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Systematic Review with meta-analysis - management of chronic refractory pouchitis with an evidence-based treatment algorithm.

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Abstract

Background

Restorative proctocolectomy (RPC) with ileal pouch anal anastomosis (IPAA) is considered the procedure of choice in patients with ulcerative colitis (UC) refractory to medical therapy. The incidence of pouchitis is 40% at 5 years. Ten to 15% of patients with pouchitis experience chronic pouchitis.

Aim

To determine the efficacy of medical therapies for the treatment of chronic refractory pouchitis in patients undergoing IPAA for UC.

Methods

A systematic computer-assisted search of the on-line bibliographic database MEDLINE and EMBASE was performed between 1966 and February 2016. All original studies reporting remission rates following medical treatment for chronic pouchitis were included. All study designs were considered. Remission was defined according to the individual study. Remission endpoints ranged from 15 days to 10 weeks. Chronic pouchitis was defined by each study.

Results

Twenty-one papers were considered eligible. Results from all studies combined suggested that overall remission was obtained in 59% of patients (95% CI: 44% to 73%). Antibiotics significantly induced remission in patients with chronic pouchitis with 74% remission rate (95% CI :56% to 93%), ($p<0.001$). Biologics significantly induced remission in patients with chronic pouchitis with 76% remission rate (95% CI: 53% to 76%), ($p<0.001$). Steroids, bismuth, elemental diet and tacrolimus all can induce remission but failed to achieve significance. Faecal microbiota transplantation in a single study was not found to achieve remission.

Conclusion

Treatment of chronic refractory pouchitis remains difficult and is largely empirical. Larger randomised control trials will help aid the management of chronic pouchitis.

Introduction

Restorative proctocolectomy (RPC) with ileal pouch anal anastomosis (IPAA) is considered the procedure of choice in patients with ulcerative colitis (UC) refractory to medical therapy (1). The incidence of acute pouchitis is 20% at one year and up to 40% at five years(2).

Pouchitis is clinically characterized by variable symptoms including increased stool frequency and fluidity, haematochezia, abdominal cramping, urgency and tenesmus, incontinence, fever and extraintestinal manifestations(1). The first-line treatment of acute pouchitis is largely empirical with antibiotics. Ciprofloxacin and metronidazole are the most commonly used, often generating a rapid dramatic response(3–6). Chronic pouchitis develops in approximately 10–15% of patients with acute pouchitis and can be 'treatment responsive' or 'treatment refractory' to antibiotic therapy(7,8). Chronic pouchitis has been poorly defined, but in this review, patients will be considered to have chronic pouchitis if symptoms persist beyond four weeks of treatment.

A systematic review with meta- analysis in 2010 reviewed the efficacy of antibiotics and probiotics in pouchitis(9). A systematic review in 2015 explored the use of biologics in pouchitis(10). A further meta-analysis in 2014 reviewed the role of probiotics with the focus on maintainance of remission(11). A Cochrane review in 2015 appraised two randomised controlled trials in the treatment and prevention of chronic refractory pouchitis(12). This systematic review with meta-analysis builds on the these reviews, adding information from all studies that treated chronic refractory pouchitis. Using medical databases and other sources, we reviewed the latest evidence in treating chronic refractory pouchitis. In addition to antibiotics, there is evidence that steroids, immunomodulators and biologics all have a role in treating chronic pouchitis.

Objectives

To determine the efficacy of oral and topical medical therapies including antibiotics, probiotics, immunomodulators, steroids and biologics for the treatment of chronic refractory pouchitis in patients who have undergone IPAA for UC.

Methods

Types of studies

Randomized controlled trials, cohort studies, observational studies and case reports were considered. Studies which reported duplicate results were excluded. Those where data could not be extracted were also excluded.

Types of participants

Adults patients (age ≥ 18 years) with chronic refractory pouchitis were included. Chronic refractory pouchitis was defined by each study. For the purpose of analysis, we used each study's definition of chronic refractory pouchitis for the systematic review.

Types of outcome measures

The primary outcome was the proportion of patients with clinical improvement or remission of pouchitis. The definition of clinical improvement or remission varied from study to study, meaning that it was difficult to make comparisons across studies. The definitions of clinical improvement or remission used in each study was used for extraction of the data.

Search methods for Identification of studies

A computer assisted search of the on-line bibliographic database MEDLINE and EMBASE was carried between 1966 and February 2016 by two independent researchers (JPS and NSD). The following medical Subject Heading (MeSH) terms were used which included both the root term and text words. Synonyms and word variations were combined using the "OR" function and then combined with other key terms using the "AND" function: "refractory" "chronic", "long term", "difficult", "unmanageable", "ulcerative colitis", "UC", "colitis", "ileum", "ileostomy", "postoperative complications", "pouchitis", "colonic pouches", "pouch", "proctocolectomy"," restorative", "colitis", "IPAA","RPC", "j-pouch", "s-pouch"," w-pouch", "treatment", "management", "medication", "therapy", "therapeutics", " anti-TNF", "antibiotics", "steroids", "tumour necrosis factor-alpha", "remission", "spontaneous", "remission induction", "resolution", "cure". Manual searches of the reference list from the potentially relevant studies were performed in order to identify additional studies that may have been missed using the computer-assisted search strategy. Abstracts from conferences from the American Gastroenterological Association, American Society of Colon and Rectal Surgery, European Crohn's and Colitis, United European Gastroenterology and the British

Society of Gastroenterology were also manually searched from 1965-2016 in order to identify unpublished studies.

Data collection and analysis

Study Selection:

Potentially relevant articles were reviewed in an independent fashion by two authors (JPS and NSD) to determine whether they met the inclusion criteria. The studies were then labelled as eligible, ineligible, or having insufficient information to make a judgement as to eligibility (which were then excluded). Any discrepancies were addressed by a joint re-evaluation of the original article.

Data Collection:

Eligible articles were reviewed by JPS and NSD and the results from the included articles were extracted into tables. The proportions of patients who had clinical improvement or entered remission were derived from each study.

Risk of Bias:

Two authors (JPS and NSD) independently assessed the methodologies using the Cochrane risk of bias tool for randomised controlled trials as described in the Cochrane handbook for systematic reviews of interventions(13). Assessment of bias was judged as “yes”: low risk of bias, “No”: high risk of bias, or “unclear” unknown risk of bias. The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool was used to assess bias in non randomised controlled studies(14). Assessment of bias was judged as low bias, moderate bias, serious bias, critical bias or no information. Disagreements were resolved by consensus.

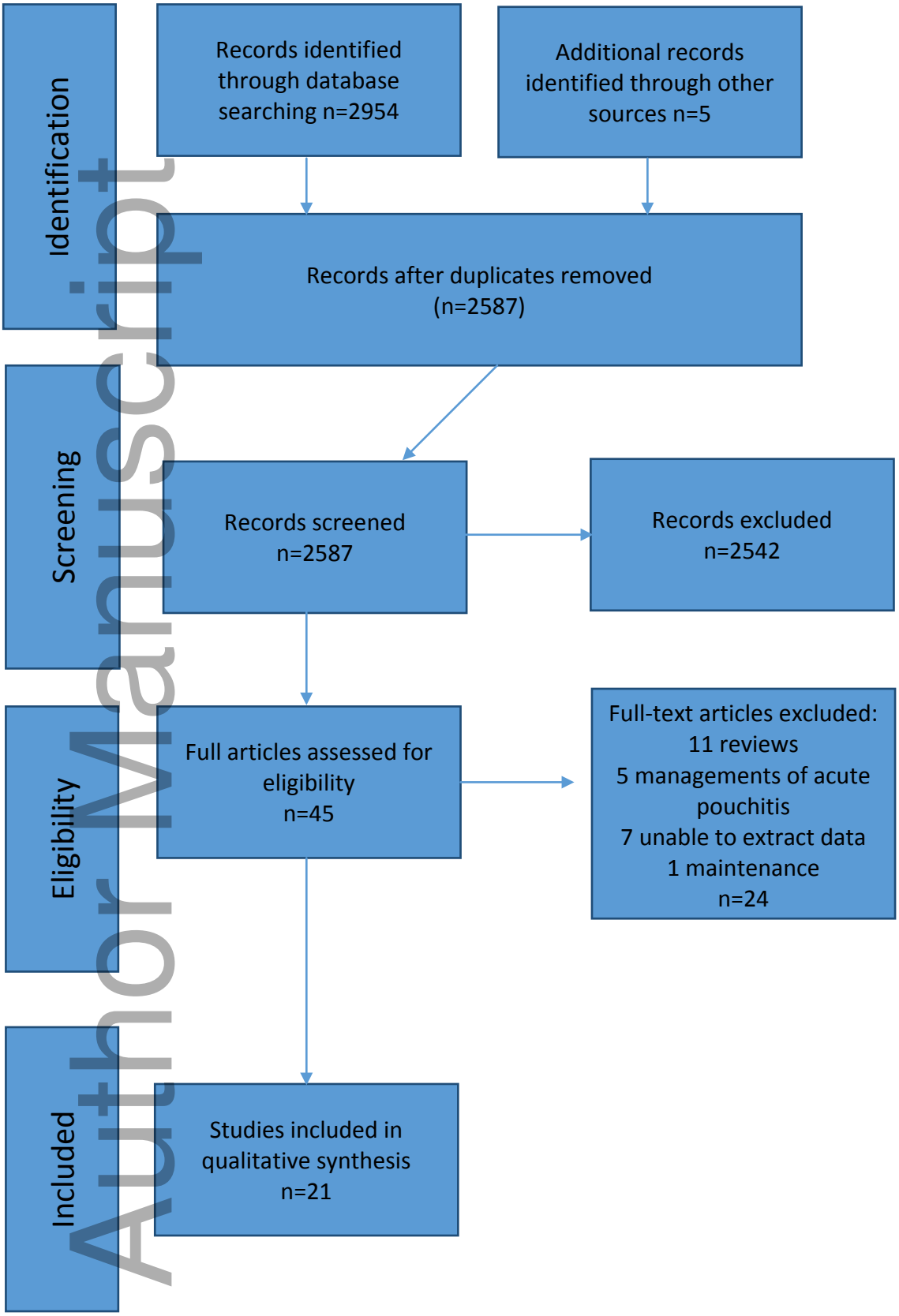
Statistical Analysis:

For analysis the outcome of remission was considered as a binary outcome (yes/no). Meta-analysis methods were used to pool the percentage of patients in remission from the various studies.The analysis was implemented using the 'metaan' package with Stata .

For each study, the standard error of the proportion in remission was calculated using the normal approximation to the binomial distribution. For studies where the outcome was not observed in any patients, or in all patients (i.e. a 0% or 100% remission occurrence), the standard error was approximated by half the width of 95% confidence calculated using the exact binomial method.

The heterogeneity between studies was assessed based on the significance of the between-study heterogeneity, and also on the size of the I^2 value. Substantial heterogeneity was assumed if the I^2 value was above 50%. If there was substantial heterogeneity between studies, studies were pooled using the DerSimonian-Laird random-effects method. A random effects model was also used if there was no heterogeneity between studies. The analyses were performed for all studies combined, and then separately for each type of medication.

Prisma Diagram



Results

Description of studies

The literature search identified a total of 2954 studies. After removing duplicates 2587 studies remained for review of title and abstracts for eligibility. Two authors (JPS and NJD) independently reviewed the titles and abstracts of these studies. After screening abstracts 45 articles were reviewed in full. After screening individual papers 16 were included in the study. Five additional papers were included after manual reference searching. A total of 21 papers were considered eligible.

Chronic refractory pouchitis was defined within each study. Sixteen out of 21 (76%) defined chronic pouchitis as greater than four weeks of symptoms despite having used antibiotics or alternative standard therapies. Three studies defined chronic pouchitis as requiring continuous antibiotics. In two studies we did not categorise the definition of chronic pouchitis.

Summary of interventions table 1

Effects of Interventions

Pouchitis defined as symptoms greater than four weeks following treatment with antibiotics or steroids.

Antibiotics

Gionchetti *et al*, 1999(15) conducted a cohort study of 18 patients with chronic pouchitis who were treated orally with rifaximin 1g BD and ciprofloxacin 500mg BD for 15 days. Pouchitis was defined as a pouch disease activity index (PDAI) $\geq$ 7. Chronic pouchitis was defined as no response after treatment with antibiotics (such as metronidazole, or ciprofloxacin or amoxycillin/clavulanic acid) for at least 4 weeks. Six out of 18 (33%) patients went into remission and 10/18 (56%) improved after 15 days. The median PDAI scores before and after therapy were 11 (range 9–17) and 4 (range 0–16), respectively ($p < 0.002$). No adverse events were reported.

Abdelrazek *et al* 2005(16) conducted a cohort study on eight patients with chronic pouchitis who were treated with two weeks of rifaximin 1g BD and ciprofloxacin 500mg BD. Pouchitis was defined using the PDAI. Chronic pouchitis was defined as no response to at least four weeks of standard antibiotic therapy or relapse immediately when antibiotic treatment was stopped or reduced. Remission was defined as an improvement of three points on the PDAI. Seven of the eight (88%) patients either went into remission (*n* = 5) or improved (*n* = 2). The median (range) PDAI scores before and after therapy were 12 (9–18) and 0 (0–15), respectively, (*P* = 0.018). There were no significant side effects reported.

Shen *et al*, 2007(17) conducted a cohort study of 16 consecutive patients with chronic pouchitis who were treated with a four week course of ciprofloxacin 1g/day and tinidazole 15mg/kg /day. A historic cohort of 10 consecutive patients with chronic pouchitis treated with oral mesalamine (4g/day) or enema (8g/day) or suppository (1g/day) were used as controls. All patients had a PDAI ≥ 7 at entry. Chronic refractory pouchitis was defined as symptoms for more than four weeks with endoscopic and histological inflammation despite treatment with single or dual antibiotics for more than four weeks. In the antibiotic group, 87.5% of patients achieved clinical remission and 88% achieved clinical response, compared to 50% in the mesalamine group for remission and 50% for response. This was however not statistically significant (p=0.069). In the antibiotic group, two patients had adverse events (peripheral neuropathy and dysgeusia) but continued treatment.

Steroids

Gionchetti *et al*, 2007(18) conducted an open-label non-randomised study in 20 consecutive patients with chronic pouchitis who were treated with budesonide controlled ileal release 9mg/day for eight weeks. Chronic pouchitis was defined as a total PDAI score of ≥ 7, and not responsive to antibiotics for four weeks. Remission was defined as a combination of PDAI of ≤ 2, endoscopic score ≤ 1 and total PDAI score ≤ 4. Fifteen of 20 patients (75%) achieved remission. The median total PDAI scores before and after therapy were, respectively, 14 (range 9-16) and 3 (range 2-10) ($P < 0.001$).

Gionchetti *et al*, 2014(19) conducted an open-label non-randomised study in 10 consecutive patients with chronic pouchitis who were treated with beclomethasone 10mg/day for eight weeks. Current active refractory pouchitis was defined as a PDAI score of ≥ 7 and no response to at least four weeks of standard antibiotic treatment (ciprofloxacin 1g once a day or metronidazole 1g once a day). Remission was defined as a combination of PDAI clinical score of ≤ 2, endoscopic score of ≤ 1 and a total PDAI score of ≤4. Eight of the 10 (80%) treated patients achieved remission, while two had only a mild improvement. The median bowel frequency decreased significantly from 10 (range 7–15) to six (range 3–11) after steroid treatment ($p < 0.001$).

Enemas

Tremaine *et al*, 1997(20) conducted a randomised, double-blind placebo controlled trial in 40 patients with chronic pouchitis who were randomly assigned either 270mg bismuth enema (n=20) or placebo (n=20). Chronic pouchitis was defined as continuous symptoms of pouchitis for more than four weeks and a PDAI score ≥7. Patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Remission was defined as a reduction in the PDAI by at least three points at three weeks. There were no significant differences between the populations at baseline. At week three, 9/20 (45%) of patients in both the bismuth and placebo groups had improved. No patient achieved remission in either group. There was no significant difference in response to therapy in the treatment or the placebo with regard to remission. One patient in the bismuth group reported a worsening of diarrhoea requiring hospital admission.

Gionchetti *et al*, 1997(21) conducted an open label non-randomized study in twelve patients with chronic pouchitis who were administered bismuth carbomer enema at night for 45 days. Chronic pouchitis was defined as continuous symptoms for more than four weeks and the need for antibiotics or steroids for more than 15 days per month to control symptoms. Clinical remission was defined as a decrease in PDAI ≥2. Ten of 12 treated patients (83%) went into remission after 45 days. No serious side effects were reported.

Milner *et al*, 2004(22) conducted an open-label, uncontrolled study in 12 patients with chronic pouchitis who were treated with 240mg alicaforsen antisense enema nightly for six weeks. Patients underwent two weeks of washout prior to enrolment. Chronic refractory pouchitis was defined as patients who had symptoms for greater than four weeks and had failed alternative therapies, with a PDAI score of ≥ 7. The primary endpoint was a reduction in PDAI from baseline at week six. At week six, 7/12 (58%) of patients were in remission with PDAI < 7. The mean decrease in PDAI from baseline was six points. No drug related serious or significant adverse effects were reported during the study.

Uchino *et al*, 2013(23) conducted a non-randomized open-label study in 10 patients with chronic refractory pouchitis who were treated with once daily tacrolimus enema (0.08mgkg^{-1}) in the morning for eight weeks. Chronic pouchitis was defined by no response to a four week course of a single antibiotic (metronidazole or ciprofloxacin) and requiring therapy of for at least four weeks of dual antibiotics. A PDAI ≥7 was used as confirmation of the diagnosis. Clinical remission and clinical response were defined a clinical sub-score of zero points and a clinical sub-score decrease of more than three points. Seven of the 10 patients achieved complete remission of clinical symptoms, and a total of nine patients were clinical responders. The mean PDAI score decreased significantly to 7.8 ± 0.8 points (range, 6–15) after eight weeks ($p < 0.01$). Three patients reported feeling mild burning in the pouch, which was not sufficient to warrant discontinuation of the eight week application.

Biologics

Ferrante *et al,* 2010(24) conducted a retrospective study in 11 patients with chronic refractory pouchitis who were treated with standard infusions of infliximab (5 mg/kg body weight). Chronic refractory pouchitis was defined as symptom duration greater than four weeks following standard treatment. A complete clinical response was defined as cessation of diarrhoea, urgency, incontinence, blood loss and abdominal pain. A partial clinical response was defined as a marked clinical improvement, but persisting symptoms. All other outcomes were defined as no short-term clinical response. Long-term response was evaluated at last follow-up. Short-term response to infliximab was evaluated at week 10. At week 10, 1/11 (9%) opatients did not show any clinical benefit and needed a permanent ileostomy, 7/11 (64%) patients had a partial clinical response, and 3/11 (27%) had a full clinical response. The modified PDAI (mPDAI) dropped significantly from nine to five (p = 0.011). In the subgroup of 10 patients with chronic refractory pouchitis in the absence of pouch fistula or prepouch ileitis who initially responded to infliximab, seven were still on infliximab after a median follow-up of 8.5 (range 2–38) months. Two patients had to stop because of a delayed hypersensitivity reaction, while one patient could be bridged to azathioprine. The remaining seven patients underwent a new endoscopy at the end of

follow-up. Four of them did not show any lesion, while three had clear endoscopic activity despite a sustained clinical benefit.

Gionchetti *et al*, 2010(25) conducted an open-label non-randomised study in 19 patients with chronic pouchitis who were treated with either 5mg/kg of infliximab at weeks zero, two, six or adalimumab 160/80mg at weeks zero and two, then 40mg every other week. Chronic pouchitis was defined as unresponsive to a month of antibiotics or two months of budesonide. Remission was defined as a PDAI score of one. Short term efficacy was measured at week 10. Twelve patients received infliximab and five adalimumab. Nine of 12 (75 %) and 5/7 (71%) showed remission respectively in the infliximab and adalimumab group. The median PDAI scores before and after therapy were 13 (range 8-18) and 2 (range 0-9) in the infliximab group($p<0.001$), and 14 (range 9-18) and 2 (range 0-10) in the adalimumab group ($p<0.001$). No serious side effects were registered.

Viazis *et al*, 2011(26) conducted an open prospective cohort study in seven patients with chronic refractory pouchitis who were treated with infliximab 5mg/kg at zero, two, and six weeks and then, every two months for a year. Chronic pouchitis was defined as no response to at least four weeks of standard antibiotic therapy (ciprofloxacin 1g BD or metronidazole 500 mg TDS). Pouchitis was defined as a total PDAI score ≥ 7 points. Complete clinical response was defined as cessation of diarrhoea, urgency, incontinence, blood loss and abdominal pain. A partial clinical response was defined as a marked clinical improvement, but with persisting symptoms. All other outcomes were defined as no response. After one year of infliximab administration, 5/7(71%) patients had a complete clinical response, 1/7 (14%) had partial response (14%) and 1/7(14%) had no response. There were no major complications from infliximab administration, apart from a minor rash seen in one of the patients. The rash appeared at the beginning of the second infusion and disappeared after reduction in the rate of the infusion.

Acosta *et al*, 2012(27) conducted a retrospective open-label multicentre study on 33 patients with chronic pouchitis who were treated with 5mg/kg of infliximab with an induction regime (infliximab at weeks zero, two, and six) at doses of 5mg/body weight and

25 (76%) continued with a maintenance scheme (infliximab every eight weeks). Among these 25 patients, nine (36%) needed dose escalation (five of them to 10mg/kg and the other four to shorter time intervals between infusions). Chronic pouchitis included all patients with clinical and endoscopic findings of pouchitis who had previously failed antibiotics for at least four consecutive weeks and probiotics or immunosuppressive drugs. Short-term infliximab efficacy was evaluated at week eight and mid-term efficacy at weeks 26 and 52.Complete response was defined as cessation of diarrhoea and urgency and partial response as marked clinical improvement but persisting symptoms. Median time of infliximab follow-up was 60 weeks. At week eight, seven patients (21%) achieved complete response and 21 (63%) showed partial clinical response. Only five of the patients (15%) did not show any response. At week 26, after an intention to treat (ITT) analysis, 11 patients (33%) were in complete response and another 11 (33%) had shown partial clinical response. After analysing only the patients who continued treatment at week 26, a complete response rate of 44% and a similar partial response rate of 44% were observed. At week 52, after an ITT analysis, nine patients (27%) were in complete clinical remission and another six (18%) had shown partial clinical response. After analysing only the patients who continued at week 52 with treatment, an observed remission rate of 56% and a response rate of 38% was found. Thirteen patients (39%) had to withdraw infliximab treatment; five (15%) due to severe adverse events, (one lupus like reaction, four infusion reactions), four (12%) lost response to infliximab during the trial period and four (12%) were primary non-responders.

Acosta *et al,*2012(28)conducted a retrospective open-label study on eight patients with chronic pouchitis who had previously failed infliximab. Patients were treated with adalimumab 160/40mg as induction, followed by 40mg every alternate week. Chronic refractory pouchitis was defined by both clinical and endoscopic features of pouchitis that had failed to show a response to at least four weeks of antibiotics. Complete clinical remission was defined as cessation of diarrhoea, urgency and haematochezia. A partial response was defined as marked clinical improvement, but persistence of symptoms. Outcomes were measured at weeks 8,26 and 52. At week eight 1/8 (13%) achieved remission and 5/8 (63%) showed a clinical response. At week 26 following an ITT analysis 1/8 (13%) was in complete remission and 3/8 (38%) showed a clinical response. At week 52

after an intention-to-treat analysis 2/8 (25%) were in clinical remission and 2/8 (25%) showed a clinical response. There were no significant adverse events reported.

Other treatments

Landy *et al*, 2013(29) conducted a non-randomised study in eight patients with chronic pouchitis who were given a 30g fresh donor stool via a nasogastric tube on a single occasion. Chronic pouchitis was defined as patients with PDAI≥7 who had not responded to standardized therapy. The outcome measure was remission at four weeks after FMT. At four weeks post FMT, no patient achieved remission however, two patients regained sensitivity to ciprofloxacin. No adverse events were reported.

McLaughlin *et al* 2013(30) conducted a non-randomized prospective study in seven patients who received 28 days of exclusive elemental diet enough to reach their daily energy requirements. Chronic pouchitis was defined as patients with a PDAI ≥7 who were unresponsive to four weeks of combined antibiotic treatment. Outcome was reduction in stool frequency at day 28 and reduction in PDAI. Treatment with elemental diet resulted in a significant reduction in stool frequency (from median 12 to 6, p = 0.028) and the PDAI symptom score (from 4 to 1, p = 0.039). There was a non-significant trend towards an improvement in the ability to defer defecation (from 25 to 60 min, p = 0.078). There were no adverse events reported.

Interventions when chronic pouchitis was defined as requiring continuous antibiotics

Antibiotics

Mimura *et al*, 2002(6) conducted a cohort study of 44 patients with chronic pouchitis who were treated using a combination of metronidazole 400mg (UK population) or 500mg (Italian population) twice daily and ciprofloxacin twice daily for 28 days. Chronic pouchitis was defined as a history of pouchitis at least twice in the last 12 months or persistent

pouchitis requiring continual antibiotics and a PDAI ≥ 7. Thirty six of 44 patients (82%) achieved remission. One patient withdrew from the trial as they developed nausea and dysgeusia to metronidazole.

Biologics

Viscido *et al*, 2004(31) conducted an open-label non-randomised study in a subgroup of seven patients with chronic pouchitis who were treated with 5mg/kg of infliximab at week zero, two and six. Treatment after this was "on demand" only. Patients also received 2.5mg/kg of azathioprine at the time of the first infliximab infusion. Chronic refractory pouchitis was defined as persistent active pouchitis unresponsive to continuous antibiotics. Complete response was defined as improvement in well-being and cessation of diarrhoea, urgency/incontinence, stool blood, abdominal pain. A partial response was defined as an improvement or reduction of the symptoms. All other outcomes were defined as no response. Among the seven patients with pouchitis who received infliximab, six had a complete clinical response, and one patient had partial clinical response 10 weeks after the first infusion. At six month follow-up, one patient had developed a thoracic herpes simplex virus infection, which required treatment with acyclovir (4 g/day for 10 days), without withdrawal of immunosuppressive treatment.

Lizuka *et al*, 2014(32) reported a case of a 29-year woman with chronic pouchitis who was treated with infliximab at weeks zero, two, six and then every eight weeks up until a year. Chronic refractory pouchitis was defined as a PDAI of >10 after two years of antibiotic treatment. After 40 weeks of treatment the patient's abdominal pain and clinical symptoms subsided and her PDAI was five. She continued treatment for a year and remained in remission.

Effects of interventions when chronic pouchitis definition cannot be categorised

Antibiotics

Madden *et al,* 1994(3) conducted a double-blind crossover trial in 13 patients with chronic pouchitis who were treated with metronidazole 400mg or placebo. Patients were randomized to receive either metronidazole 400mg by mouth three times a day or placebo for two weeks. The drug was stopped for a wash out period. Remission was not defined but improvement in stool frequency was used an assessment of improvement. There were 11/13 subjects who completed the trial; one withdrew due to an episode of intestinal obstruction. Stool frequency improved in 8/11 (73%) receiving metronidazole, worsened in two and was unchanged in one. Placebo had no effect on stool frequency in the 11 patients who received treatment. Metronidazole improved stool frequency by four actions/day ($p<0.05$ 95% CI). Six patients (55%) reported side effects whilst on metronidazole including an unpleasant taste (2), nausea (2), vomiting (1), abdominal discomfort (1), headache (1), skin rash (1).

Tacrolimus

Ng *et al*, 2006(33) conducted a retrospective single centre review of all patients with inflammatory bowel disease that received tacrolimus 0.05mg/kg twice daily orally. A sub group of patients with chronic pouchitis were included. Chronic pouchitis was defined as patients experiencing moderate to severe chronic active disease, were steroid dependent or had failed conventional therapy (azathioprine, 6-mercaptopurine or infliximab). Clinical remission was defined as a modified PDAI <5 at week four of treatment. All patients received an initial dose of 0.1mg/kg/day in two divided doses then dose was adjusted to reach a trough level of 5-10 ng/ml. One patient with chronic pouchitis took part in the study and achieved remission with a reduction of mPDAI from eight to four and a reduction of stool frequency from 25 to 12 times per day. There were no reported adverse events in this patient.

The pooled results for all studies, and for each medication separately, are summarised in the next table. These show the number of studies, and details of the heterogeneity both in terms of the significance and the I^2 value. The pooled results are also shown, and are the pooled percentage in remission, along with corresponding confidence intervals.

Table 2.

Graphical illustrations of the results for the individual studies are shown in the subsequent Forrest plots.

Results for all therapies for chronic pouchitis. Figure 1.

Results for antibiotics for chronic pouchitis. Figure 2.

Results for biologics for chronic pouchitis. Figure 3.

Discussion

The results from all studies combined suggested that, overall, remission was obtained in 59% of patients (95% CI: 44% to 73%).There was considerable heterogeneity between the different studies, with statistically significant heterogeneity and a high I^2 value of 88%.

The results for different types of medication showed varying results, ranging from a 0% remission for FMT and up to a 77% remission for steroids. For most although not all types of medication, there was considerable heterogeneity between studies.

Antibiotics significantly induced remission in patients with chronic pouchitis with 70% remission rate (95% CI: 50% to 90%) ($p<0.001$). Biologics significantly induced remission in patients with chronic pouchitis with 76% remission rate (95% CI: 53% to 76%), ($p<0.001$). Bismuth significantly induced remission in patients with chronic pouchitis in 41% (95% CI: 0% to 100%), ($p<0.001$) but had a large confidence interval suggesting that the true effect is not known. Steroids induced remission in 77% of patients (95% CI 62% to 92%) but failed to achieve significance ($p=0.75$). Tacrolimus induced remission in 72% (95% CI 45% to 100%) but failed to achieve significance ($p=0.57$). Alicaforsen and elemental diets had remission rates of 58% (95% CI 28% to 85%) and 71% (95% CI 29% to 96%) respectively but these were based on a single study. FMT failed to achieve remission in patients with chronic pouchitis with remission rates of 0% (95% CI: 0% to 37%) in a single study.

The treatment of chronic pouchitis with the aim of achieving remission remains a challenge. This likely reflects our limited knowledge on the pathogenesis of pouchitis (34). Pouchitis not only causes morbidity to the patient but is also associated with financial and economic

burden (35).Antibiotics, usually in combination such as metronidazole and ciprofloxacin are generally first line therapy, with rifaximin and tinidazole being alternative agents to try in combination. Second line treatment options include corticosteroids such as beclomethasone or budesonide. Biologics including infliximab and adalimumab are third line agents that can be used to treat chronic pouchitis. Less well studied agents such as bismuth, tacrolimus and alicaforsen may be considered as alternatives to the above therapies.

Studies presented in this review must be interpreted with caution due to the small number of trials, lack of randomised placebo controlled trials and small patient numbers. Only one of the studies was considered to be of moderate quality with the rest of the studies considered low or very low in quality. The lack of high quality head to head trials makes it difficult to measure the benefit of one drug or agent over another and it is not possible to draw conclusions about the comparative efficacy of each agent. Due to small sample populations, it is also difficult to draw conclusions about the tolerability of each agent.

In many trials, there is a lack of agreement on what defines chronic pouchitis and what defines remission. A consensus definition of chronic pouchitis with standardised outcome measures would help the analysis and interpretation of the true efficacy of each treatment. Many studies only reported short term safety outcomes. It is also important to ensure that long term safety data is available for each agent and this should be taken into account when designing future studies.

A clinical algorithm based on the evidence in this review and St Mark's experience is suggested for the treatment of chronic pouchitis.

(See figure 4)

Conclusion

The treatment of chronic pouchitis remains difficult and is largely empirical. Our knowledge of the treatment of this condition is based on small studies with often poor study designs. Studies are mostly single centred with small patient numbers which reflects a condition that is rare and that requires specialist treatment. There is also a paucity of data exploring the long term safety of some treatment options available to patients with chronic pouchitis. To improve data, larger randomised controlled trials will be beneficial. To overcome some of the limitations addressed in this review, a multi-centre, multi-national approach is needed.

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Table 1

Study	Year	Intervention	Study Design	n	Summary Outcomes	Assessment of Bias
Antibiotics						
Madden[3]	1994	Metronidazole 400mg vs Placebo	RCT	11	8/11 (73%) improved in stool frequency in antibiotic group 0/11 (0%) improvement of stool frequency in placebo group	low
Gionchetti[4]	1999	Rifaximin 1g BD and Ciprofloaxacin 500mg BD for 15 days	Observational	18	6/18 (33%) achieved remission	low
Mimura[6]	2002	Metronidazole (400mg or 500mg) BD and Ciprofloxacin 500mg BD for 28 days	Observational	42	36/42 (82%) achieved remission	low
Abdelrazek [9]	2005	Rifaximin and 1g BD and ciprofloxacin 500mg BD for 14 days	Observational	8	5/8(63%) achieved remission	low
Shen[16]	2007	Ciprofloxacin 1g/day and Tinidazole 15mg/kg for four weeks	Observational	16	14/16 (88%) achieved remission	low
Steroids						
Gionchetti[17]	2007	Budesonide 9mg/day for eight weeks	Observational	20	15/20 (75%) achieved remission	low
Gionchetti[18]	2014	Beclomethasone Dipropionate 10mg/day for eight weeks	Observational	10	8/10 (80%) achieved remission	low
Biologics						
Viscido[31]	2004	Infliximab 5mg/kg (week 0,2,6 then every eight weeks for a year)	Observational	7	6/7 (86%) achieved remission	low
Gionchetti[24]	2010	Infliximab 5mg/kg (week 0,2,6) for 10 weeks or Adalimumab 160/80mg induction then 40mg alternate weeks	Observational	12	9/12 (75%) achieved remission in infliximab group 5/7 (72%) achieved remission in adalimumab group	low
Ferrante[23]	2010	Infliximab 5mg/kg (week 0,2,6) for 10 weeks	Observational	11	3/11 (27%) achieved remission	low

Viazis[25]	2012	Infliximab 5mg/kg (week 0,2,6 then every eight weeks for a year)	Observational	7	5/7 (72%) achieved remission	low
Barreiro-de Acosta[26]	2012	Infliximab 5mg/kg (week 0,2,6) Followed by 5mg/kg every eight weeks or 10mg/kg every 10 weeks based on clinical need	Observational	33	7/33 (21%) achieved remission at week eight 11/33(34%) achieved remission at 26 weeks 9/33 (27%) achieved remission at 52 weeks	low
Barreiro-de Acosta[27]	2012	Adalimumab 160/80mg induction followed by 40mg alternate weeks for 26 weeks	Observational	8	1/8 (13%) achieved remission at eight weeks 1/8 (13%) achieved remission at 26 weeks	low
Lizuka[32]	2014	Infliximab 5mg/kg (week 0,2,6 then every eight weeks for a year)	Observational	1	1/1 (100%) achieved remission	low
Bismuth enema						
Tremaine[19]	1997	Bismuth Carbomer enema 270mg vs placebo	RCT	20	0/20 (0%) achieved remission in bismuth group 0/20 (0%) achieved remission in placebo group	low
Gionchetti[20]	1997	Bismuth Carbomer enema at night for 45 days	Observational	12	10/12 (83%) achieved remission	low
Alicaforsen enema						
Milner[21]	2004	Alicaforsen 240mg enema at night for six weeks	Observational	12	7/12 (58%) achieved remission	low
Tacrolimus						
Ng[30]	2006	Tacrolimus 0.1mg/kg/day to reach a trough level of 5-10ng/ml	Observational	1	1/1 (100%) achieved remission	Serious

Uchino[22]	2013	Tacrolimus enema 0.08mg/kg every morning for eight weeks	Observational	10	7/10 (70%) achieved remission	low
FMT						
Landy[28]	2013	30g of fresh donor stool via nasogastric tube	Observational	8	0/8 (0%) achieved remission	low
Elemental Diet						
McLaughlin[29]	2013	Elemental diet for 28 days	Observational	7	5/7 (71%) reported a reduction in stool frequency	low

Table 2

Medication	Number studies	Heterogeneity		Pooled % (95% CI)
		p-value	I^2	
All combined	22	<0.001	88%	59% (44%, 73%)
Antibiotics	5	<0.001	80%	70% (50%, 90%)
Steroids	2	0.75	0%	77% (62%, 92%)
Biologics	8	<0.001	83%	76% (53%, 76%)
Bismuth	2	<0.001	97%	41% (0%, 100%)
Alicaforsen	1	-	-	58% (28%, 85%)

Tacrolimus	2	0.57	0%	72% (45%, 100%)
FMT	1	-	-	0% (0%, 37%)
Elemental diet	1	-	-	71% (29%, 96%)

Figures 1

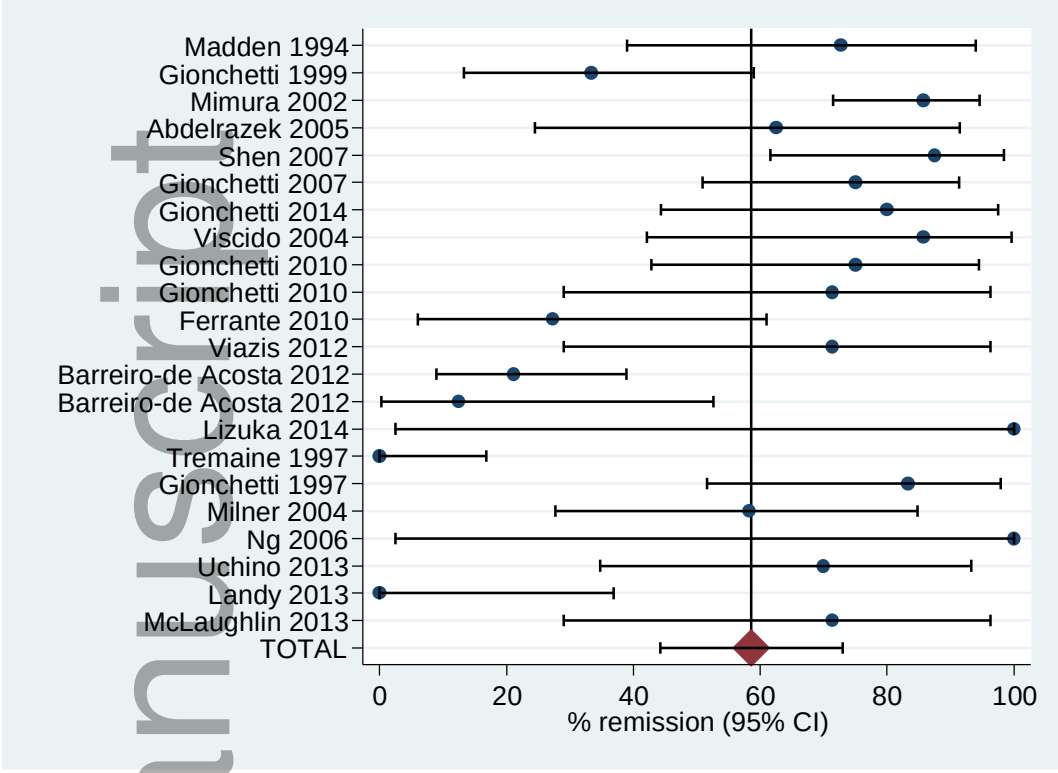

Figure 2

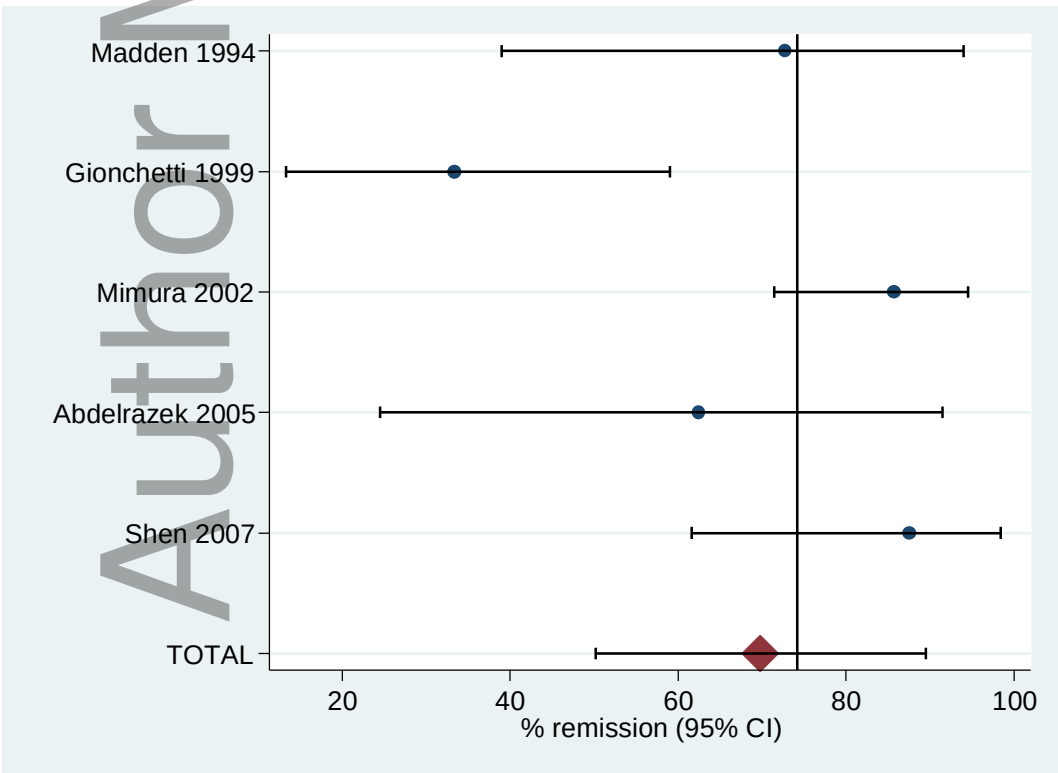

Figure 3

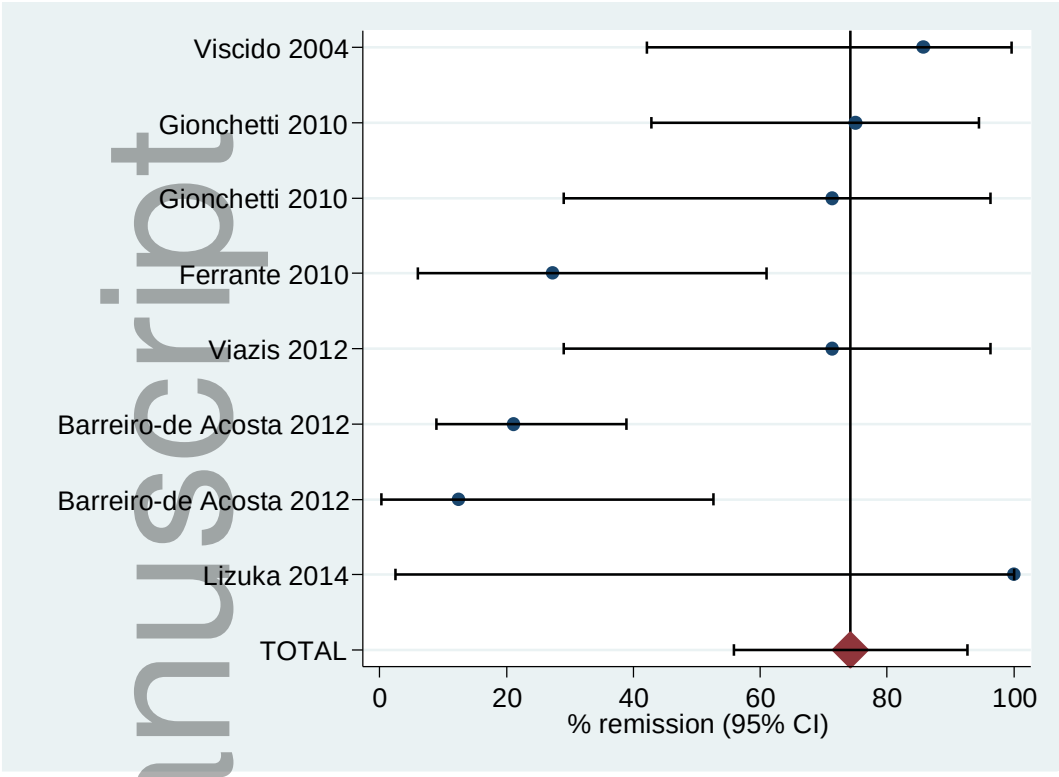

Figure 4