; antibiotic-dependent pouchitis a condition with frequent episodes ($\geq$4 episodes per yr) of pouchitis or with persistent symptoms requiring long-term, continuous antibiotic or probiotic therapy; antibiotic-refractory pouchitis as a condition in which patients fail to respond to a 2–4 wk course of a single antibiotic (metronidazole or ciprofloxacin), require therapy over 4 wks with 2 antibiotics, 5-aminosalicylate, corticosteroid or immunomodulator therapy (Table 1). Until diagnostic criteria are standardized we find the current classification clinically helpful. For example, the prognosis of antibiotic-responsive pouchitis and antibiotic-refractory pouchitis is different. Antibiotic-refractory pouchitis is a common cause of pouch failure, defined as a failure to maintain a functional pouch, leading to pouch resection. In a study consisting of 100 consecutive UC patients who underwent restorative proctocolectomy and IPAA, 5 patients developed chronic, antibiotic-refractory pouchitis, 2 of whom had pouch failure with pouch resection (31).

Treatment

Various classification systems have been used in clinical trials, making outcome comparison difficult. Here we attempt to "unify" the different classification systems into antibiotic-responsive, antibiotic-dependent, and antibiotic-refractory types when results of these trials are presented. For antibiotic-responsive pouchitis, metronidazole and ciprofloxacin are most commonly used (2, 33, 34, 35). Madden *et al.* (36) conducted a crossover, placebo-controlled trial of 7-day oral metronidazole 1.2 g per day in 11 patients with active pouchitis. The overall response rate was 73% for metronidazole compared with 9% for placebo. In a small case series, 8 of 11 pouchitis patients (94%) with failure or intolerance to metronidazole responded to a 7-day course of ciprofloxacin 1 g per day (4). Both ciprofloxacin and metronidazole significantly lowered PDAI symptom, endoscopic, and histologic inflammation scores, but patients treated with ciprofloxacin experienced significantly greater reductions in the PDAI scores and fewer adverse effects than metronidazole (35). Other antibiotic and nonantibiotic agents reported in noncontrolled trials include tetracycline, clarithromycin, amoxicillin/clavulanic acid, doxycycline, or rifaximin (24, 35), and budesonide enema (37).

Relapse of pouchitis is common. Of patients with acute pouchitis, 39% have a single acute episode that responds to antibiotic therapy whereas the remaining 61% go on to develop at least one recurrence (10). Approximately 5–19% patients with acute pouchitis develop refractory or rapidly relapsing symptoms that require frequent and/or protracted antibiotic therapy (38–40). Although effective antibiotic therapy often resolves pouchitis and decreases fecal aerobic and

Table 1. Diagnosis, Classification, and Treatment of Pouchitis

Diagnosis and Classification		Management	
Based on disease course	Based on response to antibiotic therapy	Treatment	Maintenance therapy
Acute pouchitis	Antibiotic-responsive pouchitis	Antibiotics	Not needed
Relapsing pouchitis	Antibiotic-dependent pouchitis	Antibiotics	Probiotics Antibiotics
Chronic pouchitis	Antibiotic-refractory pouchitis	Prolonged combined two antibiotics Topical/oral 5-aminosalicylates Topical/oral corticosteroids Immunomodulators Infliximab?	Topical/oral 5-aminosalicylates Topical corticosteroids? Immunomodulators? Infliximab?

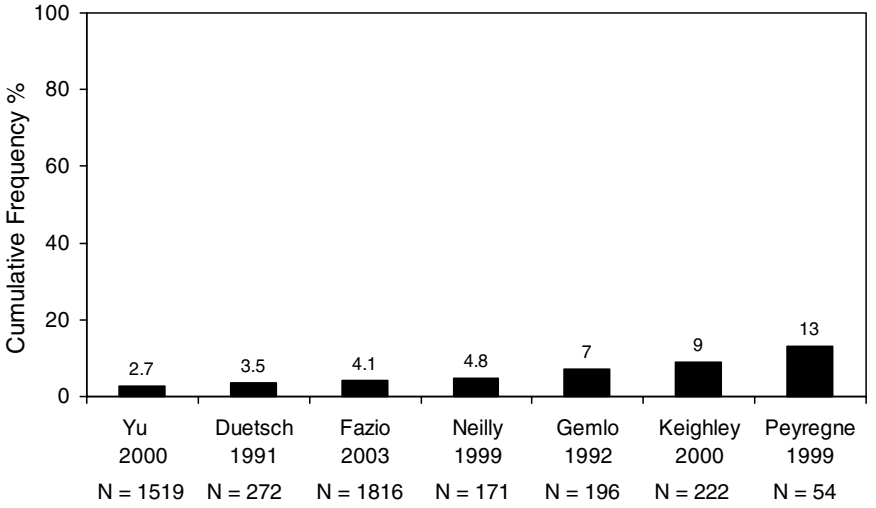

Figure 3. Cumulative frequency of postoperative Crohn's disease in patients with a preoperative diagnosis of ulcerative colitis, which varies depending on diagnostic criteria, inclusion of a preoperative diagnosis of indeterminate colitis, and duration and intensity of follow-up (19, 55, 56, 58–61).

anaerobic bacterial levels (24), a transient reduction in bacterial concentration would not be adequate to prevent relapse of pouchitis (41). These patients are classified as having antibiotic-dependent pouchitis and often require long-term antibiotic treatment to keep the disease in remission, either with a low-dose maintenance therapy or with pulse therapy. Several topical agents as alternatives to antibiotics have been tried with modest success, including bismuth carbomer enema (42), short-chain fatty acids, and glutamine (43). In patients with antibiotic-dependent pouchitis, proximal small bowel bacterial overgrowth should be excluded. Hydrogen breath testing may be useful, but its use in patients with IPAA has not been standardized or validated.

Probiotics appear to be effective in preventing flare-ups of pouchitis (37, 42, 44, 45), although their mechanism of action in pouchitis is not entirely clear. A randomized trial of a probiotic named VSL#3® was conducted. VSL#3® was given at a dose of 6 g per day containing viable lyophilized bacteria of four strains of *Lactobacillus*, three *Bifidobacterium* species, and *Streptococcus salivarius* subsp. *thermophillus* for the maintenance therapy for relapsing pouchitis after remission was induced by ciprofloxacin and rifaximin. During the 9-month trial involving 40 patients with relapsing pouchitis, only 15% in the probiotic group relapsed *versus* 100% in the placebo group (41). During probiotic treatment, fecal concentrations of *Lactobacillus*, *Bifidobacterium*, and *S. salivarius* increased by 10^2–10^6 colony-forming units/g stool, with no change in other commensal bacteria. In a separate randomized, placebo-controlled trial of VSL#3® in patients with antibiotic-dependent pouchitis, Mimura *et al.* (45) showed that 17 of 20 patients (85%) in the VSL#3® group maintained clinical remission, compared to 1 of 16 patients (6%) in the placebo group.

Since the majority of patients who develop acute pouchitis do so within the first year after IPAA (46), VSL#3® was also evaluated for the prophylaxis of the initial episode of pouchitis. Two of 20 patients (10%) treated with VSL#3® developed pouchitis within 12 months after IPAA, while 8 of 20 patients (40%) experienced pouchitis in the placebo group (47). There are no published trials on VSL#3® from the United States in pouchitis. The efficacy and applicability to routine clinical practice of the agent warrant further evaluation.

Antibiotic-refractory pouchitis is a common cause of pouch failure (31). Patients usually do not respond to full-dose, single-agent antibiotic therapy. It is important to investigate why patients do not respond to antibiotic therapy. Possible causes include NSAID use (18), concurrent *C. difficile* (48) or CMV infection (49, 50), celiac disease, cuffitis, and CD. For patients without obvious causes, there are several treatment options. We defined antibiotic-refractory pouchitis as a condition in which patients fail to respond to 2–4 wk single antibiotic therapy. The group of patients, however, still may benefit from prolonged, combined antibiotic therapy. In an open-label study of 18 patients with chronic antibiotic-refractory pouchitis, combined ciprofloxacin (1 g per day) and rifaximin (2 g per day) therapy with a prolonged course (4 wks) resulted in symptomatic improvement in 10 patients (56%) and remission in 6 patients (33%) (24). In another open-label trial, 82% of patients (36/44) with relapsing pouchitis or chronic pouchitis who received a combination therapy of ciprofloxacin and metronidazole for 4 wks experienced remission (51). In addition to antibiotics, nonantibiotic therapy has also been used in pouchitis. In an open-label trial of the enema form of alicaforsen, an antisense inhibitor of intercellular adhesion molecules-1 in chronic refractory pouchitis, 7 of 12 patients (58%) achieved remission at week 6 (52). Topically active 5-aminosalicylate and corticosteroid agents have been used for antibiotic-refractory pouchitis. In an open-label trial of 8-wk oral budesonide (9 mg per day) in 16 patients with metronidazole-refractory pouchitis, 72%

went to remission with improved PDAI and IBD Questionnaire scores (53). If a patient responds to corticosteroid therapy, immunomodulators such as 6-mercaptopurine should be considered as corticosteroid-sparing agents. There are limited data available on immunomodulators or infliximab in antibiotic-refractory pouchitis. In a small case series of 7 patients with chronic refractory pouchitis complicated by perianal fistulae (excluding CD), short-term infliximab infusion with azathioprine resulted in a complete clinical response in 6 patients and complete fistular closure in 5 patients at 10 wks (54) (Table 1).

CROHN'S DISEASE OF THE POUCH

The true incidence of CD of the pouch in patients who initially undergo surgery for UC is not known. Reported cumulative frequencies range from 2.7% to 13% (19, 55–61), depending on preoperative and postoperative diagnostic criteria for IBD subsets (UC or CD), inclusion of indeterminate colitis as a denominator, and duration and intensity of postoperative follow-up (Fig. 3). In a large series of 1,816 patients with a preoperative diagnosis of UC or indeterminate colitis for IPAA, we found 74 patients (4.1%) with CD who were diagnosed based on pre- and postoperative pathology of colon specimens or ileal pouches (19).

The identification of pre- and postoperative risk factors for CD of the pouch is important but often difficult largely because CD of the pouch develops infrequently and there are a small number of patients available for meaningful statistical analysis (62, 63). The most significant risk factors for CD of the pouch are the preoperative diagnosis of CD or indeterminate colitis (64) and being a smoker (17). Other possible risk factors include longer duration of IPAA (17) and female gender in a pediatric population (65). Of 115 patients with a preoperative diagnosis of indeterminate colitis, 4.3% had postoperative, pathologically proven CD. In contrast, of 231 patients with a preoperative diagnosis of UC, 0.4% developed postoperative CD (64). Active smokers had 4.77 times the odds (95% CI: 1.39, 16.25) of having CD compared to those who self-reported being a nonsmoker (17).

CD of the pouch can occur after IPAA is intentionally performed in a selected group of patients with Crohn's colitis with no small intestinal or perianal diseases (66); CD also is inadvertently found in colectomy specimens of patients with a preoperative diagnosis of UC (55, 56, 58, 62, 64, 67). Often the patients may have been labeled as indeterminate colitis, because severe or toxic colitis may prevent a firm pathological diagnosis of CD or UC (62). Finally, *de novo* CD of the pouch may develop weeks or years after IPAA and a reassessment of proctocolectomy specimens shows no evidence of CD (57, 58). These patients who may be called "converters," comprise the majority of those with CD of the pouch. Patients with UC scheduled for restorative proctocolectomy and IPAA should be informed of possible postoperative development of CD.

Diagnosis

Clinical symptoms of CD of the pouch consist of diarrhea, abdominal pain, and pelvic discomfort, similar to that in pouchitis, cuffitis, and IPS (3). Patients with CD of the pouch can present with obstructive symptoms. CD should be considered if a patient is an active smoker and presents with fever, weight loss, nausea, vomiting, malnutrition, iron deficiency anemia, osteoporosis, and/or perianal fistulae. The presence of granulomas in mucosal biopsy outside suture lines, although rarely detected, may help confirm the diagnosis of CD (3). Perianal disease and fistulae outside the pouch-anal anastomosis (including pouch-cutaneous, pouch-vesicular and pouch-vaginal fistulae) in the absence of postsurgical complications, such as abscess, anastomotic leak, or sepsis, would suggest a diagnosis of CD. Perianal fistulae or abscesses may result from pouch surgery itself or from CD. Whether the complication is indicative of CD is determined by several factors, including the location and time of development of fistulae or abscesses, concurrent small bowel or afferent limb diseases, and presence or absence of characteristic histologic features (such as granulomas). Generally, a diagnosis of CD should be considered if fistulae or abscesses develop greater than 12 months after IPAA in the area outside pouch-anal anastomosis; and if there are granulomas on histology. Ulcerated lesions in the afferent limb proximal to the pouch (68) and ulcerated strictures at the pouch inlet, afferent limb, or mid-pouch (69) in the absence of current NSAID use are also suggestive of CD (Fig. 4).

Accurate diagnosis is important for the management and prediction of prognosis. The diagnosis of CD of the pouch can be challenging, especially when trying to distinguish it from chronic refractory pouchitis. Smoking status may provide a clue for the differential diagnosis of pouchitis and CD of the pouch, since it has a contrasting effect for the two disease entities (*i.e.*, smoking, while being a risk factor for CD, is a protective factor for pouchitis) (17). Endoscopy and histology evaluation, and sometimes radiographic assessment and examination under anesthesia, are indicated. Suture line ulcers are nonspecific and common in patients with IPAA and do not necessarily indicate an inflammatory disease (pouchitis, cuffitis, or CD of the pouch). Clinicians should resist the temptation to take biopsies from the suture line or ulcers along the suture line, since foreign body granulomas in mucosal biopsy may be mistakenly interpreted as a sign of CD. For the diagnosis of CD, the demonstration of small bowel involvement by endoscopy or small bowel contrast radiography often is helpful. The role of push enteroscopy, capsule endoscopy, or serologic markers in patients with IPAA requires further evaluation.

Treatment

Patients who are diagnosed with CD of the pouch will require long-term maintenance therapy. Some patients may retain their pouch with proper medical, endoscopic, or surgical treatment. However, data on safe and effective therapy are limited. Patients with CD of the pouch with

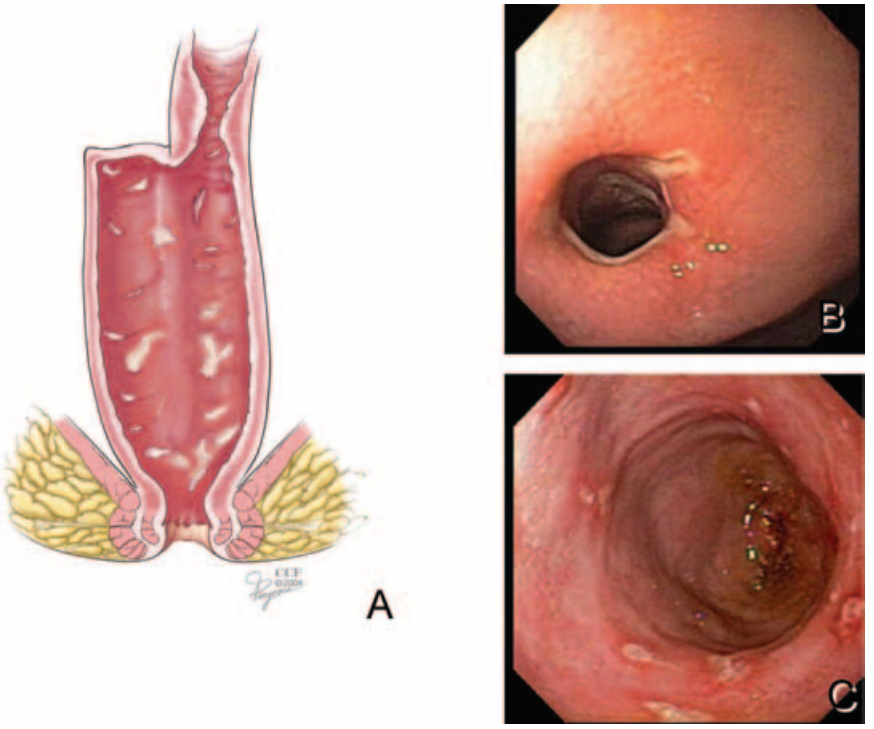

Figure 4. Crohn's disease of the pouch. (*A*) Discrete deep ulcers in the pouch and afferent limb and pouch intet stricture. (*B*) Ulcerated pouch inlet stricture and (*C*) discrete ulcers in the afferent limb.

predominantly mucosal inflammation may first be treated with topical or oral 5-aminosalicylates, corticosteroids, or oral antibiotics. Patients with strictures or fistulae may benefit from immunomodulators. Those without sepsis or strictures may be treated with antitumor necrosis factor therapy. In a case series of 26 patients with CD of the pouch, 62% had a complete response to infliximab infusion and 23% had a partial response. After a median follow-up of 22 months, 33% lost their pouch, while the pouch was functional in the remaining 67% of patients (70). In a recent study, 19 patients with pouch inlet and outlet strictures, including 11 patients with CD of the pouch, were treated with endoscopic balloon dilations. Inlet strictures were seen only in patients with CD of the pouch. All strictures were successfully dilated with the endoscopic balloon without complication. Stricture scores immediately, 8 and 16 wks after the dilation were significantly improved compared with the predilation baseline scores. Symptom and quality of life significantly improved

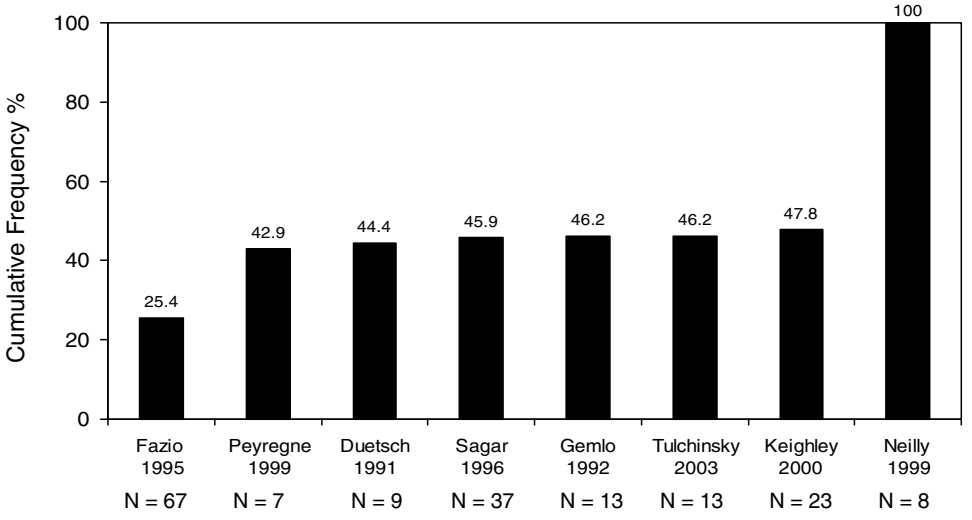

Figure 5. Cumulative frequency of pouch failure in patients with Crohn's disease of the pouch, which varies depending on diagnostic criteria, duration and intensity of follow-up, and relevant therapy (1, 55, 56, 58, 60, 61, 71, 73).

too. Endoscopic balloon dilation in conjunction with medical therapy appears safe and effective for pouch strictures (69). Surgical stricturoplasty for pouch stricture from CD has also been performed with success.

CD of the pouch can lead to pouch failure, fistulae, and septic complications (62, 65, 71, 72). Pouch failure from CD leading to pouch resection ranges from 25% to 100%, depending on the duration and intensity of follow-up after IPAA, use of medical or endoscopic therapy, and threshold of initiating pouch resection operation (1, 55–58, 60, 61, 71, 73) (Fig. 5). However, reported studies were performed before the era of routine use of immunomodulators and antitumor necrosis factor therapy. Despite the limited duration of follow-up in most studies, the majority of patients appear to be able to retain their pouches with medical and endoscopic therapy (62, 69–71).

CUFFITIS

One of two anastomotic techniques is used to construct IPAA: a hand-sewn anastomosis with mucosectomy of the anal transitional zone (ATZ) mucosa (also named rectal columnar cuff mucosa) or a stapled anastomosis at the level of the anorectal ring without mucosectomy (74). To remove the rectal columnar mucosa as completely as possible, a mucosectomy with hand-sewn anastomosis is necessary. This technique takes longer and has a relatively higher risk for postoperative functional problems such as seepage and incontinence due to anal canal manipulations. In contrast, when the IPAA is stapled, the procedure is simpler and less likely to result in functional or septic complications (75).

Stapled IPAA without mucosectomy has been routinely advocated at our institution for patients with medically refractory UC who require surgery, unless there is synchronous colorectal cancer or rectal dysplasia. The preservation of the ATZ is meant to optimize anal canal sensation, eliminate sphincter stretching, and preserve normal postoperative resting and squeeze pressures (74, 76, 77). However, in order to allow transanal insertion of the stapler head, it is normally necessary to leave a 1–2-cm strip of the rectal columnar cuff which is at risk for developing symptomatic inflammation (cuffitis) or dysplasia (20, 75, 78–80). The risk of development of dysplasia was significantly associated with a preoperative or postoperative diagnosis of dysplasia or cancer (75, 79). Digital pouch examination and surveillance endoscopy is recommended every 1–3 yr.

Dysplasia and cuffitis are the main adverse sequelae in patients with stapled IPAA without mucosectomy as compared with hand-sewn IPAA with mucosectomy. Because of the risk of dysplasia, hand-sewn IPAA with mucosectomy is routinely performed in patients with UC with dysplasia or FAP after proctocolectomy. However, patients with hand-sewn IPAA with mucosectomy may not be immune to dysplasia or cuffitis, since islands of the rectal columnar mucosa can regrow or may have been preserved due to incomplete mucosectomy (81). In a study of 178 patients who underwent IPAA and had serial endoscopic surveillance biopsy of the ATZ and followed for a minimum of 10 yr, Remzi *et al.* (79) found dysplasia in 4.5% (2 patients with high-grade and 6 patients with low-grade dysplasia). No cancer was found in the ATZ. In patients with persistent dysplasia, mucosectomy and perianal pouch advancement and neo-IPAA are recommended (79).

Diagnosis

Cuffitis may be considered a form of UC. While some patients with cuff inflammation on endoscopy and histology may be asymptomatic (20), others present with symptoms similar to those of pouchitis, CD of the pouch, and IPS (3). In a study of consecutive 61 symptomatic patients with IPAA, 7% had cuffitis (82). Bleeding ranging from blood on tissue paper to frank blood or blood clots was significantly more common in cuffitis than in pouchitis, CD of the pouch, or IPS (3) (Fig. 6). In fact, bleeding is a rather specific symptom for cuffitis. Occasionally, cuffitis with persistent bleeding can lead to iron deficiency anemia. Extraintestinal manifestations of IBD, such as arthralgias, are also common in patients with cuffitis (78). Pouch outlet strictures in some patients may be attributed to concurrent cuffitis (69). Endoscopic and histologic features of mucosal inflammation in cuffitis and pouchitis such as friability, ulceration, nodularity, erythema, and neutrophil infiltration are similar (78) (Fig. 7). Cuffitis is an under-recognized disease with limited data in the literature. No standardized diagnostic instrument has been proposed, although the Cuffitis Activity Index, adopted from components of the PDAI, has been used in one clinical trial (78).

Treatment

Cuffitis may be treated with topical 5-aminosalicylate or corticosteroid agents. Topical mesalamine appears to be well tolerated and effective in cuffitis. It improves symptoms and endoscopic and histologic inflammation. In an open-label trial of 14 patients with cuffitis, mesalamine suppositories

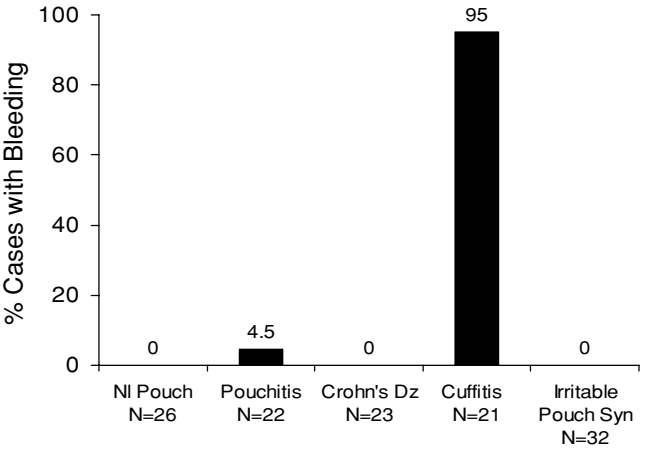

Figure 6. Bleeding is a specific sign of cuffitis 3.

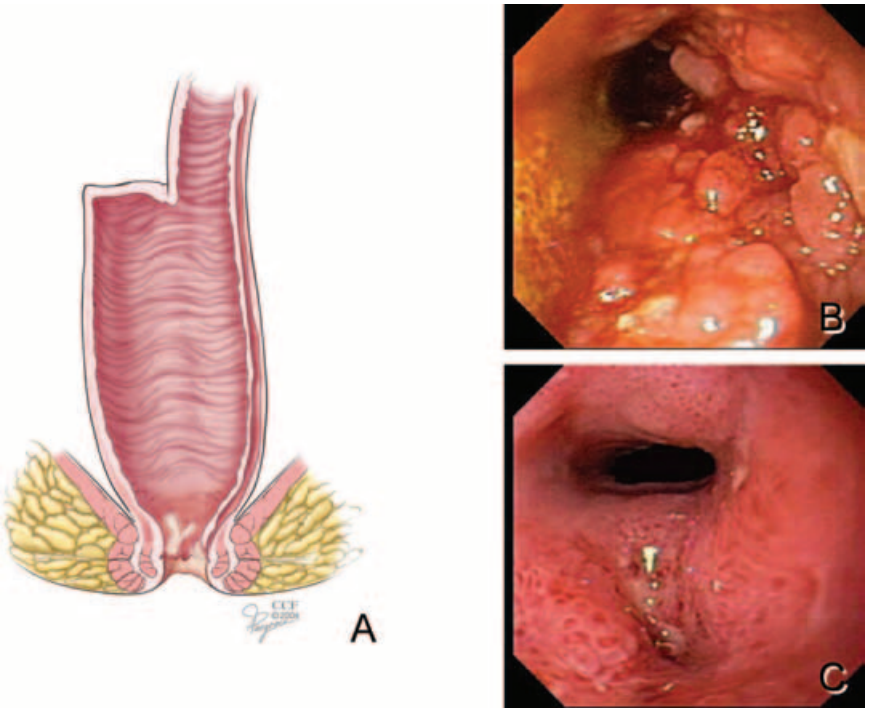

Figure 7. Cuffitis. (*A*) Linear ulcers at the rectal columnar cuff or anal transitional zone. (*B*) Severe cuffitis with cobble-stoning, nodularity, friability, edema, erythema, and loss of vascular pattern. (*C*) Mild cuffitis with an anastomotic sinus.

(1 g per day) resulted in a significant reduction in symptom, endoscopy, and histology inflammation scores with no adverse effects. Ninety-two percent of patients with bleeding and 70% patients with arthralgias improved after the therapy (78). In patients who do not tolerate or respond to topical 5-aminosalicylate agents, topical corticosteroid is a reasonable alternative. Occasionally, immunomodulators such as 6-mercaptopurine may be used. In patients with concurrent cuffitis and pouch outlet stricture, combined topical pharmaceutical therapy with endoscopic balloon dilation can be helpful (69). Oral antibiotic agents generally are not effective. In patients with coexisting pouchitis and cuffitis, we found that topical 5-aminosalicylate is often effective for both diseases.

Some questions remain unanswered: Do pouchitis, particularly antibiotic-refractory pouchitis, and cuffitis share common etiology and pathogenesis? Are patients who have frequent episodes of cuffitis at risk for developing dysplasia in the ATZ? What is the proper duration of therapy using topical agents? Could recent data on chemoprevention of dysplasia by 5-aminosalicylates in UC be extrapolated in cuffitis? Is there any role for endoscopic or surgical mucosectomy in the treatment of refractory cuffitis?

IRRITABLE POUCH SYNDROME

IPS is a newly described functional disorder in patients with IPAA (82). In a study involving 61 consecutive symptomatic patients with UC, total proctocolectomy, and IPAA (excluding CD of the pouch and surgically-related complications), 51% had pouchitis, 7% had cuffitis; and 43% had IPS, based on a combined assessment of symptoms, endoscopy, and histology (82). However, the relative prevalence of diseases of IPAA may have been affected by referral bias. Patients with IPS have significantly poorer quality-of-life scores than patients with healthy pouches (3). The etiology and pathophysiology are not clear. Functional bowel disease is not confined to the colon. Studies have shown that patients with irritable bowel syndrome (IBS) have gastrointestinal dysmotility and visceral hypersensitivity of the small intestine as well as the colon (83–85). It is therefore reasonable to speculate that patients with IPAA could present with symptoms similar to those seen in IBS.

IPS may coexist with inflammatory diseases of IPAA (*e.g.,* pouchitis, CD of the pouch, and cuffitis) as IBS may concurrently occur in IBD (86). This may explain why some patients with pouchitis, CD of the pouch, or cuffitis have disproportionately severe symptoms while endoscopic and histologic evaluation reveal only mild mucosal inflammation (25). In a study evaluating the frequency of symptoms of IBS in 98 patients with inactive UC, 33% of the patients met the criteria for IBS *versus* 7% of the healthy controls (87). Gastric emptying and small bowel transit are sometimes abnormal in patients with inactive UC (88). It has been noted that an IBS-like condition may be seen following IBD-related surgery (89).

Physiological studies on the ileal pouch may help explain the IPS symptoms. In a study of the afferent innervation of

the ileal pouch in 8 UC patients with IPAA, Bernstein *et al.* (90) found that patients with an ileal pouch had a lower volume threshold for stool sensation, poorer compliance, and more frequent referred abdominal pain when the pouch was distended than healthy volunteers with a normal rectum. Similar findings also were seen in patients with IBS who had no underlying UC and did not have proctocolectomy and IPAA (91). These results suggest that there are altered sensorymotor activities in the ileal pouch—even in normal healthy pouch—and that the alteration in pain threshold and poor compliance may predispose patients to the development of IPS.

The barostat technique is commonly used to study biomechanical features and visceral sensitivity of ileal pouches under normal physiological conditions (92–95). For example, the barostat examination has shown that increased pouch compliance is associated with decreased 24-h stool frequency (92) and that increased postprandial pouch tone is related to increased stool frequency. Our recent study demonstrated that pouch compliance and tone in IPS patients were similar to those in patients with healthy pouches. However, there was decreased threshold for perception of gas, urge to defecate, and pain in patients with IPS, indicating visceral hypersensitivity of the ileal pouch (96). These pathophysiologic features resemble those seen in IBS.

The etiology and pathophysiology of IPS are likely multifactorial. A recent study showed that patients using antidepressants or antianxiety agents would have a higher risk of having IPS, suggesting that psychological factors may play a role in the pathogenesis (17). It is not clear whether patients with a preoperative diagnosis of IBS have a higher risk of developing postoperative IPS or whether colectomy or bowel reconstruction surgery contributes to the development of the disease. On the other hand, cellular or molecular mechanisms of IPS warrant exploration. Enterochromaffin cell hyperplasia with increased numbers of serotonin-expressing cells in the pouch mucosa has been demonstrated in patients with IPS, indicating a possible role of overactivation of the neuroenteric system (97).

Diagnosis

Patients may present as IPS alone or IPS coexisting with inflammatory diseases of the ileal pouch. Currently, IPS is a diagnosis of exclusion based on the presence of symptoms of increased frequency of bowel movement with change in stool consistency, abdominal pain or cramping, and perianal or pelvic discomfort in the absence of endoscopic and histologic inflammation. "Red-flag" symptoms and signs such as nausea, vomiting, weight loss, fever, bloody bowel movement, and anemia are not consistent with IPS. Occasionally patients with celiac disease or proximal small bowel bacterial overgrowth may have similar presentations. Therefore, for patients with IPS who fail to respond to medical therapy, celiac serology and hydrogen breath test for proximal small bowel bacterial overgrowth may be helpful. It is not clear whether there is a separate entity of constipation-predominant IPS as a counterpart to constipation-predominant IBS. Diagnostic criteria for IPS need to be standardized. Some components of ROME-II criteria for IBS can be adopted (17). However, this diagnostic approach should be validated.

Treatment

Treatment of IPS is empiric. There are no published trials or established algorithms for the management of IPS. The common clinical features shared by patients with IPS and IBS suggest that the pathophysiology of the two diseases may overlap. Therefore, it is reasonable to speculate that the treatment modalities effective in IBS may also be successful in IPS. We found that dietary fibers are often not helpful in patients with IPS. However, dietary modifications such as low-fat and low-carbohydrate diet and avoidance of dairy products, excessive caffeine or alcohol sometimes help to relieve symptoms. Occasionally, patients may report improvement in symptoms with antibiotic therapy. This may be explained by the fact that some of patients with IPS may in fact have proximal small bowel bacterial overgrowth.

Pharmaceutical therapy includes antispasmodic agents (*e.g.,* hyoscyamine, dicyclomine, and cimetropium bromide), antidiarrheal agents (diphenoxylate, loperamide, cholestyramine, and opium), and tricyclic antidepressants. Our anecdotal experience suggests that tricyclic antidepressants (such as amitriptyline 25–50 mg QHS) and/or antispasmodic agents (such as hyoscyamine 0.375 mg b.i.d.) are safe and effective in the majority of patients with IPS. Patients with severe perianal spasm or discomfort may benefit from topical nitroglycerin or opium suppositories. The role of serotonin-receptor modulator therapy should be evaluated based on the fact that the neuroenteric systems may be overactivated in IPS as evidenced by enterochromaffin cell hyperplasia.

SUMMARY

Patients with inflammatory and noninflammatory diseases after IPAA often present with nonspecific symptoms that compromise their quality of life. Pouch endoscopy is the key to accurate diagnosis, and it may also play a potential role in therapy. The classification of pouchitis and the differential diagnosis of pouch disorders is important for proper clinical management. IPAA and the pathologic conditions it creates could be considered as "man-made" models for the study of infectious diarrhea, IBD, and IBS.

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REFERENCES

1. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomosis: Complications and function in 1005 patients. Ann Surg 1995;222:120–7.
2. Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis: Definition, pathogenesis, and treatment. Gastroenterology 1994;107:1856–60.
3. Shen B, Fazio VW, Remzi FH, et al. Comprehensive evaluation of inflammatory and non-inflammatory sequelae of ileal pouch-anal anastomosis. Am J Gastroenterol 2005;100:93–101.
4. Hurst RD, Molinari M, Chung TP, et al. Prospective study of the incidence, timing, and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. Arch Surg 1996;131:497–502.
5. Meagher AP, Farouk R, Dozois RR, et al. J ileal pouch-anal anastomosis from chronic ulcerative colitis: Complications and long-term outcome in 1,310 patients. Br J Surg 1998;85:800–3.
6. 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;38:234–9.
7. Simchuk EJ, Thirlby RC. Risk factors and true incidence of pouchitis in patients after ileal pouch-anal anastomosis. World J Surg 2000;24:851–6.
8. Schmidt CM, Lazenby AJ, Hendrickson RJ, et al. Preoperative terminal ileal and colonic resection histopathology predicts risk of pouchitis in patients after ileoanal pull-through procedure. Ann Surg 1998;227:654–62.
9. Shepherd NA, Hulten L, Tytgat GNJ. Workshop: Pouchitis. Int J Colorectal Dis 1989;4:205–29.
10. Lohmuller JL, Pemberton HJ, Dozois RR, et al. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg 1990;211:622–9.
11. Hata K, Watanabe T, Shinozaki M, et al. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: Multivariate analysis. Scand J Gastroenterol 2003;38:1055–8.
12. 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;49:671–7.
13. Kuisma J, Jarvinen H, Kahri A, et al. Factors associated with disease activity of pouchitis after surgery for ulcerative colitis. Scand J Gastroenterol 2004;39:544–8.
14. Carter K, 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;121:805–11.
15. Brett PM, Yasuda N, Yiannakou JY, et al. Genetic and immunological markers in pouchitis. Eur J Gastroenterol Hepatol 1996;8:951–5.
16. Merrett MN, Mortensen N, Kettlewell M, et al. Smoking may prevent pouchitis in patients with restorative proctocolectomy for ulcerative colitis. Gut 1996;38:362–4.
17. Shen B, Fazio VW, Remzi FH, et al. Risk Factors for inflammatory and non-inflammatory complications of ileal pouch-anal anastomosis. Am J Gastroenterol 2004;99:A798.
18. Achkar J-P, Al-Haddad M, Lashner B, et al. Differentiating risk factors for acute and chronic pouchitis. Clin Gastroenterol Hepatol 2005;3:60–6.
19. Fazio VW, Tekkis PP, Remzi FH, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. Ann Surg 2003;238:605–17.
20. Lavery IC, Sirimarco MT, Ziv T, et al. Anal canal inflammation after ileal pouch-anal anastomosis. The need for treatment. Dis Colon Rectum 1995;38:803–6.
21. Duffy M, O'Mahony L, Coffey JC, et al. Sulfate-reducing bacteria colonize pouches formed for ulcerative colitis but not for familial adenomatous polyposis. Dis Colon Rectum 2002;45:384–8.
22. Nasmyth DG, Godwin PGR, Dixon MF, et al. Ileal ecology after pouch anal anastomosis or ileostomy. Gastroenterology 1989;96:817–24.
23. Gosselink MP, Schouten WR, Van Lieshout LM, et al. Eradication of pathogenic bacteria and restoration of normal pouch flora: Comparison of metronidazole and ciprofloxacin in the treatment of pouchitis. Dis Colon Rectum 2004;47:1519–25.
24. Gionchetti P, Rizzello F, Venturi A, et al. Antibiotic combination therapy in patients with chronic, treatment resistant pouchitis. Aliment Pharmacol Ther 1999;13:713–8.
25. Shen B, Achkar J-P, Lashner BA, et al. Endoscopic and histologic evaluations together with symptom assessment are required to diagnose pouchitis. Gastroenterology 2001;121:261–7.
26. 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;1:167–74.
27. Heuschen UA, Autschbach F, Allemeyer EH, et al. Long-term follow-up after ileoanal pouch procedure. Algorithm for diagnosis, classification, and management of pouchitis. Dis Colon Rectum 2001;44:487–99.
28. Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis after ileal pouch-anal anastomosis: A pouchitis disease activity index. Mayo Clin Proc 1994;69:409–15.
29. Shen B, Shermock KM, Fazio VW, et al. A cost-effectiveness analysis of diagnostic strategies in symptomatic patients with ileal pouch-anal anastomosis. Am J Gastroenterol 2003;98:2460–7.
30. Parsi MA, Shen B, Achkar JP, et al. Fecal lactoferrin for diagnosis of symptomatic patients with ileal pouch-anal anastomosis. Gastroenterology 2004;126:1280–6.
31. Sandborn WJ. Pouchitis: Risk factors, frequency, natural history, classification and public health perspective. In: McLeod RS, Martin F, Sutherland LR, Wallace JL, Williams CN, eds. Trends in inflammatory bowel disease 1996. Lancaster, UK: Kluwer Academic Publishers, 1997:51–63.
32. Shen B. Diagnosis and management of patients with pouchitis. Drugs 2003;65:453–61.
33. Sandborn WJ, Pardi DS. Clinical management of pouchitis. Gastroenterology 2004;127:1809–14.
34. Zuccaro G, Fazio VW, Church JM, et al. Pouch ileitis. Dig Dis Sci 1989;34:1505–10.
35. Shen B, Achkar JP, Lashner BA, et al. A randomized trial of ciprofloxacin and metronidazole in treating acute pouchitis. Inflamm Bowel Dis 2001;7:301–5.
36. Madden MV, McIntyre AS, Nicholls RJ. Double-blinded crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. Dig Dis Sci 1994;39:1193–6.
37. Sambuelli A, Boerr L, Negreira S, et al. Budesonide enema

in pouchitis: A double-blinded, double dummy, controlled trial. Aliment Pharmacol Ther 2002;16:27–34.
38. Mowschenson PM, Critchlow JF, Peppercorn MA. Ileoanal pouch operation: Long-term outcome with or without diverting ileostomy. Arch Surg 2000;135:463–5.
39. Hurst RD, Chung TP, Rubin M, et al. Implications of acute pouchitis on the long-term functional results after restorative proctocolectomy. Inflamm Bowel Dis 1998;4:280–4.
40. Madiba TE, Bartolo DC. Pouchitis following restorative proctocolectomy for ulcerative colitis: Incidence and therapeutic outcome. J R Coll Surg Edinb 2001;46:334–7.
41. 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;119:305–9.
42. Tremaine WJ, Sandborn WJ, Wolff BG, et al. Bismuth carbomer foam enemas for active chronic pouchitis: A randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 1997;11:1041–6.
43. Wischmeyer P, Pemberton JH, Philips SF. Chronic pouchitis after ileal pouch-anal anastomosis: Responses to butyrate and glutamine suppositories in a pilot study. Mayo Clin Proc 1993;68:978–81.
44. Sartor RB. Probiotics in chronic pouchitis. Restoring luminal microbial balance. Gastroenterology 2000;119:584–5.
45. 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;53:108–14.
46. Stahlberg D, Gullberg K, Liljeqvist L, et al. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. Dis Colon Rectum 1996;39:1012–8.
47. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: A double-blind, placebo-controlled trial. Gastroenterology 2003;124:1202–9.
48. Mann SD, Pitt J, Springall RG, et al. *Clostridium difficile* infection—An unusual cause of refractory pouchitis: Report of a case. Dis Colon Rectum 2003;46:267–70.
49. Munoz-Juarez M, Pemberton JH, Sandborn WJ, et al. Misdiagnosis of specific cytomegalovirus infection of ileoanal pouch as a refractory idiopathic chronic pouchitis. Report of two cases. Dis Colon Rectum 1999;42:117–20.
50. Mooka D, Furth EE, MacDermott RP, et al. Pouchitis associated with primary cytomegalovirus infection. Am J Gastroenterol 1998;93:264–6.
51. Mimura T, Rizzello R, 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;16:909–17.
52. Miner P, Wedel M, Bane B, et al. An enema formulation of alicaforsen, an antisense inhibitor of intercellular adhesion molecule-1, in the treatment of chronic, unremitting pouchitis. Aliment Pharmacol Ther 2004;19:281–6.
53. Gionchetti P, Rizzello F, Morselli C, et al. Eight-week trial of oral budesonide for the treatment of refractory pouchitis. Gastroenterology 2004;126:A123.
54. Viscido A, Habib FI, Kohn A, et al. Infliximab in refractory pouchitis complicated by fistulae following ileoanal pouch for ulcerative colitis. Aliment Pharmacol Ther 2003;17:1263–71.
55. Keighley MRB. The final diagnosis in pouch patients for presumed ulcerative colitis may change to Crohn's disease: Patients should be warned of the consequences. Acta Chir lugosl 2000;47(4 suppl):27–31.
56. Peyregne V, Francois Y, Gilly F-N, et al. Outcome of ileal pouch after secondary diagnosis of Crohn's disease. Int J Colorectal Dis 2000;15:49–53.
57. Goldstein NS, Sanford WW, Bodzin JH. Crohn's like complications in patients with ulcerative colitis after total proctocolectomy and ileal pouch-anal anastomosis. Am J Surg Pathol 1997;21:1343–53.
58. Deutch AA, McLeod RS, Cullen J, et al. Results of the pelvic-pouch procedure in patients with Crohn's disease. Dis Colon Rectum 1991;34:475–7.
59. Yu CS, Pemberton JH, Larson D. Ileal pouch-anal anastomosis in patients with indeterminate colitis: Long-term results. Dis Colon Rectum 2000;43:1487–96.
60. Neilly P, Neill ME, Hill GL. Restorative proctolectomy with ileal pouch-anal anastomosis in 203 patients: The Auckland experience. Aust N Z J Surg 1999;69:22–7.
61. Gemlo B, Wong D, Rothenberger DA, et al. Ileal pouch-anal anastomosis: Patterns of failure. Arch Surg 1992;127:784–7.
62. Hartley JE, Fazio VW, Femzi FH, et al. Analysis of the outcome of ileal pouch-anal anastomosis in patients with Crohn's disease. Dis Colon Rectum 2004;47:1808–15.
63. Chhablani RK, Campbell MS, Su C, et al. Clinical features cannot be used to predict Crohn's disease in patients with ileoanal pouches. Gastroenterology 2004;126(suppl 2):A630
64. Delaney CP, Remzi FH, Gramlich T, et al. Equivalent function, quality of life and pouch survival rates after ileal pouch-anal anastomosis for indeterminate and ulcerative colitis. Ann Surg 2002;236:43–8.
65. Alexander F, Sarigol S, DiFiore J, et al. Fate of the pouch in 151 pediatric patients after ileal pouch anal anastomosis. J Pediatr Surg 2003;38:78–82.
66. Panis Y, Poupard B, Nemeth J, et al. Ileal pouch-anal anastomosis for Crohn's disease. Lancet 1996;347:854–7.
67. Hyman NH, Fazio VW, Tuckson WB, et al. Consequences of ileal pouch-anal anastomosis for Crohn's colitis. Dis Colon Rectum 1991;34:653–7.
68. Wolf JM, Achkar J-P, Lashner BA, et al. Afferent limb ulcers predict Crohn's disease in patients with ileal pouch-anal anastomosis. Gastroenterology 2004;126:1686–91.
69. Shen B, Fazio VF, Remzi FH, et al. Endoscopic balloon dilation of ileal pouch strictures. Am J Gastroenterol 2004;99:2340–7.
70. Colombel J-F, Richart E, Loftus EV, et al. Management of Crohn's disease of the ileoanal pouch with infliximab. Am J Gastroenterol 2003;98:2239–44.
71. Sagar PM, Dozois RR, Wolff BG. Long-term results of ileal pouch-anal anastomosis in patients with Crohn's disease. Dis Colon Rectum 1996;39:893–8.
72. Grobler SP, Hosie KB, Affie E, et al. Outcome of restorative proctocolectomy when the diagnosis is suggestive of Crohn's disease. Gut 1993;34:1384–8.
73. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. Ann Surg 2003;238:229–34.
74. Heald RJ, Allen DR. Stapled ileo-anal anastomosis: A technique to avoid mucosal proctectomy in the ileal pouch operation. Br J Surg 1986;73:571–2.
75. Ziv Y, Fazio VW, Sirimarco MT, et al. Incidence, risk factors, and treatment of dysplasia in the anal transitional zone after ileal pouch-anal anastomosis. Dis Colon Rectum 1994;37:1281–5.
76. Williams NS. Stapling technique for pouch-anal anastomosis without the need for purse-string stricture. Br J Surg 1989;76:348–9.
77. Kmiot WA, Keighley MR. Totally stapled abdominal restorative proctocolectomy. Br J Surg 1989;76:961–4.
78. Shen B, Lashner BA, Bennett A, 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;99:1527–31.
79. Remzi FH, Fazio VW, Delaney CP, et al. Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: Results of prospective evaluation after a minimum of ten years. Dis Colon Rectum 2003;46:6–13.
80. O'Riordain MG, Fazio VW, Lavery IC, et al. Incidence and natural history of dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: Results of a five-year to ten-year follow-up. Dis Colon Rectum 2000;43:1660–5.
81. Heppell J, Weiland L, Perrault J, et al. Fate of the rectal mucosa after rectal mucosectomy and ileoanal anastomosis. Dis Colon Rectum 1983;26:768–71.
82. 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;97:972–7.
83. Chun A, Desautels S, Slivka A, et al. Visceral algesia in irritable bowel syndrome, fibromyalgia, and sphincter of Oddi dysfunction, type III. Dig Dis Sci 1999;44:631–6.
84. Simrén M, Castedal M, Svedlund J, et al. Abnormal propagation pattern of duodenal pressure waves in the irritable bowel syndrome (IBS). Dig Dis Sci 2000;45:2151–61.
85. Evans PR, Kellow JE. Physiological modulation of jejunal sensitivity in health and in irritable bowel syndrome. Am J Gastroenterol 1998;93:2191–6.
86. Bayless TM. Coexistent irritable bowel syndrome and inflammatory bowel disease. In: Bayless TM, Hanauer SB, eds. Advanced therapy of inflammatory bowel disease, 1st ed. Hamilton, Ontario: B.C. Decker, 2001:91–94.
87. Isgar B, Hartman M, Kaye MD, et al. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. Gut 1983;24:190–2.
88. Rao SSC, Read NW, Brown C, et al. Studies on the mechanism of bowel disturbance in ulcerative colitis. Gastroenterology 1987;93:934–40.
89. Schiller LR. Diarrhea following small bowel resection. In: Bayless TM, Hanauer SB, eds. Advanced therapy of inflammatory bowel disease, 1st ed. Hamilton, Ontario: B.C. Decker, 2001:471–4.
90. Bernstein CN, Rollandilli R, Niazi N, et al. Characterization of afferent mechanisms in ileoanal pouches. Am J Gastroenterol 1997;92:103–8.
91. Bouin M, Plourde V, Boivin M, et al. Rectal distention testing in patients with irritable bowel syndrome: Sensitivity, specificity, and predictive values of pain sensory thresholds. Gastroenterology 2002;122:1771–7.
92. Steen J, Penning C, Brussee J, et al. Prospective evaluation of ileoanal pouch characteristics measured by barostat. Dis Colon Rectum 2002;45:1295–303.
93. Mularczyk A, Contessini-Avesani E, Cesana B, et al. Local regulation of postprandial motor response in ileal pouches. Gut 1999;45:575–80.
94. Steens J, Penning C, Bemelman WA, et al. Comparison of ileoanal pouch and rectal function measured by barostat. Dig Dis Sci 2001;46:731–8.
95. Steens J, Bemelman WA, Meijerink WJHJ, et al. Ileoanal pouch function is related with postprandial pouch tone. Br J Surg 2001;88:1492–7.
96. Shen B, Sanmiguel C, Parsi M, et al. Irritable pouch syndrome (IPS) is characterized by visceral hypersensitivity and poor quality of life (QOL) score. Gastroenterology 2004;126(suppl 2):A124
97. Shen B, Liu W, Remzi F, et al. Enterochromaffin cell (EC) cell hyperplasia and alteration of mucosal immune cells in irritable pouch syndrome. Gastroenterology 2005;127(suppl 2):A314.