TITLE: Medical Management Following Surgical Therapy in Inflammatory Bowel Disease: Evidence from Cochrane Reviews

AUTHORS: Nilesh Chande[1],MD, Siddharth Singh[2], MD, Neeraj Narula[3],MD MPH, Morris Gordon[4],MD, M Ellen Kuenzig[5,6], PhD, Tran M. Nguyen[7],MSc, John K. MacDonald[7], MA, Brian G. Feagan[7,8,9], MD.

AFFILIATIONS:

[1]Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada; [2]Division of Gastroenterology, University of California San Diego, La Jolla, California, USA; [3]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; [4]School of Medicine, University of Central Lancashire, Preston, United Kingdom; [5]Children's Hospital of Eastern Ontario (CHEO) Inflammatory Bowel Disease Centre, Division of Gastroenterology & Hepatology, Ottawa, Ontario, Canada; [6]CHEO Research Institute, Ottawa, Ontario, Canada; [7]Alimentiv Inc. London, Ontario, Canada; [8]Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada; [9]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

CORRESPONDENCE: Brian G. Feagan, MD, Western University, London, Ontario, CANADA N6A 5B6.

E-mail: brian.feagan@alimentiv.com; phone: (226) 270-0780; fax: (519) 931-5705

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ABBREVIATIONS:

5-ASA, 5-aminosalicylates; AZA, azathioprine; CD, Crohn's disease; CI, confidence interval; Crl, credible interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; 6-MP, 6-mercaptopurine; NMA, network meta-analysis; OR, Odds ratio; PDAI, Pouchitis Disease Activity Index; RCT, randomized control trial; RR, risk ratio; TNF-α, tumor necrosis factor-aplha; UC, ulcerative colitis

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SUMMARY:

The Cochrane Inflammatory Bowel Diseases Group presented a symposium at Digestive Diseases Week 2019 entitled “Medical Management Following Surgical Therapy in Inflammatory Bowel Disease: Evidence from Cochrane Reviews”. This article summarizes the data presented at this symposium.

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INTRODUCTION

Although medical therapy for inflammatory bowel disease (IBD) has greatly improved over the past two decades, surgery continues to be an integral part of the management of ulcerative colitis (UC) and Crohn's disease (CD). This article reviews data from Cochrane reviews relevant to the medical management of IBD in surgical patients including treatment and prevention of pouchitis in UC patients with an ileal pouch-anal anastomosis, the risk of post-operative infectious complications from medical therapies, infertility following IBD surgery, and prevention of recurrence following bowel resection for CD. A summary of the overall certainty of evidence was assessed using Grading of Recommendations Assessment (GRADE) (**Table 1**) and a summary of the results of these reviews is provided in **Table 2**.

TREATMENT AND PREVENTION OF POUCHITIS AFTER ILEAL POUCH-ANAL ANASTOMOSIS FOR ULCERATIVE COLITIS

Pouchitis is an chronic inflammatory disease that may occur in the ileal pouch after proctocolectomy in patients undergoing ileal pouch-anal anastomosis (IPAA).[1] The risk of pouchitis is substantially higher in patients undergoing IPAA for UC compared to patients undergoing this procedure for familial adenomatous polyposis. Most patients present with a combination of symptoms including increased stool frequency, abdominal cramping, tenesmus, fecal urgency, and incontinence. A clinical diagnosis should be confirmed by endoscopy and biopsy of the pouch. Patients with pouchitis can be classified according to disease activity and symptom duration.[2, 3] Disease activity can be classified as remission (i.e. no active pouchitis), mild-to-moderately active disease (i.e. increased stool frequency, urgency, infrequent incontinence) or severely active disease (i.e. hospitalization for dehydration, frequent incontinence). The Pouchitis Disease Activity Index (PDAI) is a 19-point composite index of pouchitis activity based upon clinical symptoms, endoscopy and histology findings.[4] Active pouchitis is defined as a PDAI ≥ 7 with

remission defined as a PDAI < 7. Clinical response to treatment is based on a reduction in the PDAI score ≥ 3 from baseline. It should be noted that the PDAI was developed empirically and has not been rigorously validated. Symptom duration can be classified as acute (i.e. ≤ 4 weeks duration) or chronic (i.e. > 4 weeks duration).

A Cochrane review conducted by Nguyen et al included 15 randomized controlled trials (RCTs) (N = 547) that evaluated the treatment of active pouchitis or the prevention of pouchitis after IPAA for UC.[5] Several different interventions were assessed including antibiotics, probiotics, budesonide, adalimumab, bismuth carbomer foam enema and allopurinol.

Efficacy of interventions for acute pouchitis

Four RCTs evaluated the efficacy of medical interventions for treatment of acute pouchitis. The overall body of evidence in support of any intervention over another treatment or placebo was deemed to be of very low quality. Based on one small RCT of 16 patients, ciprofloxacin (1,000 mg/d) may be more effective than metronidazole (20 mg/kg/d) for induction of remission at 2 weeks (100% [7/7] vs. 33% [3/9]; risk ratio [RR] 2.68, 95% confidence interval [CI] 1.13-6.35).[6] Due to a high risk of bias and a very small number of events generated by this small clinical trial, the certainty of evidence was rated as very low.

A second double-blind, double-dummy RCT that studied 26 patients with acute pouchitis, compared the relative efficacy of oral metronidazole (0.5 g twice daily) to budesonide enemas (2 mg/100 mL daily) for induction of remission.[7] No statistically significant differences in clinical remission or clinical response rates were found between metronidazole and budesonide. At six weeks, 43% (6/14) of patients in the metronidazole group achieved clinical remission, in comparison to 50% (6/12) of budesonide patients (RR 0.86, 95% CI 0.37-1.96). Clinical response was achieved by 50% (7/14) of metronidazole patients, in comparison to 58% (7/12) of budesonide patients (RR 0.86, 95% CI 0.42-1.74). The GRADE analysis

determined the certainty of evidence supporting these outcomes was very low because of an unclear risk of bias and the small number of patients evaluated.

Another small placebo-controlled study that evaluated rifaximin (400 mg) induction therapy showed a statistically non-significant difference in remission rates (25% [2/8] vs. 0% [0/10], RR 6.11, 95% CI 0.33-111.71).[8] Finally, the probiotic, Lactobacillus GG (0.5-10) x 10^{10} colony-forming units/capsule twice daily was compared to placebo in a small RCT for induction of remission with equivocal results (10% [1/10] vs. 0% [0/10], RR 3.00, 95% CI 0.14-65.90).[9] The certainty of evidence for both the rifaximin and Lactobacillus GG outcomes was rated as very low due to unclear risk of bias and very limited data.

Efficacy of interventions for chronic pouchitis

Five RCTs were identified that evaluated the efficacy of interventions for maintaining remission in patients with chronic pouchitis. Based upon two RCTs, VSL#3 formulation (6 g/day) may be superior to placebo for maintaining remission at 9 to 12 months (85% [34/40] vs. 3% [1/36], RR 20.24, 95% CI 4.28-95.81).[10, 11] Despite the very strong summary efficacy estimate generated using the aggregate data from these two trials, the certainty of evidence supporting this finding was low due to a limited amount of data.

Results from a small trial, suggested that glutamine suppositories (1 g twice daily) may be more effective than butyrate suppositories (40 mmol twice daily) for induction of remission at 3 weeks (60% [6/10] vs. 33% [3/9], RR 1.80, 95% CI 0.63-5.16).[12] The certainty of evidence was determined to be very low because of unclear risk of bias and very limited data. Another RCT that evaluated topical maintenance therapy found no benefit of bismuth carbomer foam enema (metallic bismuth 270 mg) over placebo for clinical improvement at 3 weeks (45% [9/20] vs. 45% [9/20], RR 1.00, 95% CI 0.50-1.98).[13] However, the certainty of evidence supporting this outcome was very low due to unclear risk of bias and very limited data.

Finally, in a small RCT that was terminated prematurely, the benefit of adalimumab (standard induction and maintenance dose of 160 mg, followed by 80 mg followed by 40 mg every fortnightly) over placebo

for clinical improvement at 4 weeks in patients with chronic, antibiotic-refractory pouchitis was equivocal (50% [3/6] vs. 43% [3/7], RR, 1.17, 95% CI 0.36-3.76).[14] The certainty of evidence supporting this outcome was rated as low due to very limited data.

Interventions for prevention of pouchitis

Six RCTs evaluated the efficacy of interventions for prevention of pouchitis after IPAA. The efficacy of VSL#3 in comparison to placebo or a no treatment control group was assessed in two RCTs, evaluating the proportion of patients with no episodes of pouchitis 12 months after IPAA. In the first trial 90% (18/20) of patients receiving VSL#3 (one packet per day) did not experience any episodes of pouchitis at 12 months compared with 60% (12/20) of placebo patients (RR 1.50, 95% CI 1.02-2.21).[15] The results of the second trial were also favorable for VSL#3 (two packets once per day), 100% (16/16) of VSL#3 patients did not experience any episodes of pouchitis at 12 months in comparison to 92% (11/12) of the no treatment control group (RR 1.10, 95% 0.89-1.36).[16] A GRADE analysis indicated that the certainty of evidence was low due to very limited data for the placebo-controlled study and very low due to high risk of bias and very limited data for the study with a no treatment comparison group.

The efficacy of another probiotic formulation, *Bifidobacterium longum* over placebo for preventing pouchitis was evaluated in a single study that yielded uncertain results. At 6 months, 86% (6/7) of patients in the probiotics group did not experience any episodes of pouchitis in comparison to 60% (3/5) of the placebo group (RR 1.43, 95% CI 0.66-3.11; very low certainty evidence).[17] Likewise, a second trial that evaluated a, *Clostridium butyricum MIYAIRI* formulation (20 mg three tabs daily) also generated inconclusive results. At 24 months, 11% [1/9] of the probiotics group did not experience any episodes of pouchitis in comparison to 50% (4/8) of the placebo group (RR 0.22, 95% CI 0.03-1.60; very low certainty evidence).[18]

The efficacy of tinidazole (500 mg daily) was compared to placebo in a single study. At 12 months, 81% (21/26) of patients in the tinidazole group did not experience any episodes of pouchitis compared with 58% (7/12) of placebo patients (RR 1.38, 95% CI 0.83-2.31; very low certainty evidence).[19] Finally, allopurinol (100 mg twice daily) was compared to placebo in a single study. At 24 months, 46% (43/94) of allopurinol patients did not develop pouchitis compared with 43% (39/90) of the placebo group (RR 1.06, 95% CI 0.76-1.46; low certainty evidence).[20] The certainty of evidence for tinidazole and allopurinol were both rated as very low due to unclear risk of bias and very limited data.

In summary, the currently available data show that the efficacy of antibiotics, probiotics and other pouchitis therapies are largely uncertain for both induction and maintenance therapy. Although clinical experience indicates that broad spectrum antibiotics are an appropriate first line treatment strategy for pouchitis, multiple unmet needs exist. Specifically, adequately powered and well-designed trials are required to establish the best therapy for both induction of remission and prevention of pouchitis.

RISK OF POST-OPERATIVE INFECTIOUS COMPLICATIONS FROM MEDICAL THERAPIES IN INFLAMMATORY BOWEL DISEASE

Many medications used to treat IBD may be associated with an increased risk of infection due to their immunosuppressive effects.[21] Furthermore, patients with IBD commonly undergo surgical procedures, both for management of their disease or other conditions. The immunosuppressive and anti-inflammatory effects of IBD therapy raises concerns regarding whether use of these agents in the peri-operative period convey an increased risk of post-operative complications, including infections. As a result of these fears, some surgeons recommend patients discontinue IBD medications for several weeks prior to undergoing elective surgery. [22] However, this strategy may be associated with other risks, including the reactivation of IBD. For patients using biologics, a drug holiday could also lead to immunogenicity and loss of response to the biologic following resumption of treatment post-operatively. Studies evaluating the association between peri-operative medications and post-operative

infections have yielded mixed results, particularly the studies examining risk of post-operative infections from perioperative tumor necrosis factor-alpha (TNF-α) antagonists.[23-27]

A systematic review conducted by Law et al. evaluated the risk of post-operative infectious complications in patients using common conventional and biologic therapies for IBD.[28] Given that no appropriate RCTs have been conducted in this field, only observational studies were included in the review. A total of 63 studies satisfied the inclusion criteria for meta-analysis. The primary outcome was post-operative infectious complications within 30 days of surgery. The secondary outcome was intra-abdominal infectious complications. Pre-specified subgroup analyses reported on whether type of IBD or year of publication (prior to 1998 versus after 1998 -the year infliximab was approved by the US FDA) influenced the estimates assessed.

There were 35 eligible studies that examined the risk of infection with pre-operative corticosteroid use. Overall, patients exposed to pre-operative corticosteroids had an increased risk of developing a post-operative infectious complication compared to those not exposed to corticosteroids (Odds ratio [OR] 1.34, 95% CI 1.25-1.44). Subgroup analysis by type of IBD showed a similar risk of post-operative infectious complications in patients with CD (OR 1.27, 95% CI 1.14-1.40) and UC (OR 1.37, 95% CI 1.22-1.53). Similarly, a significantly increased risk of post-operative infectious complications was seen in studies performed before 1998 (OR 1.74, 95% CI 1.26-2.41) and after 1998 (OR 1.32; 95% CI, 1.23-1.42). A secondary analysis that specifically evaluated intra-abdominal infection also showed an increased risk with corticosteroid use (OR 1.63, 95% CI 1.33-2.00).

There were five eligible studies that examined the risk of infection with pre-operative 5-aminosalicylates (5-ASA) use. Patients exposed to 5-ASA formulations pre-operatively had a significantly lower risk of infectious complications than unexposed patients (OR 0.63, 95% CI 0.46-0.87). There was no statistically significant difference in the risk of post-operative infectious complications for studies conducted before

1998 (OR 1.08, 95% CI 0.47-2.51). However, for studies conducted after 1998, patients exposed to 5-ASA had a significantly decreased risk of post-operative infectious complications compared to unexposed patients (OR 0.57, 95% CI 0.40-0.81).

A total of 26 eligible studies evaluated the risk of post-operative infectious complications in patients receiving immunosuppressives including thiopurines, methotrexate, cyclosporine and tacrolimus. There was no statistically significant difference in post-operative infectious complications between those exposed to pre-operative immunosuppressives compared to those who did not receive immunosuppressives (OR 1.08, 95% CI 0.94-1.25). No difference in post-operative infection risk was seen in patients with CD (OR 1.06; 95% CI, 0.83-1.36) or those with UC (OR 1.07; 95% CI, 0.83-1.39). In contrast, studies published prior to 1998 demonstrated an increased risk of postoperative complications in patients treated with these agents (OR 1.85, 95% CI 1.14-3.01), however this observation was not seen in studies published after 1998 (OR 1.03, 95% CI 0.88-1.20). Prior to the introduction of biologics, immunosuppressives were used more often for those with severe disease but are now mainly reserved for patients with mild to moderate disease. Hence, the increased risk of post-operative infection in studies performed prior to 1998 may reflect confounding by disease severity rather than a true biological effect.

A total of 49 eligible studies examined post-operative infection risk in patients exposed to TNF- α antagonists. Overall, an increased risk of post-operative infectious complications was observed in patients exposed to pre-operative anti-TNF-α antagonists (OR 1.26, 95% CI 1.07-1.50). On sub-group analysis, the excess risk was restricted to patients with CD (OR 1.48, 95% CI 1.11-1.97) and was not observed in patients with UC (OR 1.05, 95% CI 0.79-1.41). In a post-hoc subgroup analysis that examined patients who received TNF-α antagonist therapy within 8 weeks of surgery, a significantly elevated risk of post-operative infection was observed (OR 1.44, 95% CI 1.08-1.93). For patients who received TNF-α

antagonist therapy greater than 8 weeks before surgery, the risk of post-operative infection was no longer statistically significant (OR 1.15, 95% CI 0.93-1.43).

There were eight eligible studies that assessed the risk of post-operative infectious complications from pre-operative anti-integrin (e.g. natalizumab or vedolizumab) use. In the overall analysis, no attributable risk of infection was identified in those using anti-integrin therapies compared to patients who were not exposed to anti-integrin therapies (OR 1.06, 95% CI 0.67-1.69). Only one study examined the risk of post-operative infection in patients treated with anti-interleukin therapies (e.g. ustekinumab) and found no significant difference in post-operative infections in patients using these therapies compared to unexposed patients (OR 0.98, 95% CI 0.58-1.66).[29]

The collective quality of evidence in these studies was very low, largely due to the observational nature of the studies included. There was a serious risk of bias detected, and high levels of imprecision in the results. Notably, the majority of these studies were unable to adequately adjust for known potential confounders, most critically disease activity and severity. The authors concluded that, although the meta-analysis revealed an increase in the odds of post-operative infections in patients using pre-operative corticosteroids and TNF-α antagonists, as well as a decrease in post-operative infection risk in patients using pre-operative 5-ASA therapies, it is difficult to draw firm conclusions from this study due to the presence of residual confounding. This issue likely explains the differences observed when studies conducted before 1998 were compared to those conducted after 1998. Before 1998, when no biologics were available, patients with more severe disease tended to use pre-operative immunosuppressives. In studies conducted before 1998 a higher risk of post-operative infectious complications was found in patients using pre-operative immunosuppressives. After 1998, patients with severe disease were more likely to be treated with biologics and accordingly were less likely to receive immunosuppressives such as azathioprine (AZA). Likewise, patients with mild disease activity and/or a good prognosis were more likely to receive 5-ASA monotherapy than patients with more severe disease. These shifts in the

treatment paradigm are a potential explanation as to why pre-operative 5-ASA therapy was associated with a decreased odds of infection compared to those not using these agents in studies conducted after 1998. Similarly, it also may explain why there was no increased risk of post-operative infection observed in patients using immunosuppressives for studies conducted after 1998.

In summary, this review found an increased odds of post-operative infectious complications in patients using pre-operative corticosteroids and TNF-α antagonists. However, the certainty of this conclusion was considered low and the authors cautioned that further prospective well-controlled studies are needed before definitive conclusions can be drawn. The decision to stop therapies prior to surgery should be individualized to each patient, considering the risks involved including disease flare and sensitization to biologic therapies. Attention should be paid to other modifiable risk factors known to increase the risk of post-operative complications including nutritional status and cigarette smoking.

However, the controversy of whether biologics increase the risk of postoperative infections is yet to be resolved. Since these results were obtained, data from the PUCCINI study, a prospective multicenter cohort study were published.[30] Cohen et al., assessed 30 day overall postoperative infectious complications in 955 patients with UC and CD. Patients who received a TNF-α antagonist within 12 weeks of surgery were included. The authors found that TNF-α antagonists were not an independent risk factor for postoperative infections. Further large prospective studies are needed to more definitively understand the risks associated with preoperative medication use in IBD.

RISK OF INFERTILITY AFTER INFLAMMATORY BOWEL DISEASE-RELATED SURGERY

Infertility is a commonly acknowledged complication of IPAA,[31, 32] which may, in part, be due to scarring of the fallopian tubes during surgery.[33] Previous systematic reviews that have addressed this topic have

faced important methodological challenges, including heterogeneity in definitions of infertility, limited capacity to adjust for relevant confounders (i.e., age) and relatively limited data.[31, 32]

A Cochrane review conducted by Lee et al evaluated the effects of IBD-related surgery on female infertility and pregnancy.[34] The primary outcome was the risk of infertility defined as the inability to become pregnant after one year of regular unprotected intercourse without the use of birth control, as well as infertility after 6 months, 18 months and 24 months. Secondary outcomes included miscarriage, use of assistive reproductive technology, delivery via caesarean section, stillbirth, preterm birth, low birth weight and small size for gestational age. A total of 16 studies were included that compared fertility rates in patients with or without a previous surgery (9 studies), open and laparoscopic IPAA (1 study), or before and after surgery (7 studies). A single study compared infertility rates between women with and without IPAA and before and after IPAA. Eight studies included infertility as an outcome; the remainder evaluated pregnancy outcomes.

Two studies including 114 women with UC, evaluated the association between previous surgery and infertility following 12 months of unprotected intercourse (RR 5.45, 95% CI 0.41-72.57). One study compared women with and without IPAA[35] and the other study compared women with and without restorative proctocolectomy with ileorectal anastomosis.[36] A third study evaluated 24-month infertility rates in 86 women with CD and in 104 women with UC. The specific type of surgical procedures were not reported in this study.[37] There was a significantly increased risk of infertility at 24 months among women with UC who had surgery (RR 5.28, 95% CI 2.9-13.34) but not among women with CD who had surgery (RR 2.03, 95% CI 0.56-7.33). A single study compared 12-month infertility rates in 37 women with UC undergoing laparoscopic and open IPAA (RR 0.70, 95% CI 0.38-1.27).[38]

Twelve-month infertility before and after surgery (restorative proctocolectomy with IPAA, restorative proctocolectomy and total colectomy with ileorectal anastomosis) was described in five studies of

women with UC. Before surgery, 21% [68/327] women were infertile compared to 63% [239/377] after surgery. Similar differences in infertility were noted at 6 months in a single study (before: 20% [1/5]; after: 60% [9/15]),[39] and at 24 months in two studies (before: 16% [14/89]; 71% [116/164]).[39 40]

In an analysis of infertility before and after surgery stratified by age at surgery, higher rates of infertility were found in patients who underwent surgery after 30 years of age relative to younger patients.[41] This is consistent with age-expected increases in infertility.[42]

All analyses of the association between previous IBD-related surgery and infertility were rated as very low certainty based on GRADE, given that all studies evaluated were observational, had a high risk of bias and generated limited data. Thus, important uncertainties exist regarding the association between previous surgery and infertility in women with IBD. The interpretation of these findings is challenging due the heterogeneity in surgical techniques and patient populations. For example, the risk of infertility might be expected to differ between 2- and 3-stage IPAA construction,[43] and between hand-sewn and stapled anastomoses.[44]

At present, there is no clear evidence of an association between previous surgery and infertility in women with IBD. This conclusion is based upon the results of the Cochrane review by Lee et al,[34] differing from previous reviews on this topic that described a positive relationship.[31, 32] Unlike previous reviews, Lee et al restricted analyses to studies using a rigorous definition of infertility and did not meta-analyze studies comparing fertility rates before and after surgery. The latter exclusion criterion was used to avoid both the effects of paired data and unmeasured confounding from increasing age in patients following surgery. A more rigorous definition of infertility eliminates bias due to 1) different durations of follow-up between women with and without a previous surgery and 2) the inclusion of women who are voluntarily infertile.

It is important to recognize the heterogeneity in patient populations evaluated in these observational studies. Women with IBD who undergo surgery may be systematically different from those who do not undergo surgery. Specifically, these patients may have more severe disease, long-term disability, or systemic effects of chronic inflammation or corticosteroid use than individuals who do not have surgery. As a result, these individuals may be less likely to want to become pregnant and their inclusion would result in perceived higher infertility rate. Furthermore, sexual dysfunction rates may be higher among women with prior surgery, which may also contribute to involuntary infertility in this population.[45, 46]

There is a need for further well-designed studies to evaluate the impact of surgical procedures on infertility in women with IBD. These studies should include detailed information on disease activity and phenotype, medical and surgical treatment, clear definitions of infertility (including the contribution of sexual dysfunction to involuntary infertility), and appropriate comparison groups and statistical analyses that adjust for the effects of important confounding variables.

MEDICAL MANAGEMENT OF SURGICALLY INDUCED REMISSION

Although surgery is an integral part of the management of CD, endoscopic recurrence and clinical relapse rates are high.[47-49] Accordingly, medical therapy for prevention of recurrence after bowel resection is one of the most important unmet medical needs in IBD. Systemic corticosteroids are arguably the most effective induction agents for CD. However, corticosteroids are not effective for maintenance of remission following medical induction therapy. [50]

Although 5-ASAs are highly effective maintenance agents for UC, they are ineffective for maintaining medically-induced remission in CD.[51] Likewise, although thiopurines, comprised of AZA and 6-mercaptopurine (6-MP), are accepted as effective maintenance therapy following medical induction therapy, their role for prevention of post-operative recurrence is controversial with different systematic

reviews reaching different conclusions.[51] This situation has led to international guidelines providing varying advice regarding the efficacy of thiopurines in the post-operative setting. A series of reviews were performed to address these issues including an update of previous reviews of 5-ASA agents[51] and thiopurines,[52] as well as a network meta-analysis (NMA) of all medical therapies for preventing post-operative recurrence.[53]

5-ASA agents

Gjuladin-Hellon et al., performed a Cochrane review that assessed the efficacy and safety of 5-ASA for preventing post-operative recurrence of CD.[51] The meta-analysis included 14 studies with 1867 participants. The sample sizes of the individual trials ranged from 51 to 324 patients. The risk of bias was considered to be unclear in seven studies, high in six and low in one. Clinical relapse as specified by the included studies was the primary endpoint.

None of the individual studies showed a statistically significant difference between 5-ASA and placebo. However, a pooled analysis of five studies, found 5-ASAs to be significantly superior to placebo for avoiding clinical relapse over a period ranging from 48 weeks to 6 years.[54-58] Relapse was reported in 36% (131/361) of 5-ASA participants compared with 43% (160/369) of placebo participants (RR 0.83, 95% CI 0.72-0.96; moderate certainty evidence). It should be noted that clinical relapse definitions varied across the studies and only one of the studies in the pooled analysis met a modern FDA definition of symptomatic relapse and endoscopic confirmation of active disease.[56]

Two studies compared sulphasalazine to placebo. Over a period ranging from 18 to 36 months, no differences in the clinical relapse rates were found between the groups. Sixty-six percent (95/143) of patients in the sulphasalazine group relapsed compared with 71% (110/155) of placebo patients (RR 0.88, 95% CI 0.56-1.38; low certainty evidence).[59, 60] A pooled analysis of four studies comparing 5-ASA

to AZA showed no significant difference in clinical relapse rates. Sixty-one percent (103/170) of 5-ASA patients relapsed compared with 67% (119/177) of AZA patients (RR 0.90, 95% CI 0.76-1.07; low certainty evidence) at 24 months.[54, 61-63] In a single trial that compared the TNF-α antagonist adalimumab to 5-ASA, 50% (9/18) of 5-ASA patients relapsed at 2 years compared with 13% (2/16) of adalimumab patients (RR 4.0, 95% CI 1.01-15.84; low certainty evidence).[63]

Thiopurines

Gjuladin-Hellon et al., assessed the benefits and harms of thiopurines (i.e. AZA or 6-MP [6-mercaptopurine]) for the prevention of post-operative recurrence of CD.[51] Ten studies (928 patients) were included. The risk of bias was thought to be low in one study, high in six studies and unlcear in three studies. Clinical relapse (defined by the included studies) was the primary endpoint.

In three trials, purine analogues were found with moderate certainty to be more effective than placebo for preventing clinical relapse over a period ranging from one to three years. Fifty-one percent (109/215) of AZA/6-MP patients and 64% (124/193) of placebo patients relapsed respectively (RR 0.79; 95% CI 0.67-92).[54, 64, 65] A pooled analysis of four trials found no significant difference in clinical relapse rates between thiopurines and 5-ASA. Sixty-four percent (113/177) of thiopurine participants relapsed in comparison to 59% (101/170) of 5-ASA participants (RR 1.05; 95% CI 0.89-1.24; low certainty evidence) at 24 months.[54, 61-63]

In a pooled analysis of three studies, AZA was found to be significantly inferior to infliximab or adalimumab for prevention of clinical relapse over a period ranging from one to two years. Forty-three percent (29/67) of AZA participants relapsed in comparison to 14% (10/72) of infliximab/adalimumab participants (RR 2.89; 95% CI 1.50-5.57; very low certainty evidence). [63, 66, 67]

Overall, moderate certainty evidence proposes that AZA and 6-MP may be superior to placebo and very low certainty evidence proposes TNF-α antagonists may be superior to AZA for the prevention of post-surgical relapse.

Network meta-analysis of medical treatments for maintenance of remission

The meta-analyses assessing the efficacy of aminosalicylates and thiopurines generated some unanswered questions regarding the relative efficacy of these agents compared to other active medications including TNF-α antagonists. The majority of studies that found a benefit for these therapies were placebo-controlled and relatively small. A GRADE analysis of the results indicates important uncertainty for these conclusions and the interpretation of how these results can best inform clinical practice is difficult. Adequately powered superiority trials are the best method for comparing the relative efficacy and safety of maintenance therapies in postoperative CD. However, in the absence of such trials an alternative option for obtaining comparative data is an NMA, where different medications are compared using both direct comparisons from RCTs and indirect comparisons across the studies using a common comparator (i.e. placebo). That is, if treatment X is compared to treatment Y in one study, and the same treatment Y is compared with treatment Z in another study, indirect information for the comparison of treatment X to treatment Z can be obtained using this technique.

A Cochrane NMA was undertaken to obtain comparative data for interventions in the setting of post-operative CD.[51] Twenty-six RCTs, (2581 patients; 9 medications) were eligible for inclusion in the NMA. The nine medications assessed included adalimumab, 5-ASA, antibiotics, budesonide, infliximab, purine analogues, probiotics, sulfasalazine, and a combination of sulfasalazine and prednisolone. This network lead to 30 direct contrasts, with 102 mixed-treatment contrasts. The overall quality of evidence was rated as low for both the clinical relapse network (21 studies; 2245 patients) and endoscopic relapse (12 studies; 1128 patients) network, due to the imprecision and inconsistency across networks.

Individual contrasts were assessed as very low or low certainty, with the exception 5-ASA compared to placebo, which was considered to be moderate certainty. Treatments were ranked based on effectiveness and certainty of the evidence. Results of the NMA are presented in **Table 3** and **4**.

Clinical relapse was reported in 21 studies in the relapse network (2245 patients). The top five ranked treatments included adalimumab, infliximab, budesonide, 5-ASA and purine analogues. However, limited evidence supports the efficacy of adalimumab for prevention of clinical relapse (Hazard ratio [HR] 0.11, 95% credible interval [CrI] 0.02-0.33; low certainty evidence) and moderate certainty evidence supports the efficacy of 5-ASA for preventing clinical relapse compared to placebo (HR 0.69, 95% CrI 0.53-0.87; moderate-certainty evidence). Budesonide may not be effective for preventing clinical relapse (HR 0.66, 95% CrI 0.27-1.34; low-certainty evidence), and lastly, the evidence regarding the effectiveness of infliximab (HR 0.36, 95% CrI 0.02-1.74; very low-certainty evidence) and thiopurines (HR 0.75, 95% CrI 0.55-1.00; low-certainty evidence) was uncertain. The certainty of evidence was very low for other medications, therefore it was unclear if they reduced clinical relapse rates. Nonetheless, further evidence from the PREVENT study (N = 297), which was not included in the NMA due to transitivity issues suggests that infliximab may be effective for prevention of clinical relapse in high risk patients.

Endoscopic relapse was reported in 12 studies (1128 patients), however due to high risk of bias and limited data across the network, the effectiveness of the assessed medications for preventing endoscopic relapse is uncertain.[55, 63, 65, 66, 68-75] The top five ranked treatments for endoscopic relapse included adalimumab, infliximab, antibiotics, purine analogues and probiotics. Some evidence suggests adalimumab may be effective for prevention of endoscopic relapse (HR 0.10, 95% CrI 0.01-0.32; low-certainty evidence), however none of the other interventions studied appeared to be effective (infliximab HR 0.24, [95% CrI 0.01-1.20]; antibiotics HR 0.80 [95% CrI 0.33-1.65]; purine analogues HR 0.85 [95% CrI 0.33-1.61]; probiotics HR 1.20 [95% CI 0.62-2.19]). Nonetheless, further evidence from the

PREVENT study (N = 297) suggests that infliximab may be effective for prevention of endoscopic relapse.[76] Further large scale trials are needed to establish the best therapy for prevention of endoscopic relapse in postoperative CD.

Direct analysis has demonstrated that both 5-ASA formulations and thiopurines are probably more effective than placebo for maintenance of surgically induced remission. However, the head to head comparisons did not show any difference in efficacy between the medications. NMA's are significantly impacted by risk of bias, heterogeneity and imprecision. The analysis demonstrated that only adalimumab and 5-ASA may be effective in maintaining clinical relapse, with no other agent demonstrating efficacy. Future research needs to consider endoscopic relapse and the role of biologics as an outcome of interest, as there is currently insufficient evidence in this area.

CONCLUSIONS

In summary, some general conclusions about the medical management of IBD can be drawn from the symposium presented at DDW 2019.

The efficacy of antibiotics, probiotics and other interventions for pouchitis are considered uncertain due to limited data and risk of bias. Although broad spectrum antibiotics may be an appropriate first line therapy for pouchitis, the optimal therapy for both induction of remission and prevention of pouchitis remains unknown. Well designed, adequately powered RCTs are required to identify the ideal treatment for pouchitis. Preoperative treatment with corticosteroids and TNF-α antagonists may increase the risk of postoperative infectious complications in individuals who have surgery for IBD. However, the certainty of the evidence supporting this conclusion is low due to the observational nature of the data. Further well-designed prospective studies are necessary to draw more definitive conclusions. The decision to stop therapy before surgery needs to be individualized to each patient based on the risk of disease flare and sensitization to biologic therapy.

At present there is no clear evidence of an association between previous surgery and infertility in women with IBD. Further well-designed studies are required to assess the impact of surgery on infertility in women with IBD. The optimal therapy for the prevention of postoperative recurrence of CD is unknown. 5-ASA may be effective for preventing clinical relapse in some patients. Adalimumab and infliximab may be effective for preventing endoscopic relapse in postoperative CD. Well designed, adequately powered RCTs are needed to determine the optimal therapy for prevention of clinical and endoscopic relapse in postoperative CD.

REFERENCES

1 Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis: definition, pathogenesis, and treatment. *Gastroenterology*. 1994;107:1856-1860.

2 Di Febo G, Miglioli M, Lauri A, et al. Endoscopic assessment of acute inflammation of the ileal reservoir after restorative ileo-anal anastomosis. *Gastrointest Endosc*. 1990;36:6-9.

3 Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. *Int J Colorectal Dis*. 1986;1:167-174.

4 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.

5 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;5:Cd001176.

6 Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis*. 2001;7:301-305.

7 Sambuelli A, Boerr L, Negreira S, et al. Budesonide enema in pouchitis--a double-blind, double-dummy, controlled trial. *Aliment Pharmacol Ther*. 2002;16:27-34.

8 Isaacs KL, Sandler RS, Abreu M, et al. Rifaximin for the treatment of active pouchitis: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis*. 2007;13:1250-1255.

9 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.

10 Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut*. 2004;53:108-114.

11 Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:305-309.

12 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.

13 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.

14 Kjaer 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.

15 Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology*.2003;124:1202-1209.

16 Pronio A, Montesani C, Butteroni C, et al. Probiotic administration in patients with ileal pouch-anal anastomosis for ulcerative colitis is associated with expansion of mucosal regulatory cells. *Inflamm Bowel Dis*. 2008;14:662-668.

17 Brown SJ MJ, Smith S, Matchet D, Elliott R. Bifidobacterium longum BB-536 and prevention of acute pouchitis. *Gastroenterology*. 2004;126:S465.

18 Yasueda A, Mizushima T, Nezu R, 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.

19 Ha CY BJ, Lazarev M, Swaminath A, Sparrow M, Murphy SJ, et al. Early institution of tinidazole may prevent pouchitis following ileal pouch-anal anastomosis (IPAA) surgery in ulcerative colitis (UC) patients. *Gastroenterology*. 2010;138:S69.

20 Joelsson M, Andersson M, Bark T, 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.

21 Rawla P, Sunkara T, Raj JP. Role of biologics and biosimilars in inflammatory bowel disease: current trends and future perspectives. *J Inflamm Res*. 2018;11:215-226.

22 Lightner AL, Shen B. Perioperative use of immunosuppressive medications in patients with Crohn's disease in the new "biological era". *Gastroenterol Rep*. 2017;5:165-177.

23 Kopylov U, Ben-Horin S, Zmora O, Eliakim R, Katz LH. Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. *Inflamm Bowel Dis*. 2012;18:2404-2413.

24 Law CCY, Narula A, Lightner AL, McKenna NP, Colombel JF, Narula N. Systematic review and meta-analysis: preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *J Crohns Colitis*. 2018;12:538-545.

25 Narula N, Charleton D, Marshall JK. Meta-analysis: peri-operative anti-TNFalpha treatment and post-operative complications in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;37:1057-1064.

26 Yang ZP, Hong L, Wu Q, Wu KC, Fan DM. Preoperative infliximab use and postoperative complications in Crohn's disease: a systematic review and meta-analysis. *Int J Surg*. 2014;12:224-230.

27 Xu Y, Yang L, An P, Zhou B, Liu G. Meta-Analysis: The influence of preoperative infliximab use on postoperative complications of Crohn's disease. *Inflamm Bowel Dis*. 2019;25:261-269.

28 Law CCY, Koh D, Bao Y, Jairath V, Narula N. Risk of Postoperative infectious complications from medical therapies in inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2020:izaa020.

29 Liang H, Jiang B, Manne S, Lissoos T, Bennett D, Dolin P. Risk factors for postoperative infection after gastrointestinal surgery among adult patients with inflammatory bowel disease: findings from a large observational US cohort study. *JGH Open*. 2018;2:182-190.

30 Cohen B, Fleshner P, Kane S, et al. Anti-tumor necrosis factor therapy is not associated with post-operative infection: results from prospective cohort of ulcerative colitis and Crohn's disease patients undergoing surgery to identify risk factors for postoperative infection I (Puccini). *Gastroenterology*. 2019;156:S80.

31 Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut*. 2006;55:1575-1580.

32 Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. *Int J Colorectal Dis*. 2011;26:1365-1374.

33 Pabby V, Oza SS, Dodge LE, et al. In vitro fertilization is successful in women with ulcerative colitis and ileal pouch anal anastomosis. *Am J Gastroenterol*. 2015;110:792-797.

34 Lee S, Crowe M, Seow CH, et al. The impact of surgical therapies for inflammatory bowel disease on female fertility. *Cochrane Database Syst Rev*. 2019;7:Cd012711.

35 Johnson P, Richard C, Ravid A, et al. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum*. 2004;47:1119-1126.

36 Koivusalo A, Pakarinen MP, Natunen J, et al. Sexual functions in adulthood after restorative proctocolectomy for paediatric onset ulcerative colitis. *Pediatr Surg Int*. 2009;25:881-884.

37 Hudson M, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet*. 1997;58:229-237.

38 Bartels SA, D'Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg*. 2012;256:1045-1048.

39 Mortier PE, Gambiez L, Karoui M, et al. Colectomy with ileorectal anastomosis preserves female fertility in ulcerative colitis. *Gastroenterol Clin Biol*. 2006;30:594-597.

40 Ording Olsen K, Juul S, Berndtsson I, Oresland T, Laurberg S. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology*. 2002;122:15-19.

41 Gorgun E, Remzi FH, Goldberg JM, et al. Fertility is reduced after restorative proctocolectomy with ileal pouch anal anastomosis: a study of 300 patients. *Surgery*. 2004;136:795-803.

42 Crawford NM, Steiner AZ. Age-related infertility. *Obstet Gynecol Clin North Am*. 2015;42:15-25.

43 Hull TL, Joyce MR, Geisler DP, Coffey JC. Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis. *Br J Surg*. 2012;99:270-275.

44 Harnoy Y, Desfourneaux V, Bouguen G, et al. Sexuality and fertility outcomes after hand sewn versus stapled ileal pouch anal anastomosis for ulcerative colitis. *J Surg Res*. 2016;200:66-72.

45 Eluri S, Cross RK, Martin C, et al. Inflammatory bowel diseases can adversely impact domains of sexual function such as satisfaction with sex life. *Dig Dis Sci*. 2018;63:1572-1582.

46 Sanders JN, Gawron LM, Friedman S. Sexual satisfaction and inflammatory bowel diseases: an interdisciplinary clinical challenge. *Am J Obstet Gynecol*. 2016;215:58-62.

47 Orlando A, Mocciaro F, Renna S, et al. Early post-operative endoscopic recurrence in Crohn's disease patients: data from an Italian Group for the study of inflammatory bowel disease (IG-IBD) study on a large prospective multicenter cohort. *J Crohns Colitis*. 2014;8:1217-1221.

48 Gklavas A, Dellaportas D, Papaconstantinou I. Risk factors for postoperative recurrence of Crohn's disease with emphasis on surgical predictors. *Ann Gastroenterol*. 2017;30:598-612.

49 Rutgeerts P. Crohn's disease recurrence can be prevented after ileal resection. *Gut*. 2002;51:152-153.

50 Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2003;4:Cd000301.

51 Gjuladin-Hellon T, Gordon M, Iheozor-Ejiofor Z, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2019;6:CD008414-CD008414.

52 Gjuladin-Hellon T, Iheozor-Ejiofor Z, Gordon M, Akobeng AK. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2019;8:-CD010233.

53 Iheozor-Ejiofor Z, Gordon M, Clegg A, et al. Interventions for maintenance of surgically induced remission in Crohn's disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2019;9:Cd013210.

54 Hanauer SB, Korelitz BI, Rutgeerts P, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology*. 2004;127:723-729.

55 Lochs H, Mayer M, Fleig WE, et al. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology*. 2000;118:264-273.

56 McLeod RS, Wolff BG, Steinhart AH, et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology*. 1995;109:404-413.

57 Sutherland LR, Martin F, Bailey RJ, et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian mesalamine for remission of Crohn's disease study group. *Gastroenterology*. 1997;112:1069-1077.

58 Brignola C, Cottone M, Pera A, et al. Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group. *Gastroenterology*. 1995;108:345-349.

59 Wenckert A, Kristensen M, Eklund AE, et al. The long-term prophylactic effect of salazosulphapyridine (Salazopyrin) in primarily resected patients with Crohn's disease. A controlled double-blind trial. *Scand J Gastroenterol*. 1978;13:161-167.

60 Ewe K, Herfarth C, Malchow H, Jesdinsky HJ. Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: a multicenter trial. *Digestion*. 1989;42:224-232.

61 Ardizzone S, Maconi G, Sampietro GM, et al. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology*. 2004;127:730-740.

62 Herfarth H, Tjaden C, Lukas M, et al. Adverse events in clinical trials with azathioprine and mesalamine for prevention of postoperative recurrence of Crohn's disease. *Gut*. 2006;55:1525-1526.

63 Savarino E, Bodini G, Dulbecco P, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. *Am J Gastroenterol*. 2013;108:1731-1742.

64 D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. *Gastroenterology*. 2008;135:1123-1129.

65 Mowat C, Arnott I, Cahill A, et al. Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2016;1:273-282.

66 Armuzzi A, Felice C, Papa A, et al. Prevention of postoperative recurrence with azathioprine or infliximab in patients with Crohn's disease: an open-label pilot study. *J Crohns Colitis*. 2013;7:623-629.

67 Lopez-Sanroman A, Vera-Mendoza I, Domenech E, et al. Adalimumab vs azathioprine in the prevention of postoperative Crohn's disease recurrence. A GETECCU randomised trial. *J Crohns Colitis*. 2017;11:1293-1301.

68 Florent C, Cortot A, Quandale P, et al. Placebo-controlled clinical trial of mesalazine in the prevention of early endoscopic recurrences after resection for Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Eur J Gastroenterol Hepatol*. 1996;8:229-233.

69 Van Gossum A, Dewit O, Louis E, et al. Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after lleo-caecal resection. *Inflamm Bowel Dis*. 2007;13:135-142.

70 Herfarth HH, Katz JA, Hanauer SB, et al. Ciprofloxacin for the prevention of postoperative recurrence in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis*. 2013;19:1073-1079.

71 Marteau P, Lémann M, Seksik P, et al. Ineffectiveness of Lactobacillus johnsonii LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut*. 2006;55:842-847.

72 Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. *Gut*. 2002;51:405-409.

73 Rutgeerts P, Van Assche G, Vermeire S, et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology*. 2005;128:856-861.

74 Scapa E MN, Kariv Y, Ben-Horin S, White ID, Santo E, et al. Early initiation of adalimumab significantly diminishes post-operative Crohn's disease recurrence, and is superior to immunomodulator therapy. Preliminary results from the POPART trial. *Gastroenterology*. 2015;148:S240.

75 Tursi A, Elisei W, Picchio M, et al. Comparison of the effectiveness of infliximab and adalimumab in preventing postoperative recurrence in patients with Crohn's disease: an open-label, pilot study. *Tech Coloproctol*. 2014;18:1041-1046.

76 Regueiro M, Feagan BG, Zou B, et al. Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection. *Gastroenterology*. 2016;150:1568-1578.

77 Chande N, Costello SP, Limketkai BN, et al. Alternative and complementary approaches for the treatment of inflammatory bowel disease: evidence from cochrane reviews. *Inflamm Bowel Dis*. 2020;26:843-851.

Table 1. Summary of GRADE ratings[77]

Study design	Quality of Evidence	Reasons to downgrade
Randomized controlled trial[1]	High[2]	**Risk of bias** - Downgrade 1 level for serious risk of bias - Downgrade 2 levels for very serious risk of bias **Inconsistency** - Downgrade 1 level for serious inconsistency - Downgrade 2 levels for very serious inconsistency **Indirectness** - Downgrade 1 level for serious indirectness - Downgrade 2 levels for very serious indirectness **Imprecision** - Downgrade 1 level for serious imprecision - Downgrade 2 levels for very serious imprecision **Publication bias** - Downgrade 1 level for likely publication bias - Downgrade 2 levels for very likely publication bias
	Moderate[3]	
Observational study[4]	Low[5]	
	Very low[6]	

[1] Randomized controlled trials start with an initial GRADE rating of high and can be downgraded for problems with risk of bias, inconsistency, indirectness, imprecision and publication bias

[2] A GRADE rating of high implies that we are very confident that the true effect lies close to that of the estimate of the effect.

[3] A GRADE rating of moderate implies that we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

[4] Observational studies start with an initial GRADE rating of low and can be downgraded for problems with risk of bias, inconsistency, indirectness, imprecision and publication bias.

[5] A GRADE rating of low implies that our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

[6] A GRADE rating of very low implies that we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Table 2. Summary of Results

Outcome	Relative effect (95% CI)	No. Participants (Studies)	Quality of Evidence (GRADE)
Pouchitis			
Ciprofloxacin vs metronidazole for acute pouchitis			
Clinical remission at 2 weeks	RR. 2.68 (1.13- 6.35)	16 (1 study)	Very low
Metronidazole vs budesonide enema for acute pouchitis			
Clinical remission at 6 weeks	RR 0.86 (0.37-1.96)	26 (1 study)	Very low
Clinical improvement at 6 weeks	RR 0.86 (0.42-1.74)	26 (1 study)	Very low
Rifaximin vs placebo for acute pouchitis			
Clinical remission at 4 weeks	RR. 6.11 (0.33-111.71)	18 (1 study)	Very low
Clinical improvement at 4 weeks	RR 1.25 (0.34-4.6)	18 (1 study)	Very low
Lactobacillus GG vs placebo for acute pouchitis			
Clinical improvement at 12 weeks	RR 3.00 (0.14-65.9)	20 (1 study)	Very low
Allopurinol vs placebo for acute pouchitis			
No. of episodes of acute pouchitis	RR 1.06 (0.76-1.46)	184 (1 study)	Low
Glutamine vs butyrate for chronic pouchitis			
Clinical remission at 3 weeks	RR 1.80 (0.63-5.16)	19 (1 study)	Very low
Bismuth enema vs placebo for chronic pouchitis			
Clinical improvement at 3 weeks	RR 1.00 (0.50-1.98)	40 (1 study)	Very low
De Simone vs placebo for chronic or prevention of pouchitis			
Clinical remission at 9-12 months	RR 20.24 (4.28-95.81)	76 (2 studies)	Low
No. episodes of acute pouchitis	RR 1.5 (1.02- 2.21)	40 (1 study)	Low
De Simone vs no treatment for prevention of pouchitis			
No. episodes of acute pouchitis	RR 1.10 (0.89-1.36)	28 (1 study)	Very low
Bifidobacterium vs placebo for prevention of pouchitis			
No. episodes of acute pouchitis	RR 1.43 (0.66-3.11)	12 (1 study)	Very low
Tinidazole vs placebo for prevention of pouchitis			
No. episodes of acute pouchitis	RR 1.38 (0.83-2.31)	38 (1 study)	Very low
Adalimumab vs placebo for chronic pouchitis			
Clinical improvement at 4 weeks	RR 1.17 (0.36-3.76)	13 (1 study)	Low
Clostridium vs placebo for prevention of pouchitis			
No. of episodes of acute pouchitis at 24 months	RR 0.22 (0.03-1.60)	17 (1 study)	Very low
Post-op infections from medical therapies for IBD participants			
Corticosteroids vs control			
Risk of infectious complications in IBD patients	OR 1.34 (1.25-1.44)	25 908 (35 studies)	
Risk of infectious complications in UC patients	OR 1.37 (1.22-1.53)	9 studies	
Risk of infectious complications in CD patients	OR 1.27 (1.14-1.40)	20 studies	
Risk of infectious complications in studies before 1998	OR 1.74 (1.26-2.41)		
Risk of infectious complications in studies after 1998	OR 1.32 (1.23-1.42)		
5-ASA vs control			
Risk of postoperative infections in IBD patients	OR 0.63 (0.46-0.87)	1161 (5 studies)	Very low

Risk of postoperative infections in studies before 1998	OR 1.08 (0.47-2.51)		Very low
Risk of postoperative infections in studies after 1998	OR 0.57 (0.40-0.81)		Very low
Immunomodulators vs control			
Risk of infectious complications in IBD patients	OR 1.08 (0.94-1.25)	8459 (26 studies)	Very low
Risk of infectious complications in UC patients	OR 1.07 (0.83-1.39)	9 studies	Very low
Risk of infectious complications in CD patients	OR 1.06 (0.83-1.36)	11 studies	Very low
Risk of infectious complications in studies before 1998	OR 1.85 (1.14-3.01)		Very low
Risk of infectious complications in studies after 1998	OR 1.03 (0.88-1.20)		Very low
Anti-TNF agents vs control			
Risk of infectious complications in IBD patients	OR 1.26 (1.07-1.50)	23 218 (49 studies)	Very low
Risk of infectious complications in UC patients	OR 1.05 (0.79-1.41)	16 studies	Very low
Risk of infectious complications in CD patients	OR 1.48 (1.11-1.97)	25 studies	Very low
Anti-integrin agents vs control			
Risk of infectious complications in IBD patients	OR 1.06 (0.67-1.69)	8 studies	Very low
Risk of infectious complications in UC patients	OR 0.61 (0.28-1.36)	2 studies	Very low
Risk of infectious complications in CD patients	OR 1.32 (0.51-3.42)	4 studies	Very low
Anti-interleukin agents vs control			
Risk of infectious complications in IBD patients	OR 0.98 (0.58-1.66)	1 study	Very low
Surgical therapies on female fertility			
Infertility among women who didn't undergo previous IBD surgery			
Infertility at 12 months	RR 5.45 (0.41-72.57)	114 (2 studies)	Very low
Infertility among women with a laparoscopic approach vs open approach			
Infertility at 12 months	RR 0.70 (0.38-1.27)	19 (1 study)	Very low
Medical Management of Surgically Induced Remission			
AZA or 6-MP vs placebo			
Clinical relapse at 12-36 months	RR 0.79 (0.67-0.92)	408 (3 studies)	Moderate
AZA or 6-MP vs 5-ASA			
Clinical relapse at 12-24 months	RR 1.05 (0.89-1.24)	347 (4 studies)	Low
AZA or 6-MP vs anti-TNF			
Clinical relapse at 12-24 months	RR 2.89 (1.50-5.57)	139 (3 studies)	Very low
5-ASA vs placebo			
Clinical relapse at 48 wk-72 months	RR 0.83 (0.72-0.96)	730 (5 studies)	Moderate
5-ASA vs purine antimetabolites			
Clinical relapse at 24 months	RR 0.90 (0.76-1.07)	347 (4 studies)	Low
5-ASA vs anti TNF- alpha			
Clinical relapse at 24 months	RR 4.00 (1.01-15.84)	34 (1 study)	Very low

Sulphasalazine vs placebo			
Clinical relapse at 18-36 months	RR 0.88 (0.56-1.38)	298 (2 studies)	Low

Abbreviations: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-Mercaptopurine; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HRQL, health-related quality of life; RR, relative risk; TNF, tumor necrosis factor

Table 3. Estimates of effects, credible intervals, and certainty of the evidence for the maintenance of surgically induced remission in Crohn's disease: Benefits

Total studies: 20 RCTs **Total participants: 2149**	**Relative effect (95% CI)**	**Quality of Evidence (GRADE)**	**Ranking (95% CrI) ****
Outcome: Clinical relapse			
Adalimumab **(2 RCTs; 26 participants)**	HR 0.11 (0.02-0.33)	Low	1 (1 to 2)
Infliximab **(2 RCTs; 21 participants)**	HR 0.36 (0.02-1.74)	Very low	2 (1 to 10)
Budesonide **(1 RCT; 43 participants)**	HR 0.66 (0.27-1.34)	Low	3 (2 to 10)
5-ASA **(9 RCTs; 542 participants)**	HR 0.69 (0.53-0.87)	Moderate	4 (2 to 7)
Purine analogues **(6 RCTs; 316 participants)**	HR 0.75 (0.55-1.00)	Low	5 (3 to 8)
Sulfasalazine **(2 RCTs; 143 participants)**	HR 0.89 (0.55-1.30)	Very low	6 (3 to 10)
Antibiotics **(2 RCTs; 57 participants)**	HR 0.98 (0.50-1.71)	Very low	7 (3 to 10)
Probiotics **(2 RCTs; 105 participants)**	HR 1.11 (0.62-1.88)	Very low	8 (3 to 10)
Sulfasalazine + Prednisolone **(1 RCT; 57 participants)**	HR 1.37 (0.50-3.07)	Very low	9 (3 to 10)
Placebo **(16 RCTs; 935 participants)**	Reference comparator	Not estimate	8 (6 to 10)

Abbreviations: 5-ASA, 5-aminosalicylic acid; CI, confidence interval; CrI, credible interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HR, hazard ratio; RCT, randomized control trial

Table 4. Estimates of effects, credible intervals, and certainty of the evidence for the maintenance of surgically induced remission in Crohn's disease: Benefits

Total studies: 12 RCTs **Total participants: 1128**	**Relative effect (95% CI)**	**Quality of Evidence (GRADE)**	**Ranking (95% CrI) ****
Outcome: Clinical relapse			
Adalimumab (3 RCTs; 37 participants)	HR 0.10 (0.01-0.32)	Low	1 (1 of 2)
Infliximab (2 RCTs; 21 participants)	HR 0.24 (0.01-1.20)	Low	2 (1 to 6)
Antibiotics (2 RCTs; 57 participants)	HR 0.80 (0.33-1.65)	Very low	3 (2 to 7)
Purine analogues (4 RCTs; 164 participants)	HR 0.85 (0.33-1.61)	Very low	4 (3 to 7)
Probiotics (3 RCTs; 108 participants)	HR 1.20 (0.62-2.19)	Very low	6 (3 to 7)
5-ASA (3 RCTs; 237 participants)	HR 1.22 (0.61-2.18)	Very low	6 (3 to 7)
Placebo (8 RCTs; 507 participants)	Reference comparator	No estimate	5 (3 to 7)

Abbreviations: 5-ASA, 5-aminosalicylic acid; CI, confidence interval; Crl, credible interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HR, hazard ratio; RCT, randomized control trial