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Treatment of acute pouchitis

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A B S T R A C T

Acute pouchitis is a common disease that affects many patients with an ileal pouch-anal anastomosis. The management of acute pouchitis remains largely empiric with the mainstay of therapy being the antibiotics ciprofloxacin and metronidazole. Probiotics may have a role in the primary and secondary prophylaxis of acute pouchitis. In addition, there are modest data that probiotics are effective in the treatment of mild acute pouchitis. There are limited data for other treatments of acute pouchitis including oral and rectal budesonide and glutamine suppositories. Diet plays a largely undefined role in the development and management of acute pouchitis, and, although many have been studied, no specific diet can currently be recommended. Larger well-designed clinical trials are necessary to confirm the efficacy of current treatments and to investigate new treatments for the management of acute pouchitis.

Introduction

Pouchitis is an idiopathic inflammatory condition of the surgically constructed pouch in a patient who has an ileal pouch-anal anastomosis (IPAA) after total proctocolectomy (TPC), usually in the setting of management of ulcerative colitis (UC) or familial adenomatous polyposis (FAP).[1] Symptoms of pouchitis include abdominal pain, increased stool frequency, incontinence, tenesmus, fecal urgency, and diarrhea. Pouchitis occurs at a rate of 31% in patients who undergo TPC with IPAA for UC as compared to only 6% in patients with a surgical indication of FAP.[2] Further, 34% of patients with a pouch will develop an episode of pouchitis that is easily treated and does not recur, 61% will suffer at least a second episode, and 16% will go on to develop chronic or refractory pouchitis.[3,4]

Pouchitis is classified based on its response to management and also based on its chronicity. The typical management categories are antibiotic responsive, antibiotic dependent, and antibiotic refractory. It can also be classified as acute, acute relapsing, and chronic or refractory.[5] Additionally, there can be infectious or other causes of pouchitis, referred to as secondary pouchitis and already discussed in the previous article.

Risk factors for the development of pouchitis include prior extensive colonic disease from UC, surgical complications after the creation of an IPAA, the presence of cuffitis, extraintestinal manifestations of inflammatory bowel disease (IBD), concurrent primary sclerosing cholangitis (PSC), possibly smoking, and the use of postoperative nonsteroidal anti-inflammatory drugs (NSAIDs).[6–10] Antineutrophil cytoplasmic antibody (ANCA) positivity has been found to be a predictor of chronic but not acute pouchitis.[11] This article focuses on the prevention and management of acute pouchitis.

Management of secondary pouchitis

Prior to committing to the management of acute idiopathic pouchitis, a thorough work-up should be undertaken to exclude specific treatable etiologies of secondary pouch inflammation, which occur in up to 30% of patients.[5] Although uncommon, both *Clostridium difficile* (*C. difficile*) and cytomegalovirus (CMV) infection can cause secondary pouchitis. These infections should always be looked for in patients with clinical symptoms suggestive of pouchitis, and, if found, treated with the appropriate antibacterial or antiviral therapy. Recently, ursodiol has shown some promise in the treatment of *C. difficile*-associated pouchitis through inhibition of spore germination and vegetative growth.[12]

NSAIDs have also been identified as contributing to the development of pouchitis, especially in antibiotic refractory disease, and should be discontinued. Other differential etiologies that, though uncommon, should be considered and managed include ischemic, autoimmune, Crohn's-related, and collagenous pouchitis.[13]

Prophylaxis of pouchitis

Probiotics have been used to try to prevent a first bout of pouchitis (primary prophylaxis) or a repeat occurrence of pouchitis

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after an initial episode (secondary prophylaxis).[14] A well-studied probiotic for prophylaxis of pouchitis is VSL #3, a high-potency probiotic that contains an 8 strains of lactic acid producing bacteria. The specific strains of bacteria included in VSL #3 are *Streptococcus thermophilus (S. thermophilus), Bifidobacterium breve (B. breve), Bifidobacterium longum (B. longum), Bifidobacterium infantis (B. infantis), Lactobacillus acidophilus (L. acidophilus), Lactobacillus plantarum (L. plantarum), Lactobacillus paracasei (L. paracasei),* and *Lactobacillus delbrueckii subspecies bulgaricus (L. delbrueckii subsp. bulgaricus)*. Studies of VSL #3 have shown that it increases the diversity and richness of the bacterial microbiota while at the same time repressing fungal flora.[15] There is a growing consensus that pouchitis is associated with a decrease in the biodiversity of the stool microbiota.[16]

In a double-blind, placebo-controlled trial of 40 patients, Gionchetti et al. evaluated VSL #3 for primary prophylaxis of acute pouchitis. Patients were randomized within the first week after pouch creation to 1 packet containing 900 billion colony forming units (CFU) once daily of VSL #3 or placebo and followed for 1 year. There was a statistically significant benefit in favor of VSL #3 as primary prophylaxis with just 2 of 20 VSL #3-treated patients compared to 8 of 20 placebo-treated patients developing an episode of acute pouchitis within the first year.[17]

However, conflicting results were seen in an open-label, parallel-arm trial of 31 patients with no statistically significant benefit for 2 packets of 450 billion CFU of VSL #3 once daily in the prevention of acute pouchitis over a 12-month period in comparison to no treatment.[18] The incidence of acute pouchitis in this trial was very low with 0 of 16 patients in the VSL #3 arm and only 1 of 12 patients in the no treatment arm developing acute pouchitis. Another difference in this study from the Gionchetti VSL #3 prophylaxis study was that patients were enrolled at variable times from their surgery, with a mean duration of 97 months from IPAA creation. Although there was no statistical significance in preventing clinical pouchitis, this study did demonstrate that VSL #3 plays a role in immune system modulation, as VSL #3 treatment was associated with a reduction in proinflammatory cytokines and an expansion in regulatory T-cells in the mucosa of the treated patients.

In a 43 patient placebo-controlled trial of the probiotic Trilac, a composite probiotic containing 600 million CFU of *L. acidophilus*, 400 million CFU of *L. delbrueckii subsp. bulgaricus*, and 600 million CFU of *Bifidobacterium bifidus (B. bifidus)*, a statistically significant reduction in the modified pouch disease activity index (PDAI) was seen. The dosing used was 2 capsules of Trilac 3 times daily for the first month and 1 capsule twice daily for the remainder of the study period. Over a 9-month period, average PDAI scores decreased and, in some cases, fell to levels (<7) below which patients would not be considered to have pouchitis. Additionally, there was a reduction in fecal calprotectin levels suggesting that the probiotics decreased pouch inflammation.[19] A more recent and slightly smaller randomized and placebo-controlled trial of 32 patients treated twice daily with a probiotic combining 5 billion CFU of *L. plantarum* and 5 billion CFU of *B. infantis* showed no improvement in PDAI after 1 month.[20] Interestingly, this study did show a correlation between PDAI and specific fecal biomarker levels including calprotectin, lactoferrin, myeloperoxidase, and eosinophilic cationic protein. These biomarkers could play a role in the assessment and management of acute pouchitis in the future.

Other trials of probiotics for the primary prophylaxis of pouchitis have also shown promise, though the data are overall limited and results conflicting. In a consecutive series of 39 patients treated with *Lactobacillus rhamnosus* GG (LGG) compared to 78 control patients with no treatment, daily intake of 14 million CFU of this bacterial strain was statistically significant at reducing the risk of developing a single episode of acute pouchitis from 29% to 7% over a 3-year period. It was notable that after stopping LGG, no LGG could be detected in the stool 48 hours later, suggesting that the probiotic effect on the pouch microflora is transient.[21] A recent randomized placebo-controlled trial of 17 patients followed for 24 months showed favorable, although not statistically significant, results for *Clostridium butyricum* MIYAIRI (CBM), dosed at 90 million CFU once daily, as a complementary therapy for the prevention of pouchitis (Table 1).[22]

In addition to probiotics, other agents have been looked at for the prophylaxis of pouchitis. A cross-sectional study of 85 patients showed an association between chronic, regular use of proton pump inhibitors (PPIs), and H2-antagonists and a decrease in the risk of developing pouchitis.[23] A large double-blind trial of 184 patients showed no benefit for 100 milligrams (mg) of allopurinol twice daily as prophylaxis over a 2-year period.[24] Additionally, although a double-blind trial of 38 patients randomized to tinidazole 500 mg daily or placebo showed no statistically significant benefit for the use of tinidazole as prophylaxis over a 1-year period, there was a trend toward preventing initial episodes.[25]

Secondary prophylaxis with VSL #3 resulted in a statistically significant higher rate of remission in patients with prior pouchitis in a double-blind, placebo-controlled trial. In this study, 40 patients with acute pouchitis were treated with antibiotics to obtain remission and then randomized to receive either 3 trillion CFU of VSL #3 or placebo for 9 months. In the VSL #3-treated group, only 3 of 20 patients developed recurrent pouchitis compared to 20 of 20 patients in the placebo group.[26] Similar results in a 36 patient randomized, placebo-controlled trial confirmed the utility of VSL #3 as an agent for secondary prophylaxis as 85% of patients who received 3 trillion CFU of VSL #3 maintained remissions compared to 6% in the placebo group at 1 year. It should be noted that this study was done in a recurrent and refractory pouchitis population.[27] *B. longum* alone showed no

Table 1
Use of probiotics to prevent the onset of pouchitis (primary prevention).

Study	No. of patients	Duration (months)	Probiotic (dose and frequency)	Control	Outcome
Gionchetti et al.[17]	40	12	VSL #3 (900 billion CFU once daily)	Placebo	90% in VSL #3 vs 60% in placebo pouchitis free*
Gosselink et al.[21]	117	36	LGG (14 million CFU once daily)	No treatment	93% in LGG vs 71% in no treatment pouchitis free*
Pronio et al.[18]	31	12	VSL #3 (900 billion CFU once daily)	No treatment	100% in VSL #3 vs 92% in no treatment pouchitis free
Tomasz et al.[19]	43	9	Trilac (2 capsules 3 times per day for 1 month then 1 capsule twice per day for 8 months)	Placebo	Average PDAI decreased from 6.3 to 4.4 in Trilac vs no change in placebo*
Yasueda et al.[22]	17	24	CBM (90 million CFU once daily)	Placebo	89% in CBM vs 50% in placebo pouchitis free
Bengtsson et al.[20]	32	1	*L. plantarum* and *B. infantis* (combination pill of 500 billion CFU of each twice per day)	Placebo	No change in PDAI in either group

* Statistical significance of the outcome.