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Pouchitis unveiled: exploring clinical features, diagnosis, and cutting-edge treatments

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***Abstract*:** Last decades led to a revolution in the management of ulcerative colitis (UC), due to the development of novel advanced therapies and the identification of increasingly ambitious therapeutic goals. Nevertheless, a subset of patients, refractory to available therapies, still requires proctocolectomy with ileal pouch-anal anastomosis (IPAA). Pouchitis, an inflammatory condition of the ileal pouch, is the most common long-term complication of IPAA, affecting almost one-half of patients in the first 10 years after surgery. Symptoms of pouchitis include increased stool frequency, urgency, and abdominal discomfort, significantly affecting patients' quality of life. Traditionally the mainstay treatment of acute pouchitis involves the use of antibiotics, but one-fifth of patients develop chronic pouchitis (CP), which may be dependent or resistant to antibiotics, posing significant challenges in the management of this condition. Currently, there is still no consensus on the optimal management for CP, though recent progress in understanding the pathophysiology of pouchitis has paved the way for innovative therapeutic approaches, based on biological therapies and small molecules. This review aims to discuss the recent advanced therapies available for pouchitis and provide a comprehensive review on the topic to guide physicians in their clinical practice.

Keywords: pouch, pouchitis, proctocolectomy, ulcerative colitis

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Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) affecting the colon, characterized by a relapsing and remitting mucosal inflammation, that can lead to severe disability.[1]

Last decades brought about a revolution in the management of UC, due to the development of novel advanced therapies and the identification of increasingly ambitious therapeutic goals.[2,3] Nevertheless, remission rates among patients with UC treated with new therapeutic agents remain modest, typically ranging from 20% to 30%, facing a so-called therapeutic ceiling.[4] Consequently, approximately 10%–15% of patients ultimately require surgery due to treatment failure.[5] Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred procedure for most UC patients requiring colectomy, whether due to acute severe ulcerative colitis or medically refractory disease.[6]

Surgical and mechanical complications of IPAA—such as anastomotic leaks, fistulae, pelvic sepsis, strictures, and pouch prolapse—are relatively common and primarily related to the procedure itself. For this reason, ileo-anal pouch surgery should be performed by experienced surgeons at high-volume centers.[7,8] Indeed, a recent analysis from the Surgical Workload and Outcomes Research Database examined pouch procedures performed in England between April 2009 and December 2016. The analysis revealed that over 80% of healthcare trusts performing these procedures did so at a very low volume, with fewer than five surgeries annually. Alarmingly, many

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surgeons carried out only one pouch procedure over a nearly 5-year period, highlighting a concerning reliance on "occasional pouch surgeons."[9]

However, beyond mechanical complications, inflammatory conditions of the pouch are even more prevalent, with pouchitis being the most common issue, affecting nearly 50% of patients within the first 2 years after IPAA.[10] Pouchitis is a nonspecific inflammatory condition affecting the ileal pouch reservoir, clinically characterized by variable symptoms, including increased stool frequency, rectal bleeding, cramping abdominal pain, urgency, tenesmus, and fever.[11]

The etiopathogenesis of pouchitis remains unclear, probably involving multiple factors, including the complex balance between the host immune response of the UC patient and the gut microbiota.[12] Notably, pouchitis occurs significantly more frequently in patients with UC compared to those with familial adenomatous polyposis (FAP) undergoing IPAA. A meta-analysis reported a pouchitis prevalence of 32% in UC patients compared to 6% in FAP patients, with an odds ratio of 4.95.[13]

Pouchitis typically occurs after the closure of the ileostomy, once fecal flow through the pouch is restored.[14] Accordingly, numerous studies have identified dysbiosis, or microbial imbalance, as a key factor in its pathogenesis.[14–16]

Histological analysis of normal ileal pouch biopsies reveals a transition from a typical ileal microbiota to one resembling the colonic microbiota. This shift is marked by an increased prevalence of Proteobacteria species and a decrease in Bacteroidetes, Firmicutes, Ruminococcaceae, and Lachnospiraceae. In addition, patients with pouchitis demonstrate reduced bacterial diversity compared to those with a healthy pouch.[17]

Genetic predispositions also appear to play a role. Polymorphisms in genes associated with innate immune responses and microbial recognition—such as *NOD2/CARD15*, the interleukin-1 (IL-1) receptor antagonist gene, and Toll-like receptor genes—have been linked to an increased risk of pouchitis.[18–20] Other contributing factors include a deficiency in short-chain fatty acids, an excess of bile acids reaching the pouch, mucosal ischemia, oxidative stress, and heightened intestinal permeability.[14]

Several risk factors for pouchitis have been identified, including an extensive UC before IPAA, backwash ileitis, extraintestinal manifestations (especially primary sclerosing cholangitis), and regular use of non-steroidal anti-inflammatory drugs (NSAIDs).[11,21] Interestingly, diet may also influence pouchitis development.[22] A higher intake of fruit appears to have a protective effect.[23] Similarly, adherence to a Mediterranean diet, rich in fiber and antioxidants, may play a beneficial role in reducing pouchitis after ileoanal pouch surgery. Specifically, studies indicate that greater adherence to this diet correlates with lower levels of inflammatory markers, such as fecal calprotectin and C-reactive protein, and a trend toward a reduced incidence of pouchitis.[24]

Pouchitis classification

Under the umbrella term of pouchitis are often grouped together different clinical scenarios (Table 1). With regard to the causes, it is mandatory to distinguish the idiopathic form of pouchitis from the secondary forms, which, based on the clinical presentation, are indistinguishable. Secondary pouchitis, accounting for 30% of cases, has several causes, including infections (e.g., *Clostridium difficile*, cytomegalovirus, etc.), ischemia, radiotherapy, and NSAID usage.[25] Moreover, other inflammatory conditions, namely cuffitis or Crohn's disease of the pouch, and mechanical disorders, such as pouch prolapse, fistulas, pouch functional outlet obstruction, and nonrelaxing pelvic floor dysfunction, should always be ruled out.[26]

Traditionally, based on disease duration, pouchitis can be defined as acute ($\leqslant$4 weeks) or chronic ($>$4 weeks), depending on the symptom duration.[27] Similarly, pouchitis is considered chronic if there are four or more episodes within a year.[28]

Moreover, this inflammatory disorder can also be classified, depending on the reaction to antibiotic treatment (which is the mainstay treatment of acute pouchitis), into antibiotic-responsive, antibiotic-dependent (if continued antibiotic therapy is necessary to maintain remission), and antibiotic-refractory (meaning it does not respond to $\geqslant$4 weeks of standard antibiotical therapy).[11]

Table 1. Classification, etiologies, and differential diagnosis of pouchitis.

Pouchitis and inflammatory disorders of the pouch (according to AGA Guidelines)	
Intermittent pouchitis	Occasional acute episodes, interspersed with long periods of normal function
CADP	Recurrent episodes responding to antibiotics but relapsing after cessation
CARP	Persistent/recurring symptoms, not responding to antibiotics
Crohn's-like disease of the pouch	Fistula/stricture of the pouch or pre-pouch ileum/(pre-pouch ileitis)
Etiologies	
Idiopathic pouchitis	Multifactorial etiology (e.g., dysbiosis and genetic predisposition)
Secondary pouchitis	Infections (e.g., *Clostridium difficile* and Cytomegalovirus), ischemia, NSAIDs usage, radiotherapy
Differential diagnosis	
Cuffitis	Inflammation of the remaining rectal cuff
Mechanical disorders of the pouch	For example, pouch prolapse, fistulas, pouch functional outlet obstruction, and nonrelaxing pelvic floor dysfunction

AGA, American Gastroenterological Association; CADP, chronic antibiotic-dependent pouchitis; CARP, chronic antibiotic-refractory pouchitis; NSAID, non-steroidal anti-inflammatory drugs.

Recently the American Gastroenterological Association (AGA) published a new clinical practical guideline on the management of pouchitis; in the paper, AGA provided pragmatic definitions of pouchitis and inflammatory disorders of the pouch[10]:

- Intermittent pouchitis: Occasional acute episodes of pouchitis, with typical symptoms, responding to antibiotics or resolving spontaneously, followed by long periods of normal pouch function.
- Chronic antibiotic-dependent pouchitis (CADP): Recurrent episodes responding to antibiotics but relapsing soon after cessation, often requiring continuous antibiotics.
- Chronic antibiotic-refractory pouchitis (CARP): Persistent or recurring symptoms not responding to antibiotics, requiring alternative treatments.
- Crohn's-like disease of the pouch: Presence of a fistula (perianal or of the pouch) that developed at least 12 months after the final stage of IPAA surgery/stricture of the pouch body or pre-pouch ileum/presence of pre-pouch ileitis. Sometimes this entity can coexist with pouchitis.

It is worth noting that the concept of "Crohn's-like disease of the pouch" is subject to lively debate. While the diagnosis of CD is relatively clear-cut when complications such as fistulae or strictures are present, the use of pre-pouch ileitis as a diagnostic criterion remains controversial.[29] Although many studies have employed pre-pouch ileitis as an indicator of de novo CD,[21] some evidence suggests that it may not be associated with the development of CD-like complications.[30,31] In addition, pre-pouch ileitis is relatively common, occurring in approximately 5% of IPAA patients.[32]

Moreover, recent interesting translational data show that Crohn's-like disease of the pouch in patients with UC likely represents a distinct entity of IBD.[33] Single-cell analyses conducted with single-cell RNA sequencing and mass cytometry, revealed that this entity is characterized by increased inflammatory immune responses, different from UC, including elevated T helper 17 cells, inflammatory monocytes, and fibroblasts, along with significant endoplasmic reticulum

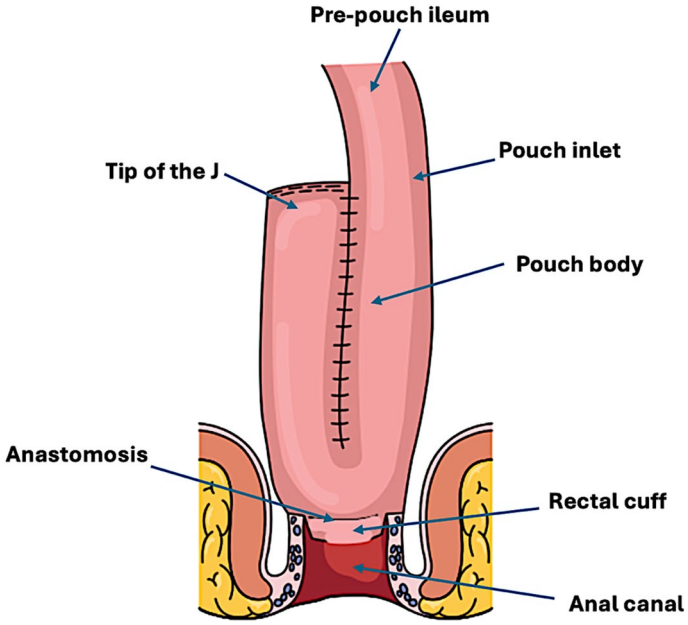

Figure 1. Normal J pouch anatomy.
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stress in both immune and nonimmune cells.[33] These findings could pave the way for new targeted therapies specifically for CADP.

Diagnosis

Patients with a functioning pouch typically report four to eight bowel movements per day and one to two bowel movements at night.[34] When a patient who underwent an IPAA presents with increased stool frequency, abdominal pain, or rectal bleeding it is important to establish the correct diagnosis to optimize the management and treatment.

In addition to an initial careful clinical evaluation (which should include the patient's drug history), it is important to prescribe blood tests and also stool tests (stool cultures, *C. Difficile* toxin, and parasites) to rule out infectious etiologies.[35]

Moreover, a contrast X-ray of the pouch, known as a "pouchogram," can be useful to evaluate pouch compliance and emptying, or the potential presence of strictures and fistulas. If there is a suspicion of fistulas, pelvic magnetic resonance imaging should be conducted too. On the other hand, in cases where fecal incontinence is the main symptom, particularly if pouch inflammation is not present, anorectal manometry and/or anal ultrasound are recommended to diagnose potential dysfunction of the anal sphincter or pelvic floor.[36]

Undoubtedly, the endoscopic and histological evaluation of the pouch body, the afferent limb, and the rectal cuff is the most important tool to make the correct diagnosis, and pouchoscopy with mucosal biopsy should be always done when symptoms of pouchitis are present.[37]

During pouchoscopy, the examiner should carefully evaluate the anal canal, rectal cuff, pouch body, afferent limb, inlet, J-tip, and anastomosis (Figure 1).

Idiopathic or primary pouchitis is typically identified endoscopically by diffuse inflammation within the pouch body, while the pre-pouch ileum, just above the pouch inlet, generally remains unaffected.[28]

Endoscopic findings of pouchitis may include mucosal edema and erythema, loss of vascular pattern, friability, granularity, bleeding, erosions, and ulcerations. However, solitary erosions or ulcers along the staple line should not be considered diagnostic indicators of pouchitis, since they can also be caused by ischemic damage.[37,38] In addition, cuffitis, an inflammation of the retained

rectal mucosa above the anal transitional zone following the anastomosis is common, occurring in up to 30.1% of pouch patients. Biopsies of the cuff can help in diagnosing cuffitis.[39]

Histological findings of pouchitis are also nonspecific and include acute inflammation with polymorphonuclear and leukocyte infiltration, crypt abscesses, ulceration, and a chronic inflammatory infiltrate.[40]

Several diagnostic tools are available to evaluate and standardize pouch inflammation.[41] Among these, the Pouchitis Disease Activity Index (PDAI) is the most widely used, whereas not validated. This index comprises subscores for symptoms (0–6 points), endoscopic findings (0–6 points), and histological features (0–6 points). A total PDAI score of $\geqslant$7 points is indicative of pouchitis.[42] In addition, a modified version of PDAI (mPDAI), excluding the histological score, has been proposed, demonstrating similar diagnostic accuracy to the traditional PDAI, with a threshold score of $\geqslant$5 for diagnosing pouchitis.[43]

Pouchitis management

The disease progression of pouchitis is variable. While around one-third of patients experience only one episode of acute pouchitis, the remaining two-thirds suffer from recurrent pouchitis. Among these, approximately one-third develop CARP.[11] Several treatments have been evaluated to prevent and treat pouchitis, such as antibiotics, probiotics, corticosteroids, and advanced immunosuppressive therapies (e.g., biologics and oral small molecule drugs). Nevertheless, there is a lack of data with strong evidence, such as from randomized controlled trials (RCTs).[44]

Treatment and prevention of acute pouchitis

Antibiotic therapy. Traditionally, despite the lack of controlled trials, acute pouchitis management involves the use of antibiotics, given the pathogenic role of fecal stasis and bacterial overgrowth in the development of this condition. Metronidazole (500 mg orally twice or 3 times daily) or ciprofloxacin (Ciprofloxacin 500 mg orally twice daily) for 2 weeks are the most commonly used antibiotics for initial therapy, with favorable responses in most cases.[10] A small, randomized trial comparing ciprofloxacin (1 g/day) and metronidazole (20 mg/kg/day) for 2 weeks found that ciprofloxacin significantly reduced the PDAI score from 10.1 ± 2.3 to 3.3 ± 1.7 ($p = 0.0001$), while metronidazole reduced it from 9.7 ± 2.3 to 5.8 ± 1.7 ($p = 0.0002$). Ciprofloxacin showed greater efficacy compared to metronidazole in terms of total PDAI ($p = 0.002$), symptom score ($p = 0.03$), and endoscopic score ($p = 0.03$), with fewer adverse events (33% vs none).[45] On the other hand, the risk of tendon ruptures with ciprofloxacin is well recognized.[46] In patients that do not respond to single-antibiotic therapy an approach using a combination of antibiotics may be more effective.[10] Several antibiotics have also been tested successfully in small uncontrolled, open-label trials. These included vancomycin, rifaximin, erythromycin, tetracycline, amoxicillin/clavulanate, and tinidazole, all of which have been utilized in clinical practice to treat acute pouchitis.[10]

Probiotics. Probiotics, such as VSL#3, can be used both to prevent the first episode of pouchitis (primary prophylaxis) and to prevent recurrence in patients with an episode of antibiotic-responsive pouchitis (secondary prophylaxis).[47,48]

An RCT evaluated the efficacy of VSL#3 in preventing pouchitis: 40 patients with IPAA for UC were randomized to receive either VSL#3 or placebo for 1 year. The results showed that only 10% of the patients treated with VSL#3 experienced an episode of acute pouchitis, compared to 40% in the placebo group ($p < 0.05$). Additionally, VSL#3 significantly improved the patient's quality of life as measured by the IBD Questionnaire, while the placebo did not have the same effect.[49]

Moreover, an RCT by Gionchetti evaluated the efficacy of VSL#3 for the secondary prophylaxis of chronic pouchitis (CP). Forty patients in endoscopic remission were randomized to receive either VSL#3 or a placebo for 9 months. Only 15% of patients in the VSL#3 group experienced a relapse, compared to 100% in the placebo group ($p < 0.001$). In addition, fecal concentrations of beneficial bacteria increased significantly in the VSL#3 group.[48]

Later on, in a randomized, placebo-controlled study involving 17 patients with UC who had undergone IPAA, the efficacy of *Clostridium butyricum* MIYAIRI in preventing pouchitis was evaluated. The participants were divided into two groups: Nine patients received MIYA-BM®, and

eight received a placebo. Over the study period from 2007 to 2013, only one out of nine patients in the MIYA-BM group developed pouchitis, compared to four out of eight in the placebo group.[50]

Similarly, a study involving 117 patients who underwent IPAA for UC evaluated the effectiveness of daily intake of the probiotic *Lactobacillus rhamnosus* GG in delaying the first onset of pouchitis. Among the 39 patients who received the probiotic immediately after surgery, only 7% developed pouchitis within 3 years, compared to 29% in the 78 patients who did not receive the probiotic ($p = 0.011$).[51]

Treatment of CADP and CARP

Antibiotic therapy. In patients with CADP, who respond to antibiotics but relapse shortly after stopping antibiotics, a strategy that could be adopted and is suggested by AGA is chronic antibiotic therapy, at the lowest effective dose (e.g., ciprofloxacin 500 mg daily or 250 mg twice daily) with intermittent gap periods (approximately 1 week per month), or use of cyclical antibiotics (e.g., changing between ciprofloxacin, metronidazole, and vancomycin every 1–2 weeks; Table 2).[10] On the other hand, an interesting observational study involving 39 patients with CADP revealed that prolonged antibiotic use led to sustained remission in just 21% of patients over a median follow-up of 102 months. Moreover, extended antibiotic administration was linked to the development of antibiotic-related adverse effects (28% of patients) and antibiotic resistance (78% of stool samples).[52]

Steroids. As already mentioned, there is also a minority of patients with recurrent pouchitis with inadequate response to antibiotics (CARP).[11] These patients may benefit from corticosteroid treatment; particularly, oral or topical budesonide is the preferred formulation. Steroids should be used for a short duration (<8–12 weeks) with consideration of steroid-sparing therapies for long-term use.[10]

Gionchetti et al. conducted a study to evaluate the effectiveness of oral budesonide in patients with CARP following IPAA for UC. The study included 20 patients with active pouchitis unresponsive to 1 month of antibiotic therapy. Patients received oral budesonide (9 mg/day) for 8 weeks. In total, 75% of patients achieved remission (clinical PDAI score of 2 or less, endoscopic score of 1 or less, and a total PDAI score of 4 or less). The median total PDAI score improved significantly from 14 before treatment to 3 after treatment ($p < 0.001$). In addition, the quality of life, measured by the IBD Questionnaire, improved significantly from a median score of 105–180 ($p < 0.001$).[53]

Similarly, Sambuelli et al. evaluated with a prospective, double-blind, double-dummy controlled trial, the efficacy and tolerability of budesonide enema compared to oral metronidazole for the treatment of pouchitis. Twenty-six patients with active pouchitis (PDAI ⩾7) and no recent treatment were randomly assigned to receive either budesonide enema (2 mg/100 mL daily) with placebo tablets or oral metronidazole (0.5 g twice daily) with placebo enema for 6-week. Results showed significant improvement in disease activity with both treatments after the first week ($p < 0.01$), though improvements moderated and stabilized by 4 weeks for both groups. Per protocol analysis indicated similar efficacy, with 58% of patients on budesonide enema and 50% on metronidazole showing significant improvement (decrease in PDAI ⩾3), with an odds ratio of 1.4 (CI 0.2–8.9). Adverse effects were more common in the metronidazole group (57%) compared to the budesonide group (25%).[54]

Advanced therapies. Current guidelines suggest, both for CARP and CADP, the use of advanced immunosuppressive therapies; in the case of CADP these therapies should be used in lieu of chronic, continuous antibiotic therapy, particularly in patients who are intolerant to antibiotics or when patients and/or providers are concerned about risks of long-term antibiotic therapy.[10] While all therapies approved for UC may be used, including TNF-a antagonists (e.g., infliximab, adalimumab, golimumab, and certolizumab pegol), vedolizumab, ustekinumab, mirikizumab, and small molecules (tofacitinib, upadacitinib, filgotinib, and ozanimod), vedolizumab is the only advanced therapy that received regulatory approval from the European Medicines Agency (EMA) for CP itself.[55]

It is worth noting that advanced therapies that patients have used before colectomy may be reconsidered,[10] even if a retrospective study by Kayal et al.[56] suggested that patients with

Table 2. Treatment strategies and considerations for CARP and CADP.

Pouchitis type	Treatment strategy	Details/considerations
CARP	**Initial approach: Steroid therapy for induction**	- Budesonide (oral or topical) for short-term use (⩽8–12 weeks) - Switch to steroid-sparing therapies after induction.
	Advanced therapies for induction and maintenance	- **Vedolizumab** (first option, EMA approved for chronic pouchitis) - Other options: TNF-α antagonists, ustekinumab, mirikizumab, small molecules (tofacitinib, upadacitinib, filgotinib, ozanimod) - **Considerations:** therapies that patients used before colectomy may be reconsidered.
CADP	**Initial approach: chronic antibiotic therapy**	- **Low-dose antibiotics** (e.g., ciprofloxacin 500 mg daily or 250 mg twice daily) - **Cyclical antibiotic therapy**: rotate antibiotics every 1–2 weeks (ciprofloxacin, metronidazole, and vancomycin) - **Considerations**: Development of antibiotic resistance (78%) and adverse effects (28%) **Consider advanced therapies early in CADP if antibiotics are not well tolerated or if long-term use presents risks.**
	If concerned about long-term antibiotic use: steroid therapy for induction	- Budesonide for short-term use (same as CARP).
	Advanced therapies for induction and maintenance (same as CARP)	- Start with **vedolizumab** (EMA approved for chronic pouchitis) - Other options include TNF-α antagonists, ustekinumab, and small molecules.

CADP, chronic antibiotic-dependent pouchitis; CARP, chronic antibiotic-refractory pouchitis; EMA, European Medicines Agency.

anti-TNF exposure prior to colectomy were less likely to achieve clinical remission with a drug of the same class, compared to patients who were anti-TNF naïve preoperatively.

Treatment of Crohn's-like disease of the pouch

Even if there is a lack of evidence on the effectiveness of corticosteroids in patients with Crohn's-like disease of the pouch, given the experience and evidence on the efficacy in patients with luminal CD, these medications are likely to be effective in the management of Crohn's-like disease of the pouch. AGA therefore suggests the use of controlled ileal-release budesonide. Steroids should generally be used for a short duration (<8 weeks) with consideration of steroid-sparing therapies for long-term use, such as advanced immunosuppressive therapies.[10]

Advanced therapies for pouchitis

Cell adhesion molecule inhibitors

Vedolizumab. Vedolizumab (VDZ) is a fully humanized monoclonal antibody that selectively targets α4β7 integrin.[55]

A recent multicenter cohort conducted in the United States enrolled 83 patients with CARP or Crohn's-like disease of the pouch, treated with VDZ. Among these, 71.1% of patients achieved clinical response and 19.3% achieved clinical remission.[57] Similarly, a German study demonstrated that 64% (9 of 14) of patients achieved clinical remission after 14 weeks of VDZ treatment.[58]

The most important data was derived from the recent, long-awaited EARNEST RCT (Figure 2). The trial enrolled 102 patients with

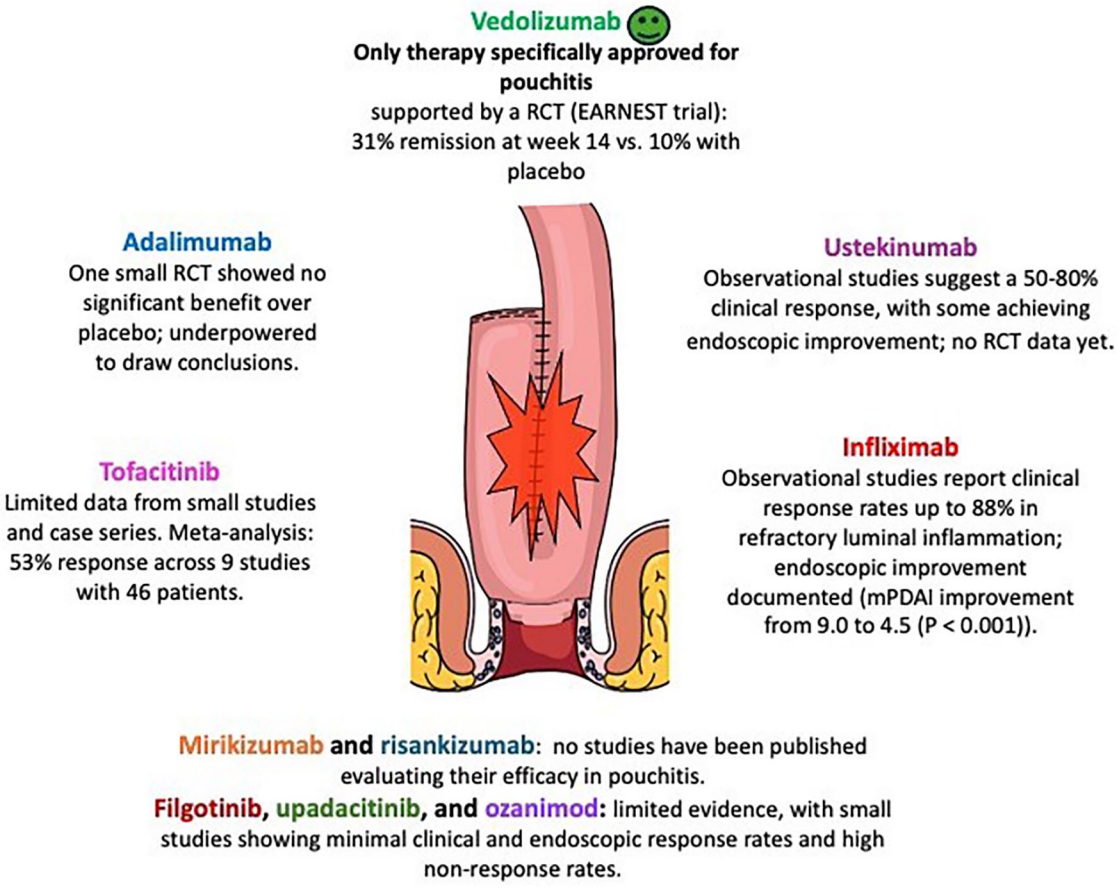

Figure 2. Available advanced therapies for pouchitis.
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CP, randomized 1:1 to receive vedolizumab or placebo. Inclusion criteria encompassed at least three episodes of recurrent pouchitis within the last 12 months, or continuous antibiotic therapy for a minimum of 4 weeks immediately prior to the baseline endoscopy. Throughout the trial, all patients received oral ciprofloxacin 500 mg twice daily from randomization until week 4, with additional antibiotics allowed in case of persistent symptoms. The primary endpoint was remission at week 14, defined as a modified PDAI (mPDAI) score <4 with a reduction of $\geqslant 2$ points from baseline.[59]

At week 14, 31% of vedolizumab-treated patients achieved remission compared to 10% in the placebo group (95% confidence interval (CI), 5–38; $p=0.01$). By week 34, remission incidence remained higher in the vedolizumab group, with a 17-percentage point difference (95% CI, 0–35).[59] Notably, among the 51 vedolizumab-treated patients, 57% reported continuous antibiotic use immediately before baseline, and 22.2% and 21.2% of patients still used antibiotics at the week 14 and week 34 assessments, respectively.[59]

Alicaforsen. Alicaforsen is a 20-base antisense oligonucleotide designed to inhibit the production of ICAM-1, a crucial molecule involved in leukocyte adhesion and migration.

An initial open-label study on 12 patients with chronic, unremitting pouchitis demonstrated that nightly administration of 240 mg alicaforsen enema for 6 weeks led to significant improvements. The PDAI decreased from 11.42 at baseline to 6.83 at week 6 ($p=0.001$). Significant reductions were observed in both endoscopic and clinical symptom subscores. Additionally, 7 out of 12 patients achieved remission by week 6. The

treatment was well tolerated with no serious side effects reported.[60]

However, a larger randomized, placebo-controlled trial on 138 subjects with CP found no significant difference in endoscopic remission between alicaforsen enemas and the placebo group. Clinical remission was achieved in 33.8% of the alicaforsen group compared to 26.2% in the placebo group, but this difference was not statistically significant.[61]

IL inhibitors

Ustekinumab. Ustekinumab is a human monoclonal antibody against the p40 subunit shared by both IL-12 and IL-23. Despite the absence of RCTs, some observational studies demonstrated the efficacy of ustekinumab (UST) for CP. A retrospective single-center study enrolled 24 patients with CARP to receive ustekinumab with standard dosing, with a median follow-up time of 12.9 months (interquartile range (IQR) 7.9–16). Twelve patients (50%) had a clinical response, with the median number of daily bowel movements decreasing from 8 to 6 ($p = 0.002$). Thirteen patients had pouchoscopies available post-ustekinumab treatment. In these patients, the median endoscopic subscore of the PDAI decreased from 5 (IQR, 3–6) to 4 (IQR, 2–5), ($p = 0.016$).[62]

Similarly, Dalal et al. demonstrated that patients with CP had a favorable response to UST therapy with standard dosing and also after dose intensification. In particular, of the 46 patients enrolled, 80.4% (37) had clinical response 8–16 weeks after UST initiation, 50.0% (23 of 46) underwent dose intensification after a median of 223 days, and 63.6% (14 of 22; 1 patient was lost to follow-up) had clinical response 8–16 weeks after dose intensification.[63]

A recent prospective study by Outtier et al. evaluated the efficacy of ustekinumab (6 mg/kg IV at baseline and 90 mg sc every 8 weeks thereafter) on 22 patients with CP. At week 16, 27.3% of patients achieved steroid-free remission (mPDAI <5 and reduction by $\geqslant 2$ points), increasing to 36.4% by week 48. The median mPDAI decreased from 8 to 7 at week 16 ($p = 0.007$) and 4 at week 48 ($p < 0.001$).[64]

Mirikizumab and risankizumab. Mirikizumab and risankizumab are second-generation IL inhibitors, targeting selectively the p19 subunit of IL-23, recently approved by the FDA and EMA for the treatment of UC and CD, respectively. The safety and efficacy of these biologic therapies in the treatment of CARP or CADP have not been described yet in the literature.

TNF-a inhibitors

Infliximab. Some observational studies assessed the efficacy of infliximab, a chimeric (human-murine) monoclonal IgG1 anti-TNF-alpha antibody, in CP. An early retrospective and multicenter study by Acosta et al. evaluated the efficacy of infliximab (IFX) for the treatment of CP in 33 patients. At week 8, 21% of patients achieved complete response, while 63% exhibited partial clinical response. At weeks 26 and 52, 33% and 27% achieved complete response and 33% and 18% showed partial clinical response, respectively.[65] Similarly, a Belgian case series by Ferrante et al. identified 28 IPAA patients who received IFX for refractory luminal inflammation (pouchitis and/or pre-pouch ileitis, $n = 25$) and/or pouch fistula ($n = 7$) and reported, at week 10, a clinical response (14 partial, 8 complete) of 88% in patients with refractory luminal inflammation. Six patients (86%) showed fistula response (three partial, three complete). The mPDAI significantly dropped from 9.0 (IQR 8.0–10.0) to 4.5 (3.0–7.0) points ($p < 0.001$).[66] In addition, Kelly et al. identified that 62.6% of patients with refractory pouchitis or Crohn's disease of the pouch had sustained response at week 48 to treatment with IFX (29.6% complete response). Complete response was defined as symptomatic and endoscopic resolution with mPDAI <5; partial response included mPDAI improvement >2.[67]

Adalimumab. In 2019 the results from an RCT evaluating the efficacy of adalimumab (ADA), a human monoclonal TNF-alpha antibody, in 13 patients with CP were published. ADA showed no benefit compared to placebo. However, as only 9 of 13 patients completed the 12-week study, definitive conclusions could not be drawn due to underpowering.[68]

Moreover, a recent systematic review and meta-analysis assessed the efficacy of anti-tumor necrosis factor therapy in patients with CARP or with Crohn's disease of the pouch. The analysis encompassed 313 patients treated with anti-TNFs (194 with infliximab and 119 with

adalimumab). In patients with CARP, while the rate of clinical remission following anti-TNF induction therapy was low (10%), the rate of long-term complete remission in the same subgroup at a median time of 12 months was 33%. Indeed, the remission rate after induction therapy seemed to be higher in Crohn's disease of the pouch (64%).

Small molecules: Janus kinase inhibitor and sphingosine 1-phosphate receptor modulator

Janus kinase inhibitors (JAKi), namely tofacitinib, upadacitinib, and filgotinib are small molecules suppressing the action of JAK, an intracellular tyrosine kinase.

Preclinical studies suggested an increased mucosal expression of STAT, coupled with its normalization through antibiotic therapy, in patients with pouchitis. This provides biological plausibility for the effectiveness of JAK-STAT signaling pathway inhibition in CADP e CARP.[69]

Tofacitinib. The initial introduction of a small molecule drug for UC came in the form of tofacitinib, which targets JAK1 and JAK3. Currently, there is limited information available regarding the utilization of tofacitinib in the treatment of chronic inflammatory pouch disorders.

In 2023, Syal et al. published the first prospective study to assess the efficacy of tofacitinib on six patients with CP. An 8-week treatment with tofacitinib 10 mg twice daily resulted in a response in two-thirds and remission in half of the patients. The primary outcome was response at 8 weeks, defined as $\geq$2-point decrease in mPDAI from baseline with at least 1-point decrease in endoscopic subscore. Response was observed in four (67%) of six and remission (defined as mPDAI $<$5 with a $\geq$2-point decrease from baseline) was achieved in three (50%) of six patients at week 8.[57]

In a recent case series conducted by Akiyama et al., involving 14 patients with CP and Crohn's-like disease of the pouch who were treated with tofacitinib, only 3 patients (23%) exhibited a clinical response after 3 months. Another three patients (23%) responded later, resulting in an overall response rate of 46%.[70]

Cataletti et al. recently conducted a systematic review on the efficacy of tofacitinib for chronic pouch disorders. The review included 9 studies and 46 patients: 30 (65%) with CP (CADP or CARP), 14 (31%) with Crohn's-like disease of the pouch, and 2 (4%) with isolated cuffitis. Primary endpoints were analyzed for 45 patients, with a response achieved in 24 (53%) patients. Clinical remission, evaluated in one study, was achieved in 4 (33%) patients at both weeks 8 and 52. Endoscopic response, available for 24 patients, was achieved in 12 (50%).[71]

Filgotinib and upadacitinib. Data on the efficacy and safety of other JAKi in CP are scarce. A retrospective ECCO-CONFER project, published in late 2023, collected data on the utilization of small molecules for CARP. A single patient received filgotinib, and at the 3-month follow-up, neither steroid and antibiotic-free clinical response nor remission was achieved. The treatment was discontinued after 4 months due to primary nonresponse. Six patients, on the other hand, were treated with upadacitinib, and at the 3-month follow-up, steroid- and antibiotic-free clinical response was achieved in two cases (33.3%), and steroid- and antibiotic-free clinical remission was attained in one case (16.7%). Four patients discontinued upadacitinib, all due to primary nonresponse. One patient reached 12 months of follow-up without achieving steroid and antibiotic-free clinical response. It is important to highlight that over 50% of the population in this study had been previously exposed to $\geq$2 classes of biologics for the treatment of CARP, with 65% of patients also being refractory to vedolizumab.[72]

Similarly, a small case series on six patients with CARP or CD of the pouch who received at least 6 weeks of upadacitinib, showed minimal or no significant clinical and endoscopic improvement was observed.[73]

Ozanimod. Ozanimod is an oral small molecule that selectively targets sphingosine 1-phosphate 1 (S1P1) and S1P5 receptors, thereby restricting the migration of activated lymphocytes from lymphoid tissues to inflamed regions in the gastrointestinal tract. The aforementioned ECCO-CONFER project reported data on the efficacy of ozanimod on two patients with CARP, showing

unsatisfactory results. Out of two patients treated with ozanimod, only one achieved a clinical response at 3 months, with no clinical remission observed. Both patients discontinued the treatment before reaching 12 months, with one patient eventually requiring pouch excision.[72]

Conclusion

Pouchitis stands out as the predominant complication following IPAA and, if one-third of patients experience only one episode of acute pouchitis, the remaining two-thirds suffer from recurrent pouchitis. Among these, one-third develop CARP,[11] which represents a daunting challenge for the clinician. Indeed, a recent international consensus recognized chronic antibiotic-refractory pouchitis as a form of "difficult-to-treat" IBD, given the lack of clear treatment targets and robust clinical guidelines.[74]

Our review focuses on the importance of the diagnostic assessment of the patient and on the currently available therapies for the various inflammatory disorders of the pouch.

In particular, the advent of novel biologic agents offers promising options for patients with CADP, CARP, or Crohn's-like disease of the pouch.

However, data on biological therapies are scarce and predominantly derived from trials with small patient cohorts, often conducted in an open-label fashion. There is an urgent need for large-scale studies, including RCTs, to provide more robust evidence and better guide clinical decision-making in this field.

Additionally, comparative studies are needed to establish optimal treatment algorithms tailored to the patients and to identify predictors of response to individual biologic agents. Overall, the advancements in biologic therapy represent a significant step forward in improving outcomes and quality of life for patients with pouchitis, but ongoing research efforts are essential to fully realize their potential in clinical practice.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Francesca Lusetti: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Camilla Almeida Martins Helfenberger: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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