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Inflammatory, infectious, and ischemic disorders of the pelvic pouch

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ABSTRACT

Pouchitis refers to a spectrum of inflammatory disorders affecting the ileal reservoir following restorative proctocolectomy and can be classified as idiopathic or secondary if a specific identifiable entity is identified. Pouchitis is a principal complication of the ileal pouch-anal anastomosis (IPAA) procedure and understanding the evaluation, diagnosis, and treatment of pouchitis is essential for the physician managing IPAA patients. Diagnosis and treatment of pouchitis is typically aided with multidisciplinary coordinated care leveraging specialized medical, pathological, and pharmacological expertise. While most mild and acute episodes of idiopathic pouchitis are easily treated, the gravity of the disease is clear – pouchitis significantly impairs the quality of life for IPAA patients and is a common cause of pouch failure.

Patients undergoing a restorative proctocolectomy are susceptible to inflammatory conditions that may cause episodic and chronic ileal pouch dysfunction.[1] Pouchitis describes a poorly understood spectrum of inflammatory disorders affecting the ileal reservoir and can be classified as idiopathic (primary) or secondary if pouch inflammation arises from a specific identifiable entity (Table 1). Pouchitis is a relatively common complication of the ileal pouch-anal anastomosis (IPAA) procedure and a substantial portion of IPAA patients experience pouchitis at least once in their lifetime. Physicians managing IPAA patients should accordingly understand the evaluation and management of pouchitis. While most episodes of pouchitis are easily treated, pouchitis detracts from quality of life for IPAA patients.[2,3] More ominously, severe chronic forms of pouchitis account for 11% of ileal pouch excisions.[4]

Idiopathic (primary) pouchitis

Idiopathic pouchitis, the most common form of pouchitis, is postulated to be a nonspecific inflammatory disease spectrum of the ileal reservoir resulting from abnormal mucosal immune responses to alterations among mucosal and luminal microflora in genetically susceptible patients.[5-7] The contemporary and prevailing theory is that pouchitis arises from an overgrowth of certain commensal bacteria altering the microflora. Host inflammatory factors play an uncertain role in idiopathic pouchitis, however it is an oversimplification to state that pouchitis is an extension of the underlying pathobiology responsible for inflammatory bowel disease (IBD).[5]

Although several definitions of idiopathic pouchitis exist, the authors prefer the clinical definition used by Fazio et al[8] (Table 2). Pouchitis can be further categorized as acute or chronic, but whether these groupings represent separate diseases or two points along a disease continuum is unclear.[9] The reported incidence of acute idiopathic pouchitis in large series ranges between 18% and 45%, whereas chronic idiopathic pouchitis can occur in approximately 10% of IPAA patients.[8,10-12] The cumulative incidence of acute idiopathic pouchitis approached 80% in a 102-patient cohort with 30 years of follow-up.[13]

The most significant risk factor for developing idiopathic pouchitis appears to be the preoperative indication for restorative proctocolectomy, as patients with ulcerative colitis (UC) and indeterminate colitis (IC) are twice as likely to develop pouchitis compared to IPAA patients with familial adenomatous polyposis (FAP).[8,10] IC and Crohn's disease (CD) are inconsistently linked with higher rates of pouchitis.[14-17] Patients undergoing restorative proctocolectomy for dysplasia were more likely to develop pouchitis, which may implicate disease severity as a risk factor.[18] Several mechanisms might explain increased rates of pouchitis in IBD patients including an adaptive metaplastic conversion of ileal pouch mucosa to a colonic subtype.[19] Compared to FAP patients, increases in sulphomucins found in the epithelial mucus layer of UC IPAA patients altered the protective mucosal architecture and conveyed higher rates of pouchitis.[20] While once thought to be limited nearly exclusively to IBD patients, recognition of pouchitis in FAP patients has been growing with a lifetime pouchitis risk that approaches 20%.[6,8]

Several perioperative risk factors are inconsistently associated with idiopathic pouchitis development. Extensive UC,[21,22]

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Table 1
Classification of pouchitis.

Idiopathic (primary) pouchitis
Secondary pouchitis
Crohn's disease of ileal pouch
Autoimmune pouchitis
Primary sclerosing cholangitis-associated
IgG4-associated
Ischemia of the pouch
Infectious pouchitis
Clostridium difficile enteritis
Cytomegalovirus pouchitis
Radiation-induced pouchitis

Table 2
Definition of primary (idiopathic) pouchitis, as modified from Fazio et al.[8]

Primary pouchitis: The clinical presentation with any of the below symptoms, and at least 1 abnormal pouch endoscopy during one of these symptomatic episodes, after excluding causes of secondary pouchitis.
• Increased number and looser consistency of bowel movements compared with baseline
• Rectal bleeding
• Fecal urgency
• Fecal incontinence
• Abdominal or pelvic cramps
Acute primary pouchitis: The presence of all of the following criteria, plus at least one pouchoscopy showing endoscopic and histological inflammation of the pouch during one of these episodes of pouchitis, after excluding causes of secondary pouchitis.
• Three or fewer episodes of pouchitis per year
• Symptoms lasting ≤4 weeks at a time with each episode
• Symptoms responding to short courses (14 days) of antibiotics
Chronic primary pouchitis: The presence of one or more of the following criteria after excluding causes of secondary pouchitis.
• Four or more episodes of pouchitis per year
• Active symptoms lasting continuously for >4 weeks despite antibiotic therapy
• Chronic antibiotic or anti-inflammatory therapy to control symptoms of pouchitis

extraintestinal IBD manifestations,[22-24] backwash ileitis,[21] preoperative thrombocytosis,[25] and postoperative nonsteroidal anti-inflammatory drug (NSAID)[26] use increase risk of pouchitis. The impact of smoking status on pouchitis is mixed.[9] Akin to IBD, underlying genetic risk factors have inconsistently been implicated in idiopathic pouchitis development. Genetic polymorphisms of the IL-1 receptor antagonist and NOD2/CARD15 may increase risk for pouchitis.[27-29] Underscoring associations with the ileal reservoir microbiome, patients with high preoperative serologic levels of perinuclear antineutrophil cytoplasmic antibody (pANCA) and anti-CBir1, an antibody that reacts to flagella of *Clostridium* species, have increased risk of idiopathic pouchitis.[30,31]

No universally accepted diagnostic criteria for pouchitis exist.[7] A constellation of symptoms prompt the clinician to initiate evaluation for pouchitis (Table 2). Increased bowel motion frequency, looser bowel motions, fecal urgency, tenesmus, increased nocturnal seepage, and crampy abdominopelvic pain are classic symptoms with variable and inconsistent penetrance. Fever, hematochezia, and development of extraintestinal symptoms are rarely seen.

A thorough work-up to exclude secondary pouchitis causes is necessary to hone a diagnosis of idiopathic pouchitis. A thorough medication history, focusing particularly on NSAID usage, may reveal an easily correctable cause of pouchitis, particularly for chronic and medically-refractory disease.[32] Endoscopic pouch evaluation (i.e., pouchoscopy) with biopsy is a necessary diagnostic component for the patient presenting with new pouchitis symptoms.[33] Characteristic, but not pathognomonic, pouchitis endoscopic findings include edema, mucosal granularity, spontaneous or contact bleeding, loss of the submucosal vascular pattern, mucus exudates, erosions, and ulcerations.[1,34] Although not always reliable, different pouchitis etiologies manifest varied inflammatory distributions within the pouch and pre-pouch afferent limb. Idiopathic pouchitis tends to cause diffuse, uniform inflammation of the pouch body sparing the pre-pouch ileal limb. Pouch body inflammation with concomitant afferent limb inflammation tends to indicate a larger inflammatory syndrome (e.g., Crohn's disease, PSC, and IgG4 associated pouchitis). Patchy inflammation, focal ulcerations, and strictures tend to be more indicative of Crohn's disease or cytomegalovirus (CMV) infection. Inflammatory polyps and loss of pouch distensibility during insufflation suggest chronicity.

Histology of the afferent limb, pouch body, and anorectal cuff is helpful to exclude hallmarks indicative of secondary pouchitis but is insufficient to diagnose idiopathic pouchitis as a sole criterion. Typically, nonspecific inflammatory changes or varying chronicity are seen with idiopathic pouchitis.[35] As common with idiopathic entities, histology is most helpful in excluding secondary etiologies of disease. The pouchitis disease activity index (PDAI) is the commonest tool which combines symptomatic, histologic, and endoscopic data to measure disease activity (Table 3).[35] Despite the fact that the PDAI is a common metric in clinical trials evaluating pouchitis treatments, it has been suggested that the symptom components of the scores correlate poorly with endoscopic and histological findings.[33,36-38]

First-line treatment of acute idiopathic pouchitis is antibiotics with a goal of altering the fecal microflora. A 14-day course of oral ciprofloxacin is more effective and better tolerated than metronidazole.[39,40] Several studies of varying quality have shown metronidazole, tetracycline, clarithromycin, amoxicillin/clavulanic acid, doxycycline, nitrofurantoin, colistin, and rifaximin are second-line agents that effectively treat idiopathic pouchitis. Budesonide enemas are equally effective and better tolerated than oral metronidazole, but lack comparison with oral ciprofloxacin.[41]

Table 3
The pouch disease activity index (PADI).[35]

Clinical	Score
Stool frequency	
Usual postoperative stool frequency	0
1-2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature >37.8°C)	
Absent	0
Present	1
Endoscopic inflammation	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudate	1
Ulceration	1
Acute histologic inflammation	
Polymorphic nuclear leukocyte infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (mean)	
<25%	1
25%-50%	2
>50%	3
Maximal total PDAI:	18

Pouchitis ≥ 7
No pouchitis < 7. These should be even with each other. This line appears to have a tab in front of it.

Approximately 5-15% of acute pouchitis patients will develop chronic pouchitis refractory to antibiotic therapy. This challenging and recalcitrant entity typically requires a "trial-and-error" approach to management. Patients failing first-line treatment should undergo re-evaluation of the underlying etiology of pouchitis to exclude occult causes of secondary pouchitis. Avoidance of Not sure if this needs an apostraphe or not may help chronic pouchitis improve.[32] Sensitivity-based antibiotic therapy derived from stool cultures might allow customized treatment specific to the patient's fecal flora.[42] Extended courses of antibiotic maintenance therapy may be helpful and present little risk in studies with intermediate follow-up.[43] Caution needs to be applied, however, given peripheral neuropathy seen with long-term metronidazole usage, and tendon weakness associated with chronic ciprofloxacin therapy.[44]

Oral bacteriotherapy may help selected patients with chronic pouchitis. Chronic relapsing pouchitis patients randomized to a polymicrobial probiotic formulation (VSL#3) experienced a 6-fold reduction in recurrent pouchitis episodes at 9 months of follow-up compared to those receiving placebo.[45] Mimura and colleagues reproduced similar outcomes and also showed bacteriotherapy patients had an improved quality of life at one year of follow-up.[46] A recent meta-analysis showed VSL#3 to be more effective than placebo for both preventing pouchitis and maintaining remission in patients with inactive disease[40] and has been supported for such use by European guidelines.[44]

Patients with chronic antibiotic resistant idiopathic pouchitis are empirically treated in a "trial-and-error" fashion until a clinical response is obtained. Treatments directed toward Crohn's disease (CD) are often employed. When medical treatments are exhausted, temporary diversion is offered. Once diverted, the pouch mucosa is allowed to heal for 3-6 months and adjunctive prophylaxis with bacteriotherapy and/or maintenance antibiotic therapy can be initiated immediately following ileostomy closure. If medically refractory chronic pouchitis persists despite a trial period of diversion, eventual pouch excision with permanent ileostomy is warranted.

Autoimmune pouchitis

While most pouchitis patients respond to antibiotics, a subset of patients has persistent symptoms requiring re-consideration of other etiologies and treatment strategies. A growing recognition of the autoimmune aspects of pouchitis is the best exemplified by primary sclerosing cholangitis- and IgG4-associated pouchitis.

Primary sclerosing cholangitis (PSC)-associated pouchitis

PSC is present in approximately 5% of UC patients and is likely a strong risk factor for chronic pouchitis.[47] An estimated 14-90% of IPAA patients with PSC will develop pouchitis.[48] It is debatable whether PSC represents a risk factor for idiopathic pouchitis or a newly recognized cause of secondary pouchitis since many hypothesize that PSC-associated IBD represents a distinct phenotype differing from UC and CD that merits specialized management.[48] The etiology of PSC pouchitis is unclear, although some propose fecal bile acid alterations contribute to the development of pouchitis[11] while others have suggested an autoimmune cause.[49] A comparison of IPAA patients with and without PSC revealed that PSC was associated with a two- and four-fold increase of the incidence of acute and chronic pouchitis, respectively.[11] Despite the increased risks of pouchitis and postoperative complications seen with PSC, restorative proctocolectomy is still the preferred surgical option for many patients presenting with UC and PSC.[11]

IgG4-associated pouchitis

IgG4-positive plasma cell infiltrates within the ileal pouch are noted in a subset of chronic antibiotic-resistant pouchitis patients and represents a newly recognized form of secondary pouchitis.[50] The unique finding of IgG4 in subsets of chronic pouchitis, patients points toward autoimmune pathways since elevation of serum IgG4 is noted in several autoimmune diseases (e.g., autoimmune pancreatitis). The mechanism behind IgG4 elevation and pouchitis is unclear but suggests a previously unrecognized alteration in B cell immunity for a subset of pouchitis patients. Current treatment strategies of IgG4 pouchitis patients leverage immunomodulation with corticosteroids, immunomodulators, and biologic agents.

Crohn's disease of the ileal pouch

IC and CD were historical contraindications for restorative proctocolectomy,[51] however some studies and guidelines suggest properly-selected and highly-motivated IC and CD patients may experience the same benefit as UC patients, albeit with increased complication rates and lower pouch survival.[52] When coupled with recent data suggesting an initial UC or IC diagnosis can eventually convert to a *de novo* diagnosis of CD for 2-19% of IPAA patients,[53] the surgeon must be prepared to recognize and treat CD pouchitis since CD pouchitis is one of the leading causes for pouch failure.[8]

CD of the pouch may occur weeks to years following IPAA creation and lacks steadfast definition which encumbers determination of the true incidence of this disease entity.[54,55] CD pouchitis may represent a delayed phenotypic conversion from UC/IC to CD. Alternatively, CD may have been unrecognized as the primary pathology at the time of initial proctocolectomy. Others have proposed IPAA creates an environment favorable for a Crohn's-like condition of the pouch to develop.

Symptoms of CD pouchitis overlap with other pouchitis etiologies. However, signs of malnutrition, fever, weight loss, obstructive symptoms, anoperineal disease, and pouch sepsis heighten suspicion of CD.[54] The timing of pouch sepsis may discern between technical IPAA complications and CD of the pouch. Most pouch sepsis occurring within 6-12 months of IPAA creation are felt to arise from technical complications. Conversely, pouch sepsis discovered more than 12 months after restoring intestinal continuity tends to arise from CD. Distinguishing between CD pouchitis and other etiologies of pouch complications is challenging, as highlighted by the fact that only 20% of pouch excisions performed for CD pouchitis contained histologic evidence of CD in the excised specimen.[55]

Pouchoscopy examining for mucosal ulcers, nodularity, hemorrhage, exudates, and inflammatory pseudopolyps leads the initial evaluation for CD pouchitis. Many characteristic endoscopic findings of acute inflammatory CD pouchitis overlap with other pouch inflammatory disorders, but long (>10 cm) segments of pre-pouch afferent limb inflammation, skip lesions, and transmural inflammation suggest a diagnosis of CD. Long-term sequella of CD pouchitis may include strictures, fistula, and anoperineal and presacral abscesses/sinuses. Biopsies are often performed to characterize endoscopic inflammation but characteristic granulomas are seen in only 12% of CD pouchitis cases.[56] Accordingly, the diagnosis is often solely based on clinical gestalt.

Selective imaging plays a role in the diagnosis of CD pouchitis depending upon phenotypic characteristics. Cross-sectional abdominopelvic imaging and contrast enemas evaluate for fibrostenotic and penetrating features of the pouch. An examination under anesthesia is useful to both diagnose and treat complicated CD of the ileal reservoir. High resolution (e.g., fistula-protocolled) pelvic magnetic resonance imaging (MRI) may be useful to localize occult sepsis. Dedicated cross-sectional small bowel enterography evaluates for synchronous foci of CD proximal to the pouch and is an important part of planning for any abdominal operation for this disease.

Despite a complex work-up, CD pouchitis will often be indiscernible from other pouchitis etiologies. In selected situations, a test trial of antibiotics, corticosteroids, or biologic agents directed at CD may elucidate a diagnosis of CD if objective clinical treatment responses are noted.[54]

No consensus exists regarding the best treatment approach for CD pouchitis patients. Septic pouch complications arising from CD should first be drained and controlled with transanal, percutaneous, or seton drainage depending upon the location of and access to the sepsis. The authors prefer to drain pelvic sepsis through transanal routes when possible to avoid creating an extrasphincteric fistula.[57] Fecal diversion in conjunction with drainage procedures may be necessary to facilitate a long-term staged approach to pouch salvage. Fibrostenotic stenosis at the ileal pouch-anal anastomosis can be dilated with rigid or pneumatic dilators, whereas pre-pouch afferent limb strictures typically require endoscopic balloon dilation or strictureplasty depending upon the location, tenacity, length, and number of strictures in relation to the pouch.

Medical therapy is typically required for CD pouchitis following control of sepsis and/or treatment of fibrostenotic disease. Acutely inflammatory disease without sepsis can be treated with antibiotics, corticosteroids, immunomodulators, and biologic agents.[58,59] Fistulizing disease is the most challenging CD phenotype to treat and conveys pouch failure rates approaching 50%.[58] To date, evidence guiding medical therapy for CD pouchitis is spartan.[60] A 2018 meta-analysis of 313 patients treated with anti-tumor necrosis factor (TNF) agents for either chronic refractory pouchitis or “Crohn's-like” IPAA disease showed sustained symptom remission in 52% of patients after one year.[61] When stratified by disease etiology, anti-TNF treatment sustained remission in 57% of CD pouchitis patients compared to 37% of chronic pouchitis patients following one year of treatment.[61]

After sepsis and active inflammation are controlled, residual IPAA complications may require definitive surgery with or without proximal fecal diversion. Fistulizing anoperineal disease may be treated with a variety of sphincter-sparing options including seton placement and pouch advancement. Short posterior pouch sinuses may be unroofed into the pouch body. Fibrostenotic disease of the afferent ileal limb refractory to endoscopic dilation may be amenable to strictureplasty, resection, or bypass. Medically refractory CD pouchitis often requires diversion and/or pouch excision with permanent ileostomy since neo-IPAA creation is unadvisable in the setting of small intestinal CD. Given the complexity and challenge of reoperative pouch surgery, referral centers provide the best chance at pouch salvage.[62,63] Despite the benefits conferred by experienced hands, the risk of pouch failure in CD pouchitis still ranges from 17% to 57%.[60]

Ischemic pouchitis

Low postoperative pouch pH serves as a surrogate for reservoir perfusion-related ischemia and correlates with increased rates of postoperative pouchitis and anastomotic complications.[64] Shen and colleagues first proposed diagnostic criteria for ischemic pouchitis based upon endoscopic asymmetric inflammation with a sharp demarcation of inflammation and one of the following: (1) refractory pouchitis (2) male, obese patients with redo pouch or multiple bowel surgeries (3) absence of mucosal hyper-enhancement on intravenously contrasted small bowel imaging (4) histologic evidence of active pouch inflammation with or without extracellular hematoidin.[65] In the initial report of 10 patients, ischemic pouchitis patients were antibiotic resistant in over 80% of cases, and 20% had evidence of prior portal venous thrombosis. Treatment of ischemic pouchitis is challenging. In the previous study, sulfasalazine and allopurinol were used but ultimately 20% of ischemic pouchitis patients required pouch excision. Of the remaining patients with a retained ileal reservoir, endoscopic disease persisted for 75% of patients despite medical therapy.

Infectious pouchitis

IPAA patients, like the general population, can develop infectious enteritis that may mimic inflammatory pouch disorders. Recent travel and dietary history as well as review of ill cohabitants and environmental exposures may point toward an infectious enteritis. Gastrointestinal symptoms following recent antibiotic treatment is a hallmark of *Clostridium difficile* enteritis, whereas cytomegalovirus (CMV) is typically seen in the immunosuppressed population.

Clostridium difficile *infection (CDI)*

Clostridium difficile has long been recognized as a common cause of colitis, but its recognition of infecting small bowel has grown since the early 2000's.[66] An estimated 10-18% of IPAA patients may develop CDI pouchitis at high-volume referral centers.[67,68] Similar to colonic infection, pouch CDI is usually precipitated by antibiotic use.[69] At this time, CDI is best confirmed with a single nucleic acid amplification test (polymerase chain reaction) of stool. Traditionally, pouchoscopy and IPAA biopsies are nondiagnostic for pouch CDI since only a small proportion of pouch CDI patients develop pseudomembranes within the pouch.[70]

The first step in treating CDI is to stop the offending antibiotic(s). Current guidelines state that adults with an initial episode of non-fulminant CDI should be treated with oral vancomycin or fidaxomicin rather than metronidazole, as the latter is inferior in head-to-head trials.[71] Recurrent episodes of *Clostridium difficile* enteritis should be managed with medications different than those used to treat the index episode. Long-term “pulsed” vancomycin treatments lasting several weeks may be used for patients with recurrent CDI.[71]

Fecal microbiota transplantation (FMT) is an emerging alternative for recurrent *Clostridium difficile* enteritis treatment, and has been shown to be more effective than antibiotics for patients with multiply recurrent colonic CDI with a published cure rate that exceeds 90%.[72] FMT may play a role in acute treatment of pouch CDI. One report showed that after an average of approximately two FMT sessions, 12 of 13 pouch CDI patients remained negative for *Clostridium difficile* in 1.2 years of follow-up, but only 58% and 23% of patients had improvement in PDAI symptom and endoscopic sub-scores, respectively.[73]

Cytomegalovirus (CMV) pouchitis

CMV plays an uncertain role in development of IBD-associated colitis but has been implicated as a rare cause of antibiotic refractory pouchitis. Latent CMV infection is ubiquitous in the adult population, with seroprevalence that approaches 90% in elderly patients[74] with reactivation typically triggered by immunosuppression. A Japanese study demonstrated a high prevalence of CMV in 41% of pouchitis patients compared to 11% of asymptomatic controls.[75] Although CMV is typically associated with patients with deficient cell-mediated immunity, several small series have implicated CMV in pouchitis in immunocompetent hosts.[76] Whether CMV is plays a causative or associative role in pouchitis is unclear.

In a series of 7 patients with CMV-associated pouchitis, 5 patients were immunosuppressed, but 2 patients were immunocompetent.[76] Symptoms of CMV pouchitis overlapped with idiopathic pouchitis. However, the presence of a high fever was felt to distinguish CMV pouchitis from idiopathic pouchitis. Ulceration tends to be a common endoscopic finding in CMV pouchitis, but CMV-associated ulceration tends to be larger and deeper than seen in other pouchitis etiologies, and the afferent ileal limb may be variably inflamed.

No standardized definition of CMV-associated pouchitis exists and reported diagnostic criteria vary considerably within the published literature. Serum CMV titers can be used to establish a high viral load and active viremia, which may be sensitive for systemic CMV infection but not specific for more mild forms of pouchitis. Serum CMV levels inconsistently correlate with intestinal disease.[76] Hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) show viral inclusion bodies in infected tissue. Highly-sensitive tissue based PCR- analysis can detect low levels of CMV otherwise

missed on traditional H&E and IHC histopathology, yet the clinical significance of detecting such low-levels of CMV is unknown since trivial quantities of CMV may not indicate an active infection.[77]

CMV pouchitis is treated with intravenous ganciclovir and/or oral valganciclovir for several weeks with a clinical resolution that typically takes several weeks. Some authors propose repeating pouchoscopy to confirm CMV eradication and assess for mucosal healing – especially when features of CD overlap with initial pouchoscopy findings (e.g., deep ulceration, afferent limb inflammation).[76]

Radiation-induced pouchitis

External beam radiation therapy (EBRT) used to treat pelvic malignancies can significantly impact ileal reservoir function. Acute radiation damage mimics acute pouchitis symptoms while chronic damage arises from intestinal vasculature injury that may lead to ischemia-type injury, fibrosis, and stricture or fistula formation.[78] EBRT of the ileal reservoir causes notoriously poor pouch function. A 2009 literature review reported 7 of 10 radiated reservoirs failed after radiation.[79] A series of 11 patients who underwent pelvic radiotherapy prior to restorative proctocolectomy found radiated patients had higher rates of chronic pouchitis (67% versus 25%) and a trend toward increased rates of pouch failure (44% versus 19%).[79] In contrast to EBRT, permanent prostate brachytherapy utilizing implantable radioactive “seeds” has been shown to be safe and efficacious for localized prostate cancer patients with an ileal reservoir after short-term follow-up.[80,81] While radiation may not be avoidable, limiting radiation exposure, targeting narrower fields, and consideration to brachytherapy are advisable when appropropriate.[53]

Treatment of radiation pouchitis is guided only by data extrapolated from radiation proctitis. Hyperbaric oxygen, sucralfate and steroid enemas, and oral sulfasalazine may be trialed to help with urgency and diarrhea. Endoscopic treatments such as argon plasma coagulation and topical formalin can be employed to control bleeding.[82,83] Unfortunately, many patients experiencing severe symptoms from radiation pouchitis may ultimately require fecal diversion and/or pouch excision.

Cuffitis

A strip of columnar anorectal mucosa of variable length and bounded by the dentate line and ileal pouch-anal anastomosis remains after creation of a stapled anastomosis. For IBD patients, this mucosal cuff can be subject to residual inflammation (“cuffitis”).

Cuffitis has been defined as endoscopic and histologic inflammation of the anorectal cuff with or without minimal inflammation of the pouch body,[84] although definitions considerably vary since cuffitis and pouchitis symptoms often overlap. Fecal urgency, abdominopelvic pain, infrequent and/or loose bowel movements, nocturnal seepage, perianal pain, diarrhea, mucus discharge, and tenesmus are common cuffitis symptoms,[85] but hematochezia tends to be more commonly seen in cuffitis than in pouchitis and can be present in over 90% of cuffitis patients.[86]

Due to underlying pathobiology, cuffitis is thought to predominantly occur in IBD patients, and less often in FAP patients. Lavery et al reported 22% of patients who underwent IPAA for IBD had both endoscopic and histologic anal canal inflammation, of which 67% where symptomatic, and approximately 10% of patients had cuffitis and concomitant pouchitis.[87] In a review of a large pouch database, pre-operative toxic megacolon, fulminant colitis, biologic agent use, and J-pouch configuration were risk factors for cuffitis in IBD patients.[84] Interestingly, in the authors’ high volume referral center, 13.6% of cuffitis patients ultimately developed pouch failure requiring excision at a median follow-up of 6 years following IPAA construction.

Endoscopy is essential to diagnose cuffitis since the entity overlaps with many pouch disorders. Endoscopic findings of cuffitis classically include erythematous, granular, hemorrhagic tissue (contact bleeding or spontaneous oozing), and ulcerations that are limited to the anorectal cuff. Acute and chronic inflammatory, as well as ischemic and collagenous changes have been described in histology of cuffitis samples leading some to believe that cuffitis, akin to pouchitis, represents a spectrum of disease.[84] Cuffitis is distinguished from pouchitis by the disease location, although cuffitis with concomitant pouchitis may be seen in 38-63% of cases depending upon the stringency of pouchitis definition.[87,88]

Due to the typically short, distal, and easily accessible nature of the rectal cuff, topical anti-inflammatory treatments are effective first-line therapies for cuffitis. An open label trial by Shen et al reported excellent symptom control of cuffitis with mesalamine suppositories in a small series.[86] Cuffitis activity index scores at 9 months of follow-up decreased for the group following a median 3.2 months of therapy. Corticosteroid suppositories, either in addition to mesalamine or as monotherapy, are also used as first-line treatment.[84]

Despite these initial results with topical agents, a larger observational study published 9 years later from the same institution showed diminished long-term efficacy of topical agents. In an analysis of 120 cuffitis patients with a median follow-up of 4 years, 48% of patients were primary non-responders and 18% of initial responders relapsed despite further treatment. Nearly one-third of non-responders were ultimately diagnosed with Crohn's disease and approximately one quarter had an occult abscess, fistula, or sinus.[84] The study findings underscore the importance of entertaining a broad list of differential diagnoses when dealing with cuffitis and other inflammatory pouch disorders. Cases of recurrent and medically refractory cuffitis should be evaluated for potential Crohn's disease and sepsis.

Cuffitis patients unresponsive to topical treatments may undergo empiric treatments with immunomodulators, systemic corticosteroids, and biologic agents until improved. The ideal treatment of cuffitis plus pouchitis remains unclear. Following exclusion of Crohn's disease and septic pouch disorders, some pundits recommend treating patients with bleeding-predominant symptoms first for cuffitis, since antibiotic therapy is felt to be anecdotally ineffective against cuffitis.[86] Proximal fecal diversion has been reported as a last-ditch effort for refractory cuffitis because this allows the inflammation to subside but ileal pouch advancement may be required.[89]

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