



REVIEW ARTICLE

Prevention of postoperative recurrence of Crohn's disease

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KEYWORDS

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Abstract

Background: Up to 75% of patients with Crohn's disease (CD) will have intestinal resection during their life. Most patients will, however, develop postoperative recurrence (endoscopic, clinical or surgical). Several medical and surgical strategies have been attempted to prevent postoperative recurrence. This review evaluates the efficacy of different drug regimens and surgical techniques in the prevention of clinical, endoscopic and surgical postoperative recurrence of CD.

Methods: A literature search for randomized controlled trials on medical or surgical interventions was performed. The endpoints for efficacy were clinical, endoscopic and surgical recurrence. Meta-analyses were performed in case two or more RCTs evaluated the same drug or surgical technique.

Results: Mesalamine is more effective in preventing clinical recurrence than placebo ($P=0.012$), as well as nitroimidazolic antibiotics at one year follow-up ($P<0.001$) and thiopurines ($P=0.018$). Nitroimidazolic antibiotics are also more effective than placebo in preventing endoscopic recurrence ($P=0.037$), as well as thiopurines ($P=0.015$) and infliximab ($P=0.006$). Budenoside, probiotics, Interleukin-10 nor any of the different surgical procedures showed any significant difference compared to placebo in postoperative recurrence rates of CD.

Conclusion: Among the different drug regimens and surgical techniques, only thiopurines and nitroimidazolic antibiotics are able to reduce postoperative clinical as well as endoscopic

Abbreviations: CD, Crohn's Disease; CDAI, Crohn's disease Activity Index; CI, Confidence Interval; IL-10, Interleukin-10; E–E, End-to-end; S–S, Side-to-side; S–E, Side-to-end; LoE, Level of Evidence; GoR, Grade of Recommendation.

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recurrence of CD. Mesalamine and infliximab also seem to be superior to placebo in preventing clinical recurrence and endoscopic recurrence, respectively. There is a paucity of trials evaluating long-term follow-up and prevention of surgical recurrence of CD.

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1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract. Most commonly it involves the terminal ileum and proximal colon. Genetic and environmental factors play a role in its etiology and pathogenesis.^{1–3} The most common age at time of diagnosis is usually during late adolescence and early adulthood, although CD can appear at almost any age. Most patients are diagnosed before the age of 40 years.^{4,5} Overall, the incidence of CD is approximately 5–10 per 100,000 per year with a prevalence of 50–100 per 100,000.^{1,2,4}

The clinical course of CD is characterized by exacerbations and remissions. Eventually, recurrent inflammation can cause bowel strictures, fistulae (often perianal) or abscesses. Extraintestinal manifestations most commonly involve the skin, eyes, joints and biliary tract.^{2,4,5}

Medical management of CD is a rapidly evolving field, with many new biologicals under investigation. There are multiple medical treatments that proved to be effective in inducing clinical response and remission. The appropriate choice for medication not only depends on the activity, location and behavior of the disease, but is also influenced by the balance between drug potency and side effects; previous response to treatment and the presence of extraintestinal manifestations, or complications.^{4,6} Operative management can be effective

in managing disease complications and improving quality of life.⁷ Eventually, around 75–80% of the patients will end up with a surgical resection.^{6,8–15} Surgery, however, does not eliminate the pathogenic process, as most patients develop recurrence of disease.^{8,11,13,16–18} Although a wide range of postoperative recurrence rates has been reported according to the definitions of recurrence (clinical, endoscopic or surgical recurrence), there is common agreement that recurrence rate steadily increases with time, reaching approximately 50% at 20 years after surgery.¹⁸ Clinical postoperative recurrence rates have been recorded between 17–55% at 5 years, 32%–76% at 10 years and 72% at 20 years, whereas postoperative surgical recurrence rates are 11%–32% at 5 years, 20%–44% at 10 years and 46%–55% at 20 years.¹⁴

Several studies have reported about prognostic factors for postoperative recurrence of CD. To date, only smoking is convincingly associated with a higher risk of recurrence.^{12–15,19,20} The identification of such risk factors is very important to select patients who may benefit from pro-active preventive measures.

Several medical and surgical strategies have been attempted to prevent postoperative recurrence. Most studies, however, only evaluate clinical and/or endoscopic recurrence. Little is known about the incidence of surgical recurrence. Therefore, this review focuses on the efficacy of different medication regimes and surgical procedures in the

prevention of clinical, endoscopic and surgical postoperative recurrence of CD.

2. Methods

2.1. Literature search

Randomized controlled clinical trials for prevention of postoperative recurrence of Crohn's disease were identified from the Medline electronic database and Embase from 1966 until July 2010. The following search terms were used: Crohn (Crohn's disease), recurrence and surgery or postoperative. The studies were limited to randomized controlled trials, humans and English language. Cross-referencing was used to identify additional articles. This resulted in 105 studies. Studies were included for analysis if they met all of the following inclusion criteria: 1) the study was a controlled study, 2) all study patients had a surgical induced remission of their CD, 3) the study reported the definition of recurrence, and 4) data on clinical and/or endoscopic and/or surgical recurrence rates were available. This resulted in 44 studies. Eleven studies were excluded based on title and abstract reading. Of five articles no full-text was available. This resulted in 28 studies available for further assessment. One study had postoperative recurrence as secondary endpoint, but the number of patients was too small to draw conclusions and was therefore excluded. One study only described the placebo group of a previously published randomized controlled trial which was already included. One

study was excluded because a more recent study analyzed the same population with longer follow-up and was already included. Eventually, 25 studies were included for analysis, Fig. 1.

2.2. Outcome measures

The efficacy endpoints are in terms of recurrence rates. Clinical recurrence was defined as symptoms associated with CD requiring therapy and/or a CD activity index (CDAI) of at least 150 points and/or a rise in CDAI of 60–100 points. Endoscopic recurrence was defined according to the criteria of Rutgeerts.²¹ The definition of surgical recurrence was the presence of clinical or endoscopic recurrence refractory to medical treatment or complications and requiring another surgical procedure.

2.3. Statistical methods

The method of analysis of the efficacy of a treatment was dependent on the details provided in the paper describing the study. If a clear description of withdrawn patients and their state of recurrence at time of withdrawal was provided, the evaluation of efficacy of the treatment was performed by a per-protocol analysis. If no reasons for withdrawal or description of recurrences were given, an intention-to-treat method, using the worst-case-model, was used. In this model, all patients who received at least one dose of a study drug were included, and patients who were not assessed with respect to the end point of the study were considered as failures. If the

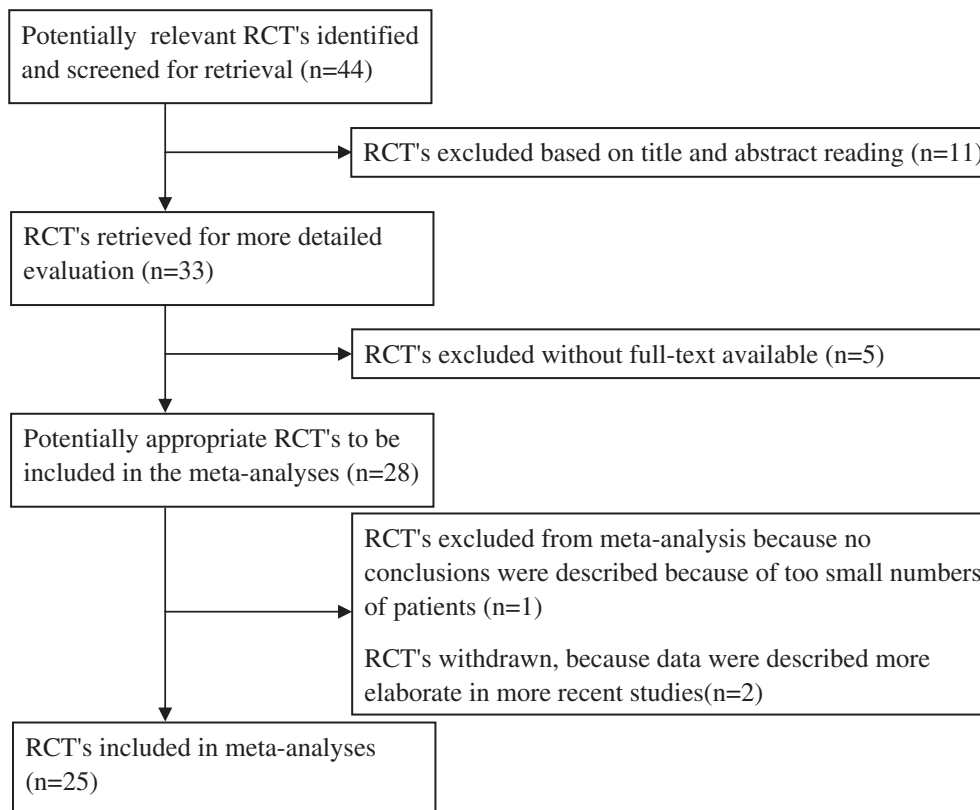


Figure 1 Flowchart of studies included in meta-analyses.

recurrence rate was reported as a percentage only, the number of patients with recurrence was extrapolated from the total number of patients.

A meta-analysis was performed for each efficacy endpoint if at least two studies evaluating the same drug or surgical procedure could be combined. Because of the differences in the methods and the follow up length, we tested for statistical heterogeneity. In case of statistical heterogeneity we used a random effect model; in case of no statistical heterogeneity a fixed effect model was used.²² To obtain an overall measure of the efficacy of treatment, the overall risk difference between the frequencies of the events in both interventional and control groups, as well as the 95% confidence intervals (CI), were calculated. Results are shown in Forrest plots when more than one study was found, with relative weights added according to sample sizes.

3. Results

3.1. Methodological quality of included studies

Of the 25 studies included in the meta-analysis 15 were judged to have adequately concealed allocation. Of the remaining 10 studies concealment of allocation was unclear or inadequate.

In Table 1 an overview of all included studies with risk of bias according to Cochrane's method is shown.²³

In Table 2 a summary of all medical and surgical interventions to prevent postoperative recurrence of CD is presented.

3.2. Drugs

3.2.1. Mesalamine

This drug has been extensively evaluated in the prevention of postoperative recurrence of CD.

Seven controlled trials have evaluated the role of mesalamine on the effect of postoperative recurrence.^{24–30}

Four trials have evaluated the role of mesalamine versus placebo and the effect on clinical recurrence.^{25,27–29} In the overall analysis mesalamine was more effective than placebo in preventing clinical recurrence (mean difference 8.8%, CI 95% 2.0–15.7%, $P=0.012$), Fig. 2a.

Endoscopic recurrence was evaluated in five trials comparing mesalamine with placebo.^{24–28} Meta-analysis of those studies did not show overall difference in postoperative endoscopic recurrence (mean difference 13.5%, CI 95% –6.0–33%, $P=0.175$), Fig. 2b.

Caprilli et al. compared two different dose regimens of mesalamine, 2.4 g vs 4 g per day. This study did not show a clinically significant difference in the prevention of postoperative endoscopic or clinical recurrence.³⁰

Surgical recurrence was not evaluated in controlled trials.

3.2.2. Metronidazole/ornidazole

Nitroimidazolic antibiotics have been shown to be effective in preventing clinical and endoscopic postoperative recurrence of CD. Rutgeerts et al. published a trial comparing metronidazole vs. placebo (for 3 months) as well as ornidazole vs. placebo (for 12 months).^{31,32} Metronidazole showed only

Table 1 Risk of bias summary.

	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting
Regueiro 2009	Yes	Yes	Yes	Yes	Yes
Caprilli 1994	Unclear	Yes	No	Yes	Yes
Brignola 1995	Yes	Yes	Yes	Yes	Yes
Florent 1996	Yes	Yes	Yes	Yes	Yes
Lochs 2000	Yes	Yes	Yes	Yes	Yes
Hanauer 2004	Yes	Yes	Yes	Yes	Unclear
McLeod 1995	Yes	Yes	Yes	Yes	Yes
Caprilli 2003	Yes	Yes	Yes	Yes	Yes
Rutgeerts 1995	Unclear	Unclear	Yes	Yes	Yes
Rutgeerts 2005	Unclear	Unclear	Yes	Yes	Yes
Ardizzone 2004	Yes	No	No	Yes	Yes
D'Haens 2008	Yes	Yes	Yes	Yes	Yes
Reinisch 2010	Yes	Yes	Yes	Yes	Yes
Ewe 1999	Yes	Yes	Yes	Yes	Yes
Hellers 1999	Unclear	Unclear	Yes	Yes	Yes
Chermesh 2007	Unclear	Unclear	Yes	No	Yes
Prantera 2002	Yes	Unclear	Yes	Yes	Yes
Marteau 2006	Yes	Yes	Yes	Yes	Yes
Van Gossum 2007	Yes	Yes	Yes	Yes	Yes
Colombel 2001	Unclear	Unclear	Yes	Yes	Yes
Fazio 1996	Yes	Unclear	Yes	Yes	Yes
Cameron 1992	Yes	Unclear	Unclear	Yes	Yes
Ikeuchi 2000	Unclear	Yes	Yes	Yes	Yes
McLeod 2009	Yes	Yes	Yes	Yes	Yes
Stocchi 2008	Yes	Unclear	No	Yes	Yes

Table 2 Overview of effectiveness of different drug therapies and surgical techniques on recurrence of CD.

Drug therapy/surgical technique	Effectiveness on recurrence	References
Mesalamine		
Endoscopic	No	24–28
Clinical	Yes	25,27–29
Surgical	Unclear	
Nitroimidazolic antibiotics		
Endoscopic	Yes	31,32
Clinical	Yes at 1 year; no at 3 years	31,32; 31,32
Surgical	Unclear	
Thiopurines		
Endoscopic	Yes	28,34,35
Clinical	No at 1 year; yes at 2 years	28,33–35; 28,33
Surgical	No	33
Budenoside		
Endoscopic	No	36,37
Clinical	No	37
Surgical	Unclear	
Probiotics		
Endoscopic	No	39–41
Clinical	No	39,40
Surgical	Unclear	
Interleukin-10		
Endoscopic	No	42
Clinical	Unclear	
Surgical	Unclear	
Infliximab		
Endoscopic	Yes	9
Clinical	No	9
Surgical	Unclear	
Length of resection margin		
Endoscopic	Unclear	
Clinical	No	43
Surgical	No	43
Type of anastomosis		
Endoscopic	No	44
Clinical	No	44,46
Surgical		
S–E vs E–E	No	44
Stapled vs handsewn	Yes at 7 years; No	45; 46
Laparoscopic vs. open resection		
Endoscopic	No	
Clinical	Unclear	47
Surgical	No	47

borderline significant difference in reducing the postoperative clinical recurrence compared to placebo at one year follow-up. Overall analysis showed that nitroimidazolic antibiotics are more effective than placebo in preventing postoperative clinical recurrence at 1 year follow-up (mean difference 24.2%, CI 95% 11.6–36.9%, $P < 0.001$), Fig. 3a. However, at 3 year follow-up there was no significant difference anymore (mean difference 9.3%, CI 95% –7.4–25.9%, $P = 0.276$), Fig. 3b.

At 3 months follow-up endoscopic recurrence was significantly reduced in an overall analysis (mean difference 23.7%,

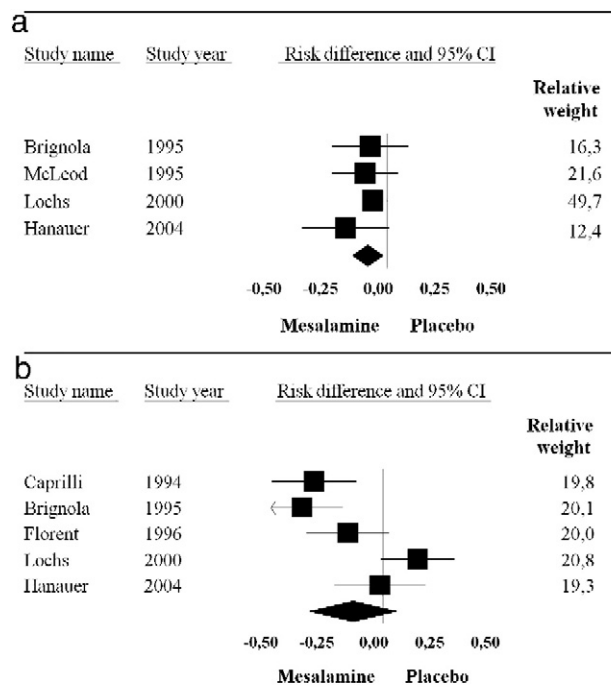


Figure 2 Overall analysis of controlled trials evaluating the effect of mesalamine versus placebo on the prevention of a. clinical recurrence (heterogeneity, $P = 0.752$). b. endoscopic recurrence (heterogeneity, $P < 0.001$).

CI 95% 6.4–41.4%, $P = 0.007$), Fig. 3c. At 1 year follow-up data were only available from the ornidazole-trial. There was still a significant difference in endoscopic recurrence rate, with 53.6% in the ornidazole group, compared with 78.8% in the placebo group ($P = 0.037$).

Surgical recurrence was not evaluated.

3.2.3. Thiopurines (azathioprine and 6-mercaptopurine)

The efficacy of thiopurine in preventing postoperative CD is still not clear. Four controlled trials comparing azathioprine or 6-MP with placebo or mesalamine have been published.^{28,33–35}

Overall analysis showed no significant difference in preventing postoperative clinical recurrence at one year follow-up, comparing AZA/6-MP to placebo or mesalamine (mean difference 3.8%, CI 95% –3.6–11.1%, $P = 0.316$), Fig. 4a. At two year follow-up only two studies were available, however, they showed that thiopurines are more effective than placebo or mesalamine in preventing clinical recurrence (mean difference 13.1%, CI 95% 2.3–23.9%, $P = 0.018$), Fig. 4b.

Endoscopic recurrence rate at one year showed a significant difference in favor of AZA/6-MP compared to placebo (mean difference 19.7%, CI 95% 8.4–31.0%, $P = 0.001$), Fig. 4c. Hanauer showed that 6-MP was more effective than placebo or mesalamine in preventing endoscopic recurrence at two years follow-up as well (difference 21.7%, CI 95% 4.3–39.2%, $P = 0.015$).

Ardiszone showed that after 24 months of treatment there was no significant difference in surgical recurrence

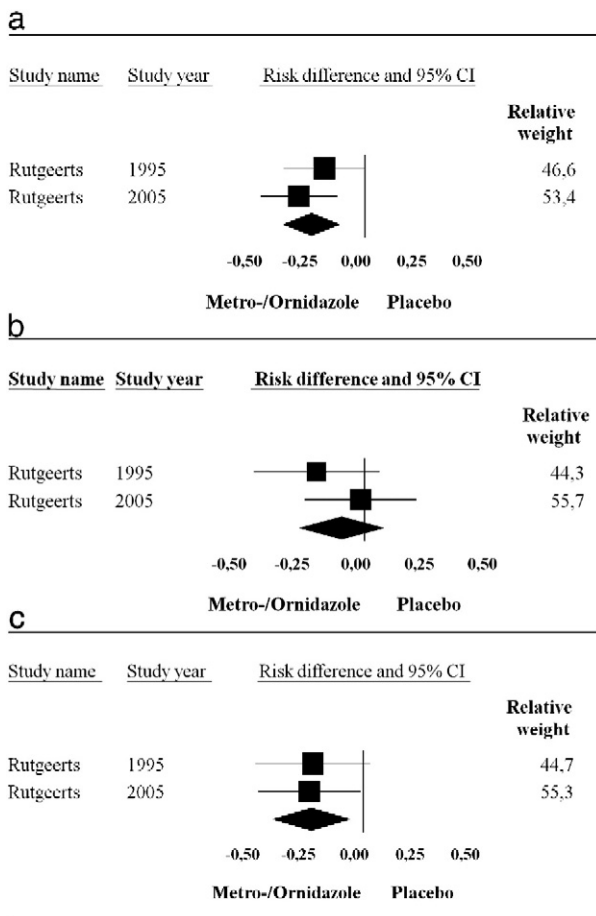


Figure 3 Overall analysis of controlled trials evaluating the effect of metro-/ornidazole versus placebo on the prevention of a. clinical recurrence at 1 year follow-up (heterogeneity, $P=0.373$). b. clinical recurrence at 3 years follow-up (heterogeneity, $P=0.309$). c. endoscopic recurrence at 3 months follow-up (heterogeneity, $P=0.927$).

between azathioprine and mesalamine, with a recurrence rate of 6% vs. 10% respectively ($P=0.5$).

3.2.4. Budesonide

Two controlled trials evaluated the effect of budesonide on the prevention of postoperative recurrence of CD.^{36,37} Overall analysis did not show any difference in endoscopic recurrence rate at one year follow-up (mean difference 7.9%, CI 95% -6.0–21.9%, $P=0.263$), Fig. 5.

Clinical recurrence, evaluated by Hellers et al., was not different after one year follow-up between budesonide and placebo (32% vs. 31% respectively).

Surgical recurrence was not evaluated.

3.2.5. Probiotics

Chermesh et al. evaluated 30 patients receiving Synbiotic 2000, a mixture of prebiotics and probiotics, including 4 lactic acid bacteria and 4 fermentable fibers, or placebo. They did not find a significant difference in mean Rutgeerts score at endoscopy at three and 24 months follow-up between both groups.³⁸

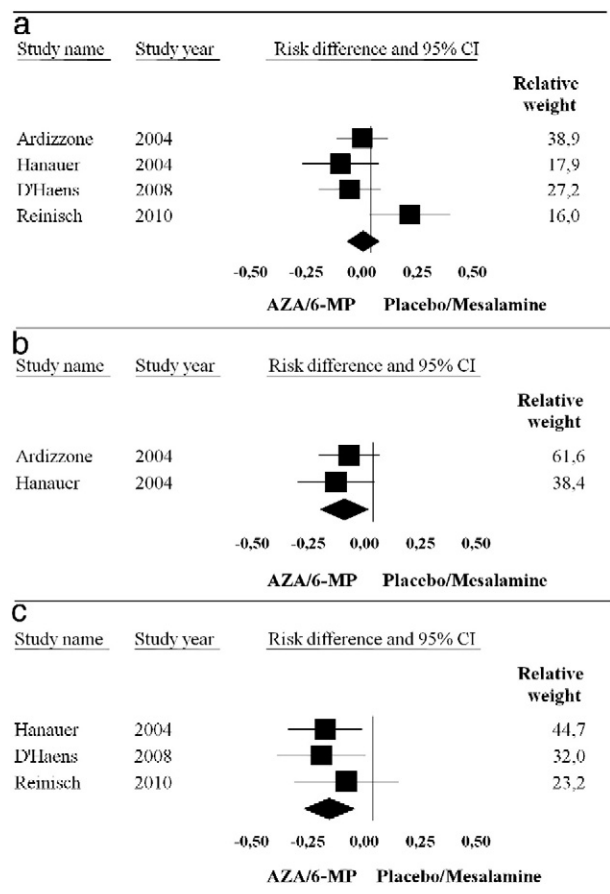


Figure 4 Overall analysis of controlled trials evaluating the effect of thiopurines versus placebo/mesalamine on the prevention of a. clinical recurrence at 1 year follow-up (heterogeneity, $P=0.069$). b. clinical recurrence at 2 years follow-up (heterogeneity, $P=0.596$). c. endoscopic recurrence at 1 year follow-up (heterogeneity, $P=0.750$).

Meta-analysis of three controlled trials did not show difference between probiotics and placebo on endoscopic recurrence (mean difference 1.5%, CI 95% -12.0–14.9%, $P=0.831$), Fig. 6a.^{39–41} Two studies did not show statistical difference on clinical recurrence as well (mean difference -3.6%, CI 95% -13.5–6.4%, $P=0.481$), Fig. 6b.

Surgical recurrence was not evaluated.

3.2.6. Interleukin-10 (IL-10)

The importance of IL-10 for regulation of mucosal inflammation has been investigated in several animal models of inflammatory bowel disease. Colombel et al. evaluated the role of subcutaneously IL-10 in preventing postoperative endoscopic recurrence in humans. There was no difference in endoscopic recurrence rates at 12 weeks follow-up (53% in IL-10 group vs. 55% in placebo).⁴²

Data about clinical and surgical recurrence were not assessed.

3.2.7. Infliximab

A recent study by Regueiro et al. evaluated the role of infliximab in preventing endoscopic and clinical recurrence

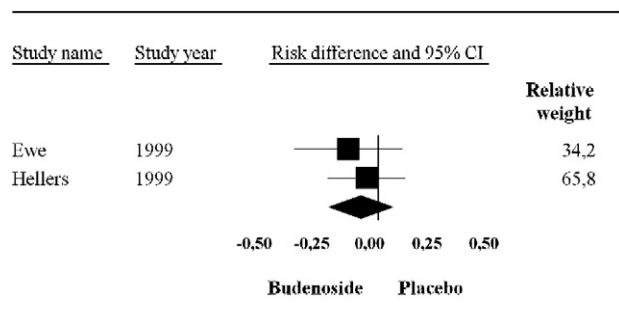


Figure 5 Overall analysis of controlled trials evaluating the effect of budesonide versus placebo on the prevention of endoscopic recurrence at 1 year follow-up (heterogeneity, $P=0.591$).

in a study with 24 patients.⁹ The endoscopic recurrence rate at one year follow-up was significantly lower in the infliximab group compared to placebo (9.1% vs. 84.6%, $P=0.0006$). The clinical recurrence rate at one year follow-up was also lower in the infliximab group, although this did not reach statistical significance (20.0% vs. 46.2%, $P=0.38$). Surgical recurrence was not evaluated.

3.3. Surgical procedure

3.3.1. Length of resection margin

Fazio et al. reported about the role of resection margins on postoperative recurrence in the small bowel.⁴³ They

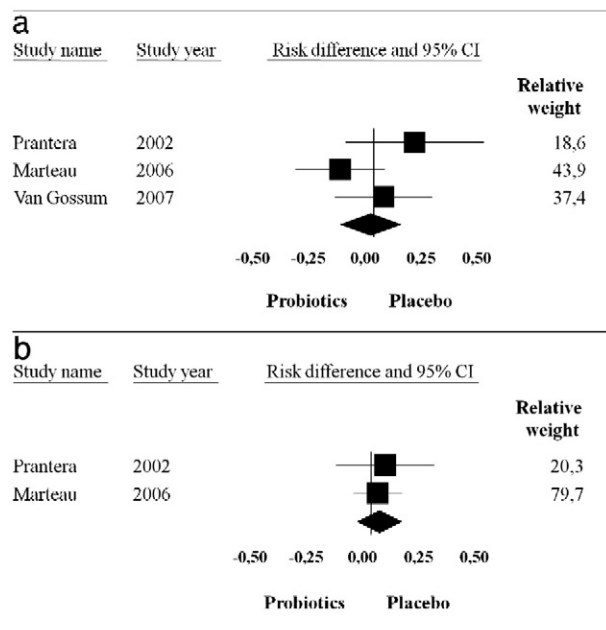


Figure 6 Overall analysis of controlled trials evaluating the effect of probiotics versus placebo on the prevention of a. endoscopic recurrence at 1 year follow-up (heterogeneity, $P=0.169$). b. clinical recurrence at 1 year follow-up (heterogeneity, $P=0.798$).

evaluated a total of 131 patients, with a mean follow-up of 55.7 months. 75 patients underwent a limited resection with a proximal margin of 2 cm of macroscopically non-involved bowel, and 56 patients underwent an extended resection with a proximal margin of 12 cm of macroscopically non-involved bowel. There was no difference in clinical recurrence with 33% vs. 29% between the limited and extended resections respectively, and also no statistical difference in surgical recurrence with 25% and 18% respectively.

3.3.2. Type of anastomosis

The type of anastomosis following resection is one of the important issues in the surgical management of Crohn's disease.

Cameron et al. compared 35 patients with a side-to-end anastomosis with 43 patients with an end-to-end anastomosis after ileocolic resection.⁴⁴ There was no difference in clinical recurrence, 51% in both groups. Endoscopic recurrence was not statistically different as well, with six patients (17%) in the side-to-end group who needed re-resection, compared with three patients (7%) in the end-to-end group.

Ikeuchi et al. showed a significant lower rate of surgical recurrence at the perianastomotic site after a stapled end-to-end anastomosis compared to a double-layer handsewn anastomosis after seven years of follow-up, 18% vs. 49% ($P=0.022$).⁴⁵

A recent multicenter study by McLeod et al. analyzed clinical and endoscopic recurrence rates in 139 patients who underwent ileocolic resection.⁴⁶ Stapled side-to-side anastomosis was performed in 66 patients and handsewn end-to-end anastomosis in 73 patients. There was no difference in clinical or endoscopic recurrence at one year follow-up, with 23% and 38% in the stapled S-S group vs. 22% and 42% in the handsewn E-E group respectively.

Overall analysis comparing S-E or S-S with E-E anastomosis did not show any statistical difference in clinical recurrence (mean difference -0.7% , CI 95% $-12.4-11.1\%$, $P=0.913$), Fig. 7.

3.3.3. Laparoscopic vs. open resection

Laparoscopic ileocolic resection has been reported to have short-term benefits compared to open resection, in terms of reducing postoperative ileus and shorter length of hospital stay. Recent studies by Stocchi et al. have evaluated the long-term results with recurrence as endpoints.⁴⁷ They evaluated 56 patients, with a mean follow-up 10.5 years. 27 patients underwent laparoscopic ileocolic resection and 29 patients open ileocolic resection. There was no difference in endoscopic recurrence with 48% after laparoscopic and 66% after open resection.

Surgical recurrence of 26% and 28%, respectively, was also not significant different between groups.

4. Discussion

In this combined systematic review with meta-analyses we analyzed multiple drug regimens and surgical techniques in preventing postoperative recurrence of CD.

The goals of treatment of CD should be to prevent postoperative recurrence that requires further medical or surgical treatment, thus to prevent clinical or surgical recurrence.

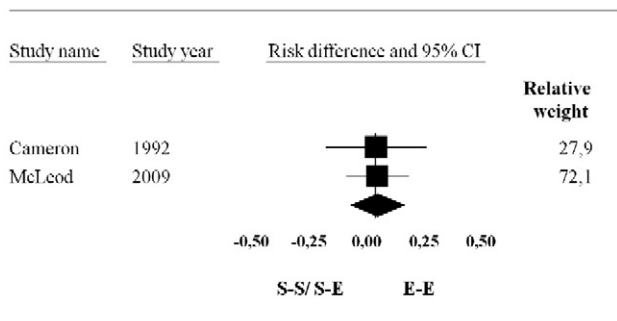


Figure 7 Overall analysis of controlled trials evaluating the effect of side–end anastomosis versus end–end anastomosis on the prevention of clinical recurrence at 1 year follow-up (heterogeneity, $P=0.968$).

Clinical recurrence is the most meaningful endpoint at short-term follow-up. Endoscopy, however, can reveal new epithelial lesions in the first year after surgery, and the severity of these lesions predicts the recurrence of clinical symptoms.²¹ Although surgical recurrence is not as relevant for the short-term follow-up, it definitely is at long-term follow-up.

Studies with mesalamine versus placebo have shown different results. Overall, mesalamine seems to be effective in moderately preventing postoperative clinical recurrence of CD. Endoscopic recurrence, however, is not prevented by mesalamine.

Nitroimidazolic antibiotics (metronidazole or ornidazole) appear to be effective in delaying the clinical recurrence, as well as to prevent endoscopic recurrence at one year follow-up. However, a high percentage of dropouts caused by side-effects was observed. More trials with larger numbers of patients are needed before stating that these drugs are really effective.

Meta-analyses of thiopurines showed significantly better results in preventing postoperative recurrence of CD. Patients treated with thiopurines have a significantly lower likelihood of postoperative clinical recurrence of CD at one and two years follow-up compared with patients treated with placebo or mesalamine. The endoscopic recurrence rate is significantly lower as well with thiopurines than with placebo or mesalamine. Surgical recurrence, analyzed in one RCT, was not different after treatment with azathioprine compared to mesalamine. The study by Hanauer et al. was criticized because the authors used a suboptimal dose of 6-MP, the high dropout rate, and the rate of clinical recurrence was higher than the endoscopic recurrence rate. However, this study had a weight of only 18% in the overall analysis of the four studies included and the impact is therefore small. Interestingly, thiopurines were still effective for the prevention of both clinical and endoscopic recurrence when excluding mesalamine arms (data not shown).

Budesonide and probiotics are not effective and will not prevent postoperative clinical and endoscopic recurrence of CD, as shown in different RCTs.

There is also no evidence that interleukin-10 can prevent endoscopic recurrence of CD. However, there is only one RCT that investigated recurrence of CD at just 12 weeks follow-up. Larger studies with longer follow-up are needed

to get more insight in the role of interleukin-10 in preventing of postoperative recurrence of CD.

In contrast, infliximab is effective in preventing endoscopic recurrence of CD. There is a higher proportion of patients in clinical remission as well, although not statistically significant. More and larger studies are necessary to investigate the results of infliximab at long-term follow-up. In this context, the PREVENT-study, an international, multicenter trial, is being conducted. In this trial, patients who underwent ileocolonic resection will be randomized to treatment with infliximab or placebo every eight weeks through week 200, with the goal to prevent recurrence of the disease after surgical resection. The primary endpoints will be clinical or endoscopic recurrence at 76 weeks.⁴⁸

The length of the resection margin does not influence the postoperative endoscopic and surgical recurrence rates of CD. Therefore, ‘radical’ resections should be avoided and a two centimeter margin of macroscopically normal bowel seems adequate.

Different trials have evaluated different types of anastomosis, but none of them seems to prevent postoperative clinical and endoscopic recurrence of CD. In one trial surgical recurrence was lower after a handsewn anastomosis than after a stapled end-to-end anastomosis at long-term follow-up. However, this trial used a very heterogeneous group of patients with different parts of bowel segments resected.

Although laparoscopic resection seems to have short-term advantage, long-term follow-up did not show any benefit in terms of postoperative clinical, endoscopic and surgical recurrence of CD. Nevertheless, especially in young patients, laparoscopic resection has a cosmetic benefit.

Variations in the definitions of recurrence and in length of follow-up in the different trials are limitations of this study. Most studies have a follow-up period that is too short to be adequate to show any difference in surgical recurrence rates. Variations in inclusion and exclusion criteria regarding disease phenotype (fistulising vs. stenosis) and type of bowel resection may influence the results as well.

Although many drug regimens and surgical techniques have been studied in RCTs, only thiopurines showed really promising results in preventing postoperative clinical as well as endoscopic recurrence of CD. Nitroimidazolic antibiotics are also effective in preventing clinical and endoscopic recurrence at one year follow-up, however, in the long-term follow-up there was no difference anymore in clinical recurrence rate. This might suggest that nitroimidazolic antibiotics are not able to prevent clinical recurrence, but only delay recurrence of disease. Mesalamine decreases the clinical recurrence rate and early endoscopic recurrence, however, does not affect the endoscopic recurrence rate after one year follow-up. Infliximab seems promising in preventing endoscopic recurrence. As surgical recurrence needs a longer follow-up to occur than clinical and endoscopic recurrence, the effect of all these regimens still remains unclear. Therefore, large controlled trials with long-term follow-up are needed to specifically study how different regimens affect or prevent surgical recurrence of CD.

4.1. Practical guidelines

To our opinion, together with the results of randomized clinical trials included in this meta-analysis the following

practical clinical guidelines can be made (Level of Evidence [LoE] and Grade of Recommendation [GoR],^{49,50} Table 3).

- Mesalamine is effective in reducing the risk of postoperative clinical recurrence.
- Maintenance therapy with thiopurines or nitroimidazolic antibiotics are both effective in reducing the risk of postoperative clinical and endoscopic recurrence (LoE 1a, GoR A).
- Infliximab is effective to reduce the risk of postoperative endoscopic recurrence and seems promising in preventing postoperative clinical recurrence, but larger studies are required (LoE 1b, GoR A).
- For the straightforward ileocolic resection for CD a two centimeter resection margin with an anastomosis of sufficient diameter is required (either side-side or end-end) (LoE 1b, GoR A).
- The type of anastomosis does not influence the postoperative recurrence rates (LoE 1a, GoR A).
- Laparoscopic surgery has the preference over open surgery, especially in young patients, because of the cosmetic benefits, but it does not influence the postoperative recurrence rates (LoE 2b, GoR B).

Because recurrence rates are high, postoperative prophylactic treatment is justified. Overall, the clinician must outweigh the risk of each postoperative treatment against the numbers needed to treat to prevent a single recurrence. So, in patients with high-risk of postoperative recurrence a more aggressive treatment is justified. Thiopurines are more effective than mesalamine in preventing postoperative clinical recurrence, as well as endoscopic recurrence. However, they are more harmful as well, and therefore should be given in patients with high-risk of recurrence only. In patients with low risk of recurrence mesalamine should be sufficient or no treatment at all, according to the CD Guidelines by the European Crohn's and Colitis Organisation.⁵¹ The role of the promising anti-TNF agents is still unclear (LoE 5, GoR D).

Conflict of interest

The review presented has no personal, financial or political interests for the authors involved in this study, nor was any

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Table 3 Levels of evidence and grade of recommendation.

Level of evidence	Grading criteria	Grade of recommendation
1a	Systematic reviews of RCTs including meta-analysis	A
1b	Individual RCT with narrow confidence interval	A
1c	All and none studies	B
2a	Systematic review of cohort studies	B
2b	Individual cohort study and low quality RCT	B
2c	Outcome research study	C
3a	Systematic review of case-control studies	C
3b	Individual case-control study	C
4	Case-series, poor quality cohort	C
5	Expert opinion	D

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