Pouchitis After Ileal Pouch-Anal Anastomosis

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Introduction

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) has emerged as the surgical procedure of choice for patients diagnosed with ulcerative colitis (UC) and familial adenomatous polyposis (FAP) syndrome since its introduction in the 1980s. In pediatric patients diagnosed with UC, specific indications for proctocolectomy include severe disease refractory to medications, toxic megacolon, perforation, and intractable bleeding. In addition, findings consistent with dysplasia or malignancy on biopsy specimens are strong indications to proceed with IPAA [1]. The latter two entities, however, are rare in pediatric patients. Patients with indeterminate colitis who undergo IPAA represent a special population. These patients have a complication rate similar to that of UC, unless the diagnosis of Crohn's disease (CD) is ultimately made [2].

Initially, restorative proctocolectomy was performed using straight ileoanal anastomosis (IAA) without construction of a pouch. The results of multiple subsequent studies have shown the superiority of IPAA in comparison to the straight ileoanal anastomosis [3, 4]. In the pediatric population, Telander et al. compared 121 children and young adults with either the straight IAA or the J-pouch procedure. They found the J-pouch to be superior in relation to stool frequency and nighttime stool patterns [3]. The IPAA procedure involves total abdominal colectomy with the upper internal anal sphincter and rectal muscular columnar cuff left intact. A pouch reservoir is then created utilizing the ileum, and an anastomotic connection is made to the anus. J-type, S-type, and W-type pouch reservoirs have been fashioned, but the most common and successful procedure involves using the J-pouch (Fig. 44.1). Temporary loop ileostomies are performed at the time of the procedure to facilitate healing of the anastomotic connection and are closed at a later date, typically 2–3 months. Contraindications to IPAA include a preoperative diagnosis of pelvic floor dysfunction and decreased anal sphincter muscle tone. Crohn's disease is a relative but not absolute contraindication, and a pouch procedure can be necessary if control of colonic disease is unable to be obtained, recognizing the potential long-term complications discussed later in the chapter [5].

Long-term results are excellent with minimal mortality related to the procedure. The majority of patients are satisfied with the IPAA procedure. Maintenance of bowel continence with a satisfactory functional outcome ranks high with these patients. However, there can be significant morbidity related to IPAA. Long-term complications include pouchitis, pouch dysfunction, stenosis, and fistulae.

Definition and Incidence

Pouchitis is defined as inflammation of the ileal reservoir in patients status post proctocolectomy with IPAA. Pouchitis is the most common long-term complication of IPAA and is a significant cause of morbidity related to the procedure. Pouchitis was first described in the literature by Kock et al. in 1977. His group described the condition as inflammation in the ileal reservoir constructed after proctocolectomy [6]. Since the initial description, multiple investigators have attempted to characterize pouchitis and delineate the underlying pathophysiology which may be multifactorial. The diagnosis of pouchitis is based on clinical symptoms, endoscopic findings, and histologic findings (Fig. 44.1).

The frequency of pouchitis reported by different groups has varied significantly. However, it is well established that the incidence of pouchitis is higher for UC patients as compared to FAP patients. Lifetime incidence of pouchitis

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P. Mamula et al. (eds.), *Pediatric Inflammatory Bowel Disease*, DOI 10.1007/978-3-319-49215-5_44

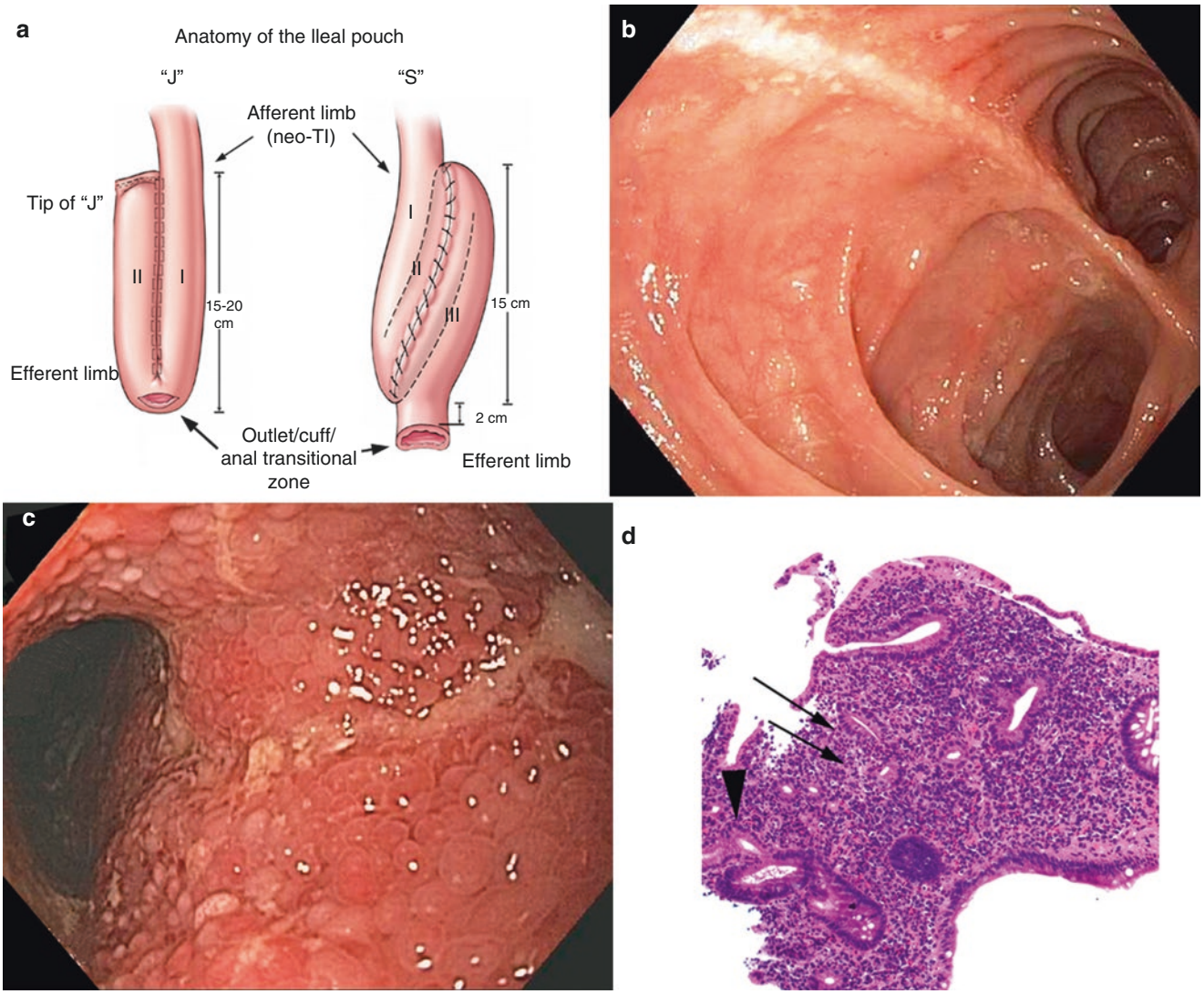

Fig. 44.1 (**a**) Schematic drawing of constructed "J"-pouch (*left*) and "S"-pouch (*right*). (**b**) Normal-appearing J-pouch with efferent (*top*) and afferent (*bottom*) giving "owl's eye" appearance. (**c**) Inflamed pouch with diffuse erythema, edema, cobblestoning, and ulceration**.** (**d**) Low-power magnification demonstrates distortion of villous architecture, expansion of lamina propria, and pyloric gland metaplasia (*arrows*). There is abundant active, neutrophil-mediated epithelial injury (*arrow head*) (hematoxylin and eosin stain, ×20) (Drawing and pictures courtesy of Bo Shen, MD. Pathology courtesy of Thomas Plesec, MD.)

in patients with UC varies between 15 and 53% [5, 7–10]. In comparison, the incidence of pouchitis in FAP patients ranges between 3 and 14% [11]. The overall incidence reported for pouchitis is related to the duration of clinical follow-up and the clinical definition used for the diagnosis of pouchitis [12]. In adult patients, Simchuk et al. reported that the incidence of pouchitis was 25% for patients followed for less than 6 months, 37% for patients followed for 1 year, and 50% for patients followed for 3 years [13].

In pediatric patients, Ozdemir et al. reviewed the outcomes of 433 pediatric patients after IPAA (83.4% with inflammatory bowel disease (IBD), 15.7% with FAP) and found an incidence of pouchitis of 31.9% with a mean follow-up of 9 years. The occurrence of pouchitis was not associated with specific pouch type in this mixed surgical group (J- vs. S-pouch) [14]. Shannon et al. reported a 45% incidence of pouchitis at a mean of 20-year postprocedure in a recent study of pediatric patients who had IPAA at the Cleveland Clinic between 1982 and 1997 for UC alone [15]. This cohort was originally reported on in 1996 and subsequently in 1999 by Sarigol et al. with shorter-term rates of pouchitis of 13% at 1.9 years and 45% at 5 years [16, 17]. Durno et al. reported a 44% incidence of at least one episode of pouchitis in pediatric patients with a J-pouch for UC in Toronto, Canada [18].

Etiology and Pathogenesis

Although there has been much interest in defining and classifying pouchitis, the etiology of pouchitis remains unknown. There are a number of proposed factors that may play a role in the pathogenesis. It is most likely that the development of pouchitis is multifactorial with several physiological and immunological factors contributing in a susceptible host. The frequency of pouchitis may vary based on the center, surgical experience, and follow-up medical care. Table 44.1 lists the proposed etiological factors that contribute to the development of pouchitis [19].

Immune Dysregulation

One of the most pursued areas of inflammatory bowel disease research is the influence of variations of gene loci on the development of IBD. As cytokines play a major role in the inflammatory pathway that lead to disease manifestations, many studies have focused on the role of cytokines such as interleukin (IL)-1 alpha, beta, and receptor antagonist (RA) in the etiology of IBD. IL-1 alpha and beta are proinflammatory cytokines, whereas IL-1RA is the natural inhibitor of these cytokines. Genetic polymorphisms that lead to a reduction in the ratio of IL-1 alpha and beta to IL-1RA will potentially lead to increased and/or chronic inflammation [20].

It is also possible that an imbalance in the ratio of IL-1 alpha and beta to IL-1RA may influence the initiation of inflammation leading to pouchitis in patients status post IPAA. In 2001, Carter et al. reported that patients that developed pouchitis had a higher IL-1RN*2 carrier rate as compared to patients that did not have the particular allele, 72% versus 45%, respectively [7]. IL-1RN*2 represents a polymorphism in the IL-1 gene cluster that has been associated with a change in the ratio of IL-1 alpha and beta to IL-1RA and the development of UC. This finding suggests patients with UC that carry this allele may have an increased tendency of developing pouchitis after IPAA.

Table 44.1 Proposed etiological factors of pouchitis

Immune dysregulation
Bacterial overgrowth and dysbiosis
Fecal stasis
Malnutrition
Mucosal ischemia (tension, torsion, or vascular)
Crohn's disease, undiagnosed
Colonic metaplasia associated with ulceration
Extraintestinal manifestations, including primary sclerosing cholangitis
Smoking
pANCA status

Adapted from Macafee et al. [19]

More recent studies have identified other genetic polymorphisms and cell membrane receptors that are associated with pouchitis. The NOD2/CARD15 mutations have been shown to be associated with the development of pouchitis and, in some instances, a more severe manifestation of the disease [21–23]. These mutations are associated with several markers of disease severity in pediatric CD [24]. It is therefore highly probable that these patients may actually have CD involving the pouch.

Intestinal epithelial expression of the innate Toll-like receptors (TLRs) 2, 4, and 5 is activated by bacterial peptidoglycan, lipopolysaccharides, and flagellin and leads to a complex downstream cascade of inflammatory signaling mediated by NF-κB. These TLRs have shown to be upregulated in patients with pouchitis [25]. Lammers et al. showed that patients who possess Toll-like receptor (TLR) 9-1237C and CD14-260 T alleles have a higher risk of developing chronic or relapsing pouchitis [26]. Alterations in tight junction claudin-1 and claudin-2 expression in biopsies of patients with pouchitis also indicate increased barrier dysfunction as a result of the inflammation [27].

A novel concept of immunoglobulin G4 (IgG4)-associated pouchitis has been described [28, 29]. Seril et al. demonstrated a high prevalence of IgG4-expressing plasma cells in the pouch of patients with chronic antibiotic-refractory pouchitis (CARP). Patients with CARP were also more likely to have autoimmune thyroid disease, primary sclerosing cholangitis (PSC), and serum microsomal antibodies suggestive of an autoimmune-mediated pouchitis [30]. Future studies are needed to further investigate the role of IgG4 in the etiology, pathogenesis, and prognosis of patients with pouchitis.

Fecal Stasis and Dysbiosis

The favorable response of the majority of acute episodes of pouchitis to antibiotic therapy and more recently to administration of probiotics suggests that bacterial populations are important etiological factors in the development of pouchitis. Pouchitis also rarely occurs until after takedown of the ileostomy with resultant resumption of fecal flow to the neoileum pouch. However, to date, no single microbial factor has been identified as the causative factor. Fecal stasis in the pouch may also be a contributing factor. A study of rats who received IPAA after colectomy had longer fecal retention and higher rates of inflammation in the pouch compared to rats who underwent straight ileorectal anastomosis [31]. As in patients with IBD prior to IPAA, 16 S ribosomal RNA sequencing has demonstrated altered microbial diversity in patients with pouchitis at multiple taxonomic levels with an increase in Fusobacteria and Enterobacteriaceae and a decrease in Bacteroidetes [32–34].

Other studies have looked at the role of serological markers, such as antibodies to bacteria fragments, in the pathogenesis of inflammatory bowel disease and also pouchitis. Serological markers such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been found to be associated with postoperative fistula formation after restorative proctocolectomy (RPC) [35]. Antibodies to OmpC, an outer membrane porin from *E. coli* and I2 (antigen to *Pseudomonas fluorescens*), were found to be predictive of postoperative continuous inflammation of the pouch [36]. In 2001, Fleshner et al. studied the relationship between pouchitis and serum perinuclear antineutrophil cytoplasmic antibody (pANCA) in a prospective study. They did not find an overall significant difference in the occurrence of pouchitis in the pANCA-positive versus pANCA-negative groups. They did, however, demonstrate a significant relationship between the development of chronic pouchitis in patients with a high level of pANCA (>100 EU/ml) as compared to patients with a medium level (40–100 EU/ml), low level (<40 EU/ml), or undetectable level of pANCA [10]. A more recent study investigating the impact of preoperative pANCA and anti-CBir1 flagellin on the development of acute or chronic pouchitis showed that both pANCA and anti-CBir1 expression are associated with pouchitis after IPAA. Anti-CBir1 increases the incidence of acute pouchitis only in patients who have low-level pANCA expression and increases the incidence of chronic pouchitis in patients who have high-level pANCA expression [37]. These findings are suggestive of a pathogenic immune response to bacterial antigens.

Infection with *Clostridium difficile* has been increasingly recognized as a problematic cause of diarrhea in IBD patients with both pre- and postcolectomy with IPAA. *C. difficile* as a cause of pathogen-associated pouchitis is diagnosed in up to 10% of adults with increased risk in patients with recent hospitalization, receiving antibiotics, and males [38, 39]. When possible, PCR testing for *C. difficile* toxin B is more sensitive than enzyme immunoassay though neither is specific, and clinical context needs to be considered for patients who may be colonized [40]. Evaluation with either endoscopy or fecal calprotectin helps to establish inflammation in the setting of symptoms in patients positive for *C. difficile*. As many of the patients have already been on metronidazole, consider vancomycin as the first-line treatment. Recurrent or persistent *C. difficile* may also require fecal microbial transplant to eradicate [41].

Mucosal Ischemia

During pouchoscopy, if the pattern of inflammation is isolated to specific limb or wall of the pouch, ischemia should be considered as an etiology of the pouchitis. Ischemia can arise from tension on the pouch when it is pulled into the pelvis during surgery, either from torsion of the pouch when attached to the cuff or by leaving a long cuff resulting in a mobile base for the pouch to rotate on. Ischemia can also occur from decreased tissue perfusion as a vasculitic component of the underlying disease [42]. Ischemic pouchitis can be evaluated under fluoroscopy and by a surgeon for tension-induced ischemia which may require revision. If there is no evidence of tension on the pouch, a more global ischemic process may be the cause. Ischemia has been proposed as a contributing factor in intestinal inflammation after the observation that IBD patients improved after treatment with hyperbaric oxygen therapy (HBOT). A 1994 study demonstrated improvement in 8 of 10 patients with perianal CD, 5 of which had complete resolution [43]. A follow-up study showed decreased levels of IL-1, IL-6, and TNF-α in these patients after HBOT [44]. A 2014 review by Dulai et al. evaluated 17 studies in which HBOT was administered for either UC or CD (including perianal disease) with varying protocols of which 86% responded (n = 613, 8924 treatments). The most common complication from treatment was middle ear barotrauma and tympanic membrane perforation (1.5% patients, 0.1% of all treatments) [45]. A recent case report of a patient with chronic antibiotic refractory pouchitis had significant improvement in symptoms after treatment with HBOT [46]. More studies including randomized controlled trials should be completed to further evaluate such a therapeutic endeavor.

Crohn's Disease

Undiagnosed CD can present clinically as chronic pouchitis following IPAA. In adults, a 2008 study by Melmed et al. reported 16/238 (7%) patients who underwent IPAA for UC or IBD-U were later diagnosed as having CD with significant risk factors of family history of CD and/or presence of serum ASCA-IgA. Four of these patients (25%) failed medical management and had a diverting ileostomy [47]. A 2012 study by Coukos et al. also demonstrated association of ASCA-IgA, ASCA-IgG, and anti-CBir1 flagellin in the development of CD of the pouch or fistula in patients with UC after IPAA [48]. In pediatrics, Wewer et al. reported approximately a 6% detection rate for CD in 30 patients aged 7–17 years status post IPAA with a median follow-up of 3.7 years [4]. Ozdemir et al. reviewed the outcomes of 361 pediatric patients who underwent IPAA over a 27-year period and found 18 patients (5%) to be later diagnosed with CD [14]. In a more recent 2016 single-center study follow-up of 74 pediatric patients (15–30 years later) after IPAA, Shannon et al. reported 28% were ultimately diagnosed as having CD, of which 40% required take down of the pouch for pouch failure [15]. The most common manifestations of CD noted for patients status post IPAA are fistulizing disease of the pouch and prepouch ileitis.

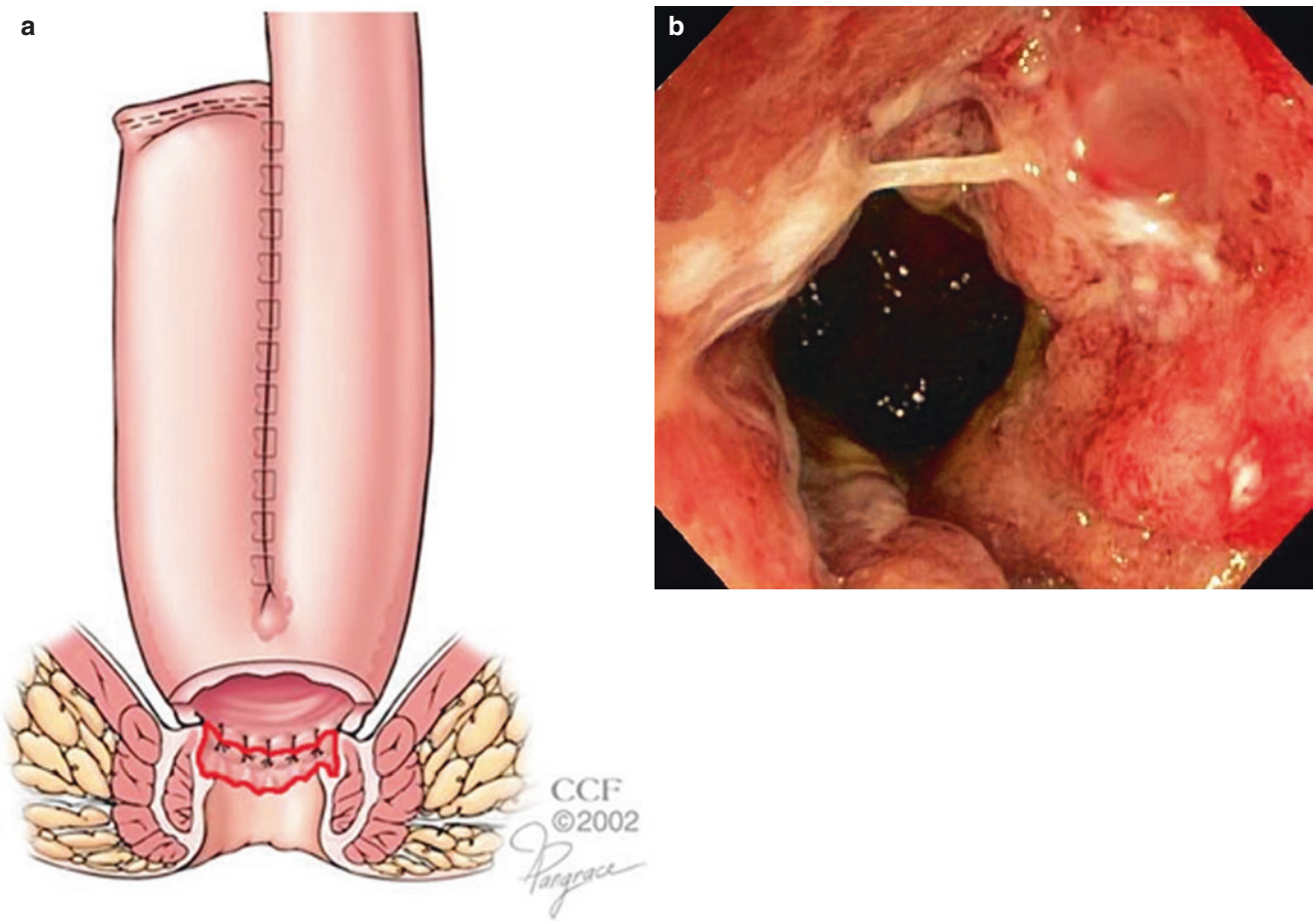

Fig. 44.2 (**a**) Schematic drawing of constructed "J"-pouch with cuff outlined in red. (**b**) Inflamed cuff or "cuffitis" at the distal end of J-pouch

Extraintestinal Manifestations

The presence of extraintestinal manifestations related to inflammatory bowel disease has been studied as possible predictors of the development and severity of pouchitis. Lohmuller et al. looked at extraintestinal manifestations such as erythema nodosum, arthritis, and uveitis to determine a relationship. Their group found that pouchitis occurred in 39% of patients with preoperative extraintestinal manifestations as compared to 26% of UC patients with no preoperative extraintestinal manifestations ($p < 0.001$). They also found an increased risk of pouchitis if postoperative extraintestinal manifestations were diagnosed [8].

Multiple groups have specifically analyzed the relationship between primary sclerosing cholangitis (PSC) and the development of pouchitis. Penna et al. found that pouchitis occurred in 63% of the patients with PSC, while pouchitis only occurred in 32% of the patients without this particular extraintestinal manifestation ($p < 0.001$). This group also reported an increased frequency of chronic pouchitis in patients with PSC versus patients without this disease, 60% and 15%, respectively ($p < 0.001$) [9]. In 2005, a study by Gorgun et al. refuted this claim. This group reported a higher overall mortality for patients with PSC status post IPAA; however, they did not find a statistically significant relationship between chronic pouchitis and UC in patients with preoperative PSC [49]. A review of the available literature by Rahman et al. concluded that pouchitis appears to be more common in the subset of patients that have both UC and PSC [50]. Shen et al. also demonstrated that concurrent PSC appears to be associated with a significant pre-pouch ileitis on endoscopy and histology in patients with IPAA [51].

Cuffitis

After IPAA a region of colonic columnar mucosa remains unless a mucosectomy is performed [52]. It has been shown that patients have markedly better pouch function when mucosectomy is not performed, and this is the preferred treatment modality in the absence of dysplasia. As a result, a "cuff" remains above the anal transitional zone (Fig. 44.2). The length of the cuff is dependent on the type of IPAA performed. After a stapled IPAA, the preferred method by adult colorectal surgeons, a region of 1.5–2 cm of diseased mucosa, remains. A hand-sewn IPAA has traditionally been performed

by pediatric surgeons and leaves a variably smaller cuff region. Neither method is superior to the other as far as complication rate, but the stapled IPAA may offer improved nocturnal continence with higher resting and squeeze pressures of the pouch demonstrated by anorectal manometry [53].

As expected, remaining diseased columnar mucosa can develop inflammation, a term coined "cuffitis." Patient symptoms include anal pain or discomfort, bleeding, discharge, or diarrhea and endoscopic features typical of colitis in the cuff region (erythema, friability, ulceration). Thompson-Fawcett et al. biopsied the cuff of 113 patients after stapled IPAA and found 13% had evidence of acute inflammation, most of which was mild and 9% were symptomatic [54]. Wu et al. followed 120 patients with cuffitis (12.9%) from their registry of 931 pouch patients over a median of 4 years and found no difference in the demographics, risk factors, and extent or severity of disease compared to controls without cuffitis. Of these patients, 33% responded to topical 5-ASA/steroid therapy, 18% relapsed after initial response to 5-ASA/steroid therapy, and 48% did not respond to topical therapy and required immunotherapy. Sixteen patients (13%) with cuffitis ultimately had failure of the pouch due to CD of the pouch, refractory cuffitis, or surgical complications (fistula, sinus) requiring diversion or pouch reconstruction [55]. As a small segment of colonic mucosa remains in situ, the risk for dysplasia remains equally present in the cuff as in the pouch [56].

Smoking

It has previously been established that cigarette smoking is associated with a reduction in the risk of developing UC. In 1996, Merrett et al. also described a link between smoking and a reduction in the incidence of pouchitis in patients after IPAA. Their study documented that 18/72 (25%) nonsmokers were diagnosed with pouchitis, while 1/17 smokers (5%) were diagnosed with pouchitis. The reason for these findings is unclear, but may be related to the effect of smoking on gut mucosal permeability [57]. Fleshner et al. performed a multivariate analysis of clinical factors associated with pouchitis after IPAA. He showed that smoking and the use of steroids prior to colectomy were associated with acute pouchitis, while smoking in of itself appeared to protect against the development of chronic pouchitis [58].

Diagnosis

The first episode of pouchitis occurs most often in the first 6 months after closure of the loop ileostomy; however, it can occur any time after IPAA is performed [11]. To accurately make a diagnosis, a combination of clinical symptoms, endoscopic appearance, and histologic findings is typically utilized. In practice, a presumptive diagnosis of pouchitis is often made on clinical symptoms alone. However, endoscopic and histologic inflammation may not correspond to the degree of symptoms, for example, in irritable pouch syndrome. Pouchoscopy still remains the main tool for establishing a diagnosis and also for evaluating other differential diagnoses in suspected cases of pouchitis [59].

The clinical presentation of pouchitis typically includes a combination of increased stool frequency, abdominal cramping, hematochezia, bowel incontinence, and/or low-grade fever. Endoscopic findings involve assessing the severity of inflammation of the pouch mucosa. Signs of inflammation include erythema, edema, granularity, mucosal ulceration, and friability. The afferent and efferent limp of the pouch are most often affected and should routinely be biopsied (Fig. 44.1). In addition, if inflammation of the neoterminal ileum is visualized, this finding is suggestive of CD. Cheifetz et al. suggest that the presence of a single aphthous lesion in the terminal ileum does not confirm the diagnosis; rather the presence of serpiginous ulcers are more suggestive [60]. Histology of the pouch is graded on an ABC scale. Type A mucosa is described as normal mucosa or mild villous atrophy with no or minimal inflammation. Type B mucosa is described as transient atrophy with temporary moderate to severe inflammation followed by normalization of the architecture. Type C mucosa is described as persistent atrophy with permanent subtotal or total villous atrophy developing from the early functioning period accompanied by severe pouchitis and thus requires follow-up pouchoscopy to diagnose [61]. Type B and C mucosa are most often found in pouchitis. When a diagnosis of pouchitis is made, evidence of acute and/or chronic inflammation is typically present on biopsy samples. Chronic lymphocytic infiltrate, crypt hyperplasia, crypt abscesses, pyloric gland metaplasia, and fibromuscular obliteration of the lamina propria are specific findings that aid in the diagnosis [62].

Histologic evaluation is also invaluable in identifying some of the other secondary causes of pouchitis such as pathogens like cytomegalovirus (CMV) or Candida, ischemia, mucosal prolapse, granulomas, and dysplasia [63]. Other laboratory tests such as stool studies for *Clostridium difficile* infection may be important especially in patients with chronic antibiotic refractory pouchitis [63]. Inflammatory markers in the serum may be useful noninvasive adjuncts in the evaluation of patients with suspected pouchitis. Studies evaluating the erythrocyte sedimentation rate (ESR) as a marker of pouchitis have shown that despite its role as a nonspecific marker of inflammation, it does correlate with the pouchitis disease activity index (PDAI) and episodes of pouchitis [64, 65]. Elevation of the serum C-reactive protein is a nonspecific marker of inflammation, but this was also found to correlate with the PDAI score and the presence of endoscopic inflammation in the pouch and

Table 44.2 Pouchitis disease activity index (PDAI)

Clinical criteria	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 cramping	
None	0
Occasional	1
Usual	2
Fever (>100.5 °F)	
Absent	0
Present	1
Endoscopic criteria	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucus exudates	1
Ulceration	1
Acute histologic pattern	
Polymorphonuclear infiltration	
Mild	1
Moderate with crypt abscesses	2
Severe with crypt abscesses	3
Ulceration per low-power field (mean)	
<25%	1
25–50%	2
>50%	3

Adapted from Sandborn et al. [11]
Pouchitis defined as a total PDAI score of 7 or above

afferent limb [59, 64]. Fecal inflammatory markers usually are reflective of the presence of intestinal inflammation. The fecal pyruvate kinase, calprotectin, and lactoferrin levels have been found to correlate with pouchitis and PDAI scores in a number of studies [66–68]. These fecal markers could serve as potential adjunctive tests in the initial evaluation of patients with pouchitis, but their role in the overall management of these patients still needs to be clearly elucidated.

Several scales for grading pouchitis have been developed over the last two decades. The most commonly used and referenced scales include the pouchitis disease activity index (PDAI) (Table 44.2), Moskowitz criteria (Table 44.3), and the Heidelberg Pouchitis Activity Score [11, 69, 70]. Another well-validated scoring system is the Cleveland Global Quality of Life (CGQL) which has patients score their current quality of life, quality of health, and energy level on a 0–10 scale (0:worst; 10:best). The total of the three items is then divided by 30 to determine their CGQL [71].

Table 44.3 Moskowitz criteria

Acute changes	Score
Acute inflammatory cell infiltrate	
Mild and patchy infiltrate in the surface of the epithelium	1
Moderate with crypt abscesses	2
Severe with crypt abscesses	3
Ulceration per low power field	
<25%	1
≥25–≤50%	2
>50%	3
Total possible	6
Chronic changes	
Chronic inflammatory cell infiltration	
Mild	1
Moderate	2
Severe	3
Villous atrophy	
Partial	1
Subtotal	2
Total	3
Total possible	6

Adapted from Moskowitz et al. [69]

Classification

The classification of pouchitis can be made based upon several different factors (Table 44.4). Severity varies from remission to severely active. Duration varies from acute (less than 4 weeks) to chronic (more than 4 weeks or more than three episodes of pouchitis in a 12-month period). Frequency varies from infrequent to continuous. Pouchitis can also be graded according to response to therapy. Response to therapy is described as antibiotic responsive, antibiotic dependent, or antibiotic resistant (refractory) [5, 73]. In addition, it must be considered that not all patients status post IPAA with symptoms of diarrhea and abdominal pain will truly have pouchitis. Other disease entities that may present similarly to pouchitis include irritable pouch syndrome, cuffitis, stenosis of the pouch, CD, celiac disease, and infectious bowel disease (most often secondary to *Clostridium difficile* or Cytomegalovirus).

Treatment

There are currently less than 20 randomized controlled trials that address the treatment or prophylaxis of pouchitis. None of these trials have been performed in pediatric patients. Therefore, the majority of treatment regimens for pouchitis are based on empiric data alone. Treatment approaches include both primary prophylaxis and treatment following development of symptoms.

Table 44.4 Classification of pouchitis

Classification	Description
Severity	Remission
	Mildly active
	Moderately active
	Severely active
Duration	Acute (less than 4 weeks)
	Chronic (more than 4 weeks)
Frequency	Infrequent (1–2 episodes)
	Relapsing (more than 3 episodes)
	Continuous
Response to therapy	Antibiotic responsive
	Antibiotic dependent
	Antibiotic refractory

Adapted from Wu and Shen [92]

Prophylaxis

The use of probiotics is proposed to increase the normal, healthy flora of the colon such that concentrations of unhealthy microflora are reduced and the incidence and severity of pouchitis are decreased. VSL#3® (Sigma-Tau, Gaithersburg, MD) contains four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and *Streptococcus thermophilus*. One week after ileostomy closure, a randomized controlled trial demonstrated 10% (2/20) of patients treated with one packet of VSL#3® (900 billion bacteria) developed acute pouchitis within 12 months versus 40% (8/20) of patients who received placebo [74]. The first episode of pouchitis has also shown to be delayed in patients given *Lactobacillus rhamnosus* GG following IPAA [75]. There is an ever-growing number of probiotics now on the market, while there is a paucity of randomized controlled trials to evaluate primary prophylaxis of pouchitis or if one particular brand of probiotics is more effective than another.

Acute Pouchitis

Acute episodes of pouchitis respond to antibiotic therapy 95% of the time. The first-line antibiotics of choice for acute pouchitis are a 14-day course of metronidazole (15–20 mg/kg/day) or ciprofloxacin (20–30 mg/kg/day). Fluoroquinolones have been associated with arthropathy and tendon rupture in all ages and should be considered when prescribing to children. In the past metronidazole alone was considered to be first-line therapy. The first controlled studies with this drug were published by Madden et al. in 1994. They performed a double-blind, crossover trail comparing metronidazole with placebo. They reported that patients with pouchitis treated with metronidazole had statistically significant improvement in their stool frequency as compared with placebo [76]. Later studies showed the efficacy of ciprofloxacin. In an unblinded randomized controlled trial by Shen et al., it was reported that both ciprofloxacin and metronidazole significantly improved PDAI scores. In addition, the ciprofloxacin group experienced significantly larger reductions in PDAI scores and decreased side effects as compared with metronidazole [77]. Both metronidazole and ciprofloxacin are now considered first-line therapy for acute pouchitis (Fig. 44.3).

Chronic Pouchitis

The medical treatment of chronic pouchitis is less clear. Other antibiotic combinations such as tinidazole and rifaximin have been used in the treatment of chronic pouchitis. Rifaximin, an inhibitor of bacterial DNA-dependent RNA polymerase, has been used as monotherapy in a pilot study by Isaacs et al. This study showed clinical remission occurred more frequently in patients on rifaximin compared to the placebo but the difference was not significant [78]. Shen et al. conducted an open-label trial using rifaximin as a maintenance agent for adult patients with antibiotic-dependent pouchitis. These patients demonstrated a favorable response to therapy [79]. Larger trials with long-term follow-up of patients are needed to fully understand the benefits that may accrue from the use of rifaximin in the treatment of patients with pouchitis.

Tinidazole, a nitroimidazole derivative, has been used in combination with ciprofloxacin in the treatment of chronic antibiotic-refractory pouchitis (CARP). This combination led to a significant reduction in the PDAI scores and also improvement in quality of life scores after 4 weeks of therapy [80]. In 2004, a study evaluating the effectiveness of combination therapy of rifaximin and ciprofloxacin was published in patients with CARP. Eight patients with chronic pouchitis refractory to ciprofloxacin alone were treated with rifaximin and ciprofloxacin for 2 weeks. Eighty-eight percent (7/8) of the patients responded to therapy, and five went into remission for at least 6 months [81]. Additional medications that have been used in the treatment of CARP include 5-ASA products (i.e., oral mesalamine, rectal mesalamine suppositories and enemas), topical and oral steroids (i.e., prednisone or budesonide enemas), bismuth-containing products, and anti-TNF therapy.

In their randomized controlled trial published in 2000, Gionchetti et al. showed that treatment with VSL#3® for 9 months following antibiotic treatment compared with antibiotic treatment alone was statistically significant in maintaining remission from pouchitis [82]. In 2005, a double-blind placebo-controlled trial examined the expression of proinflammatory cytokines in patients diagnosed with pouchitis who were treated with VSL#3®. The results revealed that the expression of mRNA for the proinflammatory cytokines IL-1 beta, IL-8, and IFN-gamma in patients treated with VSL#3®

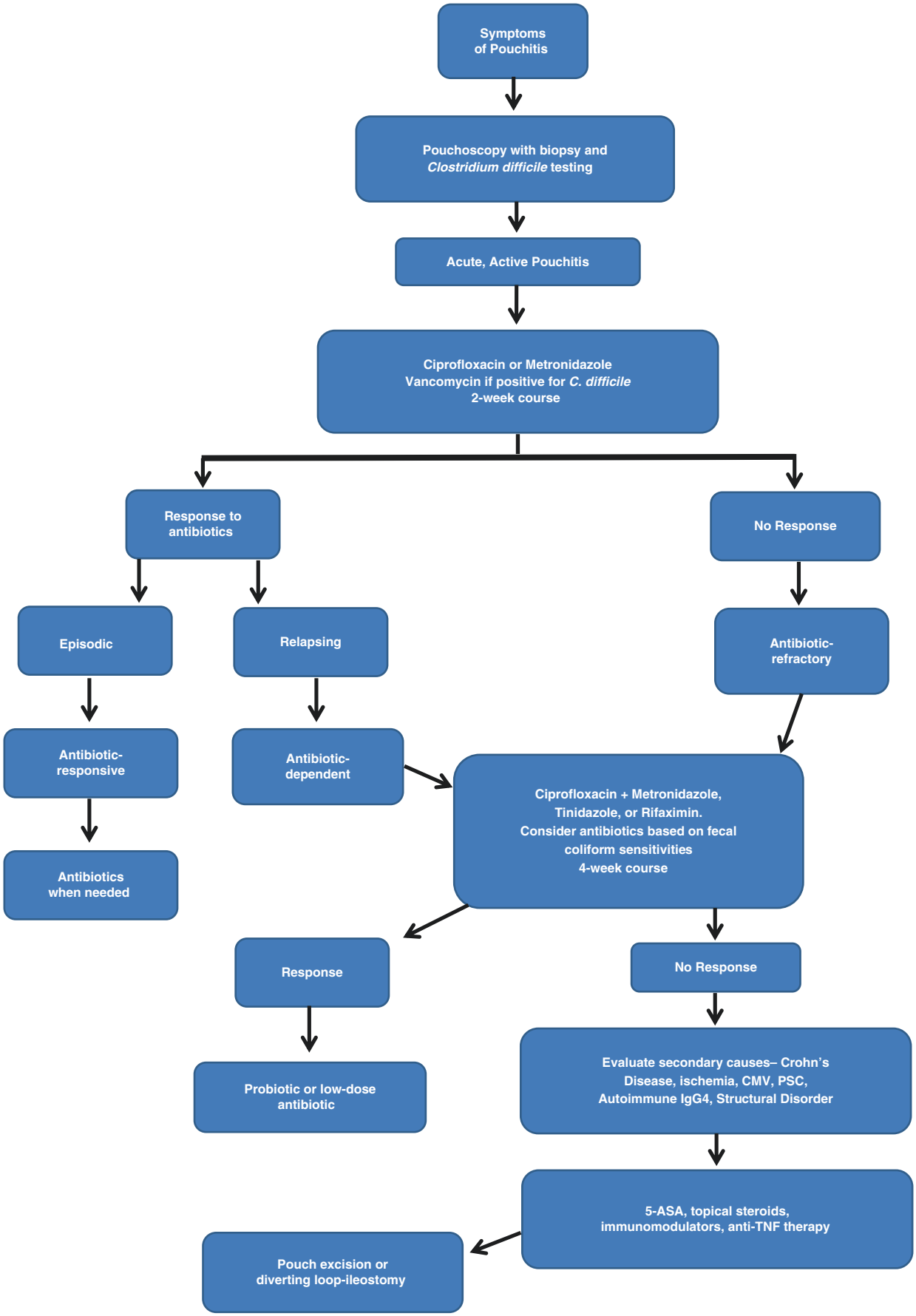

Fig. 44.3 Treatment algorithm for the management of pouchitis (Adapted from Shen [5])

was significantly decreased as compared with placebo. The levels of all of these cytokines were decreased at least two-fold [83]. A pooled meta-analysis of randomized, placebo-controlled trials on the use of probiotics showed that probiotics were beneficial in the management of pouchitis, though each study evaluated patients in different stages of disease [84].

For patients status post IPAA who are subsequently diagnosed with CD or CARP, infliximab therapy is an option that has been utilized as part of the treatment regimen. In the adult population, Columbel et al. reported in their 2003 case series that 85% percent of the patients (22/26) with CD after IPAA experienced clinical response to infliximab. Of these responders, 62% (16/26) had a complete response [85]. There is one case series in the pediatric literature supporting these findings. In this case series, four patients with CD diagnosed after IPAA were studied. The Pediatric Crohn's Disease Activity Index improved from 32.5–42.5 to 0–10 for these patients after infliximab infusions were initiated [86]. Multiple studies have since found benefit to the use of anti-TNF therapy in patients with CARP, which one could argue is on the spectrum with CD of the pouch [87–89].

The medical treatment algorithm for acute and chronic pouchitis is shown in Fig. 44.3. The antibiotic treatment of the first acute episode of pouchitis should be either metronidazole three times per day for 14 days or ciprofloxacin twice per day for 14 days. If a patient is diagnosed with antibiotic-dependent or antibiotic refractory pouchitis, alternative therapies include prolonged antibiotic therapy or combination of various antibiotic therapies with the option of additional therapy with probiotics such as VSL#3®. Failure of response to these therapeutic options should warrant the consideration of other secondary causes of pouchitis such as *Clostridium difficile* and other pathogens in the stool. The addition of anti-inflammatory or immunosuppressive therapy to the treatment regimen should be considered at this point.

Surgical

Pouch failure is an unfortunate consequence that results from a number of complications with the most common being pouch dysfunction, pouch fistulae, refractory pouchitis, pelvic sepsis, anastomotic leak, pouch prolapse, stricture, and development of CD. In adults, pouch failure occurs more commonly in CD than UC (13.3% vs. 5.1%) [73]. In pediatrics, with a mixed series of indications for IPAA over a 27-year period and mean follow-up of 9 years, 9% (39/433) had pouch failure requiring small bowel diversion or excision of the pouch, of which four were for pouchitis and three for CD [14]. Pouch failure can result in excision of the pouch, diversion with a proximal loop ileostomy, or an unreversed diverting ileostomy from primary colectomy.

Outcome

One of the most concerning potential complications of long-term inflammation of the surgically created pouch is dysplasia and progression to malignancy. Overall, the incidence of dysplasia in the pouch is more common for patients with FAP than with UC. For patients with FAP, dysplasia is more often related to the development of adenomas in the pouch. For patients with IBD, the development of dysplasia is related to chronic inflammation. A 2015 meta-analysis reported a pooled prevalence of dysplasia in the pouch of 0.6% and 3.0% at 5 and 20 years, respectively, in adults with IBD [90].

To date, no evidence of dysplasia has been noted in the biopsy specimens of pediatric patients within 5 years after the pouch has been created. Ten percent of the patients followed did have severe inflammation and villous atrophy noted in biopsy specimens which is concerning for possible neoplasia in the future [17]. No long-term studies have been performed to delineate the overall risk of malignancy in this patient population. Gullberg et al. compared the risk of dysplasia in patients status post IPAA with type A histology of the pouch (normal mucosa or mild villous atrophy) compared with type C histology of the pouch (persistent atrophy with severe inflammation). They determined that 5/7 patients with type C mucosa developed dysplasia while no patients with type A mucosa developed dysplasia [91]. These findings are consistent with other research and confirm that patients with type C mucosa are a higher risk of dysplasia and possibly malignant lesions in the pouch. Fifteen cases of adenocarcinoma in the pelvic pouches of adult patients have been described in the literature. Eight of these cases occurred with UC patients and seven occurred with FAP patients [1]. There are currently no consensus guidelines for endoscopic surveillance for dysplasia in place for adults or pediatric patients who are status post IPAA.

Summary

Ileal pouch-anal anastomosis is the surgical procedure of choice for pediatric patients with ulcerative colitis or FAP. The procedure is generally well tolerated; however, pouchitis is the most frequent cause of morbidity. The majority of patients will experience isolated acute episodes of pouchitis. However, up to 41% of adults with IPAA will ultimately be diagnosed with chronic pouchitis [72]. Pouchoscopy remains the main tool for establishing the diagnosis of pouchitis; however, other emerging noninvasive tests may serve as useful adjuncts in the diagnostic process. Therapeutic guidelines are generally empirically derived. Most patients do respond to antibiotic treatment with ciprofloxacin or metronidazole. Others may be treated with a

combination of probiotics, antibiotics, anti-inflammatory medications, and/or immunosuppressive medications. Takedown of the pouch is uncommon and occurs only in a small minority of patients. There is however an increased incidence in the development of CD in pediatric patients with longer-term follow-up, but change in diagnosis to CD does not inevitably result in pouch failure. Dysplasia and malignancy are concerns for patients with chronic pouchitis and severe inflammatory changes. To date, dysplasia and malignancy of the pouch have not been diagnosed in pediatric-aged patients although they may be at a higher risk for these complications in their lifetime due to the long duration of the disease and other yet undetermined factors.

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