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Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis

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Abstract

Background—Pouchitis occurs in approximately 50% of patients following ileal pouch-anal anastomosis (IPAA) for chronic ulcerative colitis.

Objectives—The primary objective was to determine the efficacy and safety of medical therapies (including antibiotics, probiotics, and other agents) for prevention or treatment of acute or chronic pouchitis.

Search methods—We searched MEDLINE, EMBASE and the Cochrane Library from inception to October 2014.

Selection criteria—Randomized controlled trials of prevention or treatment of acute or chronic pouchitis in adults who underwent IPAA for ulcerative colitis were considered for inclusion.

Data collection and analysis—Two authors independently screened studies for eligibility, extracted data and assessed study quality. Methodological quality was assessed using the Cochrane risk of bias tool. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria. The primary outcome was the proportion of patients with clinical improvement or remission of pouchitis in patients with acute or chronic pouchitis, or the proportion of patients with no episodes of pouchitis after IPAA. The proportion of patients who developed at least one adverse event was a secondary outcome. We calculated the risk ratio (RR) and corresponding 95% confidence interval (CI) for each dichotomous outcome.

Main results—Thirteen studies (517 participants) were included in the review. Four studies assessed treatment of acute pouchitis. One study (16 participants) compared ciprofloxacin and metronidazole; another (26 participants) compared metronidazole to budesonide enemas; another (18 participants) compared rifaximin to placebo; and the fourth study (20 participants) compared *Lactobacillus GG* to placebo. Four studies assessed treatment of chronic pouchitis. One study (19

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participants) compared glutamine to butyrate suppositories; another (40 participants) compared bismuth enemas to placebo; and two studies (76 participants) compared VSL#3 to placebo. Five studies assessed prevention of pouchitis. One study (40 participants) compared VSL#3 to placebo; another (28 participants) compared VLS# 3 to no treatment; one study (184 participants) compared allopurinol to placebo; another (12 participants) compared the probiotic *Bifidobacterium longum* to placebo; and one study (38 participants) compared tinidazole to placebo. Three studies were judged to be of high quality. Two studies were judged to be low quality and the quality of the other studies was unclear.

Treatment of acute pouchitis: The results of one small study (16 participants) suggest that ciprofloxacin may be more effective than metronidazole for the treatment of acute pouchitis. One hundred per cent (7/7) of ciprofloxacin patients achieved remission at two weeks compared to 33% (3/9) of metronidazole patients. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias (no blinding) and very sparse data (10 events). There was no difference in the proportion of patients who had at least one adverse event (RR 0.18, 95% CI 0.01 to 2.98). Adverse events included vomiting, dysgeusia or transient peripheral neuropathy. There were no differences between metronidazole and budesonide enemas in terms of clinical remission, clinical improvement or adverse events. Adverse events included anorexia, nausea, headache, asthenia, metallic taste, vomiting, paraesthesia, and depression. There were no differences between rifaximin and placebo in terms of clinical remission, clinical improvement, or adverse events. Adverse events included diarrhea, flatulence, nausea, proctalgia, vomiting, thirst, candida, upper respiratory tract infection, increased hepatic enzyme, and cluster headache. There was no difference in clinical improvement between *Lactobacillus GG* and placebo. The results of these studies are uncertain due to very low quality evidence.

Treatment of chronic pouchitis: A pooled analysis of two studies (76 participants) suggests that VSL#3 may be more effective than placebo for maintenance of remission. Eighty-five per cent (34/40) of VLS#3 patients maintained remission at 9 to 12 months compared to 3% (1/36) of placebo patients (RR 20.24, 95% CI 4.28 to 95.81). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (35 events). Adverse events included abdominal cramps, vomiting and diarrhea. There was no difference in effectiveness between glutamine and butyrate suppositories for maintenance of remission. There was no difference in clinical improvement or adverse event rates between bismuth carbomer foam enemas and placebo. Adverse events included diarrhea, worsening symptoms, cramping, sinusitis, and abdominal pain. The results of these studies are uncertain due to very low quality evidence.

Prevention of pouchitis: The results of one small study (40 participants) suggest that VSL#3 may be more effective than placebo for prevention of pouchitis. Ninety per cent (18/20) of VSL#3 patients had no episodes of acute pouchitis during the 12 month study compared to 60% (12/20) of placebo patients (RR 1.50, 95% CI 1.02 to 2.21). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (30 events). Another small study (28 participants) found that VLS# 3 was not more effective than no treatment for prevention of pouchitis. *Bifidobacterium longum*, allopurinol and tinidazole were not more effective than placebo for prevention of pouchitis. The results of these studies are uncertain due to very low quality evidence.

Authors' conclusions—For acute pouchitis, very low quality evidence suggests that ciprofloxacin may be more effective than metronidazole. For chronic pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo for maintenance of remission. For the prevention of pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo. Well designed, adequately powered studies are needed to determine the optimal therapy for the treatment and prevention of pouchitis.

PLAIN LANGUAGE SUMMARY

Therapy for treatment and prevention of pouchitis

What is pouchitis?—Some patients with ulcerative colitis have their colon and rectum removed with construction of a pouch (made from a loop of small intestine) to serve in place of the rectum. This is known as ileal pouch-anal anastomosis (IPAA) surgery. Pouchitis is inflammation of the surgically constructed pouch. Symptoms of active pouchitis include diarrhea, increased stool frequency, abdominal cramping, fecal urgency, tenesmus (feeling of constantly needing to pass stools), and incontinence. Periods when symptoms stop are called 'remission'.

What therapies are used for pouchitis?—Therapies used for pouchitis include antibiotics (drugs that fight bacteria infections), budesonide enemas (a steroid drug), probiotics (good or helpful bacteria), glutamine suppositories (an amino acid), butyrate suppositories (short chain fatty acid), bismuth enemas (diarrhea medication), allopurinol (a purine analogue drug), and tinidazole (an anti-parasitic drug).

What did the researchers investigate?—The researchers investigated whether these medications produce remission in people with active pouchitis, maintain remission in people with inactive pouchitis or prevent pouchitis in people who've had IPAA surgery and whether these medications cause any side-effects. The researchers searched the medical literature up to October 31, 2014.

What did the researchers find?—We found 13 studies that included a total of 517 participants. Four studies assessed treatment of acute pouchitis. One study (16 participants) compared the antibiotics ciprofloxacin and metronidazole; another (26 participants) compared metronidazole to budesonide enemas; another (18 participants) compared the antibiotic rifaximin to placebo (sugar pill); and the fourth study (20 participants) compared the probiotic *Lactobacillus GG* to placebo. Four studies assessed treatment of chronic pouchitis. One study (19 participants) compared glutamine to butyrate suppositories; another (40 participants) compared bismuth enemas to placebo; and two studies (76 participants) compared the probiotic VSL#3 to placebo. Five studies assessed prevention of pouchitis. One study (40 participants) compared the probiotic VSL#3 to placebo; another (28 participants) compared VLS#3 to no treatment; one study (184 participants) compared allopurinol to placebo; another (12 participants) compared the probiotic *Bifidobacterium longum* to placebo; and one study (38 participants) compared tinidazole to placebo. Three studies were judged to be of high quality. Two studies were judged to be of low quality and the quality of the other studies was unclear.

Treatment of acute pouchitis: Very low quality evidence suggests that ciprofloxacin may be more effective than metronidazole for the treatment of acute pouchitis. Side effects included vomiting, dysgeusia (metallic taste in mouth) or transient peripheral neuropathy (damage to nerves). There were no differences between metronidazole and budesonide enemas in terms of clinical remission, symptom improvement or side effects. Side effects included anorexia (an eating disorder), nausea, headache, asthenia (lack of energy and strength), metallic taste, vomiting, paraesthesia (pins and needles), and depression. There were no differences between rifaximin and placebo in terms of clinical remission, symptom improvement, or side effects. Side effects included diarrhea, flatulence, nausea, proctalgia (rectal pain), vomiting, thirst, candida (yeast infection), upper respiratory tract infection (cold or flu), increased hepatic enzyme (measure of liver function), and cluster headache. There was no difference between *Lactobacillus GG* and placebo in symptom improvement. The results of these studies are uncertain due to very low quality evidence.

Treatment of chronic pouchitis: Low quality evidence suggests that VSL#3 may be more effective than placebo for maintaining remission in people with inactive disease. Side effects included abdominal cramps, vomiting and diarrhea. There was no difference in effectiveness between glutamine and butyrate suppositories for maintenance of remission. There was no difference in symptom improvement or side effects between bismuth carbomer foam enemas and placebo. Side effects included diarrhea, worsening symptoms, cramping, sinusitis (sinus infection), and abdominal pain. The results of these studies are uncertain due to very low quality evidence.

Prevention of pouchitis: Low quality evidence suggests that VSL#3 may be more effective than placebo for prevention of pouchitis. However, one study found that VLS#3 was not more effective than no treatment for prevention of pouchitis. *Bifidobacterium longum*, allopurinol and tinidazole were not more effective than placebo for prevention of pouchitis. However, the results of these studies are uncertain due to very low quality evidence.

More research is needed to determine which of these different medications are best for treatment of pouchitis.