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Review

Refractory Pouchitis: Antibiotic-Resistant Chronic Refractory Pouchitis

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Abstract

Restorative proctocolectomy with ileal pouch–anal anastomosis is a widely recognized surgical procedure commonly employed in the management of ulcerative colitis patients. The surgical intervention results in the formation of a novel anatomical structure, which subsequently gives rise to a range of structural, inflammatory, and physiological effects in the short, medium, and long term. According to the guidelines released by the International Ileal Pouch Consortium in 2021, chronic antibiotic-refractory pouchitis was delineated as a condition characterized by a lack of clinical and endoscopic response or minimal response following conventional antibiotic therapy lasting 2-4 weeks, regardless of any prior positive response to antibiotic treatment. If the aforementioned alterations are not subjected to thorough evaluation and effectively managed, they have the potential to lead to the loss of a pouch and the subsequent establishment of a permanent ileostomy.

Keywords: Pauchitis, refractory pouchitis, ulcerative colitis

INTRODUCTION

Despite the considerable progress obtained in the treatment of inflammatory bowel disease (IBD) with biological agents over the last 2 decades, there remains a subset of patients for whom surgical intervention remains necessary.[1] Restorative proctocolectomy with ileal pouch–anal anastomosis (RP-IPAA) is a widely recognized surgical procedure commonly employed in the management of ulcerative colitis (UC) patients.[2] Refractoriness to medical treatment, colorectal dysplasia, and colon cancer are the main indications for surgery.[3] After careful preliminary evaluation, RP-IPAA may also be considered in a select group of Crohn's disease (CD) patients with isolated colonic involvement without perianal disease.[4] In addition to IBD, RP-IPAA is employed in individuals diagnosed with familial polyposis coli as a preventative intervention aimed at mitigating the likelihood of developing colorectal cancer. In order to maintain intestinal continuity, avoid permanent ileostomy, and improve the quality of life of patients, reservoirs (pouches) of different configurations (such as J, S, and W) are created from the ileum in addition to total proctocolectomy. Currently, the J pouch is the prevailing choice.

The surgical intervention results in the formation of a novel anatomical structure, which subsequently gives rise to a range of structural, inflammatory, and physiological effects in the short, medium, and long term.[5] If the aforementioned alterations are not subjected to thorough evaluation and effectively managed, they have the potential to lead to the loss of a pouch and the subsequent establishment of a permanent ileostomy.

DEFINITION OF POUCHITIS, FREQUENCY (THE MAGNITUDE OF THE ISSUE), AND THE NATURAL COURSE

Pouchitis is a pathological condition characterized by inflammation and observable changes at both the macroscopic and microscopic levels in the mucosa of a surgically created reservoir derived from the ileum. The condition can be categorized into idiopathic or secondary based on its etiopathogenesis, acute (lasting less than 4 weeks) or chronic (lasting 4 weeks or longer) based on its duration, antibiotic responsive, antibiotic dependent, or antibiotic resistant based on its response to antibiotics, and rare (less than 4 attacks per year), frequent (4 attacks per year or more), and persistent based on the frequency of attacks.[6] Pouchitis represents the prevailing complication following RP-IPAA procedures. The incidence of pouchitis demonstrates a cumulative rise in proportion to the duration of the follow-up period. Pouchitis is observed to occur at a significantly higher rate in instances of UC compared to familial polyposis, with an approximate occurrence of 40% within the initial year following surgery.[7] After a span of 3 decades, the incidence rate of pouchitis has escalated to 80%.[8] The etiopathogenesis of acute idiopathic pouchitis has not been fully elucidated. The development of pouchitis has been attributed to factors such as fecal stasis resulting from alterations in anatomy following surgery, dysbiosis in the intestinal microbiota, and genetic susceptibility.[9] Etiological uncertainty impedes the development of targeted treatments. Hence, within the conventional management approach for acute idiopathic pouchitis, a 2-week course of antibiotics is administered empirically as the initial intervention. It is recommended to utilize ciprofloxacin at a dosage of 1 g per day or metronidazole at a dosage of 1 g per day. In the event that an insufficient response is detected by the conclusion of the second week, it is advisable to prolong the course of treatment by an additional

2 weeks using a second antibiotic (ciprofloxacin or metronidazole).[10] While approximately 80% of the cases respond to 2-4 weeks of antibiotic treatment, relapse develops in 7%-20% of the cases. In instances of relapsed cases, the readministration of antibiotic therapy leads to the development of chronic antibiotic-dependent pouchitis (CADP) in approximately 80% of cases, while the remaining 10%-20% of unresponsive cases are classified as chronic antibiotic-refractory pouchitis (CARP).[11]

CHRONIC ANTIBIOTIC-REFRACTORY POUCHITIS

Numerous researchers have formulated various conceptualizations of the term "chronic antibiotic-refractory pouchitis." According to Dalal et al,[6] CARP refers to cases where clinical and endoscopic evidence of inflammation persists in patients despite repeated antibiotic and probiotic treatments. According to the guidelines released by the International Ileal Pouch Consortium in 2021, the term CARP was delineated as a condition characterized by a lack of clinical and endoscopic response or minimal response following conventional antibiotic therapy lasting 2-4 weeks, regardless of any prior positive response to antibiotic treatment.[5] Santiago et al[11] expanded the definition by incorporating the absence of responses to mesalamine, corticosteroids, immunomodulators, and antibiotics.[11] The management of CARP requires a careful and holistic approach. In 20%-30% of CARP cases, there is an identifiable cause.[12] In this particular scenario, the condition is referred to as "secondary pouchitis" (SP). The management of secondary pouchitis should primarily focus on addressing the underlying cause. If the cause of pouchitis is not found and effective treatment is not performed, additional morbidities, reoperations, and eventually pouch loss may develop. Conversely, in cases where the clinical presentation is attributed to functional factors (such as irritable pouch syndrome) or structural issues resulting from surgical procedures, there is a risk of administering unnecessary interventions to the patient.

EVALUATION OF CHRONIC ANTIBIOTIC-REFRACTORY POUCHITIS CASES

The comprehensive assessment of CARP cases necessitates the inclusion of various diagnostic procedures, such as medical history, physical examination, biochemical and microbiological analyses, endoscopic evaluation of the pouch, histopathologic interpretation, and cross-sectional imaging of the pouch.

Medical History

- Information about the phenotype of IBD includes age at diagnosis/disease, preoperative definitive diagnosis, anatomical extent of the disease, clinical behavior, presence of extraintestinal manifestations, the presence of dysplasia and/or colorectal cancer, previous perianal fistula, abscess, fissure, etc. symptoms that may indicate perianal disease,
- Habits and medications, previous treatment experiences, smoking, use of nonsteroidal anti-inflammatory drugs (NSAIDs),
- Information about the operation should include the date of the operation, indication, number of operation stages, type of pouch, type of anastomosis (stapler or hand sewing), whether a cuff was left, details about the surgical intervention such as the length of the cuff, the pathological diagnosis of the colectomy material, the time of appearance of the clinical picture, and the relationship with the closure of the ileostomy.
- Classically, signs of pouchitis appear 6-12 months after ileostomy closure. Hence, it is more appropriate to attribute early symptoms to operative morbidities or structural diseases of the pouch.
- Clinical findings indicating pouch inflammation should be questioned: bloody, mucous stools and increased number of stools, urgency, tenesmus, abdominal and pelvic pain. If bleeding is the predominant symptom, cuffitis should be considered.[10,11,13] The presence of symptoms such as constipation, incomplete evacuation, and the need for manual assistance during defecation may indicate the presence of pouch-emptying difficulties.[14]

Physical Examination

A general systemic examination should be performed; extraintestinal findings should not be overlooked, especially focusing on the perianal region; the presence of perianal fistulas, fissures, abscesses, hemorrhoids, skin tags, and anal sphincter tone should be investigated; and their characteristics, if any, should be recorded.

Laboratory Investigations

Routine hemogram, CRP, fecal calprotectin,[15] a complete biochemical analysis, *Clostridium difficile* toxin A and B if there is a clinical possibility of infection, and microbiological examination of stool may be required.

Endoscopic Evaluation of the Pouch (Pouchoscopy)

- A detailed perianal examination should be performed before pouchoscopy. In this examination, the perianal fistula, if any, its number, whether it is discharging or not, the location of the external openings, the anal fissure, if any, its location, number, depth, whether it is painful or not, findings suggestive of an abscess in the perianal region (e.g., pain, swelling, temperature increase, color change), the anal sphincter tone on rectal touch, and the presence of anal stenosis should be investigated.
- Currently, the J pouch is the preferred option in RP-IPAA. The comprehensive assessment of the endoscopic examination should encompass the examination of various regions, namely the pouch afferent (prepouch ileum), pouch apex, body, pouch efferent, pouch–rectal anastomosis, and cuff, if present. It is imperative that each of these regions be thoroughly examined and documented in the report.
- Mucosal changes in classic idiopathic pouchitis include edema, granularity, ulcerations, increased mucus, loss of submucosal vascular structures, and fragility.
- The extent and symmetry of macroscopic changes detected during pouchoscopy, the presence of lesions in the prepouch ileum, the relationship with anastomosis and stapler lines, the presence of fistulas, strictures, and deep ulcers, the presence of anastomotic strictures, whether they can be easily passed, whether there is angulation in the prepouch ileum, and whether there is pouch prolapse should be investigated.[10,11,14]
- A detailed endoscopic evaluation of the pouch provides valuable diagnostic clues.[16] For instance:
- Diffuse inflammatory changes localized only to the pouch body: idiopathic pouchitis, infections (e.g., *C. difficile*, etc.).
- Diffuse pouchitis and prepouch ileitis may indicate autoimmune pouchitis, pouchitis with PSC, or IgG4-related pouchitis.
- Segmental pouchitis, fistulas and strictures, and/or prepouch ileitis: CD.
- Asymmetric pouchitis: ischemic pouchitis.
- Cuffitis is diagnosed when there are indications of inflammation specifically confined to the cuff region.
- If pouch mucosa, prepouch ileum, and cuff are completely normal, functional pouch diseases should be considered.

Imaging

Cross-sectional imaging modalities, such as magnetic resonance imaging and computed tomography, are employed in the evaluation of pouchitis. These tools are utilized to identify potential surgical complications during the early postoperative phase and to investigate structural abnormalities of the pouch, secondary pouchitis, and pathologies like Crohn's disease and malignancy during the late postoperative period. The utilization of barium pouch defacography can be employed as a diagnostic procedure to visually illustrate the presence of dyssynergic defecation.[12]

CHRONIC ANTIBIOTIC-REFRACTORY POUCHITIS AND ITS TREATMENT

When planning the treatment of cases of CARP, it is imperative to exclude the possibility of secondary pouchitis. While several medications employed to manage SP are also utilized to treat idiopathic CARP, certain distinctions may exist due to the etiology of SP.

- In non-SP CARP cases and CADP cases, fecal coliform sensitivity testing and antibiotic treatment according to the results were recommended.[17] However, it has not entered routine clinical use. In the absence of coliform sensitivity testing, small cohorts of cases were subjected to 2-week treatment regimens involving combinations of ciprofloxacin with rifaximin and ciprofloxacin with tinidazole. The reported rates of remission ranged from 63% to 88%.[18]
- Shen et al[19] compared the ciprofloxacin+tinidazole combination with mesalamine oral 4 g/day+8 g/day enema or 1 g/day suppository for 4 weeks in CARP cases and found that the antibiotic combination was significantly more effective than mesalamine. However, 50% remission has also been reported with the mesalamine combination. In order to minimize the necessity of prolonged antibiotic usage, the utilization of a combination therapy involving mesalamine can be considered a viable alternative. However, during the consensus meetings on this subject, neither comments nor recommendations were made regarding the use of mesalamine in CARP.[20]
- Oral controlled-release budesonide (9 mg/day) was used in CARP treatment, and 75% remission, a significant reduction in the number of stools, and an improvement in quality of life were achieved. It seems that budesonide exhibits greater efficacy in the treatment of CARP that arises via immunologic mechanisms.[21] Budesonide has been recommended by the GETECCU group in cases of chronic pouchitis refractory to antibiotic therapy.[22] Budesonide has been found to be effective in maintaining remission when administered at modest levels, often ranging from 3 to 6 mg per day. However, it is important to consider the potential occurrence of corticosteroid-related side effects as a potential drawback.[20] Gionchetti et al[23] reported 80% remission in a small series of 10 patients who received 10 mg/day of oral beclomethasone.
- Insufficient data exists to provide a definitive assessment of the efficacy of immunomodulators as an induction therapy for CARP, whether utilized independently or in conjunction with biologic agents.[6,20,24] However, they can be used as an option for remission maintenance.[20]
- Bismuth, bismuth carbomer, and alicaforsen enema in CARP treatment have reported conflicting results.[18,24] On the contrary, it was observed that topical tacrolimus and cyclosporine exhibited efficacy in cases of CARP.[20,25-27]
- Biological agents are utilized as rescue therapy in CARP treatment for patients who do not respond to budesonide.[13]
    - o *Anti-TNF agents*: Infliximab (IFX) and adalimumab (ADA) were initially administered to a restricted subset of patients on an empirical basis. The short- and long-term effects of anti-TNFs were then investigated in large patient groups. The groups in these studies were heterogeneous and included mixed non-SP CARP and SP CARP cases. The data from publications involving a small number of patient groups are contradictory. Huguet et al[28] conducted a meta-analysis that examined the short-term (eighth week) and long-term (12th month) effects of anti-TNF agents on 313 cases from 21 studies and 3 abstracts. 194 patients received IFX, and 119 patients received ADA. At week 8, the IFX group exhibited 56% clinical remission compared to 38% in the ADA group. By week 52, the IFX group had achieved 52% clinical remission, while the ADA group had only achieved 30%. The efficacy of anti-TNF was also assessed in cases of Crohn's-like CARP in the meta-analysis. Compared to the general average and non-CD-like CARP cases, anti-TNF efficacy was found to be 64% at week 8 and 57% at week 52.[28]
    - o *Anti-integrin agents*: Verstockt et al's[29] study, which is based on the experiences of a single center, provides the opportunity to compare the efficacy of anti-TNF and anti-integrin agents in the treatment of CARP. The outcomes of the utilization of 48 biologic agents in 33 cases of CARP were retrospectively examined in this publication. Infliximab (n=23), ADA (n=13), and vedolizumab (VDZ) (n=15) were used. At week 14, IFX promoted clinical remission by 43%, ADA by 38.5%, and VDZ by 60%. When the long-term results covering 156 weeks were analyzed, it was found that those treated with anti-TNF agents were significantly more likely to discontinue treatment compared to VDZ, with an HR of 3.0 (95% CI, 1.1-8.7; $P=.04$). The frequency of permanent ileostomies was 0% in the VDZ group, 17% in the IFX group, and 14.5% in the ADA group. The authors of this study concluded that VDZ is a safe and effective alternative in cases of CARP.[29] The occurrence of prior anti-TNF therapy experience and subsequent failure or loss of response prior to colectomy does not have an impact on the responses to anti-TNF and VDZ treatments in the management of pouchitis.[30] The efficacy of VDZ was examined in the placebo-controlled EARNEST study, where it was found to be more effective than placebo in achieving clinical remission at weeks 14 and 32. Additionally, VDZ demonstrated comparable side effects to placebo.[31] The International Ileal Pouch Consortium[20] and some authors recommend the use of VDZ as the first step if biologic agents are to be used.[32]
    - o *IL-12/23 blockers:* Rocchi et al[33] conducted a systematic review that included 2 retrospective studies and 5 case reports. The objective of the review was to assess the efficacy of ustekinumab (UST) in a total of 51 patients with CD pouchitis and 35 patients with chronic pouchitis. Clinical response was 63% in cases of CARP and 85% in cases of CARP-CD at week 12. At week 52, clinical remission (the absence of all clinical findings) was observed in 10% of CARP cases and 27% of CARP-CD cases. Low clinical response and remission values were attributed to an elevated body mass index, a greater frequency of defecations prior to treatment, and prior administration of anti-TNF agents. No association with CRP was established. The study conducted by Brewer et al[34] employed a meta-analysis approach to evaluate the findings of 2 retrospective observational studies involving 26 cases of CARP and 1 retrospective observational study involving 52 cases of CARP-CD. The results indicated that the rate of complete response observed at an average of 7 months was 50% in CARP cases. However, the rate of durable response was

significantly lower at 7%, and there were reports of pouch loss at a rate of 7%. Ustekinumab demonstrated superior outcomes in cases of CARP-CD, with a complete response rate of 5.8% and a partial response rate of 78.8% at 3 months, a permanent response rate of 36.4% and a partial permanent response rate of 54.5% at 12 months, and no pouch loss in any circumstance. A 50% clinical response was observed with a follow-up of 12.9 months in the single-center retrospective study of Ollech et al,[35] which included 24 non-CD CARP patients and investigated endoscopic mucosal improvement in addition to clinical evaluation. Among the 13 patients for whom complete pouchoscopic data was available, it was observed that 69% of them exhibited an ulcerated area greater than 10% in the pouch prior to treatment. Subsequently, during the follow-up period, an endoscopic evaluation conducted at an average of 7.4 months revealed that 31% of the patients had an ulcerated area exceeding 10%. Upon comprehensive evaluation of the aforementioned studies, the guidelines suggest that the utilization of UST may be considered a viable alternative in the treatment of CARP.[20,22]

SECONDARY POUCHITIS AND TREATMENT

- The most challenging clinical presentations to manage are CD that develops de novo in the pouch (Crohn-like disease in the pouch, CLDP) and recurrence of CD in the pouch in extremely rare cases of CD without involvement of the perianal region and small intestine.[36] The prevalence of CLDP increases over the years in patients who underwent IPAA for UC or indeterminate colitis (IC), depending on the follow-up period, and rises to 10%-19.5%.[37,38] The mean duration of emergence exhibits a range of 8.4-11.6 years.[38] Compared to UC patients, IC patients have a 4.5-fold increased risk of developing CLDP.[39] However, pouchitis prophylaxis is not recommended in IC cases. In these cases, a pouchoscopic evaluation is recommended at 6 months.[20] Criteria for the diagnosis of prepouch ileitis were established by the International Ileal Pouch Consortium. These included the development of fistulas and abscesses in the late period (6-12 months after ileostomy closure), strictures, and segmental or bypass lesions in the pouch or small intestine, as well as non-caseating granulomas in biopsies obtained from all anatomical regions of the J pouch, excluding those caused by crypt rupture.[5] The presence of fistulas and strictures should not be linked to anastomotic sites. The time of fistula development is important in differentiating surgical causes, or CLDP. Fistulas that develop in the early postoperative period are related to surgical causes, while fistulas that develop after 6-12 months are related to CD.[39] Imaging-detected transmural inflammation is not specific to CLDP; it can also manifest in chronic pouchitis caused by other etiologies. Risk factors include family history of CD, prolonged ileal pouch duration, active smoking, preoperative diagnosis of unclassified IBD, Saccharomyces Cerevicea Antibody (ASCA) IgA positivity, and Anti-CBir 1 flagellin Antibody positivity.[40] Crohn-like disease in the pouch clinically shows 3 different behaviors: inflammatory, fistulizing, and stricturing. Crohn-like disease in the pouch is treated and managed in the same manner as CD itself. Oral and topical 5-ASA preparations are not recommended for the treatment of CLDP.[20] Ileal-release budesonide, immunomodulatory drugs, and antibiotics can be used. Biologic agents demonstrate greater efficacy in cases of CLDP compared to cases of CARP arising from alternative etiologies. In instances involving stricture, interventions such as endoscopic balloon dilatation, stricturectomy, or surgical strictoplasty may be employed. The treatment approach for patients with fistulas is identical to that of classical CD. However, between 12.4% and 15% of cases return to permanent ileostomies, with CLDP being the most prevalent cause of pouch loss.[37,38]
- Pouchitis in the presence of primary sclerosing cholangitis (PSC) exhibits distinct characteristics when compared to cases without PSC. Comparing 182 cases of pouchitis with PSC and 182 cases of pouchitis with UC, the study revealed that pouchitis with PSC was more frequently associated with prepouch ileitis (34.1% vs. 11.5%), was more frequently converted to CARP (17.6% vs. 7.7%), and exhibited more severe inflammation (54.9% vs. 32.4%).[41] Primary sclerosing cholangitis pouchitis is characterized endoscopically by severe and diffuse pouchitis accompanied by long segmental prepouch ileitis.[11,20,41] Although ciprofloxacin, metronidazole, or a combination thereof is advised as the initial course of treatment,[41] certain authorities rely on oral vancomycin[11] as the first-line treatment. In treatment, oral and topical mesalamine, oral budesonide, and anti-TNF agents are administered. Nevertheless, it was observed that the efficacy of oral budesonide was comparatively lower in the pouches of patients with PSC.[41]
- Cytomegalovirus (CMV) and *C. difficile* can cause pouch infections in rare instances. When recurrent pouchitis occurs, infectious pouchitis should be taken into consideration. The endoscopic findings lack specificity. Pseudomembranes are rarely found in pouchitis due to *C. difficile*.[14] For diagnosis, *C. difficile* toxin A and B in the stool should be evaluated. Obesity, male gender, preoperative antibiotic use, and a recent history of hospitalization can be considered risk factors.[20] Oral vancomycin has been recommended as a first-line treatment. Fecal microbiota transplantation is recommended for recurrent *C. difficile* infection.[20,42] The presence of immunosuppression increases the susceptibility to CMV infection. In addition to pouchitis findings, the diagnosis is established through the utilization of immunohistochemical analysis of pouch biopsies, quantitative measurement of CMV DNA via polymerase chain reaction technique, and fever and splenomegaly. The course of treatment remains consistent with that of a CMV infection.
- Ischemic pouchitis should be considered in conjunction with chronic pouchitis symptoms when pouchoscopy reveals a well-circumscribed, asymmetrical, and localized area of inflammation at a single site. Extracellular hematoid accumulation in the biopsy provides additional support for the diagnosis.[5,11] Strain or damage to the vascular structures supplying the distal ileum, mesenteric strain, or torsion increases the likelihood of ischemic pouchitis. Males, individuals with obesity, and those who experience excessive weight gain following surgery are more susceptible to increased risk.[14] Despite being utilized as the primary course of treatment, antibiotics exhibit a considerable degree of limited effectiveness. Hyperbaric oxygen therapy or surgical intervention (a redo pouch) may be required in severe cases.[11]
- *Cuffitis* is the inflammation of the rectal mucosa that remains as a remnant in pouch–anal anastomoses created with a stapler. In other words, it is ulcerative colitis of the remaining rectal mucosa. The predominant symptom is bleeding. Normal pouch mucosa and prepouch ileum are characteristics of classic instances of cuffitis. Nevertheless, the co-occurrence of cuffitis and pouchitis is also observed.[5,11,14] Oral and topical 5-ASA compounds and topical corticosteroids can be used in treatment. In cases of treatment-resistant cuffitis, inflammatory pathologies, CD, pouch prolapse, and malignancy should be taken into account.[43]

ADDITIONAL TREATMENT MODALITIES

- Since NSAIDs may cause prepouch ileitis, strictures, and ulcers in the pouch, the use of NSAIDs should be avoided in the preoperative, perioperative, and postoperative periods.
- A diet rich in fruit, micronutrients, and fermentable fiber should be recommended to patients, as it may reduce the development of pouchitis.[44] The available literature on exclusive enteral nutrition presents divergent findings, as it reports clinical amelioration but lacks substantial evidence of improvement in inflammatory activity. As a result, it is not advised for the treatment of CARP.[44,45]
- Probiotics have been found to be more effective than placebo in maintaining remission in CADP if remission is achieved with antibiotics. Therefore, they can be utilized for the purpose of sustaining remission.[46] Fecal microbiota transplantation is not recommended for CARP treatment.[20,42,46]

LOSS OF POUCH AND SURGICAL TREATMENT

Pouch loss can be characterized as the complete removal of the pouch, the implementation of a temporary or permanent fecal diversion by ileostomy, or the surgical redo-pouch creation.[13] Pouch loss is 5%-10% in ileal pouch anal anastomosis cases. The occurrence of pouch loss within the initial 12-month period subsequent to ileostomy closure has been found to be linked to surgical problems. However, after this timeframe, the primary factors contributing to pouch loss are identified as CLDP and CARP.[13,47]

CONCLUSION

Chronic antibiotic-refractory pouchitis is a challenging clinical manifestation that results in significant morbidity and constitutes an estimated 10%-20% of cases involving chronic pouchitis. Approximately 30% of CARP cases have an identifiable cause. When first-line antibiotic therapy fails to alleviate acute and chronic pouchitis, it is advisable to reevaluate the diagnosis. The timing between the onset of symptoms and closure of the ileostomy should be determined, and surgical causes and structural problems of the pouch (anastomotic leak, strictures, fistulas, pelvic abscesses and sepsis, afferent loop syndrome, floppy pouch complex, etc.) should be investigated in the early postoperative period. The etiology of inflammation should be established through the utilization of endoscopic, imaging, laboratory, and histopathologic techniques. Functional pouch diseases such as irritable pouch syndrome and dyssynergic defecation warrant investigation in the absence of inflammation.

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