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Nguyen N, Zhang B, Holubar SD, Pardi DS, Singh S

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Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD001176.

DOI: 10.1002/14651858.CD001176.pub4.

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

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Editorial group: Cochrane IBD Group.

Publication status and date: Edited (no change to conclusions), published in Issue 6, 2019.

Citation: Nguyen N, Zhang B, Holubar SD, Pardi DS, Singh S. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database of Systematic Reviews* 2019, Issue 5. Art. No.: CD001176. DOI: 10.1002/14651858.CD001176.pub4.

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ABSTRACT

Background

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

Objectives

The primary objective was to determine the efficacy and safety of medical therapies for prevention or treatment of acute or chronic pouchitis.

Search methods

We searched MEDLINE, Embase and CENTRAL from inception to 25 July 2018. We also searched references, trials registers, and conference proceedings.

Selection criteria

Randomized controlled trials of prevention or treatment of acute or chronic pouchitis in adults who underwent IPAA for UC were considered for inclusion.

Data collection and analysis

Two authors independently screened studies for eligibility, extracted data and assessed the risk of bias. The certainty of the evidence was evaluated using GRADE. The primary outcome was clinical improvement or remission in participants with acute or chronic pouchitis, or the proportion of participants with no episodes of pouchitis after IPAA. Adverse events (AEs) was a secondary outcome. We calculated the risk ratio (RR) and corresponding 95% confidence interval (CI) for each dichotomous outcome.

Main results

Fifteen studies (547 participants) were included. Four studies assessed treatment of acute pouchitis. Five studies assessed treatment of chronic pouchitis. Six studies assessed prevention of pouchitis. Three studies were low risk of bias. Three studies were high risk of bias and the other studies were unclear.

Acute pouchitis: All ciprofloxacin participants (7/7) achieved remission at two weeks compared to 33% (3/9) of metronidazole participants (RR 2.68, 95% CI 1.13 to 6.35, very low certainty evidence). No ciprofloxacin participants (0/7) had an AE compared to 33% (3/9) of metronidazole participants (RR 0.18, 95% CI 0.01 to 2.98; very low certainty evidence). AEs included vomiting, dysgeusia or transient peripheral neuropathy. Forty-three per cent (6/14) of metronidazole participants achieved remission at 6 weeks compared to 50% (6/12) of budesonide enema participants (RR 0.86, 95% CI 0.37 to 1.96, very low certainty evidence). Fifty per cent (7/14) of metronidazole participants improved clinically at 6 weeks compared to 58% (7/12) of budesonide enema participants (RR 0.86, 95% CI 0.42 to 1.74, very low certainty evidence). Fifty-seven per cent (8/14) of metronidazole participants had an AE compared to 25% (3/12) of budesonide enema participants (RR 2.29, 95% CI 0.78 to 6.73, very low certainty evidence). AEs included anorexia, nausea, headache, asthenia, metallic taste, vomiting, paraesthesia, and depression. Twenty-five per cent (2/8) of rifaximin participants achieved remission at 4 weeks compared to 0% (0/10) of placebo participants (RR 6.11, 95% CI 0.33 to 111.71, very low certainty evidence). Thirty-eight per cent (3/8) of rifaximin participants improved clinically at 4 weeks compared to 30% (3/10) of placebo participants (RR 1.25, 95% CI 0.34 to 4.60, very low certainty evidence). Seventy-five per cent (6/8) of rifaximin participants had an AE compared to 50% (5/10) of placebo participants (RR 1.50, 95% CI 0.72 to 3.14, very low certainty evidence). AEs included diarrhea, flatulence, nausea, proctalgia, vomiting, thirst, candida, upper respiratory tract infection, increased hepatic enzyme, and cluster headache. Ten per cent (1/10) of *Lactobacillus GG* participants improved clinically at 12 weeks compared to 0% (0/10) of placebo participants (RR 3.00, 95% CI 0.14 to 65.90, very low certainty evidence).

Chronic pouchitis: Eighty-five per cent (34/40) of De Simone Formulation (a probiotic formulation) participants maintained remission at 9 to 12 months compared to 3% (1/36) of placebo participants (RR 20.24, 95% CI 4.28 to 95.81, 2 studies; low certainty evidence). Two per cent (1/40) of De Simone Formulation participants had an AE compared to 0% (0/36) of placebo participants (RR 2.43, 95% CI 0.11 to 55.89; low certainty evidence). AEs included abdominal cramps, vomiting and diarrhea. Fifty per cent (3/6) of adalimumab patients achieved clinical improvement at 4 weeks compared to 43% (3/7) of placebo participants (RR, 1.17, 95% CI 0.36 to 3.76, low certainty evidence). Sixty per cent (6/10) of glutamine participants maintained remission at 3 weeks compared to 33% (3/9) of butyrate participants (RR 1.80, 95% CI 0.63 to 5.16, very low certainty evidence). Forty-five per cent (9/20) of patients treated with bismuth carbomer foam enema improved clinically at 3 weeks compared to 45% (9/20) of placebo participants (RR 1.00, 95% CI 0.50 to 1.98, very low certainty evidence). Twenty-five per cent (5/20) of participants in the bismuth carbomer foam enema group had an AE compared to 35% (7/20) of placebo participants (RR 0.71, 95% CI 0.27 to 1.88, very low certainty evidence). Adverse events included diarrhea, worsening symptoms, cramping, sinusitis, and abdominal pain.

Prevention: At 12 months, 90% (18/20) of De Simone Formulation participants had no episodes of acute pouchitis compared to 60% (12/20) of placebo participants (RR 1.50, 95% CI 1.02 to 2.21, low certainty evidence). Another study found 100% (16/16) of De Simone Formulation participants had no episodes of acute pouchitis at 12 months compared to 92% (11/12) of the no treatment control group (RR 1.10, 95% CI 0.89 to 1.36, very low certainty evidence). Eighty-six per cent (6/7) of *Bifidobacterium longum* participants had no episodes of acute pouchitis at 6 months compared to 60% (3/5) of placebo participants (RR 1.43, 95% CI 0.66 to 3.11, very low certainty evidence). Eleven per cent (1/9) of *Clostridium butyricum* MIYAIRI participants had no episodes of acute pouchitis at 24 months compared to 50% (4/8) of placebo participants (RR 0.22, 95% CI 0.03 to 1.60, very low certainty evidence). Forty-six per cent (43/94) of allopurinol participants had no episodes of pouchitis at 24 months compared to 43% (39/90) of placebo participants (RR 1.06, 95% CI 0.76 to 1.46; low certainty evidence). Eighty-one per cent (21/26) of tinidazole participants had no episodes of pouchitis over 12 months compared to 58% (7/12) of placebo participants (RR 1.38, 95% CI 0.83 to 2.31, very low certainty evidence).

Authors' conclusions

The effects of antibiotics, probiotics and other interventions for treating and preventing pouchitis are uncertain. 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 people with ulcerative colitis have their colon and rectum removed with construction of a pouch (made from a loop of small intestine) in place of the rectum - 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. Acute refers to symptoms that last less than four weeks while chronic refers to symptoms that last more than four weeks. Periods when symptoms stop are called 'remission'.

What therapies are used for pouchitis?

Therapies used for pouchitis include antibiotics (drugs for bacteria infections), budesonide enemas (a steroid drug), probiotics (helpful bacteria), biologic agents that target tumor necrosis factor, 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. Side effects were also assessed. The medical literature was searched up to 25 July 2018.

What did the researchers find?

We found 15 studies with a total of 547 participants. Four studies assessed treatment of acute pouchitis. Five studies assessed treatment of chronic pouchitis. Six studies assessed prevention of pouchitis.

Acute pouchitis: It is uncertain whether ciprofloxacin is more effective than metronidazole for treatment of acute pouchitis (1 study, 16 participants). Side effects included vomiting, metallic taste and temporary damage to nerves. It is unclear whether there are any differences between metronidazole and budesonide enemas in terms of clinical remission, symptom improvement or side effects (1 study, 26 participants). Side effects included anorexia, nausea, headache, lack of energy and strength, metallic taste, vomiting, pins and needles, and depression. It is uncertain whether there are any differences between rifaximin and placebo in terms of clinical remission, symptom improvement, or side effects (1 study, 18 participants). Side effects included diarrhea, flatulence, nausea, rectal pain, vomiting, thirst, yeast infection, common cold, increased liver enzymes, and cluster headache. It is uncertain whether there is any difference between *Lactobacillus GG* and placebo in symptom improvement (1 study, 20 participants). The results of these studies are uncertain due to low event numbers caused by the small numbers of people who participated in the studies.

Chronic pouchitis: It is uncertain whether De Simone Formulation (a probiotic formulation) is more effective than placebo for maintaining remission in people with inactive disease (2 studies, 76 participants). Side effects included abdominal cramps, vomiting and diarrhea. It is unclear whether there is any difference in effectiveness between adalimumab and placebo for treating chronic pouchitis (1 study, 13 participants). It is unclear whether there is any difference between glutamine and butyrate suppositories for maintenance of remission (1 study, 19 participants). It is unclear whether there are any differences in symptom improvement or side effects between bismuth carbomer foam enemas and placebo (1 study, 40 participants). Side effects included diarrhea, worsening symptoms, cramping, sinus infection, and abdominal pain. The results of these studies are uncertain due to the small number of people who participated in the studies.

Prevention of pouchitis: It is uncertain whether De Simone Formulation is more effective than placebo for prevention of pouchitis (1 study, 40 participants). However, it is unclear whether there is any difference in prevention of pouchitis between De Simone Formulation and a no treatment control group (1 study, 28 participants). It is unclear whether there are any differences in prevention of pouchitis between *Clostridium butyricum* MIYAIRI and placebo (1 study, 17 participants), *Bifidobacterium longum* and placebo (1 study, 12 participants), allopurinol and placebo (1 study, 184 participants) and tinidazole and placebo (1 study, 38 participants). The results of these studies are uncertain due to the small number of people who participated in the studies.

The effects of antibiotics, probiotics and other interventions for treating and preventing pouchitis are uncertain. More research is needed to determine which of these different medications are best for treatment of pouchitis.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Ciprofloxacin versus metronidazole for treatment of acute pouchitis						
Patient or population: Patients with acute pouchitis Settings: Outpatient Intervention: Ciprofloxacin versus metronidazole						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Metronidazole	Ciprofloxacin				
Clinical remission Follow-up: 2 weeks	333 per 1000 ¹	893 per 1000 (377 to 1000)	RR 2.68 (1.13 to 6.35)	16 (1 study)	⊕○○○ very low ^{2,3}	Clinical remission defined as defined as PDAI score < 7
Clinical improvement	Not reported					
Maintenance of clinical remission	Not reported					
No episodes acute pouchitis	Not reported					
Adverse events Follow-up: 2 weeks	333 per 1000 ¹	60 per 1000 (3 to 993)	RR 0.18 (0.01 to 2.98)	16 (1 study)	⊕○○○ very low ^{2,4}	Adverse events include vomiting, dysgeusia or transient peripheral neuropathy
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to high risk of bias (no blinding).

³ Downgraded two levels due to very sparse data (10 events).

⁴ Downgraded two levels due to very sparse data (3 events).

BACKGROUND

Description of the condition

Pouchitis is an idiopathic chronic inflammatory disease that may occur in the ileal pouch after restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) (Sandborn 1994a). Although pouchitis can occur after construction of pouches for either chronic ulcerative colitis or familial adenomatous polyposis, pouchitis occurs much less frequently in the latter, providing evidence that pouchitis is less related to the structure of the pouch, but is a function of the patients' underlying immune dysregulation interacting with the pouch. The diagnosis of pouchitis is suggested by variable clinical symptoms including increased stool frequency, abdominal cramping, fecal urgency and tenesmus, incontinence, and occasionally rectal bleeding and fever. A clinical diagnosis should ideally be confirmed by endoscopy and mucosal biopsy of the pouch. Endoscopic examination shows inflammatory changes that may include mucosal edema, granularity, contact bleeding, loss of vascular pattern, hemorrhage, and ulceration (Di Febo 1990; Moskowitz 1986). Histologic examination shows acute inflammation, including neutrophil infiltration and mucosal ulceration superimposed on a background of chronic inflammation including villous atrophy, crypt hyperplasia, and chronic inflammatory cell infiltration (Moskowitz 1986; Shepherd 1987). Patients with pouchitis can be classified according to disease activity and symptom duration (Pardi 2009; Sandborn 1997). Disease activity can be classified as: remission (no active pouchitis); mild-to-moderately active (increased stool frequency, urgency, infrequent incontinence); or severely active (hospitalisation for dehydration, frequent incontinence). Symptom duration can be classified as: acute (≤ 4 weeks); or chronic (> 4 weeks). The Pouchitis Disease Activity Index (PDAI) is a 19 point index of pouchitis activity based on both clinical symptoms and endoscopic and histologic findings (Sandborn 1994b). Active pouchitis is defined as a PDAI ≥ 7 and remission is defined as a PDAI < 7 . Clinical response to treatment can also be quantified by reduction in the PDAI (e.g. a reduction in the PDAI score ≥ 3 from baseline).

After IPAA, the primary function of the terminal ileum changes from absorption to storage, and bacterial overgrowth occurs with bacterial concentrations increasing to levels which are intermediate between an end ileostomy and the colon (Sandborn 1995; Shepherd 1989). However, there is no correlation between fecal bacterial concentrations and histologic changes of acute inflammation (Sandborn 1995; Shepherd 1989), demonstrating that pouchitis is not directly related to the quantity of bacterial overgrowth. However, anaerobic bacterial overgrowth of the pouch is associated with transformation of the ileal mucosa to a 'colon-like' morphology (villous atrophy, chronic inflammatory cell infiltration) (Natori 1992; Sandborn 1995). Thus, pouch bacterial overgrowth may indirectly set the stage for pouchitis to the extent that 'colon-

like' ileal mucosa may be more susceptible to a recurrence of UC-like inflammation.

Description of the intervention

A variety of medical therapies have been investigated in the treatment of pouchitis including antibiotics, probiotics, steroid therapies, glutamine suppositories, butyrate suppositories, bismuth enemas, allopurinol, tinidazole, and anti-TNF therapy.

How the intervention might work

While there are many different medical therapies for pouchitis, it is unclear which medical therapy may be best for the treatment and prevention of pouchitis. Strategies directed towards reducing fecal concentrations of anaerobic bacteria through the use of antibiotics, or altering the relative balance of anaerobes and other bacteria using probiotic bacteria therapy, may be useful for treating pouchitis. Using this rationale, clinicians have empirically treated participants with antibiotics and have observed that most participants with pouchitis experience clinical improvement. In the absence of adequately powered, well conducted randomized trials to guide therapy, antibiotics have become the de facto 'standard' medical therapy for pouchitis. In the past, the most commonly used antibiotic for pouchitis was metronidazole (Boerr 1995; Boerr 1996; Bonello 1981; Hurst 1996; Kelly 1983; Klein 1983; Kmiot 1993; Knobler 1986; Lohmuller 1990; Moskowitz 1986; Sandborn 1994a; Scott 1989; Svaninger 1993; Tytgat 1988; Zuccaro 1989). More recently, ciprofloxacin has become the more commonly used antibiotic for pouchitis (Pardi 2006; Pardi 2009). Amoxicillin or clavulanic acid, erythromycin, and tetracycline have also been reported to be of benefit (Scott 1989). Most participants with pouchitis initially respond to ciprofloxacin at a dose of 500 to 1000 mg/day or metronidazole at doses of 750 to 1500 mg/day. Symptomatic improvement usually occurs within 1 to 2 days. Participants with relapsing or continuous pouchitis may require chronic maintenance therapy with ciprofloxacin with doses ranging from 250 mg every third day up to 1000 mg/day. Based on the Sambuelli 2002 study, budesonide enemas and metronidazole appear to have similar efficacy (58% and 50%). Although the authors of that study suggested that the enema preparation may be more tolerable than oral metronidazole, which is known to produce a metallic taste when it comes in contact with the tongue, many participants prefer oral administration to administration per anus. Nonetheless, the results of that study suggest that additional study of budesonide, whether administered orally or as a suppository, is warranted. There are two uncontrolled reports supporting this conclusion (Chopra 2006; Gionchetti 2007).

To a limited extent, this empiric approach to the manipulation of pouch bacterial flora has been validated by controlled trials of metronidazole and the De Simone Formulation (formally known as

the oral probiotic formulation VSL#3) in participants with chronic pouchitis. [Madden 1994](#) reported that the odds ratio for a decrease in stool frequency following metronidazole therapy compared with placebo in participants with active chronic pouchitis was 12.34 (95% CI 2.34 to 64.94). The single patient 'n-of-1' study of metronidazole for active chronic pouchitis also suggested benefit ([McLeod 1986](#)). However, despite the decrease in stool frequency, there was no difference between metronidazole and placebo for changes in endoscopic inflammation, general well-being, stool blood, and histologic inflammation ([Madden 1994](#)). The pooled risk ratio for maintenance of remission in participants with chronic pouchitis during administration of the oral probiotic bacteria formulation De Simone Formulation was 20.24 (95% CI 4.28 to 95.81) ([Gionchetti 2000](#); [Mimura 2004](#)). However, when examining the efficacy of the De Simone Formulation for prevention of pouchitis, conflicting results were obtained, with the De Simone Formulation being more efficacious than placebo ([Gionchetti 2003](#)) but not more efficacious than no treatment ([Pronio 2008](#)). The reason for this discrepancy is not clear. Thus, while antibiotic and probiotic bacterial therapies appear to be efficacious, antibiotic selection, dose, and duration of therapy remain empiric. Ingestion of other *Lactobacillus*-based formulations such as *Lactobacillus GG* do not appear to be as effective as the De Simone Formulation probiotic therapy. At the present time, based on the limited controlled clinical trial data available, it is reasonable to treat pouchitis with antibiotics and perhaps probiotic bacterial therapy (at least for chronic pouchitis), but additional controlled trials are needed to optimize therapy.

In the well-functioning ileal pouch, the bacterial flora produce short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate at concentrations similar to those in the colon of healthy controls, and increased compared to stomal SCFA concentrations in ileostomy patients ([Nasmyth 1989](#); [Sandborn 1995](#)). In the colon, SCFAs are the preferred fuel for colonic epithelial cell metabolism, whereas in the small bowel, glutamine is the preferred fuel for enterocyte metabolism. Some ([Clausen 1992](#); [Wischmeyer 1993](#)), but not all studies ([Sandborn 1995](#)), have reported that patients with pouchitis have lower fecal concentrations of SCFAs than patients with well-functioning IPAA, perhaps as a result of dilution ([Clausen 1992](#)). Strategies directed at replacing 'nutritional deficits' of SCFAs or glutamine in the ileal pouch by administering SCFA or glutamine enemas or suppositories may be useful for treating pouchitis. However, small uncontrolled studies of SCFA enemas have, for the most part, shown low overall clinical response rates, suggesting that SCFA enemas are not beneficial for pouchitis ([De Silva 1989](#); [den Hoed 1996](#); [Tremaine 1994](#)). This lack of efficacy of SCFA-based therapies is supported by the [Welters 2002](#) study, which examined the use of inulin, a sugar which is fermented to SCFA, which was not clinically effective for the prevention of pouchitis; although it did produce a reduction in mean PDAI scores. [Wischmeyer 1993](#) found no difference in the proportion of patients who maintained remission between

glutamine suppositories and butyrate suppositories. It is not clear from this single controlled trial whether glutamine and butyrate suppositories are equally effective or equally ineffective, but considering the low overall response rates observed during open therapy with SCFA enemas, it appears that 'nutritional replacement' with SCFA, butyrate, or glutamine is probably not beneficial for pouchitis.

Bismuth has both anti-microbial and anti-diarrheal properties, and has been useful for the treatment of travellers' diarrhea and collagenous colitis. A randomized, double-blind, controlled trial suggested that bismuth citrate may have efficacy comparable to mesalamine for the treatment of left-sided ulcerative colitis ([Pullan 1993](#)). Given the proven benefit of bismuth in travellers' diarrhea, and its potential benefit in ulcerative colitis and collagenous colitis, therapeutic trials of bismuth in patients with acute pouchitis seemed reasonable. An uncontrolled study of bismuth complexed to carbomer suggested beneficial effects for both inducing and maintaining remission in patients with chronic pouchitis ([Gionchetti 1997](#)), while another uncontrolled study suggested that bismuth subsalicylate may also be of benefit in chronic pouchitis ([Tremaine 1998](#)). In contrast, a placebo-controlled trial with the bismuth carbomer formulation in patients with active chronic pouchitis showed no benefit ([Tremaine 1997](#)). It is possible that the xanthan gum placebo in this study was actually a positive control ([Gupta 1997](#)). Additional controlled trials using an inactive placebo are needed to determine with certainty whether or not bismuth is effective for pouchitis. Allopurinol did not appear to be clinically effective for the prevention of pouchitis ([Joelsson 2001](#)). An initial uncontrolled prospective trial indicated that allopurinol, a oxygen-related free radical scavenger, may be efficacious in decreasing inflammation hypothesized to be related to chronic ischemia and subsequent free radical damage ([Levin 1992](#)). However the results of the [Joelsson 2001](#) trial, the largest randomized trial of any treatment for any form of pouchitis (184 patients randomized) have refuted this hypothesis.

Why it is important to do this review

At the time of the previous Cochrane review of this topic ([Holubar 2010](#)), there were 13 randomised trials on treatment and prevention of pouchitis. This updated Cochrane review examines the results from a total of 15 randomised controlled trials to determine which of the currently utilized empiric medical therapies for pouchitis can be substantiated with valid data from controlled trials.

OBJECTIVES

The primary objective was to determine the efficacy and safety of various oral and topical (per rectum) medical therapies (including

antibiotics, probiotics, and modulators of inflammation) for the treatment of acute pouchitis, chronic pouchitis, and the prevention of pouchitis in patients undergoing IPAA for ulcerative colitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized, controlled trials were considered for inclusion. Study designs could include parallel arm placebo-controlled trials, crossover placebo-controlled trials, and trials comparing two active agents.

Types of participants

Adult participants (age ≥ 18 years) who had undergone IPAA for chronic ulcerative colitis and were at risk of, or had developed acute or chronic pouchitis were considered for inclusion. Pouchitis was variably defined by 1) solely clinical criteria; 2) clinical criteria in combination with endoscopic and histologic criteria; or 3) PDAI. Pouchitis was categorized by disease activity, as active (defined clinically as the presence of mild-to-severe symptoms or by a PDAI ≥ 7) or in remission (absence of symptoms or by a PDAI < 7), or by disease duration as acute (symptom duration ≤ 4 weeks) or chronic (symptom duration > 4 weeks).

Types of interventions

Any active therapy for treatment or prevention of pouchitis was considered for inclusion. Therapies used for pouchitis include antibiotics (e.g. oral metronidazole, ciprofloxacin or rifaximin), budesonide enemas, probiotics (e.g. De Simone Formulation, *Lactobacillus GG*, *Bifidobacterium longum* BB-536, or *Clostridium butyricum* MIYAIRI), biologic agents (e.g. adalimumab), glutamine suppositories, butyrate suppositories, bismuth enemas, allopurinol, and tinidazole.

Types of outcome measures

Primary outcomes

The primary outcome was the proportion of participants with clinical improvement or remission of pouchitis in participants with acute or chronic pouchitis (treatment of pouchitis), or the proportion of participants with no episodes of pouchitis after IPAA (prevention of pouchitis). The exact definition of improvement and remission varied from study to study limiting the ability to make

comparisons across studies. However, the definition of improvement or remission used in each study was used for extraction of data from the individual studies for the purposes of this systematic review.

Secondary outcomes

The proportion of participants who developed at least one adverse event was a secondary outcome.

Search methods for identification of studies

Electronic searches

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane IBD Group Specialized Register from inception to 25 July 2018 to identify relevant publications. The search strategies are reported in [Appendix 1](#).

Searching other resources

Review papers on pouchitis and references from identified papers were also searched in an effort to identify additional studies. Abstracts from major gastroenterological meetings were searched to identify research published in abstract form only.

Data collection and analysis

Selection of studies

Potentially relevant articles were reviewed in an independent unblinded fashion by two authors (SS, NHN) to determine if they met the criteria specified above. The studies were then rated as being eligible, ineligible, or as having insufficient information to make a judgment as to eligibility.

Data extraction and management

Eligible articles were reviewed in duplicate (SS, NHN) and the results of the primary research trials were abstracted into specially designed data extraction forms. The proportion of participants who had clinical improvement in the active treatment and control groups of each study was derived from life tables, survival curves, or where possible, by calculating life tables from the data provided.

Assessment of risk of bias in included studies

Two authors (SS, NHN) independently assessed methodological quality, using the Cochrane risk of bias tool as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Briefly, an assessment was made of the method of allocation generation (i.e. was the allocation sequence adequately generated?), allocation concealment (i.e. was allocation adequately concealed?), blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?), incomplete outcome data (i.e. were incomplete outcome data adequately addressed?); and selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?). A judgment of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias. Disagreements were resolved by consensus.

The overall certainty of evidence supporting the primary and secondary outcomes was evaluated using the GRADE approach (Guyatt 2008; Schünemann 2011). Outcome data were rated as being of high, moderate, low or very low certainty evidence. Data from randomized controlled trials begin as high certainty but can be downgraded based on the following criteria:

1. Risk of bias in the included trials;
2. Indirect evidence;
3. Inconsistency (including unexplained heterogeneity);
4. Imprecision (i.e. sparse data or wide confidence interval or both); and
5. Reporting bias.

The different certainty ratings are interpreted as the likelihood that future research would affect the estimate of effect. An estimate of effect based on high certainty evidence is unlikely to change with further research. If the overall evidence is of moderate certainty further research may have an impact on our confidence in the estimate and may change the estimate. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate when the evidence is rated as low certainty. Very low certainty research means that we are very uncertain about the finding (Schünemann 2011).

Measures of treatment effect

We calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI) for dichotomous outcomes.

Unit of analysis issues

Data extracted from the original research articles were converted into individual 2X2 tables (response versus no response, medical therapy versus placebo, or medical therapy versus medical therapy).

Dealing with missing data

The primary analysis was an intention-to-treat analysis where all subjects assigned to treatment were included in the denominator with all people lost to follow-up assumed to not have the outcome.

Assessment of heterogeneity

If adequate number of studies are available, we plan to assess heterogeneity by using the Chi² test with a P value of 0.10 to indicate statistical significance and the I² statistic of 50% to indicate significant statistical heterogeneity.

Assessment of reporting biases

We planned to assess the potential for publication bias by constructing funnel plots. However, none of the pooled analyses included 10 or more studies, so we didn't conduct any funnel plot analyses.

Data synthesis

We used Review Manager 5 (RevMan 5) to perform a meta-analysis on the data of included studies. Data from individual studies were pooled when interventions, patient groups and outcomes were sufficiently similar (determined by consensus). A fixed-effect model was used for the pooling of data.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of studies, we did not perform subgroup analysis.

Sensitivity analysis

Due to the limited number of studies, we did not perform a sensitivity analysis.

RESULTS

Description of studies

Results of the search

The literature search identified a total of 891 studies. After removing duplicates, a total of 553 records remained for review of titles and abstracts. Two authors (SS and NHN) independently reviewed the titles and abstracts of these trials and 26 records were selected for full text review (see Figure 1).

Figure 1. Study flow diagram.

Included studies

A total of 15 trials (547 participants) satisfied the inclusion criteria ([Brown 2004](#); [Gionchetti 2000](#); [Gionchetti 2003](#); [Ha 2010](#); [Isaacs 2007](#); [Joelsson 2001](#); [Kjaer 2019](#); [Kuisma 2003](#); [Mimura 2004](#); [Pronio 2008](#); [Sambuelli 2002](#); [Shen 2001](#); [Tremaine 1997](#); [Wischmeyer 1993](#); [Yasueda 2016](#)).

Excluded studies

Eleven studies were excluded (see table of excluded studies), including a single patient 'n-of-1' trial for active chronic pouchitis (metronidazole versus placebo), a randomized trial of probiotics versus placebo in participants with poor pouch function (not pouchitis), two randomized trials of alicaforsen enema versus mesalazine enema for ulcerative colitis (not pouchitis), a non-randomized sub-study (De Simone Formulation), two non-randomized follow-up studies of Cultura (a fermented milk probiotic),

two randomized cross-over trials of metronidazole and of inulin both without outcome data from before the first cross-over, a randomized trial of probiotics (*Lactobacillus* and *Bifidobacterium*) in which all participants with IPAA regardless of indication (chronic ulcerative colitis or familial adenomatous polyposis) were included and a trial of octreotide for prevention of diarrhea (not pouchitis) after IPAA.

Risk of bias in included studies

The Cochrane risk of bias tool indicates that the risk of bias was low for 3 of the 15 included studies (See [Figure 2](#)). The risk of bias in the other studies was high for blinding in two studies (open-label studies), high for selective reporting in one study, and high for other potential sources of bias in two studies. Some quality items were unclear in 12 studies (due to inadequate descriptions of methods used for sequence generation, allocation concealment and blinding and possible reporting or other bias).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brown 2004	?	?	+	+	+	?
Gionchetti 2000	+	+	+	+	+	+
Gionchetti 2003	+	+	+	+	+	+
Ha 2010	?	?	?	?	+	?
Isaacs 2007	+	?	+	+	+	+
Joelsson 2001	?	?	+	+	+	+
Kjaer 2019	+	?	+	+	+	+
Kuisma 2003	?	?	+	+	+	+
Mimura 2004	+	+	+	+	+	+
Pronio 2008	?	?	-	+	+	+
Sambuelli 2002	?	?	+	+	+	+
Shen 2001	?	?	-	?	?	?
Tremaine 1997	+	?	+	+	+	+
Wischmeyer 1993	?	?	?	+	+	+
Yasueda 2016	?	?	?	-	-	+

Allocation

Gionchetti 2000; Gionchetti 2003; Kjaer 2019; and Mimura 2004 had low risk of bias due to use of random sequence generation by a computer and the procedures of allocation were described in the studies.

All other studies did not describe allocation concealment procedures so the risk of bias was unclear.

Blinding

Shen 2001 did not use blinding while Pronio 2008 was an open-label study with participants aware of their treatment assignments, so the risk of performance and detection bias were high in these studies.

The risk of bias was unclear for Ha 2010, since it was not clear whether the outcome assessors were blinded, while blinding was not described in the studies by Wischmeyer 1993 and Yasueda 2016.

All other studies had low risk of bias as there was a clear description of the blinding procedure in the methodology section.

Incomplete outcome data

The risk of bias was high in Yasueda 2016 due to differential attrition with two dropouts from intervention group due to "difficulty in taking medication" and none from placebo.

Ha 2010 and Shen 2001 did not describe their plan for accounting drop-outs, so the risk of bias was unclear.

All other studies had low risk of bias as the authors either used intention-to-treat analysis or reported per-protocol analysis.

Selective reporting

Yasueda 2016 was rated as having high risk of bias since there was no protocol available and no prespecified secondary outcomes.

Shen 2001 was rated as having unclear risk of bias as selective reporting was not described by the authors.

All other studies had low risk of bias.

Other potential sources of bias

Brown 2004; Ha 2010; and Shen 2001 were rated as unclear risk for other potential sources of bias, since they were published as abstracts only, without access to full study protocol. All other studies had low risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Ciprofloxacin versus metronidazole for treatment of acute pouchitis; [Summary of findings 2](#) Metronidazole versus budesonide enema for treatment of acute pouchitis; [Summary of findings 3](#) Rifaximin versus placebo for treatment of acute pouchitis; [Summary of findings 4](#) Lactobacillus GG versus placebo for treatment of acute pouchitis; [Summary of findings 5](#) Glutamine versus butyrate for treatment of chronic pouchitis; [Summary of findings 6](#) Bismuth enema versus placebo for treatment of chronic pouchitis; [Summary of findings 7](#) De Simone Formulation versus placebo for treatment of chronic pouchitis or prevention of pouchitis in patients with ileal pouch-anal anastomosis; [Summary of findings 8](#) De Simone Formulation versus no treatment for prevention of pouchitis in patients with ileal pouch-anal anastomosis; [Summary of findings 9](#) Bifidobacterium longum versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis; [Summary of findings 10](#) Allopurinol versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis; [Summary of findings 11](#) Tinidazole versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis; [Summary of findings 12](#) Adalimumab versus placebo for treatment of chronic pouchitis; [Summary of findings 13](#) Clostridium probiotic vs. placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis

The 15 included studies had a variety of designs (although all were randomized controlled trials) and categories of outcomes. For analysis, these 15 studies were categorized according to the type of study 1) treatment of acute pouchitis, 2) treatment, or maintenance of remission, for chronic pouchitis, and 3) prevention of pouchitis.

1. Treatment of Acute Pouchitis - 4 Studies, 5 agents

Ciprofloxacin versus metronidazole

Shen 2001 was a randomized, non-blinded, parallel-arm trial of ciprofloxacin compared to metronidazole for the induction of remission of acute pouchitis. All participants had a PDAI score ≥ 7 at entry, and there was no difference in mean baseline PDAI scores between groups. A total of 16 participants were enrolled; 7 participants received ciprofloxacin and 9 received metronidazole for two-weeks. After two weeks of therapy, both groups had lower PDAI scores compared to baseline. There was a difference in remission rates (defined as PDAI score < 7) at two weeks. Overall 100% (7/7) of the ciprofloxacin group achieved remission, compared to 33% (3/9) of the metronidazole group (RR 2.68, 95% CI 1.13 to 6.35; See [Analysis 1.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to high risk of bias (no blinding) and very sparse data

(10 events, See [Summary of findings for the main comparison](#)). There was no difference in the proportion of participants who experienced at least one adverse event. None of the participants in the ciprofloxacin group developed adverse effects compared to three participants in the metronidazole group (33%) who developed vomiting, dysgeusia or transient peripheral neuropathy (RR 0.18, 95% CI 0.01 to 2.98; See [Analysis 1.2](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to high risk of bias and very sparse data (3 events, See [Summary of findings for the main comparison](#)).

Metronidazole versus budesonide enema

[Sambuelli 2002](#) was a randomized, double-blind, double dummy, placebo-controlled, parallel-arm trial of budesonide enemas plus placebo tablets compared to placebo enemas and metronidazole tablets for the induction of remission of acute pouchitis ([Sambuelli 2002](#)). At entry participants had a PDAI score ≥ 7 and no treatment during the previous month. A total of 26 participants were enrolled; 12 received budesonide enemas plus placebo tablets and 14 received placebo enema plus metronidazole tablets for 6 weeks. Of note, the randomization resulted in un-balanced groups with respect to age (metronidazole group older, $P = 0.044$). There was no difference in clinical remission (PDAI < 7) rates at six weeks. Forty-three per cent (6/14) of metronidazole participants achieved remission at week 6 compared to 50% (6/12) of budesonide enema participants (RR 0.86, 95% CI 0.37 to 1.96; See [Analysis 2.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (random sequence generation and allocation concealment) and very sparse data (12 events, See [Summary of findings 2](#)). There was no difference in clinical improvement (a reduction in the PDAI score ≥ 3 from baseline) rates at six weeks. Overall, 50% (7/14) of the metronidazole participants improved clinically compared to 58% (7/12) of the budesonide group (RR 0.86, 95% CI 0.42 to 1.74; See [Analysis 2.2](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias and very sparse data (14 events, See [Summary of findings 2](#)). There was no difference in the proportion of participants who experienced at least one adverse event. Fifty-seven per cent (8/14) of metronidazole participants experienced at least one adverse event compared to 25% (3/12) of budesonide participants (RR 2.29, 95% CI 0.78 to 6.73; See [Analysis 2.3](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias and very sparse data (11 events, See [Summary of findings 2](#)). Adverse events included anorexia, nausea, headache, asthenia, metallic taste, vomiting, paraesthesia, and depression. No serious adverse events were reported.

Rifaximin versus placebo

[Isaacs 2007](#) was a randomized, double-blind, placebo-controlled, parallel-arm, multi-center trial of rifaximin tablets compared to placebo for induction of remission in acute pouchitis. A total of 18 participants were enrolled; 8 participants received rifaximin and

10 participants received placebo for 4 weeks. There was no difference in clinical remission (defined as a PDAI score < 7 and an improvement of at least 3 points from baseline) rates at week four. Twenty-five per cent (2/8) of rifaximin participants achieved remission compared to 0% (0/10) of placebo participants (RR 6.11, 95% CI 0.33 to 111.71; See [Analysis 3.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (allocation concealment) and very sparse data (2 events, See [Summary of findings 3](#)). There was no difference in clinical improvement rates at week four. Thirty-eight per cent (3/8) of rifaximin participants improved clinically at week 4 compared to 30% (3/10) of placebo participants (RR 1.25, 95% CI 0.34 to 4.60; See [Analysis 3.2](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias and very sparse data (6 events, See [Summary of findings 3](#)). There was no difference in the proportion of participants who had at least one adverse event. Seventy-five per cent (6/8) of rifaximin participants had at least one adverse event compared to 50% (5/10) of placebo participants (RR 1.50, 95% CI 0.72 to 3.14; See [Analysis 3.3](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias and very sparse data (11 events, See [Summary of findings 3](#)). Six participants in the rifaximin group experienced 10 adverse events including diarrhea ($n = 1$), flatulence ($n = 1$), nausea ($n = 1$), proctalgia ($n = 1$), vomiting ($n = 1$), thirst ($n = 1$), candida ($n = 1$), upper respiratory tract infection ($n = 1$), increased hepatic enzyme ($n = 1$), and cluster headache ($n = 1$). Five participants in the placebo group experienced 16 adverse events including eye pain ($n = 1$), eye irritation ($n = 1$), abdominal pain ($n = 3$), defecation urgency ($n = 1$), diarrhea ($n = 1$), frequent bowel movements ($n = 1$), nausea ($n = 1$), rectal hemorrhage ($n = 1$), vomiting ($n = 1$), arthropod bite ($n = 1$), headache ($n = 1$), acne ($n = 1$), rash ($n = 1$) and mole excision ($n = 1$).

Lactobacillus GG versus placebo

[Kuisma 2003](#) was a randomized, double-blind, placebo-controlled, parallel arm trial comparing *Lactobacillus GG* to placebo for inducing clinical response in acute pouchitis. All participants had a previous history of pouchitis and endoscopic inflammation. Participants who had received antibiotics within one month were excluded, as were active chronic pouchitis (intermittent or continuous medical treatment) or symptoms [fever, bleeding, and increased number of stools (> 2 /day within 1 week)] indicative of an acute exacerbation of pouchitis. A total of 22 participants were enrolled. Two participants were excluded after enrollment for severe endoscopic pouchitis requiring immediate antibiotics. The assigned group of these two participants was not reported; hence only per protocol analysis results were available. A total of 10 participants received *Lactobacillus GG* and 10 participants received placebo for 3 months. There was no difference in the proportion of participants who had a clinical response (defined as a PDAI score reduction of ≥ 3). Ten per cent (1/10) of *Lactobacillus GG* partic-

ipants had a clinical response compared to 0% (0/10) of placebo participants (RR 3.00, 95% CI 0.14 to 65.90; See [Analysis 4.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (random sequence generation and allocation concealment) and very sparse data (1 event, See [Summary of findings 4](#)). The authors reported that *Lactobacillus GG* was well tolerated and that no participants were withdrawn due to adverse events.

2. Treatment of Chronic Pouchitis - 5 studies, 5 agents

Glutamine versus butyrate suppositories

[Wischmeyer 1993](#) was a randomized, double-blind trial of glutamine compared to butyrate suppositories for maintenance of remission in participants with chronic pouchitis after withdrawal of other suppressive medical therapy. All participants had chronic pouchitis (defined as at least 4 episodes of pouchitis within one year and the need for suppressive medications for at least 6 of the prior 12 months) and all discontinued suppressive medical therapy 7 days prior to study entry. At entry, participants could have either active or remitted pouchitis following the recent withdrawal of suppressive medical therapy. A total of 19 participants were enrolled into a single study; 10 received glutamine suppositories and 9 received butyrate suppositories. There was no difference in the proportion of participants who maintained remission at three weeks. Sixty per cent (6/10) of glutamine participants maintained remission at three weeks compared to 33% (3/9) of butyrate participants (RR 1.80, 95% CI 0.63 to 5.16; See [Analysis 5.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (random sequence generation, allocation concealment and blinding) and very sparse data (9 events, See [Summary of findings 5](#)).

Bismuth carbomer foam enemas versus placebo

[Tremaine 1997](#) was a randomized, double-blind, placebo-controlled, parallel-arm trial of bismuth carbomer enemas for induction of clinical response in active chronic pouchitis. All participants had active, chronic pouchitis (defined as a PDAI score ≥ 7 points and failure or intolerance to treatment with antibiotics and other medical therapies). A total 40 participants were enrolled; 20 received bismuth carbomer foam enemas and 20 received placebo. There was no difference in the proportion of participants with clinical improvement (defined by a decrease in the PDAI score of ≥ 3 points from baseline). At three weeks, 45% (9/20) of participants in the bismuth carbomer foam enema group improved clinically compared to 45% (9/20) of placebo participants (RR 1.00, 95% CI 0.50 to 1.98; See [Analysis 6.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (allocation concealment) and very sparse data (18 events, See [Summary of findings 6](#)). There was no difference in the proportion of participants who experienced at least one adverse event. Twenty-five per cent (5/20) of participants in the bismuth carbomer foam enema group had at least one adverse event compared to 35% (7/20) of placebo participants (RR 0.71, 95% CI 0.27 to 1.88; See [Analysis 6.2](#)). A

GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias and very sparse data (12 events, See [Summary of findings 6](#)). Adverse events included worsening of diarrhea, worsening symptoms, cramping discomfort, sinusitis, and abdominal pain.

Oral probiotic bacteria (De Simone Formulation) versus placebo (2 studies):

[Gionchetti 2000](#) was a randomized, double-blind, placebo-controlled, parallel-arm trial of probiotic bacteria (De Simone Formulation) for maintenance of remission in chronic pouchitis. All participants were in remission (defined as a PDAI score of 0 following open-label induction with antibiotics) and had chronic pouchitis (history of requiring continuing medical suppressive therapy and recurrence within a few weeks of discontinuing suppression). In total, 40 participants were enrolled; 20 received probiotic bacteria and 20 received placebo. The relapse rate at nine months, as measured by an increase ≥ 2 points in the 6 point clinical portion of the PDAI, was 15% (3/20) for probiotic therapy compared to 100% (20/20) for placebo.

[Mimura 2004](#) was a randomized, placebo-controlled, multicenter, parallel-arm trial of probiotic bacteria (De Simone Formulation) for maintenance of remission in chronic pouchitis. All participants had pouchitis at least twice in the previous year or requiring continuous antibiotics, associated with a PDAI ≥ 7 , in whom remission was induced by four weeks of combined metronidazole and ciprofloxacin. Active refractory or recurrent pouchitis was defined as a total PDAI score of >7 and a history of relapsing or persistent pouchitis. A total of 36 participants were enrolled for 1 year of treatment; 20 participants received the De Simone Formulation and 16 participants received placebo. Remission at one year, as defined by a clinical PDAI score ≤ 2 and endoscopic PDAI ≤ 1 , was maintained in 85% (17/20) in the De Simone Formulation group and 6% (1/16) in the placebo group.

A pooled analysis of two studies (76 participants) showed a difference in the proportion of participants who maintained remission at 9 to 12 months. Eighty-five per cent (34/40) of participants in the De Simone Formulation group maintained remission compared to 3% (1/36) of placebo participants (RR 20.24, 95% CI 4.28 to 95.81; See [Analysis 7.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was low due to very sparse data (35 events, See [Summary of findings 7](#)). [Gionchetti 2000](#) reported no adverse events in either group. Data from the [Mimura 2004](#) study showed no difference in the proportion of participants who experienced at least one adverse event. Five per cent (1/20) of De Simone Formulation participants experienced at least one adverse event compared to 0% (0/16) of placebo participants (RR 2.43, 95% CI 0.11 to 55.89; See [Analysis 7.2](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was low due to very sparse data (1 event, See [Summary of findings 7](#)). The one patient in the De Simone Formulation group experienced three adverse events including abdominal cramps, vomiting and diarrhea.

Adalimumab versus placebo (1 study):

[Kjaer 2019](#) was a multicenter, randomized double-blind, placebo-controlled trial of adalimumab for treatment of chronic pouchitis. All participants had active pouchitis (PDAI ≥ 7) for 4 weeks despite treatment with antibiotics. Participants were treated with adalimumab (standard induction and maintenance dose of 160mg, followed by 80mg followed by 40mg every 2 weeks) or placebo. Of 32 participants screened, only 13 participants met inclusion criteria and were randomized to adalimumab (n = 6) or placebo (n = 7). Clinical improvement in chronic pouchitis (defined as reduction in modified PDAI ≥ 2 at any time within the 12 weeks of treatment) was achieved by 50% (3/6) in the adalimumab group and 43% (3/7) in the placebo group (RR 2.92, 95% CI 0.86 to 9.93, See [Analysis 12.1](#)). A GRADE analysis indicated that the certainty of evidence supporting adalimumab over placebo had no serious risk of bias (See [Summary of findings 12](#)). Three serious adverse events were reported but it was unclear which participants experienced adverse events.

3. Prevention of Pouchitis - 6 studies, 5 agents

Oral Probiotic Bacteria versus placebo or no treatment (4 studies): [Gionchetti 2003](#) was a randomized, double-blind, placebo-controlled, parallel-arm trial which assessed the efficacy of oral probiotic therapy with the De Simone Formulation for the prevention of pouchitis. All participants were randomized within one week of ileostomy closure after IPAA. A total of 40 participants were enrolled for 12 months of treatment. Twenty participants received the De Simone Formulation and 20 received placebo. There was a difference in the proportion of participants who developed an acute episode of pouchitis over the 12 month treatment period. Ninety per cent (18/20) of De Simone Formulation participants had no episodes of acute pouchitis during the 12 month period compared to 60% (12/20) of placebo participants (RR 1.50, 95% CI 1.02 to 2.21; See [Analysis 7.3](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was low due to very sparse data (30 events, See [Summary of findings 7](#)).

[Pronio 2008](#) was a randomized, open-label, parallel-arm trial which assessed the efficacy of oral probiotic therapy with the De Simone Formulation compared to no treatment for the prevention of pouchitis. All participants were taking no medication at entry. Exclusion criteria included participants with active pouchitis (PDAI ≥ 7), perianal disease (including abscess, fissure, stricture, or anal sphincter weakness), and pregnant or lactating women. A total of 31 participants were enrolled for 12 months. There was no difference in the proportion of participants who developed an acute episode of pouchitis over the 12 month treatment period. One hundred per cent (16/16) of the De Simone Formulation group (16/16) had no acute episodes of pouchitis compared to 92% (11/12) of the control group (RR 1.10, 95% CI 0.89 to 1.36; See [Analysis 8.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to high risk of bias (no blinding) and very sparse data (27 events, See [Summary of findings 8](#)). This study did not report on adverse events.

[Brown 2004](#) reported a randomized, double-blind, placebo-controlled trial which assessed the efficacy of a six months of treatment with a single probiotic, *Bifidobacterium longum* BB-536 compared with placebo, for the prevention of pouchitis in 12 participants who had undergone IPAA for ulcerative colitis. Participants had no evidence of active pouchitis. The study was published as an abstract. The primary end point was PDAI score six months after therapy, and a secondary end point was the proportion of participants who remained free of pouchitis at the end of six months. The baseline mean PDAI scores were similar in both groups (active vs. placebo; mean $\pm$ standard error of mean PDAI, 2.14 $\pm$ 0.46 vs. 2.40 $\pm$ 1.29, P = 0.64). After 6 months of therapy a difference in mean PDAI scores was apparent (1.83 $\pm$ 0.91 vs. 5.40 $\pm$ 1.17 P = 0.035), which was contributed to by all three components of the PDAI score (clinical 0.17 $\pm$ 0.17 vs. 1.60 $\pm$ 0.68; endoscopic 1.0 $\pm$ 0.37 vs. 2.0 $\pm$ 0.84; histological 0.67 $\pm$ 0.67 vs. 1.80 $\pm$ 0.49). There was no difference in the proportion of participants who had no acute episodes of pouchitis over the six month treatment period. Eighty-six per cent (6/7) of participants in the *Bifidobacterium longum* group had no episodes of acute pouchitis compared to 60% (3/5) of the placebo group (RR 1.43, 95% CI 0.66 to 3.11; See [Analysis 9.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (random sequence generation, allocation concealment and other potential sources of bias) and very sparse data (9 events, See [Summary of findings 9](#)). This study did not report on adverse events as an outcome.

[Yasueda 2016](#) performed a randomized, placebo-controlled trial comparing MIYA-BM[®] (Miyarisan Pharmaceutical Co., Ltd., Tokyo, Japan) tablets containing 20mg spore-forming bacteria *Clostridium butyricum* MIYAIRI 3 tabs daily (n = 9) versus placebo (n = 8) for 24 months, in participants immediately after IPAA for UC. The primary endpoint was development of acute pouchitis defined based on modified PDAI (≥ 4); endoscopy was performed in all participants who met this criteria. Over the course of 24 months, 11% (1/9) of participants treated with *Clostridium butyricum* MIYAIRI and 50% (4/8) participants treated with placebo developed acute pouchitis (RR 0.22, 95% CI 0.03 to 1.60; See [Analysis 13.1](#)). The study did not report scheme of sequence generation, allocation concealment or randomization of participants, physicians or outcome assessors. For the secondary aim of analyzing microbiome, only data from 1/2 sites was included since data from the other site was not reproducible, leading to selective reporting. A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to high risk of bias with regards to incomplete outcome data and selective reporting; unclear risk of bias with regards to random sequence generation, allocation concealment, and blinding; and very sparse data (See [Summary of findings 13](#)). This study did not report on adverse events as an outcome.

Allopurinol versus placebo

[Joelsson 2001](#) was a randomized, double-blind, multi-center,

placebo-controlled, parallel-arm study assessing the efficacy of allopurinol for the prevention of pouchitis. All participants were randomized one week after IPAA surgery. A total of 184 participants were enrolled for 24 months; 94 participants received allopurinol and 90 placebo. Of these participants, 63% (116) completed the study. There was no difference in the proportion of participants who had no episodes of acute pouchitis at one year. Forty-six per cent (43/94) of allopurinol participants had no episodes of pouchitis compared to 43% (39/90) of placebo participants (RR 1.43, 95% CI 0.66 to 3.11; See [Analysis 10.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was low due to unclear risk of bias (random sequence generation and allocation concealment) and sparse data (82 events, See [Summary of findings 10](#)). Eight adverse events that were suspected to be drug-related were reported in the allopurinol group. These events included pruritus (n = 3), headache (n = 1), mild allergic reaction (n = 1), gynecomastia (n = 1), malaise (n = 1) and abnormal liver test (n = 1).

Tinidazole versus placebo

[Ha 2010](#) reported a randomized, double-blind, placebo-controlled trial which assessed the efficacy of 12-month treatment with tinidazole 500 mg daily started within 1 month of ileostomy closure after IPAA, compared with placebo, for the prevention of pouchitis (published only in abstract form). A total of 38 participants were randomized 2:1 to tinidazole or placebo. There was no significant difference in the proportion of participants who had no episodes of acute pouchitis at 12 months. Eighty-one per cent (21/26) of tinidazole participants had no episodes of pouchitis over the 12 month treatment period compared to 58% (7/12) of placebo-treated participants (RR 1.38, 95% CI 0.83 to 2.31; See [Analysis 11.1](#)). A GRADE analysis indicated that the certainty of evidence supporting this outcome was very low due to unclear risk of bias (random sequence generation, allocation concealment, blinding, incomplete outcome data and other potential sources of bias) and very sparse data (28 events, See [Summary of findings 11](#)). There was no difference in the number of adverse events between the two groups (P = 0.64).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Metronidazole versus budesonide enema for treatment of acute pouchitis						
Patient or population: Patients with acute pouchitis Settings: Outpatient Intervention: Metronidazole versus budesonide enema						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Budesonide enema	Metronidazole				
Clinical remission Follow-up: 6 weeks	500 per 1000 ¹	430 per 1000 (185 to 980)	RR 0.86 (0.37 to 1.96)	26 (1 study)	⊕○○○ very low ^{2,3}	Clinical remission defined as PDAI score < 7
Clinical improvement Follow-up: 6 weeks	583 per 1000 ¹	502 per 1000 (245 to 1000)	RR 0.86 (0.42 to 1.74)	26 (1 study)	⊕○○○ very low ^{2,4}	Clinical improvement defined as a reduction in the PDAI score ≥ 3 from baseline
Maintenance of clinical remission	Not reported					
No episodes acute pouchitis	Not reported					
Adverse events Follow-up: 6 weeks	250 per 1000 ¹	572 per 1000 (195 to 1000)	RR 2.29 (0.78 to 6.73)	26 (1 study)	⊕○○○ very low ^{2,5}	Adverse events included anorexia, nausea, headache, asthenia, metallic taste, vomiting, paraesthesia, and depression

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for random sequence generation and allocation concealment.

³ Downgraded two levels due to very sparse data (12 events).

⁴ Downgraded two levels due to very sparse data (14 events).

⁵ Downgraded two levels due to very sparse data (11 events).

Rifaximin versus placebo for treatment of acute pouchitis						
Patient or population: Patients with acute pouchitis Settings: Outpatient Intervention: Rifaximin versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Rifaximin				
Clinical remission Follow-up: 4 weeks	0 per 1000 ¹	0 per 1000 (0 to 0)	RR 6.11 (0.33 to 111.71)	18 (1 study)	⊕○○○ very low ^{2,3}	Clinical remission defined as PDAI score < 7 25% (2/8) of rifaximin participants achieved remission at 4 weeks compared to 0% (0/10) of placebo participants
Clinical improvement Follow-up: 4 weeks	300 per 1000 ¹	375 per 1000 (102 to 1000)	RR 1.25 (0.34 to 4.6)	18 (1 study)	⊕○○○ very low ^{2,4}	Clinical improvement defined as a reduction in the PDAI score ≥ 3 from baseline
Maintenance of clinical remission	Not reported					
No episodes acute pouchitis	Not reported					
Adverse events Follow-up: 4 weeks	500 per 1000 ¹	750 per 1000 (360 to 1000)	RR 1.5 (0.72 to 3.14)	18 (1 study)	⊕○○○ very low ^{2,5}	Adverse events included diarrhea, flatulence, nausea, proctalgia, vomiting and nausea

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for allocation concealment.

³ Downgraded two levels due to very sparse data (2 events).

⁴ Downgraded two levels due to very sparse data (6 events).

⁵ Downgraded two levels due to very sparse data (11 events).

The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for random sequence generation and allocation concealment.

³ Downgraded two levels due to very sparse data (1 event).

Glutamine versus butyrate for treatment of chronic pouchitis						
Patient or population: Patients with chronic pouchitis Settings: Outpatient Intervention: Glutamine versus butyrate						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Butyrate	Glutamine				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission Follow-up: 3 weeks	333 per 1000	600 per 1000 (210 to 1000)	RR 1.8 (0.63 to 5.16)	19 (1 study)	⊕○○○ very low ^{1,2}	Maintenance of clinical remission defined as defined as PDAI score < 7
No episodes acute pouchitis	Not reported					
Adverse events	Not reported					
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for random sequence generation, allocation concealment and blinding.

³ Downgraded two levels due to very sparse data (9 events).

Bismuth enema versus placebo for treatment of chronic pouchitis						
Patient or population: Patients with chronic pouchitis Settings: Outpatient Intervention: Bismuth enema versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Bismuth enema				
Clinical remission	Not reported					
Clinical improvement Follow-up: 3 weeks	450 per 1000	450 per 1000 (225 to 891)	RR 1 (0.5 to 1.98)	40 (1 study)	⊕○○○ very low ^{2,3}	Clinical improvement defined as a decrease in the PDAI score of ≥ 3 points from baseline
Maintenance of clinical remission	Not reported					
No episodes acute pouchitis	Nor reported					
Adverse events Follow-up: 3 weeks	350 per 1000	248 per 1000 (95 to 658)	RR 0.71 (0.27 to 1.88)	40 (1 study)	⊕○○○ very low ^{2,4}	Adverse events include worsening of diarrhea, worsening symptoms, cramping discomfort, sinusitis, and abdominal pain
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for allocation concealment.

³ Downgraded two levels due to very sparse data (18 events).

⁴ Downgraded two levels due to very sparse data (12 events).

De Simone Formulation versus placebo for treatment of chronic pouchitis or prevention of pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with chronic pouchitis or ileal pouch-anal anastomosis Settings: Outpatient Intervention: De Simone Formulation versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	De Simone Formulation				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission Follow-up: 9-12 months	28 per 1000 ¹	562 per 1000 (119 to 1000)	RR 20.24 (4.28 to 95.81)	76 (2 studies)	⊕⊕○○ low ²	Maintenance of clinical remission defined as a PDAI score of 0 following open-label induction with antibiotics or PDAI score ≤ 2
No episodes of acute pouchitis Follow-up: 9 months	600 per 1000 ¹	900 per 1000 (612 to 1000)	RR 1.5 (1.02 to 2.21)	40 (1 study)	⊕⊕○○ low ³	Acute pouchitis defined as
Adverse events	0 per 1000 ¹	0 per 1000 (0 to 0)	RR 2.43 (0.11 to 55.89)	76 (2 studies)	⊕⊕○○ low ⁴	Adverse events included abdominal cramps, vomiting and diarrhea 5% (1/20) of De Simone Formulation participants experienced at least one adverse

		event compared to 0% (0/16) of placebo participants
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded two levels due to very sparse data (35 events).

³ Downgraded two levels due to very sparse data (30 events).

⁴ Downgraded two levels due to very sparse data (1 event).

De Simone Formulation versus no treatment for prevention of pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with ileal pouch-anal anastomosis						
Settings: Outpatient						
Intervention: De Simone Formulation versus no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	De Simone Formulation				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission	Not reported					
No episodes of acute pouchitis Follow-up: 12 months	917 per 1000 ¹	1000 per 1000 (816 to 1000)	RR 1.1 (0.89 to 1.36)	28 (1 study)	⊕○○○ very low ^{2,3}	
Adverse events	Not reported					
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio;</p>						
GRADE Working Group grades of evidence						
High quality: Further research is very unlikely to change our confidence in the estimate of effect.						
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.						
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.						
Very low quality: We are very uncertain about the estimate.						

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

- ² Downgraded one level due to high risk of bias (no blinding).
- ³ Downgraded two levels due to very sparse data (27 events).

Bifidobacterium longum versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with ileal pouch-anal anastomosis Settings: Outpatient Intervention: Bifidobacterium longum versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Bifidobacterium longum				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission	Not reported					
No episodes of acute pouchitis Follow-up: 6 months	600 per 1000 ¹	858 per 1000 (396 to 1000)	RR 1.43 (0.66 to 3.11)	12 (1 study)	⊕○○○ very low ^{2,3}	
Adverse events	Not reported					
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio;</p>						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for random sequence generation, allocation concealment, and other potential sources of bias.

³ Downgraded two levels due to very sparse data (9 events).

Allopurinol versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with ileal pouch-anal anastomosis						
Settings: Outpatient						
Intervention: Allopurinol versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Allopurinol				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission	Not reported					
No episodes of acute pouchitis Follow-up: 24 months	433 per 1000 ¹	459 per 1000 (329 to 633)	RR 1.43 (0.66 to 3.11)	184 (1 study)	⊕⊕○○ low ^{2,3}	
Adverse events	Not reported					
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio;</p>						
GRADE Working Group grades of evidence						
High quality: Further research is very unlikely to change our confidence in the estimate of effect.						
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.						
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.						
Very low quality: We are very uncertain about the estimate.						

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

- ² Downgraded one level due to unclear risk of bias for random sequence generation and allocation concealment.
- ³ Downgraded one level due to sparse data (82 events).

Tinidazole versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with ileal pouch-anal anastomosis Settings: Outpatient Intervention: Tinidazole versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tinidazole				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission	Not reported					
No episodes of acute pouchitis Follow-up: 12 months	583 per 1000 ¹	805 per 1000 (484 to 1000)	RR 1.38 (0.83 to 2.31)	38 (1 study)	⊕○○○ very low ^{2,3}	
Adverse events	Not reported					
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio</p>						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

- ² Downgraded one level due to unclear risk of bias for random sequence generation, allocation concealment, blinding, incomplete outcome data and other potential sources of bias.
- ³ Downgraded two levels due to very sparse data (28 events).

Adalimumab versus placebo for treatment of chronic pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with ileal pouch-anal anastomosis						
Settings: Outpatient						
Intervention: Adalimumab versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Adalimumab				
Clinical remission	Not reported					
Clinical improvement Follow-up: 4 weeks	429 per 1000 ¹	501 per 1000 (154 to 1000)	RR 1.17 (0.36 to 3.76)	13 (1 study)	⊕⊕○○ low ²	Clinical improvement defined as reduction in modified PDAI ≥2 at any time within the 12 weeks of treatment
Maintenance of clinical remission	Not reported					
No of episodes of acute pouchitis	Not reported					
Adverse events	Not reported					
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Very sparse data (7 events)

Clostridium probiotic versus placebo for prevention of pouchitis in patients with ileal pouch-anal anastomosis						
Patient or population: Patients with ileal pouch-anal anastomosis						
Settings: Outpatient						
Intervention: Clostridium probiotic versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Clostridium probiotic				
Clinical remission	Not reported					
Clinical improvement	Not reported					
Maintenance of clinical remission	Not reported					
No of episodes of acute pouchitis Follow-up: 24 months	500 per 1000 ¹	110 per 1000 (15 to 800)	RR 0.22 (0.03 to 1.60)	17 (1 study)	⊕○○○ very low ^{2,3}	
Adverse events	Not reported					
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials

- ² Downgraded one level due to unclear risk of bias
- ³ Downgraded two levels due to very sparse data (5 events)

DISCUSSION

Summary of main results

Based on the results of this systematic review the following conclusions may be drawn. It is uncertain whether ciprofloxacin is more effective than metronidazole for the treatment of acute pouchitis. There was no difference in adverse events rates between the two antibiotics. It is important to note that the U.S. Food and Drug Administration has issued black-box warnings for fluoroquinolones including ciprofloxacin related to risk of tendinitis, tendon rupture and peripheral neuropathy and risk of hypoglycaemia. For treatment of acute pouchitis, it is unclear whether there are any differences between metronidazole and budesonide enemas in terms of clinical remission, clinical improvement or adverse event rates. However, these results are uncertain due to very low certainty evidence. Due to low certainty evidence, it is unclear whether there are any differences between rifaximin and placebo in terms of clinical remission, clinical improvement or adverse event rates. Due to very low certainty evidence, it is unclear whether there is any difference in clinical improvement rates between *Lactobacillus GG* and placebo. For the treatment of chronic pouchitis, it is uncertain whether the De Simone Formulation is more effective than placebo for maintaining remission. Due to very low certainty evidence, it is unclear whether there is any difference in efficacy between glutamine suppositories and butyrate suppositories for maintenance of remission. It is unclear whether there are any differences in clinical improvement or adverse event rates between bismuth carbomer foam enemas and placebo enemas, or between adalimumab and placebo. However, these results are uncertain due to very low certainty evidence. For the prevention of pouchitis, it is uncertain whether the De Simone Formulation is more effective than placebo due to low certainty evidence. However, due to very low certainty evidence, it is unclear whether there is any difference in prevention of pouchitis between the De Simone Formulation and no treatment. Hence the efficacy of the De Simone Formulation for prevention of pouchitis is questionable. More research is needed to determine the efficacy of the De Simone Formulation for preventing pouchitis. Due to very low certainty evidence, it is unclear whether there are any differences between *Clostridium butyricum* MIYAIRI and placebo, allopurinol and placebo and tinidazole and placebo for prevention of pouchitis.

Two cross-over studies which were excluded (because of lack of data prior to cross-over) merit further discussion. Madden 1994 was a randomized, double-blind, placebo-controlled, cross-over trial of metronidazole for induction of clinical response in active chronic pouchitis. All participants had active pouchitis (defined as chronic, recurrent clinical symptoms, > 6 stools/24 hours, and endoscopic inflammation) at entry. In total 13 participants were enrolled, and 11 participants completed both arms of the cross-over trial. The overall response, as measured by a reduction in stool

frequency of at least 3 stools/24 hours, was 73% (8/11) for metronidazole compared to 9% (1/11) for placebo ($P = 0.003$). Welters 2002 was a randomized, double-blind, placebo-controlled, cross-over study assessing the efficacy of inulin for the prevention of pouchitis. Participants with IPAA for chronic ulcerative colitis or familial adenomatous polyposis were included. Participants with a history of pouchitis were not excluded, none of the included participants had overt clinical pouchitis at the time of the study, and none were taking pouchitis-related medications. A total of 20 participants were enrolled to receive inulin followed by placebo, or placebo followed by insulin, for three weeks each. One patient who started in the placebo group dropped out due to lactose intolerance. Overall, there was no difference in pouchitis prevention, as measured by the final mean PDAI score, which was 1.42 for inulin and 1.66 for the placebo. However, the modified intention-to-treat mean difference in PDAI for the prevention of pouchitis by inulin compared to placebo was 1.34 (95% CI 0.85 to 1.83), a difference that is not likely to be clinically significant. Some participants with chronic pouchitis become refractory to standard medical treatment and may require a permanent ileostomy. Although few treatment options exist for these participants several retrospective cohort studies and case series suggest that TNF-alpha antagonists (infliximab and adalimumab) or anti-integrin agents (vedolizumab) may provide benefit (Bär 2018; Herfarth 2015; Zippi 2013). In one underpowered clinical trial comparing adalimumab to placebo in participants with chronic antibiotic-refractory pouchitis, there was no difference in efficacy in adalimumab over placebo (Kjaer 2019). There are ongoing trials of alicaforsen enema, and of vedolizumab, for treatment of chronic pouchitis, which would further inform and expand the treatment options for chronic pouchitis.

Overall completeness and applicability of evidence

This systematic review comprehensively investigates available therapies for the prevention of pouchitis (in patients with IPAA) as well as treatment of acute and chronic pouchitis in patients who develop pouchitis. Patients included in the body of evidence are representative of patients commonly seen in practice, and all available therapies commonly discussed in practice and clinical guidelines have been addressed. Outcomes of interest, likewise, are those commonly used in clinical practice, and of importance to patients. However, the body of evidence is limited in number and size of studies, particularly of modern therapies like immunosuppressive or biologic agents for treatment of pouchitis, leading to very low confidence in some estimates. Moreover, there is paucity of comparative data.

The results presented in this review must be interpreted with extreme caution given the small numbers of trials and participants evaluated for any one comparison. For each comparison, the confidence intervals about the risk ratio were wide. This indicates a

moderate amount of uncertainty in the effect estimate. For example, for the comparison of oral ciprofloxacin versus metronidazole, we are 95% confident that the true estimate of effect falls between 1.13 and 6.35. The estimate of the therapeutic advantage of oral ciprofloxacin over metronidazole is uncertain.

Additionally for each comparison, with the exception of the De Simone Formulation versus placebo for chronic pouchitis, only one trial was eligible. Therefore, the generalizability and external validity of these results must be questioned. GRADE analyses indicate that the overall certainty of evidence derived from this systematic review ranges from low for the comparisons De Simone Formulation versus placebo (for both maintenance of remission and prevention of acute pouchitis) and allopurinol versus placebo (for prevention of acute pouchitis) to very low for all other comparisons. These ratings were due to high or unclear risk of bias in the included studies and very serious imprecision. The reader must exercise clinical judgment, and ensure the patient populations (those being generalized to, and those in the trials) are similar before these findings can be implemented into clinical practice.

Quality of the evidence

Most of the included interventions for prevention and treatment of pouchitis were studied in one to three trials, which limited the ability to perform a meta-analysis. While the included studies were generally at low risk of bias, some studies were at unclear risk of selection bias because the methods used for random sequence generation and allocation concealment were not reported. Due to very serious imprecision (sparse data), the certainty of the evidence for most of the outcomes assessed in this review ranged from low to very low.

Potential biases in the review process

The systematic review followed an a priori defined protocol with comprehensive search of multiple electronic databases including conference proceedings, and followed steps as recommended in the PRISMA guidelines for reporting systematic reviews. Study identification, risk of bias assessment and data abstraction was performed in duplicate. There are specific limitations. When all outcomes were not reported, we did not reach out to individual authors for unpublished data. Due to paucity of number of trials for specific interventions, quantitative synthesis and subgroup analyses could not be performed.

Agreements and disagreements with other studies or reviews

The evidence summarized in this review is of low quality and comparisons with other reviews may be difficult since previous sys-

tematic reviews had narrower scopes of investigation and included observational studies, which are at high risk of bias.

The results of a systematic review and meta-analysis of antibiotics and probiotics in pouchitis are consistent with the results of our review and suggest that antibiotics and probiotics may be effective for the treatment of pouchitis, although efficacy may depend on the types of probiotics or antibiotics that are used (Nikfar 2010). Although our systemic review did not include studies that evaluated the use of infliximab for the treatment of pouchitis, previous retrospective studies suggest a potential benefit for infliximab. A systematic review in 2015 explored the use of biologics in pouchitis and included a total of 17 full length articles and 2 abstracts, most of these studies were retrospective case series that reported on treatment with either infliximab or adalimumab (Herfarth 2015). Overall, infliximab appears to have good clinical effectiveness achieving response rates of up to 80% in the short-term and response rates of around 50% in the long-term. There were limited data available to draw conclusions for adalimumab. Segal 2017 investigated the efficacy of medical therapies for the treatment of chronic refractory pouchitis and included 21 studies (which included RCTs, cohort studies, and observational studies) that reviewed the data on steroids, bismuth, elemental diet, tacrolimus, and fecal microbiota transplantation. Ultimately, the authors concluded that steroids, bismuth, elemental diet could induce remission in chronic pouchitis, but this finding did not reach statistical significance. Fecal microbiota transplantation did not demonstrate any efficacy for achieving remission in chronic pouchitis (Segal 2017).

In summary, there are limited data to guide therapy in pouchitis. More high quality studies with larger numbers of patients are required to assess the efficacy and safety of medical therapy for the treatment and prevention of pouchitis.

AUTHORS' CONCLUSIONS

Implications for practice

The effects of antibiotics, probiotics and other interventions for treating and preventing pouchitis are uncertain.

Implications for research

The medical therapy of pouchitis remains largely empiric. We identified single small trials for most comparisons. Well designed, adequately powered multicenter, randomized, double-blind, placebo-controlled, dose-ranging trials of antibiotics, probiotic bacteria, and other therapies known to be beneficial in ulcerative colitis such as mesalamine and corticosteroids are needed. Trials of the De Simone Formulation compared to ciprofloxacin or metronidazole for the treatment and maintenance of remission of chronic pouchitis are warranted, and perhaps additional trials of

rifaximin and inulin. In addition, larger trials of biologic therapies including TNF-alpha antagonists (e.g. infliximab or adalimumab) as well as anti-integrin agents (e.g. vedolizumab) and janus kinase inhibitors (e.g. tofacitinib), need to be performed in order to establish the true efficacy of these agents prior to widespread clinical application. In future trials, treatment indications such as active acute or chronic pouchitis and maintenance of remission for acute or chronic pouchitis should be clearly defined using the gold stan-

dard PDAI definitions.

ACKNOWLEDGEMENTS

Funding for the Cochrane IBD Group (May 1, 2017 - April 30, 2022) has been provided by Crohn's and Colitis Canada (CCC).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brown 2004

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 12)	
Participants	Participants with IPAA for ulcerative colitis with no active pouchitis	
Interventions	Bifidobacterium longum BB-536 (n = 7) or placebo (n = 5) for 6 months	
Outcomes	Prevention of acute pouchitis Study also reports mean change in PDAI pre- and post-intervention	
Notes	Intention-to-treat analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, endoscopists and pathologists were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Published reported includes all relevant outcomes
Other bias	Unclear risk	Abstract publication

Gionchetti 2000

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 40)	
Participants	Participants with pouchitis in remission (defined as a PDAI = 0) and chronic pouchitis (require continuing medical suppression therapy and recur within a few weeks of discontinuing suppression) Prior to study entry participants were treated with open antibiotics (types not specified) to induce remission Antibiotic therapy was discontinued at study entry	

Gionchetti 2000 (Continued)

Interventions	VSL#3 (now known as the De Simone Formulation), 6 grams per day (n = 20) versus placebo (n = 20) for 36 weeks	
Outcomes	Maintenance of remission Relapse was defined as an increase by 2 points in the 6 point clinical portion of the PDAI, from a baseline score of 0	
Notes	Intention-to-treat analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Centralized randomization by pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Gionchetti 2003

2009

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 40)
Participants	Participants were randomized within one week of ileostomy closure after ileal pouch-anal anastomosis for ulcerative colitis
Interventions	VSL#3 (now known as the De Simone Formulation), 1 packet per day (n = 20) versus 3 g/day maize placebo (n = 20) for 12 months
Outcomes	Prophylaxis. Primary endpoint was pouchitis, defined as PDAI score ≥ 7 , with symptoms, histologic, and endoscopic evidence of inflammation. Secondary endpoints included IBDQ score, fecal bacterial concentrations, and stool frequency
Notes	Intention-to-treat analysis
<i>Risk of bias</i>	

Gionchetti 2003 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization by pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Ha 2010

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 38)
Participants	Participants were randomized within one month of ileostomy closure after ileal pouch-anal anastomosis for ulcerative colitis
Interventions	Tinidazole 500 mg daily (n = 26) versus placebo (n = 12) for 12 months
Outcomes	Prevention of acute pouchitis
Notes	Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described

Ha 2010 (Continued)

Selective reporting (reporting bias)	Low risk	Relevant outcomes reported
Other bias	Unclear risk	Abstract publication

Isaacs 2007

Methods	Randomized, double-blind, multi-center, placebo-controlled, parallel-arm trial (N = 18)
Participants	Participants with active pouchitis defined as a PDAI score of at least 7
Interventions	Oral rifaximin 400 mg or placebo (n =10) 3 times per day for 4 weeks
Outcomes	Clinical remission defined as a PDAI score < 7 points and a decrease in the baseline PDAI score of 3 points
Notes	Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated with permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants withdrew from placebo group due to lack of efficacy These participants were classified as treatment failures
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Joelsson 2001

Methods	Randomized, double-blind, multi-center, placebo-controlled, parallel-arm trial (N = 184)	
Participants	Participants with IPAA for UC were randomized 1 week after surgery Excluded: age < 18 or > 75 years, breastfeeding, pregnancy or planned pregnancy during the coming year, psychiatric disease, known alcohol abuse, other disease of relevance according to the clinician judgement, allergy/intolerance to allopurinol, or current azathioprine, 6-mercaptopurine, cyclophosphamide, cyclosporine or anticoagulation use	
Interventions	Allopurinol 100 mg twice daily (n = 94) or placebo (n = 90) for 24 months	
Outcomes	Prevention of acute pouchitis Pouchitis defined by a functional score (similar to PDAI)	
Notes	Per protocol analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Kjaer 2019

Methods	Multicenter, randomized double-blind, placebo-controlled trial	
Participants	Participants with IPAA for UC, with chronic refractory pouchitis (PDAI $\geq$ 7 and symptoms lasting for more than 4 weeks despite antibiotic treatment)	
Interventions	Adalimumab (n=6) vs. Placebo (n =7), for 12 weeks	

Outcomes	Reduction in modified PDAI ≥ 2 at any time within the 12 weeks of treatment	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Performed within each center according to a computer-generated randomization schedule with permuted blocks
Allocation concealment (selection bias)	Unclear risk	Placebo was supplied in identical packets containing syringes
Blinding (performance bias and detection bias) All outcomes	Low risk	Per protocol, quadruple-blinded (Participant, Care Provider, Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants are accounted for
Selective reporting (reporting bias)	Low risk	Clinical improvement and adverse events reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Kuisma 2003

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 20)
Participants	Participants with a previous history of pouchitis and endoscopic inflammation. Participants who had received antibiotics within one month were excluded, as were active chronic pouchitis (intermittent or continuous medical treatment) or symptoms [fever, bleeding, increased number of stools (> 2/day within 1 week)] indicative of an acute exacerbation of pouchitis
Interventions	Lactobacillus GG in two gelatine capsules orally twice daily (n = 10) versus microcrystalline cellulose-only gelatine placebo capsules (n = 10) for 3 months
Outcomes	Clinical improvement Total PDAI score and quantitative bacterial culture of fresh fecal samples and biopsies taken from the pouch were performed before and after supplementation
Notes	Per protocol analysis After randomization 2 participants were excluded after the first endoscopy because of severe endoscopic pouchitis (large ulcers, stricture) requiring immediate antibiotic therapy

Kuisma 2003 (Continued)

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<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were excluded because of severe disease before treatment began. No participants dropped out
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Mimura 2004

Methods	Randomized, placebo-controlled, multi-center, parallel-arm trial (N = 36)	
Participants	Participants with pouchitis at least twice in the previous year or requiring continuous antibiotics, associated with a PDAI ≥ 7 , in whom remission was induced by four weeks of combined metronidazole and ciprofloxacin. Active refractory or recurrent pouchitis was defined as a total PDAI score of > 7 and a history of relapsing or persistent pouchitis	
Interventions	VSL#3 (now known as the De Simone Formulation) 3 g orally twice per day (n = 20) versus maize placebo (n = 16) for 12 months	
Outcomes	Maintenance of remission Remission was defined as a clinical PDAI ≤ 2 and endoscopic PDAI ≤ 1 Relapse was defined as an increased clinical PDAI score ≥ 2 and increased endoscopic PDAI score ≥ 3	
Notes	Intention-to-treat analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Mimura 2004 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated in blocks of four at each institution
Allocation concealment (selection bias)	Low risk	Pharmacy randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient dropped out from the De Simone Formulation group due to adverse events
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Pronio 2008

Methods	Randomized, open-label, parallel-arm trial (N = 28)
Participants	Participants had no active disease, no chronic pouchitis, and were taking no medication Excluded participants with acute pouchitis (PDAI ≥ 7), participants with perianal disease including abscess, fissure, stricture, or anal sphincter weakness, and pregnant or lactating women
Interventions	VSL#3 (now known as the De Simone Formulation), 2 packets once per day (n = 16) versus no treatment (n = 12) for 12 months
Outcomes	Prevention of acute pouchitis defined as a PDAI score ≥ 7 Secondary endpoint included prevalence of regulatory T-cells
Notes	Modified intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study

Pronio 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants in the De Simone Formulation group dropped out (refusals) and one control patient developed anal carcinoma
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Sambuelli 2002

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 26)	
Participants	Participants with an active episode of pouchitis, defined as a PDAI score ≥ 7 and no treatment during the previous month or during the trial Participants were defined as having chronic pouchitis, if they presented with recurrence of symptoms at least four times a year or if they needed therapy for more than 6 months in the last year, and required a 1 month treatment-free period prior to enrollment	
Interventions	Budesonide enema (2 mg/100 mL at bedtime) plus placebo tablets or oral metronidazole (0.5 g twice per day.) plus placebo enema for 6 weeks	
Outcomes	Clinical remission (PDAI < 7 points with a decrease of ≥ 3 points from baseline) Clinical improvement (decrease in PDAI ≥ 3 from baseline)	
Notes	Intention-to-treat analysis	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes

Sambuelli 2002 (Continued)

Other bias	Low risk	The study appeared to be free of other sources of bias
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Shen 2001

Methods	Randomized, open-label, parallel-arm trial design (N = 16)
Participants	Participants with acute pouchitis, defined as a PDAI score of ≥ 7 and symptom duration of 4 weeks or less who had not received any treatment for pouchitis within 2-weeks prior to enrollment Excluded participants with chronic pouchitis defined as symptoms lasting 4 weeks or longer
Interventions	Oral ciprofloxacin 1 g/day (n = 7) or metronidazole 20 mg/kg/day (n = 9) for 2 weeks
Outcomes	Acute treatment. Total PDAI score as well as in the symptom, endoscopy, and histology subscores
Notes	Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not used (pouch biopsies were blindly scored by a GI pathologist)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs were not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Abstract publication

Tremaine 1997

Methods	Randomized, double-blind, placebo-controlled, parallel-arm trial (N = 40)
Participants	Participants with pouchitis that was active (defined as a PDAI ≥ 7) and chronic (defined as failure or intolerance to treatment with antibiotics and other medical therapies)

Tremaine 1997 (Continued)

Interventions	Bismuth carbomer foam enemas (n = 20) containing bismuth citrate 513 mg (metallic bismuth 270 mg) complexed with carbomer (a synthetic high molecular weight polymer of acrylic acid cross linked with polyalkenyl polyether) versus placebo (n = 20) administered nightly for 3 weeks	
Outcomes	Clinical improvement or remission defined as a decrease in the PDAI ≥ 3 or a PDAI of 0, respectively	
Notes	Intention-to-treat analysis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants in the bismuth carbomer foam group with missing data at the end of treatment were considered to be treatment failures
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Wischmeyer 1993

Methods	Randomized, double-blind, parallel-arm trial (N = 19)
Participants	<p>Participants with pouchitis that was chronic (defined as at least 4 episodes of recurrent pouchitis within one year and the need for suppressive medications for at least 6 of the prior 12 months)</p> <p>Eligible participants with chronic pouchitis discontinued all concomitant medications for 7 days and then began investigational therapy</p> <p>At the time that the investigational therapy was begun, the participants could have either active or remitted pouchitis following discontinuation of suppressive medical therapy</p>

Wischmeyer 1993 (Continued)

Interventions	L-glutamine 1 g in a polyethylene glycol base suppository (n = 10) versus sodium butyrate 40 mmol in a polyethylene glycol base suppository (n = 9) administered twice per day for 3 weeks	
Outcomes	Induction of symptomatic remission (resolution of increased stool frequency, urgency and cramping, fever, and blood in stools), if necessary, and subsequent maintenance of symptomatic remission (asymptomatic) after discontinuing other suppressive medical therapy	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient withdrew from each group
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Yasueda 2016

Methods	Randomized, placebo-controlled trial (N=17)	
Participants	Participants with ulcerative colitis undergoing IPAA, without any prior episodes of pouchitis	
Interventions	MIYA-BM® (Miyarisan Pharmaceutical Co., Ltd., Tokyo, Japan) tablets containing 20 mg spore-forming bacteria <i>Clostridium butyricum</i> MIYAIRI (CBM) 3 tabs daily (n=9) versus placebo (containing lactose, provided by Miyarisan Pharmaceutical Co., Ltd.) (n=8) for 24 months after IPAA	
Outcomes	Development of pouchitis based on modified PDAI (mPDAI ≥ 4)	
Notes		

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential attrition with 2 dropouts from intervention group due to "difficulty in taking medication" and none from placebo
Selective reporting (reporting bias)	High risk	No protocol available and no pre-specified secondary outcomes
Other bias	Low risk	The study appeared to be free of other sources of bias

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bengtsson 2016	Randomized, double-blind, placebo-controlled study of probiotics (<i>Lactobacillus plantarum</i> 299 and <i>Bifidobacterium infantis</i> Cure 21). Included participants with "poor pouch function", rather than pouchitis (subset had pouchitis); outcomes reported as absolute change in pouch function score or PDAI, but not as proportion of participants with or without pouchitis
Kuhbacher 2006	Non-randomized sub-study
Laake 2005	Non-randomized follow-up study
Madden 1994	Data were not available before the first cross-over
McLeod 1986	Randomized, double-blind, placebo-controlled "n-of-1" trial in a single patient with chronic pouchitis in a Kock pouch Five 14 day treatment courses with oral metronidazole 250 mg/day and five 14 day treatment courses with placebo, administered in random order Overall, the study demonstrated a beneficial effect for metronidazole as compared to placebo The study was excluded from the analysis because the purpose of such trials is to determine whether a given intervention is beneficial for a single patient, not to determine whether one intervention is more effective than

(Continued)

	another in groups of participants with a given disease
Meijer 2000	Follow-up study (actually published before the main results) of the randomized trial by Welters et al in 2002
Miner 2006	Not pouchitis but mild to moderate active left-sided ulcerative colitis
Tomasz 2014	Randomized trial of probiotics (<i>Lactobacillus</i> and <i>Bifidobacterium</i>) in which all participants with IPAA regardless of indication (chronic ulcerative colitis or familial adenomatous polyposis) were included
van Assche 2012	Trial of octreotide for prevention of diarrhea (not pouchitis) after IPAA
van Deventer 2006	Not pouchitis but mild to moderate left-sided ulcerative colitis
Welters 2002	Data were not available before the first cross-over

DATA AND ANALYSES

Comparison 1. Ciprofloxacin versus metronidazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission at 2 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Metronidazole versus budesonide enema

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission at 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical improvement at 6 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Rifaximin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical remission at 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Clinical improvement at 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. *Lactobacillus GG* versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical improvement at 12 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Glutamine versus butyrate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maintenance of clinical remission at 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 6. Bismuth enema versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical improvement at 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. De Simone Formulation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maintenance of clinical remission at 9 to 12 months	2	76	Risk Ratio (M-H, Fixed, 95% CI)	20.24 [4.28, 95.81]
2 Adverse events	2	76	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.11, 55.89]
3 No episodes of acute pouchitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. De Simone Formulation versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No episodes of acute pouchitis at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 9. *Bifidobacterium longum* versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No episodes of acute pouchitis at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 10. Allopurinol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No episodes of acute pouchitis at 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Tinidazole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No episodes of acute pouchitis at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 12. Adalimumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical improvement at 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 13. Clostridium probiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No episodes of acute pouchitis at 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Ciprofloxacin versus metronidazole, Outcome 1 Clinical remission at 2 weeks.

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

Comparison: 1 Ciprofloxacin versus metronidazole

Outcome: 1 Clinical remission at 2 weeks

Analysis 1.2. Comparison 1 Ciprofloxacin versus metronidazole, Outcome 2 Adverse events.

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

Comparison: 1 Ciprofloxacin versus metronidazole

Outcome: 2 Adverse events

Analysis 2.1. Comparison 2 Metronidazole versus budesonide enema, Outcome 1 Clinical remission at 6 weeks.

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

Comparison: 2 Metronidazole versus budesonide enema

Outcome: 1 Clinical remission at 6 weeks

Analysis 2.2. Comparison 2 Metronidazole versus budesonide enema, Outcome 2 Clinical improvement at 6 weeks.

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

Comparison: 2 Metronidazole versus budesonide enema

Outcome: 2 Clinical improvement at 6 weeks

Analysis 2.3. Comparison 2 Metronidazole versus budesonide enema, Outcome 3 Adverse events.

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

Comparison: 2 Metronidazole versus budesonide enema

Outcome: 3 Adverse events

Analysis 3.1. Comparison 3 Rifaximin versus placebo, Outcome 1 Clinical remission at 4 weeks.

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

Comparison: 3 Rifaximin versus placebo

Outcome: 1 Clinical remission at 4 weeks

Analysis 3.2. Comparison 3 Rifaximin versus placebo, Outcome 2 Clinical improvement at 4 weeks.

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

Comparison: 3 Rifaximin versus placebo

Outcome: 2 Clinical improvement at 4 weeks

Analysis 3.3. Comparison 3 Rifaximin versus placebo, Outcome 3 Adverse events.

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

Comparison: 3 Rifaximin versus placebo

Outcome: 3 Adverse events

Analysis 4.1. Comparison 4 *Lactobacillus GG* versus placebo, Outcome 1 Clinical improvement at 12 weeks.

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

Comparison: 4 *Lactobacillus GG* versus placebo

Outcome: 1 Clinical improvement at 12 weeks

Analysis 5.1. Comparison 5 Glutamine versus butyrate, Outcome 1 Maintenance of clinical remission at 3 weeks.

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

Comparison: 5 Glutamine versus butyrate

Outcome: 1 Maintenance of clinical remission at 3 weeks

Analysis 6.1. Comparison 6 Bismuth enema versus placebo, Outcome 1 Clinical improvement at 3 weeks.

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

Comparison: 6 Bismuth enema versus placebo

Outcome: 1 Clinical improvement at 3 weeks

Analysis 6.2. Comparison 6 Bismuth enema versus placebo, Outcome 2 Adverse events.

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

Comparison: 6 Bismuth enema versus placebo

Outcome: 2 Adverse events

Analysis 7.1. Comparison 7 De Simone Formulation versus placebo, Outcome 1 Maintenance of clinical remission at 9 to 12 months.

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

Comparison: 7 De Simone Formulation versus placebo

Outcome: 1 Maintenance of clinical remission at 9 to 12 months

Analysis 7.2. Comparison 7 De Simone Formulation versus placebo, Outcome 2 Adverse events.

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

Comparison: 7 De Simone Formulation versus placebo

Outcome: 2 Adverse events

Analysis 7.3. Comparison 7 De Simone Formulation versus placebo, Outcome 3 No episodes of acute pouchitis.

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

Comparison: 7 De Simone Formulation versus placebo

Outcome: 3 No episodes of acute pouchitis

Analysis 8.1. Comparison 8 De Simone Formulation versus no treatment, Outcome 1 No episodes of acute pouchitis at 12 months.

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

Comparison: 8 De Simone Formulation versus no treatment

Outcome: 1 No episodes of acute pouchitis at 12 months

Analysis 9.1. Comparison 9 *Bifidobacterium longum* versus placebo, Outcome 1 No episodes of acute pouchitis at 6 months.

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

Comparison: 9 *Bifidobacterium longum* versus placebo

Outcome: 1 No episodes of acute pouchitis at 6 months

Analysis 10.1. Comparison 10 Allopurinol versus placebo, Outcome 1 No episodes of acute pouchitis at 24 months.

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

Comparison: 10 Allopurinol versus placebo

Outcome: 1 No episodes of acute pouchitis at 24 months

Analysis 11.1. Comparison 11 Tinidazole versus placebo, Outcome 1 No episodes of acute pouchitis at 12 months.

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

Comparison: 11 Tinidazole versus placebo

Outcome: 1 No episodes of acute pouchitis at 12 months

Analysis 12.1. Comparison 12 Adalimumab versus placebo, Outcome 1 Clinical improvement at 4 weeks.

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

Comparison: 12 Adalimumab versus placebo

Outcome: 1 Clinical improvement at 4 weeks

Analysis 13.1. Comparison 13 Clostridium probiotic versus placebo, Outcome 1 No episodes of acute pouchitis at 24 months.

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

Comparison: 13 Clostridium probiotic versus placebo

Outcome: 1 No episodes of acute pouchitis at 24 months

APPENDICES

Appendix I. Search strategies

1. Search strategy for Embase (via OVID)

1. random\$.tw.
2. factorial\$.tw.
3. (crossover\$ or cross over\$ or cross-over\$).tw.
4. placebo\$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).tw.
9. (double\$ adj blind\$).tw.
10. (tripl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (colitis and ulcerat*).mp.
20. ulcerative colitis.mp. or exp ulcerative colitis/
21. (inflammatory bowel disease* or IBD).mp.
22. or/19-21
23. Ex pouchitis/
24. Pouch Ileitis.mp.

25. Pouch*.mp.
26. Ileitis.mp.
27. or/23-26
28. 18 and 22 and 27

2. Search strategy for MEDLINE

1. random\$.tw.
2. factorial\$.tw.
3. (crossover\$ or cross over\$ or cross-over\$).tw.
4. placebo\$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).tw.
9. (double\$ adj blind\$).tw.
10. (tripl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. randomized controlled trial/
14. or/1-13
15. (colitis and ulcerat*).mp.
16. ulcerative colitis.mp. or exp ulcerative colitis/
17. (inflammatory bowel disease* or IBD).mp.
18. or/15-17
19. Ex pouchitis/
20. Pouch Ileitis.mp.
21. Pouch*.mp.
22. Ileitis.mp.
23. or/19-22
24. 14 and 18 and 23

3. Cochrane Central Register of Controlled Trials (CENTRAL)

- #1 MeSH descriptor: [Colitis, Ulcerative] explode all trees
- #2 colitis OR UC OR IBD OR inflammatory bowel disease
- #3 # 1 or #2
- #4 MeSH descriptor: [Pouchitis] explode all trees
- #5 Pouch Ileitis
- #6 Pouch*
- #7 Ileitis
- #8 #4 or #5 or #6 or #7
- #9 #3 and #8

4. SR-IBD (IBD Group Specialized Register)

Abstract OR Title OR Keyword: "Pouchitis" and "ulcerative colitis"
 "Pouch Ileitis" and "ulcerative colitis"
 "Pouchitis" and "Inflammatory Bowel Disease"

Clinical trials.gov

1. Pouchitis and ulcerative colitis
2. Pouchitis and Inflammatory Bowel Disease

WHO trial registry

1. Pouchitis and ulcerative colitis
2. Pouchitis and Inflammatory Bowel Disease

WHAT'S NEW

Date	Event	Description
24 June 2019	Amended	Correction: Three of the included studies in this review assessed a probiotic formulation known as VSL#3. The probiotic formulation that was assessed in these studies is now known by the generic name 'De Simone Formulation'. To the best of our knowledge, there are no randomized trials that have assessed the current product known as VSL#3 in people with pouchitis. The current product known as VSL#3 is not the same formulation as the original product invented by Professor De Simone. De Simone Formulation is available under the brand names Visbiome in the USA and Vivomixx in the EU

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 3, 1998

Date	Event	Description
25 July 2018	New citation required but conclusions have not changed	Updated review with new authors
25 July 2018	New search has been performed	New search, two new studies added

CONTRIBUTIONS OF AUTHORS

Dr. Nguyen - data analysis, drafting of review, critical revision

Dr. Zhang - critical revision

Dr. Holubar - drafting of review, critical revision.

Dr. Pardi - data analysis, critical revision.

Dr. Singh - data analysis, drafting of review, critical revision

DECLARATIONS OF INTEREST

Nghia Nguyen: None known

Bing Zhang: None known

Stefan D Holubar: None known

Darrell S Pardi: has received consulting fees from Assembly Bioscience, C3 Jian, Ferring, Janssen, Nestle, Merck, Otsuka, Salix, Seres, Gilead; research grants from Atlantic, Finch, Janssen, Merck, Pfizer, Salix, Seres, Takeda, Vedanta

Siddharth Singh - has received consulting fees from AbbVie, Takeda, AMAG Pharmaceuticals; research grants from Pfizer and AbbVie; and honorarium for grant review from Pfizer.

SOURCES OF SUPPORT

Internal sources

- none, Other.

External sources

- none, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

Anastomosis, Surgical [*adverse effects]; Anti-Bacterial Agents [adverse effects; therapeutic use]; Budesonide [adverse effects; therapeutic use]; Ciprofloxacin [adverse effects; therapeutic use]; Colitis, Ulcerative [*surgery]; Enema; Gastrointestinal Agents [adverse effects; therapeutic use]; Metronidazole [adverse effects; therapeutic use]; Postoperative Complications [drug therapy; prevention & control]; Pouchitis [*drug therapy; etiology; prevention & control]; Probiotics; Randomized Controlled Trials as Topic; Remission Induction

MeSH check words

Humans