ClinicalEvidence

Crohn's disease

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ABSTRACT

INTRODUCTION: Crohn's disease is a chronic condition of the gastrointestinal tract. It is characterised by transmural, granulomatous inflammation that occurs in a discontinuous pattern, with a tendency to form fistulae. The cause is unknown but may depend on interactions between genetic predisposition, environmental triggers, and mucosal immunity. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of medical treatments to induce remission in adults with Crohn's disease? What are the effects of surgical interventions to induce and maintain remission in adults with small-bowel Crohn's disease? What are the effects of surgical interventions to induce remission in adults with colonic Crohn's disease? What are the effects of medical interventions to maintain remission in adults with Crohn's disease; and to maintain remission following surgery? What are the effects of lifestyle interventions to maintain remission in adults with Crohn's disease? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 93 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: aminosalicylates, antibiotics, azathioprine/mercaptopurine, ciclosporin, corticosteroids (oral), enteral nutrition, fish oil, infliximab, methotrexate, probiotics, resection, segmental colectomy, smoking cessation, and strictureplasty.

QUESTIONS

INTERVENTIONS

MEDICAL TREATMENTS TO INDUCE REMISSION IN ADULTS

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unlikely to be beneficial

Likely to be ineffective or harmful

SURGERY TO INDUCE AND MAINTAIN REMISSION IN ADULTS WITH SMALL BOWEL CROHN'S

Likely to be beneficial

Unknown effectiveness

SURGERY TO INDUCE REMISSION IN ADULTS WITH COLONIC CROHN'S

Likely to be beneficial

MEDICAL INTERVENTIONS TO MAINTAIN REMISSION IN ADULTS

Likely to be beneficial

Trade off between benefits and harms

Likely to be ineffective or harmful

Key points

- Crohn's disease is a chronic condition of the gastrointestinal tract.

  It is characterised by transmural, granulomatous inflammation that occurs in a discontinuous pattern, with a tendency to form fistulae.

  The cause is unknown but may depend on interactions between genetic predisposition, environmental triggers, and mucosal immunity.
- First-line treatment to induce remission of acute disease is corticosteroids.

  Budesonide is generally recommended in mild to moderate ileocaecal disease because it is only slightly less effective in inducing remission than prednisolone and has a superior adverse-effect profile.

  Prednisolone or methylprednisolone are generally recommended for severe or more extensive disease because of their superior efficacy.
- Azathioprine and mercaptopurine are effective in inducing remission and healing fistulae in Crohn's disease, provided that at least 17 weeks of treatment are given. Monitoring for myelosuppression is obligatory.

  Aminosalicylates (mesalazine, sulfasalazine) may reduce disease activity, but we don't know which regimen is best to induce remission.

  Methotrexate 25 mg weekly increases remission rates and has a corticosteroid-sparing effect. There is consensus that it is also effective for maintenance.

  Infliximab (a cytokine inhibitor) is effective in inducing and maintaining remission in Crohn's disease, but the long-term adverse-effect profile is unclear; infliximab is therefore generally reserved for treatment of disease that is refractory to treatment with corticosteroids or other immunomodulators.

  Antibiotics and ciclosporin are unlikely to be beneficial in inducing remission.
- Bowel-sparing surgery to induce remission may be preferable to extensive resection, to avoid short-bowel syndrome. Segmental and sub-total colectomy have similar remission rates.
- Laparoscopic resection may reduce postoperative hospital stay, but we don't know whether strictureplasty is effective.
- Azathioprine has been shown to be beneficial in maintaining remission in Crohn's disease, either alone or after surgery, and has a corticosteroid-sparing effect, but it is associated with important adverse effects.

  Ciclosporin, or oral corticosteroids, alone are unlikely to be beneficial in maintaining remission after medical treatment.

  Methotrexate and infliximab may also maintain remission compared with placebo.

  Smoking cessation reduces the risk of relapse, and enteral nutrition may be effective.

  Fish oil and probiotics have not been shown to be effective.
- Mesalazine seems effective in maintaining medically induced remission, but we don't know how effective other aminosalicylates are in maintaining remission.

DEFINITION Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract, characterised by transmural granulomatous inflammation, a discontinuous pattern of distribution, and fistulae. [1] Although any part of the digestive tract from mouth to anus may be affected, Crohn's disease most frequently occurs in the terminal ileum, ileocaecal region, colon, and perianal region. The disease may be further classified into inflammatory, fistulating, and stricturing disease. [2] The symptoms vary but commonly include diarrhoea, abdominal pain, weight loss, blood or mucus in the stool,

perineal pain, discharge, and irritation resulting from perianal fistulae. Extraintestinal manifestations of the disease include arthritis, uveitis, and skin rash. [3] **Diagnosis:** There is no single gold standard for the diagnosis of Crohn's disease. Diagnosis is made by clinical evaluation and a combination of endoscopic, histological, radiological, and biochemical investigations. Internationally accepted criteria for the diagnosis of Crohn's disease have been defined by Lennard-Jones. [4] After exclusion of infection, ischaemia, irradiation, and malignancy as causes for intestinal inflammation, a combination of 3 or more of the following findings on clinical examination, radiological investigation, endoscopy, and histological examination of endoscopic biopsies or excised specimens is considered diagnostic: chronic inflammatory lesions of the oral cavity, pylorus or duodenum, small bowel or anus; a discontinuous disease distribution (areas of abnormal mucosa separated by normal mucosa); transmural inflammation (fissuring ulcer, abscess, or fistula); fibrosis (stricture); lymphoid aggregates or aphthoid ulcers; retention of colonic mucin on biopsy in the presence of active inflammation; and granulomata (of the non-caseating type and not caused by foreign bodies). Further macroscopic findings not included in the Lennard-Jones classification that are considered diagnostic for Crohn's disease include fat wrapping, cobblestoning, and thickening of the intestinal wall. Laboratory findings consistent with Crohn's disease include anaemia, thrombocytosis, raised C-reactive protein levels, and a raised erythrocyte sedimentation rate. [3] It may be difficult to distinguish Crohn's disease from ulcerative colitis, particularly when only the colon is affected. In 10% to 15% of patients originally diagnosed as having Crohn's disease, the diagnosis changes to ulcerative colitis during the first year. [3]

INCIDENCE/ PREVALENCE

Estimates of the incidence of Crohn's disease worldwide vary considerably. In Europe, incidence rates range from 0.7 (Croatia) to 9.8 (Scotland) new cases per 100,000 people per year, whereas in North America these range from 3.6 (California) to 15.6 (Manitoba, Canada). The incidence of Crohn's disease is increasing, with incidence rates in the UK, Italy, Iceland, Finland, and the USA having doubled between 1955 and 1995. [5] Crohn's disease is most commonly diagnosed in late adolescence and early adulthood, but the mean age at diagnosis in North American studies ranges from 33.4 to 45 years. [6] Crohn's disease appears to affect women more commonly than men. In a systematic review of North American cohort studies of Crohn's disease, the percentage of females affected by the disease varied from 48% to 66%, and was above 50% in 9 out of 11 studies. [6]

AETIOLOGY/ RISK FACTORS

The true aetiology of Crohn's disease remains unknown. Current aetiological theories suggest that the disease results from a genetic predisposition, regulatory defects in the gut mucosal immune system, and environmental triggers. [7] Defects in the gut mucosal immune system are mainly related to disordered activity of T cells (a type of white blood cell). Environmental triggers that have been linked with Crohn's disease include smoking, diet (high sugar intake), and the balance of beneficial and harmful bacteria in the gut. [5] Finally, debate has raged since *Mycobacterium avium paratuberculosis* was cultured from intestinal tissue of people with Crohn's disease, with little agreement on whether this bacterium is an infective cause of Crohn's disease. [8]

PROGNOSIS

Crohn's disease is a lifelong condition, with periods of active disease alternating with periods of remission. The disease causes significant disability, with only 75% of sufferers being fully capable of work in the year of diagnosis, and 15% of people unable to work after 5 to 10 years of disease. [2] At least 50% of people with Crohn's disease require surgical treatment during the first 10 years of disease, and approximately 70% to 80% will require surgery during their lifetime. [9] People with Crohn's disease are at higher risk than those without the disease of developing colorectal and small bowel cancer. [10] **Mortality:** Mortality rates among people with Crohn's disease are slightly higher than in those without it. A systematic review of 7 population-based cohort studies found that estimates of standardised mortality ratios were >1 in 6 of the 7 studies, with estimates ranging from 0.72 (95% CI 0.49 to 1.01) to 2.16 (95% CI 1.54 to 2.94). [11] The review also found that mortality rates in Crohn's disease have not changed during the past 40 years.

AIMS OF INTERVENTION

To induce remission, prevent recurrence, allow return to normal activities, and improve quality of life, while minimising the adverse effects of treatment.

OUTCOMES

Remission rate (includes reporting on results for inducing complete remission and also improvement in symptoms that are part of the same spectrum of improvement, as measured using the Crohn's Disease Activity Index, Disease Activity Score, and Harvey–Bradshaw Index, increase in crude remission rates) **Relapse rate** (includes crude rates of clinical relapse, reduction in endoscopic recurrence rates [as measured using Rutgeerts' classification], reduction in radiological recurrence rates) **Re-operation rate**, **Quality of life** (as measured by using the Inflammatory Bowel Disease Questionnaire), **Adverse effects** (corticosteroid-related adverse effects [e.g., moon face, buffalo hump, bruising, striae, central obesity, hirsutism, hypertension], other adverse effects [infection, drug hypersensitivity reactions, impaired renal function, drug-induced lupus syndrome, serum sickness, gastrointestinal bleeding, nausea, vomiting, heartburn, diarrhoea, leukopenia, headache,

back pain, gingival hyperplasia, alopecia], duration of postoperative stay in hospital, death, and postoperative adverse effects [enterocutaneous fistula, gastrointestinal haemorrhage, wound infection, abdominal sepsis, bowel obstruction, anastomotic leak]).

METHODS

Clinical Evidence search and appraisal December 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2009, Embase 1980 to December 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we did an observational harms search for specific harms as highlighted by the contributor, peer reviewer and editor. We searched for prospective and retrospective cohort studies on specific harms for azathioprine and infliximab. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 36). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of medical treatments to induce remission in adults with Crohn's disease?**

OPTION CORTICOSTEROIDS (ORAL) TO INDUCE REMISSION

Remission rate

Methylprednisolone or prednisolone compared with placebo Methylprednisolone and prednisolone (combined analysis) are more effective at increasing remission rates at 15 weeks and longer in people with Crohn's disease (high-quality evidence).

Different methylprednisolone regimens compared with each other We don't know how methylprednisolone tapered over 7 weeks compares with methylprednisolone tapered over 15 weeks at increasing remission rates in people with Crohn's disease (low-quality evidence).

Budesonide compared with placebo Budesonide is more effective at increasing the rate of clinical remission at 12, 24, and 38 weeks in people with ileocolonic Crohn's disease not extending beyond the hepatic flexure (high-quality evidence).

Different budesonide regimens compared with each other We don't know how different dosing regimens of budesonide compare with each other at improving remission rates in people with Crohn's disease (low-quality evidence).

Budesonide compared with methylprednisolone or prednisolone Budesonide and methylprednisolone or prednisolone seem equally effective at increasing remission rates in the shorter term (12 weeks) in people with Crohn's disease, but budesonide seems less effective at increasing remission rates in the longer term (24–28 weeks) in people with Crohn's disease (high-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Methylprednisolone or prednisolone versus placebo:

We found one systematic review (search date 2008, 2 RCTs) comparing corticosteroids versus placebo. [12] The two RCTs included in the pooled data of the review compared methylprednisolone

or prednisolone versus placebo. [13] [14] The review found that corticosteroids significantly increased remission rates at least 15 weeks compared with placebo (2 RCTs, 267 people; 79/132 [60%] with corticosteroids *v* 42/135 [31%] with placebo; RR 1.99, 95% CI 1.51 to 2.64; P <0.00001). [12]

Different methylprednisolone regimens versus each other:
We found no systematic review but found one RCT. [15] It found similar remission rates when methylprednisolone 40 mg daily for 3 weeks was tapered over 7 weeks compared with the same initial methylprednisolone dose tapered over 15 weeks. However, participant numbers were small (1 RCT, 54 people, Crohn's Disease Activity Index [CDAI] 280–380; AR: 22/27 [81%] after a 7-week course *v* 23/27 [85%] after a 15-week course; P value not reported).

Budesonide versus placebo:
We found one systematic review (search date 2008, 2 RCTs, 327 people aged at least 18 years, with ileocolonic Crohn's disease not extending beyond the hepatic flexure). [16] It found that, compared with placebo, budesonide 9 mg daily significantly increased the proportion of people who achieved clinical remission (defined as CDAI <150) at 12 weeks (2 RCTs, 327 people; 75/220 [34%] with budesonide *v* 12/107 [9%] with placebo; RR 2.97, 95% CI 1.67 to 5.29; P = 0.00022), 24 weeks (2 RCTs, 327 people; 94/220 [48%] with budesonide *v* 24/107 [22%] with placebo; RR 1.67, 95% CI 1.12 to 2.47; P = 0.011), and 38 weeks (2 RCTs, 327 people; 109/220 [50%] with budesonide *v* 26/107 [24%] with placebo; RR 1.96, 95% CI 1.19 to 3.23; P = 0.0082). [16]

Different budesonide regimens versus each other:
We found one systematic review (search date 2002, 2 RCTs [17] [18]) [19] and two additional RCTs. [20] [21]

The first RCT identified by the review included 4 arms: budesonide 15 mg, 9 mg, and 3 mg, and placebo, all given in two daily divided doses for 8 weeks. [17] It found that, compared with budesonide 3 mg, budesonide 9 mg significantly increased the proportion of people who achieved remission (see table 1, p 34).

The second RCT identified by the review found no significant difference in the proportion of people who achieved remission at 8 weeks between budesonide 9 mg daily in a single dose, budesonide 9 mg daily in two divided doses, and prednisolone 40 mg daily (reducing to 5 mg/day after 9 weeks) (see table 1, p 34). [18]

The first additional RCT found that similar proportions of people achieved remission at 8 weeks with budesonide 9 mg daily in a single dose and with budesonide 9 mg daily in two divided doses; however, no significance assessment was performed. (see table 1, p 34). [20]

The second additional RCT compared budesonide 6 mg, 9 mg, and 18 mg (each in 3 daily divided doses). It found that, compared with budesonide 6 mg, the 9 mg and 18 mg dosages increased the proportion of people in remission at 6 weeks, although this reached significance only in the 18 mg group (see table 1, p 34). [21]

Budesonide versus methylprednisolone or prednisolone:
We found one systematic review (search date 2008) comparing budesonide 9 mg versus conventional corticosteroids (methylprednisolone and prednisolone; combined analysis). [16] The review found no significant difference between groups for clinical remission (defined as CDAI <150) at 12 weeks (3 RCTs, 397 people; 94/227 [41%] with budesonide *v* 81/170 [48%] with methylprednisolone or prednisolone; RR 0.91, 95% CI 0.72 to 1.13; P = 0.39). However, the review found that significantly fewer people achieved clinical remission at 24 and 38 weeks with budesonide compared with methylprednisolone or prednisolone (24 weeks: 4 RCTs, 430 people; 112/246 [46%] with budesonide *v* 119/184 [67%] with methylprednisolone or prednisolone; RR 0.71, 95% CI 0.59 to 0.85; P = 0.00016; 38 weeks: 8 RCTs, 750 people; 211/406 [52%] with budesonide *v* 210/344 [61%] with methylprednisolone or prednisolone; RR 0.85, 95% CI 0.75 to 0.97; P = 0.012). [16]

Harms:

Methylprednisolone or prednisolone versus placebo:
The review reported that corticosteroids significantly increased the risk of any adverse event compared with placebo (1 RCT, 162 people; 27/85 [32%] with corticosteroids *v* 5/77 [6%] with placebo; RR 4.89, 95% CI 1.98 to 12.07). [12] The review also reported that a significantly larger proportion of people withdrew from the studies owing to adverse effects with corticosteroids compared with placebo (2 RCTs, 267 people; 6/132 [5%] with corticosteroids *v* 1/135 [<1%] with placebo; RR 4.57, 95% CI 0.75 to 27.83). [12]

One additional RCT assessing adverse effects of treatment (119 people randomised to azathioprine, prednisolone, sulfasalazine, or placebo) found that at 17 weeks, compared with placebo, prednisolone significantly increased petechial bleeding, ecchymosis, striae, moon face, acne, hyperten-

sion, and infection (petechial bleeding: 6% with prednisolone *v* 0% with placebo; P <0.05; ecchymosis: 17% with prednisolone *v* 3% with placebo; P <0.01; striae: 6% with prednisolone *v* 0% with placebo; P <0.05; moon face: 47% with prednisolone *v* 3% with placebo; P <0.01; acne: 30% with prednisolone *v* 7% with placebo; P <0.01; hypertension: 13% with prednisolone *v* 0% with placebo; P <0.01; infection: 27% with prednisolone *v* 10% with placebo; P <0.01). [22] It also found that prednisolone significantly reduced nausea and vomiting and anorexia at 17 weeks compared with placebo (nausea and vomiting: 38% with placebo *v* 19% with prednisolone; P <0.05; anorexia: 25% with placebo *v* 8% with prednisolone; P <0.01). [22]

Budesonide versus placebo:
The review reported no significant difference in adverse effects at between budesonide 9 mg daily and placebo (2 RCTs, 332 people; 115/225 [51%] with budesonide *v* 43/107 [40%] with placebo; RR 0.98, 95% CI 0.77 to 1.24; P = 0.84). [16] However, there was a significantly higher incidence of abnormal ACTH test result in the budesonide group (2 RCTs, 327 people; 105/220 [48%] with budesonide *v* 20/107 [19%] with placebo; RR 2.60, 95% CI 1.69 to 4.00; P = 0.000014). [16]

Different budesonide regimens versus each other:
The review [19] and two additional RCTs [20] [21] gave no information on adverse effects.

Budesonide versus methylprednisolone or prednisolone:
The review found that a significantly smaller proportion of people experienced an adverse effect with budesonide compared with conventional corticosteroids (methylprednisolone or prednisolone; combined analysis) (6 RCTs, 703 people; 156/383 [41%] with budesonide *v* 203/320 [63%] with methylprednisolone or prednisolone; RR 0.64, 95% CI 0.54 to 0.76; P <0.00001). [16] Budesonide was also associated with a significantly lower risk of plasma cortisol level below the normal range compared with methylprednisolone or prednisolone (3 RCTs, 401 people; 81/229 [35%] with budesonide *v* 109/172 [63%] with methylprednisolone or prednisolone; RR 0.53, 95% CI 0.43 to 0.65; P <0.0001). There was a significantly lower incidence of an abnormal ACTH test result in the budesonide group (3 RCTs, 244 people; 75/154 [49%] with budesonide *v* 66/90 [73%] with methylprednisolone or prednisolone; RR 0.65, 95% CI 0.55 to 0.78; P <0.0001).

There was no significant difference between groups in the proportion of people who withdrew from the studies because of adverse effects (5 RCTs, 522 people; AR: 6/259 [2%] with budesonide *v* 13/263 [5%] with methylprednisolone or prednisolone; RR 0.57, 95% CI 0.18 to 1.84; P = 0.35). There was no significant difference between groups in the decrease of osteocalcin levels (221 people; WMD –2.49, 95% CI –10.52 to +5.54; P = 0.54).

We found one RCT that examined the effects on bone mineral density (BMD) of budesonide 9 mg daily and prednisolone 40 mg daily. [23] It found no significant difference in BMD between budesonide and prednisolone, although people who received budesonide had smaller reductions in BMD at 2 years (1 RCT, 98 corticosteroid-naïve people aged 20–70 years, CDAI >150; BMD change from baseline: –1.04% with budesonide *v* –3.84% with prednisolone; P = 0.084).

Cohort studies
One large population-based study (47,163 people, 5539 people with Crohn's disease and 41,624 healthy controls) found that those treated with corticosteroids had a higher relative hazard of death than those who did not receive corticosteroids (HR corticosteroid treated versus corticosteroid naive 2.48, 95% CI 1.85 to 3.31). [24] However, the study could not clarify whether this was due to the medication or the underlying disease severity. [24]

A second large cohort study (120,131 people, 8581 people with Crohn's disease and 111,550 controls) found that, compared with people with Crohn's disease who had never received corticosteroids, those receiving corticosteroids were at higher risk of dementia, candidiasis, and sepsis (dementia: HR 1.47, 95% CI 1.03 to 2.10; candidiasis: HR 3.68, 95% CI 2.37 to 5.71; sepsis: HR 1.61, 95% CI 1.27 to 2.04). [25] When adverse events were grouped, corticosteroid treatment was associated with a non-significantly higher risk of cervical dysplasia or human papillomavirus (HR 1.18, 95% CI 0.65 to 2.16), and of opportunistic infections, candidiasis, or tuberculosis (HR 3.20, 95% CI 2.12 to 4.84). There was no difference in the incidence of solid tumours (HR 1.07, 95% CI 0.87 to 1.31). Again, the study could not determine whether the increased risk of adverse events was related to corticosteroid treatment or underlying disease severity. [25]

Comment:

Clinical guide:
In mild to moderate ileocaecal Crohn's disease, budesonide's favourable adverse-effect profile makes it preferable to methylprednisolone or prednisolone. [3] Both RCTs in the systematic review comparing the efficacy of budesonide versus placebo excluded people with disease extending beyond the hepatic flexure. [26] Of the 5 RCTs comparing the efficacy of budesonide versus that of methylprednisolone or prednisolone, only two included people with disease extending beyond

the hepatic flexure. The efficacy of budesonide for colonic Crohn's disease is, therefore, less well established. Consequently, when ileocaecal disease is severe, or where there is extensive small bowel or colonic disease, methylprednisolone or prednisolone are often used because of their superior efficacy compared with budesonide. [3] Although one systematic review found no difference in adverse effects between budesonide and placebo in the short term, all corticosteroids have significant adverse effects with long-term or repeated use, and these must be weighed against the benefits of treatment while taking into account the recipient's wishes. [3] [26] [23]

OPTION AMINOSALICYLATES TO INDUCE REMISSION

Remission rate

Mesalazine compared with placebo Mesalazine seems more effective at reducing Crohn's Disease Activity Index scores at 3 months, but not at increasing remission at 6 weeks or 4 months, in people with Crohn's disease (moderate-quality evidence).

Olsalazine compared with placebo Olsalazine seems less effective at increasing remission rates in people with Crohn's disease (moderate-quality evidence).

Sulfasalazine compared with placebo Sulfasalazine seems more effective at increasing remission rates at 17 weeks in people with Crohn's disease (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

We found 3 systematic reviews and one additional RCT comparing aminosalicylates with placebo to induce remission in people with Crohn's disease. [27] [28] [29] [13]

Mesalazine versus placebo:

The first review (search date 1998) [27] included 3 RCTs comparing mesalazine 4 g daily versus placebo. [30] [31] [32] It found that mesalazine 4 g significantly reduced Crohn's Disease Activity Index (CDAI) compared with placebo at 3 months (3 RCTs, 625 people aged 16–82 years, CDAI 77–300; change in CDAI: –63 with mesalazine *v* –45 with placebo; P = 0.04).

The second and third reviews (search dates 1999 [28] and 2000 [29]) did not include a meta-analysis for the clinical outcomes of interest. They identified 3 further RCTs. [33] [34] [35]

The first RCT found no significant difference in remission rates at 16 weeks between mesalazine 1.5 g daily and placebo (1 RCT, 67 people aged 14–79 years with mild to moderate disease; improvement [subjective clinical and endoscopic]: AR: 12/30 [40%] with mesalazine *v* 11/37 [30%] with placebo; P >0.2). [33]

The second RCT found no significant difference in remission rates at 6 weeks (defined as decrease in Harvey–Bradshaw Index of at least 2 points) between mesalazine 1.5 g daily and placebo (1 RCT, 40 people aged 18–74; AR: 9/20 [45%] with mesalazine *v* 7/20 [35%] with placebo; P >0.10). [34]

Olsalazine versus placebo:

The third RCT (91 people) included in the second and third review found that a significantly smaller proportion of people achieved remission with olsalazine 2 g daily (in 2 divided doses) compared with placebo (remission: 8/46 [17%] with olsalazine *v* 22/45 [49%] with placebo; P <0.03). [35]

Sulfasalazine versus placebo:

The additional RCT, which found that sulfasalazine (1 g/day/15 kg body weight) significantly increased remission rates (defined as CDAI <150) compared with placebo at 17 weeks after the start of treatment (1 RCT, 159 people randomised to placebo [mean age 33.7 years] or sulfasalazine [mean age 29.6 years], matched for disease severity, body weight, prior abdominal surgery, sex, and race; AR: 20/77 [26%] with placebo *v* 28/74 [38%] with sulfasalazine; P = 0.0175). [13]

Harms:

We found one systematic review (search date 2006) specifically addressing the question of aminosalicylates causing nephrotoxicity in people with inflammatory bowel disease. [36] It found that, in 2671 people with 3070 patient-years of follow-up, the mean annual nephrotoxicity rate was 0.26% per patient-year (95% CI 0.13% per patient-year to 0.5% per patient-year). [36]

Mesalazine versus placebo:

We found 5 RCTs reporting on adverse effects. [22] [30] [33] [34] [35] One RCT found that proportionately more people taking mesalazine than placebo had adverse effects (AR: 11/30 [37%] with mesalazine *v* 12/37 [32%] with placebo; significance not reported). [33] Another RCT found that 3 people stopped taking mesalazine because of abdominal distension and pain (1/20 [5%]) or malaise

(2/20 [10%]) with mesalazine, compared with one person withdrawing from the placebo group because of nausea (1/20 [5%]; significance not reported). [34] One RCT found that mesalazine (1 g, 2 g, or 4 g) significantly increased the proportion of people with adverse effects compared with placebo (17/80 [21%] with mesalazine 1 g *v* 23/75 [31%] with mesalazine 2 g *v* 20/75 [27%] with mesalazine 4 g *v* 15/80 [19%] with placebo; significance not reported). [30]

Olsalazine versus placebo:
Another RCT reported a significantly higher rate of withdrawals caused by adverse effects with olsalazine (diarrhoea, vomiting, pain, and anorexia) compared with placebo (91 people; AR for withdrawal: 15/46 [33%] with olsalazine *v* 3/45 [7%] with placebo; P value not reported). [35]

Sulfasalazine versus placebo:
The final RCT did not report on adverse effects with mesalazine or sulfasalazine. [13] A further RCT found no significant difference in adverse effects between sulfasalazine and placebo when used for induction of remission (reported as not significant; P value not reported). [22] The most commonly reported adverse effects were headache, nausea, and diarrhoea.

Comment:

Clinical guide:
Aminosalicylates may be used for induction of remission in ambulatory people with mild to moderate disease who can tolerate oral intake. However, evidence suggests that benefit over placebo is marginal, and previous response to aminosalicylates should be taken into account when deciding whether to prescribe these drugs. Treatment decisions are often based on the site of disease and whether it is active, but there are not enough participant numbers in the RCTs to confirm this approach.

OPTION ANTIBIOTICS TO INDUCE REMISSION

Remission rate
Broad-spectrum antibiotics compared with placebo Broad-spectrum antibiotics may be more effective at improving clinical symptoms of Crohn's disease. However, these results should be interpreted with caution, as they came from a review of low quality, which pooled data from studies with different antibiotic regimes, and used a fixed-effects model (very low-quality evidence).

Metronidazole compared with sulfasalazine Metronidazole may be no more effective at reducing disease activity scores at 4 months in people with Crohn's disease (low-quality evidence).

Rifaximin compared with placebo Rifaximin may be no more effective at increasing remission rates at 12 weeks in people with Crohn's disease (low-quality evidence).

Ciprofloxacin plus metronidazole compared with methylprednisolone Ciprofloxacin plus metronidazole may be no more effective at increasing rates of remission at 12 weeks in people with ileal, colonic, or ileal and colonic disease Crohn's disease (low-quality evidence).

Ciprofloxacin plus metronidazole plus budesonide compared with budesonide alone Adding ciprofloxacin plus metronidazole to budesonide seems no more effective than budesonide alone at increasing rates of remission at 8 weeks in people with ileal, colonic, or ileal and colonic disease to mid-transverse colon Crohn's disease (moderate-quality evidence).

Clofazimine plus prednisolone compared with placebo plus prednisolone Clofazimine plus prednisolone may be no more effective at increasing remission rates at 3 months in people with Crohn's disease (low-quality evidence).

Clarithromycin plus rifabutin plus clofazimine plus prednisolone compared with placebo plus prednisolone Clarithromycin plus rifabutin plus clofazimine plus prednisolone is more effective at increasing remission rates at 16 weeks in people with Crohn's disease; however, this benefit is not sustained in long-term follow-up 16 to 156 weeks (high-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Broad-spectrum antibiotics versus placebo:
We found one systematic review (search date 2006, 6 RCTs, 804 people with Crohn's disease) comparing broad-spectrum antibiotics (including: metronidazole alone [135 people], ciprofloxacin alone [128 people], trimethoprim–sulfamethoxazole [co-trimoxazole; TMP-SMX] alone [46 people], metronidazole plus ciprofloxacin [66 people], TMP-SMX plus metronidazole [56 people]), and placebo (373 people) versus placebo. [37] Concomitant treatment included salazosulfapyridine, prednisolone, budesonide, mesalazine, 6-mercaptopurine, methotrexate, azathioprine, and infliximab. [37] The review found that broad-spectrum antibiotics significantly improved the clinical symptoms of Crohn's disease compared with placebo (230/431 [53%] with antibiotics *v* 134/373 [36%] with

placebo; OR 2.25, 95% CI, 1.67 to 3.03; P <0.001). However, these results should be interpreted with caution, as the review was of low quality, pooled data from studies with different antibiotic regimes, and used a fixed-effects model. [37]

Metronidazole versus placebo:
We found one RCT, [38] which was too small to meet our quality criteria (see Methods) and has been excluded.

Metronidazole versus sulfasalazine:
One RCT (78 people, Crohn's Disease Activity Index [CDAI] >150) compared metronidazole versus sulfasalazine. [39] After 4 months of treatment it found no significant difference in response rates between the two drugs (reduction in CDAI [mean ± standard error]: from 262 ± 13 to 113 ± 16 with metronidazole *v* from 257 ± 10 to 120 ± 16 with sulfasalazine; reported as not significant). Participants did not receive any other concomitant treatment.

Ciprofloxacin versus placebo or other treatments:
We found no RCTs comparing ciprofloxacin versus placebo or other treatments.

Rifaximin versus placebo:
We found one RCT (83 people with ileal or colonic disease, CDAI 200–400), which was a 3-arm trial comparing rifaximin 800 mg twice daily versus rifaximin 800 mg once daily plus placebo versus placebo alone. [40] It found no significant difference in remission rates (defined as CDAI <150) after 12 weeks of treatment between rifaximin and placebo (AR: 14/27 [52%] with rifaximin 800 mg twice daily *v* 8/25 [32%] with rifaximin 800 mg once daily plus placebo *v* 9/27 [33%] with placebo; P value not reported; reported as not significant). [40]

Ciprofloxacin plus metronidazole versus methylprednisolone:
We found no systematic review but found one RCT. [41] The RCT (41 people aged 18–75 years, CDAI >200; and with ileal, colonic, or ileal and colonic disease) compared antibiotics versus corticosteroids. [41] It found no difference after 12 weeks in remission rates (defined as CDAI <150) between people receiving ciprofloxacin 500 mg twice daily plus metronidazole 250 mg 4 times daily and those receiving a tapering regimen of methylprednisolone 0.7 to 1 mg/kg (AR: 10/22 [46%] with antibiotics *v* 12/19 [63%] with methylprednisolone; reported as not significant; P value not reported).

Ciprofloxacin plus metronidazole plus budesonide versus budesonide alone:
We found no systematic review but found one RCT. [42] The RCT (130 people aged at least 14 years, CDAI 200–400, ileal or colonic disease to mid-transverse colon) compared antibiotics (ciprofloxacin plus metronidazole, both 500 mg twice daily) versus placebo, both in addition to oral budesonide 9 mg once daily. [42] It found no significant difference in remission rates (defined as CDAI <150) at 8 weeks between antibiotics and placebo (AR: 21/64 [33%] with antibiotics *v* 25/66 [38%] with placebo; P = 0.55). Antibiotics increased remission rates compared with placebo in a subgroup of people with colonic disease, but the increase was not significant (33 people with ileocolonic disease; AR: 9/17 [53%] with antibiotics *v* 4/16 [25%] with placebo; P = 0.10).

Clofazimine plus prednisolone versus placebo plus prednisolone:
We found no systematic review but found one RCT. [43] The RCT (49 people aged 14–46 years with ileal and colonic disease) found no significant difference in remission rates after 3 months between people treated with clofazimine 100 mg daily and placebo, both in combination with a reducing regimen of prednisolone 45 mg (Disease Activity Score reduction: from 10 ± 4.4 to 3.1 ± 3.4 with clofazimine *v* from 10 ± 4 to 3.6 ± 3.7 with placebo; reported as not significant; P value not reported). [43]

Clarithromycin plus rifabutin plus clofazimine plus prednisolone versus placebo plus prednisolone:
We found no systematic review but found one RCT. [44] The RCT (213 people with ileal and colonic Crohn's disease, CDAI at least 200) compared clarithromycin (750 mg/day) plus rifabutin (450 mg/day) plus clofazimine (50 mg/day) versus placebo to assess the efficacy of antibiotics specifically for the eradication of *Mycobacterium avium* subspecies *paratuberculosis* for 2 years, with a further 1 year of follow-up to assess maintenance of remission (CDAI <150). [44] All participants were started on a tapering course of prednisolone (40 mg) at randomisation. The RCT found that antibiotics significantly increased rates of remission at 16 weeks (67/102 [66%] with antibiotics *v* 55/111 [50%] with placebo; OR 0.51, 95% CI 0.30 to 0.90; P = 0.02; NNT 6). However, the RCT found that this benefit was not sustained, with no significant difference in relapse rates during weeks 16 to 52, 53 to 104, and 105-156 (weeks 16–52: 26/67 [39%] with antibiotics *v* 31/51 [56%] with placebo; P = 0.054; weeks 53–104: 11/42 [26%] with antibiotics *v* 12/28 [43%] with placebo; P = 0.14; weeks 105–156: 20/34 [59%] with antibiotics *v* 10/20 [50%] with placebo; P = 0.54). [44]

Harms:

Broad-spectrum antibiotics versus placebo:
The review gave no information on adverse effects. [37]

Metronidazole versus placebo:
We found one RCT, [38] which was too small to meet our quality criteria (see Methods) and has been excluded.

Metronidazole versus sulfasalazine:
The RCT found that, after treatment with metronidazole 400 mg twice daily for 4 months, 40 participants experienced the following adverse effects: nausea (38%), fatigue (30%), anorexia (25%), itching (20%), rash (13%), and paraesthesia (5%). [39] The incidence of the same adverse effects was similar when people crossed over to sulfasalazine. No participants withdrew from the trial because of adverse effects.

Ciprofloxacin versus placebo or other treatments:
We found no RCTs.

Rifaximin versus placebo:
The most common adverse events reported by the RCT (see comment below) included gastrointestinal disorders, infections and infestations, and skin and subcutaneous tissue disorders (number of people experiencing adverse events: 12/27 [44%] with rifaximin 800 mg twice daily *v* 10/25 [40%] with rifaximin 800 mg once daily plus placebo *v* 16/27 [50%] with placebo alone; gastrointestinal disorders: 5/27 [19%] with rifaximin 800 mg twice daily *v* 17/27 [63%] with rifaximin 800 mg once daily plus placebo *v* 16/27 [59%] with placebo alone; infections and infestations: 2/27 [7%] with rifaximin 800 mg twice daily *v* 2/25 [8%] with rifaximin 800 mg once daily plus placebo *v* 6/27 [22%] with placebo alone; skin and subcutaneous tissue disorders: 4/27 [15%] with rifaximin 800 mg twice daily *v* 1/25 [4%] with rifaximin 800 mg once daily plus placebo *v* 2/27 [7%] with placebo alone; P values and significance not reported). Five people withdrew because of adverse events (3/27 [11%] with rifaximin 800 mg twice daily *v* 0/25 [0%] with rifaximin 800 mg once daily plus placebo *v* 2/27 [7%] with placebo alone; P value and significance not reported). [40]

Ciprofloxacin plus metronidazole versus methylprednisolone:
The RCT reported the following adverse effects with ciprofloxacin plus metronidazole (both 500 mg/day) in 22 people after 8 weeks: nausea (32%), metallic taste (32%), and heartburn (23%). [41] Six people (27%) withdrew from the trial because of adverse effects. By comparison, 79% of people in the corticosteroid group had adverse effects, and one person withdrew from the trial.

Ciprofloxacin plus metronidazole plus budesonide versus budesonide alone:
The RCT, which administered the same antibiotic combination (ciprofloxacin plus metronidazole, both 500 mg twice daily) to 66 people, plus budesonide 9 mg daily for 12 weeks, reported a significantly higher proportion of the following non corticosteroid-related adverse effects in people in the antibiotic group compared with the placebo group: taste disturbance, dizziness, diarrhoea, vaginitis, and oral candidiasis (taste disturbance: 27% with ciprofloxacin plus metronidazole *v* 0% with placebo; dizziness: 21% with ciprofloxacin plus metronidazole *v* 6% with placebo; diarrhoea: 20% with ciprofloxacin plus metronidazole *v* 6% with placebo; vaginitis: 17% with ciprofloxacin plus metronidazole *v* 0% with placebo; oral candidiasis: 14% with ciprofloxacin plus metronidazole *v* 0% with placebo; P <0.05 for all comparisons). [42] Thirteen people (20%) stopped antibiotic treatment because of adverse effects compared with none in the placebo group (P <0.001).

Clofazimine plus prednisolone versus placebo plus prednisolone:
The RCT reported that, of 25 people treated with clofazimine 100 mg plus prednisolone for 12 weeks, 12 (48%) developed skin pigmentation and 3 (12%) developed rash; in comparison, 5 people in the placebo group (21%) developed skin pigmentation and none developed rash (P value not reported). [43]

Clarithromycin plus rifabutin plus clofazimine plus prednisolone versus placebo plus prednisolone:
The RCT reported no difference in withdrawal rates caused by adverse effects (8 people in each group, including 5 each in the induction phase). [44] The RCT reported that several adverse effects were more common in the antibiotic group than in the placebo group during the induction phase: abnormal liver function (2.0% with antibiotics *v* 0.3% with placebo), vaginal candidiasis (4% with antibiotics *v* 1% with placebo), abdominal distention (3% with antibiotics *v* 1% with placebo), myalgia (2.0% with antibiotics *v* 0.3% with placebo), and urine discoloration (3.0% with antibiotics *v* 0.3% with placebo). Between weeks 17 and 52, arthralgia (4% with antibiotics *v* 1% with placebo) and tooth discoloration (2.0% with antibiotics *v* 0.2% with placebo) were the only adverse effects more common in those given antibiotics than in those given placebo. The number needed to harm (NNH) during the induction phase was 77; calculated over the whole study period it was 40. [44]

Comment:

Rifaximin versus placebo:
Two people in the placebo group experienced adverse events (severe nausea and eye oedema), which the investigators ascribed to the study medication. The substance used as placebo was not described accurately, thus it is possible that genuine differences between the adverse-effect profiles of rifaximin and placebo were masked by the use as placebo of a non-inert substance. [40]

Clinical guide:
At present there is little evidence of benefit from antibiotics (including antimycobacterial treatment), either as a substitute for or as an adjunct to corticosteroids or mesalazine, for inducing remission in ileal or colonic Crohn's disease. However, ciprofloxacin and metronidazole are indicated by general consensus in the treatment of septic complications of Crohn's disease, symptoms attributable to bacterial overgrowth, and perineal disease. [3]

OPTION AZATHIOPRINE OR MERCAPTOPURINE TO INDUCE REMISSION

Remission rate
Compared with placebo Azathioprine or mercaptopurine seem more effective at increasing remission rates at 17 weeks in people with Crohn's disease (moderate-quality evidence).

Note
Azathioprine and mercaptopurine have been associated with pancreatitis, leukopenia, nausea, allergy, and infection.

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Azathioprine/mercaptopurine versus placebo:
We found one systematic review (search date 1997, 8 RCTs, 425 people, age range not reported, with active disease [Crohn's Disease Activity Index {CDAI} >150 or Harvey–Bradshaw Index 7 or greater]). [46] It found that, compared with placebo, azathioprine or mercaptopurine significantly increased remission rates (remission was defined as either CDAI <150 or Harvey–Bradshaw Index 3 or less; AR: 113/209 [54%] with azathioprine or mercaptopurine *v* 72/216 [33%] with placebo; OR 2.36, 95% CI 1.57 to 3.53; P <0.001). The review found that azathioprine or mercaptopurine were more effective at inducing remission when the duration of treatment was at least 17 weeks (treatment at least 17 weeks: OR 2.51, 95% CI 1.63 to 3.88; treatment <17 weeks: OR 1.56, 95% CI 0.52 to 4.69).

Harms:

Azathioprine or mercaptopurine versus placebo:
The systematic review reported adverse effects severe enough to cause withdrawal in proportionately more people with azathioprine or mercaptopurine than with placebo (AR: 20/214 [9%] with azathioprine or mercaptopurine *v* 5/215 [2%] with placebo; OR 3.01, 95% CI 1.30 to 6.96). [46] Common adverse effects included pancreatitis, leukopenia, nausea, allergy, and infection (absolute numbers not reported).

We found one additional study reporting adverse effects from azathioprine or mercaptopurine (1 cohort study, 50 people, aged 19–71 years). [47] Adverse effects occurred in 15/50 (30%) people; 3 people required hospitalisation (pancreatitis, high fever, pneumonia), two people developed leukopenia that resolved on discontinuation of treatment, and 4 people had nausea. Most adverse effects occurred at doses of at least 100 mg/kg.

One large population-based study (47,163 people, 5539 people with Crohn's disease and 41,624 healthy controls) found that there was no difference in the relative hazard of death between those people with Crohn's disease who received thiopurines and those who did not (HR thiopurine-treated *v* thiopurine naive 0.83, 95% CI 0.37 to 1.86). [24]

Comment: None.

OPTION METHOTREXATE TO INDUCE REMISSION

Remission rate
Compared with placebo Intramuscular methotrexate seems more effective at inducing remission at 16 weeks in people with chronic active Crohn's disease (moderate-quality evidence).

Quality of life
Compared with placebo Intramuscular methotrexate seems more effective at improving quality-of-life scores at 16 weeks in people with chronic active Crohn's disease (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Methotrexate versus placebo:
We found one systematic review (search date 2004), which did not include a meta-analysis for the clinical outcomes of interest. [48] It identified one RCT that met our inclusion criteria. [49] The RCT found that, compared with placebo, intramuscular methotrexate 25 mg weekly achieved higher rates of remission at 16 weeks (1 RCT, 141 people, mean age 35 years, corticosteroid dependent [>12.5 mg/day prednisolone]; AR: 37/94 [39%] for methotrexate *v* 9/47 [19%] with placebo; P = 0.025; RR 1.95, 95% CI 1.09 to 3.48; NNT 5). Quality of life at 16 weeks was found to be greater (as measured using the Inflammatory Bowel Disease Questionnaire) in the methotrexate group compared with placebo (169 ± 4 for methotrexate *v* 151 ± 6 for placebo; P <0.002).

Harms:

Methotrexate versus placebo:
The RCT found that proportionately more people withdrew from treatment because of adverse effects with methotrexate than with placebo (AR: 16/94 [17%] with methotrexate *v* 1/47 [2%] with placebo; P = 0.012). Adverse effects with methotrexate resulting in withdrawal were: abnormal liver function tests (7/94 [7%]), nausea (6/94 [6%]), skin rash (1/94 [1%]), pneumonia (1/94 [1%]), and optic neuritis (1/94 [1%]). [49]

Comment:

Clinical guide:
Intramuscular methotrexate 25 mg weekly may be used for induction of remission in refractory Crohn's disease. Subcutaneous injection may be used as an alternative, with fewer injection site reactions and greater comfort. Caution must be exercised in people with known hepatic impairment. Regular liver-function testing and monitoring of haematological parameters is obligatory. Methotrexate is contraindicated in women who may become pregnant and in men who may father a child during and for 3 months after administration.

OPTION INFLIXIMAB TO INDUCE REMISSION

Remission rate
Compared with placebo Infliximab seems more effective at increasing remission rates at 4 weeks in people with moderate to severe Crohn's disease (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Infliximab versus placebo:
We found two systematic reviews (search dates 2003 [50] and 2001; [51] neither performed a meta-analysis), which included one RCT that met our inclusion criteria. [52] The RCT found that single-dose infliximab significantly increased remission rates compared with placebo at 4 weeks, in people with moderate to severe Crohn's disease refractory to aminosalicylates, corticosteroids, and immunomodulators (1 RCT, 181 adults with Crohn's Disease Activity Index 220–400, matched for age, sex, disease duration, ileal and colonic disease distribution, and concomitant medical treatment; AR: 27/83 [33%] with infliximab *v* 1/25 [4%] with placebo; RR 8.1, 95% CI 1.2 to 56.9; NNT 4, 95% CI 1.6 to 10.1). Participants received infliximab doses of 5 mg/kg (27 people), 10 mg/kg (28 people), or 20 mg/kg (28 people). No dose response was seen at 4 weeks, and the authors of the RCT concluded that 5 mg/kg was therefore the most appropriate dose.

Harms:

Infliximab versus placebo:
The RCT found no significant difference in the incidence of adverse effects over a period of 12 weeks after placebo or a single infusion of infliximab (5 mg/kg, 10 mg/kg, or 20 mg/kg) for the induction of remission in Crohn's disease. [52] For long-term adverse effects see harms of infliximab under question on medical interventions to maintain remission in adults with Crohn's disease, p 18 .

In 2008, the US Food and Drug Administration (FDA) issued a drug safety alert on the risk of opportunistic fungal infections associated with TNF-alpha blockers (tumour necrosis factor alpha-blockers). Twelve of 240 cases of fungal infections in people treated with TNF-alpha blockers (including infliximab) reported in the USA were fatal. As this review concerns itself exclusively with adults over 18 years of age, the alert regarding children and adolescents is probably irrelevant (http://www.fda.gov).

Comment:

Clinical guide:
Infliximab is indicated in the treatment of moderate or severe Crohn's disease that is refractory to treatment with corticosteroids and other immunomodulators. [3] The drug's high cost means that the decision to prescribe infliximab may be influenced by national guidelines. Long-term studies have shown that the presence of sepsis is an absolute contraindication to infliximab treatment, because it may lead to overwhelming septicaemia. [53] Infliximab also increases 4- or 5-fold the risk of contracting tuberculosis, and people should be appropriately screened. [3] Infliximab should be used with caution in people with congestive heart failure because it may exacerbate the condition.

[54] [53] The long-term safety profile of the drug remains to be determined; it is unclear whether infliximab is associated with an increased risk of malignancy, and whether people should be monitored for this.

OPTION CICLOSPORIN TO INDUCE REMISSION

Remission rate
Compared with placebo Ciclosporin may be no more effective at increasing rates of remission in people with Crohn's disease (low-quality evidence).

Note
Adverse effects included paraesthesia, hypertrichosis, dyspepsia, hypertension, rash, vertigo, diarrhoea, headaches, mouth ulcers, ocular photosensitivity, nausea, vomiting, epigastric pain, tremor, back pain, weight increase, gingival hyperplasia, and impaired renal function.

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Ciclosporin versus placebo:
We found one systematic review (search date 2004, 4 RCTs). [55]

The review found that ciclosporin (5 mg/kg/day) did not significantly increase rates of remission after 16 weeks compared with placebo (2 RCTs, [56] [57] 176 people aged 18–70 years, remission defined as Crohn's Disease Activity Index (CDAI) >150 or requiring continuous corticosteroid treatment: 25/85 [29%] with ciclosporin *v* 16/91 [18%] with placebo; OR 1.96, 95% CI 0.97 to 3.93; P = 0.06). [55]

The third included RCT compared ciclosporin 5 mg/kg daily versus placebo in people taking prednisolone. It found no significant difference between groups in rates of clinical improvement (defined as freedom from symptoms or clinically significant improvement plus successful withdrawal or reduction below initial dose of prednisolone) after 12 weeks (1 RCT, 146 people; 26/72 [36%] with ciclosporin *v* 32/74 [43%] with placebo; OR 0.74, 95% CI 0.38 to 1.44; P = 0.4). [58]

The fourth included RCT compared ciclosporin (5−7.5 mg/kg/day) versus placebo. Although it found that a significantly greater proportion of people had clinical improvement after 12 weeks with ciclosporin, assessed using a non-validated modified clinical grading scale (71 people; 22/37 [60%] with ciclosporin *v* 11/34 [32%] with placebo; OR 3.07, 95% CI 1.16 to 8.11; P <0.02), it found no significant difference in median CDAI values between groups after 12 weeks (71 people; median CDAI value: 227 with ciclosporin *v* 245 with placebo; weighted mean difference –18.0, 95% CI –82.3 to +46.3). [59]

Harms:

Ciclosporin versus placebo:
The systematic review reported that a greater proportion of people had adverse effects severe enough to cause withdrawal with ciclosporin compared with placebo (124/198 [63%] with ciclosporin *v* 16/201 [8%] with placebo; OR 16.63, 95% CI 10.65 to 25.95; P <0.00001). [55] Adverse effects included paraesthesia, hypertrichosis, dyspepsia, hypertension, rash, vertigo, diarrhoea, headaches, mouth ulcers, ocular photosensitivity, nausea, vomiting, epigastric pain, tremor, back pain, weight increase, gingival hyperplasia, impaired renal function (3 with ciclosporin *v* 0 with placebo), and increases in serum creatinine level (numbers not reported). [55]

Comment: None.

QUESTION What are the effects of surgical interventions to induce and maintain remission in adults with small bowel Crohn's disease?

OPTION STRICTUREPLASTY

Relapse rate
Compared with resection We don't know how strictureplasty and resection compare at reducing medical and surgical recurrence at 39 to 85 months (very low-quality evidence).

Finney procedure compared with Heineke–Mikulicz procedure The Finney procedure may be more effective at reducing the risk of recurrence at 30 months (very low-quality evidence).

Reoperation rates
Finney procedure compared with Heineke–Mikulicz procedure The Finney procedure may be more effective at reducing the risk of reoperation rates at 30 months (very low-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Strictureplasty versus resection:
We found one systematic review (search date 2006, 7 non-randomised studies, 688 people, mean follow-up in individual studies ranging from 39 to 85 months) comparing strictureplasty (311 people) versus resection with or without strictureplasty (377 people). [60] The review found no significant difference in recurrence rates (medical or surgical) after strictureplasty alone compared with resection (medical recurrence; 12% with strictureplasty *v* 18% with resection; OR 0.80, 95% CI 0.09 to 6.85; P = 0.84; absolute numbers not reported; surgical recurrence; 38% with strictureplasty *v* 31% with resection; OR 1.36, 95% CI 0.96 to 1.93; P = 0.09; absolute numbers not reported). [60]

Finney versus Heineke–Mikulicz procedure:
We found one low-quality systematic review (search date 1999, 15 non-randomised retrospective studies, 506 people [aged 24–43 years] undergoing 1825 strictureplasties). [61] It found that, at 30 months, Finney strictureplasty significantly reduced recurrence and reoperation rates compared with Heineke–Mikulicz (recurrence: 0% recurrence with Finney *v* 32% with Heineke–Mikulicz; P = 0.008; reoperation rates: 0% reoperations with Finney *v* 23% with Heineke–Mikulicz; P = 0.005; absolute numbers not reported). The review gave no data on sample size for the outcome of interest.

Harms:

Strictureplasty versus resection:
The review found no significant difference in complication rates after strictureplasty alone compared with resection (overall early postoperative complications: 17/134 [13%] with strictureplasty *v* 36/188 [19%] with resection; OR 0.57, 95% CI 0.30 to 1.09; P = 0.09; bowel obstruction: 2% with strictureplasty *v* 5% with resection; OR 0.49, 95% CI 0.11 to 2.15; P = 0.34; absolute numbers not reported; intestinal haemorrhage: 3% with strictureplasty *v* 7% with resection; OR 0.51, 95% CI 0.13 to 2.00; P = 0.33; absolute numbers not reported; septic complications: 8% with strictureplasty *v* 11% with resection; OR 0.67, 95% CI 0.27 to 1.67; P = 0.39; absolute numbers not reported). [60] There was also no significant difference in overall complications (OR 0.60, 95% CI 0.31 to 1.16; P = 0.13; absolute numbers not reported). Postoperative mortality was 2/311 (0.6%) in the strictureplasty group and 1/377 (0.2%) in the resection group. [60]

We found one systematic review (search date 2005, 21 non-randomised trials, 1112 people who underwent 3259 strictureplasties for Crohn's disease), which assessed postoperative complications for strictureplasty. [62] The types of procedure assessed included Heineke–Mikulicz (81%), Finney (10%), and side-to-side isoperistaltic (5%). The sites of strictureplasty were jejunum, ileum, or jejunum and ileum (94%), previous anastomosis (4%), duodenum (1%), and colon (1%). The review found that 142/1057 (13%) people included in these studies developed postoperative complications. Septic complications (defined as anastomotic leak, fistula, and abscess) occurred in 39/1057 (4%) people of whom 17/39 (44%) required laparotomy for the sepsis. The review reported that other postoperative complications included haemorrhage (35/1057 [3%]), ileus (24/1057 [2%]), wound infection (19/1057 [2%]), and bowel obstruction (11/1057 [1%]). [62]

Finney versus Heineke–Mikulicz procedure:
The review reported postoperative complications in 66/506 (13%) people. [61] Adverse effects were enterocutaneous fistula (23%), gastrointestinal haemorrhage (11%), wound infection (8%), abdominal sepsis (5%), bowel obstruction (4%), and anastomotic leak (3%). Overall recurrence was 26%. The review did not compare Finney versus Heineke–Mikulicz strictureplasty when assessing complications.

Comment:

Clinical guide:
Strictureplasty is generally considered a safe and effective procedure for small bowel stenosis in Crohn's disease.

OPTION LIMITED VERSUS EXTENDED RESECTION

Relapse rate
Compared with extended resection Limited resection may be as effective as extended resection at reducing surgical recurrence rates in people with Crohn's disease (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Limited versus extended resection:
We identified one RCT (131 people, median age 33.2 years, median follow-up 55.7 months, indications for surgery: bowel obstruction 42/131 [32%], perforating disease 29/131 [22%], non-perforating and perforating disease 34/131 [26%], other disease 26/131 [20%]). [63] It found no evidence that extended resection margins reduced surgical recurrence rates (AR: 10/56 [18%] for extended resection *v* 19/75 [25%] for limited resection; P = 0.38).

Harms:

Limited versus extended resection:
The RCT did not compare limited versus extended resection when assessing harms. [63] A total of 20/131 (15%) people experienced an adverse event; of whom 9/131 (7%) experienced postoperative ileus, 6/131 (5%) developed a wound infection, 2/131 (2%) required blood transfusion, 1/131 (1%) developed intra-abdominal sepsis, 1/131 (1%) developed pneumonia, and 1/131 (1%) developed pyrexia with no focal sepsis.

Comment:

Clinical guide:
Bowel-sparing surgery with mini-resections is preferable to extensive resection in Crohn's disease in an attempt to avoid the short-bowel syndrome.

OPTION LAPAROSCOPIC VERSUS OPEN ILEOCAECAL RESECTION

We found no clinically important results from RCTs about laparoscopic versus open ileocaecal resection in people with Crohn's disease.

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Laparoscopic versus open ileocaecal resection:
We found 4 systematic reviews (search dates 2004, [64] 2005, [65] and 2006 [66] [67]), which did not report on the effects of surgery on remission rates in Crohn's disease.

Harms:

We found 4 systematic reviews (search dates 2004, [64] 2005, [65] and 2006 [66] [67]). The third review [66] included studies on colonic resections for Crohn's disease, and the fourth review [67] did not include any outcomes of interest for this review, so we have reported results from the second review, [65] as the most recent, inclusive, highest-quality review.

The review [65] found that laparoscopic surgery significantly reduced length of postoperative hospital stay compared with open ileocaecal resection (1 RCT, 6 prospective non-randomised, and 8 retrospective studies; 783 people, follow-up 1−63 years: WMD –2.97 days, 95% CI –3.89 days to –2.04 days; P <0.001). [65] It also found that time to recovery of enteric function was significantly shorter after laparoscopic surgery compared with open surgery (time to first flatus, 4 studies, 191 people; WMD –0.68 days, 95% CI –1.2 days to –0.17 days; P = 0.009; time to first bowel movement, 5 studies, 253 people; WMD –0.58 days, 95% CI –1.12 days to –0.03 days; P = 0.04). [65] The review found no significant difference between groups in postoperative adverse effects (anastomotic leak: 7 studies, 406 people; OR 1.33, 95% CI 0.4 to 4.43; P = 0.64; wound infection: 10 studies, 525 people; OR 1.25, 95% CI 0.57 to 2.77; P = 0.57; chest infection: 5 studies, 329 people; OR 0.60, 95% CI 0.15 to 2.43; P = 0.48; intra-abdominal abscess: 6 studies, 254 people; OR 0.83, 95% CI 0.22 to 3.17; P = 0.79). [65]

Comment:

Clinical guide:
There is evidence to suggest that laparoscopic ileocaecal resection for Crohn's disease is equivalent to open surgery in terms of clinical outcomes. [68] The main benefit of laparoscopic surgery is an earlier postoperative recovery. The indications for laparoscopic versus open surgery remain undefined.

QUESTION What are the effects of surgical interventions to induce remission in adults with colonic Crohn's disease?

OPTION SEGMENTAL VERSUS SUB-TOTAL COLECTOMY

Relapse rate
Compared with sub-total colectomy Segmental colectomy may be as effective at reducing the risk of recurrence; however, recurrence may occur earlier with segmental colectomy (very low-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Segmental versus sub-total colectomy:
We found one systematic review (search date 2005). [69] It found no significant difference in recurrence rates between people who had a segmental colectomy and those who had a sub-total colectomy (5 non-randomised studies, 248 people, aged 11–78 years, mean follow-up range 4.6–15.3 years; AR: 55/111 [50%] with sub-total *v* 63/137 [46%] with segmental; OR 1.08, 95% CI 0.39 to 2.95; P = 0.88). The timing of recurrence was found to be earlier in the segmental colectomy group (WMD 4.43 years, 95% CI 3.08 years to 5.78 years).

Harms: There was no evidence that overall adverse effects differed postoperatively between segmental colectomy and sub-total colectomy (OR 1.24, 95% CI 0.17 to 8.89; specific adverse effects not reported). [69]

Comment: There is some evidence to suggest quality of life is better after segmental than after sub-total colectomy. The difference is mainly accounted for by improved continence after segmental colectomy. Sub-total colectomy is normally performed for more diffuse disease.

QUESTION What are the effects of medical interventions to maintain remission in adults with Crohn's disease?

OPTION AMINOSALICYLATES TO MAINTAIN REMISSION

Relapse rate

Compared with placebo Aminosalicylates (mesalazine or olsalazine) seem no more effective at reducing recurrence in people with Crohn's disease in medically induced remission (moderate-quality evidence).

Mesalazine compared with placebo Mesalazine is more effective at maintaining medically induced remission in people with Crohn's disease. pH7-dependent mesalazine is more effective at maintaining remission in people with medically induced remission, but pH6-dependent and controlled-release mesalazine are no more effective at maintaining medically induced remission in people with Crohn's disease (high-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits: We found two systematic reviews. [70] [71]

Aminosalicylates (mesalazine or olsalazine) versus placebo:
The first review (search date 2004, 6 RCTs, 1339 people, with Crohn's Disease Activity Index [CDAI] <150) compared aminosalicylates (ASA; mesalazine or olsalazine) versus placebo. [70] It found no significant difference between aminosalicylates (mesalazine or olsalazine) and placebo in recurrence rates at 12 months in people with medically induced remission (6 RCTs, 1339 people; 362/663 [54.6%] with 5-ASA *v* 370/676 [54.7%] with placebo; OR 1.0, 95% CI 0.80 to 1.24). At 24 months, the difference between groups in remission rate remained not significant (1 RCT, 161 people; with CDAI <150; AR: 54/80 [67.5%] with 5-ASA *v* 55/81 [67.9%] with placebo; OR 0.98, 95% CI 0.51 to 1.90). [70]

Mesalazine versus placebo:
The second review (search date 2006, 13 RCTs [5 RCTs also included in the first review], 2034 people with CDAI <150, follow-up 4–72 months) compared mesalazine (1–4 g/day) versus placebo. [71] It found that, compared with placebo, mesalazine significantly increased the proportion of people who maintained medically induced remission (9 RCTs, 1305 people; OR [for risk of relapse] 0.70, 95% CI 0.52 to 0.93; P = 0.013; NNT 16; absolute numbers not reported).

Similarly, the review found that, in people with medically induced remission, pH7-dependent mesalazine significantly reduced the rate of relapse compared with placebo (1 RCT, 125 people; OR 0.38, 95% CI 0.18 to 0.80; P = 0.010; NNT 5), whereas pH6-dependent mesalazine (4 RCTs, 710 people; OR 0.75, 95% CI 0.43 to 1.31; P = 0.318; NNT 23) and controlled-release mesalazine (4 RCTs, 470 people; OR 0.71, 95% CI 0.49 to 1.04; P = 0.080; NNT 16) did not. [71]

Harms:

Aminosalicylates versus placebo:
The first systematic review reported on harms. [70] There was no meta-analysis of adverse effects. Only one of the included studies found that people treated with 5-ASA suffered significantly more adverse effects than with placebo. Adverse effects were predominantly diarrhoea and nausea (1 RCT, 327 people; AR for gastrointestinal adverse effects: 54/167 [32%] with olsalazine *v* 27/160 [17%] with placebo; P = 0.001). [72]

Mesalazine versus placebo:
The second review gave no information on adverse effects. [71]

Comment:

Clinical guide:
Although previously published reviews found no benefit for aminosalicylates in maintenance of remission, the possibility of a minor beneficial effect in maintaining remission, combined with the relative safety of this drug and the suggestion that mesalazine may have a role in reducing cancer risk in inflammatory bowel disease, means that in practice many people have remained on aminosalicylates in the long term. [73]

The most recent review suggests that pH7-dependent mesalazine formulations, which are predominantly released in the terminal ileum and colon, seem to produce a significant treatment benefit, whereas pH6-dependent and controlled-release preparations do not. This benefit was, however, demonstrated in single RCTs with trial populations of about 100 people, therefore further trials are required to corroborate this observation. [71]

OPTION AZATHIOPRINE TO MAINTAIN REMISSION

Relapse rate

Compared with placebo Azathioprine is more effective at maintaining remission in people with Crohn's disease at 6 to 24 months (high-quality evidence).

Compared with budesonide Azathioprine and budesonide seem equally effective at maintaining remission at 12 months in people with Crohn's disease (moderate-quality evidence).

Note

With azathioprine use, regular monitoring for myelosuppression is obligatory.

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Azathioprine versus placebo:

We found one systematic review (search date 2008, 7 RCTs) comparing azathioprine versus placebo. [74] It found that azathioprine significantly increased the proportion of people who maintained remission compared with placebo over a treatment period of 6 to 24 months (7 RCTs, including 2 withdrawal trials, 463 people; 147/208 [71%] with azathioprine *v* 141/255 [55%] with placebo; OR 2.32, 95% CI 1.55 to 3.49; P = 0.00005; NNT 6). [74]

Azathioprine versus budesonide:

We found one RCT (77 people with corticosteroid-dependent Crohn's ileocolitis or proximal colitis who achieved clinical remission (Crohn's Disease Activity Index [CDAI] <150) with conventional corticosteroids), which compared azathioprine (2.0–2.5 mg/kg/day) versus budesonide (6–9 mg/day). [75] The RCT found no significant difference in clinical remission rates between groups at 12 months (32/38 [84%] with azathioprine *v* 25/39 [64%] with budesonide; P = 0.07). [75] The RCT found that azathioprine significantly increased the rate of endoscopic remission (Crohn's Disease Endoscopic Index of Severity (CDEIS) score: mean difference: 2.58 with azathioprine *v* 3.20 with budesonide; P <0.001). [75]

Harms:

Azathioprine versus placebo:

The systematic review found that azathioprine significantly increased the rate of withdrawals due to adverse effects compared with placebo (6 RCTs, 530 people; 14/231 [6%] with azathioprine *v* 5/299 [2%] with placebo; OR 3.74, 95% CI 1.48 to 9.45, NNH 20). [74] The review reported that common adverse effects included pancreatitis, leukopenia, nausea, allergy, and infection. [74]

Azathioprine versus budesonide:

The RCT reported no lethal adverse effects, but found numerically more adverse effects with azathioprine (112 people) compared with budesonide (83 people), but did not perform a significance assessment. [75] Two people treated with azathioprine were withdrawn for pancreatitis and severe, reversible leukopenia. Twenty-five people treated with azathioprine and 14 treated with budesonide developed infections, mainly from the upper respiratory tract; one person on azathioprine suffered a herpes zoster infection. Twenty-three people treated with azathioprine and 17 people treated with budesonide had transient abdominal pain, diarrhoea, or both. Other azathioprine-related adverse effects included paraesthesias, hair loss, and elevated transaminases. Other budesonide-related adverse effects were mild acne, moon face, and transient hair loss (no comparisons were made between groups). Mean white blood cell counts were significantly lower with azathioprine compared with budesonide (4.330 with azathioprine *v* 8.950 with budesonide; P <0.0001), as were mean platelet counts (285.000 with azathioprine *v* 300.000 with budesonide; P <0.01). [75]

Cohort studies:

One large prospective observational cohort study (19,486 people, 11,759 with Crohn's disease and 7727 with ulcerative colitis) found that people receiving azathioprine or 6-mercaptopurine had a significantly increased risk of developing lymphoproliferative disorders. [76] The multivariate-adjusted hazard ratio of lymphoproliferative disorder between people receiving thiopurines and those who had never received the drugs was 5.28 (95% CI 2.01 to 13.90; P = 0.0007). [76]

One small retrospective cohort study (100 people) compared azathioprine (2.0–2.5 mg/kg) for 2 to 4 years (Group A, 58 people) versus 4 to 8 years (Group B, 42 people). [77] It found no significant difference between groups in the rates of transient (2 in Group A *v* 1 in Group B) or significant (1

in Group A *v* 1 in Group B) leukopenia or infections (9 in Group A *v* 7 in Group B). No malignancies were reported in either group. Other reported adverse effects included headache, paraesthesia and transient psoriatic rash (headache: 7 in Group A *v* 10 in Group B; paraesthesia: 0 in Group A *v* 1 in Group B; transient psoriatic rash: 1 in Group A *v* 0 in Group B; P values not reported, reported as not significant). [77]

Comment: Azathioprine is beneficial in maintaining remission in Crohn's disease, and there is some evidence that azathioprine has a corticosteroid-sparing effect, although the sample size is very small. The drug should be used in people who are corticosteroid dependent or resistant, and regular monitoring for myelosuppression is obligatory.

OPTION METHOTREXATE TO MAINTAIN REMISSION

Relapse rate
Compared with placebo Methotrexate seems more effective at maintaining clinical remission in people with Crohn's disease (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits: **Methotrexate versus placebo:**
We found two systematic reviews comparing methotrexate versus placebo. [78] [79]

The first review (search date 2001) did not include a meta-analysis for the clinical outcomes of interest, and only included one RCT that met *Clinical Evidence* inclusion criteria. [78] The RCT is also included in the more recent review, [79] and therefore only data from this review are reported here.

The review (search date 2009, 3 RCTs, 125 people) found that methotrexate (12.5–15 mg/week orally or intramuscularly) significantly increased the proportion of people who maintained clinical remission (2 RCTs, 98 people; 35/50 [70%] with methotrexate *v* 22/48 [46%] with placebo; OR 3.11, 95% CI 1.31 to 7.41; P = 0.01; NNT 4). [79]

Harms: **Methotrexate versus placebo:**
The review reported that adverse effects were generally mild in nature and resolved upon discontinuation or with folic acid supplementation. [79] Common adverse events included nausea and vomiting, symptoms of a cold, abdominal pain, headache, joint pain or arthralgia, and fatigue. The review reported no serious adverse effects. [79]

The largest RCT included in the review reported no severe adverse effects (leukopenia, myelotoxicity, liver impairment, or serious infections) with methotrexate. [80] Mild adverse effects were nausea and vomiting, coryzal symptoms, influenza-like illness, abdominal pain, headache, arthralgia, fatigue, diarrhoea, abdominal bloating or distention, and insomnia (nausea and vomiting: 16/40 [40%] with methotrexate *v* 9/36 [25%] with placebo; coryzal symptoms: 10/40 [25%] with methotrexate *v* 10/36 [28%] with placebo; influenza-like illness: 2/40 [5%] with methotrexate *v* 2/36 [6%] with placebo; abdominal pain: 7/40[18%] with methotrexate *v* 9/36 [25%] with placebo; headache: 7/40 [18%] with methotrexate *v* 6/36 [17%] with placebo; arthralgia: 5/40 [12%] with methotrexate *v* 10/36 [28%] with placebo; fatigue: 5/40 [12%] with methotrexate *v* 5/36 [14%] with placebo; diarrhoea: 1/40 [2%] with methotrexate *v* 7/36 [19%] with placebo; abdominal bloating or distention: 1/40 [2%] with methotrexate *v* 1/36 [3%] with placebo; rash: 2/40 [5%] with methotrexate *v* 4/36 [11%] with placebo; insomnia: 1/40 [2%] with methotrexate *v* 0/36 [0%] with placebo; significance not reported).

Comment: In people unresponsive to azathioprine, methotrexate may be very effective. See also comment on methotrexate to induce remission in Crohn's disease, p 11 .

OPTION INFLIXIMAB TO MAINTAIN REMISSION

Relapse rate
Compared with placebo Infliximab is more effective at maintaining clinical remission in people with Crohn's disease at 44 to 54 weeks (high-quality evidence).

Different doses of infliximab compared with each other Infliximab 10 mg may be no more effective than infliximab 5 mg at maintaining remission at 30 to 50 weeks in people with Crohn's disease. Scheduled treatment with infliximab every 8 weeks seems more effective at maintaining remission at 14 weeks, but not at 30 to 50 weeks in people with Crohn's disease (moderate-quality evidence).

Quality of life
Compared with placebo Infliximab may be more effective at improving quality of life (assessed using IBDQ and SF-36 questionnaire) at 54 weeks in people with Crohn's disease (low-quality evidence).

Note:
Infliximab is associated with serious adverse effects, including infusion reactions, serum sickness, drug-induced lupus syndrome, fatal sepsis, and tuberculosis.

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Infliximab versus placebo:
We found 3 systematic reviews [51] [81] [82] assessing the use of infliximab versus placebo.

The first review (search date 2001, 2 RCTs) reported on the same two RCTs included in the second and third review, so will not be reported further here. [51]

The second review (search date not reported, 14 RCTs) compared any tumour necrosis factor (TNF) antagonist versus placebo. The review did not include a subgroup for infliximab, but included 3 RCTs comparing infliximab with placebo. [81] All 3 of these RCTs are also included in the third and most recent review. [82]

The most recent review (search date 2007, 3 RCTs) found that infliximab (5 mg or 10 mg every 8 weeks) significantly increased the proportion of people who maintained clinical remission at 44 to 54 weeks (2 RCTs, 404 people, Crohn's Disease Activity Index [CDAI] <150 after induction of remission with infliximab: 93/259 [36%] with infliximab *v* 22/145 [15%] with placebo; RR 2.50, 95% CI 1.64 to 3.80; P = 0.00001). [82] The review identified a further RCT that assessed maintenance of enterocutaneous and perineal fistula healing after induction of remission with 3 doses of infliximab 5 mg/kg. It found that, compared with placebo, infliximab (5 mg/kg every 8 weeks) significantly increased the proportion of people who maintained clinical remission (defined as the absence of a draining fistula) after 54 weeks (1 RCT; 33/91 [34%] with infliximab *v* 19/98 [19%] with placebo, 198 people; RR 1.87, 95% CI 1.15 to 3.04; P = 0.009). [82]

People from one RCT identified by the review were assessed for quality of life in a separate study, which found that infliximab treatment achieved a greater improvement in quality-of-life scores, as assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 instruments, at 54 weeks compared with placebo (change from baseline in IBDQ score: 22.1 with 5 mg/kg [P <0.05] *v* 30.2 with 10 mg/kg [P <0.001] *v* 8.9 with placebo; change from baseline in SF-36 score: 6.1 with 5 mg/kg [P <0.05] *v* 7.2 with 10 mg/kg [P <0.01] *v* 2.5 with placebo). [83]

Different dosing regimens versus each other:
We found one RCT. [84] It found no significant difference in remission rates (defined as CDAI <150) at weeks 30 or 54, between people treated with infliximab 5 mg/kg and 10 mg/kg, given every 8 weeks (225 people, median age 35 years, CDAI 220–400, gastroduodenal, ileal, and colonic disease refractory to corticosteroids, aminosalicylates, or other immunomodulators; week 30: OR 1.3, 95% CI 0.74 to 2.20; week 54: OR 1.58, 95% CI 0.90 to 2.80). [84] The same cohort was analysed in a separate study, which found that, at 14 weeks, scheduled treatment with infliximab 5 mg/kg or 10 mg/kg every 8 weeks resulted in a higher proportion of people in remission compared with episodic treatment when clinical need arose with infliximab 5, 10, or 15 mg/kg (573 people, CDAI 220–400, gastroduodenal, ileal, and colonic disease refractory to corticosteroids, aminosalicylates, or immunomodulators; remission; remission defined as an increase in CDAI of 70 points or 35% from baseline, or introduction of new treatment for Crohn's disease: P = 0.006; absolute numbers or percentages not reported). [85] However, this benefit was not maintained at week 30 or 54 (week 30: 155/385 [40%] with scheduled infliximab *v* 61/188 [32%] with episodic infliximab; P = 0.07; week 54: 158/385 [41%] with scheduled infliximab *v* 65/188 [35%] with episodic infliximab; P value not reported). [85]

Harms:

In 2008, the US Food and Drug Administration (FDA) issued a drug safety alert on the risk of opportunistic fungal infections associated with TNF-alpha blockers (tumour necrosis factor alpha-blockers). Twelve of 240 cases of fungal infections in people treated with TNF-alpha blockers (including infliximab) reported in the USA were fatal. As this review concerns itself exclusively with adults aged over 18 years, the alert regarding children and adolescents is probably irrelevant here (http://www.fda.gov).

Infliximab versus placebo:
The systematic review did not pool data for adverse effects. [82] The first RCT included in the review found a similar overall incidence of adverse effects between placebo or infliximab 10 mg/kg every 8 weeks for 36 weeks, after an initial dose of 5, 10, or 20 mg/kg (73 people; 35/36 [97%] with placebo *v* 35/37 [95%] with infliximab). Common adverse effects were upper respiratory tract infection (24%), headache (16%), abdominal pain (14%), nausea (19%), fever (11%), bronchitis (16%), and pharyngitis (19%). Of 47 evaluable people, 7 developed antibodies to infliximab.

The second RCT included in the review compared doses of 5 and 10 mg/kg of infliximab, given every 8 weeks, versus placebo, after an initial dose of infliximab 5 mg/kg in all 3 groups. Headache, abdominal pain, and upper respiratory tract infection were the most frequently occurring adverse effects (incidences not reported). [82] After 54 weeks, the most common adverse effects leading to discontinuation of infliximab were infusion reactions (1%), allergic reaction (1%), arthralgia (1%), serum sickness (1%), and rash (1%). Infections requiring treatment occurred in 32% of people, and were considered serious in 4% of the study population; one person died from sepsis secondary to bowel obstruction. One person developed tuberculosis following infliximab treatment. Malignancy occurred in 1% of study participants. Two people developed a lupus-like syndrome, 11% to 34% of people developed anti-double stranded DNA antibodies, and 35% to 56% of people developed anti-nuclear antibodies. Because the study design allowed approximately half of the people in the placebo group to cross over to episodic treatment with infliximab on clinical worsening, a direct comparison between adverse effects in the infliximab and placebo groups was not possible. However, the study did report no significant difference in serious adverse effects between people receiving a single infusion of infliximab and those receiving multiple infusions up to week 14 of the study (AR: 22/88 [12%] with single infusion *v* 38/385 [10%] with multiple infusions; P = 0.561). [82]

We found a second systematic review (search date 2002), which reported the following additional adverse effects, which were summarised from RCTs and post-marketing case reports of infliximab treatment for Crohn's disease and rheumatoid arthritis. [53] Mild infusion reactions occurred in 22% of all those treated with infliximab and in 9% of those treated with placebo. Of approximately 170,000 people treated with infliximab worldwide, 84 developed tuberculosis, which was fatal in 14 cases. Histoplasmosis infection was reported in 9 of 170,000 people and was fatal in one case. Exacerbation of demyelinating disease (e.g., multiple sclerosis) was reported in 3 cases. [53]

Infliximab versus no treatment:
We found 4 large prospective cohort studies. [86] [87] [88] [89] [90]

The largest study was reported in two papers. [86] [87] It compared adverse effects in people receiving infliximab versus in people not receiving infliximab. Although univariate analysis found that infliximab significantly increased rates of intestinal stenosis, stricture, or obstruction (SSO) at a median follow-up of 1.8 years (5336 people; 1.95 events per 100 patient-years with infliximab *v* 0.99 events per 100 patient-years without infliximab; P <0.001), multivariate analysis found no significant difference in SSO rates between groups (SSO hazard ratio: 1.11, 95% CI 0.72 to 1.73; P = 0.63). It also found no significant difference in mortality between infliximab and no infliximab (6290 people; mortality: 0.53 per 100 patient-years with infliximab *v* 0.43 per 100 patient-years without infliximab; RR 1.24, 95% CI: 0.73 to 2.10). [87] Univariate analysis found a significantly higher rate of serious infections with infliximab compared with no infliximab (6253 people; AR: 1.37 per 100 patient-years with infliximab *v* 0.65 per 100 patient-years without infliximab; RR 2.15, 95% CI 1.44 to 3.21; P <0.001). However, multivariate analysis adjusted for previous corticosteroid use found that infliximab was not a significant independent predictor of serious infection (6253 people; OR 0.99, 95% CI 0.64 to 1.54; P = 0.97). [86]

The second cohort study (1400 people, 734 people with inflammatory bowel disease [IBD] [77% with Crohn's disease] treated with infliximab, and 666 control not treated with infliximab) performed retrospective case note review over a 14-year period. [89] The median follow-up time was 58 months (interquartile range 33 to 88 months) in the infliximab group and 144 months (interquartile range 83 to 163 months) for controls. The study reported that 112 severe adverse effects occurred in 93/734 [13%] people with infliximab, compared with 157 events in 126/666 [19%] controls (OR 1.33, 95% CI 0.56 to 3.00; P = 0.45). There was no difference between the two groups in the rates of mortality, malignancy, and infection. Tuberculosis was diagnosed in two patients receiving infliximab who had negative skin tests at baseline, whereas none of 16 people in the infliximab group with positive skin tests who received prophylaxis developed tuberculosis. Concomitant treatment with corticosteroids was the only independent risk factor for infections in people treated with infliximab (OR 2.69, 95% CI 1.18 to 6.12; P = 0.018). The most commonly observed systemic adverse effects were skin eruptions, including psoriasiform eruptions in 150/734 (20%) people. The authors of the study concluded that infliximab had a good long-term safety profile. [89]

The third study performed retrospective case note review of a Danish population-based IBD cohort receiving infliximab over 6 years (651 people, 619 with Crohn's disease, 15 with ulcerative colitis, 17 with indeterminate colitis). In total, 3351 infusions were administered, with a median of 3 infusions per person. [88] The study reported that infusion reactions occurred in 146/3351 (4%) of infusions. The study found that a significantly smaller proportion of people suffered infusion reactions when they also received azathioprine or methotrexate compared with people who did not receive azathioprine or methotrexate (63/2079 [3%] with azathioprine or methotrexate *v* 83/1272 [7%] without azathioprine or methotrexate; P <0.001). Severe adverse effects were observed after 112/3351 (3%) infusions in a total of 95 people. The study also reported that 4 people developed cancer

versus the 5.9 people expected (standardised incidence ratio 0.7, 95% CI 0.2 to 1.7) and 13 people died versus the 6.9 people expected (standardised mortality ratio 1.9, 95% CI 1.0 to 3.2). Two deaths caused by infections were possibly related to infliximab. [88]

The fourth study (202 people, 157 with Crohn's disease, 42 with ulcerative colitis, and 3 with coeliac disease) performed retrospective case note review over an 8-year period. [90] The median follow-up was 2.4 years (range 1.0–4.9 years), with a total of 620 patient-years' follow-up. The study reported that 19% of people with Crohn's disease were subsequently treated with adalimumab. The study found that 7/202 (3%) deaths occurred during follow-up; only one death was <1 year post-infliximab (at day 72, from lung cancer). A total of 6 malignancies (3 haematological, 3 bronchogenic) and 6 cases of suspected demyelination (3 with confirmed neurological disease) were reported. In the 90 days following infliximab, 95 adverse effects (36 serious) occurred in 58/202 (29%) of people. The study found that, overall, 42/202 (21%) people had an infectious event (22 serious) and 27/202 (13%) of people had an infusion reaction; 19 were acute (4 serious) and 8 delayed (3 serious). The authors of the study concluded that serious infections, malignancies, and neurological disease can complicate anti-TNF use in clinical practice, although evidence for causality was unclear. [90]

Infliximab versus other immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, corticosteroids):
We found one retrospective cohort study examining a putative association between opportunistic infection and the use of infliximab or corticosteroids compared with other immunomodulating drugs (azathioprine, 6-mercaptopurine, and methotrexate) using data from 10,662 people with IBD, 60% of whom had Crohn's disease, over a 5-year period. [91] The outcome of interest was serious bacterial infections requiring hospitalisation, including *Clostridium difficile*. The incidence of bacteraemia was not significantly higher for infliximab at 7.4 per 1000 person-years (95% CI 3.3 per 1000 person-years to 19.3 per 1000 person-years), compared with 3.8 per 1000 person-years (95% CI 2.1 per 1000 person-years to 6.2 per 1000 person-years) for azathioprine, 6-mercaptopurine, and methotrexate (RR 1.4, 95% CI 0.47 to 4.24). *Clostridium difficile* infections occurred in 0 per 1000 patient-years (95% CI 0 per 1000 person-years to 5.4 per 1000 person-years) among 521 infliximab initiations and in 14 per 1000 patient-years (95% CI 10.6 per 1000 person-years to 18.2 per 1000 person-years) for corticosteroids. [91] The authors of the study concluded that no meaningful association existed between infliximab and serious bacterial infections. [91]

Different dosing regimens versus each other:
We found one RCT, reported in 3 publications. [92] [86] [93] The RCT compared groups of people receiving infliximab 5 mg/kg and 10 mg/kg every 8 weeks, and found no significant difference after 54 weeks in serious adverse effects, serious infections, infusion reactions, and serum sickness-like reactions (serious adverse effects: 15/193 [8%] with 5 mg/kg *v* 11/192 [6%] with 10 mg/kg; serious infections: 8/193 [4%] with 5 mg/kg *v* 6/192 [3%] with 10 mg/kg; infusion reactions: 44/193 [23%] with 5 mg/kg *v* 36/192 [19%] with 10 mg/kg; serum sickness-like reactions: 5/193 [3%] with 5 mg/kg *v* 6/192 [3%] with 10 mg/kg; P values not reported). The same cohort was analysed and compared episodic infliximab treatment (5, 10, or 15 mg/kg on-demand) versus regular infliximab treatment (5 or 10 mg/kg every 8 weeks). [92] At 54 weeks, the investigators found similar rates between groups in serious infections, malignancy, serious infusion reactions, and serum sickness-like reactions (serious infections: 8/188 [4%] with episodic infliximab *v* 8/192 [4%] with regular 5 mg/kg *v* 6/193 [3%] with regular 10 mg/kg; malignancy: 2/188 [1%] with episodic infliximab *v* 3/192 [2%] with regular 5 mg/kg *v* 1/193 [0.5%] with regular 10 mg/kg; serious infusion reactions: 1/188 [0.5%] with episodic infliximab *v* 4/192 [2%] with regular 5 mg/kg *v* 1/193 [0.5%] with regular 10 mg/kg; serum sickness-like reactions: 3/188 [2%] with episodic infliximab *v* 5/192 [3%] with regular 5 mg/kg *v* 6/193 [3%] with regular 10 mg/kg; P values not reported). Compared with the episodic treatment group, a greater proportion of people in the regular-treatment group developed anti-double-stranded DNA antibodies and anti-nuclear antibodies (anti-double-stranded DNA antibodies: 34% with regular infliximab *v* 11% with episodic infliximab; anti-nuclear antibodies: 56% with regular infliximab *v* 35% with episodic infliximab; P values not reported). However, only one person in the regular-treatment group developed a clinical lupus-like syndrome. People who received episodic treatment with infliximab had significantly higher levels of antibodies to infliximab than those who received regular treatment (51/170 [30%] with episodic *v* 29/344 [8%] with regular treatment; OR 0.21, 95% CI 0.13 to 0.36; P <0.0001). [93] People in all 3 treatment groups experienced similar rates of intestinal stenosis, stricture, or obstruction (573 people; AR: 12/188 [6%] with episodic infliximab treatment *v* 10/192 [5%] with infliximab 5 mg/kg *v* 13/193 [7%] with infliximab 10 mg/kg; significance and P values not reported). [86]

Comment:

Clinical guide:
There is good evidence to support the use of infliximab to maintain remission in people with Crohn's disease that is refractory to corticosteroids or conventional immunosuppressants (azathioprine, mercaptopurine, and methotrexate), after successful 3-dose induction treatment. Scheduled treat-

ment with infliximab every 8 weeks seems superior to episodic treatment with respect to some but not all clinical end points. This superiority may be due to the lower incidence of antibody development to the drug in a scheduled regimen. Small trials have suggested that concomitant use of azathioprine during the first 6 months also decreases antibody levels. [94] However, many centres still use an episodic policy, converting to scheduled treatment regimens in those who relapse quickly. Large cohort studies seem to suggest that infliximab is safe over the long term. For clinical guidance on infliximab, see comment on infliximab to induce remission in Crohn's disease, p 12 .

OPTION CICLOSPORIN TO MAINTAIN REMISSION

Relapse rate
Compared with placebo Ciclosporin may be no more effective at maintaining remission in people with Crohn's disease at 12 to 18 months (low-quality evidence).

Note
Ciclosporin has been associated with increases in serum creatinine levels, hypertension, tingling, headaches, and hirsutism.

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Ciclosporin versus placebo:
We found no systematic review but found two RCTs. [56] [57]

The first RCT found that ciclosporin (5 mg/kg daily in 2 divided doses) worsened (defined as an increase in Crohn's Disease Activity Index [CDAI] of 100 points) quiescent Crohn's disease in proportionately more people compared with placebo, although this difference did not reach significance (305 people, age 18–65 years, CDAI <150, ileal and colonic disease, concomitant prednisolone or mesalazine treatment; AR: 91/151 [60%] with ciclosporin *v* 80/154 [52%] with placebo; P = 0.11). [56] People in the ciclosporin group also had significantly higher CDAI scores than those in the placebo group (repeated measures analysis, absolute difference not reported; P = 0.02), and there was no significant difference in Inflammatory Bowel Disease Questionnaire scores between the groups (repeated measures analysis; P = 0.24) over the study period of 18 months.

The second RCT found no difference after 12 months in remission rates (defined as CDAI <150) in people with quiescent or mildly active Crohn's disease treated with oral ciclosporin (5 mg/kg daily in 2 divided doses) and placebo (118 people, age 18–60 years, CDAI <200, ileal and colonic disease; AR: 16/56 [29%] with ciclosporin *v* 16/62 [26%] with placebo; P value not reported). [57]

Different dosing regimens:
We found no systematic review or RCTs comparing different dosing regimens of oral ciclosporin for maintaining remission in Crohn's disease.

Harms:

Ciclosporin versus placebo:
We found no systematic review but found two RCTs reporting on harms. [56] [57] The first RCT reported a significantly higher rate of withdrawals caused by adverse effects (increases in serum creatinine levels, hypertension, tingling, headaches, and hirsutism) with oral ciclosporin (5 mg/kg daily in 2 divided doses) for 18 months compared with placebo (305 people, age 18–65 years; AR: 22/151 [15%] with ciclosporin *v* 5/154 [3%] with placebo; P = 0.003). [56]

The second RCT (182 people treated with oral ciclosporin 5 mg/kg daily in 2 divided doses or placebo) reported that the following adverse effects occurred notably (but not significantly) more often in the ciclosporin group: tingling (31%), increased hair growth (24%), back pain (11%), weight gain (8%), tremor (7%), gingival hyperplasia (7%), and impaired renal function (7%). [57] Seven people taking ciclosporin and 4 people taking placebo stopped treatment because of adverse effects. Ciclosporin was associated with a 10% increase in serum creatinine levels, and a blood pressure rise of between 3 mmHg and 8 mmHg.

Comment:

Clinical guide:
Although there is debate about the effectiveness of short courses of oral or intravenous ciclosporin to induce remission in active Crohn's disease, [3] current evidence does not support the use of oral ciclosporin for maintenance of remission.

OPTION CORTICOSTEROIDS (ORAL) TO MAINTAIN REMISSION

Relapse rate
Methylprednisolone or prednisolone compared with placebo Methylprednisolone or prednisolone may be no more effective at reducing relapse in people with Crohn's disease at 6, 12, or 24 months (high-quality evidence).

Budesonide compared with placebo Budesonide 6 mg is no more effective at maintaining clinical remission at 3, 6, or 12 months in people with Crohn's disease. Budesonide 3 mg is more effective at maintaining clinical remission at 3 months, but not at 6 or 12 months, in people with Crohn's disease (high-quality evidence).

Different budesonide regimens compared with each other Budesonide at a dose of 6 mg seems no more effective than a dose of 3 mg at maintaining clinical remission at 3 to 12 months in people with Crohn's disease. Budesonide 9 mg seems no more effective than a dose of 6 mg at maintaining clinical remission in people with Crohn's disease (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Methylprednisolone or prednisolone versus placebo:
We found one systematic review (search date 2003, 3 RCTs) comparing maintenance treatment using conventional corticosteroids (prednisolone 0.25 mg/kg/day, prednisolone 7.5 mg/day, or 6-methylprednisolone 8 mg/day) versus placebo in people with quiescent Crohn's disease (defined as Crohn's Disease Activity Index [CDAI] <150 or absence of symptoms). [95] Meta-analysis of the 3 RCTs found no significant difference in rates of relapse (defined as CDAI >150 or recurrence of symptoms) at 6, 12, or 24 months between treatment and placebo groups (relapse at 6 months: 303 people; 23/142 [16%] with corticosteroids *v* 33/161 [20%] with placebo; OR 0.71, 95% CI 0.38 to 1.31; P = 0.3; relapse at 12 months: 269 people; 37/131 [28%] with corticosteroids *v* 43/138 [31%] with placebo; OR 0.82, 95% CI 0.47 to 1.43; P = 0.5; relapse at 24 months: 182 people; 36/95 [38%] with corticosteroids *v* 39/87 [45%] with placebo; OR 0.72, 95% CI 0.38 to 1.35; P = 0.3).

Budesonide versus placebo:
We found one systematic review (search date 2008, 11 RCTs) comparing budesonide versus placebo or different regimens of budesonide with each other. [96] The review found no significant difference between budesonide 6 mg and placebo in the rate of continued clinical remission at 3, 6, or 12 months (6 months: 6 RCTs; 173/268 [65%] with budesonide *v* 142/272 [52%] with placebo; RR 1.25, 95% CI 1.00 to 1.58; P = 0.05; 6 months: 5 RCTs; 127/208 [54%] with budesonide *v* 111/212 [52%] with placebo; RR 1.15, 95 % CI 0.95 to 1.39; P= 0.14; 12 months: 5 RCTs; 114/208 [55%] with budesonide *v* 101/212 [48%] with placebo; RR 1.13, 95% CI 0.94 to 1.35; P = 0.19). The review found that budesonide 3 mg significantly increased the rate of continued clinical remission compared with placebo at 3 months (4 RCTs; 76/133 [57%] with budesonide *v* 57/130 [44%] with placebo; RR 1.31, 95% CI 1.03 to 1.67; P = 0.03), but not at 6 months (3 RCTs; 44/90 [49%] with budesonide *v* 40/90 [44%] with placebo; RR 1.10, 95% CI 0.81 to 1.50; P = 0.53) or 12 months (5 RCTs; 92/217 [42%] with budesonide *v* 90/225 [40%] with placebo; RR 1.04, 95% CI 0.84 to 1.30; P = 0.70). [96]

Different budesonide regimens versus each other:
We found one systematic review (search date 2008, 11 RCTs) comparing budesonide versus placebo or different regimens of budesonide with each other. [96] The review found no significant difference between budesonide 3 mg and budesonide 6 mg in rate of continued clinical remission at 3, 6, or 12 months (3 months: 3 RCTs; 56/90 [62%] with budesonide 6 mg *v* 53/90 [59%] with budesonide 3 mg; RR 1.07, 95% CI 0.84 to 1.35; P = 0.59; 6 months: 3 RCTs; 50/90 [56%] with budesonide 6 mg *v* 44/90 [49%] with budesonide 3 mg; RR 1.16, 95% CI 0.88 to 1.53; P = 0.30; 12 months: 3 RCTs; 42/90 [47%] with budesonide 6 mg *v* 35/90 [39%] with budesonide 3 mg; RR 1.23, 95% CI 0.88 to 1.72; P = 0.22). The review also included one RCT that compared budesonide 9 mg versus budesonide 6 mg. It found no significant difference between groups in continued clinical remission (1 RCT, 66/81 [81%] with budesonide 9 mg *v* 58/76 [76%] with budesonide 6 mg; RR 1.07, 95% CI 0.91 to 1.26). [96]

Harms:

Methylprednisolone or prednisolone versus placebo:
See harms of corticosteroids to induce remission, p 4 .

Budesonide versus placebo:
The review reported no significant difference in rates withdrawal due to adverse effects between budesonide 6 mg or 3 mg compared with placebo (budesonide 6 mg: 5 RCTs; 20/231 [7%] with budesonide 6 mg *v* 19/235 [8%] with placebo; RR 1.06, 95% CI 0.60 to 1.88; P = 0.83; budesonide 3 mg: 4 RCTs; 4/184 [2%] with budesonide 3 mg *v* 7/189 [4%] with placebo; RR 0.64, 95% CI 0.21 to 1.91; P = 0.42). [96]

Different budesonide regimens versus each other:
The review found no significant difference in rates of withdrawal due to adverse effects between budesonide 6 mg and budesonide 3 mg (2 RCTs; 1/54 [2%] with 6 mg *v* 1/57 [2%] with 3 mg; RR 1.18, 95 % CI 0.08 to 17.82; P = 0.90) or budesonide 9 mg and budesonide 6 mg (1 RCT, 1/81 [1%] with 9 mg *v* 3/76 [4%] with 6 mg; RR 0.31, 95% CI 0.03 to 2.94). [96]

Comment: **Clinical guide:**
Conventional corticosteroids have no place in maintenance treatment for Crohn's disease. Although budesonide may delay the time to relapse, it has not been shown to maintain remission over 12 months. [97]

QUESTION What are the effects of medical interventions to maintain remission after surgery in adults with Crohn's disease?

OPTION AMINOSALICYLATES TO MAINTAIN REMISSION AFTER SURGERY

Relapse rate
Mesalazine compared with placebo Mesalazine seems more effective at maintaining clinical and endoscopic remission in people with Crohn's disease. pH7-dependent mesalazine seems more effective than placebo at reducing relapse rate, but pH6-dependent and controlled-release mesalazine seem no more effective at reducing relapse rates in people with Crohn's disease (moderate-quality evidence).

Different mesalazine regimens compared with each other Mesalazine 2.4 g daily seems as effective as mesalazine 4 g daily at increasing clinical or endoscopic remission at 12 months in people with Crohn's disease (moderate-quality evidence).

Sulfasalazine compared with placebo Sulfasalazine seems more effective at reducing relapse rates at 1 year in people with Crohn's disease, but we don't about at periods up to 3 years (moderate-quality evidence).

Mesalazine compared with azathioprine or 6-mercaptopurine Mesalazine is as effective as azathioprine at reducing clinical recurrence at 12 or 24 months, but is less effective at reducing endoscopic recurrence at 12 months in people with Crohn's disease (high-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits: **Mesalazine versus placebo:**
We found 4 systematic reviews comparing mesalazine versus placebo. [28] [98] [99] [71]

The first review (search date 1997), [28] the second review (search date 2000), [98] and the third review (search date 2009) [99] all included some variation of the same 5 RCTs. Therefore only the most recent review is reported here. [99] The fourth review (search date 2006) [71] had different inclusion criteria, and therefore is reported in full.

The third review (search date 2009, 5 RCTs, 788 people) compared 5-ASA (mesalazine) versus placebo. [99] It found that mesalazine significantly reduced risk of clinical recurrence after surgery and severe endoscopic recurrence after surgery compared with placebo (risk of clinical recurrence after surgery: 4 RCTs; 96/327 [29%] with mesalazine *v* 122/325 [38%] with placebo; RR 0.76, 95% CI 0.62 to 0.94; NNT 12; P = 0.012; severe endoscopic recurrence after surgery: 3 RCTs; 18/153 [12%] with mesalazine *v* 34/144 [24%] with placebo; RR 0.50, 95% CI 0.29 to 0.84; NNT 8; P = 0.04). [99]

The fourth review (search date 2006, 13 RCTs [3 RCTs also included in the third review], 2034 people with Crohn's Disease Activity Index [CDAI] <150, follow-up 4–72 months) compared mesalazine (1–4 g/day) versus placebo. [71] It found that, compared with placebo, mesalazine significantly increased the proportion of people who maintained surgically induced remission (5 RCTs, 729 people; OR [for risk of relapse] 0.58, 95% CI 0.40 to 0.86; P = 0.006; NNT 10; absolute numbers not reported). [71]

In subgroup analysis, pH7-dependent mesalazine significantly reduced the rate of relapse in people with surgically induced remission compared with placebo (1 RCT, 95 people; OR 0.28, 95% CI 0.12 to 0.65; P = 0.003; NNT 4), whereas pH6-dependent mesalazine (1 RCT, 163 people; OR 0.65, 95% CI 0.34 to 1.24; P = 0.195; NNT 11) and controlled-release mesalazine (3 RCTs, 471 people; OR 0.72, 95% CI 0.47 to 1.08; P = 0.111; NNT 15) did not. [71]

Different mesalazine regimens versus each other:
We found one RCT. [100] It found no significant difference between mesalazine 4 g daily compared with 2.4 g daily in maintaining severe endoscopic or clinical remission at 12 months (165 people, age 18–65 years, terminal ileal disease, CDAI <150; severe endoscopic recurrence: AR: 23/84 [27%] with 4 g/day *v* 30/81 [37%] with 2.4 g/day; risk difference –0.097, 95% CI –0.238 to +0.045; P = 0.18; clinical recurrence [CDAI >150 or increase by 100 points]: AR: 11/84 [12%] with 4 g/day *v* 13/81 [14%] with 2.4 g/day; risk difference –0.027, 95% CI –0.124 to +0.069; P = 0.58). However, the RCT found that mesalazine 4 g daily significantly reduced the risk of mild endoscopic recurrence

compared with mesalazine 2.4 g daily (mild endoscopic recurrence: AR: 39/84 [46%] with 4 g/day *v* 50/81 [62%] with 2.4 g/day; risk difference –0.153, 95% CI –0.303 to –0.003; P = 0.04).

Sulfasalazine versus placebo:
We found no systematic review but found two RCTs. [101] [102] The first RCT found that, compared with placebo, sulfasalazine significantly reduced relapse at 1 and 2 years, but not at 3 years (232 people, age 15–66 years, 113 males and 119 females, who had had resections considered curative at the time of surgery: at 1 year: AR: 18/111 [16%] with sulfasalazine *v* 34/121 [28%] with placebo; P <0.01; at year 2: AR: 9/111 [8%] with sulfasalazine *v* 12/121 [10%] with placebo; P <0.01; at year 3: AR: 42/111 [38%] with sulfasalazine *v* 58/121 [48%] with placebo; P = 0.09). [101]

The second RCT found that, compared with placebo, sulfasalazine 3 g daily did not significantly reduce relapse rates at 18 months (66 people, age 15–59 years with normal erythrocyte sedimentation rate; AR: 4/32 [13%] for sulfasalazine *v* 9/34 [26%] for placebo; P >0.1). [102] Relapse was defined clinically based on the presence or absence of fever, diarrhoea, rectal haemorrhage, abdominal pain, extra-intestinal manifestations, palpable abdominal masses, fistulae, abscesses, and possible loss of working days (see comment below).

Mesalazine versus azathioprine or 6-mercaptopurine (6-MP):
We found one systematic review (search date 2009, 4 RCTs, 349 people) that compared 5-ASA (mesalazine) versus azathioprine/6-MP. [71] It found no significant difference between groups in the rate of clinical recurrence at 12 or 24 months (12 months: 4 RCTs, 349 people; 39/173 [23%] with mesalazine *v* 28/176 [16%] with azathioprine; RR 1.43, 95% CI 0.95 to 2.16; P = 0.09; 24 months: 3 RCTs, 270 people; 52/136 [38%] with mesalazine *v* 40/134 [30%] with azathioprine; RR 1.31, 95% CI 0.95 to 1.81; P = 0.09). However the review reported that mesalazine significantly increased the risk of endoscopic recurrence at 12 months (2 RCTs, 130 people; 39/65 [60%] with mesalazine *v* 27/65 [42%] with azathioprine; RR 1.45, 95% CI 1.03 to 2.06; P = 0.03). [71]

Harms:

Mesalazine versus placebo:
The third review found no significant difference between mesalazine and placebo in the proportion of people who withdrew from the RCTs owing to adverse effects (5 RCTs, 788 people; 107/402 [27%] with mesalazine *v* 96/386 [25%] with placebo; RR 1.12, 95% CI 0.89 to 1.39; P = 0.33), or who experienced serious adverse effects (5 RCTs, 788 people; 30/402 [7.5%] with mesalazine *v* 28/386 [7.3%] with placebo; RR 1.01, 95% CI 0.62 to 1.66; P = 0.95). [99]

The fourth review gave no information on adverse effects. [71]

Different mesalazine regimens versus each other:
The RCT reported similar adverse effect rates with mesalazine 4 g daily and 2.4 g daily (2/101 [2%] with 4 g/day *v* 2/105 [2%] with 2.4 g/day; significance not reported). [100] In the 4 g daily group both people experienced severe dyspepsia; in the 2.4 g daily group one person had lower-limb cramps and the other had elevated liver function tests.

Sulfasalazine versus placebo:
The RCTs gave no information on adverse effects. [102] [101]

Mesalazine versus azathioprine or 6-MP:
The review found that mesalazine significant reduced the risk of serious adverse effects compared with azathioprine or 6-MP (4 RCTs, 374 people; 16/171 [9%] with mesalazine *v* 33/176 [19%] with azathioprine; RR 0.51, 95% CI 0.30 to 0.89; P = 0.01). [71] However, the review reported no significant difference in withdrawal rates due to adverse effects between groups (3 RCTs, 268 people; 29/134 [22%] with mesalazine *v* 35/134 [26%] with azathioprine; RR 0.86, 95% CI 0.59 to 1.26; P = 0.43).

Comment:

Sulfasalazine versus placebo:
The second RCT was planned in 1969 and did not base relapse rates on an index calculation such as CDAI. [102]

Clinical guide:
Aminosalicylates may have a role in preventing postoperative recurrence in Crohn's disease. Although the RCT comparing mesalazine 4 g daily and 2.4 g daily found no significant difference in clinical recurrence at 12 months between doses, the improvements in endoscopic recurrence rates in the 4 g daily group suggest that a total daily mesalazine dose of 4 g may be more effective than a total daily dose of 2.4 g. pH7-dependent mesalazine may be more effective than pH6-dependent or controlled-release formulations, and further trials in this area are warranted. However, for people at high risk of recurrence after surgery, such as those who have had a second operation, expert opinion would generally suggest commencing with an immunomodulator, such as azathioprine.

OPTION AZATHIOPRINE/MERCAPTOPURINE TO MAINTAIN REMISSION AFTER SURGERY

Relapse rate
Azathioprine compared with placebo Azathioprine seems more effective at reducing clinical and severe endoscopic recurrence in people with Crohn's disease at 12 months (moderate-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

We found two systematic reviews [103] [99] comparing purine analogues (azathioprine and 6-mercaptopurine [6-MP]) with placebo [99] or control arms (placebo, with and without antibiotic treatment and mesalazine). [103]

Azathioprine versus placebo:
The first review (search date 2008) included all purine analogues and did not report a subgroup for azathioprine. [103] However the review did include two RCTs comparing azathioprine versus placebo, which are also included in the second, more recent review. [99]

The second review (search date 2009, 2 RCTs 168 people) found that, compared with placebo, azathioprine/6-MP significantly reduced risk of clinical recurrence and severe endoscopic recurrence at 12 months after surgery (clinical recurrence: 2 RCTs, 168 people; 20/87 [23%] with azathioprine *v* 30/81 [37%] with placebo; RR 0.59, 95% CI 0.38 to 0.92; NNT 7; P = 0.02; severe endoscopic recurrence: 2 RCTs, 168 people; 28/87 [32%] with azathioprine *v* 41/81 [51%] with placebo; RR 0.64, 95% CI 0.44 to 0.92; NNT 4). [99]

Different regimens versus each other:
We found no systematic review or RCTs that compared different doses of azathioprine or mercaptopurine in the prevention of postoperative recurrence in Crohn's disease.

Azathioprine versus mesalazine:
See benefits of aminosalicylates to maintain remission after surgery, p 24 .

Harms:

Azathioprine versus placebo:
The review found no significant difference between azathioprine and placebo in the rate of serious adverse effects or rate of withdrawal (serious adverse effects: 2 RCTs, 168 people; 14/87 [16%] with azathioprine *v* 8/81 [9%] with placebo; RR 1.61, 95% CI 0.71 to 3.66; P = 0.25; rate of withdrawal: 2 RCTs, 168 people; 31/87 [36%] with azathioprine *v* 39/81 [48%] with placebo; RR 0.71, 95% CI 0.51 to 1.00; P = 0.052). [99]

Different regimens versus each other:
We found no RCTs.

Azathioprine versus mesalazine:
See harms of aminosalicylates to maintain remission after surgery, p 24 .

We found one retrospective case note review (data from 343 consecutive abdominal operations in people with Crohn's disease), which found that that intra-abdominal septic complications occurred in 26/343 (8%) of operations. [104] The study found that thiopurine treatment is associated with a significantly increased risk of intra-abdominal septic complications (16% with treatment *v* 6% without treatment; P = 0.044). [104]

Comment:

There is growing evidence that thiopurines reduce clinical and endoscopic recurrence in ileocaecal Crohn's disease following surgical resection. However, the long-term benefit of treatment beyond 2 years has not been established. Thiopurines are probably the drug of choice for people at high risk of relapse, particularly after second episodes of surgery.

QUESTION What are the effects of lifestyle interventions to maintain remission in adults with Crohn's disease?

OPTION OMEGA 3 OIL

Relapse rate
Compared with placebo We don't know whether fish oil is more effective at increasing the proportion of people with Crohn's disease who maintained remission at least 1 year (low-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Fish oil versus placebo:
We found two systematic reviews (search dates 2001 [54] and 2008 [105]). We report only the more recent review [105] as it includes all the RCTs from the earlier review. [54]

The review (search date 2008, 6 RCTs) compared n-3 fatty acid (fish oil) versus placebo for maintenance of remission in people with Crohn's disease for at least 6 months. [105] It found that n-3 fatty acid significantly increased the proportion of people who maintained remission (6 RCTs, 1039 people, proportion of people who relapsed: 202/523 [37%] with n-3 fatty acid *v* 243/516 [47%] with placebo; RR 0.77, 95% CI 0.61 to 0.98; P = 0.03). However, the review reported that the studies were both clinically and statistically heterogeneous (P = 0.03, I^2 = 58%) and there was evidence of publication bias (results presented graphically).

Owing to the heterogeneity in the pooled analysis, the review reported the two largest included RCTs individually, both of which found negative results.

The first large RCT included in the review (374 people in remission [Crohn's Disease Activity Index {CDAI} <150]) compared omega-3 fatty acids 4 g daily (188 people) versus placebo (186 people) for 52 weeks. Participants had to be in remission for at least 3 but for no longer than 12 months. No other treatments for Crohn's disease were permitted. Clinical relapse was defined as CDAI >150 or an increase of 70 from baseline. The RCT found no significant difference in relapse rates between groups at 1 year (32% with omega-3 fatty acids *v* 36% with placebo, HR 0.82, 95% CI 0.51 to 1.19; P = 0.30; absolute numbers not reported).

The second large RCT included in the review (379 people with active Crohn's disease) compared prednisolone (40 mg/day) versus budesonide (9 mg/day) for induction of remission. Patients were eligible for randomisation at 8 weeks if the CDAI was <150. In addition to a further 8-week tapering course of prednisolone or budesonide, 189 people were randomised to 4 g daily of omega-3 fatty acid versus 190 who received placebo. The RCT found no significant difference in relapse rates at 58 weeks (48% with omega-3 fatty acid *v* 49% with placebo, HR 0.90, 95% CI 0.67 to 1.21; P = 0.48; absolute numbers not reported).

Harms:

Fish oil versus placebo:
The review reported that no serious adverse effects were recorded in any of the included RCTs, but found in the pooled analysis that n-3 fatty acid significantly increased the rate of diarrhoea and symptoms of the upper gastrointestinal tract (nausea, vomiting, bloating, dyspepsia, altered taste, or halitosis) compared with placebo (diarrhoea: 4 RCTs, 862 people; 84/433 [19%] with n-3 fatty acid *v* 60/429 [14%] with placebo; RR 1.36, 95% CI 1.01 to 1.84; P = 0.045; symptoms of the upper gastrointestinal tract : 5 RCTs, 609 people; 106/503 [21%] with n-3 fatty acid *v* 61/496 [12%] with placebo; RR 1.98, 95% CI 1.38 to 2.85; P = 0.00002). [105]

Comment:

Omega-3 fatty acids are safe, but likely to be ineffective for maintenance of remission in Crohn's disease.

OPTION ENTERAL NUTRITION

Relapse rate
Half-elemental diet compared with unrestricted diet Half-elemental diet seems more effective at reducing the rate of relapse in people ileal and colonic Crohn's disease at 2 years (moderate-quality evidence).

Quality of life
Half-elemental diet compared with unrestricted diet Half-elemental diet may be as effective at improving quality of life in people with ileal and colonic Crohn's disease at 1 and 13 months (low-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Half-elemental diet versus unrestricted diet:
We found systematic review (search date 2007, 2 RCTs, 84 people) that compared half-elemental diet versus unrestricted diet. [106] Only one of the included RCTs met *Clinical Evidence* inclusion criteria. [107] The RCT (51 people with ileal and colonic disease and Crohn's Disease Activity Index [CDAI] <150) included in the review compared "half-elemental diet" (where half the person's daily calorie intake was given by elemental diet [900−1200 kcal a day; 240−320 g as powder, 900−1200 mL as solution in water, through self-inserted tube or by oral intake] and half by an unrestricted diet) versus an unrestricted diet. [107] It found that the half-elemental diet reduced rates of relapse (defined as CDAI >200 or need for medical treatment to induce remission) at 2 years compared with an unrestricted diet (9/26 [35%] with half-elemental diet *v* 16/25 [64%] with unrestricted diet; HR: 0.40, 95% CI 0.16 to 0.98). [107] A secondary analysis of the same RCT included in the review found that, after adjusting for confounding factors, there was no significant difference

between groups for quality of life (measured by Inflammatory Bowel Disease Questionnaire [IBDQ] score) at 1 or 13 months (IBDQ score at 1 month: 167 with half-elemental diet *v* 169.4 control group; IBDQ score at 13 months: 171.9 half-elemental diet group *v* 176.6 control group; P values not reported, reported as not significant). [108]

Harms: The review and the subsequent RCT gave no information on adverse effects. [106] [108]

Comment: Enteral nutrition has an established role in the treatment of children with Crohn's disease, [109] and evidence suggests that it may also be beneficial in maintaining remission in adults. Although elemental diet has been shown to be less effective than corticosteroids for inducing remission in adults with Crohn's disease, [110] it is used in some centres because of its favourable adverse-effects profile when compared with corticosteroids. [2]

OPTION PROBIOTICS

Relapse rate

Probiotics compared with placebo We don't know whether probiotics are more effective at reducing clinical and endoscopic relapse in people with Crohn's disease (low-quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits:

Lactobacilli versus placebo:
We found 3 systematic reviews (search dates 2005 [111] and 2007 [45] [112]) comparing lactobacilli versus placebo.

The first review found no RCTs that met *Clinical Evidence* inclusion criteria. [111]

The second review compared probiotics versus placebo; it included 6 RCTs comparing lactobacilli versus placebo that are also included in the most recent review, and is therefore not reported further here. [45]

The most recent review found no significant difference in overall clinical relapse rate between lactobacilli and placebo (6 RCTs, 359 people; 78/179 [44%] with lactobacilli *v* 68/180 [38%] with placebo; RR 1.15, 95% CI 0.90 to 1.48; P = 0.26). [112] The review also found no significant difference between groups in the rate of endoscopic relapse (3 RCTs, 200 people; 11/97 [11%] with lactobacilli *v* 9/103 [8%] with placebo; RR 1.31, 95% CI 0.57 to 3.00; P = 0.53). Subgroup analysis found that, compared with placebo, *Lactobacillus johnsonii* did not significantly reduce clinical relapse rates (2 RCTs, 168 people; 41/82 [50%] with *Lactobacillus johnsonii v* 47/86 [54%] with placebo; RR 0.91, 95% CI 0.68 to 1.23; P = 0.55), but that *Lactobacillus rhamnosus* strain *GG* significantly increased clinical relapse rates (4 RCTs, 191 people; 35/97 [36%] with *Lactobacillus rhamnosus v* 21/94 [22%] with placebo; RR 1.68, 95% CI 1.07 to 2.64; P = 0.03). [112]

Other probiotics:
We found no systematic review or RCTs comparing other probiotics versus placebo in Crohn's disease.

Harms:

Lactobacilli versus placebo:
The systematic review found no significant difference in the rate of adverse effects between lactobacilli and placebo (5 RCTs, 350 people; 44/175 [25%] with lactobacilli *v* 54/175 [31%] with placebo; RR 0.83, 95% CI 0.61 to 1.12; P = 0.23). [112]

Comment:

Clinical guide:
Based on current evidence, treatment with probiotics cannot be recommended for maintenance of remission in Crohn's disease. It should be noted that a number of trials too small to meet our inclusion criteria have shown beneficial effects of probiotic strains other than *Lactobacillus johnsonii* LA1, and that negative results for one bacterium or strain cannot be extrapolated to another. Furthermore, this calls into question the validity of pooling results for different strains of lactobacilli.

OPTION SMOKING CESSATION

Relapse rate

Compared with no smoking cessation Smoking cessation may be more effective at reducing the risk of clinical relapse. Smoking cessation may reduce the risk of flare-ups and the use of immunosuppressive treatment at 1 year. Former smokers may have lower rates of clinical relapse compared with smokers, but may have higher rates of clinical relapse compared with non-smokers (very low-quality evidence).

Reoperation rates

Compared with no smoking cessation Smoking cessation may reduce the risk of reoperation. Former smokers may have lower reoperation rates than smokers, but may have higher reoperation rates than non-smokers (very-low quality evidence).

For GRADE evaluation of interventions for Crohn's disease, see table, p 36 .

Benefits: We found two systematic reviews (search dates 1999 [113] and 2004; [114] neither contained a meta-analysis) that largely included the same studies. Between them the two reviews reported on 10 cohort studies matching our inclusion criteria, 9 of which compared clinical relapse or reoperation rates in people with Crohn's disease in remission in relation to smoking status. All but one study found that non-smokers had between 16% and 33% fewer episodes of clinical relapse and between 7% and 34% fewer reoperations compared with non-smokers (table 2, p 35). Former smokers were universally found to have lower rates of clinical relapse and reoperation than smokers, but tended to have higher relapse and reoperation rates than non-smokers (table 2, p 35). One cohort study found that people who stopped smoking for >1 year had significantly fewer flare-ups and required significantly less immunosuppressive treatment than those who continued smoking, and had the same risk of flare-ups as non-smokers after 4 years of observation (1 cohort study, 177 people matched for age, sex, disease location and activity, concurrent medical treatment, and previous smoking habit; Kaplan–Meier life table analysis: P <0.001). [115]

Harms: None of the studies reported harms associated with smoking cessation.

Comment: **Clinical guide:**
There is good evidence that smoking cessation in people with Crohn's disease reduces the frequency of clinical relapse and the need for immunosuppressive medication as well as surgery. All people with Crohn's disease who smoke should be urged to give up smoking, and should be offered support through evidence-based, structured smoking-cessation programmes. [115]

GLOSSARY

Elemental diet A liquid diet, made up of simple forms of protein, carbohydrates, and fats that can be absorbed without further digestion. They are given either as total nutritional support to induce remission, or to support an exclusion diet or to supplement a normal diet. They are taken diluted in water, either orally or via a nasogastric tube or a percutaneous enterostomy tube.

Harvey-Bradshaw Index A validated clinical index used for Crohn's disease. It includes general well being, abdominal pain, number of liquid stools, abdominal mass and complications, and ranges from 0 to 25, with remission defined as a score below 5.

Olsalazine is broken down by the colonic flora into two molecules of mesalazine

Rutgeerts' classification Score grading the severity of recurrence of Crohn's disease following surgical resection of the terminal ileum, which is based on the following endoscopic findings: number of isolated aphthous ulcers (< 5 = 1 and > 5 = 2), generalised inflammation (diffuse ileitis = 3), and mucosal irregularity with narrowing (= 4) in the neoterminal ileum. A score of 0 denotes no recurrence, and 4 denotes severe recurrence.

Crohn's disease activity index (CDAI) Validated composite score grading the severity of Crohn's disease based on the following clinical parameters measured over 7 days: number of soft or liquid stools, use of antidiarrhoeal medication (0 or 1), abdominal pain (0–3), general well being (0–4), number of extraintestinal manifestations, abdominal mass (0, 2, or 5), haematocrit (% decrease from expected), and body weight (% decrease from expected). The scores achieved for each parameter are multiplied by a predefined factor, and the products are added to give a final score. Scores range from 0 to approximately 600. A CDAI score below 150 is generally considered to mean quiescent disease, whereas a score above 450 generally signifies very severe disease.

Disease Activity Score A non-validated composite score grading the severity of Crohn's disease based on the following parameters: number of soft or liquid stools, use of antidiarrhoeal medication, abdominal pain, general well being, number of extra-intestinal manifestations, abdominal mass, weight loss, fever, hypoalbumenaemia, anaemia, and increase in erythrocyte sedimentation rate. Scores range from 0 to 10. A CDAI score <5 signifies quiescent disease, whereas a score of >10 signifies severe disease.

Fistula An abnormal communication between two epithelial surfaces (e.g., bowel lumen and skin).

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

Inflammatory Bowel Disease Questionnaire (IBDQ) The IBDQ is a validated health-related quality-of-life questionnaire. It contains 32 questions, which are divided into four health domains: bowel symptoms (10 questions), systemic symptoms (5 questions), emotional function (12 questions), and social function (5 questions). The total IBDQ score ranges from 32 to 224, with higher scores reflecting better well being.

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

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

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Aminosalicylates to maintain remission after surgery Two systematic reviews added comparing mesalazine versus placebo or azathioprine/6-mercaptopurine. [99] [71] The first review found that mesalazine reduced the rate of clinical and endoscopic recurrence after surgery compared with placebo, but found no difference between mesalazine and azathioprine for clinical recurrence rates at 12 or 24 months. However, the review also found that mesalazine increased the risk of endoscopic recurrence after surgery compared with azathioprine at 12 months. [71] The second review found that mesalazine increased the proportion of people who maintained remission after surgery compared with placebo. [99] A subgroup analysis of the people with surgically induced remission found that pH7-dependent mesalazine reduced the rate of relapse compared with placebo whereas pH6-dependent mesalazine and controlled-release mesalazine did not. Categorisation unchanged; Likely to be beneficial.

Antibiotics to induce remission One systematic review and one RCT added. [45] [44] The review found that broad-spectrum antibiotics improved the clinical symptoms of Crohn's disease compared with placebo. [45] However, these results should be interpreted with caution, as the review was of low quality, pooled data from studies with different antibiotic regimes, and used a fixed-effects model. The RCT found that antibiotics plus prednisolone increased rates of remission at 16 weeks compared with placebo plus prednisolone; however, these benefits were not sustained at longer-term follow-up. [44] Categorisation unchanged (Unlikely to be beneficial).

Azathioprine to maintain remission One systematic review and one RCT added. [74] [75] The review found that azathioprine increased the proportion of people who maintained remission compared with placebo over a treatment period of 6 to 24 months. It also found that 6-mercaptopurine increased the proportion of people who maintained remission over 2 years compared with placebo. [74] The RCT found no significant difference in the rate of clinical remission between azathioprine and budesonide, but found that azathioprine increased the rate of endoscopic remission compared with budesonide. [75] One cohort study found that azathioprine increased the risk of lymphoproliferative disorders in people with Crohn's disease or ulcerative colitis. [76] Categorisation unchanged (Trade-off between benefits and harms).

Azathioprine/mercaptopurine to maintain remission after surgery One systematic review added. [99] It found that, compared with placebo, azathioprine/6-mercaptopurine reduced the risk of clinical recurrence after surgery and severe endoscopic recurrence after surgery at 12 months. Categorisation unchanged (Likely to be beneficial).

Corticosteroids (oral) to induce remission Two reviews updated. [12] [16] The first review found that conventional corticosteroids increased remission rates at 15 or more weeks compared with placebo. [12] The second review found that budesonide increased the rate of clinical remission at 12, 24, and 38 weeks compared with placebo. [16] It also found that proportionately fewer people achieved clinical remission with budesonide compared with methylprednisolone or prednisolone at 24 and 38 weeks. No significant differences were found between groups at 12 weeks. [16] Categorisation unchanged (Beneficial).

Corticosteroids (oral) to maintain remission One systematic review added comparing budesonide versus placebo or different regimens of budesonide versus each other. [96] The review found no difference between budesonide 3 or 6 mg and placebo in maintenance of clinical remission at 3, 6, or 12 months. [96] The review also reported no significant difference in maintenance of clinical remission between budesonide 3 mg and 6 mg at 3, 6, or 12 months, or between budesonide 6 mg and 9 mg. [96] Categorisation unchanged (Likely to be ineffective or harmful).

Enteral nutrition One systematic review and one secondary analysis added. [106] [108] The review found that, at 2 years, the half-elemental diet reduced rates of relapse (defined as Crohn's Disease Activity Index >200 or need for medical treatment to induce remission) compared with an unrestricted diet. [106] A secondary analysis of the RCT included in the review found no difference between groups in quality of life. [108] Categorisation unchanged (Likely to be beneficial).

Infliximab to maintain remission Two systematic reviews added to the benefits section that assessed the use of infliximab versus placebo. [81] [82] They found that infliximab increased the proportion of people who maintained clinical remission at 44 to 54 weeks. [81] [82] Four cohort studies were added to the harms section. [88] [89] [90] [91] The trend of this evidence suggests that infliximab is safe to use in the long term. [88] [89] [90] [91] Categorisation unchanged (Likely to be beneficial).

Laparoscopic versus open ileocaecal resection Two systematic reviews added, which did not report the effects of surgery on remission of Crohn's disease. [66] [67] Categorisation unchanged; Likely to be beneficial.

Methotrexate to maintain remission One systematic review added comparing methotrexate versus placebo or 6-mercaptopurine. [79] It found that methotrexate increased the proportion of people who maintained clinical remission compared with placebo. [79] Categorisation unchanged; Likely to be beneficial.

Probiotics Two systematic review added. [45] [112] Both reviews identified the same 6 RCTs comparing lactobacilli versus placebo. The most recent review found no differences between groups for either clinical or endoscopic relapse

rates. [112] Categorisation remains Unknown effectiveness as there remains insufficient evidence to assess the effects of probiotics on Crohn's disease.

Strictureplasty One systematic review added that assessed non-randomised trials. [60] It found no difference in rates of medical or surgical recurrence, or postoperative complications between strictureplasty compared with resection. [60] Categorisation unchanged; Unknown effectiveness, as there remains insufficient good-quality evidence to assess the effects of strictureplasty.

Aminosalicylates to maintain remission One review updated. [70] No further data added. One systematic review added comparing mesalazine (1–4 g/day) versus placebo. [71] It found that mesalazine significantly increased the proportion of people who maintained medically induced remission. Categorisation changed from Likely to be ineffective or harmful to Likely to be beneficial.

Fish oil One systematic review added comparing fish oil versus placebo. [105] The review reported that a larger proportion of people taking fish oil than placebo maintained remission, based on a pooled analysis of 6 RCTs; however, the review also reported that the RCTs included in the pooled analysis were clinically and statistically heterogeneous. [105] When the review analysed the studies individually, it found that the two largest RCTs identified found no significant difference between groups in relapse rates. [105] Categorisation unchanged (unknown effectiveness)

REFERENCES

1. Jewell DP. Crohn's disease. In: Warrell DA, Cox TM, Firth JD, et al, eds. *Oxford textbook of medicine*. 4th ed. Oxford: Oxford University Press, 2005.
2. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53(Suppl 5):V1–V16.[PubMed]
3. Travis SP, Stange EF, Lemann M, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006;55(Suppl 1):i16–i35.[PubMed]
4. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;170:2–6; discussion 16–19.[PubMed]
5. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126:1504–1517.[PubMed]
6. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther* 2002;16:51–60.[PubMed]
7. Isaacs KL, Lewis JD, Sandborn WJ, et al. State of the art: IBD therapy and clinical trials in IBD. *Inflamm Bowel Dis* 2005;11(Suppl 1):S3–S12.[PubMed]
8. Grant IR. Zoonotic potential of *Mycobacterium avium* spp. *paratuberculosis:* the current position. *J Appl Microbiol* 2005;98:1282–1293.
9. Loftus EV Jr. Crohn's disease: why the disparity in mortality? *Gut* 2006;55:447–449.[PubMed]
10. von Roon AC, Reese GE, Teare J, et al. The risk of cancer in Crohn's disease. *Dis Colon Rectum* 2007;50:839–855.
11. Wolters FL, Russel MG, Stockbrugger RW. Systematic review: has disease outcome in Crohn's disease changed during the last four decades? *Aliment Pharmacol Ther* 2004;20:483–496.
12. Benchimol EI, Seow CH, Steinhart AH, et al. Traditional corticosteroids for induction of remission in Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
13. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847–869.
14. Malchow H, Ewe K, Brandes JW, *et al*. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;86:249–266.
15. Brignola C, De Simone G, Iannone P, et al. Influence of steroid treatment's duration in patients with active Crohn's disease. *Agents Actions* 1992;Spec No:C90–C92.[PubMed]
16. Seow CH, Benchimol EI, Griffiths AM, et al. Budesonide for induction of remission in Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.[PubMed]
17. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994;331:836–841.[PubMed]
18. Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;41:209–214.[PubMed]
19. Hofer KN. Oral budesonide in the management of Crohn's disease. *Ann Pharmacother* 2003;37:1457–1464.[PubMed]
20. Tremaine WJ, Hanauer SB, Katz S, et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002;97:1748–1754.[PubMed]
21. Herfarth H, Gross V, Andus T, et al. Analysis of the therapeutic efficacy of different doses of budesonide in patients with active Crohn's ileocolitis depending on disease activity and localization. *Int J Colorectal Dis* 2004;19:147–152.[PubMed]
22. Singleton JW, Law DH, Kelley ML Jr, et al. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. *Gastroenterology* 1979;77:870–882.
23. Schoon EJ, Bollani S, Mills PR, et al. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. *Clin Gastroenterol Hepatol* 2005;3:113–121.
24. Lewis JD, Gelfand JM, Troxel AB, et al. Immunosuppressant medications and mortality in inflammatory bowel disease. *Am J Gastroenterol* 2008;103:1428–1435.[PubMed]
25. Marehbian J, Arrighi HM, Hass S, et al. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol* 2009;104:2524–2533.[PubMed]
26. Otley A, Steinhart AH. Budesonide for induction of remission in Crohn's disease. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date not reported.
27. Hanauer SB, Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004;2:379–388.[PubMed]
28. Gisbert JP, Gomollon F, Mate J, et al. Role of 5-aminosalicylic acid (5-ASA) in treatment of inflammatory bowel disease: a systematic review. *Dig Dis Sci* 2002;47:471–488. Search date 2000.[PubMed]
29. Klotz U. The role of aminosalicylates at the beginning of the new millennium in the treatment of chronic inflammatory bowel disease. *Eur J Clin Pharmacol* 2000;56:353–362.
30. Singleton JW, Hanauer SB, Gitnick GL, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993;104:1293–1301.[PubMed]
31. Nordic Research Inc. *Clinical research report: efficacy and safety of oral Pentasa in the treatment of active Crohn's disease*. Nordic Research Inc., 1991.
32. Hoechst Marion Roussel Inc. Clinical study report: *Efficacy and safety of oral Pentasa in the treatment of active Crohn's disease*. Hoechst Marion Roussel Inc., 1997, Frankfurt, Germany.
33. Rasmussen SN, Lauritsen K, Tage-Jensen U, et al. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. *Scand J Gastroenterol* 1987;22:877–883.[PubMed]
34. Mahida YR, Jewell DP. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. *Digestion* 1990;45:88–92.[PubMed]
35. Wright JP, Modigliani R, Malchow H. A randomized, double blind, placebo controlled trial of olsalazine for active Crohn's disease. *Inflamm Bowel Dis* 1995;1:241–246.
36. Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflam Bowel Dis* 2007;13:629–638.[PubMed]
37. Rahimi R, Nikfar S, Rezaie A, et al. A meta-analysis of broad-spectrum antibiotic therapy in patients with active Crohn's disease. *Clin Ther* 2006;28:1983–1988.[PubMed]
38. Blichfeldt P, Blomhoff JP, Myhre E, et al. Metronidazole in Crohn's disease. A double blind cross-over clinical trial. *Scand J Gastroenterol* 1978;13:123–127.
39. Ursing B, Alm T, Barany F, et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. II. Result. *Gastroenterology* 1982;83:550–562.
40. Prantera C, Lochs H, Campieri M, et al. Antibiotic treatment of Crohn's disease: results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. *Aliment Pharmacol Therap* 2006;23:1117–1125.[PubMed]
41. Prantera C, Zannoni F, Scribano ML, et al. An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996;91:328–332.[PubMed]
42. Steinhart AH, Feagan BG, Wong CJ, et al. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology* 2002;123:33–40.[PubMed]
43. Afdhal NH, Long A, Lennon J, et al. Controlled trial of antimycobacterial therapy in Crohn's disease. Clofazimine versus placebo. *Dig Dis Sci* 1991;36:449–453.
44. Selby W, Pavli P, Crotty B, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology* 2007;132:2313–2319.[PubMed]
45. Rahimi R, Nikfar S, Rahimi F, et al. A meta-analysis on the efficacy of probiotics for maintenance of remission and prevention of clinical and endoscopic relapse in Crohn's disease. *Digest Dis Sci* 2008;53:2524–2531.[PubMed]
46. Sandborn W, Sutherland L, Pearson D, et al. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 1997.
47. de Jong DJ, Goullet M, Naber TH. Side effects of azathioprine in patients with Crohn's disease. *Eur J Gastroenterol Hepatol* 2004;16:207–212.[PubMed]
48. Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004.

49. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;332:292–297.[PubMed]
50. Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003.
51. Clark W, Raftery J, Song F, et al. Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease. *Health Technol Assess* 2003;7:1–67. Search date 2001.
52. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;337:1029–1035.[PubMed]
53. Nahar IK, Shojania K, Marra CA, et al. Infliximab treatment of rheumatoid arthritis and Crohn's disease. *Ann Pharmacother* 2003;37:1256–1265. Search date 2002.[PubMed]
54. MacLean CH, Mojica WA, Newberry SJ, et al. Systematic review of the effects of n-3 fatty acids in inflammatory bowel disease. *Am J Clin Nutr* 2005;82:611–619. Search date 2003.[PubMed]
55. McDonald JW, Feagan BG, Jewell D, et al. Cyclosporine for induction of remission in Crohn's disease. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd.
56. Feagan BG, McDonald JW, Rochon J, et al. Low-dose cyclosporine for the treatment of Crohn's disease. The Canadian Crohn's Relapse Prevention Trial Investigators. *N Engl J Med* 1994;330:1846–1851.[PubMed]
57. Stange EF, Modigliani R, Pena AS, Wood AJ, Feutren G, Smith PR. European trial of cyclosporine in chronic active Crohn's disease: a 12-month study. The European Study Group. *Gastroenterology* 1995;109:774–782.[PubMed]
58. Jewell DP, Lennard-Jones JE, Lowes J, et al. Oral cyclosporin for chronic active Crohn's disease: A multicentre controlled trial. *Eur J Gastroenterol Hepatol* 1994;6:499–505.
59. Brynskov J, Freund L, Rasmussen SN, et al. A placebo-controlled, double-blind, randomized trial of cyclosporine therapy in active chronic Crohn's disease. *N Engl J Med* 1989;321:845–850.
60. Reese GE, Purkayastha S, Tilney HS, et al. Strictureplasty vs resection in small bowel Crohn's disease: an evaluation of short-term outcomes and recurrence. *Colorect Dis* 2007;9:686–694.[PubMed]
61. Tichansky D, Cagir B, Yoo E, et al. Strictureplasty for Crohn's disease: meta-analysis. *Dis Colon Rectum* 2000;43:911–919. Search date 1999.
62. Yamamoto T, Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2007;50:1968–1986.
63. Fazio VW, Marchetti F, Church M, et al. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. *Ann Surg* 1996;224:563–571; discussion 71–73.[PubMed]
64. Rosman AS, Melis M, Fichera A. Metaanalysis of trials comparing laparoscopic and open surgery for Crohn's disease. *Surg Endosc* 2005;19:1549–1555.
65. Tilney HS, Constantinides VA, Heriot AG, et al. Comparison of laparoscopic and open ileocecal resection for Crohn's disease: a metaanalysis. *Surg Endosc* 2006;20:1036–1044.
66. Tan JJ, Tjandra JJ. Laparoscopic surgery for Crohn's disease: a meta-analysis. *Dis Col Rec* 2007;50:576–585.[PubMed]
67. Polle SW, Wind J, Ubbink DT, et al. Short-term outcomes after laparoscopic ileocolic resection for Crohn's disease. A systematic review. *Dig Surg* 2006;23:346–357.[PubMed]
68. Polle SW, Bemelman WA, et al. Surgery insight: minimally invasive surgery for IBD. *Nature Clin Pr Gastroenterol Hepatol* 2007;4:324–335.[PubMed]
69. Tekkis PP, Purkayastha S, Lanitis S, et al. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. *Colorectal Dis* 2006;8:82–90. Search date 2005.[PubMed]
70. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd.
71. Steinhart AH, Forbes A, Mills EC, et al. Systematic review: the potential influence of mesalazine formulation on maintenance of remission in Crohn's disease. *Aliment Pharmacol Therap* 2007;25:1389–1399.[PubMed]
72. Mahmud N, Kamm MA, Dupas JL, et al. Olsalazine is not superior to placebo in maintaining remission of inactive Crohn's colitis and ileocolitis: a double blind, parallel, randomised, multicentre study. *Gut* 2001;49:552–556.[PubMed]
73. Binder V. Epidemiology of IBD during the twentieth century: an integrated view. *Best Pract Res Clin Gastroenterol* 2004;18:463–479.[PubMed]
74. Prefontaine E, Sutherland LR, MacDonald JK, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
75. Mantzaris GJ, Christidou A, Sfakianakis M, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. *Inflam Bowel Dis* 2009;15:375–382.[PubMed]
76. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617–1625.[PubMed]
77. Mantzaris GJ, Roussos A, Christidou A, et al. The long-term efficacy of azathioprine does not wane after four years of continuous treatment in patients with steroid-dependent luminal Crohn's disease. *J Crohn's Colitis* 2007;1:28–34.
78. Vandell AG, DiPiro JT. Low-dosage methotrexate for treatment and maintenance of remission in patients with inflammatory bowel disease. *Pharmacotherapy* 2002;22:613–620. Search date 2001.[PubMed]
79. Patel V, MacDonald JK, Donald-John WD, et al. Methotrexate for maintenance of remission in Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2009.
80. Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000;342:1627–1632.[PubMed]
81. Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008;6:644–653.[PubMed]
82. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. In: The Cochrane Librar, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.
83. Feagan BG, Yan S, Bala M, et al. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastroenterol* 2003;98:2232–2238.
84. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541–1549.[PubMed]
85. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;126:402–413.[PubMed]
86. Lichtenstein GR, Olson A, Travers S, et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. *Am J Gastroenterol* 2006;101:1030–1038.
87. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;4:621–630.
88. Caspersen S, Elkjaer M, Riis L, et al. Infliximab for inflammatory bowel disease in Denmark 1999-2005: clinical outcome and follow-up evaluation of malignancy and mortality. *Clin Gastroenterol Hepatol* 2008;6:1212–1217.[PubMed]
89. Fidder H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;58:501–508.[PubMed]
90. Lees CW, Ali AI, Thompson AI, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther* 2009;29:286–297.[PubMed]
91. Schneeweiss S, Korzenik J, Solomon DH, et al. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther* 2009;30:253–264.[PubMed]
92. Rutgeerts P, D Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;117:761–769.
93. Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004;2:542–553.[PubMed]
94. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601–608.[PubMed]
95. Steinhart AH, Ewe K, Griffiths AM, et al. Corticosteroids for maintaining remission of Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd.
96. Benchimol EI, Seow CH, Otley AR, et al. Budesonide for maintenance of remission in Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
97. Hanauer S, Sandborn WJ, Persson A, et al. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. *Aliment Pharmacol Ther* 2005;21:363–371.
98. Camma C, Giunta M, Rosselli M, et al. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables. *Gastroenterology* 1997;113:1465–1473. Search date 1997.[PubMed]
99. Doherty G, Bennett G, Patil S, et al. Interventions for prevention of post-operative recurrence of Crohn's disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2009.
100. Caprilli R, Cottone M, Tonelli F, et al. Two mesalazine regimens in the prevention of the post-operative recurrence of Crohn's disease: a pragmatic, double-blind, randomized controlled trial. *Aliment Pharmacol Ther* 2003;17:517–523.[PubMed]
101. Ewe K, Herfarth C, Malchow H, et al. Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: a multicenter trial. *Digestion* 1989;42:224–232.[PubMed]
102. 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.
103. Peyrin-Biroulet L, Deltenre P, Ardizzone S, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2009;104:2089–2096.[PubMed]
104. Myrelid P, Olaison G, Sjodahl R, et al. Thiopurine therapy is associated with postoperative intra-abdominal septic complications in abdominal surgery for Crohn's disease. *Dis Col Rect* 2009;52:1387–1394.[PubMed]
105. Turner D, Zlotkin SH, Shah PS, et al. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. In: The Cochrane Library, Issue 1, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.[PubMed]
106. Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. In: The Cochrane Library, Issue 3, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.
107. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: a randomized-controlled trial. *Aliment Pharmacol Ther* 2006;24:1333–1340.[PubMed]
108. Takagi S, Utsunomiya K, Kuriyama S, et al. Quality of life of patients and medical cost of "half elemental diet" as maintenance therapy for Crohn's disease: secondary outcomes of a randomised controlled trial. *Dig Liver Dis* 2009;41:390–394.[PubMed]
109. Zachos M, Tondeur M, Griffiths A. Enteral nutritional therapy for induction of remission in Crohn's disease (Cochrane review). In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd.
110. Goh J, O'Morain A. Review article: nutrition and adult inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;17:307–320.[PubMed]
111. Rolfe VE, Fortun PJ, Hawkey CJ, et al. Probiotics for maintenance of remission in Crohn's disease. In: The Cochrane Library, Issue 1, 2007. Chichester, UK: John Wiley & Sons, Ltd.

112. Shen J, Ran HZ, Yin MH, et al. Meta-analysis: the effect and adverse events of Lactobacilli versus placebo in maintenance therapy for Crohn disease. *Int Med J* 2009;39:103–109.[PubMed]
113. Johnson GJ, Cosnes J, Mansfield JC. Review article: smoking cessation as primary therapy to modify the course of Crohn's disease. *Aliment Pharmacol Ther* 2005;21:921–931. Search date 2004.[PubMed]
114. Yamamoto T, Keighley MR. Smoking and disease recurrence after operation for Crohn's disease. *Br J Surg* 2000;87:398–404. Search date 1999.[PubMed]
115. Cosnes J, Beaugerie L, Carbonnel F, et al. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001;120:1093–1099.[PubMed]
116. Lindberg E, Jarnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and clinical course. *Gut* 1992;33:779–782.[PubMed]
117. Cottone M, Rosselli M, Orlando A, et al. Smoking habits and recurrence in Crohn's disease. *Gastroenterology* 1994;106:643–648.[PubMed]
118. Breuer-Katschinski BD, Hollander N, Goebell H. Effect of cigarette smoking on the course of Crohn's disease. *Eur J Gastroenterol Hepatol* 1996;8:225–228.[PubMed]
119. Cosnes J, Carbonnel F, Beaugerie L, et al. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;110:424–431.[PubMed]
120. Timmer A, Sutherland LR, Martin F. Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1998;114:1143–1150.[PubMed]
121. Yamamoto T, Keighley MR. The association of cigarette smoking with a high risk of recurrence after ileocolonic resection for ileocecal Crohn's disease. *Surg Today* 1999;29:579–580.
122. Yamamoto T, Allan RN, Keighley MR. Smoking is a predictive factor for outcome after colectomy and ileorectal anastomosis in patients with Crohn's colitis. *Br J Surg* 1999;86:1069–1070.[PubMed]
123. Cosnes J, Carbonnel F, Carrat F, et al. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. *Aliment Pharmacol Ther* 1999;13:1403–1411.[PubMed]

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Disclaimer

TABLE 1 **Randomised controlled trials comparing different dosing regimens of oral budesonide for inducing remission in active Crohn's disease (see text, p 4).**

Reference	Methods	Participants	Interventions	Outcomes	Results	P value
[17]	RCT	Age >18 years, CDAI >200, ileal or ileocaecal Crohn's disease up to the hepatic flexure	15 mg, 9 mg, 3 mg, and placebo daily in two divided doses for 8 weeks	Proportion of people achieving remission	AR: 28/64 (43%) with 15 mg *v* 31/61 (51%) with 9 mg *v* 22/67 (33%) with 3 mg	9 mg *v* 3 mg; P = 0.03 15 mg *v* 9 mg; P value not reported 15 mg v 3 mg; P value not reported
[18]	RCT	Age >18 years, CDAI >200, ileal or ileocaecal Crohn's disease up to the hepatic flexure	Budesonide 9 mg in a single dose, budesonide 9 mg in 2 divided doses, and prednisolone 40 mg (reducing to 5 mg after 9 weeks) for 8 weeks	Proportion of people achieving remission	AR: 35/58 (60%) with single dose *v* 26/61 (42%) with divided dose *v* 35/58 (60%) with prednisolone	P = 0.062 for all comparisons
[20]	RCT	Age >18 years, CDAI 200 to 450, ileal or ileocaecal Crohn's disease up to the hepatic flexure	Budesonide 9 mg in a single dose, budesonide 9 mg in 2 divided doses, and placebo for 8 weeks	Proportion of people achieving remission	AR: 37/80 (48%) with single dose *v* 41/79 (53%) with divided dose *v* 13/41 (33%) with placebo	P value not reported
[21]	RCT	Age 18 to 70 years, CDAI >150, ileal, ileocaecal, or colonic Crohn's disease	Budesonide 6 mg, 9 mg, or 18 mg in 3 divided doses daily	Proportion of people achieving remission	AR: 21/32 (66%) with 18 mg *v* 18/33 (55%) with 9 mg *v* 14/39 (36%) with 6 mg	18 mg *v* 6 mg; P = 0.017 9 mg *v* 6 mg; P value not reported

CDAI, Crohn's Disease Activity Index.

TABLE 2 **Cohort studies comparing the relationship of disease recurrence and smoking in people with Crohn's disease in remission (see text, p 28).**

Reference	Methods	Participants	Site of disease	Length of follow-up	Outcome	P value
[116]	Cohort study after surgical resection	85 smokers, 89 non-smokers	SB + IC + LB	Mean 10.8 years	Reoperation rate (non-smokers *v* smokers): 5 years: 29% *v* 36% 10 years: 41% *v* 70%	P = 0.007 (RR 2.1)
[117]	Cohort study after surgical resection	81 smokers, 54 non-smokers	SB + IC + LB	10 years	Reoperation rate after 10 years (non-smokers *v* smokers): 26% *v* 42%	P = 0.015* (RR 1.79)
[118]	Cohort study after surgical resection	53 smokers, 110 non-smokers, 19 ex-smokers	SB + IC + LB	Mean 8.2 years	Clinical recurrence rate after 6 years (non-smokers *v* smokers *v* ex-smokers): 40% *v* 73% *v* 59%	P = 0.006* (RR 1.4)
					Reoperation rate after 6 years (non-smokers *v* smokers *v* ex-smokers): 8% *v* 24% *v* 21%	P = 0.005* (RR 2.0)
					Endoscopic recurrence rate after 1 year (non-smokers *v* smokers *v* ex-smokers): 35% *v* 70% *v* 27%	P = 0.002* (RR 4.3)
[119]	Cohort study after surgical resection	143 smokers, 144 non-smokers	SB + IC + LB	Not documented	Reoperation rate (non-smokers *v* smokers): 5 years: 26% *v* 43% 10 years: 33% *v* 64%	P <0.001 (RR 3.1)
[120]	Cohort study after surgical resection	89 smokers, 115 non-smokers	SB + IC + LB	Not documented	Crude reoperation rate (non-smokers *v* smokers): 22% *v* 30%	NS
[121]	Cohort study after surgical resection	53 smokers, 59 non-smokers, 40 ex-smokers	SB + IC + LB	48 weeks	Relapse rate after 48 weeks (non-smokers *v* smokers *v* ex-smokers): 30% *v* 53% *v* 35%	P = 0.02* (RR 2.1)
[122]	Cohort after ileocaecal resection	79 smokers, 62 non-smokers	IC only	Median 8.1 years	Reoperation rate (non-smokers *v* smokers): 5 years: 19% *v* 35% 10 years: 36% *v* 55%	P = 0.007 (RR 2.3)
[123]	Cohort after colectomy and ileorectal anastomosis	36 smokers, 33 non-smokers	LB only	Median 18.6 years	Reoperation rate (non-smokers *v* smokers): 5 years: 11% *v* 25% 10 years: 15% *v* 46% 15 years: 18% *v* 52%	P = 0.005 (RR 3.0)
[115]	Cohort study of consecutive outpatients	303 smokers, 262 non-smokers, 57 ex-smokers	SB + IC + LB + perineum	12 to 18 months	Clinically active disease (CDAI >150) after 12 months (non-smokers *v* smokers *v* ex-smokers): 30% *v* 46% *v* 23%	P = 0.005*†

CDAI, Crohn's Disease Activity Index; IC, ileocaecal; LB, large bowel, SB, small bowel; *Smokers versus non-smokers; †smokers versus ex-smokers.

TABLE **GRADE evaluation of interventions for Crohn's disease**

Important outcomes	**Remission rate, Relapse rate, Re-operation rate, Quality of life, Adverse effects.**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of medical treatments to induce remission in adults with Crohn's disease?									
1 (267) [12]	Remission rate	Methylprednisolone or prednisolone *v* placebo	4	0	0	0	0	High	
1 (54) [15]	Remission rate	Different regiments of methylprednisolone *v* each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (327) [16]	Remission rate	Budesonide *v* placebo	4	0	0	0	0	High	
4 (660) [18] [20] [21] [17]	Remission rate	Different regimens of budesonide *v* each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of data. Directness point for the inclusion of prednisolone
at least 8 (at least 750) [16]	Remission rate	Budesonide *v* methylprednisolone or prednisolone	4	0	0	0	0	High	
5 (732) [27] [33] [34]	Remission rate	Mesalazine *v* placebo	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (91) [35]	Remission rate	Olsalazine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (159) [13]	Remission rate	Sulfasalazine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
6 (804) [37]	Remission rate	Antibiotics *v* placebo	4	0	–1	–2	0	Very low	Consistency point deducted for the use of different types of antibiotics. Directness points deducted for use of concomitant treatment and uncertainty of measure used to assess outcome
1 (78) [39]	Remission rate	Metronidazole *v* sulfasalazine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (83) [40]	Remission rate	Rifaximin *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (41) [41]	Remission rate	Ciprofloxacin plus metronidazole *v* methylprednisolone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (130) [42]	Remission rate	Ciprofloxacin plus metronidazole plus budesonide *v* budesonide alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (49) [43]	Remission rate	Clofazimine plus prednisolone *v* placebo plus prednisolone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (213) [44]	Remission rate	Clarithromycin plus rifabutin plus clofazimine plus prednisolone *v* placebo plus prednisolone	4	0	0	0	0	High	
8 (425) [46]	Remission rate	Azathioprine or mercaptopurine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (141) [48]	Remission rate	Methotrexate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	**Remission rate, Relapse rate, Re-operation rate, Quality of life, Adverse effects.**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (141) [48]	Quality of life	Methotrexate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (181) [51] [50]	Remission rate	Infliximab *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
4 (176) [55]	Remission rate	Ciclosporin *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
What are the effects of surgical interventions to induce and maintain remission in adults with small bowel Crohn's disease?									
7 non-randomised trials (688) [60]	Relapse rate	Strictureplasty *v* resection	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
15 non-randomised trials (506) [61]	Relapse rate	Finney *v* Heineke–Mikulicz procedure	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
15 non-randomised trials (560) [61]	Reoperation rate	Finney *v* Heineke–Mikulicz procedure	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
1 (131) [63]	Relapse rate	Limited *v* extended resection	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of surgical interventions to induce remission in adults with colonic Crohn's disease?									
5 non-randomised trials (248) [69]	Relapse rate	Segmental colectomy *v* sub-total colectomy	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
What are the effects of medical interventions to maintain remission in adults with Crohn's disease?									
6 (1339) [70]	Relapse rate	Aminosalicylates (mesalazine or olsalazine) *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for including mesalazine and olsalazine
at least 9 (at least 1305) [71]	Relapse rate	Mesalazine *v* placebo	4	0	0	0	0	High	
7 (463) [74]	Relapse rate	Azathioprine *v* placebo	4	0	0	0	0	High	
1 (77) [75]	Relapse rate	Azathioprine *v* budesonide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (98) [79]	Relapse rate	Methotrexate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (602) [82]	Relapse rate	Infliximab v placebo	4	0	0	0	0	High	
1 (225) [84]	Relapse rate	Different doses of infliximab v each other	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (unclear) [82]	Quality of life	Infliximab *v* placebo	4	–2	0	0	0	Low	Quality points deducted for unclear population size and incomplete reporting of results
2 (423) [56] [57]	Relapse rate	Ciclosporin *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting or results. Consistency point deducted for conflicting results
3 (303) [95]	Relapse rate	Methylprednisolone or prednisolone *v* placebo	4	0	0	0	0	High	
6 (maximum 540) [96]	Relapse rate	Budesonide *v* placebo	4	0	0	0	0	High	
3 (180) [96]	Relapse rate	Different regimens of budesonide v each other	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	**Remission rate, Relapse rate, Re-operation rate, Quality of life, Adverse effects.**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of medical interventions to maintain remission after surgery in adults with Crohn's disease?									
5 (maximum 788) [99] [71]	Relapse rate	Mesalazine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (165) [100]	Relapse rate	Different regimens of mesalazine versus each other	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (298) [101] [102]	Relapse rate	Sulfasalazine *v* placebo	4	0	–1	0	0	Moderate	Consistency point deducted for different results at different time frames
3 (349) [71]	Relapse rate	Mesalazine *v* azathioprine or 6-MP	4	0	0	0	0	High	
2 (168) [99]	Relapse rate	Azathioprine/6-MP *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of lifestyle interventions to maintain remission in adults with Crohn's disease?									
6 (1039) [105]	Relapse rate	Fish oil *v* placebo	4	0	–2	0	0	Low	Consistency points deducted for conflicting results, publication bias and heterogeneity among studies (clinical and statistical)
1 (51) [106]	Relapse rate	Half-elemental diet *v* unrestricted diet	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (51) [108]	Quality of life	Half-elemental diet *v* unrestricted diet	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
6 (209) [112]	Relapse rate	Probiotics *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results with different strains. Directness point deducted for inclusion a co intervention.
3 cohort studies (956) [113] [114]	Relapse rate	Smoking cessation *v* no smoking cessation	2	–1	0	0	0	Very low	Quality point deducted for incomplete results
7 cohort studies (1192) [113] [114]	Reoperation rate	Smoking cessation *v* no smoking cessation	2	–1	0	0	0	Very low	Quality point deducted for incomplete results

Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies; Directness: generalisability of population or outcomes; Effect size: based on relative risk or odds ratio; 6-MP, 6-mercaptopurine.