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Ileal Pouch-Anal Anastomosis: A Gastroenterology Perspective

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Total proctocolectomy with an ileal pouch-anal anastomosis (IPAA) is the treatment of choice in medically refractory ulcerative colitis. Patients with an IPAA are at risk of developing pouch disorders, ranging from pouchitis, Crohn disease of the pouch, cuffitis, pouch neoplasia, and irritable pouch syndrome. Pouchitis is an aberrant mucosal immune response to altered luminal microflora and constitutes the leading cause of pouch dysfunction. A combination of clinical, serologic, and genetic factors may predict the likelihood of developing pouchitis. Endoscopy remains the gold standard in diagnosing pouch disorders. Inflammatory markers in blood as well as stool are useful in monitoring disease activity and can be followed for accurate prognostication. Most patients with pouchitis respond to a course of antibiotics; however, a few develop chronic relapsing pouchitis that may require long-term antibiotics or probiotics. All patients with chronic antibiotic refractory pouchitis should undergo evaluation for underlying enteric infections as well as Crohn disease. Treatment of Crohn disease of the pouch may require immunomodulators or biological agents. IPAA decreases but does not eliminate the risk of subsequent neoplasia in the residual rectal mucosa or the pouch itself. A systematic approach to diagnosing and classifying pouch disorders is imperative in managing patients' post-IPAA.
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The past few decades have witnessed a surge in the incidence of inflammatory bowel disease (IBD). The prevalence of ulcerative colitis (UC) is estimated to approach 200/100,000 in the West, with rising incidence in developing countries[1] Despite strides in medical treatment of UC with the advent of biologics, almost 10%-36% of patients do not respond to medical therapy and require colectomy.[2] Total proctocolectomy with an ileal pouch-anal anastomosis (IPAA) is the surgical procedure of choice for patients with UC who are refractory to medical management, develop colonic dysplasia or colon cancer, as well as for patients with familial adenomatous polyposis syndrome. Most surgeons have abandoned the 4-loop W pouch in favor of the 2-loop J pouch. The pouch-anal anastomosis can be stapled or hand sewn. The former technique leaves behind a cuff of rectal mucosa[3] that can be a site for subsequent inflammation (cuffitis) or dysplasia. A rectal mucosectomy followed by a hand-sewn anastomosis just proximal to the dentate line removes virtually all the rectal mucosa, thereby eliminating risk of subsequent cuffitis or dysplasia. Patients undergoing IPAA generally report improved health-related quality of life scores and health status after the surgery. The improved health-related quality of life scores remain durable over time.[4,5] However, the improved functional outcome comes at the price of pouch-related complications. The cumulative incidence of pouch failure is estimated at 4%. Pelvic sepsis remains the leading cause of pouch failure, with an estimated incidence of 7.5%,[6] followed by Crohn disease (CD) of the pouch and chronic pouchitis.[7-9] Pelvic sepsis usually requires surgical intervention for anastomotic leaks, pouch sinus, wound dehiscence, or fistulae that typically occur in the early postoperative period with a limited role for the gastroenterologist in their management. Patients with an ileal pouch need to be followed up at regular intervals after their surgery, as they remain at risk for subsequent inflammatory and non-inflammatory complications of the pouch, such as pouchitis and CD that can lead to pouch failure.

Pouchitis

Pouchitis remains the most common cause of pouch dysfunction. A recent meta-analysis of 53 studies covering almost 15,000 patients reported a pooled incidence of 26.8% for pouchitis in studies published since 2000[6] Other studies

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have estimated the incidence at as high as 40%.[10,11] It is safe to assume that almost half of all patients undergoing IPAA surgery will experience at least 1 episode of pouchitis, with the majority developing within the first year after ileostomy closure[12] The natural history of pouchitis is not well understood. Almost all patients with acute pouchitis respond well to antibiotics; however, relapses are common, and up to 19% of patients develop recurring episodes of pouchitis.[13,14] Although there are no universally accepted classification systems, pouchitis can be classified based on response to antibiotics (antibiotic responsive, antibiotic dependent, and antibiotic refractory), duration of symptoms (acute vs chronic with a cutoff duration of 4 weeks), and etiology (idiopathic vs secondary).[15] With the rising incidence of UC, gastroenterologists can expect to see an increasing number of patients with pouch disorders in their clinical practice. An accurate diagnosis, classification, and identification of specific etiologies are necessary to initiate appropriate therapy.

Etiopathogenesis of Pouchitis

Pouchitis occurs almost exclusively in patients with underlying UC and not in patients with familial adenomatous polyposis after an IPAA.[16,17] An abnormal mucosal immune response to altered luminal microflora is thought to cause inflammation of the pouch in genetically susceptible individuals (dysbiosis). The microbial load in the pouch promotes morphologic changes in the ileal mucosa mimicking the colonic epithelium, resulting in colonic metaplasia; characterized by villous blunting, crypt cell hyperplasia, and colonic epithelium-specific antigens expression.[18] Colonic metaplasia of the pouch in UC results in sulfomucin production by the metaplastic goblet cell.[18,19] The abundance of sulfomucin allows colonization of sulfate-reducing bacteria, thereby promoting dysbiosis by triggering cellular apoptosis via production of hydrogen sulfide, resulting in mucosal inflammation.[20,21] Previous studies of pouch microbiota have demonstrated an abundance of *Lactobacilli* and anaerobes in the absence of inflammation. During episodes of pouchitis, there is an increase in the number of aerobic bacteria, hemolytic strains of *Escherichia coli* and *Clostridium perfringens*, with a decrease in the numbers of *Lactobacilli.*[22] Treatment with ciprofloxacin and metronidazole was noted to eradicate the pathogens and restore normal flora.

In conjunction with altered luminal microflora alteration in the innate and adaptive mucosal immunity contribute to the development of pouchitis. Altered mucosal permeability and impaired barrier function have been noted in the small bowel mucosa after IPAA.[23,24] Pouchitis is characterized by an altered adaptive immune response as well, such as proliferation of immature plasma cells and increased production of proinflammatory cytokines, cell adhesion molecules, platelet-activating factor, and other mediators of inflammation.[25-28] In summary, there are numerous changes in the mucosal immune responses in the pouch mucosa that indicate activation of a nonspecific inflammatory cascade in response to altered luminal microflora, leading to acute or chronic inflammation of the pouch.

Risk Factors for Pouchitis

Numerous studies have attempted to identify risk factors for pouchitis, in an effort to better prognosticate clinical course after IPAA. Numerous clinical, serologic, and genetic parameters have been identified as predictive of an increased risk of pouchitis.

Genetic polymorphisms of interleukin-1 receptor antagonist and *NOD2/CARD15* genes, combined carriership of specific TLR9 and CD14 alleles, and noncarrier status of tumor-necrosis factor allele 2 are associated with increased risk of pouchitis.[29-32]

IBD serologies can help identify patients at an increased risk of pouchitis after IPAA. In a study by Fleshner et al,[33] 95 patients with UC undergoing IPAA were followed prospectively for a median duration of 32 months. Pouchitis was seen in 42% of peri-nuclear anti-neutrophil cytoplasmic antibody (pANCA)-positive patients compared with 20% of pANCA-negative patients. A high pANCA titer (>100 ELISA units [EU]/mL) was associated with the 56% cumulative risk of developing pouchitis. A more recent study by the same group followed 238 patients with antibiotic responsive as well as antibiotic-dependent pouchitis for a median duration of 47 months. The presence of pANCA (36% vs 16%) and anti-CBir1 (anti flagellin [CBir1] antibody) (46% vs 26%) was associated with a greater risk of pouchitis when compared with patients with negative serologies.[10]

In this population, a family history of CD or preoperative anti-*Saccharomyces cerevisiae* immunoglobulin A (ASCA IgA) seropositivity was associated with a subsequent diagnosis of CD of the pouch.[34]

Additional predictors of pouchitis following IPAA include presence of primary sclerosing cholangitis, extensive UC, the presence of backwash ileitis, preoperative thrombocytosis, being a nonsmoker, and concomitant arthropathy.[12,35-41] The use of nonsteroidal antiinflammatory medications is an additional risk factor for pouchitis.

Diagnosis of Pouchitis

Patients with pouchitis can present with a wide array of symptoms, ranging from increased frequency of bowel movements to urgency, blood in stool, nocturnal diarrhea, incontinence, abdominal and/or pelvic pain, and fever. These symptoms are not specific to pouchitis and can be seen with cuffitis or CD; hence, a diagnosis of pouchitis should never be made based on symptoms alone.

An Endoscopic Assessment With a Pouchoscopy

An endoscopic assessment with a pouchoscopy is indispensable in evaluating patients presenting with the aforementioned symptoms after an IPAA. An endoscopic examination of the pouch should include intubation of the afferent limb to examine the "pre-pouch" ileum as well as a careful examination of the anal transition zone for a residual rectal cuff. Biopsies should be obtained, as histologic assessment of the

mucosa may provide clues to the underlying etiology of inflammation, such as the presence of granulomas (CD), pyloric gland metaplasia (chronic inflammation), or viral inclusions on H&E stain or immunostain (cytomegalovirus [CMV]). The Pouchitis Disease Activity Index (PDAI)[42] and the Heidelberg Pouchitis Activity Score[43] were developed to aid in diagnosis of pouchitis based on symptoms, endoscopic appearance, and histologic assessment. These scoring systems are of limited utility in routine clinical practice and used primarily as research tools.

In addition to pouch endoscopy, certain laboratory parameters are helpful in diagnosis and prognostication of pouchitis.

Fecal Inflammatory Markers

Fecal inflammatory markers have been studied in IBD and demonstrate strong correlation with the degree of luminal inflammation. Calprotectin is a neutrophil cytosolic protein that is detectable in stool during active inflammation and resists bacterial degradation, making it a convenient, reliable, and reproducible marker of mucosal inflammation.[44,45] Fecal calprotectin levels have been shown to correlate with endoscopic and histologic scores in pouchitis as well as the PDAI scores.[46,47] This simple cost-effective test can be used in monitoring patients' response to antibiotics as well as in differentiating pouchitis from the noninflammatory condition of irritable pouch syndrome.

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) is a nonspecific marker of inflammation. In studies investigating the role of ESR as a marker of inflammation in pouchitis, a significant correlation was observed between ESR levels and PDAI scores as well as episodes of pouchitis.[48,49]

C-reactive Protein

C-reactive protein (CRP) is an acute-phase reactant secreted by the hepatocytes in response to circulating inflammatory cytokines. CRP has a shorter half-life compared with ESR and is a useful marker of inflammation in IBD. CRP levels have been shown to correlate significantly with the PDAI in pouchitis.[48]

Stool *Clostridium difficile* and Bacterial Culture and Sensitivity Testing

Stool *C difficile* and bacterial culture and sensitivity testing should be performed in patients with antibiotic refractory pouchitis. There has been a significant increase in the rates and severity of *C. difficile* infection (CDI) in the United States and Europe, particularly in patients with IBD. CDI has been reported in patients with IPAA.[50] and should be excluded in pouch patients with active symptoms, particularly if they remain refractory to antibiotics. Occasionally, other enteric pathogens may be identified on stool testing, such as *Campylobacter jejuni* or *Salmonella typhi*.

CMV infection is associated with increased risk of complications in UC. In a study of 34 patients with IPAA, immunostaining of the biopsy samples was performed for CMV detection. The rate of CMV detection was significantly higher in patients with pouchitis (41%) compared with those with normal pouches (11%).[51] CMV infection in patients with IPAA mimics chronic pouchitis and should be considered in the differential diagnosis of refractory pouchitis, even in an immunocompetent patient.[52,53]

Laboratory Evaluation for the Long-term Metabolic Sequelae of IPAA

Laboratory evaluation for the long-term metabolic sequelae of IPAA should be performed periodically, even in the absence of inflammation of the pouch. Anemia is common in patients with IPAA and UC.[54] It is usually multifactorial and may be a secondary to chronic inflammation, low iron, and vitamin B12 levels. Iron-deficiency anemia may occur in the absence of overt gastrointestinal bleeding and reflect underlying pouchitis or CD of the pouch.[55] Patients with IPAA are predisposed to low vitamin B12 levels because of resection of a portion of the terminal ileum.[56] Lastly, all patients with IPAA should undergo screening for osteopenia and osteoporosis, with a baseline bone densitometry, as the prevalence of low bone mineral density approaches 30% in this population.[57]

There is no consensus on the diagnostic criteria for pouchitis and when and what specific tests should be ordered in evaluating these patients. It is certainly reasonable to treat an initial episode of pouchitis with an empiric course of antibiotics; however, recurrent or worsening symptoms, fever, weight loss, anemia, or persistent blood in stool should warrant a more thorough evaluation as detailed earlier in the text.

Treatment of Pouchitis

Most cases of pouchitis are thought to be the sequela of an abnormal immune response to altered luminal microflora (dysbiosis) and antibiotic comprise the first line of therapy in the treatment of pouchitis. In a small randomized trial of ciprofloxacin (1000 mg/d) and metronidazole (20 mg/kg/d), both ciprofloxacin and metronidazole were effective in treating acute pouchitis with significant reduction in the PDAI scores. Patients receiving ciprofloxacin reported fewer medication-related adverse effects than the metronidazole group.[58] The efficacy of rifaximin (a poorly absorbed, nonaminoglycoside, semisynthetic antibiotic derived from rifamycin O) in treatment of acute pouchitis was studied in placebo-controlled pilot trial with 18 patients. Rifaximin, 400 mg 3 times a day for 4 weeks, was only marginally better than placebo in treating acute pouchitis.[59] A 28-day regimen comprising of ciprofloxacin (500 mg twice a day) and metronidazole (400 mg twice a day) was shown to be effective in treating pouchitis with concurrent pre-pouch ileitis.[60] Open-label trials of other agents, such as tetracycline, doxycycline, clarithromycin and amoxicillin/clavulanic acid, and budesonide enemas, have shown varying degrees of success in treatment of pouchitis.[61]

Patients with antibiotic-responsive pouchitis often become

antibiotic dependent, requiring long-term maintenance therapy to prevent recurrent episodes. In an open-label study evaluating the efficacy of rifaximin in maintaining remission in patients with antibiotic-dependent pouchitis, 65% of patients maintained remission at 3 months, with a median dose of rifaximin, 200 mg/d (range: 200-1800 mg/d).[62]

In addition to rifaximin, probiotics have also been used as maintenance therapy for prevention of relapse in antibiotic-dependant pouchitis. In a randomized controlled trial, the probiotic formulation VSL#3 maintained clinical remission in 85% (n = 17) of patients with antibiotic-dependent pouchitis.[63] Similar efficacy in maintaining clinical remission with VSL#3 was also seen in a trial for secondary prophylaxis of relapse of pouchitis following treatment with ciprofloxacin and rifaximin.[64] The high rates of clinical remission with probiotics have not been reproduced in subsequent postmarket open-label studies.[65,66]

A meta-analysis of 5 randomized placebo-controlled trials of probiotics administered for prevention or treatment of pouchitis, an odds ratio of 0.04 (95% CI: 0.01-0.14, $P < 0.0001$) was noted in favor of treatment with probiotics.[67] The studies included in the meta-analysis displayed significant heterogeneity, as they included probiotics for treatment as well as prevention of relapse of acute and chronic pouchitis.

The most challenging subset of patients with IPAA is of chronic antibiotic-refractory pouchitis. A thorough evaluation for potential causes of antibiotic refractoriness, such as CD of the pouch, ongoing non-steroidal anti-inflammatory drugs (NSAID) intake, concurrent CDI or CMV infection, celiac disease, or cuffitis, should be undertaken. In a small study of 8 patients with chronic refractory pouchitis, a combination of ciprofloxacin (500 mg twice a day) and rifaximin (1000 mg/d twice a day) for 2 weeks was effective in inducing remission. Of 8 patients, 7 responded to this combination and reported satisfactory pouch function at 30 months.[68] Other open-label trials with metronidazole, 500 mg twice a day or combination of ciprofloxacin (1000 mg/d with tinidazole (100-1500 mg/d) for 4 weeks have shown efficacy in treating chronic refractory pouchitis.[69,70]

In addition to antibiotics, budesonide 9 mg/d for 8 weeks induced remission in 75% (n = 15) of patients with chronic refractory pouchitis in an open-label study of 20 patients.[71] Topical therapy with mesalamine enemas, short-chain fatty acid enemas, bismuth carbomer enemas, and glutamine enemas has been used in chronic pouchitis; however, the experience remains restricted to small studies.[66]

Prophylaxis for Pouchitis

Pouchitis occurs in approximately 40% of all UC patients with IPAA. As majority of patients develop their first episode within the first year after IPAA surgery,[9-11] it is certainly reasonable to institute prophylactic therapy, especially in patients at high risk of developing pouchitis.[67] Various probiotic formulations have been studied for prophylaxis of pouchitis. In a randomized control trial of primary prophylaxis of pouchitis, the probiotic formulation VSL#3 (comprising of 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and *Streptococcus salivarius thermophilus*) decreased the incidence of pouchitis within the first year following IPAA (10% in the VSL#3 group vs 40% with placebo).[72] In a larger study encompassing 127 patients, a probiotic formulation containing *Lactobacillus rhamnosus GG* was shown to delay the first episode of pouchitis.[73] Lastly, IPAA surgery results in loss of the valve mechanism, thereby allowing reflux into the small bowel, increasing the likelihood of developing small bowel bacterial overgrowth. Although studies done thus far have failed to demonstrate a link between pouchitis and small bowel bacterial overgrowth as detected with hydrogen breath testing[74,75] a diet devoid of poorly absorbed short-chain carbohydrates may decrease frequency of bowel movements in patients with IPAA.[66,76] In summary, despite relative paucity of data, probiotics may be used for primary as well as secondary prophylaxis of pouchitis.

CD of the Pouch

CD of the pouch can occur in setting of a known diagnosis of CD after an intentional IPAA surgery for Crohn colitis. Alternatively, CD may develop de novo, years after IPAA for UC. The latter appears to have a poorer prognosis, with a higher likelihood of progressing to pouch failure.[77,78] A family history of CD and ASCA IgA seropositivity are risk factors for CD of the pouch.[34] Presence of neural hypertrophy in the resected colon may predict CD of the pouch.[79] Pouch fistulas arising >6 months after ileostomy closure, pouch strictures as well as inflammation involving the afferent limb of the pouch, should prompt a thorough evaluation for CD of the pouch. An upper endoscopy and wireless capsule study are often necessary to evaluate the proximal small bowel.

CD of the pouch can be treated with oral as well a topical 5-aminosalicylate (5-ASA) formulations, often in combination with steroid enemas. More severe disease warrants escalation of therapy. Budesonide, with its time-controlled release in the distal small bowel can be used in the treatment of CD of the pouch. Patients with disease that remains refractory to first-line agents and those with fistulizing or structuring phenotype require escalation of therapy. In a small open-label trial of patients with chronic refractory pouchitis complicated by fistulae, treatment with infliximab (2.5 mg/kg at 0, 2, and 6 weeks) in combination with azathioprine (2.5 mg/kg) resulted in fistula closure in 5 of 7 patients at 10 weeks.[80] In a subsequent open-label trial of infliximab (5 mg/kg at 0, 2, and 6 weeks) in patients with chronic refractory pouchitis complicated by ileitis, 8 of 10 patients achieved and maintained complete endoscopic remission at 6 months.[81] Data on maintenance treatment for CD of the pouch are sparse and restricted to case series. Ferrante et al[82] reported a case series of 28 IPAA patients treated with infliximab (2.5 mg/kg at 0, 2, and 6 weeks followed by every 8 weeks thereafter) for refractory pouchitis with ileitis (n = 25) and fistulae (n = 7). At 20 months, 40% of patients with refractory pouchitis and ileitis achieved endoscopic healing, and 3 of 7 patients with fistulae had complete cessation of drainage Thus, despite relative paucity of data, infliximab has

shown good short- and mid-term efficacy in treating CD of the pouch.[83] Data on adalimumab use in this scenario remain restricted to case reports.[84]

Cuffitis

The aim of a restorative proctocolectomy is to remove all disease-prone mucosa; however, depending on the surgical technique used, a cuff of rectal mucosa may have been left intact to allow stapling of the ileoanal anastomosis.[3] Symptoms of residual inflammation in the retained cuff of rectal mucosa constitute cuffitis. Patients with cuffitis experience significant urgency, bloody stool, and rectal discomfort. Cuffitis is diagnosed on careful examination of the anorectal region on endoscopy. Biopsies from the cuff will reveal inflamed colonic mucosa. Topical mesalamine suppositories or corticosteroid formulations are used in treatment of cuffitis.[85] There are anecdotal reports of treatment of cuffitis refractory to topical therapy with endoscopic injection of long-acting corticosteroids.[77] Chronic cuffitis can lead to anastomotic strictures and, in rare instances, pouch failure. Anastomotic strictures are amenable to endoscopic or bougie dilations.[86,87] Lastly, patients with refractory cuffitis should undergo evaluation to rule out CD of the pouch.

Irritable Pouch Syndrome

Irritable pouch syndrome is a functional disorder of the pouch that has a significant negative impact on health-related quality of life of patients.[88] Although the exact etiology and pathophysiology remain unclear, it is characterized by visceral hypersensitivity and enterochromaffin cell hyperplasia on biopsies.[89,90] Inflammation is not a component of irritable pouch syndrome, and it remains a diagnosis of exclusion. As in irritable bowel syndrome, treatment is symptomatic and empiric. Antidiarrheals, tricyclic antidepressants, antispasmodics, and, occasionally, oral narcotics are used for treatment of irritable pouch syndrome.[77]

Pouch Neoplasia

The risk of neoplasia is reduced significantly after proctocolectomy with IPAA; however, dysplasia or adenocarcinoma may still occur in the rectal cuff or the pouch. The neoplastic lesion can present as a flat or polypoid lesion.[77,91-93] A study covering almost 3200 patients with IPAA estimated the cumulative incidence of pouch neoplasia at 10, 15, 20, and 25 years was 1.3%, 1.9%, 4.2%, and 5.1%, respectively. Rectal mucosectomy did not eliminate risk of subsequent neoplasia of the pouch and a preoperative diagnosis of cancer, or dysplasia of the colon was the most significant risk factor for pouch neoplasia.[94] Additional risk factors for pouch neoplasia include persistent severe villous atrophy of the pouch mucosa, pancolitis with backwash ileitis, chronic pouchitis, and primary sclerosing cholangitis.[95-98] Pouch endoscopy with biopsies remains the gold standard for neoplasia detection; however, there are no guidelines regarding the frequency of pouch endoscopy for dysplasia surveillance.

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