Network meta-analysis: efficacy of treatment for acute, chronic, and prevention of pouchitis in ulcerative colitis

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Introduction Pouchitis is a clinically significant complication of ileal pouch-anal anastomosis. There is a paucity of head-to-head comparisons between treatments and no data were available about how each treatment rank against each other. A network meta-analysis of the different treatments used for acute, chronic and prevention of pouchitis was conducted.
Methods Biomedical databases and the Cochrane Central registry were searched between 1978 and 2021 for randomised controlled trials examining treatment for acute, chronic and prevention of pouchitis. A network meta-analysis was performed using the frequentist model with pooled relative risks and *P* scores used to rank treatments.
Results 18 studies were included from a screen of 4291 abstracts. When compared to placebo, rifaximin was found to be the best antibiotic for acute pouchitis whereas ciprofloxacin ranked highest against metronidazole. For chronic pouchitis, metronidazole followed by probiotics was statistically significant and effective treatments in inducing remission although metronidazole had the highest adverse events. Adalimumab and bismuth were also found to be superior to placebo; however, they did not reach statistical significance. Probiotics proved superior to placebo in the prevention of pouchitis development.
Conclusions This is the first network meta-analysis which compares the efficacy and tolerability of treatments in the management and prevention of acute and chronic pouchitis. It confirms that antimicrobial therapy remains the mainstay of treatment and adds weight to current guideline recommendations. Our results demonstrate that rifaximin and probiotics may deserve a more prominent role. While biologics are starting to show promise, large-scale head-to-head comparisons are warranted to validate the efficacy of these treatments. Eur J Gastroenterol Hepatol 34: 518–528

Introduction

Restorative proctocolectomy may be offered to patients with ulcerative colitis who despite medical therapy remains burdened by their inflammatory bowel disease. Functional outcomes with restorative proctocolectomy remain good, but complications, such as pouchitis remain a major cause of morbidity in this patient group.

Pouchitis has no specific definition but is considered when there is inflammation of the ileoanal pouch [1]. Pouchitis is diagnosed using a combined assessment of symptoms which include increased stool frequency, urgency, incontinence, nocturnal seepage, abdominal cramping and pelvic discomfort; together with classical endoscopic and histologic findings of inflammation. The most commonly used composite scoring system is the pouch disease activity index (PDAI) which incorporates these elements and allows disease assessment and monitoring [2].

Pouchitis prevalence has been estimated to be 18% for acute pouchitis and 13% for chronic pouchitis [3]. Risk factors for pouchitis include a concomitant autoimmune disorder, extensive colonic disease, smoking, arthritis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis and presence of the NOD2insC variant gene [4].

Pouchitis can be both acute and chronic, where acute pouchitis refers to inflammation of the pouch that usually responds to a short course of antibiotics, whereas chronic pouchitis refers to frequent relapsing episodes of acute pouchitis (≥3 per 12 months), which can be antibiotic responsive or antibiotic resistance. Chronic pouchitis remains a difficult-to-treat condition and relies on empirical therapy with rotating antibiotics and steroids. Newer treatments aimed at controlling inflammation, such as biologic therapy, faecal microbiota transplantation and probiotics have since emerged, highlighted by a number of meta-analyses [5]. Pouchitis carries a 10% [6] incidence of pouch failure and hence there is a need to determine the best available medical therapy as this carries significant implications in terms of quality of life and the need for surgical intervention. However, there remains no data about where each treatment ranks against each other. This is predominately due to studies having different comparators.

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We, therefore, conducted a network meta-analysis to rank treatments for pouchitis according to efficacy and tolerability and circumnavigate the lack of head-to-head trials in pouchitis.

Methods

Search strategy and study selection

A search of the medical literature was conducted using *MEDLINE* (1978 to May 2021), *EMBASE* and *EMBASE classic* (1978 to May 2021), the Cochrane central register of controlled trials (Issue 2 May 2021) and the Cochrane Specialized Trials Register. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week and the Asian Pacific Digestive Week) between 2006 and 2020 to identify studies published only in abstract form.

Randomised Controlled Trials (RCTs) examining the efficacy of medical therapies versus placebo or another therapy for pouchitis were included. We included only an adult population where at least 90% of the subjects were over 16 years old. The first period of any cross over study was also eligible. For induction of remission, trials had to report one or more of the following endpoints: a composite of clinical and endoscopic remission; clinical remission; endoscopic remission or histological remission. Chronic pouchitis studies had to report on patients who were defined with pouchitis for at least 4 weeks. For maintenance studies patients were required to be in remission and report how many patients remained in remission at the end of the study period. The study protocol was published on the PROSPERO international prospective register of systematic reviews (PROSPERO ID: CRD42021273564). Ethical approval for this study was not required.

Studies were identified with the terms pouchitis, restorative proctocolectomy both as medical subject headings or free text terms. These were combined using the set operator AND with studies identified with the terms (Supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJGH/A750*). There were no language restrictions, and we translated manuscripts where appropriate using Google Translate. The abstracts from the search were screened against eligibility criteria and those that were deemed to potentially fit were examined in greater detail using the whole manuscript. Bibliographies of included articles were also interrogated for further studies that may reach the inclusion criteria. If a study was potentially relevant but was missing data required, we contacted the authors for clarification. Eligibility assessment was performed by two independent authors (S.P. and D.S.) using predefined eligibility forms. We resolved any disagreements by consensus and measured the degree of agreement with a kappa statistic.

Outcome assessment

The primary outcome was the efficacy of medical therapies at achieving remission in acute and chronic pouchitis. Secondary outcomes included the efficacy of medical therapies at maintaining remission in pouchitis, adverse events occurring due to therapy, including total numbers of adverse events, and adverse events leading to study withdrawal.

Data extraction

Data were extracted onto a Microsoft Excel spreadsheet by two independent investigators (S.P. and D.S.). We extracted the following clinical data for each trial, where available: number of centres, country of origin, endpoints used to define remission or relapse, dosage, route, schedule of medication used, duration of therapy and number of individuals incurring each (or any) of the adverse events of interest. We extracted data as intention-to-treat analyses, with all dropouts assumed to be treatment failures (i.e. failed to achieve remission in active microscopic colitis).

Risk of bias assessment

We used the Cochrane Risk of Bias 2.0 tool to assess the studies [7]. Two investigators (S.P. and D.S.) assessed study quality independently, with disagreements resolved by discussion. For all RCTs, we recorded the method used to generate the randomisation schedule, deviations from the intended interventions, methods used to deal with missing outcome data, how the outcome was measured and how the reported result was selected.

Data synthesis and statistical analysis

We performed a network meta-analysis using the frequentist model [8] with the statistical package netmeta (version 0.9-0), in R (version 3.4.6) to compare (directly and indirectly) the efficacy and safety of each treatment of interest across studies. The results were reported according to the preferred reporting items for systematic reviews and meta-analyses extension statement for network meta-analyses [9]. Network meta-analysis results usually give a more precise estimate of relative efficacy and safety than results from standard pairwise analyses and allow treatments to be ranked in terms of efficacy to help inform clinical decisions.

We generated comparison-adjusted funnel plots [10] to assess publication bias and small-study bias for all available treatment comparisons versus each other or placebo, where sufficient studies (≥10) existed. If symmetry around the effect estimate line is found this indicates the absence of publication bias or small-study bias.

For each treatment in the meta-analysis, we generated a pooled relative risk (RR) with 95% confidence intervals (CIs) to compare the effect of each comparison tested using a random-effects model. We calculated the RR of failure to achieve remission, values of less than 1 that does not cross 1, highlights that there is a significant benefit of one treatment over another, or over placebo. As there were direct comparison between some of the treatments for several endpoints of interest.

We furthermore assessed global statistical heterogeneity using the I^2 measure [11]. The I^2 measure of heterogeneity ranges from 0 to 100%. A result of 25–49% indicates low study heterogeneity, 50–74% indicates moderate

heterogeneity and 75% and above indicates high heterogeneity [12].

Heat plots were also used to assess inconsistency in the network meta-analysis by comparing direct and indirect evidence (when available) [12]. The grey squares in these plots represent the size of the contribution of the direct estimate in columns, compared with the network estimates in rows [12]. The coloured squares represent the degree of inconsistency.

The *P*-score [8] was used to rank treatments which generate a value between 0 and 1. They measure the extent of certainty that one treatment is superior to another. Therefore, the higher the score the more likely they are superior to another treatment.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The search revealed 4291 studies. After the abstract screening, there were 24 studies remaining and after full-text screening, 18 studies were analysed (Fig. 1). The treatments analysed include bifidobacterium longum subsp. longum (BB536), VSL#3, tinidazole, rifaximin, allopurinol, faecal microbiota transplantation (FMT), adalimumab, serum leucine-rich alpha-2 glycoprotein (LRG), metronidazole, budesonide, ciprofloxacin, LAP (lactobacillus acidophilus, lactobacillus delbrueckii subsp. bulgaricus, and bifidobacterium bifidus), bismuth, octreotide, butyrate, glutamine and clostridium butyricum miyairi (CBM). The three studies included that report on VSL#3 used the 'De Simone Formulation' of the drug which is now sold under the brand name Visbiome [13]. The characteristics of all the studies are displayed in Table 1.

Acute pouchitis: remission

There were four RCTs that reported clinical remission in acute pouchitis to include 83 patients. Two studies (Van Assche *et al*., [29] and Isaacs *et al*., [18]) used a placebo as the comparator against eight patients taking rifaximin and 12 patients taking octreotide, respectively. Two studies (Sambuelli et al. [25] and Shen et al.[26]) used metronidazole as the comparator against 12 patients taking budesonide and seven patients taking ciprofloxacin, respectively. The duration of treatment across the studies varied from 2 to 6 weeks. Due to the small number of studies, an I^2 was 0% and no funnel plot or heat plot was possible. The definition of clinical remission used by each study is outlined in Table 1.

Placebo vs. rifaximin and octreotide

In the placebo-controlled studies; Van Assche *et al*. [29] reported that 2/12 (16%) achieved clinical remission in the octreotide group and 2/11(18%) in the placebo group, and Isaacs *et al*. [18] reported that 2/8 (25%) achieved clinical remission in the rifaximin group and 0/10 (0%) in the placebo group. The forest plot showed that rifaximin (RR, 6.18; 95% CI, 0.34–112.09) performed better than placebo whereas octreotide (RR, 0.92; 95% CI, 0.15–5.44) did not, with both results not being statistically significant

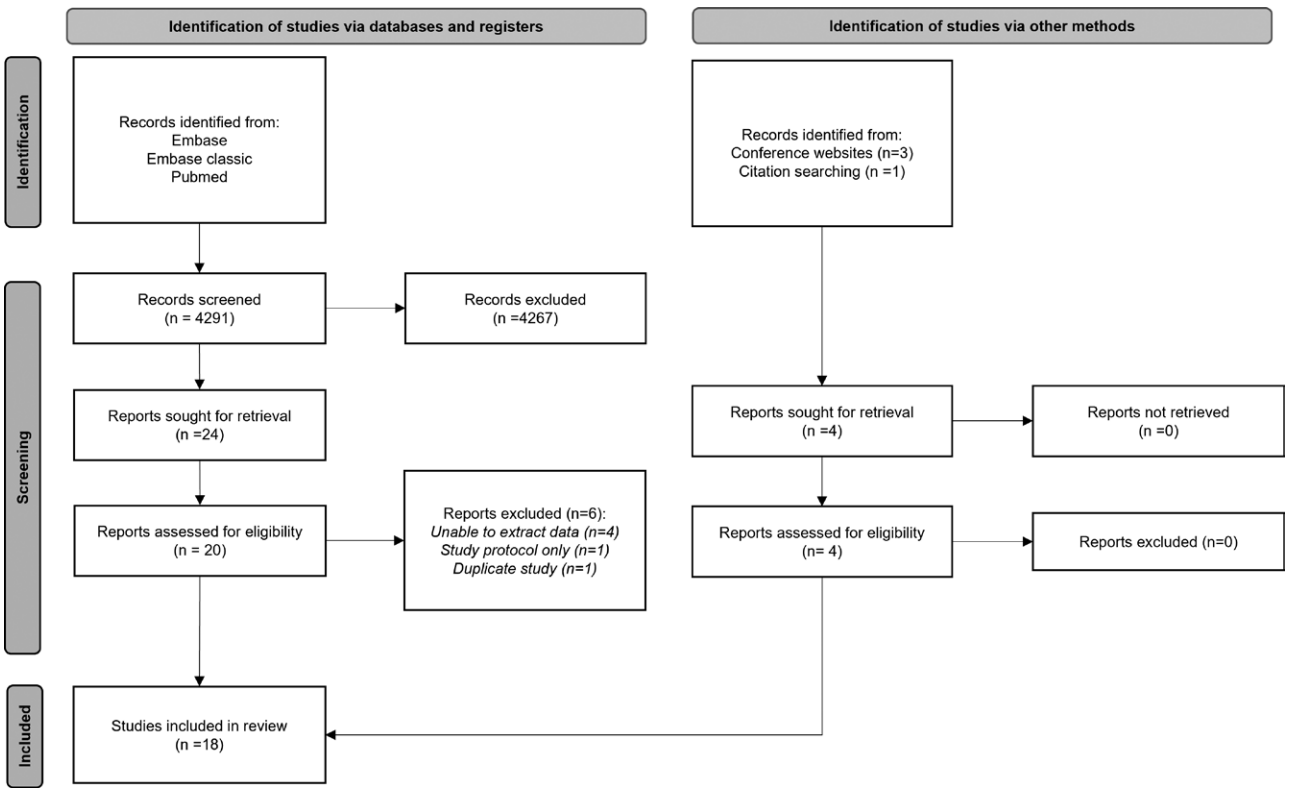

Fig. 1 PRISMA 2020 diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Table 1 Characteristics of studies included

Study	Country	Treatment	% Male	Number of patients receiving treatment	End point	Definition of end point	Follow up period	Definition of pouchitis
Brown *et al*., (2004) [14]	USA	BB536	Unknown	7	Prevention of pouchitis	PDAI score ≤ 7 after 6 months	6 months	PDAI >7
Gionchetti *et al*., (2000) [15]	Italy	VSL#3	57.5	20	Prevention of chronic pouchitis	PDAI score increase <2	9 months	Not stated
Gionchetti *et al*., (2003) [16]	Italy	VSL#3	57.5	20	Prevention of pouchitis	PDAI score ≤7	12 months	PDAI>7
Ha *et al*., (2010) [17]	USA	Tinidazole	Unknown	24	Prevention of pouchitis	Not stated	12 months	Not stated
Isaccs *et al*., (2007) [18]	USA	Rifaximin	82.35	8	Remission of acute pouchitis	PDAI <7 points and decrease ≥3 from baseline	1 month	PDAI >7
Joelsson *et al*., (2001) [19]	Sweden	Allopurinol	59.78	62	Prevention of pouchitis	Own scoring system	24 months	Own scoring system
Karjalainen *et al*., (2021) [20]	Finland	FMT	57.69	13	Remission of chronic pouchitis	PDAI score <7 and no need for antibiotics	12 months	PDAI>7
Kjaer *et al*., (2019) [21]	Denmark	Adalimumab	53.85	6	Remission of chronic pouchitis	Reduction in clinical PDAI of >2 after 12 weeks	3 months	PDAI>7 with symptoms for >4 weeks not responsive to treatment
Kuisma *et al*., (2003) [22]	Finland	LRG	55	10	Prevention of pouchitis	Reduction in PDAI ≥3 after 12 weeks	9 months	PDAI >7
Madden *et al*., (1994) [23]	UK	Metronidazole	Unknown	12	Remission of chronic pouchitis	Reduction in stool frequency	1 month	Not stated
Mimura *et al*., (2004) [24]	Italy and UK	VSL#3	55.56	20	Remission of chronic pouchitis	PDAI score <7	12 months	PDAI >7 with persistent symptoms
Sambuelli *et al*., (2002) [25]	Argentina	Budesonide vs. Metronidazole	69.23	12 vs. 14	Remission of acute pouchitis	PDAI <7 points and decrease ≥3 from baseline	6 weeks	PDAI >7
Shen *et al*., (2001) [26]	USA	Ciprofloxacin vs. metronidazole	56.25	7 vs. 9	Remission of acute pouchitis	PDAI score <7	9 months	PDAI >7
Tomasz *et al*., (2014) [27]	Poland	LAP	53.49	19	Prevention of pouchitis	PDAI score ≤7	9 months	PDAI >7
Tremaine *et al*., (1997) [28]	USA	Bismuth	55	20	Remission of chronic pouchitis	Reduction in the PDAI to 0	3 weeks	PDAI >7 with symptoms > 4 weeks
Van Assche *et al*., (2012) [29]	Belgium	Octreotide	73.33	12	Remission of acute pouchitis	Reduction in stool frequency ≥3 stools per day and reduction in frequency ≥30% after 7 days	6 months	Not stated
Wischmeyer *et al*., (1993) [30]	USA	Butyrate vs. glutamine	47.62	9 vs. 10	Remission of chronic pouchitis	Recurrence of symptoms	3 weeks	Symptoms that occur ≥3 times a year
Yasueda *et al*., (2016) [31]	Japan	CBM	52.94	9	Prevention of pouchitis	mPDAI <4	24 months	mPDAI ≥4

BB536, bifidobacterium longum subsp. longum; CBM, clostridium butyricum miyairi; FMT, faecal microbiota transplantation; LAP, lactobacillus acidophilus, lactobacillus delbrueckii subsp. bulgaricus, and bifidobacterium bifidus, LRG, serum leucine-rich alpha-2 glycoprotein; PDAI, pouch disease activity index.

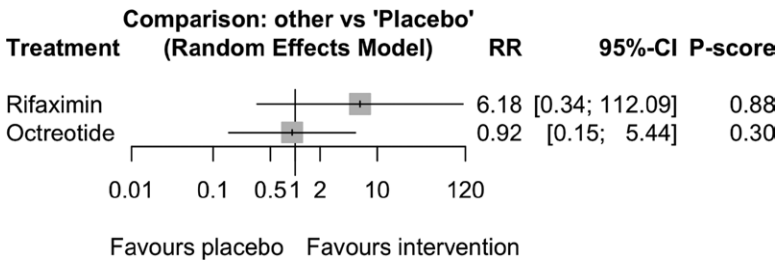

Fig. 2 Forest plot of acute pouchitis treatments vs. placebo.

(Fig. 2). The summary of treatment effect ranking is demonstrated in Table 2 and the network plot in Fig. 3. In addition to octreotide being less favourable when compared to placebo and rifaximin, it also has the worst adverse events and withdrawal rate when compared to placebo and to rifaximin. The network plots, forest plots, funnel plots and

effect ranking for adverse events and withdrawals can be found in the Supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJGH/A750*.

Metronidazole vs. ciprofloxacin and budesonide

In the metronidazole-controlled studies, Sambuelli *et al*. [25] reported 7/12 (58%) achieved clinical remission in the budesonide group and 7/14(50%) in the metronidazole group, and Shen et al. [26] reported 7/7(100%) achieved clinical remission in the ciprofloxacin group and 6/9 (66%) in the metronidazole group. The forest plot showed that both ciprofloxacin (RR, 1.46; 95% CI, 0.95–2.25) and budesonide (RR, 1.17; 95% CI, 0.57–2.37) outperformed metronidazole but the results were not statistically significant (Fig. 4). The network plot is shown in Fig. 5 and the summary of treatment effects ranking in Table 3. Both treatments had a less favourable adverse event rate than metronidazole with budesonide having a less favourable withdrawal rate than metronidazole too. However, these results were not statistically significant. The network plots, forest plots, funnel plots and effect ranking for adverse events and withdrawals can be found in the Supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJGH/A750*.

Table 2 Summary of treatment effect rankings acute pouchitis vs. placebo

Rifaximin	6.18 (0.34–112.09)	
6.18 (0.34–112.09)	Placebo	1.09 (0.18–6.48)
6.74 (0.22–202.31)	1.09 (0.18–6.48)	Octreotide

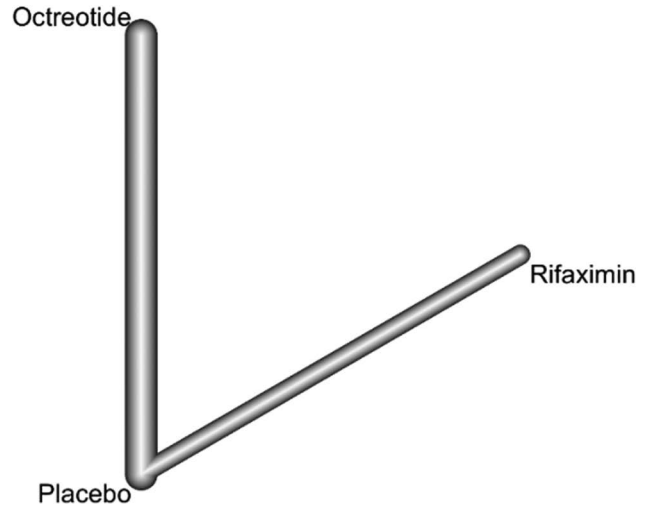

Fig. 3 Network plot of acute pouchitis treatments vs. placebo.

Chronic pouchitis

There were six RCTs that compared treatments for chronic pouchitis to include 157 patients. In total 13 patients received FMT, 6 adalimumab, 12 metronidazole, 20 VSL#3, 20 bismuth, 10 glutamine and 9 butyrate, respectively. All but one study were placebo-controlled – this trial compared butyrate with glutamine to evaluate the rate of recurrence of pouchitis. The duration of treatment varied across studies from 2 to 52 weeks. All studies assessed the effect of these treatments on remission of chronic pouchitis, except for one using metronidazole by Madden et al., [23] which assessed reduction of stool frequency. The definition of clinical remission used by each study is outlined in Table 1. Due to the small number of studies, an I^2 was 0% (0.0%; 84.7%) and no funnel plot or heat plot was possible.

Placebo vs. FMT, adalimumab, metronidazole, VSL#3 and bismuth

The forest plot shows that all treatments but one (faecal microbiota transplantation) performed better than placebo at inducing remission in chronic pouchitis (Fig. 6). Metronidazole ranked the most superior and statistically significant, resulting in a reduction in stool frequency in 9/12 (75%) patients compared to 0/11 (0%) in the placebo group (RR, 17.48; 95% CI, 1.14–267.68). This is followed by VSL#3 which induced remission in 17/20 (85%) vs. 1/16 (6%) patients in the placebo group (RR, 13.60; 95% CI, 2.02–91.53). While not statistically significant,

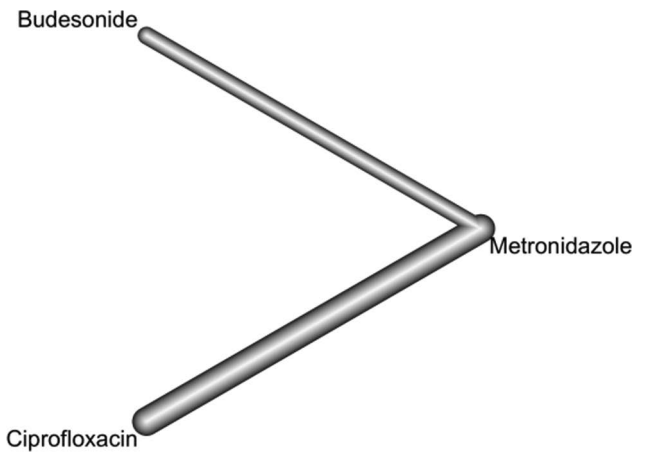

Fig. 5 Network plot of acute pouchitis treatments vs. metronidazole.

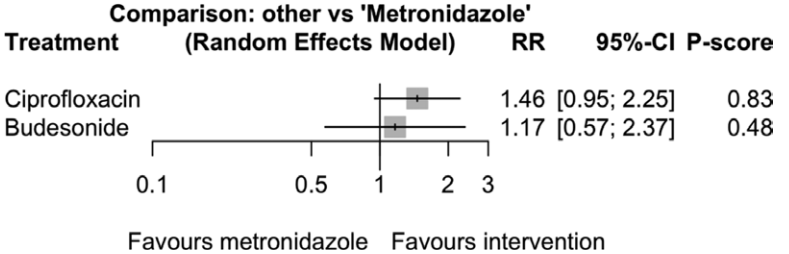

Fig. 4. Forest plot of acute pouchitis treatments vs. metronidazole.

adalimumab (RR, 1.17; 95% CI, 0.09–14.92) and bismuth (RR, 1.00; 95% CI, 0.02–48.03) ranked above placebo in inducing remission of chronic pouchitis, whereas FMT was inferior (RR, 0.80; 95% CI, 0.28–2.32). The summary of treatment effect ranking is demonstrated in Table 4 and the network plot in Fig. 7.

While metronidazole showed the best treatment effect, it also ranked highest in terms of adverse outcomes (RR, 15.00; 95% CI, 0.97–233.13). The most commonly reported side effects include nausea, dysgeusia and peripheral neuropathy, however, no one withdrew from this study. This is followed by FMT, VSL#3 and adalimumab which ranked higher than placebo in terms of adverse outcomes; however, none of these associations are statistically significant. VSL#3 produced the highest RR of withdrawal resulting from recurrent abdominal cramps, diarrhoea and vomiting in one patient (RR, 2.41; 95% CI, 0.1051–55.4690) although this is again not statistically significant. The network plots, forest plots, funnel plots and effect ranking for adverse events and withdrawals can be found in the Supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJGH/A750*.

Butyrate vs. glutamine

Butyrate was compared to glutamine in the study by Wischmeyer *et al*. [30] with 3/9 (33%) of patients in the butyrate group and 6/10 (60%) of patients in the glutamine group. None of the patients suffered from any side effects nor did they withdraw from the study. Due to no further studies comparing these treatments no further analysis could be carried out.

Prevention of pouchitis

There were seven RCTs reporting on the prevention of pouchitis that include 281 patients. In total 20 patients received VSL#3, 10 LRG, 24 tinidazole, 9 CBM, 7 BB536, 19 LAP and 62 allopurinol. All studies were placebo-controlled with treatment duration varying from 3 months to 2 years. The definition of prevention used by each study is outlined in Table 1. Due to the small number of studies, the Eggers test or a heatmap could not be performed but the $I^2 = 79.9\%$ (13.3–95.3%).

Table 3 Summary of treatment effect rankings acute pouchitis vs. metronidazole

Ciprofloxacin		1.46 (0.95–2.25)
1.25 (0.55–2.87)	Budesonide	1.17 (0.57–2.37)
1.46 (0.95–2.25)	1.17 (0.57–2.37)	Metronidazole

Placebo vs. VSL#3, LRG, tinidazole, CBM, BB536, LAP and allopurinol

All treatments except for allopurinol were better than placebo for maintaining the prevention of pouchitis. However, none of the studies produced statistically significant results (Fig. 8). VSL#3 was superior with 18/20 (90%) patients not developing pouchitis compared with 12/20 (60%) in the placebo group (RR, 5.34; 95% CI, 0.26–110.38). LRG ranked next with 1/10 (10%) patients not developing pouchitis after being in remission from acute pouchitis at the start of the study compared to 0/10 (0%) in the placebo group (RR, 3; 95% CI, 0.02–433.38). This was followed by tinidazole (RR, 1.90; 95% CI, 0.04–100.01), CBM (RR, 1.78; 95% CI, 0.03–94.09), BB536 (RR, 1.43; 95% CI, 0.03–76.28), LAP (RR, 1.36; 95% CI, 0.03–68.58) and last was allopurinol (RR, 0.96; 95% CI, 0.02–47.83). The summary of treatment effect ranking is demonstrated in Table 5 and the network plot in Fig. 9. The funnel plot (Fig, 10) did not demonstrate a publication bias. Adverse events and withdrawal from the study were reported with VSL#3, LAP, CBM and allopurinol. Allopurinol had the highest risk of adverse events and CBM withdrawal (RR, 3.83; 95% CI, 0.84–17.55) had the highest risk of withdrawal (RR, 4.47; 95% CI, 4.47–80.65). The network plots, forest plots, funnel plots and effect ranking for adverse events and withdrawals can be found in the Supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJGH/A750*.

Risk of bias assessment

Assessment of bias was carried out using the Cochrane risk of bias tool for randomised trials [7]. The tool found that four studies had a high risk of bias, one study with some concerns of bias and 13 studies had a low risk of bias. This is demonstrated in Table 6 and Fig. 11.

Discussion

This is the first network meta-analysis which provides up-to-date evidence comparing the efficacy and safety profile of various treatments in the management and prevention of acute and chronic pouchitis. The results of our study support the current accepted practice of antimicrobial therapy the mainstay of treatment in acute pouchitis, with ciprofloxacin or metronidazole as preferred options [5]. While none of these treatments achieved statistical significance, our study suggests that rifaximin is an

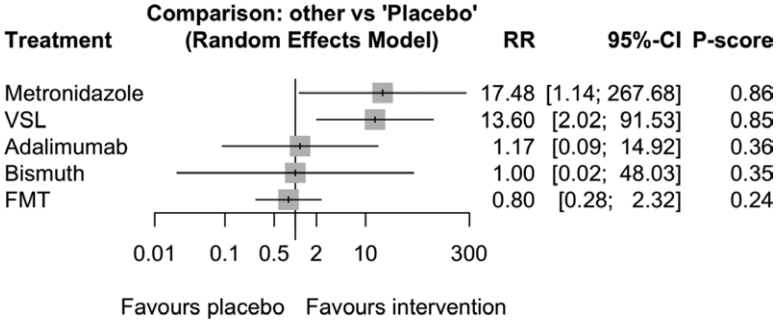

Fig. 6 Forest plot chronic pouchitis treatments vs. placebo.

Table 4 Summary of treatment effect rankings chronic pouchitis

Metronidazole				17.48 (1.14–267.68)	
1.29 (0.05–35.87)	VSL#3			13.60 (2.02–91.53)	
14.98 (0.36–626.73)	11.66 (0.48–281.06)	Adalimumab		1.17 (0.09–14.92)	
17.48 (0.15–1993.86)	13.60 (0.18–1018.30)	1.17 (0.01–120.22)	Bismuth	1.00 (0.02–48.03)	
17.48 (1.14–267.68)	13.60 (2.02–91.53)	1.17 (0.09–14.92)	1.00 (0.02–48.03)	Placebo	1.25 (0.43–3.63)
21.85 (1.17–409.11)	17.00 (1.91–151.10)	1.46 (0.09–23.10)	1.25 (0.02–69.35)	1.25 (0.43–3.63)	FMT

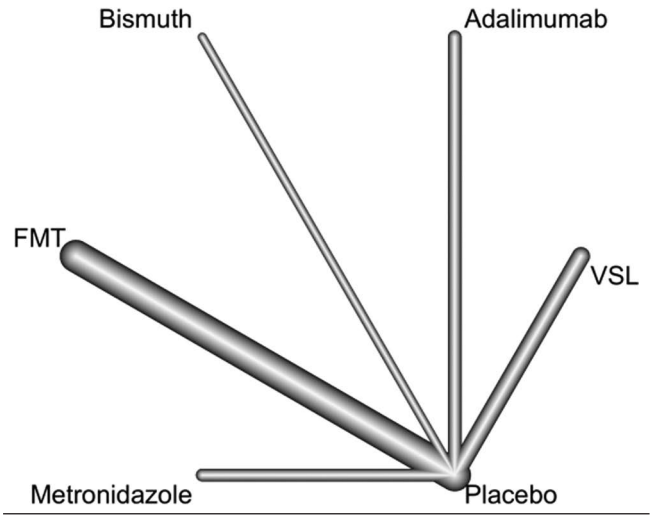

Fig. 7 Network plot of chronic treatments vs. placebo.

effective and well-tolerated treatment strategy compared to placebo (RR, 6.13), whereas ciprofloxacin and budesonide enema were superior to metronidazole in inducing remission for acute pouchitis. Ciprofloxacin and budesonide enema also appear to have a better tolerability profile compared to metronidazole and patients' preference on the route of administration will aid clinical decision making.

The management of chronic pouchitis remains a significant challenge in the absence of high-quality evidence with treatment being largely empirical with combined antibiotic therapy or oral steroids, or both [5,32]. In keeping with this, metronidazole ranked highest in the treatment of chronic pouchitis (RR, 17.48) although this was accompanied with drug-related side-effects. Importantly, metronidazole is associated with peripheral neuropathies and hence long-term use should be avoided where possible. Interestingly this was followed by VSL#3 which significantly induced remission in chronic pouchitis with a RR of 13.6 and indeed ranked highest in the maintenance of remission. Lactobacillus rhamnosus GG ranked second in the prevention of acute pouchitis, however, it may be difficult to apply these findings to the general pouch population because their patient cohort was recently treated for and thus likely predisposed to acute pouchitis. It has been well documented that pouchitis is related to perturbations in the pouch microbiome [33], hence probiotics may have a positive influence on gut bacteria resulting in the reduction of pouch inflammation. Our data suggest that probiotics do have a role in the prevention of pouchitis and further studies are warranted to validate the beneficial effects of VSL#3 on gut micro-diversity and select patients who will most likely benefit from this therapy.

In keeping with the pouch dysbiosis hypothesis, faecal microbiota transplantation is a recently proposed albeit contentious treatment in pouchitis. While FMT has shown promise in *Clostridioides difficile* infection and ulcerative colitis, its impact on pouchitis is controversial and research has been limited [34]. Recently, two pilot open-label studies report symptomatic benefit in patients with chronic pouchitis although this improvement was not necessarily reflected endoscopically [35,36]. Our results demonstrate that FMT was both inferior to placebo at inducing remission in chronic pouchitis while carrying a high adverse event profile, suggesting that this should not be recommended in clinical practice. A better understanding of gut biodiversity and the intricate interactions between the intestinal flora and host immune response are required to restore balance to the gut microbiome and allow us to determine potential therapeutic targets.

There has been an increasing body of evidence supporting the use of biologic therapy in the short- and long-term management of chronic pouchitis with clinical improvement in 62.3% treated with infliximab and 58.7% treated with adalimumab [37]. While not statistically significant, adalimumab ranked superior compared to placebo (RR, 1.17) and has been proposed as a third-line strategy in the treatment of chronic pouchitis [32]. Importantly there are many nonrandomised and observational studies that support the use of other biologics, such as vedolizumab and ustekinumab for inflammatory pouch disorders and further head-to-head data will help guide their position in the treatment algorithm [38,39].

The aetiopathogenesis of pouchitis is multifactorial, and it may be that a multi-hit approach together with individualised patient-centred management is required to tackle this difficult-to-treat disease. Our network meta-analysis builds on the current body of evidence and appraises treatments according to efficacy and tolerability, which can help guide clinical practice [40]. Our study supports the British Society of Gastroenterology guidelines on the management of pouchitis but is the first to rank treatments in that order [5]. It is possible that probiotics are currently underutilised in the maintenance of a healthy pouch and our work suggests that this may have some potential benefit. The National Institute for Clinical Excellence (NICE) guidance [41] supports the use of rifaximin in acute pouchitis but this remains off-label while the European Crohn's and Colitis Organisation (ECCO) guidance suggests that rifaximin should be used as second-line therapy [42]. Our results suggest that in fact, rifaximin may be more beneficial than other antibiotics and thus may be considered earlier in the disease course. Biologic therapy and biosimilars are recently developed treatments which are gaining momentum in pouchitis management through the reduction of gut-specific inflammation, however, prospective

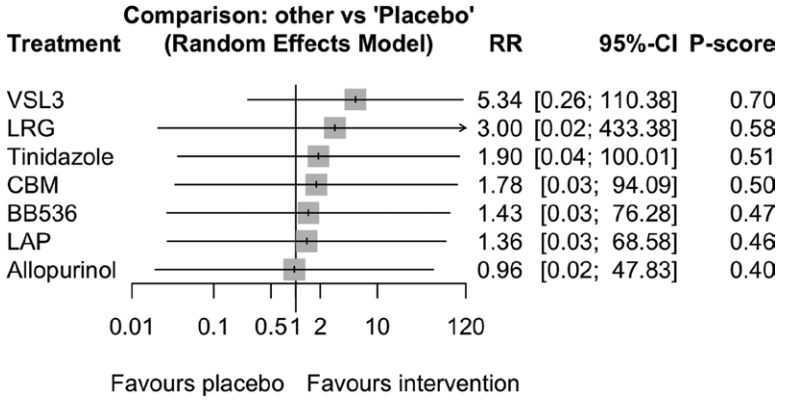

Fig. 8 Forest plot of treatments for the prevention of pouchitis vs. placebo.

Table 5 Summary of treatment effect rankings prevention of pouchitis

VSL#3							5.34 (0.26–110.38)
1.78 (0.01–601.52)	LRG						3.00 (0.02–433.38)
2.8114 (0.02–412.27)	1.58 (0.00–912.29)	Tinidazole					1.90 (0.04–100.01)
3.00 (0.02–442.53)	1.69 (0.00–978.33)	1.07(0.00–291.63)	CBM				1.78 (0.03–94.09)
3.74 (0.03–554.58)	2.10 (0.00–1224.21)	1.33 (0.00–365.19)	1.24 (0.00–343.02)	BB536			1.43 (0.03–76.28)
3.93 (0.03–556.48)	2.21 (0.00–1240.56)	1.40 (0.01–368.29)	1.31 (0.00–345.94)	1.05 (0.00–279.74)	LAP		1.36 (0.03–68.58)
5.56 (0.04–780.70)	3.12 (0.01–1744.09)	1.98 (0.01–517.24)	1.85 (0.01–485.85)	1.49 (0.01–392.88)	1.42 (0.01–359.16)	Allopurinol	0.96 (0.02–47.83)
5.34 (0.26–110.38)	3.00 (0.02–433.38)	1.90 (0.04–100.01)	1.78 (0.03–94.09)	1.43 (0.02–76.28)	1.36 (0.03–68.58)	0.96 (0.01–47.83)	Placebo

BB536, bifidobacterium longum subsp. longum; CBM, clostridium butyricum miyairi; LAP, lactobacillus acidophilus, lactobacillus delbrueckii subsp. bulgaricus, and bifidobacterium bifidus, LRG, serum leucine-rich alpha-2 glycoprotein.

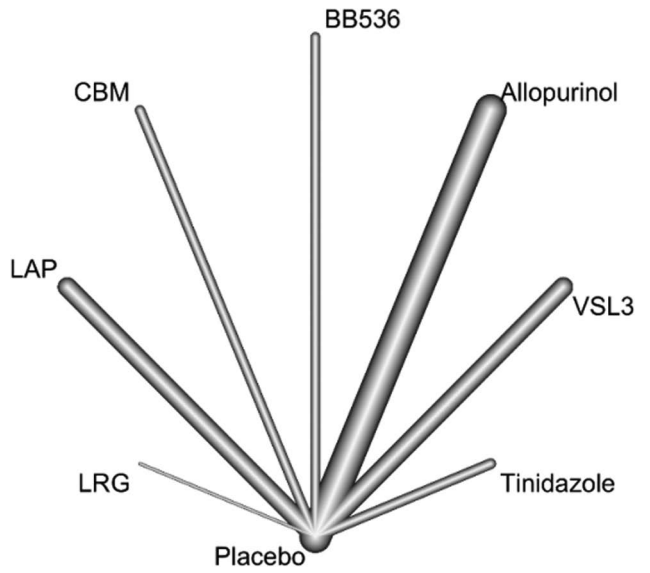

Fig. 9 Network plot of treatments for the prevention of pouchitis vs. placebo.

RCTs against current best-practice treatments are needed to evaluate its efficacy and long-term safety.

The limitations of this study are inherent to any meta-analysis. There was significant heterogeneity between studies and variations in defining disease activity, treatment response and clinical remission; due to limited data, robust heterogeneity analyses could not be performed. The results from our network meta-analysis need to be interpreted with caution as our study is limited by a small number of randomised controlled trials, with only a small number of patients included in each study. As such heat plots were unable to be generated. There were very few head-to-head comparisons and any indirect analyses may result in biases due to inter-study heterogeneity. This analysis did not include any observational studies that evaluate the impact of other real-world treatments, which may limit the generalisability of our findings. Furthermore, the RCTs included in this analysis were mainly conducted on a western population hence may not be applicable to the rest of the world. Some studies had a high risk of biases related to allocation concealment, randomisation and outcome measurements.

A significant limitation in pouchitis management is the limited number of high-quality head-to-head randomised controlled trials with well-defined clinical and endoscopic outcome measures. Larger prospective randomised controlled trials with head-to-head comparisons using standardised definitions of pouchitis and validated outcome measures will allow accurate interpretation and comparison of results. The attainment and maintenance of clinical remission were the main denominator in most of the included trials, which may not necessarily reflect endoscopic and histological remission. Future trials should ideally combine both clinical symptomatology and endoscopic pouch assessments in their analysis, while proactive and timely pouchoscopies should be considered in asymptomatic individuals.

Conclusion

This network meta-analysis supports current treatment algorithms in the management of acute and chronic pouchitis, however, highlights the emerging roles of unlicensed treatments, such as rifaximin, probiotics and biologic therapy and the need for large head-to-head trials to perform meaningful comparative evaluations.

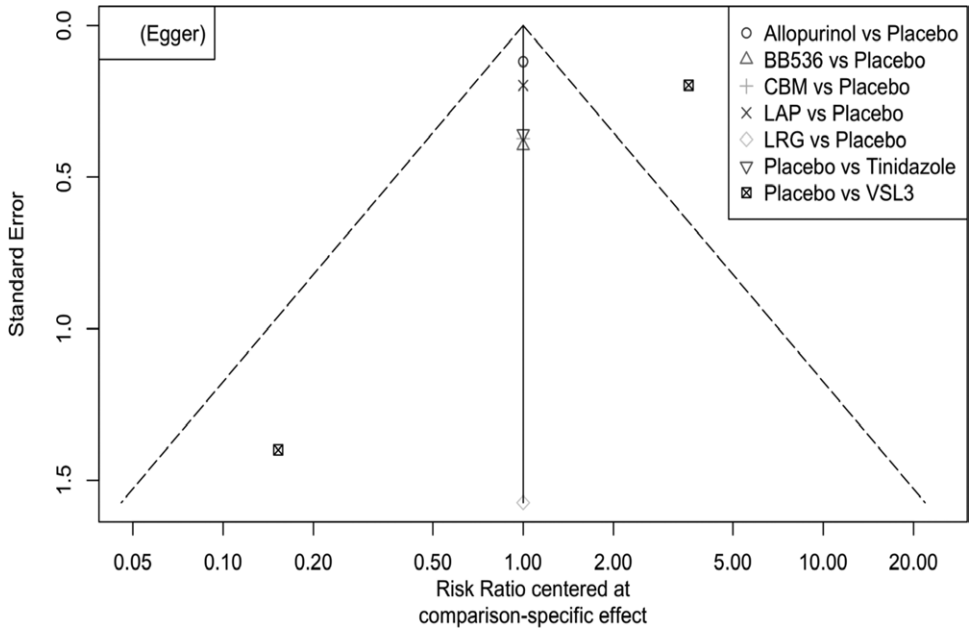

Fig. 10 Funnel plot of treatments for the prevention of pouchitis vs. placebo.

Table 6 Assessment of bias

	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Brown *et al*., (2004) [14]	Low	Low	Low	Low	Low	Low
Gionchetti *et al*., (2000) [15]	Low	Low	Low	Low	Low	Low
Gionchetti *et al*., (2003) [16]	Low	Low	Low	Low	Low	Low
Ha *et al*., (2010) [17]	Low	Low	High	Low	Low	High
Isaccs *et al*., (2007) [18]	High	Some concerns	Low	High	Low	High
Joelsson *et al*., (2001) [19]	Low	High	Some concern	Low	Low	High
Karjalainen *et al*., (2021) [20]	Low	Low	Low	Low	Low	Low
Kjaer *et al*., (2019) [21]	Low	Low	Low	Low	Low	Low
Kuisma *et al*., (2003) [22]	Low	Low	Low	Low	Low	Low
Madden *et al*., (1994) [23]	Low	Low	Low	Low	Low	Low
Mimura *et al*., (2004) [24]	Low	Low	Low	Low	Low	Low
Sambuelli *et al*., (2002) [25]	Low	Low	Low	Low	Low	Low
Shen *et al*., (2001) [26]	Low	Low	Low	Low	Low	Low
Tomasz *et al*., (2014) [27]	Low	Low	Low	Low	Low	Low
Tremaine *et al*., (1997) [28]	Low	Low	Low	Low	Low	Low
Van Assche *et al*., (2012) [29]	High	Low	Low	Low	Low	High
Wischmeyer *et al*., (1993) [30]	Low	Low	Low	Low	Low	Low
Yasueda *et al*., (2016) [31]	Some concerns	Low	Low	Low	Low	Some concerns

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J.P.S. came up with the concept. J.P.S., S.P. and D.S. conducted the literature review, performed the data extraction and drafted the article. J.P.S. performed the analysis. All authors agreed to the final version of the article.

J.P.S is the guarantor of article.

The data underlying this article are available in the article and in its online supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJGH/A750*.

Conflicts of interest

J.P.S. has received speaker fees for Janssen, Abbvie and Takeda. For the remaining authors, there are no conflicts of interest.

References

1 Krielen P, Stommel MWJ, Pargmae P, Bouvy ND, Bakkum EA, Ellis H, *et al*. Adhesion-related readmissions after open and laparoscopic surgery: a retrospective cohort study (SCAR update). *Lancet* 2020; 395:33–41.

2 Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a pouchitis disease activity index. *Mayo Clin Proc* 1994; 69:409–415.

3 Sriranganathan D, Kilic Y, Nabil Quraishi M, Segal JP. Prevalence of pouchitis in both ulcerative colitis and familial adenomatous polyposis: A systematic review and meta-analysis. *Colorectal Dis* 2022; 24:27–39.

4 Szeto W, Farraye FA. Incidence, prevalence, and risk factors for pouchitis. *Semin Colon Rectal Surg* 2017; 28:116–120.

5 Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, *et al*.; IBD Guidelines eDelphi Consensus Group. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; 68:s1–s106.

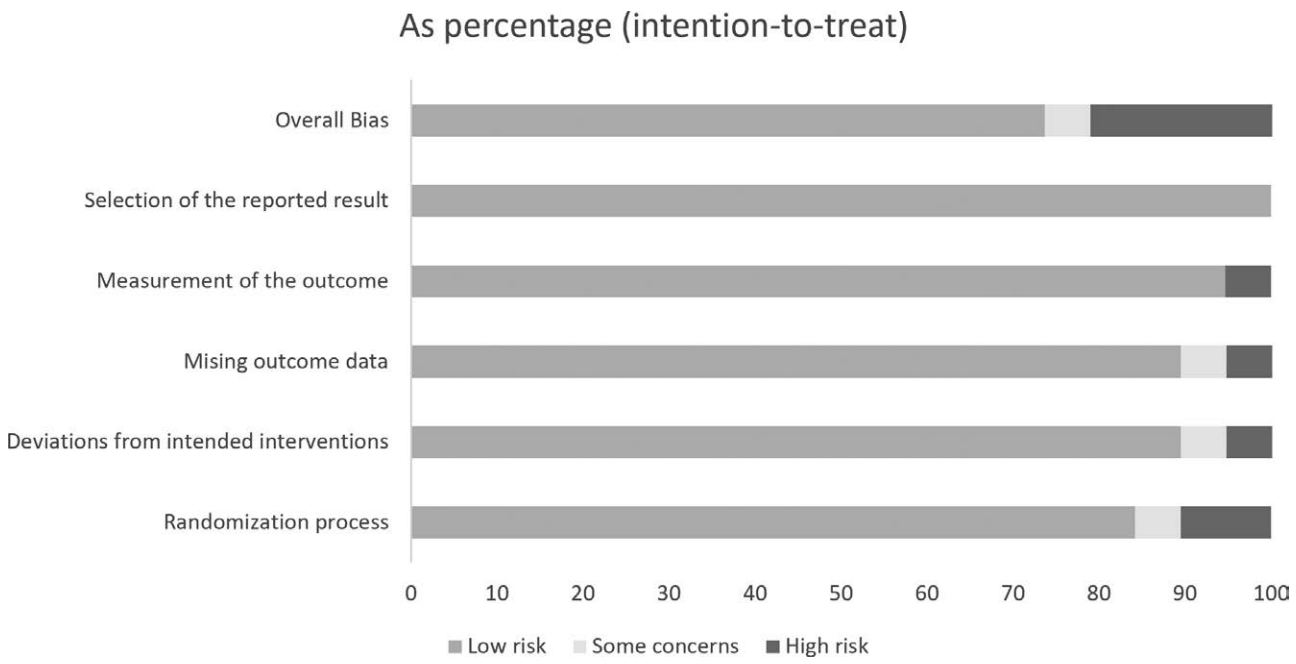

Fig. 11. Risk of bias analysis.

6 Akiyama S, Rai V, Rubin DT. Pouchitis in inflammatory bowel disease: a review of diagnosis, prognosis, and treatment. *Intest Res* 2021; 19:1–11.
7 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898.
8 Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015; 15:58.
9 Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162:777–784.
10 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634.
11 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539–1558.
12 Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013; 13:35.
13 Visbiome. *Note to healthcare professionals and patients.* Visbiome. 2019.
14 Brown S. Bifidobacterium longum BB-536 and prevention of acute pouchitis. *Gastroenterology* 2004; 4(Supplement 2):S465–S465.
15 Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, *et al*. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119:305–309.
16 Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, *et al*. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003; 124:1202–1209.
17 Ha CY, Bauer JJ, Lazarev M, Swaminath A, Sparrow M, Murphy SJ, *et al*. 488 Early Institution of Tinidazole may prevent pouchitis following Ileal-Pouch Anal Anastomosis (IPAA) surgery in Ulcerative Colitis (UC) patients. *Gastroenterology* 2010; 138:S69.
18 Isaacs KL, Sandler RS, Abreu M, Picco MF, Hanauer SB, Bickston SJ, *et al*.; Crohn's and Colitis Foundation of America Clinical Alliance. Rifaximin for the treatment of active pouchitis: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2007; 13:1250–1255.
19 Joelsson M, Andersson M, Bark T, Gullberg K, Hallgren T, Jiborn H, *et al*. Allopurinol as prophylaxis against pouchitis following ileal pouch-anal anastomosis for ulcerative colitis: a randomized placebo-controlled double-blind study. *Scand J Gastroenterol* 2001; 36:1179–1184.
20 Karjalainen EK, Renkonen-Sinisalo L, Satokari R, Mustonen H, Ristimäki A, Arkkila P, Lepistö AH. Fecal microbiota transplantation in chronic pouchitis: a randomized, parallel, double-blinded clinical trial. *Inflamm Bowel Dis* 2021; 27:1766–1772.
21 Kjær MD, Qvist N, Nordgaard-Lassen I, Christensen LA, Kjeldsen J. Adalimumab in the treatment of chronic pouchitis. A randomized double-blind, placebo-controlled trial. *Scand J Gastroenterol* 2019; 54:188–193.
22 Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther* 2003; 17:509–515.
23 Madden MV, McIntyre AS, Nicholls RJ. Double-blind crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. *Dig Dis Sci* 1994; 39:1193–1196.
24 Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, *et al*. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004; 53:108–114.
25 Sambuelli A, Boerr L, Negreira S, Gil A, Camartino G, Huernos S, *et al*. Budesonide enema in pouchitis–a double-blind, double-dummy, controlled trial. *Aliment Pharmacol Ther* 2002; 16:27–34.
26 Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Brzezinski A, *et al*. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis* 2001; 7:301–305.
27 Tomasz B, Zoran S, Jarosław W, Ryszard M, Marcin G, Robert B, *et al*. Long-term use of probiotics Lactobacillus and Bifidobacterium has a prophylactic effect on the occurrence and severity of pouchitis: a randomized prospective study. *Biomed Res Int* 2014; 2014:208064.
28 Tremaine WJ, Sandborn WJ, Wolff BG, Carpenter HA, Zinsmeister AR, Metzger PP. Bismuth carbomer foam enemas for active chronic pouchitis: a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 1997; 11:1041–1046.
29 Van Assche G, Ferrante M, Vermeire S, Noman M, Rans K, Van der Biest L, *et al*. Octreotide for the treatment of diarrhoea in patients with ileal pouch anal anastomosis: a placebo-controlled crossover study. *Colorectal Dis* 2012; 14:e181–e186.
30 Wischmeyer P, Pemberton JH, Phillips SF. Chronic pouchitis after ileal pouch-anal anastomosis: responses to butyrate and glutamine suppositories in a pilot study. *Mayo Clin Proc* 1993; 68:978–981.
31 Yasueda A, Mizushima T, Nezu R, Sumi R, Tanaka M, Nishimura J, *et al.* The effect of Clostridium butyricum MIYAIRI on the prevention of pouchitis and alteration of the microbiota profile in patients with ulcerative colitis. *Surg Today* 2016;46:939–949.
32 Segal JP, Ding NS, Worley G, Mclaughlin S, Preston S, Faiz OD, *et al.* Systematic review with meta-analysis: the management of chronic refractory pouchitis with an evidence-based treatment algorithm. *Aliment Pharmacol Ther* 2017; 45:581–592.
33 Segal JP, Oke S, Hold GL, Clark SK, Faiz OD, Hart AL. Systematic review: ileoanal pouch microbiota in health and disease. *Aliment Pharmacol Ther* 2018; 47:466–477.

34 Stallmach A, Lange K, Buening J, Sina C, Vital M, Pieper DH. Fecal microbiota transfer in patients with chronic antibiotic-refractory pouchitis. *Am J Gastroenterol* 2016; 111:441–443.
35 Selvig D, Piceno Y, Terdiman J, Zydek M, Umetsu SE, Balitzer D, *et al*. Fecal microbiota transplantation in pouchitis: clinical, endoscopic, histologic, and microbiota results from a pilot study. *Dig Dis Sci* 2020; 65:1099–1106.
36 Kousgaard SJ, Michaelsen TY, Nielsen HL, Kirk KF, Brandt J, Albertsen M, Thorlacius-Ussing O. Clinical results and microbiota changes after faecal microbiota transplantation for chronic pouchitis: a pilot study. *Scand J Gastroenterol* 2020; 55:421–429.
37 Chandan S, Mohan BP, Kumar A, Khan SR, Chandan OC, Kassab LL, *et al*. Safety and efficacy of biological therapy in chronic antibiotic refractory pouchitis: a systematic review with meta-analysis. *J Clin Gastroenterol* 2021; 55:481–491.
38 Ribaldone DG, Pellicano R, Saracco GM, Morino M, Astegiano M. Vedolizumab for treatment of chronic refractory pouchitis: a systematic review with pool analysis. *Rev Esp Enferm Dig* 2020; 112:59–63.
39 Ollech JE, Rubin DT, Glick L, Weisshof R, El Jurdi K, Israel A, *et al*. Ustekinumab is effective for the treatment of chronic antibiotic-refractory pouchitis. *Dig Dis Sci* 2019; 64:3596–3601.
40 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 Syst Rev* 2019; 11:1-58.
41 National Institute for Health and Care Excellence (NICE). Pouchitis: rifaximin (NICE Guideline ESUOM30). 2014; 1–25.
42 Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A, *et al*.; European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: special situations. *J Crohns Colitis* 2008; 2:63–92.