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TREATMENT STRATEGIES FOR POUCHITIS: STEP-UP VERSUS EARLY BIOLOGIC THERAPY

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ABSTRACT

Research objectives: This systematic review aims to assess and summarize the available evidence comparing step-up strategies versus early biologic therapy for pouchitis. The goal is to clarify their relative effectiveness, safety profiles, and impact on clinical outcomes to inform evidence-based treatment algorithms and identify gaps for future research.
Methods: A systematic review was conducted using PubMed, Google Scholar, and ResearchGate. Eligible studies included clinical trials, observational studies, systematic reviews, meta-analyses, and international guidelines published after 1990. Search terms combined RPC-IPAA, acute pouchitis, chronic pouchitis, step-up therapy, biologic therapy, antibiotics, immunosuppressants, and advanced therapies.
Key findings: Most patients with acute pouchitis treated with antibiotics achieved a short-term clinical response, although relapses and progression to chronic disease were common. Chronic combination antibiotic therapy maintained remission in approximately three-quarters of patients but was associated with bacterial resistance and adverse events. Biologic agents achieved response rates of approximately 60%, while remission remained ≤50%. Vedolizumab and ustekinumab showed higher long-term tolerability and treatment persistence than TNF inhibitors. Evidence of early biologic therapy was limited, and no clear association between early initiation and clinical outcomes was identified.
Conclusions: Step-up antibiotic therapy remains justified as the first-line treatment for pouchitis due to its high short-term efficacy. Biologic agents represent a valuable option for chronic or refractory disease but do not appear to be superior to antibiotics as initial treatment. Current evidence does not support routine early biologic therapy for all patients, although selected high-risk groups may benefit. Future prospective studies are needed to define optimal timing of biologic therapy.

KEYWORDS

Pouchitis, Chronic Antibiotic-Refractory Pouchitis, Chronic Antibiotic-Dependent Pouchitis, Antibiotics, Biologic Agents

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Introduction

Pouchitis is the most common complication following restorative proctocolectomy with ileal pouch-anal anastomosis (RPC-IPAA), a surgical procedure primarily performed for refractory ulcerative colitis (UC) or familial adenomatous polyposis (FAP) [1-4]. This procedure is associated with pouchitis in 54% of patients within 2 years postoperatively, which may negatively affect quality of life and require additional treatment [1, 2, 5]. Pouchitis remains a condition of unproven, multifactorial etiology [6-10]. The main factors implicated in its pathogenesis include alterations in the gut microbiome and dysregulated immune responses [7, 9-12]. Clinical presentation includes increased stool frequency, urgency, abdominal pain, and hematochezia [1, 2, 13-16]. Diagnosis is based on clinical presentation and findings from endoscopic and histopathological examinations, with pouchoscopy as the gold standard [1, 89, 90]. Histopathological assessment may be required in selected cases [1]. Disease activity is commonly assessed using validated indices, including the Pouchitis Disease Activity Index (PDAI) and its modified version (mPDAI) [1, 19].

Pouchitis is classified as acute or chronic based on symptom duration [20, 21]. Acute pouchitis is defined by symptom resolution within <4 weeks [9, 20, 21]. At least one relapse following the first episode occurs in >50% of patients [22]. Recurrent acute pouchitis involves <4 documented relapses per year, and it is responsive to a short course of antibiotics [21, 23]. If the disease does not resolve within <4 weeks or recurs ≥4 times per year, it is considered chronic pouchitis, affecting 13.0-29.3% of patients overall, with higher progression rates (around 29-39%) within the first year after diagnosis of acute pouchitis [2, 9, 14, 24]. Although most cases of acute pouchitis respond well to antibiotics, some patients may develop either chronic antibiotic-dependent pouchitis (CADP) or chronic antibiotic-refractory pouchitis (CARP) [2, 9, 21, 25]. CADP refers to pouchitis with a good initial response to antibiotics that relapses shortly after discontinuation,

requiring prolonged or repeated treatment [2]. In contrast, CARP is characterized by persistent symptoms despite antibiotic therapy, after exclusion of secondary causes and alternative diagnoses [2, 21].

Pouchitis management generally follows a step-up treatment strategy, with antibiotics as first-line therapy [76, 98]. In patients with ongoing symptoms, escalation to locally acting steroids or conventional immunosuppressants is recommended [21, 26-28]. Advanced therapies are reserved for later stages, particularly in cases of severe or refractory disease [2, 25, 29-31]. Biologic therapy includes tumor necrosis factor (TNF) inhibitors, integrin inhibitors, and interleukin (IL) inhibitors [2, 26, 27, 29, 30, 32]. Biologic agents approved for inflammatory bowel disease (IBD), including infliximab (IFX), adalimumab (ADA), vedolizumab (VDZ), and ustekinumab (UST), have been evaluated for efficacy in treating pouchitis [31, 33, 34]. Among these agents, vedolizumab (VDZ) is currently the only therapy approved by the European Medicines Agency (EMA) for moderate-to-severe CARP [2]. Janus kinase (JAK) inhibitors are also under investigation; however, evidence for tofacitinib remains limited [35]. Current AGA, GETECCU, and ACCU guidelines recommend treating CADP with a combination of two antibiotics for at least 4 weeks at the lowest effective dose, either intermittently (approximately 1 week per month) or in a cyclical regimen (rotating among ciprofloxacin, metronidazole, and vancomycin every 1-2 weeks) [2, 20]. For CARP therapy, these guidelines suggest using advanced therapies that patients have received before RPC-IPAA [2, 20].

The proven efficacy of biologic agents in inflammatory bowel disease (IBD) has led to growing interest among clinicians in their potential benefits for treating pouchitis. Although biologics are typically used in patients with CARP, data regarding their optimal timing, particularly earlier initiation, remains limited. Therefore, given the lack of clear consensus, this review aims to synthesize the available evidence on step-up versus early biologic therapy for pouchitis.

Methodology

This study was conducted as a systematic review with a structured literature search. A comprehensive search of electronic databases and academic search platforms, including PubMed, Google Scholar, and ResearchGate, was performed to identify relevant studies on treatment strategies for pouchitis.

The search terms used were: (“acute pouchitis” OR “chronic pouchitis” OR “chronic antibiotic-refractory pouchitis” OR “chronic antibiotic-dependent pouchitis”) AND (“ileal pouch-anal anastomosis” OR “restorative proctocolectomy”) AND (“step-up therapy” OR “early biologic therapy” OR “immunosuppressants” OR “tumor necrosis factor inhibitors” OR “vedolizumab” OR “ustekinumab” OR “Janus kinase inhibitors”).

The search was limited to studies published between 1990 and 2025. Studies were eligible for inclusion if they comprised randomized controlled trials, non-randomized clinical trials, cohort studies, case-control studies, systematic reviews, meta-analyses, or international guidelines; involved patients with acute pouchitis, chronic antibiotic-dependent pouchitis, or chronic antibiotic-refractory pouchitis; evaluated treatment of pouchitis such as antibiotics, immunosuppressants, biologic agents, or JAK inhibitors; and reported clinically relevant outcomes, including response rates, remission rates, PDAI reductions, prior anti-TNF exposure, treatment discontinuations, and adverse events.

Studies were excluded if they focused exclusively on Crohn’s-like disease of the pouch or pouchitis with pre-pouch ileitis treatment. Case reports were not included in the analyses. Preclinical and non-clinical studies without relevant patient outcomes were also excluded. In addition, editorials, letters, and conference abstracts were not considered due to limited methodological robustness.

Study selection was performed through a stepwise screening process based on titles and abstracts, followed by full-text evaluation of potentially relevant articles. Relevant studies were selected based on their clinical relevance, methodological quality, and contribution to the topic. Data extraction included study design, patient characteristics, pouchitis subtype, treatment regimen, follow-up duration, and reported clinical outcomes.

Results

Role of antibiotic therapy in pouchitis

Based on a weighted analysis, clinical response to antibiotics was observed in 78.8% of cases, and all patients responded to at least 1 course of treatment [36]. Relapses were found in 66.0% of patients over 3 weeks to 13 months following therapy cessation and requiring additional antibiotic treatment [36, 41, 50].

In acute pouchitis, 2-week ciprofloxacin monotherapy (1,000 mg daily) resulted in 100% clinical response and remission rates [37]. In comparison, metronidazole monotherapy (20 mg/kg daily) was associated with clinical response and remission rates of 100% and 66.7%, respectively [37]. Rifaximin (400 mg 3 times daily) administered for 4 weeks achieved endoscopic remission in 25.0% of patients, compared to 0.0% in those receiving placebo [38].

Antibiotics were administered in chronic pouchitis for 67.3% of patients, with a median cumulative treatment duration of 425 days (range 14-1000) [36]. Combination antibiotic therapy was used for ≥4 weeks, with the most common regimens including ciprofloxacin with metronidazole, rifaximin, or tinidazole [36, 39-44]. Based on a weighted analysis, clinical response and remission rates for this approach were 88.1% and 75.6%, respectively [39-42]. Some patients were treated with vancomycin (125 mg twice daily). After 4 weeks of this therapy, a 51.2% clinical response rate was achieved in patients previously treated with multiple antibiotics; however, no significant endoscopic differences were observed between responders and non-responders [45].

Antibiotic-related adverse events occurred at a weighted rate of 24.4% (range 12.5-75%), while long-term treatment was linked to side effects in 28.2% of patients [38, 39, 44, 46]. Additionally, chronic antibiotic use was associated with drug intolerance and bacterial resistance with a frequency of 77.8% based on stool-sample analyses [36, 44, 46]. *Clostridioides difficile* infection was also observed [47]. Adverse events were more commonly reported with metronidazole than with ciprofloxacin (14.6% vs 5.1%), and included nausea, vomiting, dysgeusia (metallic taste), and peripheral neuropathy [37, 40, 44, 46, 48]. No significant increase in the risk of tendon rupture was identified with ciprofloxacin use within 30 days of exposure [49]. One study reported complications in 75.0% of patients receiving rifaximin, compared with 50.0% receiving placebo [38]. Withdrawal due to adverse events or treatment failure was noted at a weighted rate of 3.26% [38, 40-42, 48].

Role of probiotics in pouchitis

Probiotics such as VSL#3, *Lactobacillus rhamnosus GG*, or *Clostridium butyricum* MIYAIRI, used after RPC-IPAA, were linked to a lower weighted risk of developing pouchitis over 10-36 months, from 36.4% to 8.8% [51-53]. The first episode of pouch inflammation was associated with a response rate of 62.7% [53-58]. During maintenance therapy, a sustained remission rate of 86.7% was observed between 4 weeks and 24 months, compared with 45.9% in the placebo group [51, 53, 57, 59-61]. Treatment discontinuation due to relapse occurred in 74.2% of cases after 1.2 months [62]. Chronic use of probiotics reduced recurrence rates after the initial episode, from 89.8% (range, 85-100%) to 10.2% (range, 0-15%) during a 12-24 month follow-up [51, 53, 59, 61].

Probiotic use resulted in a weighted risk of adverse events of 1.5%, including abdominal cramps, vomiting, diarrhea, bleeding, bloating, constipation, and intolerance [51, 53, 55, 56, 59, 60, 62]. 6.5% of patients discontinued therapy due to side effects [62].

Treatment escalation in antibiotic-dependent and antibiotic-refractory disease

Prolonged antibiotic therapy in CADP was associated with long-term remission in 20.5% of patients over a median follow-up of 8.5 years [44]. Rifaximin (200 mg daily) was used as maintenance therapy following a 2-week induction of remission, with dose escalation to 1800 mg daily in those with a partial response [43]. Sustained remission at 3 months was observed in 64.7% of patients, among whom 57.6% maintained remission for 12 months [43]. Based on a weighted analysis of studies involving patients with CADP, vedolizumab (VDZ) achieved clinical response and remission rates of 52.6% and 19.6%, respectively, after 12-14 weeks of treatment [63,64].

In CARP, combination antibiotic therapy showed a weighted clinical remission rate of 85.4% after a treatment duration of 15 days to 6 months [39, 41, 42]. Significant reductions in PDAI scores were observed (from 11-12 to 0-4), and patients who did not achieve remission showed a decrease from 14.5 to 9.5 [39-42]. Budesonide (9 mg daily for 8 weeks, tapered by 3 mg/month) induced remission in 75.0%, while beclomethasone (10 mg daily for 8 weeks) achieved remission in 80.0-100% over 8-16 weeks [65, 66]. Previous thiopurine failure was reported in 41.9% of patients receiving biologic therapy [64, 67, 71]. Patients with inadequate response to prior treatment received advanced therapies [64, 67-73]. During short-term follow-up of 8-14 weeks, weighted response and remission rates for biologic agents were 63.3% and 28.9%,

respectively [63, 64, 67, 74-76]. Weighted long-term clinical response was 47.5% over a 1-year observation period [64, 67, 72, 75, 77]. Failure of biologic therapy before initiation of tofacitinib (5-10 mg twice daily) was reported in 38% of cases [70]. Overall, 81.5% of patients had previous exposure to biologic therapy [69, 70]. Based on a weighted analysis, response to this agent was 44.2% after 8 weeks to 3 months of short-term treatment [68-70, 78]. Following 3 months of therapy, upadacitinib and ozanimod demonstrated a weighted clinical response rate of 37.5% and a remission rate of 12.5%, while filgotinib was discontinued after 4 months due to primary non-response [68].

Higher rates of CARP following RPC-IPAA were observed in patients with primary sclerosing cholangitis (PSC) [79]. No differences in treatment response to probiotics, mesalamine, thiopurines, and biologic agents were found between PSC-pouchitis and UC-pouchitis; however, repeated courses of antibiotics were required in 12.7 percentage points more patients with PSC-pouchitis (95.1% vs 82.4%) [71]. After 1 year of therapy, endoscopic remission was achieved in 72.2% of those receiving budesonide [80].

Biologic agents

Biologic therapy was typically used after antibiotic and conventional immunosuppressive therapy [67, 72]. TNF inhibitors, integrin inhibitors, and IL-12/23 inhibitors were administered off-label to patients with pouchitis [64, 67, 72, 73, 76, 81].

Prior anti-TNF exposure before colectomy was associated with a 2.5-fold higher risk of non-response and a 4.9-fold greater likelihood of pouch failure during biologic therapy [64, 82].

At 8-10 weeks, IFX was associated with 73.4% weighted clinical response and 50.0% remission rates [67, 83-85]. Endoscopic remission was 56.3% [67, 83]. Treatment discontinuation occurred in 53.6% of patients, primarily due to lack of efficacy, loss of response, or adverse events [67, 74]. Surgical intervention, including pouch excision or permanent ileostomy, was required in 23.5% of cases [81, 84, 86].

Over 8-12 weeks of ADA treatment, a weighted clinical response rate of 57.1% and a remission rate of 14.3% were observed [75, 97]. The endoscopic response rate was 66.7% at 12 weeks [59]. Prior IFX exposure was reported in all patients [75]. Treatment discontinuation occurred in 77.0% of patients, primarily due to primary non-response, secondary loss of response, or adverse events [74]. Permanent ileostomy was required in 50.0% of cases at 52 weeks [75].

Reductions in fecal calprotectin levels and improvements in histopathological inflammation were reported following vedolizumab (VDZ) and ustekinumab (UST) therapy [36, 74, 88, 89].

Based on weighted analysis, 74.5% of patients treated with VDZ had prior exposure to TNF inhibitors [64, 76]. Over 12-14 weeks, this biologic agent resulted in a 49.1% clinical response and a 23.7% clinical remission [63,64, 90]. VDZ had an 18.2-percentage-point lower clinical response rate in patients with prior TNF inhibitor exposure than in biologic-naive patients (69.3% vs 87.5%) [64]. After 3 months, endoscopic response was observed in 47.8%, and endoscopic remission in 13.0% [64]. Treatment discontinuation rates were 18.2%, primarily due to lack of efficacy and loss of treatment persistence [74, 90]. Surgical intervention, including permanent ileostomy, redo surgery, or pouch excision, was required in 10.8% of cases [64, 76].

UST was administered as a subsequent line of therapy following prior exposure to biologic agents [72, 88, 91]. At 16 weeks, treatment resulted in weighted clinical response and remission rates of 52.2% and 27.3%, respectively [39, 63]. Endoscopic improvement was reported in selected cases; however, none of the patients achieved endoscopic remission [72]. Treatment discontinuation was observed in 41.7% [72]. Limited data were available for risankizumab, with only isolated treatment courses identified [91].

PDAI scores decreased from 8-12 to 3-7 during short-term follow-up (10-16 weeks) and from 8-13 to 4-5 during long-term follow-up (8-21 months) across studies evaluating biologic agents [63, 74, 77, 83-85, 88].

Adverse events associated with biologic therapy included infections (*Clostridioides difficile*, norovirus), recurrent pneumonia, osteomyelitis, intra-abdominal abscesses, and sepsis [64, 74, 86, 90, 92]. Other manifestations comprised herpes zoster, infusion reactions, rash, and arthralgia [74, 86, 92]. Hypersensitivity reactions were observed following re-exposure to IFX [74, 92]. Upper respiratory tract infections and headaches occurred among VDZ-treated patients [90].

Early biologic therapy

Biologic therapy was initiated at a median of 3.5 months after diagnosis of chronic pouchitis [93]. A 23.3% of patients received biologic therapy a median of 10 days after diagnosis, most commonly ADA (57.1%) [94]. Based on a weighted analysis, 48.9% of patients undergoing biologic therapy still required antibiotic treatment during follow-up [63, 64, 88, 90]. At week 14, 7.7% remained on corticosteroid therapy while receiving biologic agents [63, 90].

IFX and ADA were used for the early initiation of biologic therapy at weighted rates of 42.9% and 41.3%, respectively [91-93]. The corresponding rates for UST and VDZ were 7.9% and 4.7% [91, 93]. Monotherapy was administered to 67.9% of patients, while combination therapy was given to 32.1% [92]. Clinical remission was achieved in 32.2% of patients with a median of 5.6 months [93]. Endoscopic remission was observed in 50.0% of patients at 52 weeks [91].

Across pooled Kaplan-Meier analyses, treatment discontinuation occurred in approximately 35-45% of patients within 1 year and increased to around 70-80% over 5 years, most commonly due to primary non-response [91, 92]. Weighted persistence of first-line TNF inhibitor therapy was 25.0% at final follow-up, compared with 100% for VDZ and UST in a small cohort [91, 92]. Approximately 42.6% of patients required switching to a second- or later-line advanced therapy, including both biologic agents and small molecules [91, 92]. Pouch failure occurred in 21.7% of patients [91-93].

No significant association was observed between the timing of biologic therapy initiation and clinical, endoscopic, or pouch failure outcomes [93].

Comparison: step-up versus early biologic strategy

In patients with pouchitis, 2- to 4-week antibiotic therapy was associated with weighted short-term clinical response and remission rates of 76.0% and 66.4%, respectively [37, 40-42, 45, 50]. No recurrence after an initial episode was observed in 41.2% of cases, while relapse occurred in 58.8% [95, 96]. After RPC-IPAA, long-term antibiotic use increased from 18% at 5 years to 42% at 20 years [46]. Short-term weighted response and remission rates for biologic therapies were 67.8% and 28.0%, respectively, within 8-14 weeks [63, 64, 67, 76, 81, 84, 85, 87, 90]. During a 6-21-month follow-up, the corresponding long-term rates were reported in 51.1% and 28.9% of cases [64, 67, 72, 75, 77, 83, 84, 88].

Discussion

Key findings

Available data suggest that the step-up treatment strategy is currently the most commonly recommended approach for managing pouchitis. Antibiotics show high short-term efficacy, but their chronic use is associated with significant limitations. In contrast, biologic agents may provide long-term disease control in selected patients. For this reason, early biologic therapy remains a potential strategy requiring further investigation.

Clinical interpretation (step-up vs biologics)

The step-up treatment strategy appears to provide many benefits in the management of pouchitis, owing to the well-documented antimicrobial effects of antibiotics, which are the first-line choice in most cases. Ciprofloxacin achieves disease control in a significant proportion of patients, although relapses remain common. Antibiotic therapy also carries a risk of antibiotic resistance and adverse events. Additionally, patients may eventually develop CADP and CARP.

Some patients may experience recurrent pouchitis, sometimes shortly after completing treatment, which significantly limits the options for antimicrobial management. This may create a risk of exposing patients to chronic antibiotic use and delaying treatment escalation. However, because the substantial benefits may outweigh the risks and most patients respond well to antibiotic therapy, early initiation of biologic therapy for all patients would not be justified.

The introduction of new biologic agents for the treatment of inflammatory bowel disease (IBD) in recent years has enabled effective management of pouchitis cases that are challenging with standard antibiotic therapy. Currently, biologic therapy is most often used as a rescue treatment. TNF inhibitors appear to provide lower remission rates than antimicrobial agents. Across included studies, IFX shows higher response and remission rates and lower treatment discontinuation rates than ADA. The limited long-term efficacy and high discontinuation rate of TNF inhibitors highlight the need for alternative therapeutic options, including VDZ and UST. VDZ is characterized by an intermediate response rate and lower treatment discontinuation than those reported for TNF inhibitors. UST therapy achieved moderate response rates and intermediate risk of discontinuation. However, remission rates remain limited.

Moreover, adding probiotics to long-term treatment may provide significant benefits by helping prevent disease relapse. After antibiotic therapy fails, glucocorticosteroids may provide symptom control. The efficacy of other immunosuppressants has not been sufficiently established to support their use as an alternative to antibiotic therapy. There have also been studies on the effectiveness of small molecules as potential therapies for pouchitis; however, the available analyses are limited and do not allow for a definitive determination of whether these drugs can replace established therapeutic strategies in pouchitis management.

Patient stratification

Early biologic therapy may be considered in selected patients with chronic pouchitis who are at risk of developing antibiotic resistance and the associated therapeutic challenges due to a decreasing pool of effective drugs. In the case of CARP, high-dose combination antibiotic therapy administered for >2 weeks achieves high remission rates. This approach carries a risk of adverse events and further increases the likelihood of resistance development. Despite this risk, the benefits of antibiotic therapy may outweigh its limitations in many patients. It is important to note, however, that antibiotics currently remain a highly effective option for symptom control in most patients, and modifying this regimen may result in loss of previously achieved clinical response.

Early initiation of biologic therapy may also be considered in patients with frequent relapses of CADP, who require chronic antibiotic treatment to manage symptoms. Although antibiotics are used at the lowest effective dose, this approach still exposes patients to prolonged treatment and its consequences. To minimize these risks, periodic antibiotic rotation may be considered; however, this also has limitations, as not all antibiotics are equally effective. Metronidazole appears less beneficial than ciprofloxacin, and the therapeutic value of other antimicrobials remains uncertain. Furthermore, drug rotation may be ineffective in frequent CADP relapses, where intermittent antibiotic therapy is often used. Therefore, early biologic therapy may be considered as an alternative to prolonged antibiotic exposure in selected cases.

Biologic therapy may also be considered for patients requiring repeated antibiotic courses. Long-term low-dose antibiotic therapy may have limitations, supporting consideration of treatment modification.

Additionally, for patients with a history of intolerance to antibiotics used to treat pouchitis, early biologic therapy may represent an alternative treatment option that could reduce further antibiotic exposure. Moreover, among patients treated with VDZ, prior TNF inhibitor exposure may be associated with a lower response rate.

Safety

Short-term antibiotic therapy is generally not associated with significant risk to patients; however, prolonged use may disrupt the gut microbiome and promote antimicrobial resistance. Nevertheless, when antibiotic resistance is suspected, it may be reasonable to consider alternative treatments that do not require frequent therapeutic modification as the disease progresses. Long-term antibiotic therapy may increase the risk of adverse events. In some cases, side effects may lead to treatment discontinuation. Caution is warranted with metronidazole, as it is associated with a higher risk of adverse events, which may limit its use relative to ciprofloxacin. Therefore, antibiotic therapy remains an important treatment option despite the risk of adverse events.

It is important to note that antibiotics are not the only medications that can cause adverse effects; however, biologic agents also carry this risk. In addition, some patients (especially those previously treated with IFX) may experience hypersensitivity reactions to biologic agents, which represent a common cause of therapy discontinuation. This was reported as a cause of treatment discontinuation in selected patients.

Given the distinct safety profiles of antibiotics and biologic agents, direct comparisons remain difficult. Moreover, the significant heterogeneity in the available data makes it difficult to determine which adverse events present a greater risk to patients. As a result, each case has a different clinical course, and clinical decisions may need to be made on an individual basis.

It is worth noting, however, that probiotics appear to carry a minimal risk of adverse events compared with other medications, which may support their use in many patients with pouchitis.

Limitations

Available comparative studies were limited by a short observation period (mean ~3 months) and a relatively small number of analyses, most of which were from retrospective studies of varying methodological quality. In addition, only a few high-quality prospective randomized controlled trials exist, as most analyses exclude patients with a J-pouch. Most analyses were performed at single centers, with small patient cohorts that were insufficiently large to enable analysis of homogeneous groups. Additionally, many studies lack a reliable control group. No standardized tool has been established to predict clinical and endoscopic improvement.

In some studies analyzing multiple drugs, unequal group sizes and the collective reporting of data for different biologic agents may have affected the interpretation of results. There is also a lack of evidence on the effectiveness of combination therapies that simultaneously use antibiotics and biologic agents. Another problem is the inability to assess all known adverse events in patients with pouchitis treated with specific drugs. Additionally, not all patients underwent follow-up pouchoscopy, limiting the assessment of endoscopic

improvement. During long-term follow-up, patient withdrawal and reduced data availability represented additional limitations. Moreover, data are at high risk of bias due to prior exposure to biologic therapy.

These limitations make it difficult to identify reliable clinical and endoscopic differences and to draw clear conclusions from the available evidence. The number of studies specifically addressing treatment standards for biologic therapy in pouchitis is limited. Due to significant heterogeneity among the studied groups, it is not possible to conduct a high-quality meta-analysis that would address all necessary clinical outcomes. The marked imbalance between retrospective and prospective studies also limits the ability to synthesize the available evidence. Another challenge is the frequent inclusion of mixed patient groups, which complicates analyses across all patients without prior stratification into the well-defined clinical phenotypes of pouchitis.

Furthermore, there is no consensus on standardizing response predictors, endpoints, or outcome definitions, so analyses generate different results, making comparisons across drugs difficult. Overly positive assessments of efficacy for certain drugs used in pouchitis therapy may also be related to the exclusion of patients who were forced to discontinue treatment, resulting in the selective inclusion of only those with good treatment tolerance in the final analyses. Furthermore, insufficient data on the long-term efficacy and safety of the studied agents also limit the ability to draw meaningful conclusions.

As a consequence, it remains unclear whether earlier initiation of biologic therapy improves clinical outcomes. However, there is still insufficient evidence to support this approach as a new standard of care for the treatment of pouchitis.

Clinical implications

Current studies indicate that the step-up treatment strategy remains the primary standard of care in most cases of pouchitis. Given the well-documented efficacy of antibiotics in inducing a short-term clinical response, this therapy should not be disregarded, especially given their rapid action in first-episode pouchitis. The initiation of biologic therapy at this stage may be unwarranted, as there is no evidence that the disease is likely to become a long-term problem. Importantly, the available evidence did not demonstrate a significant association between earlier biologic initiation and improved clinical, endoscopic, or pouch failure outcomes. At the same time, it is difficult to predict how many patients will eventually develop CADP or CARP, or who will benefit most from antibiotic therapy, so antibiotics should not be completely excluded from treatment protocols or prematurely replaced by biologic agents.

Furthermore, the treatment of chronic pouchitis often requires long-term antibiotic therapy, although for some patients this may not be as effective as expected. In such cases, it is important to consider which factors may be responsible for the lack of treatment effect - whether it is related to antibiotic dependence, antibiotic resistance, or other disease-related factors. This distinction may influence the choice of further therapeutic approach. When there is no response to antibiotic treatment, and given the limitations of antibiotics in maintaining remission, a change in the current approach may be necessary.

Biologic agents generally achieve lower short-term remission rates than antibiotics, but durable remission has been reported in selected patients. However, there is no clear evidence that biologic therapy can serve as a complete replacement for antibiotic therapy. Additionally, because few reliable predictors of treatment response exist, selecting the right biologic agent is extremely challenging. IFX and ADA are associated with relatively high discontinuation rates. This suggests the potential benefits may be limited to a small group of patients who can maintain therapy. Available data suggest a favorable safety profile for VDZ and UST, although evidence remains limited. Nevertheless, VDZ is currently approved by the EMA for the treatment of CARP.

Biologic agents may be considered earlier in the treatment course, particularly in patients with antibiotic dependence or resistance. This particularly applies to patients with CADP and CARP who require long-term antibiotic therapy, in whom treatment efficacy may become more difficult to maintain with repeated disease relapses. However, early biologic therapy may also be considered in patients who do not improve with antibiotic treatment, or those with severe disease activity and frequent relapses. In these situations, biologic therapy may represent an alternative treatment option.

In summary, non-antibiotic options, including biologic agents, may represent a reasonable alternative in selected cases. However, the routine use of advanced therapies as first-line treatment appears to be generally unjustified, although it may be warranted in specific patient groups - particularly in those at high risk of antibiotic resistance or intolerance.

Future directions

Due to the limitations of available analyses, additional data are needed to draw definitive conclusions regarding pouchitis management strategies. To achieve this, it is important to conduct detailed prospective comparative studies, including adequately powered randomized controlled trials (RCTs), designed to compare the step-up treatment strategy with early biologic therapy directly.

It is also important to identify biomarkers that can predict the risk of recurrence before clinical manifestation. Furthermore, defining optimal indicators for monitoring and evaluating treatment outcomes remains essential. While PDAI and mPDAI are useful for individual assessment, they do not allow for objective standardization across studies. Due to challenges in patient recruitment, separate analyses for the CADP, CARP, and CLDP cohorts may be required. Given the significant heterogeneity of endpoints across studies, standardizing them is important for reliable comparison of disease course and clinical outcomes.

Further studies investigating the risk of developing severe relapsing disease, CADP, and CARP may help optimize therapeutic strategies to specific patient groups. Additionally, it is worth considering evaluating alternative therapeutic approaches, such as fecal microbiota transplantation (FMT).

The data obtained could serve as a starting point for further analyses concerning the appropriate selection and dosing of biologic agents, as well as the optimal timing and duration of treatment. Future studies incorporating biomarkers, genetic factors, disease history, and response to prior therapy may help account for the complexity of the processes underlying pouchitis pathogenesis and support a holistic approach to each case. It may also be important to compare the results obtained with real-world data (RWD), which would allow assessment of real-world effectiveness, determination of an acceptable safety profile, and development of the optimal treatment regimen - ultimately informing the development of clinical guidelines focused specifically on pouchitis therapy.

Conclusions

Pouchitis remains the most common long-term complication of RPC-IPAA and continues to pose a therapeutic challenge. In most cases, the currently used step-up strategy is justified, as antibiotics provide substantial short-term clinical response and remission. However, adverse events, frequent relapses, antibiotic dependence, and antimicrobial resistance limit the long-term effectiveness of this approach.

Biologic agents therefore represent a valuable therapeutic option for patients with CADP and CARP, especially when other lines of treatment have failed. Among these drugs, vedolizumab represents the most promising therapeutic option and has been approved by the EMA as the only agent for the treatment of CARP. Nevertheless, TNF inhibitors, integrin inhibitors, and IL inhibitors generally show lower short-term remission rates than antibiotics and are associated with a higher risk of treatment discontinuation or switching.

Based on the available data, it has not been possible to demonstrate a relationship between earlier initiation of biologic therapy and improvements in clinical or endoscopic outcomes, or reductions in pouch failure rates. Therefore, routine use of biologic agents as first-line therapy is not recommended. However, such treatment may be considered in selected high-risk patients, including those with antibiotic intolerance, frequent relapses, CADP, or CARP.

Probiotics appear to be the safest option for managing pouchitis. They help reduce relapse frequency and support the maintenance of remission. However, treatment should not rely solely on these agents, and probiotics should be considered only as adjunctive therapy.

Evidence for the effectiveness of other drugs remains insufficient; therefore, their use in patients with pouchitis is not recommended.

Overall, the current state of knowledge supports maintaining the step-up treatment strategy as the standard of care for all subtypes of pouchitis. However, therapeutic decisions should be made individually, based on disease phenotype, prior drug exposure, the risks associated with antibiotic therapy, and patient-specific factors. There is also a need for more prospective randomized studies to more precisely determine whether certain patient subgroups may benefit from earlier introduction of biologic therapy and to identify prognostic factors for treatment response.

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