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Review Article

Key Focus Areas in Pouchitis Therapeutic Status: A Narrative Review

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Abstract

Pouchitis, as the most common complication after ileal pouch-anal anastomosis (IPAA), has an incidence from 7% to 46%. Pouchitis treatment still represents one of the biggest gaps of knowledge in the treatment of diseases. This review has focused on achievements and challenges in the treatment of pouchitis. A combined assessment of symptoms, endoscopic findings, histologic results, quick biomarkers, and fecal calprotectin test were determined to be valuable diagnostic criteria. Conventional therapy was described as a modification of bacterial flora, mainly with antibiotics and more recently with probiotics such as bifidobacteria, lactobacilli, and streptococci. Other therapeutic approaches such as anti-tumor necrosis factor, infliximab, adalimumab, vedolizumab, ustekinumab, tacrolimus, tofacitinib, thiopurines, corticosteroids, prolyl hydroxylase–containing enzymes, povidone-iodine, dextrose spray, fecal microbiota transplantation, herbal medicines, and leukocyte apheresis have been discussed. Changes in dietary components, and administration of complementary and alternative medicine, probiotics, and fecal transplantation in addition to conventional therapies were also shown to affect the outcome of disease. Due to the potential significant impairment in quality of life caused by pouchitis, it is essential to address the gaps in knowledge for both patients and physicians in its treatment. Therefore, well-designed and adequately powered studies should assess the optimal treatment for pouchitis.

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What's Known

- After total proctocolectomy for the management of inflammatory bowel diseases (IBD) and the creation of ileal pouch-anal anastomosis (IPAA) to restore intestinal continuity, the most common complication is pouchitis.
- Antibiotics administration is also directed toward the modification of bacterial flora, but not always successful and can lead to significant impairment in quality of life.

What's New

- Changes in dietary components and administration of complementary and alternative medicine, probiotics, and fecal transplantation in addition to conventional therapies have been recommended for pouchitis treatment.
- There is a need to clarify the gaps of knowledge in the treatment of pouchitis for both patients and physicians.

Introduction

Studies have shown that 70-80% of patients with Crohn's disease (CD) and 20-30% of patients with ulcerative colitis (UC) undergo gastrointestinal surgery, specifically total proctocolectomy, as a management option for inflammatory bowel diseases (IBD) that are refractory to medical therapy.[1] Surgery as a therapeutic approach for UC patients is conducted.[2] After total proctocolectomy, ileal pouch-anal anastomosis (IPAA) as another surgical intervention is performed to restore intestinal continuity,[3] but the most common complication is acute pouchitis with an incidence rate of 70%,[3] which can significantly impair quality of life.[4] The course of pouchitis is the same as UC, which appears as a chronic condition revealing episodic symptomatic exacerbations. The first episode of pouchitis usually happens in the first year following surgery.[5] In a geographically diverse

population of 594 patients, 48% of patients with UC developed pouchitis within the first 2 years after total proctocolectomy with IPAA.[6]

Although the etiology of pouchitis has remained unclear, the gut microbiome has been hypothesized as a key factor. In patients with pouchitis, there is a decrease in bacterial diversity and an altered abundance of pouch bacteria.[7] In addition, changes in fungal composition for antibiotic-refractory patients can exacerbate pouchitis.[7] Thus, this review focuses on achievements and challenges in the treatment of pouchitis.

Categorization of Pouchitis

Pouchitis is categorized into acute or chronic forms. In acute pouchitis, symptoms last less than 4 weeks, and patients respond to 2-week courses of antibiotics. While, in chronic form, symptoms last longer than 4 weeks, and despite standard antibiotic therapy, the patients need chronic antibiotics or anti-inflammatory treatment choices.[8] About 10-15% of patients with acute pouchitis can develop chronic pouchitis, which has two difficult forms: chronic antibiotic-dependent and chronic antibiotic-resistant pouchitis.[8] Additionally, based on the duration of symptoms and the disease course, pouchitis is categorized as infrequent (less than three episodes per year), recurrent (more than three episodes per year), or continuous.[8] Considering etiology, pouchitis is described as idiopathic or secondary to infections (e.g., cytomegalovirus (CMV) or *Clostridium difficile*), surgical complications, nonsteroidal anti-inflammatory drug intake, or other autoimmune conditions (e.g., primary sclerosing cholangitis (PSC) or CD of the pouch).[8]

Pouchitis Risk Factors

Various risk factors have been mentioned for pouchitis including age, male sex, smoking, bacterial dysbiosis, nonsteroidal anti-inflammatory drugs, mucosal ischemia, oxygen-free radical injury, recurrence of UC, immune dysregulation and positive antineutrophil cytoplasmic antibody (ANCA), short change fatty acid deprivation, 3-stage IPAA, genetic predisposition, and so on.[9] It is worth mentioning that many confounders such as disease severity, extraintestinal manifestations, and dose-response effects of smoking should be considered when assessing the impact of smoking on pouchitis.[10] Chronic pouchitis with erosion secondary to sodium polystyrene sulfonate crystals has been reported in a 67-year-old woman undergoing total colectomy with IPAA, which was improved by oral steroid administration.[11] Weaver and colleagues reported that chronic antibiotic-dependent pouchitis was related to older age at the time of IPAA (J-pouch) surgery.[12] The interleukin-1β (IL-1B, rs1143627) TT genotype and preoperative extraintestinal manifestation were shown to be significant predictors of pouchitis development after IPAA in patients with UC.[13] Interleukin 17 receptor A is responsible for the pathogenesis of pouchitis through downregulation of microRNAs.[14] Younger age at colectomy, chronic active colitis as an indication for surgery, and 3-stage IPAA have increased the risk for pouchitis.[9] Vitamin-D deficiency can increase the risk for pouchitis as well.[15] Presence of a great peripouch fat was shown to be associated with a higher prevalence of chronic antibiotic refractory pouchitis, and accumulation of peripouch fat is a risk factor for pouch failure.[16] Development of pouchitis in patients with UC was demonstrated to be linked to factors such as PSC, extraintestinal manifestations of IBD, preoperative terminal ileal inflammation, extensive colonic disease, presence of interleukin-1 receptor antagonist gene allele 2, use of infliximab, having a neutrophil percentage of >65%, and presence of perinuclear antineutrophil cytoplasmic antibodies.[13-16]

Diagnosis of Pouchitis

The diagnostic criteria for pouchitis were mentioned to be dependent on the combined assessment of disease symptoms, endoscopic findings, and histologic results.[17] A lower fecal pH value in patients with hereditary colorectal cancer (CRC) after IPAA was mentioned to be a new indicator of pouchitis.[18] Around 45% of asymptomatic pouchitis patients have abnormal endoscopic and histologic results.[19] Regarding symptoms in the diagnosis of pouchitis, the most typically reported ones were an increase in the frequency of bowel movement, abdominal pain or abdominal cramping, pelvic pain, watery diarrhea, tenesmus, fecal incontinence, pelvic discomfort, fever, and urgency.[20] Extraintestinal manifestations related to chronic pouchitis can be PSC and an elevated platelet count.[21] Moreover, for disease differential diagnosis in pouchitis patients, utilizing serum or stool or functional tests, imaging assessments for infections of CMV and *C. difficile*, and examination for anal sphincter or pelvic floor dysfunction, pouch-outlet obstruction, decreased pouch compliance or emptying, CD of the pouch, anastomotic stricture, any immune-mediated intestinal inflammation, intestinal bacterial overgrowth, cuffitis, and irritable pouch syndrome should be undertaken.[20]

In endoscopic examination and pouchoscopy, the pouch, afferent ileal limb, anastomosis, and the rectal cuff should be carefully investigated.[22] The major endoscopic findings in pouchitis can be edema, erythema, hemorrhage, friability, absent vascular pattern, erosions, ulcerations, chronic inflammatory infiltrates, as well as crypt abscesses, crypt distortion, and villous atrophy that are typically distributed throughout the pouch body. A combination of the degree of mononuclear cell infiltration, segmental distribution of mononuclear cell infiltration, and eosinophil infiltration from histological criteria can have utility in the prediction of the future development of pouchitis. Therefore, taking biopsies from the pouch and afferent limb can help distinguish between pouchitis, CMV infection, CD, dysplasia, and ischemic pouchitis.[23] Another diagnostic criterion described for diagnosis of pouchitis is an assessment of Pouchitis Disease Activity Index (PDAI), while PDAI≥7 and mPDAI≥5 were established as diagnosis of pouchitis,[24] PDAI scoring system investigates stool frequency, rectal bleeding, fecal urgency, fever, and endoscopic and histologic inflammation, and a PDAI score equal to or greater than 7 verifies pouchitis.[25]

Quick biomarkers such as fecal lactoferrin have been used in the diagnosis of pouchitis. They are neutrophil-derived proteins that are stable in feces and are detected as fast as possible by quantitative enzyme-linked immunosorbent assay (ELISA) in small sample sizes in patients with gastrointestinal inflammation. They can predict clinical relapse in IBD patients in remission and also be used for early diagnosis and prediction of pouchitis after ileostomy closure following proctocolectomy. When fecal lactoferritin is applied with fecal calprotectin, the sensitivity and specificity reach 90% and 86%, respectively.[26] Fecal calprotectin is a zinc- and calcium-binding protein and another quick, reliable, and inexpensive mucosal inflammatory biomarker with a high sensitivity and good reproducibility found in the cytoplasm of neutrophils for detection of pouchitis patients using ELISA and enzyme fluoroimmunoassays. When utilized together with other biomarkers, the specificity increases.[27, 28] There are other biomarkers for the identification of acute pouchitis such as alpha-1 antitrypsin (AAT with a sensitivity of 55.6% and specificity of 100%), and fecal M2-pyruvate kinase (a glycolytic enzyme that is upregulated with cell turnover and has a sensitivity of 80% and specificity of 70.6%).[29, 30] The expression of interferon-gamma (IFN-γ) in the ileal mucosa can be an important factor in the diagnosis and pathophysiology of pouchitis.[31] The neutrophil-to-lymphocyte ratio (NLR) in 79 patients who underwent IPAA can have a diagnostic role in predicting the development of pouchitis after IPAA in clinical practice.[32] In patients with or without subsequent recurrent/chronic pouchitis who underwent IPAA, a computational miRNA-based algorithm could accurately predict recurrent/chronic pouchitis.[33]

Treatment of Puchitis

Pouchitis is characterized by inflammation, mainly in the pouch, and may be complicated by abscesses, fistulae, and stricture of the pouch–inlet, and lead to the development of pouch neoplasia by the appearance of a low- or high-grade dysplasia, or colorectal cancer (CRC) at anal transitional zone, cuff, pouch body or afferent limb. Thus, it is a condition with large unmet medical needs, even treatment of pouchitis depends on the phenotype of the disease.[34] Conventional therapy is usually directed toward the modification of bacterial flora, mainly with antibiotics and more recently with probiotics.[35]

Antibiotic Therapy

Long-term safety and efficacy of maintenance antibiotic therapy for chronic pouchitis was assessed revealing remission in 21% of patients and side effects in 28% of patients. Therefore, the use of long-term antibiotics should be weighed against potential complications.[36] The first trial of antibiotic use in the treatment of acute pouchitis was carried out by Madden and others in 11 patients utilizing metronidazole (1200 mg/day).[36] Other antibiotics such as erythromycin, tetracycline, amoxicillin/clavulanate, ciprofloxacin, rifaximin, or metronidazole were also used with success in small uncontrolled and open-label trials.[37]

Ciprofloxacin was recommended as the first-line treatment for pouchitis. Ciprofloxacin with rifaximin or metronidazole has been the most recommended combination with high rates of response (about 80%), but it increased the risk of adverse effects based on prolonged use of antibiotics.[37, 38] Ciprofloxacin (1000 mg/day) and metronidazole (20 mg/Kg/day) in 16 patients with acute pouchitis for 2 weeks improved clinical symptoms, even ciprofloxacin produced a greater clinical response with zero adverse events, while with metronidazole, they experienced adverse effects.[39] Rifaximin with ciprofloxacin has been the most suggested combination with about 80% response, but it increased the risk of adverse effects due to prolonged use of antibiotics.[38, 39] Madden and colleagues in 11 patients utilized

metronidazole (1200 mg/day) for 1 week leading to a reduction in the median frequency of stools (73%) when compared with placebo (9%).[36] Metronidazole has been utilized in the treatment of *C. difficile* infection in patients with pouchitis leading to clinical improvement; while the recurrence rate has been as high as 57%.[40] However, metronidazole was demonstrated to be tolerated hard and with adverse side effects such as nausea, dysgeusia, and peripheral neuropathy.[34] Topical metronidazole (80 mg) as enemas twice daily for 1 week was effective in four IPAA patients, and they responded to the therapy.[41]

Vancomycin was administered with clinical improvement in the treatment of *C. difficile* infection of patients with pouchitis; while the recurrence rate was as high as 57%.[40, 41] Treatment with oral vancomycin improved symptoms in 154 pouch patients who had postoperative *C. difficile* stool testing of 7.1% after final surgical stage and had symptoms of increased stool frequency, fever, incontinence, hematochezia, urgency, and abdominal and/or pelvic pain.[42] Sulfasalazine was administered with clinical improvement in the treatment of pouchitis. The use of sulfasalazine (2 g) was effective after 68 months and after therapy, pouchitis was developed just in 15% of patients in comparison to 64.5% among those not taking any drug.[43] In a rat model of pouchitis, 2,4,6-trinitrobenzene sulfonic acid as a nitroaryl oxidizing acid was documented in the treatment of pouchitis.[44]

Based on their response to antibiotics, patients are categorized into responsive (good response), dependent (need for maintenance therapy), or refractory (no response) types. It was shown that refractory or frequently relapsing pouchitis occurred in 5-19% of patients with acute pouchitis. Among 46 patients with pouchitis clinical symptoms, 25% did not present objective evidence of pouchitis on endoscopy or histology and were not responsive to treatment with antibiotics.[20] Moreover, in 20-30% of patients with pouchitis who developed antibiotic resistance, there may be a need for pouch excision or permanent diversion. The efficacy of antibiotic therapy for pouchitis can be due to the establishment of an antibiotic-resistant microbiome with low inflammatory potential, while this microbiome can cause resistance against colonization by bacteria that promote inflammation. To inhibit progression to antibiotic-dependent disease and its consequences, interventions such as short-term alternating antibiotics and nutrition- and microbiome-based interventions were targeted.[7] For the treatment of chronic pouchitis and the concern of antibiotic resistance due to the use of several antibiotics, alternative medications were recommended.[7] Davanas reported utilization of off-label medicine povidone-iodine enemas/suppositories for "terminal" pouchitis.[45]

Anti-Tumor Necrosis Factor (TNF) Drugs

In case of severe chronic refractory pouchitis, patients may benefit from biological treatment of anti-tumor necrosis factor (TNF). TNF inhibitors, including infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab are biological agents with FDA approval to treat CD. The therapeutic efficacy of anti-TNF in chronic refractory pouchitis was reported in the short- and long-term.[46] In a meta-analysis, anti-TNF therapy had higher and faster efficacy in distinguishing chronic antibiotic-refractory pouchitis from CD of the pouch.[46] Herfarth and others reported TNF-alpha (TNF-α) inhibitors are effective for the treatment of pouchitis.[47]

The first reports of biological therapy and response rate with infliximab, as a TNF inhibitor, were 50% after 1 year.[48, 49] Koumaki and colleagues reported a male case of chronic refractory pouchitis-associated pyoderma gangrenosum who was successfully treated with infliximab after proctocolectomy and IPAA undertaken for severe UC.[50] A case of refractory pouchitis complicated by CMV infection was treated with infliximab and ganciclovir demonstrating the resolving of symptoms and disappearance of CMV-positive cells without any recurrence of pouchitis.[51] Infliximab has been effective in patients with elevated serum TNF-α.[52] The effectiveness and safety of tofacitinib, as a TNF inhibitor, in patients with chronic pouchitis multi-refractory to biologics were also demonstrated.[53] Adalimumab, another TNF inhibitor, was successfully administered in patients who failed infliximab in the treatment of pouchitis.[54] In another patient, adalimumab was effectively used in the treatment of chronic pouchitis with liver transplantation for fulminant *Herpes simplex* hepatitis.[55] Kjaer and others reported treatment with adalimumab in 13 patients with refractory pouchitis in a randomized controlled trial as well.[56]

Corticosteroids

Treatment with 9 mg budesonide for 8 weeks, as a corticosteroid medication, could improve the quality of life in 20 patients with antibiotic-refractory pouchitis with a remission rate of 75%.[57] In patients with acute pouchitis, all went into remission when oral budesonide (9 mg/day for 3 months, followed by 3-6 mg/day for maintenance) was administered.[58]

Local budesonide foam (2 mg/100 mL nightly) or metronidazole (1000 mg daily) in 26 patients over 6 weeks revealed similar improvements in PDAI, endoscopic scores, and histologic scores.[59] Central serous chorioretinopathy in a 44-year-old male patient with UC and pouchitis happened after budesonide use.[60]

Monoclonal Antibodies

In active pouchitis, a severe infiltration of the mucosa by immune cells happens and an increased proportion of mucosal dendritic cells expressing integrin β7 are noted that have a pathogenic role in the pathogenesis of pouchitis. Blockade of α4β7 integrin with vedolizumab can have a promising therapeutic effect in pouchitis.[61] Several studies revealed vedolizumab to be the treatment of choice in pouchitis. Vedolizumab, a monoclonal antibody, can selectively block gut lymphocyte trafficking by interacting with α4β7 heterodimer.[61] It suppresses intestinal inflammation through inhibition of leukocyte trafficking to the digestive tract.[61] Treatment with vedolizumab was more effective than placebo in inducing remission in patients with chronic pouchitis after undergoing IPAA for UC.[62] It can better control markers of inflammation approved by improvements in endoscopic/histologic outcomes in the pouch mucosa.[63] Vedolizumab (300 mg) in chronic, antibiotic-dependent, or refractory pouchitis decreased PDAI remarkably without any serious side effects.[64] After starting vedolizumab in patients with chronic pouchitis, the rate of endoscopic response at 6 months was 58.3% and for clinical response at 12 months, it was 39.1%.[65] Successful treatment with vedolizumab was reported in a patient with chronic refractory pouchitis and primary sclerosing cholangitis as well.[66]

In a 41-year-old female with pancolonic UC who underwent a total proctocolectomy with IPAA, vedolizumab (300 mg parenterally) decreased the frequency of bowel movements without blood or mucus and improvement of abdominal pain via a gut-specific immune modulation.[67] Vedolizumab showed to have impressive endoscopic improvement for chronic, antibiotic-dependent, or refractory pouchitis in a female patient with chronic refractory pouchitis undergoing proctocolectomy with IPAA and multiple ulcers, edema, loss of vascular pattern, and fistulas in pouchoscopy.[68] In 12 patients with CD of the pouch who received vedolizumab, therapy was effective and safe in reducing the symptoms.[69] Ribaldone and colleagues reported that vedolizumab caused an effective clinical improvement in chronic refractory pouchitis in a systematic review enrolling 44 patients with chronic pouchitis and also in patients who failed to respond to other treatments such as anti-TNF agents.[70] In a male patient with pancolonic UC and primary failure of infliximab and mesalamine and intolerance of azathioprine who underwent total proctocolectomy with IPAA, vedolizumab was safely and effectively administered in the management of anti-TNF-alpha refractory pouchitis.[71] Records from 39 patients with UC and IPAA who received infliximab, adalimumab, vedolizumab, or cyclosporine for pouchitis revealed that vedolizumab was more efficacious and safe in treating chronic antibiotic-refractory pouchitis patients.[72] Vedolizumab could treat luminal disease remission in a female patient with anti-TNF refractory pouchitis and autoimmune hemolytic anemia.[73] Vedolizumab was also successfully administered in combination with etanercept in a patient with pouchitis to control the disease safely.[74] Among 19 patients with chronic antibiotic-refractory pouchitis, vedolizumab was effective and safe in treating chronic antibiotic-refractory pouchitis.[75]

Ustekinumab, as another treatment of choice for pouchitis, is a human IgG1 kappa monoclonal antibody against p40 subunit of interleukin-12/23. It improved clinical symptoms of pouchitis such as bowel movements and endoscopic subscore of the PDAI after 1 year.[76] In an open-label pilot study in patients with chronic antibiotic refractory pouchitis, maintenance therapy with ustekinumab led to a clinical and endoscopic improvement in half of the patients.[77] In another study after starting ustekinumab, the rate of clinical and endoscopic response at 6 months was 83% and 60%, respectively.[78] Additionally, ustekinumab rescue therapy in a male patient with chronic refractory pouchitis resulted in improvement of clinical symptoms at week 4 with a decrease in the frequency of defecation.[79]

Immunosuppressive Drugs

The safety and effectiveness of tacrolimus as an immunosuppressive drug in a review of 188 patients with chronic refractory pouchitis were assessed showing a clinical remission of 57.1%, 57.14%, and 70.0% in patients with proctitis, fistulizing perianal CD, and chronic pouchitis, while the most commonly reported side effects were perianal itching and burning.[80] Successful treatment of refractory pyoderma gangrenosum with pouchitis after restorative proctocolectomy for ulcerative colitis was reported using tacrolimus.[81] Uchino and colleagues also reported successful use of topical tacrolimus therapy for antibiotic-refractory pouchitis.[82]

Janus Kinase (JAK) Inhibitors

The effectiveness and safety of tofacitinib have been exhibited in patients with chronic pouchitis multi-refractory to biologics.[53, 83] A female case of refractory pouchitis who underwent surgery and did not respond to conventional conservative treatment of anti-TNF therapy, systemic steroid, and vedolizumab, was successfully treated with tofacitinib as a Janus kinase (JAK) inhibitor and a medication that is used to treat UC was administered. It resulted in improvement in her symptoms as well as the appearance of the pouch in endoscopy.[84]

Thiopurine Drugs

Thiopurines, which are purine antimetabolites widely used in the treatment of autoimmune disorders, were utilized for the biological therapy of patients with refractory pouchitis.[85] Alicaforsen is a 20-base antisense oligonucleotide that can inhibit ICAM-1 production and has a role as an adhesion molecule involved in leukocyte migration and trafficking to the site of inflammation. It showed beneficial effects in patients with chronic refractory pouchitis after restorative proctocolectomy with IPAA of UC.[86]

Prolyl Hydroxylase–Containing Enzymes

Hypoxia-inducible transcription factor prolyl hydroxylase–containing enzymes (PHD1, PHD2, and PHD3) are molecular oxygen sensors that can control adaptive gene expression through hypoxia-inducible factor (HIF) and are targeted in the treatment of intestinal inflammation. Harnoss and others established a strong therapeutic rationale for targeting PHD1 with small-molecule inhibitors in pouchitis following IPAA for UC.[87]

Leukocytapheresis

Successful treatment of chronic antibiotic refractory diversion pouchitis following IPAA for UC with diverting ileostomy by leukocytapheresis was reported before. The mucosa of the diverted pouch is less exposed to the fecal stream and pathogens. Therefore, the modified immunity plays an important role in the maintenance of diversion pouchitis.[88]

Dextrose Sprays

In recent years, hypertonic dextrose spray was successfully used in colorectal anastomosis bleeding and diversion pouchitis.[89] The first case of hypertonic glucose spray was reported for the management of diffuse diversion ileal pouch bleeding, which was safe and inexpensive and had a very low chance of causing transient hyperglycemia. It had the potential to reduce bleeding recurrence and the need for surgical interventions.[90] A patient with UC who suffered from hematochezia and diffuse mucosal bleeding in a diverted ileal pouch, was successfully treated with an endoscopic spray of 50% hypertonic glucose. It is a safe and inexpensive method with a very low risk of complications acting via osmotic dehydration and sclerosant impacts. The treatment caused long-term mural necrosis, fibrotic obliteration of mucosal vessels, and decreased bleeding. Moreover, the need for surgical interventions declined.[91]

Probiotics

Digestive microbiota plays an important role in the development of pouchitis in UC patients after restorative proctocolectomy with IPAA and wide use of antibiotics. A possible safer prophylactic and therapeutic alternative in the treatment of pouchitis is the administration of probiotics.[92] A probiotic mixture as prophylaxis after the first episode of pouchitis was recommended to reduce the risk of developing pouchitis.[93] Specific probiotic mixture with eight bacterial strains of Bifidobacteria (*Bifidobacterium longum*, *B. breve*, and *B. infantis*), Lactobacilli (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus,* and *L. delbrueckii* ssp. bulgaricus), *Streptococcus thermophilus*, and *Streptococcus salivarius* (900 billion bacteria) was used for the primary prevention of pouchitis in a trial of 40 patients, showing that 10% of patients responded to the therapy developed pouchitis after 12 months, and the quality of life was also improved.[94] Among 117 patients who underwent IPAA and received daily *L. rhamnosus*, pouchitis occurred less frequently.[95] The therapeutic potential of *L. acidophilus* for the treatment of pouchitis in a rat model was investigated leading to a decrease in pro-inflammatory factors, an increase in anti-inflammatory factors, and restoring ZO-1 expression in the mucosa.[96]

In 31 pouchitis patients receiving prophylaxis treatment with a probiotic mixture and a group of patients without any treatment, no new case of pouchitis was observed during prophylaxis treatment.[97] In 40 patients who achieved remission with antibiotics and received 6 g/day probiotic mixture for prevention of new episodes, only 15% of patients developed chronic pouchitis.[35] In 76 patients who received a probiotic mixture, 85% of patients maintained remission.[98] Among 31 patients with antibiotic-dependent pouchitis, administration of a probiotic mixture as the maintenance therapy after the induction of remission with ciprofloxacin could stop medication in 81% of patients at 8 months.[99]

In 23 patients with mild pouchitis who received once-daily high doses of probiotics twice per day for 28 days (3600 billion bacteria/day), 69% were in clinical remission based on PDAI score.[100]

Diet and Lifestyle

Dietary components in fruits and vegetables can affect pouch function through their impact on small bowel water content, upper gastrointestinal transit, and the structure and fermentative activity of the pouch microbiota. The risk of pouchitis was inversely related to the intake of fruits.[101] Fruit consumption was demonstrated to be associated with modifications in microbial composition in pouch patients, leading to lower rates of pouchitis.[102] Kousgaard and others were the only group that reported microbial diversity was not correlated with the consumption of fruit.[103]

Fecal Microbiota Transplantation

Pouchitis is an inflammatory disease that can be induced by a lack of the fecal stream and the subsequent lack of nutrients from luminal bacteria. Non-surgical interventions are the administration of antibiotics, short-chain fatty acid enemas, glucocorticoids, and 5-aminosalicylic acids, but the efficacy of these treatments has not been documented. In recent years, both positive and negative clinical outcomes of treating chronic pouchitis with fecal microbiota transplantation were demonstrated.[93] Gundling and colleagues successfully used autologous fecal transplantation as a safe and inexpensive procedure, with little risk of complications in the re-establishment of microbiota in a patient with chronic diversion colitis;[81] changing microbial composition and function was reported as the Achilles heel of therapy for pouchitis.[104] In a study conducted by Ardalan and colleagues, it was found that analyzing the pouch microbiota could provide insights into how antibiotic treatment may be effective for pouchitis offering a potential basis for enhancing antimicrobial strategies.[105] Hence, gut microbiota has a key role in the etiology of pouchitis; and transplantation of fecal microbiota is a promising new treatment for chronic pouchitis;[106] and changing fecal microbiome in patients with chronic pouchitis can lead to beneficial outcomes.[107]

Single fecal microbiota transplantation by colonoscopy was performed safely and effectively in a case series on three Japanese UC patients with chronic pouchitis after restorative proctocolectomy with IPAA.[108] Protease-producing bacteria can increase fecal proteolytic activity and lead to disruption of tight junction proteins and increased epithelial permeability in a protease-activated receptor-2 (PAR2)-dependent manner and finally to pouch inflammation.[109] In nine patients with chronic pouchitis who were treated with fecal microbiota transplantation, improvement of clinical symptoms, changes in gut microbiota, and quality of life were noted.[110] Fecal microbiota transplantation of 69 patients with chronic pouchitis led to a clinical response in 31.8% of patients at various time points, and clinical remission in 22.7% of patients without any adverse events.[111] In another study, transplantation of fecal microbiota had encouraging results in the treatment of chronic pouchitis.[112] NOD2 signaling pathway could contribute to intrinsic bacterial dysbiosis which was pre-existing and predisposed individuals to pouchitis.[113] Deepak and others targeted pouchitis treatment by specific dysbiosis in bacteria to generate secondary bile acids, specifically lithocholic acid, to reduce colitis severity and stimulation of the bile acid-responsive G-protein-coupled receptor TGR5 in immune cells.[114]

In contrast, reports are showing that fecal microbiota transplantation is not effective in the treatment of chronic pouchitis, even though the procedure is safe.[3] Fecal microbiota transplantation for 2 weeks in 20 patients with antibiotic-dependent pouchitis resulted in low clinical efficacy, revealing the absence of any superiority for fecal microbiota transplantation in antibiotic-dependent pouchitis patients.[115] In another study on 19 pouchitis patients undergoing fecal microbiota transplantation, the microbiota was tolerable and with short-term safety that could decrease bowel movements in patients with chronic pouchitis in the absence of any robust endoscopic or histologic changes.[116]

Herbal Medicines

Both patients and physicians seek complementary and alternative medicines - including a wide range of plants, herbs, and formulations, such as cannabis, curcumin, fish oil, and De Simone Formulation- for pouchitis to alleviate symptoms by targeting trigger foods and reducing inflammation levels.[117, 118] The safety and efficacy of Hange-Shashin-To (HST) as a combination of seven herbs (*Pinelliae Tuber*, *Scutellariae Radix*, *Glycyrrhizae Radix*, *Zizyphi Fructus*, *Ginseng Radix*, *Zingiberis Scicatum Rhizoma*, and *Coptidis Rhizoma*) in the treatment of chronic pouchitis was assessed in 14 patients revealing a decrease in the total ciprofloxacin dose in the absence of any adverse events.[119] Plant-based polyphenolic compounds in 78% of patients with refractory pouchitis could reduce the frequency of bowel

movements and bleeding, causing complete relief and improvement.[120]

The lack of well-designed studies due to the heterogeneity of patients should be mentioned as a limitation. Lack of culture for the majority of intestinal organisms and the absence of a murine model of pouchitis can be mentioned as well.

Conclusion

Pouchitis can develop in patients with IBD after IPAA and lead to a significant impairment in quality of life. As pouchitis treatment is still one of the biggest gaps of knowledge in IBD and efficacy of treatments for pouchitis are still uncertain, well-designed and adequately powered studies are needed to assess optimal treatments in the therapy and prevention of pouchitis. Changes in dietary components, administration of complementary and alternative medicine, probiotics, and fecal transplantation in addition to conventional therapies can affect the outcomes of the disease outcomes.

Authors' Contribution

S.M.K.H.A: Study design, collecting data, writing, reviewing, and finalizing the manuscript; G.M: collecting data, reviewing, editing, and finalizing the manuscript; S.J.M: Study design and writing the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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