Navigating Chronic Pouchitis: Pathogenesis, Diagnosis, and Management

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Abstract: Chronic pouchitis affects 13% to 17% of patients with ileal pouch–anal anastomosis and ulcerative colitis, and 20% with a history of acute pouchitis. It is classified by antibiotic responsiveness into chronic antibiotic-dependent pouchitis and chronic antibiotic-refractory pouchitis. Pathogenesis of chronic pouchitis can range from microbially mediated to more antibiotic-resistant and immune-mediated processes. A diagnostic index combining clinical, endoscopic, and histologic components is essential for clinical practice and research. In chronic antibiotic-dependent pouchitis, remission is managed with microbiota- or immune-targeted therapies. For chronic antibiotic-refractory pouchitis, immune-directed therapy is primary, with vedolizumab recommended for first-line treatment. Other advanced therapies rely on less definitive evidence, and efficacy may be reduced by precolectomy exposure. This article reviews the pathogenesis, diagnosis, and management of chronic pouchitis.

Keywords
Ulcerative colitis, pouchitis, pathogenesis, antibiotic-refractory pouchitis, vedolizumab

Restorative proctectomy with ileal pouch–anal anastomosis (IPAA) is the preferred surgical procedure for patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). This procedure creates an internal pouch from the small intestine to serve as a new rectal reservoir, avoiding the need for a permanent stoma and allowing for voluntary defecation, significantly improving quality of life. However, this complex surgery is associated with several complications, the most common of which is pouchitis, an idiopathic inflammation of the pouch mucosa.

Pouchitis can be classified by symptom duration into acute (<4 weeks) and chronic (≥4 weeks) pouchitis. Further classification incorporates antibiotic responsiveness: acute antibiotic-responsive pouchitis (<4 episodes per year that are antibiotic responsive), chronic antibiotic-dependent pouchitis (CADP; ≥4 antibiotic-responsive episodes per year or persistent symptoms requiring continuous antibiotic use), and chronic antibiotic-refractory pouchitis (CARP; refractory to conventional antibiotics for ≥4 weeks).[1] Pouchitis, particularly chronic pouchitis, by virtue of persistent symptoms and treatment challenges, is associated with a poor

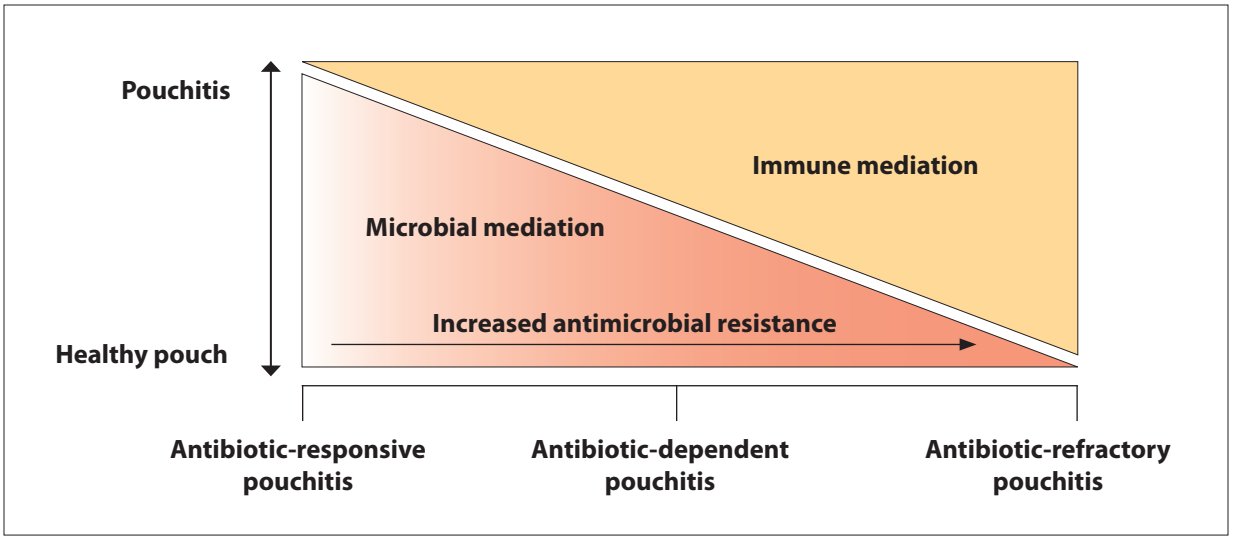

Figure 1. Pouchitis is primarily microbially mediated in antibiotic-responsive cases and immune-mediated in chronic antibiotic-refractory cases, with antibiotic-dependent pouchitis in between.

quality of life[2] and pouch failure.[3]

The prevalence of chronic pouchitis in UC pouches is reported to be around 13% to 17%. One meta-analysis of 25 studies reported a prevalence of 13%,[4] whereas another meta-analysis of 49 studies found a median prevalence of 17.1% (interquartile range, 12%-23.6%).[5] Patients who develop 1 episode of acute pouchitis are at increased risk for chronic pouchitis, with progression rates of 20% to 30%.[6] The risk is even higher for those who develop their first acute pouchitis episode within several months after stoma closure.[7]

This article aims to discuss the pathogenesis of chronic idiopathic pouchitis, present a pragmatic approach to accurately diagnose chronic pouchitis and assess its severity, and discuss the data supporting treatment strategies. The article concludes with future directions for unmet needs.

Pathogenesis of Pouchitis

Pouchitis is thought to result from disrupted innate immunity and a dysregulated adaptive immune response to altered pouch microbiota in susceptible hosts. It represents a disease spectrum, typically starting as acute antibiotic-responsive and then progressing to antibiotic-dependent and finally antibiotic-refractory disease. This progression suggests that etiopathogenesis evolves from microbially mediated inflammation to predominantly immune-mediated inflammation (Figure 1).[8]

Pouch Microbiota

The role of pouch microbiota in mediating pouchitis is supported by pouchitis onset only after continuity is restored and the pouch mucosa is exposed to feces, the correlation of certain microbial groups and reduced diversity with pouchitis and disease activity, and the effectiveness of antibiotics in treating acute pouchitis. To date, no specific microbial signature has been consistently found, possibly because of heterogeneity in study designs, sampling methods, and analysis techniques. However, changes have demonstrated reduced microbial diversity, increased abundance of pathogenic bacteria, and decreased abundance of beneficial bacteria. Studies show decreased microbial diversity in patients with UC with a history of pouchitis compared with healthy UC pouches, with further decreases in active pouchitis.[9,10] Mucin-degrading bacteria such as *Clostridium perfringens* and *Ruminococcus gnavus* are repeatedly associated with pouchitis.[9,11,12] In a prospective study of 21 patients with UC, those who developed pouchitis had increased levels of *R gnavus*, *Phocaeicola vulgatus*, and *C perfringens*, and lacked 2 *Lachnospiraceae* genera, in their precolectomy fecal samples.[11] Another study of 27 patients with UC undergoing IPAA found bacterial DNA in the mesenteric lymph nodes and mesenteric adipose tissue of patients who developed pouchitis, with *Ruminococcus*, *Bacteroides*, and Clostridiales bacteria found exclusively in those patients.[12] Studies show decreased levels of anti-inflammatory and butyrate-producing *Faecalibacterium prausnitzii* in patients with a history of or active pouchitis.[9,13] *Bacteroides* spp are also reduced in active pouchitis compared with healthy pouches.[13,14]

The microbiota of FAP pouches, which have a lower rate of pouchitis, are less studied but maintain more diversity than those of UC pouches.[9] Although not equivalent to healthy colon controls, FAP pouches exhibit fewer

microbial alterations and retain beneficial bacteria such as *Faecalibacterium*.[9] Interestingly, this difference is not owing to macro- or micronutrient intake or diet quality between patients with UC and FAP pouches.[15] This raises the possibility of a bidirectional relationship between microbiota and the pouch's innate and adaptive mucosal immune system contributing to UC pouch dysbiosis.

There is no doubt that altered pouch microbiota play a major role in mediating acute pouchitis, and targeting the microbiome is the mainstay of treatment. However, the mechanism of how altered microbiota mediate pouchitis—through direct association with the pouch mucosa, alterations of the microenvironment, or recognition as a target for a dysregulated immune response—remains unclear.

Pouch Mucosal Immune System

Disrupted or Upregulated Innate Immunity Fecal stasis in the ileal pouch reservoir results in adaptive epithelial changes to a more colon-like mucosa.[16] In UC pouches, these changes are more pronounced even without acute inflammation.[17] Additionally, UC pouches exhibit disruptions in the innate immune system, which are less commonly observed with FAP pouches, including barrier dysfunction with increased claudin-2 tight junctions, aberrant dendritic cells, increased expression of defensins (human defensins 5 and 6, human β-defensins), Toll-like receptors such as TLR4, interferon-γ expression, and signal transducer and activator of transcription (STAT) 1 activation.[18,19]

Disrupted innate immunity is further upregulated in chronic pouchitis. Patients with recurrent or chronic pouchitis show increased expression of mucosal human defensin 5 and heightened antimicrobial activity against *Escherichia coli*,[20] which dominates the microbiota in chronic pouchitis.

Dysregulated Adaptive Immunity A dysregulated immune response in chronic pouchitis is suggested by several studies and supported by the effectiveness of immunosuppressive treatments such as the α4β7 integrin inhibitor vedolizumab (Entyvio, Takeda),[21] tumor necrosis factor (TNF) inhibitors (adalimumab or infliximab),[22] potentially anti-interleukin (IL)-12 and -23 inhibitors (ustekinumab),[23] and Janus kinase (JAK)–STAT3 inhibitors such as tofacitinib (Xeljanz, Pfizer).

There is increased TNF expression in uninflamed UC pouches compared with FAP pouches and in patients with pouchitis.[24,25] The role of the IL pathway is shown by increased expression of IL-1β, IL-6, IL-8, and IL-12 in pouchitis.[25,26] Lymphocyte trafficking and adhesion molecules are implicated in chronic pouchitis. UC pouches have abundant gut-homing T cells expressing integrin α4β7 and increased mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) expression.[27] This is supported by high inhibition of circulating CD4+ T cells' adhesion to MAdCAM1 in vedolizumab-responsive patients. However, alicaforsen, an intercellular adhesion molecule-1 (ICAM-1) antisense oligonucleotide inhibitor, has not shown clear therapeutic effects in chronic pouchitis.[28] STAT protein pathways and interferon-γ are also upregulated in patients with pouchitis.[19]

Risk Factors for Progression to Chronic Pouchitis

Predicting which patients with pouches will develop chronic pouchitis is difficult but important for risk stratification and targeting modifiable risk factors to prevent or delay progression.

Early-Onset Pouchitis Multiple studies show that early-onset pouchitis predicts chronic pouchitis.[7,29] One study found that onset at a median of 1.5 years after stoma closure had an odds ratio of 5.55 (95% CI, 2.14-14.44).[30] Another study reported an earlier onset at 6 months with an odds ratio of 3.51 (95% CI, 2.07-5.94).[7]

Antimicrobial Resistance and Dysbiosis Prolonged antibiotic use may lead to dysbiosis and disease progression in pouchitis. A prospective study showed that chronic pouchitis associated with antibiotic therapy (not with biologic or immunomodulatory therapy) featured decreased levels of *Faecalibacterium*, *Roseburia*, and Lachnospiraceae, alongside increases in *Enterococcus* and Enterobacteriaceae.[9] In a cross-sectional analysis of 265 pouches, antibiotic use was linked to higher levels of *Enterococcus* spp and a chronic pouchitis phenotype, and to increased *Escherichia* spp correlating with IL-12–enriched host transcript patterns.[26] Dubinsky and colleagues found in 49 patients with ileoanal pouches that antibiotic-treated microbiota were dominated by *Escherichia*, *Enterococcus*, and *Streptococcus* spp, including multiple ciprofloxacin-resistant strains. Ceasing antibiotic usage led to a swift repopulation with pathogenic and oral bacteria, suggesting that repeated antibiotic use fosters dependence and contributes to refractory disease progression.[10]

Other Factors Other risk factors may be involved. There is a higher prevalence of pelvic dyssynergia in patients with chronic pouchitis (83% vs 62%; *P*=.01), suggesting a positive association.[31] Several autoimmune factors are linked with chronic pouchitis, including a family history of inflammatory bowel disease (IBD),[7] other autoimmune diseases,[32] extraintestinal manifestations of IBD,[32] and positivity for antineutrophil cytoplasmic antibodies.[33] Primary sclerosing cholangitis (PSC) is associated with a high risk for chronic pouchitis, prepouch ileitis, and reduced responsiveness to antibiotics.[34] Extensive colitis, backwash ileitis, and indeterminate colitis are risk factors

Table 1. Inflammatory and Noninflammatory Disorders of the Pouch Presenting With Increased Frequency and Urgency

Disorder	Incidence	Key clinical features	Diagnosis	Treatment
Idiopathic inflammatory pouch disorders				
Pouchitis	Acute: 25%-50% of UC IPAA Chronic: 13%-17% of UC IPAA	Most common inflammatory disorder of the pouch	Diagnostic indices: PDAI ≥7, mPDAI ≥5	Measures directed at microbial and immune components
Cuffitis	13%[95,96]	Rectal bleeding	Circumferential inflammation of the cuff	Managed similarly to UC recurrence
Prepouch ileitis	4.4%-11%[97]	Risk of strictures[98] When associated with pouchitis, inflammation appears to be predominately immune-mediated	Endoscopic or histologic inflammation >2 cm proximal to pouch inlet	Immune-targeted approach; consider vancomycin if PSC-associated.[60] When associated with pouchitis, management follows that of idiopathic pouchitis.
Secondary causes of CARP				
CDP	3%-13% as de novo CDP[99,100]	3 phenotypes: • Inflammatory (difficult to distinguish from CARP, granulomas in only 13%-15%)[101] • Fibrostenotic: ulcerated strictures and inflammation along the GI tract not limited to the pouch inlet or previous loop ileostomy site • Fistulizing: distinct nonanastomotic fistulas 6-12 months poststoma closure often with associated cuff inflammation	Clinical, endoscopic, histologic, and radiologic evaluation	Tailored to specific phenotype; may include anti-TNF agents, endoscopic interventions, and surgical interventions
Pelvic sepsis from anastomotic leak/sinus/abscess	3% as a late complication[94] One-third of patients presumed to have CADP in 1 study[102]	Persistent and worsening pouch function following stoma closure even in the absence of fever and pain	Diagnostic imaging (MRI) and pouchoscopy	Antibiotics, percutaneous drainage, surgical treatment; may need pouch reconstruction
Clostridioides difficile infection	10% in patients with chronic symptoms[103]	Fever, diarrhea	Detection of *C difficile* toxin	Oral or IV metronidazole, vancomycin, fidaxomicin, FMT
CMV	Rare	Fever, ulcerations in the pouch and prepouch ileum[104]	CMV inclusion bodies or positive immunohistochemistry	Oral or IV ganciclovir
Ischemia	Not clear	Anemia, inflammation affecting the distal half of the pouch, the afferent limb, the staple line, or the pouch inlet[105]	Clinical diagnosis	Hyperbaric oxygen therapy and weight loss
NSAIDs	Not clear	No unique clinical features	History of regular NSAID use	Cessation improves pouchitis
Noninflammatory disorders				
Irritable pouch syndrome	18%-43% of patients with pouch-related symptoms[106]	Associated anxiety	No evidence of endoscopic or histologic inflammation; total PDAI <7, including ePDAI ≤1	Consider low-FODMAP diet, neuropathic medications
Pelvic dyssynergia	75% with a higher incidence in chronic pouchitis[31]	Presents with incomplete emptying of the pouch	Clinical diagnosis	Biofeedback therapy[31]

CADP, chronic antibiotic-dependent pouchitis; CARP, chronic antibiotic-refractory pouchitis; CDP, Crohn's disease of the pouch; CMV, cytomegalovirus; ePDAI, Pouchitis Disease Activity Index endoscopic score; FMT, fecal microbiota transplantation; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; IPAA, ileal pouch–anal anastomosis; IV, intravenous; mPDAI, modified Pouchitis Disease Activity Index; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PDAI, Pouchitis Disease Activity Index; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UC, ulcerative colitis.

Table 2. Pouchitis Diagnostic Indices

Index	Reference, year	Components	Diagnosis criteria	Strengths	Weaknesses
St. Mark's Index	Moskowitz et al,[40] 1986	12-point histologic scoring system assessing inflammation that is • Acute (neutrophilic infiltration, ulceration) • Chronic (chronic inflammatory cell infiltration, villous atrophy)	≥4 acute histologic subscore, plus diarrhea and macroscopic inflammation	Differentiates acute and chronic inflammation	Limited use owing to stringent criteria
PDAI	Sandborn et al,[42] 1994	18-point index divided equally into 3 components: • Clinical (frequency, urgency, fever, bleeding) • Endoscopic (ulceration, friability, exudate, edema, loss of vascularity, granularity) • Histologic (acute inflammation)	Total score ≥7	Standardizes definition with a quantitative system	Issues with clinical, endoscopic, and histologic index reliability
Modified PDAI	Shen et al,[43] 2003	12-point index divided equally into 2 components: • Clinical (frequency, urgency, fever, bleeding) • Endoscopic (ulceration, friability, exudate, edema, loss of vascularity, granularity)	Score ≥5	More efficient and cost-effective without needing histology	Shares deficiencies with PDAI
Heidelberg Pouchitis Activity Score	Heuschen et al,[107] 2002	36-point index divided equally into 3 components: • Clinical (frequency, urgency/cramps, bleeding) • Endoscopic (ulceration, friability, edema, loss of vascularity, granularity, erythema, flattening of mucosal surface) • Histologic (acute and chronic inflammation) components	Score ≥13	Notes chronic inflammation features; correlates with long-term risks	Overestimates pouchitis by 11% compared with expert evaluations
Japanese Endoscopic Pouch Activity Index	Shinozaki et al,[45] 2005	Endoscopic component with 6 features: erosions, erythema, ulceration, friability, exudate, granularity	Score ≥2	Improves reliability by replacing endoscopic features of the PDAI (loss of vascularity and edema) with more reliable features (erosions and erythema)	Lacks clinical and histologic components; reliability concerns with included endoscopic items
Japanese Diagnostic Criteria for Pouchitis	Fukushima et al,[46] 2007	Combines dichotomous clinical components (increased frequency, urgency/cramps, fever, bleeding) with ordinal categories of endoscopic features divided into • Mild (edema, granularity, loss of vascular pattern, erythema) • Moderate (erosion, aphthoid ulcer, ulceration, friability, mucus) • Severe (extensive or multiple ulceration, diffuse erythema, spontaneous bleeding)	2 clinical and 1 moderate endoscopic feature or 1 severe endoscopic feature	Categorizes endoscopic features by reliability and disease severity correlation	Not widely recognized or used
Monash Pouchitis Score	Ardalan et al,[47] 2022	Combined clinical and histologic components of PDAI with a new endoscopic component comprising 3 ordinal categories: • Erosions (absent, <10, ≥10) • Bleeding (absent, contact, spontaneous) • Ulceration (absent, <10%, ≥10%)	Total score ≥7	High interrater reliability; correlates well with disease activity	Limited to single center; lacks validation and responsiveness assessment
Atlantic Pouch Index	Sedano et al,[48] 2023	Combines endoscopic and histologic components using SES-CD applied to the ileum with RHI, excluding symptomatic assessments	(3 × SES-CD) + (1 × RHI) Higher scores correlate with disease activity	High reliability and responsiveness; includes strictures in scoring	Pending validation, but lacks clinical component

PDAI, Pouchitis Disease Activity Index; RHI, Robarts Histopathology Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

for chronic pouchitis.[35] Age at colectomy as a risk factor is unclear, with some studies suggesting that younger age (<26 or <35 years)[36,37] and others suggesting that age greater than 55 years is a risk.[38]

Diagnosis

Clinical Features of Pouchitis

Patients with pouchitis often experience symptoms such as frequent and loose stools, urgency, cramps, and seepage. However, these symptoms are not unique to pouchitis; they may also present in other conditions affecting the pouch. These include idiopathic inflammatory disorders such as prepouch ileitis and cuffitis, secondary inflammatory disorders such as Crohn's disease of the pouch, infections (cytomegalovirus or *Clostridioides difficile*), ischemia, and pelvic sepsis, as well as noninflammatory disorders such as irritable pouch syndrome or pelvic dyssynergia, detailed in Table 1. Specific clinical signs can suggest certain diagnoses: for instance, bleeding, which is rare in pouchitis, more commonly indicates cuffitis, either isolated or concurrent. Systemic symptoms such as fever or night sweats might point to an infectious etiology such as cytomegalovirus or *C difficile*, penetrating Crohn's disease, or complications such as anastomotic leaks.

Given the broad overlap and variability of these symptoms, they alone are not sufficient to distinguish between inflammatory and noninflammatory causes. This underscores the need for a diagnostic tool that can objectively assess the presence, location, and severity of inflammation in patients with an ileoanal pouch.

Confirming Pouchitis: Diagnostic Approaches and Challenges

The diagnosis of pouchitis should be based on a comprehensive assessment that includes clinical symptoms and macroscopic and microscopic evaluations of the pouch mucosa. As symptoms alone do not provide a definitive diagnosis, they must be integrated with endoscopic and histologic findings, each contributing independently to confirming pouchitis.[39-41] Thus, pouchoscopy with biopsies remains the gold standard for evaluating pouch-related symptoms, allowing for the assessment of the prepouch ileum, the cuff, and any structural complications.

Several diagnostic indices have been developed that evaluate all or some of these components[40,42-48] (Table 2); however, none are fully validated, and all exhibit limitations in accuracy, reliability, and responsiveness to treatment.[8,49] The most commonly used index in both clinical practice and research is the Pouchitis Disease Activity Index (PDAI) or its modifications.[42] The PDAI is an 18-point composite index of equally weighted clinical, endoscopic, and acute histologic items. A diagnosis of pouchitis is confirmed with a PDAI score of at least 7. Alternatively, the modified PDAI (mPDAI), which omits the histologic component, has shown to be nearly as accurate and more cost-effective, with a sensitivity of 97% and a specificity of 100% for diagnosing pouchitis at a cutoff value of at least 5.[43] A subsequent study showed that the PDAI was more sensitive than the mPDAI for the diagnosis of pouchitis, with relatively high dependence of the PDAI on acute histologic subscore (r=0.6408; P<.0001) when considering histologic contribution to the PDAI.[50] Nevertheless, the mPDAI is commonly used in clinical trials and as a reference standard for pouchitis in studies assessing the accuracy of biomarkers and imaging modalities.

One of the primary challenges with existing diagnostic indices for pouchitis, particularly with the PDAI and mPDAI, is the significant variability in intra- and interrater reliability of endoscopic features. These components are largely based on the Mayo score for UC, although the clinical, endoscopic, and histologic features of pouchitis differ appreciably from those of UC. The equal weighting of all diagnostic features is a further limitation. For example, in a study analyzing 50 pouchoscopy videos reviewed by 4 central readers in random order, only the endoscopic features of ulcerations and friability/contact bleeding showed reasonable reliability. In contrast, features such as vascular pattern, granularity, and mucus exudate performed poorly.[51]

This led to the development of the Monash Pouchitis Score (MPS), which revised the endoscopic component of the PDAI to include 3 ordinal categories: bleeding (absent, contact, spontaneous), erosions (absent, <10, ≥10), and ulceration (absent, <10%, ≥10%). All 3 Monash endoscopic items had substantial intrarater reliability with intraclass correlation coefficients (ICC) greater than 0.61 (95% CI, >0.61), compared with only ulcers from the PDAI, showing a marked improvement over the PDAI.[47] Moreover, the ordinal categories of the MPS likely contribute to its stronger correlation with disease severity.[47]

Further advancements were made with the Atlantic Pouchitis Index (API), which combines the Simple Endoscopic Score for Crohn's Disease (SES-CD) applied to the ileum with the Robarts Histopathology Index, excluding symptomatic assessments.[48] The API has shown significant interrater reliability (ICC, 0.72 [95% CI, 0.60-0.79]) and a high correlation with disease severity, outperforming the PDAI in responsiveness.[48] Notably, the API is the first diagnostic index to incorporate strictures as part of the scoring for pouchitis, acknowledging their importance in disease progression.

An effective endoscopic assessment of pouchitis should document whether the inflammation is diffuse or focal, as focal inflammation is associated with better outcomes for pouch survival.[52] Additionally, the presence of ulceration at the ileal pouch inlet should be noted owing

to its association with an increased risk of developing strictures, which are a significant risk factor for pouch failure.[52] Finally, the extent and severity of associated prepouch ileitis should be documented, ideally using the SES-CD, as moderate-to-severe prepouch ileitis is also linked to a higher risk of pouch failure.[53]

Noninvasive Investigations for Pouchitis

In patients with IPAA who experience more than 3 episodes of pouchitis per year, the routine performance of a pouchoscopy with each episode can be an invasive and burdensome procedure.[54] Additionally, the empirical use of antibiotics for each episode is not cost-effective and risks exposing 25% to 35% of symptomatic patients unnecessarily to antibiotics, potentially complicating cases of irritable pouch syndrome.[39,54] Consequently, alternative noninvasive tests that can differentiate between inflammatory and noninflammatory causes, and identify the location of inflammation, are highly valuable.

Among the laboratory tests, stool biomarkers, and imaging modalities, fecal calprotectin (FCal) and, to a lesser extent, intestinal ultrasound (IUS) have shown significant utility. FCal has been extensively evaluated in numerous studies.[50,55] Earlier studies suggested cutoff values of 66 μg/g and 92.5 μg/g, which demonstrated sensitivities of approximately 85% and 81%, respectively, for diagnosing pouchitis.[50,55] However, the reliability of these findings was limited by the use of a single endoscopist and the lack of evaluation of both the cuff and prepouch ileum. A more comprehensive study involving 156 patients proposed more definitive cutoff values, where levels below 208 μg/g excluded pouchitis and levels above 550 μg/g confirmed the diagnosis.[56] A subsequent study, which used a more rigorous methodology to ensure the reference standard of pouchitis was accurate and reliable, found that cutoff values of less than 100 μg/g and greater than 350 μg/g were most useful. A level of 100 μg/g was 90% sensitive, with an area under the curve of 0.90, for excluding any inflammatory pouch disorder, whereas a level of 350 μg/g was 80% specific for confirming pouchitis.[57]

The same study highlighted the diagnostic value of IUS in assessing pouch-related symptoms. Transabdominal ultrasound was found to effectively assess prepouch ileitis, whereas transperineal ultrasound was more useful for evaluating actual pouchitis. IUS is particularly helpful in localizing inflammation in patients with FCal levels greater than 350 μg/g.[57]

Ruling Out Secondary Causes in Chronic Antibiotic-Refractory Pouchitis

In patients with confirmed pouchitis that does not respond to 4 weeks of combination antibiotic therapy, it is critical to exclude secondary causes of chronic pouchitis, as listed in Table 1.

Treatment

The primary objectives in treating chronic pouchitis, including both CADP and CARP, are to treat pouch-related symptoms, improve quality of life, optimize pouch function, and avoid long-term antibiotic use. Other key goals include resolving both endoscopic and histologic inflammation and reducing inflammation-associated complications. For CADP specifically, treatment aims also to delay progression to CARP.

The treatment approaches for CADP and CARP differ based on the evolving understanding of pouchitis pathogenesis. This model suggests a spectrum where antibiotic-responsive pouchitis is primarily microbially mediated, antibiotic-refractory pouchitis is predominantly immune-mediated, and antibiotic-dependent pouchitis lies in between. Thus, in CADP, maintaining remission involves targeting both microbial and immune components. In contrast, treatment for CARP focuses more on the immune aspect, akin to therapies used for UC or Crohn's disease, both for induction and maintenance of remission.

Targeting the Microbial Component

Therapy directed at the microbial component of pouchitis can be divided into antibiotic, probiotic, prebiotic, and microbial transplantation strategies.

Antibiotics A 2-week course of conventional antibiotics (eg, ciprofloxacin, metronidazole, tinidazole [Tindamax, Mission]) effectively induces remission in patients with CADP. For CARP, extended 4-week regimens that combine therapies such as ciprofloxacin with rifaximin (Xifaxan, Salix) or metronidazole have proven effective.[58] Vancomycin at a dose of 125 mg twice daily was 50% effective at inducing remission and 75% effective at maintaining it over 6 months in a study of 41 patients with chronic pouchitis (CADP and CARP).[59] It is also effective for PSC-associated pouchitis and prepouch ileitis.[60]

Long-term antibiotic use, however, poses safety concerns. An observational study tracking 39 patients with CADP receiving maintenance antibiotics reported an 82% remission maintenance rate but noted side effects such as dysgeusia, nausea, and transient neuropathy. Alarmingly, 78% of patients developed resistance to bacteria such as *E coli* or *Klebsiella* spp.[61]

Rifaximin is favored for long-term use owing to minimal absorption and negligible resistance. A study maintained 51 patients with CADP on rifaximin (median dose 200 mg/day), achieving a 65% remission rate at 3 months, which declined to 37% by 12 months.[62] An alternative approach to maintain remission while theoretically reducing risk of microbial resistance,[63] but not supported by clinical studies,[64] is using the lowest effective dose of

antibiotic such as ciprofloxacin or tinidazole (500 mg daily or 250 mg twice daily) with intermittent gap periods of 1 to 2 weeks per month, or use of cyclical antibiotics (such as rotating between ciprofloxacin, metronidazole, and co-amoxiclav every 1-2 weeks).

Probiotics Early studies on the De Simone Formulation (Visbiome) showed an 85% remission maintenance at 9 months in treated groups vs none in placebo groups.[65,66] However, real-world data did not replicate these results.[67] A more recent randomized controlled trial (RCT) involving 15 patients with CADP found that all 10 patients randomized to probiotics with VSL#3 (similar to De Simone Formulation) maintained endoscopic remission for 2 months, unlike any of the 5 patients randomized to placebo.[68] The study also observed significant enhancements in the total number and diversity of intestinal bacteria with VSL#3.

Prebiotics Unlike probiotics, which introduce beneficial bacteria directly into the gut, prebiotics include dietary supplements or whole diet strategies that enhance the growth and activity of beneficial bacteria already present. This can lead to improvements in gut health and potentially help maintain remission in patients with pouchitis.

Observational Studies There are currently no direct interventional studies on the efficacy of prebiotics specifically for maintaining remission in chronic pouchitis. However, observational studies provide indirect evidence supporting potential benefits. A study showed that a diet rich in fruits (over 1.45 servings per day) led to a more diverse microbiota, with increased *Faecalibacterium* and *Lachnospira* spp, and a lower incidence of pouchitis, indicating a protective effect.[69] Another study reported that individuals without pouchitis history consumed more fruits daily than those with the disease.[15] Adherence to a Mediterranean diet correlated with lower pouchitis rates (26% vs 45%) and was associated with higher intake of fiber, vitamins, minerals, and antioxidants, further supporting its preventive potential (r=0.51; P<.001).[70]

Dietary Challenges High-fiber diets rich in fruits and vegetables can be problematic for patients with chronic pouchitis. Many patients with IPAA, especially those with a history of pouchitis, report dietary intolerances and link these diets to worsening symptoms.[15] For active cases such as CARP, dietary strategies are often less tolerated. A pilot study on the Monash Pouch diet, which aimed to mitigate pouchitis by reducing hydrogen sulfide and promoting carbohydrate fermentation, showed that patients with severe CARP found the diet difficult to tolerate and experienced exacerbated symptoms.[71] In a study on the Crohn's disease exclusion diet, dropout rates reached 45%, with a negative response correlated with severe endoscopic PDAI.[72]

Given these challenges, recommending prebiotic-rich diets requires careful consideration. Tailored dietary guidance from a dietitian specialized in gastrointestinal disorders is recommended to integrate prebiotics gradually. Continuous monitoring and adjustments based on individual responses are essential for successful prebiotic implementation in pouchitis management.

Fecal Microbiota Transplantation This approach has been investigated as a treatment for both CADP and CARP. The procedure, which involves the transfer of fecal bacteria from a healthy donor to a patient via methods such as nasogastric tube, gastroscopy, colonoscopy, or enema, aims to reestablish a healthy microbiota balance. Although fecal microbiota transplantation (FMT) in chronic pouchitis has yielded variable outcomes, it is generally considered safe and shows promising results in terms of clinical response and engraftment, effectiveness of multiple FMT administrations, or restoration of antibiotic sensitivity.

Clinical remission in chronic pouchitis appears to correlate with successful microbial engraftment. An open-label study reported that 4 of 5 patients achieved sustained clinical remission after receiving multiple FMTs into the jejunum every 4 weeks. One initially nonresponsive patient achieved remission following successful engraftment from a different donor.[73] Additionally, in a smaller study, 3 of 4 patients who successfully engrafted maintained remission 6 months after daily FMT enemas for 2 weeks, unlike those who did not engraft.[74] Conversely, a placebo-controlled RCT showed that only 1 of 5 patients maintained remission post-FMT, with the majority failing to engraft and relapsing within 4 weeks.[75]

Multiple FMT administrations have been shown to increase the chances of successful engraftment and clinical response.[14,73] Although single or dual FMTs via pouchoscopy demonstrated lower success rates, protocols involving multiple administrations, either into the jejunum or via enemas, achieved better outcomes.[75,76]

FMT may help restore sensitivity to antibiotics. In an open-label study, 2 of 4 patients with ciprofloxacin-resistant coliforms regained antibiotic sensitivity after FMT, enabling more effective antimicrobial therapy for their ongoing disease management.[77]

Targeting the Immune Component

5-Aminosalicylates Limited evidence supports the use of 5-aminosalicylates (5-ASAs) in chronic pouchitis. In a case-controlled trial with 26 patients with CARP, 5-ASAs were less effective at achieving clinical response and remission, with only a 50% success rate, than combination antibiotic therapy.[78]

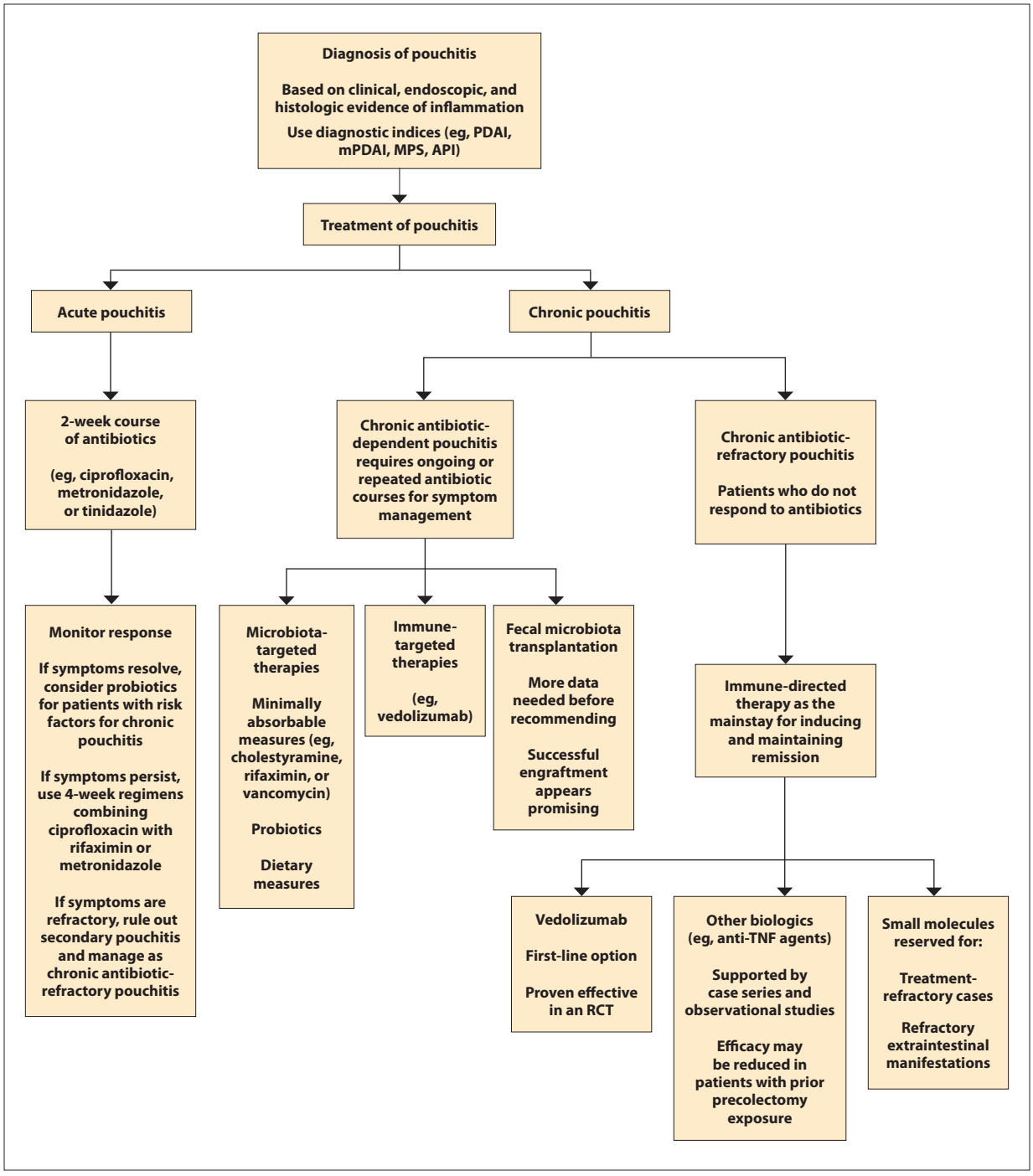

Figure 2. A step-by-step management algorithm for idiopathic pouchitis, guiding treatment decisions based on pouchitis phenotype.

API, Atlantic Pouchitis Index; mPDAI, modified Pouchitis Disease Activity Index; MPS, Monash Pouchitis Score; PDAI, Pouchitis Disease Activity Index; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Immunomodulators Azathioprine, 6-mercaptopurine, and methotrexate are seldom used as monotherapy in pouchitis. Cyclosporine and tacrolimus have shown some efficacy in case series, although their use is not widespread.[79,80]

Corticosteroids Oral budesonide is commonly used as a first-line treatment to induce remission in CARP, supported by small, open-label studies.[81,82] In 1 study, a 2-month course of budesonide 9 mg achieved complete remission in 20 patients with CARP.[82] Similarly, other

studies have shown the efficacy of oral corticosteroids in inducing remission in patients with active pouchitis refractory to antibiotics.[81]

Biologic Agents Biologic agents, particularly vedolizumab, an α4β7 integrin inhibitor, are increasingly used for both induction and maintenance therapy in CARP and as an antibiotic-sparing strategy in CADP.

Vedolizumab has become first-line treatment for CARP following the EARNEST trial, a phase 4 placebo-controlled study.[83] The trial involved 102 patients with CADP and CARP with active disease (mPDAI ≥5). Participants received 300 mg of vedolizumab or placebo intravenously at weeks 0, 2, 6, 14, and 22, along with ciprofloxacin until week 4. Remission was defined as an mPDAI score of 4 or less and a reduction from baseline of at least 2 points in the mPDAI total score. Vedolizumab achieved significant remission at week 14 in 31% of patients compared with 10% in the placebo group (P=.01). The benefits, including reduced ulcers and erosions, persisted through week 34, highlighting the potential of vedolizumab as a long-term treatment option for pouchitis.

Infliximab and adalimumab are frequently used anti-TNF agents in CARP and CADP, although data supporting their efficacy are mixed and mainly derived from retrospective studies and case series. One retrospective study showed a 45% remission rate with infliximab and 39% with adalimumab.[22] However, other studies reported lower response rates and noted that precolectomy exposure to anti-TNF agents could lead to less favorable responses.[84,85] A small RCT of adalimumab vs placebo in 13 patients with CARP failed to demonstrate efficacy for adalimumab at week 14.[86]

Ustekinumab's efficacy for treating CARP relies largely on data from case series and retrospective studies. A meta-analysis that included 2 retrospective studies and 1 case series found that ustekinumab led to a clinical response in 63% (22/35 patients) within 4 to 12 weeks, with no significant variation in response based on the dosage or interval of administration.[87] Further evidence from a multicenter open-label study involving 22 patients with CARP, of whom 12 had prior biologic treatments, demonstrated that ustekinumab achieved mPDAI-defined remission in 27% of patients at week 16 and 36% at week 48.[88]

An RCT of alicaforsen (anti–ICAM-1) therapy failed to meet any primary or major secondary endpoints (NCT02525523), although results have yet to be published in full.[89]

Small Molecules Small molecules, including JAK inhibitors (tofacitinib and upadacitinib [Rinvoq, AbbVie]) and a selective sphingosine-1 phosphate receptor modulator (ozanimod [Zeposia, Bristol Myers Squibb]), have shown mixed outcomes in treating chronic pouchitis, particularly in CARP.

As a JAK inhibitor, tofacitinib has been employed primarily for patients with CARP who did not respond to anti-TNF agents, and has shown varied effectiveness. In a pilot study involving 13 patients, clinical remission was achieved in 31%.[90] Another smaller retrospective review of 8 patients reported only 1 patient achieving a clinical response.[91] Preliminary results from a multicenter open-label induction trial with randomized withdrawal involving 33 patients (with one-third biologic-exposed) demonstrated that at week 8, 55% achieved a clinical response, defined as a reduction in clinical PDAI of more than 2, and 48% reached mPDAI-defined remission.[92]

Limited to a single case series, upadacitinib's use in CARP involved 3 patients, none of whom showed a clinical response within 6 to 16 weeks.[93]

Figure 2 outlines a management algorithm for idiopathic pouchitis.

Ancillary Measures

Pelvic dyssynergia, prevalent in up to 75% of patients with IPAA, particularly those with chronic pouchitis, can lead to symptomatic incomplete pouch emptying.[31] Biofeedback therapy has been shown to provide mild-to-moderate improvement in symptom scores and may help manage fecal stasis–associated pouchitis.[31]

Endoscopic interventions are effective for structural issues such as strictures and prolapse, which obstruct defecation and can alleviate symptoms of fecal stasis–associated pouchitis.[1] Inflammatory polyps, which are linked to CARP and can cause diarrhea, discomfort during defecation, and anemia, are especially treatable endoscopically if they are larger than 1 cm.[58]

Pouch diversion, with or without pouch excision, is also an option. Pouch failure affects 5% to 10% of patients over the first decade. For patients with therapy-resistant CARP, permanent diversion and ileostomy can significantly enhance quality of life. The choice to combine diversion with pouch excision involves complex decision-making, owing to a 35% to 40% risk of a persistent perineal sinus that may never heal.[58] Hyperbaric oxygen therapy combined with a myocutaneous flap may seal the sinus.[94] Conversely, leaving the pouch in situ risks diversion pouchitis, pouch strictures (50%-60%), and dysplasia.[58]

Future Directions

As the understanding of chronic pouchitis evolves, research continues into its complex pathogenesis, diagnostic challenges, and treatment options. Enhanced understanding of both microbial and immune components

is crucial. Studies are exploring the roles of short-chain fatty acids, hydrogen sulfide, and volatile organic compounds in the development of pouchitis.[71] Similarly, advances in immunology are identifying new cellular populations and markers such as IL-1β+LYZ+ myeloid cells, FOXP3+BATF+ T cells, and microRNAs that may influence the pathogenesis.[1] Identifying risk factors is vital for developing primary and secondary prophylaxis strategies. The DEPP study in Australia is a multicenter, longitudinal, observational study examining the impacts of diet, antibiotic use, probiotics, pelvic dyssynergia, and stress on the progression of pouchitis (ACTRN12624000016538). Current diagnostic indices for pouchitis are only partially validated, spurring research into new indices such as the MPS and API. The ideal diagnostic tool would accurately reflect disease presence and severity, incorporate reliable and easy-to-use components, and respond well to treatment changes. Research is needed to refine strategies targeting the microbial component of pouchitis, such as rotating antibiotics to manage resistance, determining optimal probiotic doses and formulations, and establishing guidelines for FMT regarding administration routes, doses, donor selection, frequency, and intervals. Studies on advanced therapies for IBD, including IL-23 p19 inhibitors such as mirikizumab (Omvoh, Lilly) and risankizumab (Skyrizi, AbbVie) as well as small molecules including rifamycin, aim to expand treatment options through case series, prospective studies, and randomized trials. Tailoring treatments based on specific inflammatory markers, although challenging, is an anticipated approach and similar for other treatments for IBD.

Conclusions

Chronic pouchitis is a challenging and common complication of IPAA, with pathogenesis evolving from microbially mediated antibiotic-sensitive to antibiotic-resistant and immune-mediated processes. However, modifiable risk factors for disease progression can be targeted. A reliable diagnostic index is needed for both clinical trials and practice. When using PDAI or mPDAI, the reduced reliability of endoscopic features should be noted, especially when diagnosing pouchitis without ulcerations or bleeding. Newer diagnostic indices appear more reliable and responsive, given the ordinal nature of their categories.

Courses of antibiotics, including for acute antibiotic-responsive pouchitis, should be followed by measures to reduce dysbiosis risk, particularly in high-risk patients. Probiotics may be considered. Although dietary adjustments to include more fruits and vegetables can be challenging because of perceived intolerances, working with an experienced dietitian may be beneficial.

In CADP, maintaining remission can be achieved through microbiota-targeted therapies (such as minimally absorbable antibiotics, probiotics, and dietary measures) or immune-targeted measures. More data are needed before recommending FMT, but successful engraftment appears promising.

In CARP, immune-directed therapy is the mainstay for inducing and maintaining remission. Vedolizumab should be considered first-line treatment, as it is the only biologic agent proven effective for CARP in an RCT. The efficacy of other biologic agents is based on case series and observational studies and may be reduced by precolectomy exposure. Small molecules may be reserved for patients with treatment-refractory disease or associated extraintestinal manifestations.

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