NCGC National Clinical Guideline Centre

# Crohn's disease

## Management in adults, children and young people

*Clinical Guideline 152*

*Methods, evidence and recommendations*

*10 October 2012*

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# Acronyms and abbreviations

| | |
|---|---|
| 5-ASA | 5-aminosalicylate treatments and sulfasalazine |
| ANOVA | Analysis of variance |
| AZA | Azathioprine |
| BNF | British National Formulary |
| BNF | British National Formulary for Children |
| CCA | Cost-consequences analysis |
| CEA | Cost-effectiveness analysis |
| CI | Confidence interval |
| CUA | Cost-utility analysis |
| DH | Department of Health |
| DSA | Deterministic Sensitivity Analysis |
| EQ-5D | EuroQol-5D |
| GDG | Guideline Development Group |
| GP | General Practitioner |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HBI | Harvey Bradshaw Index |
| HES | Hospital Episode Statistics |
| HR | Hazard Ratio |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| IBDQ | Inflammatory bowel disease questionnaire |
| ICER | Incremental cost-effectiveness ratio |
| INMB | Incremental Net Monetary Benefit |
| IRR | Inter-rater reliability |
| ITT | Intention to treat |
| LOS | Length of Stay |
| LR+ | Positive likelihood ratio |
| LY | Life-year |
| MD | Mean difference |
| MDT | Multidisciplinary team |

| | | |
|---|---|---|
| MP | Mercaptopurine |
| MTX | Methotrexate |
| NCGC | National Clinical Guideline Centre |
| NHS | National Health Service |
| NHSEED | NHS Economic Evaluation Database |
| NICE | National Institute for Health and Clinical Excellence |
| NNT | Number needed to treat |
| NPV | Negative predictive value |
| NS | Non-significant (not statistically significant) |
| OR | Odds ratio |
| PCDAI | Paediatric Crohn’s disease activity index |
| PICO | Framework incorporating patients, interventions, comparison and outcome |
| PPP | Purchasing Power Parity |
| PPV | Positive predictive value |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life year |
| RCT | Randomised controlled trial |
| ROC | Receiver operating characteristic |
| RR | Relative risk |
| SD | Standard deviation |
| SE | Standard error |
| SPC | Summary of product characteristics |
| SR | Systematic review |
| SS | Statistically significant |
| TPMT | Thiopurine methyl transferase |

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# 1 Introduction

## 1.1 Epidemiology

While the inflammatory condition which affects the distal small bowel and leads to weight loss, abdominal pain and occasional intestinal bleeding became known as Crohn's disease[52] in 1932, individual cases were documented in Poland[152] and Scotland[60] up to thirty years earlier. Typically involving distal ileum or colon, the disease can occur anywhere in the gastrointestinal tract. Since the 1960s there has been a dramatic change in the prevalence and geographical distribution of the condition. Crohn's disease was originally recognised in urban areas of Northern Europe and North America, although there are now few parts of the world where it is not found.[72] Conservative estimates during the 1990s suggested that the prevalence in the United Kingdom was about 75/100,000[214] and that this figure may have underestimated the true prevalence by 33%.[176] By the end of the century, the prevalence of Crohn's disease in the north of England was 145/100,000[228] and the most recent study from Tayside (Scotland) now indicates a prevalence of 157/100,000[263], meaning there are at least 115,000 people in the UK with Crohn's disease at the present time.

## 1.2 Aetiology

The causes of Crohn's disease are widely debated, and none have consistently met the criteria necessary to be recognised as the sole or major cause of the condition. Smoking and genetic predisposition are two important factors that are likely to play some role.[39] This limited understanding has meant that treatment is largely directed at symptom relief rather than cure, and there is need to distinguish between active treatment of acute disease (inducing remission) and the prevention of relapse (maintaining remission). Whether a relapse refers to a recurrence of symptoms, or the appearance of mucosal abnormalities before the development of symptoms, remains the subject of dispute.[220] Patients' views about treatment and the type of information they need have changed little over the last 30 years.[53,218]

## 1.3 Clinical features

Typically people with Crohn's disease have recurrent attacks, with acute exacerbations interspersed with periods of remission or less active disease. Most people with Crohn's disease lead active lives. Nevertheless, five years after onset, 15% to 20% of people are disabled by their disease to some degree [see 'Infliximab (review) and adalimumab for the treatment of Crohn's disease', NICE technology appraisal guidance 187, 2010].[198]

People with severe Crohn's disease can present with evidence of systemic toxicity (for example, fever and raised pulse rate), weight loss, diarrhoea and often other complications. Investigation may reveal severe, and sometimes extensive, intestinal inflammation, with associated biochemical and haematological evidence of clinically significant systemic disturbance (for example, raised levels of C-reactive protein and low albumin levels). People with severe Crohn's disease often may not respond to standard drug therapy, including immunosuppressives.

Crohn's disease can be complicated by the development of intestinal obstruction, fistulae or perianal disease. Fistulae can develop in about one quarter of people with Crohn's disease.[287] Perianal disease is a frequent complication of colonic and ileocolonic disease and is characterised by fissures, fistulae or abscesses. Spontaneous healing is uncommon, and surgery is often needed, although it is not always possible and may not be successful.

Other complications include stricture, acute dilation and perforation of the gastrointestinal tract, and significant haemorrhage, particularly if the disease affects the colon. As well as these intestinal

problems, the disease may be associated with abnormalities of the joints, eyes, liver and skin. These non-intestinal symptoms have been reported in more than 6% of patients, mainly in people with colonic Crohn's disease.[25] There is also evidence of an increase in the incidence of cancer of the small and large intestine in people with Crohn's disease.

## 1.4 Management

Current management options for Crohn's disease include drug therapy, attention to nutrition, smoking cessation and, in severe or chronic active disease, surgery.

### 1.4.1 Drug therapy

The aims of drug treatment are to reduce symptoms and maintain or improve quality of life, while minimising toxicity related to drugs over both the short and long term. Glucocorticosteroids, 5-aminosalicylates, antibiotics, immunosuppressive drugs and tumour necrosis factor (TNF) alpha inhibitors are current options for treating Crohn's disease.

### 1.4.2 Enteral nutrition

Enteral nutrition is currently widely used as first-line therapy in children and adolescents to facilitate growth and development.[237] Conversely, its use in adults is less common for various reasons.

### 1.4.3 Smoking Cessation

There appears to be clinical benefit from cessation of smoking with a reduction in the rate of recurrence of disease activity.[145,272] Readers are advised to emphasise the importance of smoking cessation to people with Crohn's disease and should refer to NICE guidance: Smoking cessation services PH10[195] and Smoking cessation – Varenicline TA123.[193]

### 1.4.4 Surgery

Between 50% and 80% of people with Crohn's disease will eventually need surgery.[253] The main indications for this are strictures causing symptoms of obstruction, other complications such as fistula formation, perforation or failure of medical therapy.

This guideline intends to show the place of both new and established treatments in the wider care pathway for Crohn's disease. This will be useful for clinicians and people with Crohn's disease because new drugs have been licensed for Crohn's disease in the last decade. The guideline also deals with those medications which are unlicensed for treatment of the condition, but which have been used in this way (off-label) for many years and their role is recognised in other NICE documents as well as the British National Formulary.[139] They include azathioprine, mercaptopurine and methotrexate. The guideline aims to help improve the care offered to people with Crohn's disease and provide information about the clinical and cost effectiveness of potential care pathways. Management of Crohn's disease in specific populations (for example, in pregnancy) may require special consideration.

The GDG notes a number of difficulties in the development of this guideline:

- The relative paucity of high quality data with which to inform evidence-based recommendations. Since its earliest description Crohn's disease has been the subject of considerable research including aetiology, treatment, social consequences and its long-term impact on health and quality of life. The chronic and periodic nature of the disease has limited the value of short-term studies. The diverse anatomical sites and the existence of associated extra-intestinal complications have made it difficult to conduct randomised controlled studies in which both the intervention and placebo arm contain comparable patient populations. Many published studies are under-powered and lack homogeneity. In addition outcome measures need to reflect benefits which are of clinical significance and are considered valuable by patients.
- Subgroup data stratified by severity are rare, making clinically and cost-effectiveness evidence-based recommendations for varying levels of severity for the most part unfeasible. The GDG acknowledges that severity is an important factor in management decisions and accepts that consideration of severity will fall within the discretion of the individual clinician and the person with Crohn's disease. For pragmatic reasons, the guideline primarily addresses best practice and cost-effectiveness for the "average" patient - people with moderate to severe Crohn's disease. The guidance does not consider in any detail the evidence base for management of Crohn's disease at the extreme ends of the spectrum (people with either mild or profoundly severe Crohn's disease).
- Reporting of outcomes by smoking habit was rare.
- Recommending pharmaceutical products that are used off-label in Crohn's disease, but which are widely prescribed in UK clinical practice and which are licensed for use in other conditions or populations.
- Extrapolating and generalising from adult populations to children and *vice versa* when there are no or little data for specific populations. The GDG agreed to base treatment recommendations on RCTs with extrapolation to childhood if no separate paediatric evidence was found.

## 1.5 Considerations specific to children and young people

Up to a third of patients with Crohn's disease are diagnosed before the age of 21[104] but there is a lack of studies on treatment for children and young people. Paediatric practice is often based on extrapolation from adult studies and in this guideline all recommendations relate to adults and children unless otherwise specified. Induction and maintenance of remission as well as optimisation of nutritional status and minimising possible side effects of treatment are fundamental to best practice for all people with Crohn's disease, whatever their age. There are, however, important differences to consider when treating children including.

- Childhood and adolescence are critical periods for growth and development and Crohn's disease can have a major influence on both of these. Between 15% and 40% of children have growth impairment[115,187] and this can result in permanently reduced final adult height.[115,239] This may be due to the inflammatory process itself, or to impaired nutritional status associated with malabsorption and/or reduced nutritional intake. Along with growth, puberty is often delayed and there may be an opportunity to continue growing into late adolescence. Assessment of pubertal status and bone age can be useful to assess the potential for further growth.In order to achieve optimum growth and development it is vital to induce a rapid and prolonged remission whilst optimising nutritional status and avoiding glucocorticosteroid-related growth impairment. This has led to a search for other treatments such as exclusive enteral nutrition.
- As well as growth and physical development it is also important to consider the child's or young person's psychological and emotional development and educational needs. Several studies have shown a high incidence of psychological morbidity in children and young people as well as adults with Crohn's disease.[74,120]

- Although paediatric practice is often based on adult studies most of the drugs currently used are not licensed for use in children, reflecting similar off-label use in adults. As guidance covers children, but the summaries of product characteristics for many drugs do not include children, the guideline will assume that prescribers will consult the current online version of the British National Formulary for Children.
- Ultimately the prescriber must take responsibility for using drugs outside of their licensed indications but it is important to involve the parents and, if possible the child, in a discussion about risks and potential benefits. It is implicit in all discussions with patients about their treatment that the clinician should establish that the patient has the capacity[2] to make a fully informed decision about their care, and the ability to understand the potential benefits (and risks) of treatment.
- In the case of children, clinicians would normally involve those with parental responsibility in the clinical decision-making process, and clinicians should also consider the maturity and competence of the child to understand and make decisions about their own care.[100]
- Children can consent to treatment when they are able to understand the risks and benefits but they cannot legally refuse treatment against their parents' wishes until they are 16 years old. It is important to consider the young person's cognitive developmental stage when discussing the disease and treatment options. Using appropriate terminology will help children and young people participate actively in decision-making.
- As children mature into adolescents and subsequently young people and adults they should be encouraged to take more responsibility for managing their condition. Arrangements for transition to adult care should be an integral part of the service. Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in the DH 'Transition: getting it right for young people' (available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_4132944).
- When managing Crohn's disease in children and young people, the timing of treatment should be carefully considered to avoid or minimise long-term consequences, be they either physical or psychological.

## 1.6 Patient vignettes

The GDG agreed that it was important to bring the 'lived experience' of Crohn's disease to the reader's attention whilst considering the evidence base. The reality of living with a chronic condition is a vital aspect of the guideline. The vignettes were provided by the patient and carer members of the GDG.

# 2 Development of the guideline

## 2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. Clinical guidelines are based on the best available research evidence, with the aim of improving the quality of health care. Predetermined and systematic methods are used to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

The guidelines are produced using the following steps:

- guideline topic is referred to NICE from the Department of Health
- stakeholders register an interest in the guideline and are consulted throughout the development process
- the scope is prepared by the National Clinical Guideline Centre (NCGC)
- the NCGC establishes a guideline development group (GDG)
- a draft guideline is produced after the group assesses the available evidence and makes recommendations
- there is a consultation on the draft guideline
- the final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- information for the public ('understanding NICE guidance' or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version and can be downloaded from the NCGC website at XXXX. The other versions can be downloaded from NICE at www.nice.org.uk, where pathways showing how this guideline within the context of other NICE guidance is also available.

## 2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

To prepare a clinical guideline on the management of Crohn's disease.

## 2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor John Mayberry in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every six weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded. Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B:

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

## 2.4 What this guideline covers

Sections 2.4, 2.5 and 2.6 are based upon an extract of the guideline scope document that was written before commencement of the guideline and hence the tense used is prospective (see Appendix A: for the full version of the scope).

- Adults and children with a diagnosis of Crohn's disease.
- Consideration will be given to specific needs, if any, during pregnancy and in females of child-bearing potential.

Key clinical issues that will be covered include

- Drug therapy, including the following drug categories:
  - Glucocorticosteroids – conventional glucocorticosteroids and budesonide
  - Immunosuppressives – azathioprine, mercaptopurine and methotrexate
  - 5-aminosalicylates

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

- Enteral nutrition versus medical management or combination of medical therapy and enteral nutrition
- Aspects of surgical management, for example:
  - disease limited to the distal ileum (medical versus surgical management)
  - strictures
- Information and support for people with Crohn's disease and their families and carers as appropriate.
- Monitoring for:

- osteopaenia
- early relapse.

For further details please refer to the scope in and review questions in Table 1.

## 2.5 What this guideline does not cover

- Diagnosis
- Treatment of extraintestinal manifestations of Crohn's disease
- Surgical techniques
- The following approaches to management:
  - photopheresis
  - granulocyte-macrophage colony-stimulating factor (GM-CSF)
  - probiotics
  - fish oil
  - anti-tuberculosis drugs for treatment of *Mycobacterium avium paratuberculosis*
  - cyclosporin.

## 2.6 Relationships between the guideline and other NICE guidance

**Health Technology Appraisals to be incorporated in this guidance:**

- Infliximab (review) and adalimumab for the treatment of Crohn's disease. NICE technology appraisal guidance 187 (2010). Available from www.nice.org.uk/guidance/TA187

**Related NICE Health Technology Appraisals:**

- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/guidance/TA123

**Related NICE Interventional Procedures:**

- Extracorporeal photopheresis for Crohn's disease. NICE interventional procedure guidance 288 (2009). Available from www.nice.org.uk/guidance/IPG288
- Leukapheresis for inflammatory bowel disease. NICE interventional procedure guidance 26 (2005). Available from www.nice.org.uk/guidance/IPG126
- Wireless capsule endoscopy for investigation of the small bowel. NICE interventional procedure guidance 101 (2004). Available from www.nice.org.uk/guidance/IPG101

**Related NICE Clinical Guidelines:**

- Osteoporosis: fragility fracture risk. NICE clinical guideline 146 (2012). Available from www.nice.org.uk/guidance/CG146
- Colorectal cancer: the diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011). Available from www.nice.org.uk/CG131
- Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas CG118 (2011). Available from www.nice.org.uk/CG118
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Irritable bowel syndrome in adults. NICE clinical guideline 61 (2008). Available from www.nice.org.uk/guidance/CG61
- Faecal incontinence. NICE clinical guideline 49 (2007). Available from www.nice.org.uk/guidance/CG49

- Nutrition support in adults. NICE clinical guideline 32 (2006). Available from www.nice.org.uk/guidance/CG32
- Dyspesia. NICE clinical guideline 17 (2004). Available from www.nice.org.uk/guidance/CG17
- Fertility. NICE clinical guideline 11 (2004). Available from www.nice.org.uk/guidance/CG11

**Related NICE Public Health Guidance:**

- Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10
- Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006). Available from www.nice.org.uk/guidance/PH1

# 3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009.[197]

## 3.1 Developing the review questions and outcomes

- Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of prognostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). A qualitative approach was used to frame questions related to patient experience. The questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A:). Further information on the outcome measures examined follows this section.

**Table 1: Review questions**

| Chapter | Review questions | Outcomes |
|---|---|---|
| 5 | Pharmacological induction | |
| 5 | 1. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for induction of remission<br>1.1.1 compared with placebo?<br>1.1.2 compared with 5-aminosalicylate (5-ASA) treatment?<br>1.2 *plus* 5-ASA treatment compared with placebo?<br>1.3 compared with azathioprine or mercaptopurine (AZA/MP)?<br>1.4 *plus* azathioprine or mercaptopurine (AZA/MP) compared with conventional glucocorticosteroid treatment *plus* placebo?<br>1.5 compared with methotrexate?<br>1.6 *plus* methotrexate compared with conventional glucocorticosteroid treatment *plus* placebo ? | Remission as defined by:<br>• Absence of clinical symptoms (determined by investigator)<br>• Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 points in CDAI<br>• Harvey Bradshaw Index (HBI) < 3<br>• Endoscopic healing<br>• Fistula healing<br>Adverse events<br>Withdrawal rate/premature termination<br>Inflammatory Bowel Disease Questionnaire (IBDQ) scores<br><br>In paediatric studies the main outcomes included:<br>Remission as defined by:<br>• Absence of clinical symptoms (determined by investigator)<br>• Paediatric Crohn's Disease Activity Index (PCDAI) < 10 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy<br>• Endoscopic healing<br>• Fistula healing |
| | | |
| 5 | 2. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for induction of remission compared with<br>2.1 placebo?<br>2.2 conventional glucocorticosteroid treatment?<br>2.3 5-aminosalicylate (5-ASA) treatment?<br>2.4 azathioprine or mercaptopurine (AZA/MP)?<br>2.5 methotrexate? | |
| | | |
| 5 | 3. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for induction of remission compared with<br>3.1 placebo?<br>3.2 azathioprine or mercaptopurine (AZA/MP)? | |

| Chapter | Review questions | Outcomes |
|---|---|---|
| | 3.3 methotrexate? | Adverse events<br>Withdrawal rate/premature termination<br>Growth as measured by height velocity standard deviation score (HVSDS) |
| | | |
| 5 | 4. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for induction of remission compared with<br>4.1 placebo?<br>4.2 methotrexate?<br>4.3 In individuals diagnosed with Crohn's disease what is the incidence of serious adverse events for individuals with:<br>• normal blood TPMT activity, on a standard dose of azathioprine<br>• low blood TPMT activity, on a low dose of azathioprine<br>• unknown TPMT activity, on a standard dose of azathioprine? | |
| | | |
| 5 | 5. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for induction of remission<br>5.1 compared with placebo?<br>5.2 *plus* conventional glucocorticosteroid treatment compared with placebo *plus* conventional glucocorticosteroid treatment? | |
| | | |
| 6 | Pharmacological maintenance | |
| | 6. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for maintenance of remission for 12 months or longer<br>6.1 compared with placebo?<br>6.2 compared with 5-aminosalicylate (5-ASA) treatment?<br>6.3 *plus* 5-ASA treatment with conventional glucocorticosteroid *plus* placebo ?<br>6.4 compared with azathioprine or mercaptopurine (AZA/MP)?<br>6.5 *plus* azathioprine or mercaptopurine compared with conventional glucocorticosteroid treatment *plus* placebo?<br>6.6 methotrexate? | Remission as defined by:<br>• Absence of clinical symptoms (determined by investigator)<br>• Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 points in CDAI<br>• Harvey Bradshaw Index (HBI) < 3<br>• Endoscopic healing<br>• Fistula healing<br>Adverse events<br>Withdrawal rate/premature termination<br>Inflammatory Bowel Disease Questionnaire (IBDQ) scores<br><br>In paediatric studies the main outcomes included:<br>Remission as defined by:<br>• Absence of clinical symptoms (determined by investigator)<br>• Paediatric Crohn's Disease |
| | | |
| | 7. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for maintenance of remission for 12 months or longer compared with<br>7.1 placebo?<br>7.2 conventional glucocorticosteroid treatment?<br>7.3 5-aminosalicylate (5-ASA) treatment?<br>7.4 azathioprine or mercaptopurine (AZA/MP)?<br>7.5 methotrexate? | |
| | | |

| Chapter | Review questions | Outcomes |
|---|---|---|
| 6 | 8. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for maintenance of remission compared with<br>8.1 placebo?<br>8.2 azathioprine or mercaptopurine (AZA/MP)?<br>8.3 methotrexate? | Activity Index (PCDAI) < 10 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy<br>• Endoscopic healing<br>• Fistula healing<br>Adverse events<br>Withdrawal rate/premature termination<br>Growth as measured by height velocity standard deviation score (HVSDS) |
| | | |
| 6 | 9. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for maintenance of remission for 12 months or longer<br>9.1 compared with placebo?<br>9.2 compared with methotrexate?<br>9.3 *plus* conventional glucocorticosteroid or 5-ASA treatment compared with placebo *plus* conventional glucocorticosteroid or 5-ASA treatment? | |
| | | |
| 6 | 10. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for maintenance of remission for 12 months or longer<br>10.1 compared with placebo?<br>10.2 *plus* conventional glucocorticosteroid treatment compared with placebo *plus* conventional glucocorticosteroid treatment? | |
| | | |
| 7 | Maintaining remission after surgery | |
| | 11. In adults and children what is the clinical and cost effectiveness of post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer of<br>• conventional glucocorticosteroid treatment<br>• budesonide<br>• 5-aminosalicylate treatment<br>• azathioprine<br>• mercaptopurine<br>• methotrexate<br>• metronidazole or<br>• combinations thereof<br>• or nutritional treatment<br>compared with<br>• placebo<br>• no treatment? | Maintenance of remission as defined by:<br>• Absence of clinical symptoms (determined by investigator)<br>• Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy<br>• Harvey Bradshaw Index (HBI) < 3<br>• Endoscopic evaluation (Rutgeerts score)<br>Relapse<br>Relapse + withdrawals<br>Serious adverse events<br>Withdrawal due to adverse events<br>Quality of life<br>Children:<br>• Absence of clinical symptoms (determined by investigator)<br>• Paediatric Crohn's Disease Activity Index (PCDAI) < 10 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later |

| Chapter | Review questions | Outcomes |
|---|---|---|
| | | (late) following initiation of therapy<br>• Endoscopic healing<br>• Fistula healing<br>Adverse events<br>Withdrawal rate/premature termination<br>Growth as measured by height velocity standard deviation score (HVSDS)Growth |
| | | |
| 8 | Enteral nutrition | |
| | 12.1 In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) as a sole source of nutrition for induction of remission compared with<br>• usual diet<br>• conventional glucocorticosteroid treatment<br>• budesonide<br>• a combination of conventional glucocorticosteroid treatment *plus* 5-ASA treatment<br>• a combination of conventional glucocorticosteroid treatment *plus* azathioprine or mercaptopurine<br>• a combination of conventional glucocorticosteroid treatment *plus* methotrexate<br><br>12.2 In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness for induction of remission of enteral nutrition (elemental, semi-elemental and polymeric) plus medical therapy versus usual diet. | Remission as defined by:<br>• Absence of clinical symptoms (determined by investigator)<br>• Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4 - 6 (early), weeks 10 -12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 CDAI<br>• Paediatric Crohn's Disease Activity Index (PCDAI < 10) Fistula healing<br>• Harvey Bradshaw Index (HBI) < 3<br>• Mucosal healing<br>Adverse events |
| | | |
| 8 | 13.1 What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission compared with<br>• usual diet<br>• medical treatment<br>• conventional glucocorticosteroid treatment<br>• budesonide<br>• 5-ASA treatment<br>• azathioprine or mercaptopurine<br>• methotrexate<br><br>13.2 What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission in combination with<br>• conventional glucocorticosteroid treatment<br>• budesonide | Maintenance of remission as defined by:<br>• Crohn's Disease Activity Index (CDAI) ≤ 150 after 12 months<br>• Paediatric Crohn's Disease Activity Index (PCDAI) < 10<br>• Harvey Bradshaw Index (HBI) < 3<br>• Other validated index<br>• Mucosal healing<br>• Symptomatic recurrence<br>Adverse events<br>Withdrawal due to adverse events |

| Chapter | Review questions | Outcomes |
|---|---|---|
| | • 5-ASA treatment<br>• azathioprine or mercaptopurine<br>• methotrexate?<br>compared with any of the above? | |
| | | |
| 9 | Surgery | |
| | 14. In individuals diagnosed with Crohn's disease limited to the distal ileum, what is the clinical and cost-effectiveness of surgical resection for induction and maintenance of remission compared with medical or nutritional treatment? | Adults<br>Remission as defined by:<br>• CDAI ≤ 150 +/- fall of > 70<br>• HBI < 3<br>• Endoscopic healing<br>• Fistula healing<br>• Any valid index<br>IBDQ<br>Premature termination of study<br>Adverse events including:<br>• Early (up to 30 days)<br>Infection local wound or intra-abdominal abscess, other<br>Anastomotic dehiscence<br>Length of stay is a surrogate, (inpatient v outpatient), ITU<br>Cardiovascular (MI, thromboembolism)<br>Intestinal obstruction<br>Haemorrhage<br>• Late<br>Wound herniation<br>Obstruction<br>Anaemia<br>B12 deficiency<br>Bile salt malabsorption<br>In paediatric studies<br>Remission as defined by:<br>• PCDAI ≤ 10 +/- fall of > 12.5<br>IMPACT<br>Growth (height velocity) |
| | | |
| | 15. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of surgical treatment of stricture compared with<br>15.1 balloon dilation<br>15.2 balloon dilation plus intralesional glucocorticosteroid injections<br>15.3 conservative management? | • Incidence of perioperative complications<br>• Incidence of major complications<br>• Recurrence rate of symptomatic strictures requiring repeat procedure |
| | | |
| 10 | Monitoring | |
| | 16. In adults and children diagnosed with Crohn's disease, | • Fracture rates in children under |

| Chapter | Review questions | Outcomes |
|---|---|---|
| | what is the clinical and cost effectiveness of DEXA compared with no monitoring for changes in bone mineral density on patient outcomes (fracture rate)?<br><br>Further to development of the NICE Osteoporosis Guideline, this question changed to:<br>In children with Crohn's disease what is the risk of fracture? | 18<br>• Change in bone density in children under 18<br>• Hospitalisation for fracture in children under 18 |
| | | |
| 10 | 17. Does predicting early relapse through monitoring:<br>• Unintended weight loss<br>• CRP<br>• ESR<br>• MRI<br>• Calprotectin<br>• Colonoscopy or capsule endoscopy<br>• Growth in children<br>compared with standard care, improve patient outcomes (quality of life, future surgery, hospitalisation)? | Adult disease relapse as measured by<br>• Crohn's Disease Activity Index > 150 +/- rise 70<br>• Harvey Bradshaw Index > 3<br>• Endoscopic relapse by Rutgeerts score<br>• Recurrence of fistula<br>• Hospitalisation<br>• Surgery<br>IBDQ score<br>Adverse events<br>Colorectal cancer<br>Mortality<br><br>Disease relapse in children and young people including:<br>• PCDAI ≥ 10<br>Growth as measured by height velocity or high velocity standard deviation score<br>IMPACT Questionnaire |
| | | |
| 11 | Patient information and support | |
| | 18.1 What are the primary information needs of adults with Crohn's disease in the UK?<br><br>18.2 What are the primary information needs of children and young people with Crohn's disease in the UK? | • the information people with Crohn's disease wanted or found useful<br>• any specific information requirements for people with Crohn's disease<br>• if information received changed the perception of the disease. |
| | | |
| 12 | Pregnancy | |
| | Scope: "Consideration is given to the specific needs, if any, in pregnancy and females of child-bearing potential" | |

## 3.2 Searching for evidence

### 3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions in accordance with the NICE Guidelines Manual[197]. Additional searches were conducted to retrieve material on adverse events, pregnancy and breastfeeding and fracture risk in children with Crohn's disease. Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English and studies published only in abstract form were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases: Medline, Embase, Cinahl and The Cochrane Library. All searches were updated on 13th March 2012. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D:. During the scoping stage, a search was conducted for guidelines and reports. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

### 3.2.2 Call for evidence

The GDG decided to initiate a 'call for evidence' (See Appendix K:) for part of Question 3:

"3. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for induction of remission compared with

3.1 placebo?

3.2 azathioprine or mercaptopurine (AZA/MP)?

3.3 methotrexate?"

They believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence. No previously unidentified evidence was submitted.

### 3.2.3 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to adults and children with a diagnosis of Crohn's disease in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on Medline and Embase, with a specific economic filter, from April 2010, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed.

The search strategies for health economics are included in Appendix D:. All searches were updated on 13th March 2012. Any papers published after this date were not considered.

#### 3.2.3.1 Health economic call for evidence undertaken

No health economic call for evidence was undertaken.

## 3.3 Evidence of effectiveness

The Research Fellow:

- identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- reviewed full papers against pre-specified inclusion/exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C:)
- critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual[197]
- extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix F:)
- generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - randomised studies:meta-analysis performed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - observational studies: data presented as a range of values in GRADE profiles for cohort and case control studies
  - prognostic studies: data presented in modified quality assessment profiles and forest plots
  - qualitative studies: each study summarised in adapted GRADE profiles.

### 3.3.1 Inclusion/exclusion

The inclusion/exclusion of studies was based on the review protocols (Appendix C:). The GDG were consulted about any uncertainty regarding inclusion/exclusion of selected studies.

### 3.3.2 Methods of combining clinical studies

#### 3.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: remission, relapse, relapse + withdrawal, adverse events, withdrawal/premature termination, withdrawal due to adverse events, glucocorticosteroid sparing , maintenance of remission after 12 months, cancer of the colon, height velocity, fracture rates, hospitalisation due to fracture and mortality. The continuous outcome(s) change in CDAI/PCDAI scores, change in IBDQ scores, IMPACT scores, and changes in bone density were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data were presented as a hazard ratio.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p < 0.1$ or an I-squared inconsistency statistic of > 50% to indicate significant heterogeneity. Where significant heterogeneity was present, predefined subgroup analyses for disease severity, active or quiescent disease, concurrent medications, age or disease location were carried out if the information was available in the selected studies. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow-up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

#### 3.3.2.2 Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5) software. Studies were not combined in a meta-analysis for observational studies. Sensitivity analyses were carried out on the basis of study quality and results were reported as ranges. The included studies were critically appraised using a checklist adapted from the prognostic check list in The Guidelines Manual[197] and from the Cochrane Prognosis Methods Group.[3]

### 3.3.3 Types of studies

For most intervention evidence reviews in this guideline, RCTs were included, as they are considered the most robust type of study design. Where the RCT data were not available or would not be considered to be the most appropriate study design (i.e. prognostic reviews) this is detailed in the protocols in Appendix C: and in the clinical evidence introductions.

### 3.3.4 Types of analysis

Estimates of effect from individual studies were based on intention to treat (ITT with imputation) analysis if possible. With respect to the maintenance of remission reviews both relapse and relapse plus withdrawal (ITT) analyses were presented. An ITT analysis considers all randomised participants based on the intervention and control groups to which they were originally assigned. An assumption is made that all participants in the trials who were lost to follow-up experienced the outcome of interest, i.e. relapse (categorical variable/outcome). In the case of a continuous variable/outcome the assumption is that those lost to follow-up would not considerably change the average scores of their assigned groups. ITT analysis is a conservative approach to analyse the data and therefore may under-estimate the effect and tend to bias the results towards no difference.

### 3.3.5 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The "Clinical evidence profile" includes details of the quality assessment as well as pooled outcome data, an absolute measure of intervention effect and the summary of quality of evidence for each outcome. In this table, the columns for intervention and

control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias is only taken into consideration in the quality assessment and if apparent. Clinical and Economic study characteristics are included in "Evidence tables" that can be found in Appendix F:. "Economic summary of findings" tables and Economic study characteristics are included in the Economic evidence sections of the guideline.

Each outcome was examined separately for the quality elements listed and defined in Table 2 and each graded using the quality levels listed in Table 3: The main criteria considered in the rating of these elements are discussed below (see section 3.3.6 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 4: The GRADE toolbox is currently designed only for randomised trials and observational studies. For this guideline the GRADE quality assessment elements and outcome presentation was adapted for prognostic and qualitative studies.

**Table 2: Description of quality elements in GRADE for intervention studies**

| Quality element | Description |
|---|---|
| Limitations | Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. |
| Inconsistency | Inconsistency refers to any unexplained heterogeneity of results. |
| Indirectness | Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made. |
| Imprecision | Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect, relative to the clinically important threshold. |
| Publication bias | Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. |

**Table 3: Levels of quality elements in GRADE**

| Level | Description |
|---|---|
| None | There are no serious issues with the evidence |
| Serious | The issues are serious enough to downgrade the outcome evidence by one level |
| Very serious | The issues are serious enough to downgrade the outcome evidence by two levels |

**Table 4: Overall quality of outcome evidence in GRADE**

| Level | Description |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low | 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 |
| Very low | Any estimate of effect is very uncertain |

### 3.3.6 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.3.7 to 3.3.10.

### 3.3.7 Study limitations

The main limitations for randomised controlled trials are listed in Table 5.

**Table 5: Study limitations of randomised controlled trials**

| Limitation | Explanation |
|---|---|
| Allocation concealment | Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomised trials with allocation by day of week, birth date, chart number, etc) |
| Lack of blinding | Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated |
| Incomplete accounting of patients and outcome events | Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated |
| Selective outcome reporting | Reporting of some outcomes and not others on the basis of the results |
| Other limitations | For example:<br>• Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules<br>• Use of non-validated patient-reported outcomes<br>• Carry-over effects in cross-over trials<br>• Recruitment bias in cluster randomised trials |

### 3.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity existed (Chi square $p < 0.1$ or I-squared inconsistency statistic of > 50%), but no plausible explanation could be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square

values, the decision for downgrading was also dependent on factors such as whether the intervention was associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gave a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

### 3.3.9 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

### 3.3.10 Imprecision

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered by the GDG for the evaluation of precision in this guideline for all reviews included in the health economic model. The minimal important difference (MID) was also utilised to assess precision but was only applied in this guideline to reviews which were not considered in the economic analysis. The main outputs of the economic analyses were 'costs per QALY gained' where QALYs were derived from patient questionnaires. This negates the need to consider MIDs, since QALYs explicitly incorporate important changes in quality of life related to disease burden. i.e. a clinically important difference has been ascertained directly from people with Crohn's disease.

For reviews which considered MIDs, the default MIDs of 0.75 and 1.25 for dichotomous outcomes and of 0.5 of the standardised mean difference for continuous outcomes were accepted by the GDG. The thresholds of important benefits or harms, or the MID for an outcome are considered relevant for determining whether there is a "clinically important" difference between intervention and control groups and in assessing imprecision. For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, ether beneficial or harmful, and that would lead the patient or clinician to consider a change in the management.[108,137,245,246]

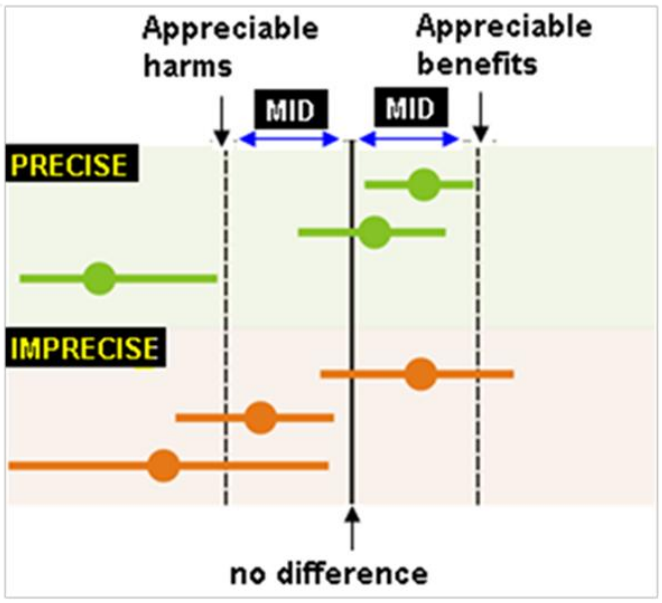
The difference between two interventions, as observed in the studies, was compared against the MID when considering whether the findings were of "clinical importance"; this is useful to guide decisions. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to strongly recommend one intervention over the other based on that outcome.

The criteria applied for imprecision are based on sample size, event rates and the resulting width of confidence intervals for reviews included in the health economic model or on the confidence intervals for pooled or the best estimate of effect for reviews not included in the health economic model, as outlined in Table 6 and illustrated in Figure 1.

**Table 6: Criteria applied to determine precision**

| Dichotomous and continuous outcomes | |
|---|---|
| 'no serious imprecision' | For reviews included in the health economic model: sample size, event rates were sufficient and the resulting width of confidence intervals were narrow.<br>For reviews not included in the health economic model: 95% CI does not cross either of the two minimal important difference (MID) thresholds (the threshold lines for appreciable benefit or harm); defined as precise. |
| 'serious' | For reviews included in the health economic model: sample size, event rates were small and the resulting width of confidence intervals were wide.<br>For reviews not included in the health economic model: 95% CI crosses one of the two MID thresholds (appreciable benefit or appreciable harm); defined as imprecise. |
| 'very serious' | For reviews included in the health economic model: sample size, event rates were very small and the resulting width of confidence intervals were very wide.<br>For reviews not included in the health economic model: 95% CI crosses both of the two MID thresholds (appreciable benefit and appreciable harm); defined as imprecise. |

**Figure 1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a f**




*Source: Figure adapted from GRADEPro software*

The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results.

## 3.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the treatment options in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them.[197] Thus, if the evidence suggests that an intervention provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook:

- a systematic review of the economic literature
- new cost-effectiveness analysis in priority areas

### 3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual.[197]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix F:).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

#### 3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-Organisation for Economic Co-operation and Development [OECD] country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual[197]) and the health economics research protocol in Appendix C:

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of

applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual.[197] It also shows incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and the incremental cost-effectiveness ratio, as well as information about the assessment of uncertainty in the analysis. See Appendix F: for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[208]

**Table 7: Content of NICE economic profile**

| Item | Description |
|---|---|
| Study | First author name, reference, date of study publication and country perspective. |
| Applicability | An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*:<br>Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness.<br>Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness.<br>Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness. |
| Limitations | An assessment of methodological quality of the study*:<br>Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness.<br>Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness.<br>Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table. |
| Other comments | Particular issues that should be considered when interpreting the study. |
| Incremental cost | The mean cost associated with one strategy minus the mean cost of a comparator strategy. |
| Incremental effects | The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy. |
| Cost effectiveness | Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects. |
| Uncertainty | A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate. |

* Applicability and limitations and were assessed using the economic evaluation checklist from The Guidelines Manual.[197]

### 3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified drug induction of remission and drug maintenance of remission as the highest priority areas for an original economic model. These models analyse a large proportion of resource use for the majority of Crohn's patients. The GDG also wished to prioritise surgical versus medical induction of remission but the evidence was considered too limited to develop such a model.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[194]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available GDG expert opinion was used to populate the model.

- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

To parameterise treatment effects in the model, a network meta-analysis (NMA) based on a conditional logistic regression was carried out. The aim of the NMA was to calculate treatment-specific odds ratios for withdrawal and remission conditional upon people not withdrawing. Separate analyses were carried out for:

- first-line induction and
- second-line induction following failure of glucocorticosteroid treatment.

The NICE Technical Support Unit wrote the WinBUGS code for these NMA analyses.

Full methods for the cost-effectiveness analysis are described in Appendix H:.

### 3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[197]

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[196]

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

### 3.4.4 In the absence of cost-effectiveness evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between comparators and relevant UK NHS unit costs alongside the results of the clinical review of effectiveness evidence.

## 3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix F:
- Summary of clinical and economic evidence and quality (as presented in chapters 5 - 12)
- Forest plots in Appendix G:
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix H:).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, having taken into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations included the balance between potential harms and benefits, economic implications compared with the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through an on-line survey and follow-up discussions in the GDG meeting resolved any differences of opinion. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Appendix I:).

The main considerations specific to each recommendation are outlined in the 'Linking evidence to recommendations' section preceding the recommendations for each review question.

### 3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

### 3.5.2 Validation process

The guidance was subject to a five week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders were responded to and posted on the NICE website.

### 3.5.3 Updating the guideline

Following publication, NICE undertake a review for update according to the guideline manual.[197]

### 3.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise, resources and drug licencing issues.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

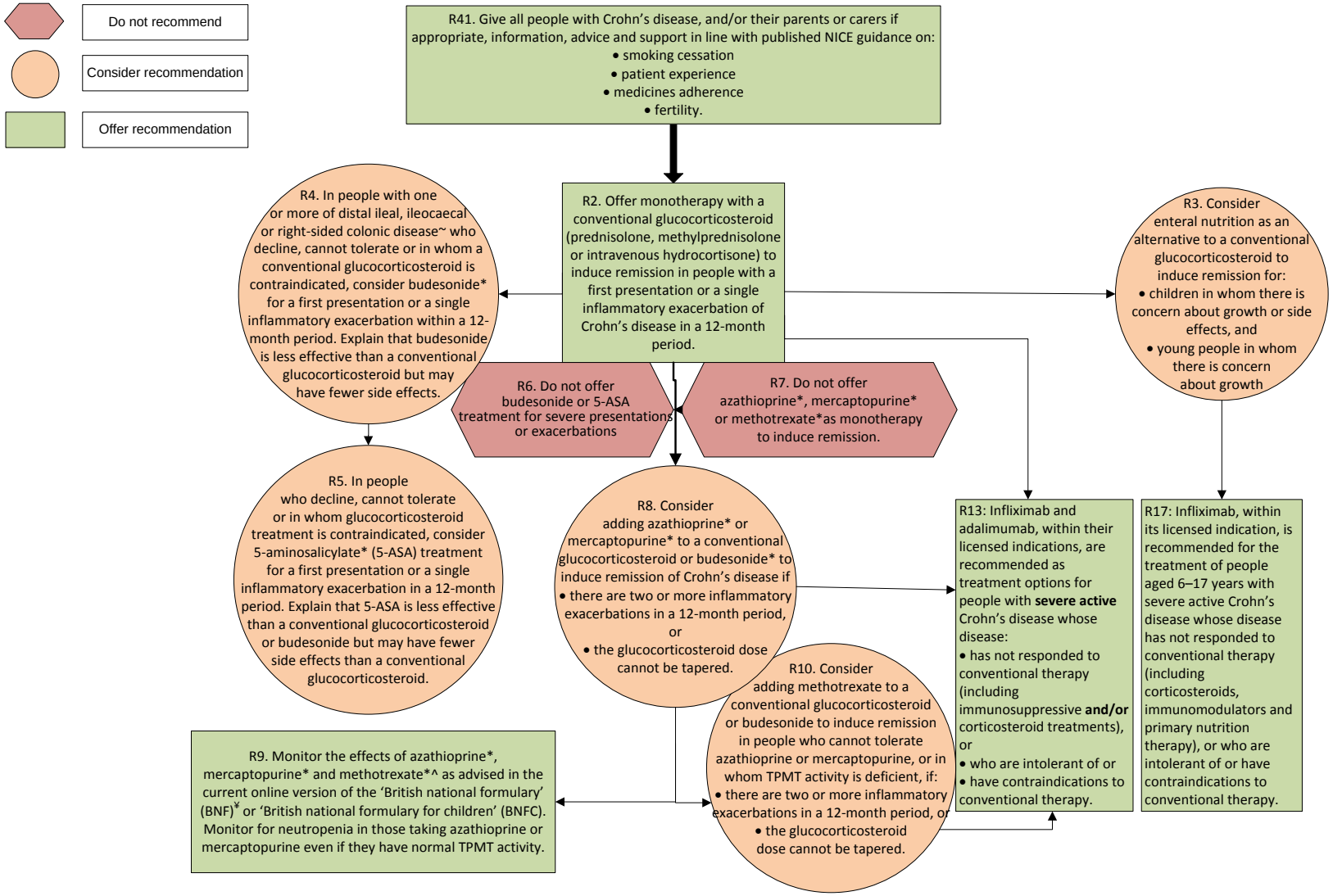
### 3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

# 4 Guideline summary

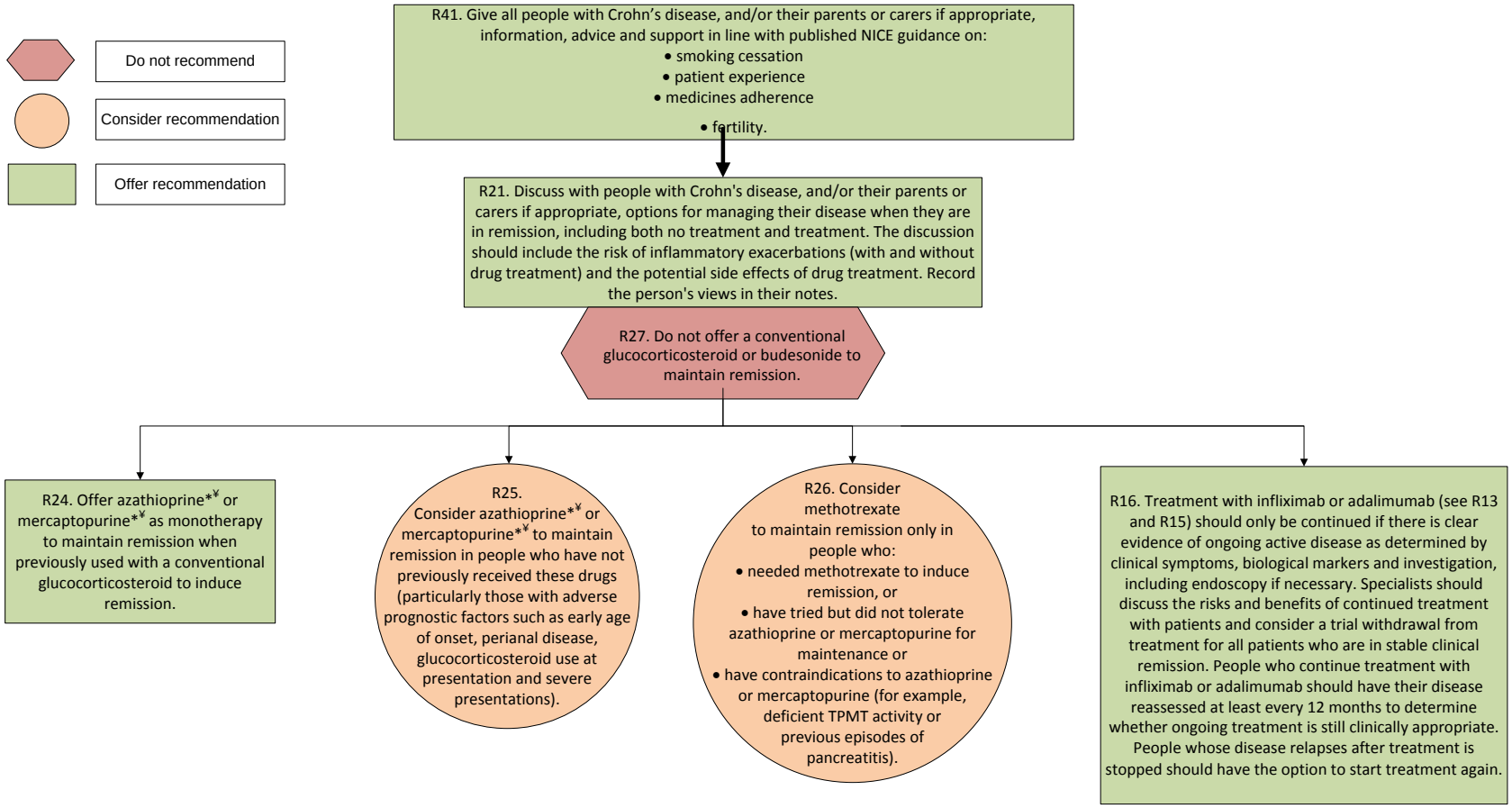
## 4.1 Algorithms

**Figure 2: Inducing remission in Crohn's disease**




~See recommendation 31 and 32 for when to consider surgery early in the course of the disease for people whose disease is limited to the distal ileum *Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine, mercaptopurine, methotrexate, mesalazine, olsalazine and balsalazide did not have UK marketing authorisation for inducing remission in Crohn's disease and budesonide did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. ^ Follow BNF/BNFC cautions on prescribing methotrexate. ¥Advice on monitoring of immunosuppressives can be found in the BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.

## Figure 3: Maintaining remission in Crohn's disease




* Although use is common in UK clinical practice, at the time of publication (October 2012), azathioprine, mercaptopurine and methotrexate did not have UK marketing authorisation for maintaining remission in Crohn's disease. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. ^Follow BNF/BNFC cautions on prescribing methotrexate. ¥Advice on monitoring of immunosuppressives can be found in the BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.

## 4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected nine key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual.[197] They are not listed in order of importance.

39. Ensure that information and advice about Crohn's disease:

- is age appropriate
- is of the appropriate cognitive and literacy level, and
- meets the cultural and linguistic needs of the local community.

1. Discuss treatment options and monitoring with the person with Crohn's disease, and/or their parent or carer if appropriate, and within the multidisciplinary team. Apply the principles outlined in 'Patient experience in adult NHS services' (NICE clinical guidance 138).

42. Give people with Crohn's disease, and/or their parents or carers if appropriate, additional information on the following when appropriate:

- possible delay of growth and puberty in children and young people
- diet and nutrition
- fertility and sexual relationships
- prognosis
- side effects of their treatment
- cancer risk
- surgery
- care of young people in transition between paediatric and adult services
- contact details for support groups.

43. Offer adults, children and young people, and/or their parents or carers, age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education.

9. Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine[a]. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).

11. Monitor the effects of azathioprine, mercaptopurine[a] and methotrexate[b,c] as advised in the current online version of the 'British national formulary' (BNF)[d] or 'British national formulary for children' (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity.

12. Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate.

19. Discuss with people with Crohn's disease, and/or their carer if appropriate, options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. Record the person's views in their notes.

26. Do not offer a conventional glucocorticosteroid or budesonide to maintain remission.

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*a Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*b Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine, mercaptopurine and methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*c Follow BNF/BNFC cautions on prescribing methotrexate.*

*d Advice on monitoring of immunosuppressives can be found in the current online version of BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.*

## 4.3 Full list of recommendations

All recommendations relate to adults and children unless otherwise specified.

**Inducing remission in Crohn's disease**

1. Discuss treatment options and monitoring with the person with Crohn's disease, and/or their parent or carer if appropriate, and within the multidisciplinary team. Apply the principles outlined in 'Patient experience in adult NHS services' (NICE clinical guidance 138).

**Monotherapy**

2. Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.

3. Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:

- children in whom there is concern about growth or side effects, and
- young people in whom there is concern about growth.

4. In people with one or more of distal ileal, ileocaecal or right-sided colonic disease[e] who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide[f] for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects.

5. In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment[g] for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid.

6. Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations.

7. Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission.

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*e See recommendations 31 and 32 for when to consider surgery early in the course of the disease for people whose disease is limited to the distal ileum.*

*f Although use is common in UK clinical practice, at the time of publication (October 2012), budesonide did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.*

*g Although use is common in UK clinical practice, at the time of publication (October 2012) mesalazine, olsalazine and balsalazide did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

**Add-on treatment**

8. Consider adding azathioprine or mercaptopurine[a] to a conventional glucocorticosteroid or budesonide[f] to induce remission of Crohn's disease if:

- there are two or more inflammatory exacerbations in a 12-month period, or
- the glucocorticosteroid dose cannot be tapered.

9. Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine[a]. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).

10. Consider adding methotrexate[b,c] to a conventional glucocorticosteroid or budesonide[f] to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:

- there are two or more inflammatory exacerbations in a 12-month period, or
- the glucocorticosteroid dose cannot be tapered.

11. Monitor the effects of azathioprine, mercaptopurine[a] and methotrexate[b,c] as advised in the current online version of the 'British national formulary' (BNF)[d] or 'British national formulary for children' (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity.

12. Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate.

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*a Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*b Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine, mercaptopurine and methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*c Follow BNF/BNFC cautions on prescribing methotrexate.*

*d Advice on monitoring of immunosuppressives can be found in the current online version of BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.*

*f Although use is common in UK clinical practice, at the time of publication (October 2012), budesonide did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.*

**Infliximab and adalimumab**

The recommendations in the following section are from 'Infliximab and adalimumab for the treatment of Crohn's disease' (NICE technology appraisal guidance 187).

13. Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see recommendation 18) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 16) to determine whether ongoing treatment is still clinically appropriate.

14. Treatment as described in recommendation 13 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.

15. Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 16) to determine whether ongoing treatment is still clinically appropriate.

16. Treatment with infliximab or adalimumab (see recommendations 13 and 15) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.

17. Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.

18. For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.

19. When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate.

20. Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.

**Maintaining remission in Crohn's disease**

21. Discuss with people with Crohn's disease, and/or their parents or carers if appropriate, options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. Record the person's views in their notes.

22. Offer colonoscopic surveillance in line with 'Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas' (NICE clinical guideline 118).

**Follow-up during remission for those who choose not to receive maintenance treatment**

23. When people choose not to receive maintenance treatment:

• discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see

• ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill-health)

• ensure they know how to access the healthcare system if they experience a relapse

• discuss the importance of not smoking.

**Maintenance treatment for those who choose this option**

24. Offer azathioprine or mercaptopurine[h] as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission.

25. Consider azathioprine or mercaptopurine[h] to maintain remission in people who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations).

26. Consider methotrexate[c,i] to maintain remission only in people who:

• needed methotrexate to induce remission, or

• have tried but did not tolerate azathioprine or mercaptopurine for maintenance or

• have contraindications to azathioprine or mercaptopurine (for example, deficient TPMT activity or previous episodes of pancreatitis).

27. Do not offer a conventional glucocorticosteroid or budesonide to maintain remission.

See recommendation 11 and 12 for guidance on monitoring the effects of azathioprine mercaptopurine and methotrexate.

See recommendation 16 for when to continue infliximab or adalimumab during remission.

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*c Follow BNF/BNFC cautions on prescribing methotrexate.*

*h Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*i Although use is common in UK clinical practice, at the time of publication (October 2012) methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

**Maintaining remission in Crohn's disease after surgery**

28. Consider azathioprine or mercaptopurine[j] to maintain remission after surgery in people with adverse prognostic factors such as:

- more than one resection, or
- previously complicated or debilitating disease (for example, abscess, involvement of adjacent structures, fistulising or penetrating disease).

29. Consider 5-ASA treatment[k] to maintain remission after surgery.

30. Do not offer budesonide or enteral nutrition to maintain remission after surgery.

**Surgery**

**Crohn's disease limited to the distal ileum**

31. Consider surgery as an alternative to medical treatment early in the course of the disease for people whose disease is limited to the distal ileum, taking into account the following:

- benefits and risks of medical treatment and surgery
- risk of recurrence after surgery[l]
- individual preferences and any personal or cultural considerations.

Record the person's views in their notes.

32. Consider surgery early in the course of the disease or before or early in puberty for children and young peoplewhose disease is limited to the distal ileum and who have:

- growth impairment despite optimal medical treatment and/or
- refractory disease.

Discuss treatment options within the multidisciplinary team and with the person's parent or carer and, if appropriate, the child or young person.

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*j Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*k Although use is common in UK clinical practice, at the time of publication (October 2012) olsalazine, balsalazide and sulfasalazine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information. Some forms of mesalazine (Octasa MR, Mesren MR, Asacol MR) are licensed for maintaining remission in Crohn's ileo-colitis.*

*l Appendix N contains observational data on recurrence rates after surgery.*

**Managing strictures**

33. Consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy.

34. Discuss the benefits and risks of balloon dilation and surgical interventions for managing strictures[m] with:

- the person with Crohn's disease and/or their parent or carer, if appropriate
- a surgeon and
- a gastroenterologist

35. Take into account the following factors when assessing options for managing a stricture:

- whether medical therapy has been optimised
- the number and extent of previous resections
- the rapidity of past recurrence (if appropriate)
- the potential for further resections
- the consequence of short bowel syndrome
- the person's preference, and how their lifestyle and cultural background might affect management.

36. Ensure that abdominal surgery is available for managing complications or failure of balloon dilation.

**Monitoring for osteopenia and assessing fracture risk**

Refer to 'Osteoporosis: assessing the risk of fragility fracture' (NICE clinical guideline 146) for recommendations on assessing the risk of fragility fracture in adults. Crohn's disease is a cause of secondary osteoporosis.

37. Do not routinely monitor for changes in bone mineral density in children and young people.

38. Consider monitoring for changes in bone mineral density in children and young people with risk factors, such as low body mass index (BMI), low trauma fracture or continued or repeated glucocorticosteroid use.

**Patient information and support**

39. Ensure that information and advice about Crohn's disease:

- is age appropriate
- is of the appropriate cognitive and literacy level, and
- meets the cultural and linguistic needs of the local community.

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*m Appendix O contains observational data on efficacy, safety, quality of life and time to recurrence for balloon dilation and surgery for stricture.*

40. Discuss the possible nature, frequency and severity of side effects[n] of drug treatment (see appendices L and M)[m] with people with Crohn's disease, and/or their parents or carers if appropriate.

41. Give all people with Crohn's disease, and/or their parents or carers if appropriate, information, advice and support in line with published NICE guidance on:

- smoking cessation
- patient experience
- medicines adherence
- fertility.

See 'Relationships between the guideline and other NICE guidance' section 2.6.

42. Give people with Crohn's disease, and/or their parents or carers if appropriate, additional information on the following when appropriate:

- possible delay of growth and puberty in children
- diet and nutrition
- fertility and sexual relationships
- prognosis
- side effects of their treatment
- cancer risk
- surgery
- care of young people in transition between paediatric and adult services
- contact details for support groups.

43. Offer adults, children and young people, and/or their parents or carers, age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education.

**Conception and pregnancy**

44. Give information about the possible effects of Crohn's disease on pregnancy, including the potential risks and benefits of medical treatment and the possible effects of Crohn's disease on fertility.

45. Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gastroenterology) in the care of pregnant women with Crohn's disease.

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*m Appendix O contains observational data on efficacy, safety, quality of life and time to recurrence for balloon dilation and surgery for stricture.*

*n Appendices L and M contain observational data on adverse events associated with 5-ASA treatment and immunosuppressives.*

## 4.4 Key research recommendations

1. For patients with intestinal Crohn's disease, does the addition of azathioprine to glucocorticosteroid treatment at diagnosis, improve the long-term outcome compared with glucocorticosteroid treatment alone?

2. Following successful medical induction of remission of Crohn's disease of the colon, is mesalazine more clinically and cost effective than no treatment?

3. What are the benefits, risks and cost effectiveness of enteral nutrition compared with glucocorticosteroid treatment in adults, children and young people?

4. What is the effect on quality of life of medical treatment (immunosuppressive or biological therapy) compared with early surgery for Crohn's disease limited to the distal ileum?

5. What are the information needs of people with Crohn's disease, as defined by people with the condition, and can education and support based on these needs lead to better clinical and quality-of-life outcomes?

# 5 Induction of remission

## 5.1 Clinical introduction

As yet, the cause of Crohn's disease remains unknown. Partly for this reason, treatment is directed at symptom control rather than cure and subsequently at maintaining remission. However, due to its chronic nature and patchy distribution, it is difficult to define when remission has been achieved. Is it when symptoms are at an acceptable level to the patient, or assessing clinician, or when measures of disease activity (for example, Crohn's disease activity index [CDAI] and Harvey Bradshaw index [HBI]) suggest that there is no on-going inflammation? Even with these scoring systems there remains the difficulty of identifying a level at which the disease is considered inactive. Objective measures include mucosal healing[17,94] on endoscopy and the absence of inflammation in tissue biopsy, but with the patchy distribution typical of Crohn's disease, samples examined may not necessarily be representative of the whole bowel. With these limitations in current measurements of disease activity, we need to interpret clinical trials from both the perspective of the patient and his or her symptoms as well as laboratory-based assessments. The purpose of such an approach is to ensure that new treatments lead to a symptom-free patient with objective evidence of healing of diseased tissue and improved quality of life.

Induction of remission in patients with Crohn's disease may involve drug therapy, specific nutritional therapy, and surgery, in addition to cessation of smoking.

Pharmacological therapy largely includes four groups of drugs – glucocorticosteroid treatment, 5-aminosalicylates, immunosuppressives, and biological treatments. It is worth noting that the health economics relevant to induction of remission will be influenced more by the costs of monitoring and serious side effects, than the actual costs of most of the pharmaceutical agents. Before the recent advance of biological treatments, the field was dominated by agents prescribed generically, with budesonide being a branded exception.

- Glucocorticosteroids were first shown to be effective in the management of ulcerative colitis in 1955 by Truelove & Witts.[289] Subsequently they were also found to play a role in the treatment of Crohn's disease.[270] Glucocorticosteroids suppress the production of a large number of pro-inflammatory proteins, such as interleukin, interferon, tumour necrosis factor, adhesion molecules, E-selectin, lymphocyte adhesion molecules, colony-stimulating factor, prostaglandins, and leukotrienes. They can also inhibit protein synthesis at the post-transcription level by altering messenger RNA stability.[310]. Current concerns, both amongst patients and clinicians, include long-term side effects and thus there is a general desire to minimise exposure to these agents.
- Sulfasalazine, the original 5-aminosalicylate (5-ASA), was probably the first designer drug in history. It was found to have a role in the treatment of inflammatory bowel disease by Nanna Svartz at the Karolinska Institute as early as 1942, when she and her colleagues successfully treated patients with ulcerative colitis.[273] Subsequent work showed that 5-ASA is the active ingredient of sulfasalazine.[15] For the purposes of this guidance, 5-ASA as used to denote plurality, refers to both 5-aminosalicylates (mesalazine, including Pentasa MR, Mesren MR, Asacol MR and Octasa MR; olsalazine, balsalazide) and sulfasalazine (Salazopyridine).
- The immunosuppressives azathioprine and mercaptopurine have long been used for the prevention of relapse[223], but were considered to have potentially serious side effects leading to concern about their use in both the short and long term.[212] Although their original use was as glucocorticosteroid-sparing agents, their value as agents in the treatment of Crohn's disease in their own right soon emerged. Mercaptopurine and its pro-drug, azathioprine, are purine analogues that inhibit cell growth by directly interfering with nucleic acid synthesis.[212] Azathioprine is non-enzymatically converted to mercaptopurine upon ingestion, and is for pragmatic and clinical purposes considered to be the same entity as mercaptopurine.

Methotrexate has been investigated as another immunosuppressive that may be effective in Crohn's disease because of its efficacy in rheumatoid arthritis and its potential as an alternative to azathioprine and mercaptopurine in this situation.[7] These three drugs are used extensively in Crohn's disease and their role is acknowledged in the British National Formulary[138] and in the NICE technology appraisal 187: Infliximab (review) and adalimumab for the treatment of Crohn's disease[198], despite the fact that azathioprine, methotrexate and mercaptopurine are not licensed to treat Crohn's disease.

- Biological treatments (such as infliximab and adalimumab) are not the subject of systematic review within this guideline as they are covered in a NICE Technology Appraisal. Recommendations from TA187[198] are incorporated into the present guidance.

Patient vignette 1

*Sometimes the treatment can seem worse than the illness.*

# 5.2 Conventional glucocorticosteroid treatment for induction of remission

## 5.2.1 Clinical questions

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for induction of remission

- compared with placebo?
- compared with 5-aminosalicylate (5-ASA) treatment?
- *plus* 5-ASA treatment compared with placebo?
- compared with azathioprine or mercaptopurine (AZA/MP)?
- *plus* azathioprine or mercaptopurine (AZA/MP) compared with conventional glucocorticosteroid treatment *plus* placebo?
- compared with methotrexate?
- *plus* methotrexate compared with conventional glucocorticosteroid treatment *plus* placebo?

## 5.2.2 Conventional glucocorticosteroid versus placebo or 5-ASA treatment

### 5.2.2.1 Clinical evidence

A Cochrane systematic review[22] was identified and quality assessed and accepted for this review.The Cochrane review was based upon six studies, two of which[166,270] evaluated conventional glucocorticosteroid versus placebo and six of which evaluated conventional glucocorticosteroid treatment versus 5-ASA treatment.[119,166,172,210,242,270]. A full systematic update search was also conducted and no additional studies were identified. No paediatric reviews were identified.

The primary objective of the Cochrane review[22] was to assess the efficacy and safety of conventional glucocorticosteroid treatment (given orally or intravenously) with placebo or 5-ASA treatment for induction of remission. Pooling of data in the Cochrane review was limited by design quality of the included studies and the unavailability of raw data. The conclusions of the authors (see evidence statements) were based upon two, large, high or moderate-quality studies: Malchow et al, 1984 European Cooperative Crohn's Disease Study (ECCDS)[166] and Summers/Singleton et al, 1979 National Cooperative Crohn's Disease Study (NCCDS).[258,270]

**Table 8: Evidence profile: conventional glucocorticosteroid treatment versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid | Placebo | Relative (95% CI) | Absolute | Quality |
| **Induction of remission (CDAI < 150, follow-up 15 weeks);** Malchow 1984, Summers 1979 in Bechimol 2008 | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 79/132 (59.8%) | 42/135 (31.1%) | RR 1.99 (1.51 to 2.64) | 308 more per 1000 (from 159 more to 510 more) | HIGH |
| **Adverse events (follow-up 17 weeks);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 27/85 (31.8%) | 5/77 (6.5%) | RR 4.89 (1.98 to 12.07) | 253 more per 1000 (from 64 more to 719 more) | HIGH |
| **Withdrawal due to adverse events (follow-up 17-18 weeks);** Malchow 1984, Singleton 1979 in Bechimol 2008 | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious imprecision[1] | none | 6/132 (4.5%) | 1/135 (0.7%) | RR 4.57 (0.75 to 27.83) | 26 more per 1000 (from 2 fewer to 199 more) | MODERATE |

*1 Confidence interval crosses 1.25.*

**Table 9: Evidence profile: conventional glucocorticosteroid versus 5-ASA treatment**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid | 5-ASA | Relative (95% CI) | Absolute | |
| **Induction of remission (CDAI < 150, follow-up 15 weeks);** Malchow 1984, Scholmerich 1990, Summers 1979 in Bechimol 2008 | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111/164 (67.7%) | 66/158 (41.8%) | RR 1.65 (1.33 to 2.03) | 272 more per 1000 (from 138 more to 430 more) | HIGH |
| **Withdrawal due to adverse events (follow-up 15 weeks);** Gross 1995, Malchow 1984, Martin 1990, Prantera 1999, Scholmerich 1990, Singleton 1979 in Bechimol 2008 | | | | | | | | | | | |
| 6 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious imprecision[1] | none | 16/250 (6.4%) | 12/228 (5.3%) | RR 1.18 (0.61 to 2.29) | 9 more per 1000 (from 21 fewer to 68 more) | LOW |
| **Adverse events (all dose ranges) (follow-up 15 weeks) [fixed effect];** Gross 1995, Martin 1990, Prantera 1999, Scholmerich 1990, Singleton 1979 in Bechimol 2008 | | | | | | | | | | | |
| 5 | randomised trials | no serious risk of bias | serious inconsistency[2] | no serious indirectness | no serious imprecision | none | 74/192 (38.5%) | 28/204 (13.7%) | RR 2.53 (1.77 to 3.63) | 210 more per 1000 (from 106 more to 361more) | MODERATE |
| **Adverse events (all dose ranges) (follow-up 15 weeks) [random effects];** Gross 1995, Martin 1990, Prantera 1999, Scholmerich 1990, Singleton 1979 in Bechimol 2008 | | | | | | | | | | | |
| 5 | randomised trials | no serious risk of bias | serious inconsistency[1] | no serious indirectness | serious imprecision[3] | none | 74/192 (38.5%) | 28/204 (13.7%) | RR 3.13 (0.99 to 9.90) | 292 more per 1000 (from 1 fewer to 1222 more) | LOW |

*1 Confidence interval crosses 0.75 and 1.25.*

*2 $I^2$ > 50%.*

*3 Confidence interval crosses 1.25.*

### 5.2.3 Conventional glucocorticosteroid plus 5-ASA treatment versus conventional glucocorticosteroid treatment plus placebo

#### 5.2.3.1 Clinical evidence

Two arms of the Malchow 1984 study[166] were included in the Cochrane review[22] of conventional glucocorticosteroid treatment vs. placebo and glucocorticosteroid vs. 5-ASA treatment. A further arm of this study assessed the use of a combination of sulfasalazine and prednisone. It was possible to analyse this arm of the study in comparison with the prednisone-only arm. One additional study was identified[259] which evaluated sulfasalazine as adjunctive therapy. These two studies have been meta-analysed.

**Table 10: Evidence profile: conventional glucocorticosteroid plus sulfasalazine versus conventional glucocorticosteroid plus placebo**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid plus sulfasalazine | Conventional glucocorticosteroid | Relative (95% CI) | Absolute | |
| **Induction of remission (CDAI < 150, follow-up 8-15 weeks)** Malchow, 1984; Singleton, 1979 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | 63/99 (63.6%) | 73/93 (73.7%) | RR 0.88 (0.74 to 1.04) | 88 fewer per 1000 (from 192 fewer to 29 more) | LOW |

*1 Method of randomisation and allocation concealment not described in one study.*

*2 Confidence interval crosses 0.75.*

### 5.2.4 Conventional glucocorticosteroid versus azathioprine or mercaptopurine AND conventional glucocorticosteroid plus azathioprine or mercaptopurine vs. conventional glucocorticosteroid plus placebo (adjunctive therapy)

#### 5.2.4.1 Clinical evidence

A Cochrane systematic review[212] was quality assessed and accepted for this review. The Cochrane review was based on eight studies.[38,80,148,207,213,224,270,302] The objective was to determine the effectiveness of azathioprine and mercaptopurine for induction of remission in Crohn's disease. One study included in the Cochrane review[270] provided evidence of a head-to-head study of azathioprine versus conventional glucocorticosteroid treatment. All other studies in the review[38,80,148,207,213,224,302] assessed azathioprine or mercaptopurine as adjunctive therapy to concurrent conventional glucocorticosteroid treatment. A full update search and a further paediatric search were conducted. Two additional studies which were not included in the Cochrane review above[212] were added to this review.These were a mixed age study by Rosenberg et al[227] and a paediatric study by Markowitz et al.[170]

Please refer to the Prefontaine et al Cochrane review[212] for individual study evidence reviews.

**Table 11: Evidence profile: conventional glucocorticosteroid versus azathioprine/mercaptopurine and conventional glucocorticosteroid plus azathioprine/mercaptopurine versus conventional glucocorticosteroid +/- placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid +/- placebo | AZA+/- glucocorticosteroid | Relative (95% CI) | Absolute | Quality |
| **Induction of remission (remission by CDAI or researcher definition) (follow-up mean 16 weeks) [fixed effect];** Prefontaine, 2009 | | | | | | | | | | | |
| 8 | randomised trials | no serious risk of bias | serious inconsistency[1,2] | no serious indirectness | no serious imprecision | none | 72/216 (33.3%) | 113/210 (53.8%) | RR 1.57 (1.26 to 1.96) | 190 more per 1000 (from 87 more to 320 more) | MODERATE |
| **Induction of remission (remission by CDAI or researcher definition) (follow-up mean 16 weeks) [random effects];** Prefontaine, 2009 | | | | | | | | | | | |
| 8 | randomised trials | no serious risk of bias | serious inconsistency[1,2] | no serious indirectness | serious imprecision[3] | none | 72/216 (33.3%) | 113/210 (53.8%) | RR 1.59 (1.03 to 2.43) | 197 more per 1000 (from 10 more to 477 more) | LOW |
| **Glucocorticosteroid-sparing effect final prednisone dose < 10 mg/day (follow-up mean 16 weeks); [fixed effect]** Prefontaine, 2009 | | | | | | | | | | | |
| 5 | randomised trials | no serious risk of bias | serious inconsistency[2] | no serious indirectness | no serious imprecision | none | 39/109 (35.8%) | 76/117 (65%) | RR 1.81 (1.38 to 2.38) | 293 more per 1000 (from 132 more to 469 more) | MODERATE |
| **Glucocorticosteroid-sparing effect final prednisone dose < 10 mg/day (follow-up mean 16 weeks) [random effects];** Prefontaine, 2009 | | | | | | | | | | | |
| 5 | randomised trials | no serious risk of bias | serious inconsistency[2] | no serious indirectness | serious imprecision[3] | none | 39/109 (35.8%) | 76/117 (65%) | RR 1.80 (1.01 to 3.20) | 286 more per 1000 (from 4 more to 787 more) | LOW |
| **Fistula improvement (follow-up mean 16 weeks);** Prefontaine, 2009 | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4] | none | 2/7 (28.6%) | 6/11 (54.5%) | RR 2.00 (0.67 to 5.93) | 260 more per 1000 (from 134 fewer to 1694 more) | LOW |
| **Adverse events (follow-up mean 16 weeks);** Prefontaine, 2009 | | | | | | | | | | | |
| 7 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 5/215 (2.3%) | 20/214 (9.3%) | RR 2.81 (1.28 to 6.17) | 169 fewer per 1000 (from 26 more to 483 | HIGH |

*1 In seven studies patients were also taking conventional glucocorticosteroid or tapering a conventional glucocorticosteroid dose. In one study there was no concurrent glucocorticosteroid treatment.*

*2 $I^2$ > 50%.*

*3 Confidence interval crosses 1.25.*

*4 Confidence interval crosses 0.75 and 1.25.*

**Table 12: Evidence profile: conventional glucocorticosteroid plus azathioprine/mercaptopurine versus conventional glucocorticosteroid plus placebo in a mixed age population**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Mean reduction in conventional glucocorticosteroid dose | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | AZA/MP + conventional glucocorticosteroid | Placebo + conventional glucocorticosteroid | Relative (95% CI) | Absolute | |
| **Glucocorticosteroid-sparing: reduction in glucocorticosteroid dosage (follow-up 26 weeks; better indicated by higher values);** Rosenberg 1975 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | not assessable[2] | none | -15.5 mg | -6.1 mg | - | Mean Difference 9.4mg higher (Confidence interval not available) $p < 0.05$. | VERY LOW |

*1 Method of randomisation and allocation concealment not described.*

*2 Standard deviations not reported.*

**Table 13: Evidence profile: conventional glucocorticosteroid plus mercaptopurine versus conventional glucocorticosteroid plus placebo in children**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid + mercaptopurine | Conventional glucocorticosteroid + placebo | Relative (95% CI) | Absolute | Quality |
| **Glucocorticosteroid-sparing: days on prednisone (follow-up 18 months; Better indicated by lower values);** Markowitz 2000 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | not assessable[2] | none | 0.73 days | 1.34 days | p < 0.001 | | VERY LOW |
| **Remission after one month by Harvey Bradshaw Index;** Markowitz 2000 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 25/27 (92.6%) | 22/28 (78.6%) | RR 1.18 (0.94-1.47) | 141 more per 1000 (from 47 fewer to 369 more) | MODERATE |

*1 The 18-month trial was completed by 21 of 27 patients in the MP group but only 11 of 28 controls.*

*2 Standard deviations not reported.*

*3 Confidence interval crosses 1.25.*

### 5.2.5 Conventional glucocorticosteroid plus methotrexate versus conventional glucocorticosteroid plus placebo (adjunctive therapy)

#### 5.2.5.1 Clinical Evidence

A Cochrane systematic review[7] was identified and quality assessed and accepted for this review. The objective of this Cochrane review was to perform a systematic review of the evidence for effectiveness of methotrexate for induction of remission of refractory Crohn's disease. The Cochrane outcomes of interest were based upon three studies.[14,85,207]

The primary outcome measure for the Cochrane review was *failure to enter remission*. For consistency with GDG-defined outcome measures, the data were re-analysed and the meta-analysis was re-run to assess for successful achievement of remission. In two studies[14,207] patients were permitted to continue their concurrent medications. In the Feagan et al study[83] patients all received a standard dose of glucocorticosteroid in addition to the study drugs.

**Table 14: Evidence profile: conventional glucocorticosteroid plus methotrexate versus conventional glucocorticosteroid plus placebo (16 week follow-up)**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid + methotrexate | Conventional glucocorticosteroid + placebo | Relative (95% CI) | Absolute | Quality |
| **Induction of remission at 16 weeks (CDAI ≤ 150 or Harvey Bradshaw Index ≤ 3) [fixed effect];** Aurora 1999, Oren 1997, Feagan 1995 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | serious inconsistency[3] | no serious indirectness | serious imprecision[2] | none | 54/133 (40.6%) | 24/88 (27.3%) | RR 1.25 (0.86 to 1.80) | 85 more per 1000 (from 48 fewer to 273more) | VERY LOW |
| **Induction of remission at 16 weeks (CDAI ≤ 150 or Harvey Bradshaw Index ≤ 3) [random effects];** Aurora 1999, Oren 1997, Feagan 1995 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | serious inconsistency[3] | no serious indirectness | very serious imprecision[4] | none | 54/133 (40.6%) | 24/88 (27.3%) | RR 1.09 (0.48 to 2.47) | 31more per 1000 (from 177 fewer to 501 more) | VERY LOW |
| **Withdrawal due to adverse events (follow-up 18 months);** Aurora 1999, Oren 1997, Feagan 1995 in Alfadhli Ahmad, 2004 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 20/135 (14.8%) | 1/91 (1.1%) | RR 6.97 (1.61 to 30.1) | 66 more per 1000 (from 7 more to 320 more) | MODERATE |

*1 Allocation concealment not described in three studies.*

*2 Confidence interval crosses 1.25.*

*3 $I^2$ > 50%.*

*4 Confidence interval crosses 0.75 and 1.25.*

### 5.2.6 Economic evidence

No published data were found relating to the cost effectiveness of conventional glucocorticosteroid treatment for the induction of remission of Crohn's disease.

For primary health economic modelling, please see the health economic induction model summary, section 5.6 and Appendix H: for the full health economic report.

#### 5.2.6.1 Evidence statements – clinical

- In a meta-analysis of two RCTs (n = 260) with a follow-up period of 15 weeks, conventional glucocorticosteroid treatment was more effective than placebo for induction of remission (RR 1.99 [1.51 to 2.64])[166,270] [HIGH QUALITY]
- In a meta-analysis to two RCTs (n=192) of patients receiving conventional glucocorticosteroid plus 5-ASA (sulfasalazine) versus conventional glucocorticosteroid treatment there was no significant difference in induction of remission (RR 0.88[0.74,1.04])[166,259] [LOW QUALITY]
- Conventional glucocorticosteroid treatment was more effective than 5-ASA at inducing remission in three studies (n = 322)with follow-up > 15 weeks (RR 1.65 [1.33 to 2.03])[166,242,270] [HIGH QUALITY]
- In a meta-analysis[212] of eight studies[38,80,148,207,213,224,270,302] (n = 425) conventional glucocorticosteroid plus AZA/MP was significantly more effective for inducing remission in active Crohn's disease than placebo RR 1.57 [1.26 to 1.96](fixed effect) and RR 1.59 [1.03 to 2.43](random effects).[MODERATE QUALITY]
- In one paediatric study (n = 55) there was no significant difference in induction of remission between groups receiving mercaptopurine plus conventional glucocorticosteroid treatment versus conventional glucocorticosteroid treatment plus placebo (RR 1.18 [0.94 to 1.47]).[170] [LOWQUALITY]
- In three RCTs (n = 221) there was no significant difference in induction of remission between groups receiving conventional glucocorticosteroid treatment plus methotrexate versus conventional glucocorticosteroid treatment plus placebo (RR 1.25 [0.86 to 1.80] fixed effect; RR 1.09 (0.48 to 2.47) random effects).[14,85,207] [VERY LOW QUALITY]
- In one study with a 17-week duration (n = 162)[258] there were significantly more adverse events in the conventional glucocorticosteroid treatment group compared with placebo (RR 4.89 [1.98 to 12.07]).[HIGH QUALITY]
- In a meta-analysis of five RCTs (n = 396) there were more adverse events in the conventional glucocorticosteroid treatment group compared with 5-ASA in all dose ranges (RR 2.53 [1.77,3.63])(fixed effect), (RR 3.13 [0.99 to 9.90])(random effects).[119,172,210,242,259] [LOW QUALITY]
- In a meta-analysis[212] of seven RCTs (n = 429)[38,80,148,213,224,270,302] there were significantly more adverse events when conventional glucocorticosteroid treatment plus azathioprine was compared with conventional glucocorticosteroid treatment plus placebo (RR 2.81 [1.28 to 6.17]).[HIGH QUALITY]
- In two studies (n = 267) of withdrawal due to adverse events, there was no significant difference in withdrawal due to adverse events between groups receiving conventional glucocorticosteroid or placbo (RR 4.57 [0.75 to 27.83]).[166,258][HIGH QUALITY]
- In six studies (n = 478) comparing withdrawal due to adverse events ofconventional glucocorticosteroid treatment versus 5-ASA treatment there was no significant difference between the groups (RR 1.18 [0.61 to 2.29]).[119,166,172,210,242,258] [HIGH QUALITY]
- In three studies (n = 226) comparing withdrawal due to adverse events of conventional glucocorticosteroid treatment plus methotrexate vs. conventional glucocorticosteroid treatment plus placebo, there were significantly more withdrawals in the methotrexate group (RR 6.97 [1.61 to 30.10]).[14,85,207] [MODERATE QUALITY]
- One RCT (n = 19) demonstrated that the addition of mercaptopurine to a regimen of conventional glucocorticosteroid decreased the need for prednisone (-15.5 vs. -6.1 mg).[227] [VERY LOW]
- In a meta-analysis[212] of five studies (n = 226)[38,80,148,213,302], AZA/MP was significantly more effective for glucocorticosteroid sparing (< 10 g/day) compared with placebo (RR1.81 [1.38 to 2.38] fixed effect; RR 1.80 [1.01 to 3.20] random effects).[MODERATE QUALITY]

- In one paediatric study (n = 55) there were 0.73 days on prednisone in the mercaptopurine plus conventional glucocorticosteroid arm compared with 1.34 days on prednisone in the conventional glucocorticosteroid arm alone.[170] [VERY LOW ]
- In a meta-analysis[212] of three studies (n = 18)[148,224,302], there was no significant difference in fistula healing between conventional glucocorticosterid plus azathioprine versus conventional glucocorticosteroid treatment plus placebo (RR 2.00 [0.67 to 5.93]).[LOW QUALITY]

#### 5.2.6.2 Evidence statements – economic

Please refer to the Health economic induction model summary, section 5.6

# 5.3 Budesonide for induction of remission

## 5.3.1 Clinical question

The clinical question searched in the review of budesonide for induction of remission in Crohn's disease was:

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for induction of remission compared with

- placebo?
- conventional glucocorticosteroid treatment?
- 5-aminosalicylate (5-ASA) treatment?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

## 5.3.2 Budesonide versus placebo

### 5.3.2.1 Clinical evidence

A Cochrane systematic review[249] was identified, quality assessed and accepted for this review. The Cochrane review was based upon fourteen studies, two of which[109,285] evaluated budesonide versus placebo; eight of which evaluated budesonide versus conventional glucocorticosteroid treatment[19,35,75,117,153,232,290,293] and one of which compared budesonide with 5-ASA treatment.[279] Two further studies were included in evaluation of change in CDAI scores[57] and change in IBDQ scores.[136]

A further update search was conducted and one additional study was identified[288] which provided efficacy and safety data for budesonide vs. 5-ASA treatment.

Paediatric studies were meta-analysed as a subgroup. No studies were identified comparing budesonide with immunosuppressives.

**Table 15: Evidence profile: budesonide versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide 9 mg | placebo | Relative (95% CI) | Absolute | |
| **Induction of clinical remission - 8 weeks (CDAI ≤ 150);** Greenberg 1994 and Tremaine 2002 in Seow 2008 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | 109/220 (49.5%) | 26/107 (24.3%) | RR 1.96 (1.19 to 3.23) | 233 more per 1000 (from 46 more to 542 more) | LOW |
| **Withdrawal due to adverse events 8-10 weeks;** Greenberg 1994 and Tremaine 2002 in Seow 2008 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious imprecision[3] | none | 17/220 (7.7%) | 6/107 (5.6%) | RR 1.16 (0.45 to 2.99) | 9 more per 1000 (from 31 fewer to 112 more) | VERY LOW |
| **Change in IBDQ score (better indicated by lower values) 8-10 weeks [fixed effect];** Irvine 2000 and Tremaine 2002 in Seow 2008 | | | | | | | | | | | |
| 2 | randomised trials | serious[1,] | Serious[4] | no serious indirectness | serious imprecision[5] | none | 40.1 (37.3) - Irvine & 34.1 (35.2) - Tremaine | 11.7 (31.5) - Irvine & 29.3 (35.7) - Tremaine | - | Mean Difference 17.84 higher (8.88 lower to 26.81 higher) | VERY LOW |
| **Change in IBDQ score (better indicated by lower values) 8-10 weeks [random effects];** Irvine 2000 and Tremaine 2002 in Seow 2008 | | | | | | | | | | | |
| 2 | randomised trials | serious[1,] | serious[2] | no serious indirectness | serious imprecision[5] | none | 40.1 (37.3) – Irving & 34.1 (35.2) - Tremaine | 11.7 (31.5) - Irvine & 29.3 (35.7) - Tremaine | - | Mean Difference 16.79 higher (6.34 lower to 39.91 higher) | VERY LOW |

*1 Allocation concealment not described in two RCTs.*
*2 Confidence interval crosses 1.25.*
*3 Confidence interval crosses 0.75 and 1.25.*
*4 $I^2$ > 50%.*
*5 Confidence interval crosses 16.8.*

### 5.3.3 Budesonide versus conventional glucocorticosteroid treatment

#### 5.3.3.1 Clinical evidence

The Seow 2008 Cochrane systematic review[249] was quality assessed and accepted for this review. Eight studies[19,35,75,117,153,232,290,293] which evaluated budesonide versus conventional glucocorticosteroid treatment underwent meta-analysis.

**Table 16: Evidence profile: budesonide versus conventional glucocorticosteroid treatment**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Conventional glucocorticosteroid | Relative (95% CI) | Absolute | |
| **Induction of clinical remission (assessed with CDAI ≤ 150; follow-up eight weeks);** Bar-Meir, 1998;Campieri, 1997;Escher, 2004;Gross, 1996;Levine, 2003;Rutgeerts, 1994;Tursi, 2006;Van Ierssel, 1995 in Seow et al 2008 | | | | | | | | | | | |
| 8 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 211/406 (52%) | 210/344 (61%) | RR 0.85 (0.75 to 0.97) | 92 fewer per 1000 (from 18 fewer to 153 fewer) | MODERATE |
| **Induction of clinical remission (assessed with CDAI ≤ 150; follow-up twelve weeks);** Campieri, 1997;Escher, 2004;Levine, 2003 in Seow et al 2008 | | | | | | | | | | | |
| 3 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 87/160 (54.4%) | 52/98 (53.1%) | RR 1.02 (0.81 to 1.3) | 11 more per 1000 (from 101 fewer to 159 more) | LOW |
| **Induction of clinical remission in severe disease (assessed with CDAI ≤ 150 in those with CDAI ≥ 300 at trial entry; follow-up eight weeks);** Campieri ,1997; Gross, 1996 | | | | | | | | | | | |
| 2 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[5] | none | 11/41 (26.8%) | 13/23 (56.5%) | RR 0.52 (0.28 to 0.95) | 271 fewer per 1000 (from 28 fewer to 407 fewer) | LOW |
| **Induction of clinical remission ileal or right-sided ileocolonic disease (assessed with CDAI; follow-up eight weeks);** Bar-Meir, 1998;Campieri, 1997;Escher, 2004;Gross, 1996;Rutgeerts, 1994;Van Ierssel, 1995 | | | | | | | | | | | |
| 6 | randomised trials | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 161/305 (52.8%) | 157/256 (61.3%) | RR 0.86 (0.75 to 1) | 86 fewer per 1000 (from 153 fewer to 0 more) | LOW |
| **Change in CDAI (measured with CDAI; Better indicated by lower values) [fixed effect];** Bar-Meir, 1998;D'Haens, 1998;Escher, 2004;Gross, 1996;Rutgeerts, 1994; Van Ierssel, 1995 in Seow et al 2008 | | | | | | | | | | | |
| 6 | randomised trials | serious[7] | serious[8] | no serious indirectness | no serious imprecision | none | 269 | 270 | - | MD 33.83 lower (45.68 to 21.97 lower) | LOW |
| **Change in CDAI (measured with CDAI; Better indicated by lower values) [random effects];** Bar-Meir, 1998;D'Haens, 1998;Escher, 2004;Gross, 1996;Rutgeerts, 1994; Van Ierssel, 1995 in Seow et al 2008 | | | | | | | | | | | |
| 6 | randomised trials | serious[7] | serious[8] | no serious indirectness | no serious imprecision | none | 269 | 270 | - | MD 42.27 lower (69.67 to 14.86 lower) | LOW |
| **Withdrawal due to adverse events;** Bar-Meir, 1998;Escher, 2004;Gross, 1996;Levine, 2003; Rutgeerts, 1994; Tursi, 2006 in Seow et al 2008 | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | randomised trials | serious[9] | no serious inconsistency | no serious indirectness | very serious[10] | none | 6/259 (2.3%) | 13/263 (4.9%) | RR 0.57 (0.18 to 1.84) | 21 fewer per 1000 (from 41 fewer to 42 more) | VERY LOW |
| **Glucocorticosteroid-related adverse events (follow-up eight weeks) [fixed effect];** Bar-Meir, 1998; Campieri, 1997; Escher, 2004; Gross, 1996; Levine, 2003; Rutgeerts, 1994 | | | | | | | | | | | |
| 6 | randomised trials | serious[11] | serious[8] | no serious indirectness | no serious imprecision | none | 222/594 (37.4%) | 372/594 (62.6%) | RR 0.60 (0.53 to 0.67) | 251 fewer per 1000 (from 207 fewer to 294 fewer) | LOW |
| **Glucocorticosteroid-related adverse events (follow-up eight weeks) [random effects];** Bar-Meir, 1998; Campieri, 1997; Escher, 2004; Gross, 1996; Levine, 2003; Rutgeerts, 1994 | | | | | | | | | | | |
| 6 | randomised trials | serious[11] | no serious indirectness | serious[8] | Serious[5] | none | 222/594 (37.4%) | 372/594 (62.6%) | RR 0.59 (0.46 to 0.77) | 257 fewer per 1000 (from 144 fewer to 338 fewer) | VERY LOW |
| **Glucocorticosteroid-related adverse events in adults (follow-up eight weeks) [fixed effect];** Bar-Meir, 1998; Campieri, 1997; Gross, 1996; Rutgeerts, 1994 | | | | | | | | | | | |
| 4 | randomised trials | serious[11] | serious[8] | no serious indirectness | no serious imprecision | none | 183/509 (36%) | 326/509 (64%) | RR 0.56 (0.49 to 0.64) | 282 fewer per 1000 (from 231 fewer to 327 fewer) | LOW |
| **Glucocorticosteroid-related adverse events in adults (follow-up eight weeks) [random effects];** Bar-Meir, 1998; Campieri, 1997; Gross, 1996; Rutgeerts, 1994 | | | | | | | | | | | |
| 4 | randomised trials | serious[12] | serious[8] | no serious indirectness | no serious imprecision | none | 183/509 (36%) | 326/509 (64%) | RR 0.53 (0.40 to 0.69) | 301 fewer per 1000 (from 199 fewer to 384 fewer) | LOW |

*1 Allocation concealment not described in eight studies. One study unblinded. Randomisation not described in five studies.*
*2 Allocation concealment not described in three studies. One study unblinded. Randomisation not described in one study.*
*3 Confidence interval crosses 1.25.*
*4 Allocation concealment not described in two studies. Randomisation not described in one study.*
*5 Confidence interval crosses 0.75.*
*6 Allocation concealment not described in six studies. Randomisation not described in three studies.*
*7 Allocation concealment not described in six studies. Blinding not described in two studies. Randomisation not described in three studies.*
*8 $I^2 > 50\%$.*
*9 Allocation concealment not described in five studies. Randomisation not described in three studies.*
*10 Confidence interval crosses 0.75 and 1.25.*
*11 Allocation concealment not described in six studies. Blinding not described in one study. Randomisation not described in three studies.*
*12 Allocation concealment not described in five studies. Blinding not described in one study. Randomisation not described in three studies.*

## 5.3.14 Budesonide versus 5-ASA treatment

### 5.3.421 Clinical evidence

The Seow 2008 Cochrane systematic review[249] was quality assessed and accepted for this review. One study[279] evaluated budesonide versus 5-ASA treatment for efficacy at 8 and 12 weeks and one additional study[288] was identified in the updated search which provided some additional efficacy and safety data.

**Table 17: Evidence profile: budesonide versus 5-ASA treatment**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other conside rations | Budesonide 9 mg | Mesalazine | Relative (95% CI) | Absolute | Quality |
| **Induction of remission (CDAI, follow-up eight weeks) [fixed effect];** Thomsen 1998 in Seow 2008;Tromm 2010 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | serious inconsistency[2] | no serious indirectness | serious imprecision[3] | none | 170/247 (68.8%) | 132/242 (54.5%) | RR 1.26 (1.10 to 1.46) | 142 more per 1000 (from 55 more to 251 more) | VERY LOW |
| **Induction of remission (CDAI, follow-up eight weeks) [random effects];** Thomsen 1998 in Seow 2008;Tromm 2010 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | serious inconsistency[2] | no serious indirectness | serious imprecision[3] | none | 170/247 (68.8%) | 132/242 (54.5%) | RR 1.33 (0.91 to 1.92) | 180 more per 1000 (from 49 fewer to 502more) | VERY LOW |
| **Induction of clinical remission (CDAI ≤ 150, follow-up twelve weeks);** Thomsen 1998 in Seow 2008 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[3] | none | 58/93 (62.4%) | 35/89 (39.3%) | RR 1.59 (1.17 to 2.15) | 232 more per 1000 (from 67 more to 452 more) | LOW |
| **Withdrawal due to adverse events; (follow-up eight weeks);**Thomsen, 1998 in Seow 2008;Tromm 2010 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[4] | none | 7/247 (2.8%) | 16/242 (6.6%) | RR 0.43 (0.18 to 1.02) | 38 fewer per 1000 (from 54 fewer to 1 more) | LOW |
| **Change in CDAI score (better indicated by lower CDAI values, follow-up eight weeks);** Tromm 2010 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | -149 (91) | -130 (108) | - | MD 19 lower (41.35 lower to | MODERATE |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 3.35 higher) | |
| **Total adverse events (follow-up eight weeks);** Tromm 2010 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 142/154 (92.2%) | 151/153 (98.7%) | RR 0.93 (0.89 to 0.98) | 69 fewer per 1000 (from 20 fewer to 109 fewer) | MODERATE |

*1 Allocation concealment not described.*
*2 $I^2$ > 50%.*
*3 Confidence interval crosses 1.25.*
*4 Confidence interval crosses 0.75.*

### 5.3.5 Children

#### 5.3.5.1 Budesonide versus conventional glucocorticosteroid treatment in children

#### 5.3.5.2 Clinical evidence

The data for this subgroup analysis were taken from the Seow 2008 Cochrane Review[249] and are based on two studies.[75,153]

**Table 18: Evidence profile: budesonide versus conventional glucocorticosteroid treatment in children**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Conventional glucocorticosteroid | Relative (95% CI) | Absolute | |
| **Induction of remission at eight weeks (follow-up eight weeks; assessed with: PCDAI);** Escher, 2004;Levine, 2003 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 20/41 (48.8%) | 23/40 (57.5%) | RR 0.88 (0.58 to 1.33) | 69 fewer per 1000 (from 242 fewer to 190 more) | VERY LOW |
| **Induction of remission at 12 weeks (follow-up 12 weeks; assessed with: PCDAI);** Escher, 2004; Levine, 2003 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 21/41 (51.2%) | 6/40 (15%) | RR 0.99 (0.65 to 1.5) | 1 fewer per 1000 (from 53 fewer to 75 more) | VERY LOW |
| **Induction of remission at eight weeks - ileal or right-sided ileocolonic disease (follow-up eight weeks; assessed with: PCDAI);** Escher, 2004 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[2] | none | 12/22 (54.5%) | 17/26 (65.4%) | RR 0.83 (0.52 to 1.34) | 111 fewer per 1000 (from 314 fewer to 222 more) | VERY LOW |
| **Change in PCDAI (follow-up eight weeks; measured with: PCDAI; range of scores: 0-100; Better indicated by higher values);** Escher, 2004 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | not assessable[4] | none | 19 | 14 | - | MD 4.10 lower (0 to 4.57 higher) | VERY LOW |
| **Glucoorticosteroid-related adverse events (follow-up eight weeks; assessed with: PCDAI);** Escher, 2004; Levine, 2003 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 17/41 (41.5%) | 30/40 (75%) | RR 0.57 (0.38 to 0.85) | 322 fewer per 1000 (from 112 fewer to 465 fewer) | VERY LOW |
| **Withdrawal due to adverse events (follow-up eight weeks; assessed with: PCDAI);** Escher, 2004 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/22 (4.5%) | 7/26 (26.9%) | RR 0.17 (0.02 to 1.27) | 223 fewer per 1000 (from 264 fewer to 73 more) | VERY LOW |

*1 Allocation concealment not described. One study was not blinded and randomisation method was not described.*

*2 Confidence interval crosses 0.75 and 1.25.*

*3 Allocation concealment not described*

*4 Standard deviations not reported.*

#### 5.3.5.3 Evidence statements - clinical

- In two RCTs (n = 327)[109,285] budesonide 9 mg was more effective than placebo (RR 1.96 [1.19 to 3.23]) for induction of remission for ileal or ileal colonic disease at eight weeks in Crohn's disease.[LOW QUALITY]
- In two RCTs (n = 327)[109,285] there was no significant difference in withdrawal due to adverse events between budesonide and placebo (RR 1.16 [0.45 to 2.99]).[VERY LOW QUALITY]
- In two RCTs (n = 247)[136,285] there was no significant difference in change in IBDQ scores between budesonide and placebo in the random effects model (MD 16.79 [-6.34 to 39.91]). However the fixed effect model favoured budesonide (MD 17.84 [-8.88,26.81]).[VERY LOW QUALITY]
- In eight RCTs (n = 750)[19,35,75,117,153,232,290,293] budesonide was significantly less effective for induction of remission at eight weeks compared with conventional glucocorticosteroid treatment (RR 0.85 [0.75 to 0.97]).[MODERATE QUALITY]
- In three RCTs (n = 258)[35,75,153] there was no significant difference in induction of remission at 12 weeks in patients treated with budesonide compared with conventional glucocorticosteroid treatment (RR 1.02 [0.81 to 1.30]).[LOW QUALITY]
- In two RCTs (n = 64)[35,117] conventional glucocorticosteroid treatment was significantly more effective at eight weeks than budesonide (RR 0.52 [0.28 to 0.95])for induction of clinical remission in patients with severe disease (CDAI > 300).[LOW QUALITY]
- In six RCTs (n = 561)[19,35,75,117,232,293] the relative risk approached significance (RR 0.86 [0.75 to 1]) favouring conventional glucocorticosteriods over budesonide for induction of clinical remission in patients with ileal or right-sided ileocolonic disease.[LOW QUALITY]
- In six RCTs (n = 539)[19,75,117,232,293] change in CDAI score was lower in budesonide compared with conventional glucocorticosteroid treatment MD -33.83 [-45.68 to -21.97] (fixed effect) and MD -42.27 [-69.67 to -14.86] (random effects).[LOW QUALITY]
- In five RCTs (n = 522)[19,75,117,232,290] there was no significant difference in withdrawal due to adverse events between budesonide and conventional glucocorticosteroid treatment (RR 0.57 [0.18 to 1.84]).[VERY LOW QUALITY]
- In six RCTs (n = 594)[19,35,75,117,153,232] including adults and children, there were significantly fewer glucocorticosteroid-related adverse events in participants receiving budesonide compared to a conventional glucocorticosteroid (RR 0.60 [0.53 to 0.67] [fixed effect]; RR 0.59 [0.46 to 0.77] [random effects]).[VERY LOW QUALITY]
- In four RCTs (n = 509)[19,35,75,117,153,232] in adults only, there were significantly fewer glucocorticosteroid-related adverse events in patients receiving budesonide compared to a conventional glucocorticosteroid (RR 0.56 [0.49 to 0.64] [fixed effect]; RR 0.53 [0.4 to 0.69] [random effects]).[LOW QUALITY]
- In two RCTs (n = 489)[279,288] budesonide was significantly more effective than 5-ASA (mesalazine) for induction of remission at eight weeks in the fixed effect analysis (RR 1.26 [1.10 to 1.46]) but not statistically significant in the random effects analysis (RR 1.33 [0.91 to 1.92]).[VERY LOW QUALITY]
- In one RCT (n = 182)[279] budesonide was significantly more effective than 5-ASA treatment (mesalazine) for induction of remission at 12 weeks (RR 1.59 [1.17 to 2.15]).[LOW QUALITY]
- In two RCTs (n = 489)[279,288] there was no significant difference in withdrawal due to adverse events between budesonide and mesalazine (RR 0.43 [0.18 to 1.02]).[LOW QUALITY]
- In one RCT (n = 307)[288] there were significantly fewer total adverse events in the budesonide group when compared with 5-ASA treatment (mesalazine) (RR 0.93 [0.89 to 0.98]).[MODERATE QUALITY]

- In one RCT (n = 307)[288] there was no significant difference in change in CDAI score between budesonide vs. 5-ASA treatment (MD 19 lower [41.35 lower to 3.35 higher]).[MODERATE QUALITY]
- In a meta-analysis of two paediatric studies (n = 81)[75,153], there was no significant difference in induction of remission at eight weeks between budesonide and conventional glucocorticosteroid treatment (regardless of disease site or severity) (RR 0.88 [0.58 to 1.33]).[VERY LOW QUALITY]
- In a meta-analysis of two paediatric studies (n = 81)[75,153], there was no significant difference in induction of remission at 12 weeks between budesonide and conventional glucocorticosteroid treatment (RR 0.99 [0.65 to 1.50]).[VERY LOW QUALITY]
- In one paediatric RCT (n = 33)[75] the change in PCDAI score was less with budesonide than conventional glucocorticosteroid treatment (Mean Difference 4.10 lower [12.77 lower to 4.57 higher]).[VERY LOW QUALITY]
- In a meta-analysis of two paediatric RCTs (n = 81)[75,153], there were significantly fewer glucocorticosteroid-related side effects in the budesonide treatment group compared to the conventional glucocorticosteroid treatment group (RR 0.57 (0.38 to 0.85).[VERY LOW QUALITY]
- In one paediatric RCT (n = 48) [75] there was no significant difference in withdrawal due to adverse events between budesonide and a conventional glucocorticosteroid (RR 0.17 (0.02 to 1.27).[VERY LOW QUALITY]

### 5.3.6 Economic evidence

No published data were found relating to the cost effectiveness of corticosteroid treatment for the induction of remission of Crohn's disease.

For primary health economic modelling, please see the health economic induction model summary, section 5.6 and Appendix H: for the full health economic report.

# 5.4 5-ASA treatment for induction of remission

## 5.4.1 Clinical questions

The clinical questions searched in the review of 5-ASA[a] treatment for induction of remission in Crohn's disease included:

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for induction of remission compared with

- placebo?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

## 5.4.2 5-ASA treatment versus placebo

### 5.4.2.1 Clinical evidence

A systematic search of the literature was conducted and nine studies[113,162,166,173,217,257,258,270,286] were identified which compared 5-ASA treatment with placebo. One of these studies[113] was a paediatric study. The Singleton studies[256-258] and Summers[270] paper evaluated different outcomes for the same trial.

The studies reviewed included patients with active disease who were not receiving any other medical treatment[113,162,166,217,257,258,270] or patients who were taking stable does of prednisone or immunosuppressives.[173,286] In the Mate-Jimenez 2000 study all participants had active disease and were glucocorticosteroid-dependent. In the Tremain study, participants on a stable dose of glucocorticosteroid or immunosuppressive treatment were included in the study population; subgroup analyses of participants on adjunctive therapy were not presented in the trial results.

The particular 5-ASA compound as described by the investigator is noted in the evidence tables (see Appendix F:), as the site of action has been purported to vary between treatments in this class of drug.

All included papers within the review were quality assessed using GRADE criteria. Meta-analysis was performed to provide summary statistics when possible. Results of paediatric papers are presented separately.

In December 2010, "Aminosalicylates for induction of remission or response in Crohn's disease"[154] was published by the Cochrane collaboration. This review included 16 RCTs which evaluated the efficacy of sulfasalazine and mesalazine. The review differs from the Crohn's guideline review of 5-ASA for induction in the following ways and thus was not included:

- The review was in adults only.
- Sulfasalazine and mesalazine were assessed independently.
- 5-ASA dosages were compared.
- The following studies which were included in the Cochrane review were excluded from the Crohn's guideline review. The reasons for exclusion were as follows:
  - Van Hees 1981[292]: Sulfasalazine vs. placebo; GDG criteria for assessment of remission not met (Van Hees Index [VHI] used).

[a] 5-ASA treatment is used to denote plurality. It includes both 5-aminosalicylates: mesalazine (Mesren MR, Asacol MR and Octasa MR), olsalazine, balsalazide; and the aminosalicylates: sulfasalazine (Salazosulfapyridine). Readers should be aware that not all 5-ASA treatments are licensed for maintenance of remission in Crohn's disease.

- Rijk 1991[226]: comparison of two indices of remission (CDAI and VHI) (change in activity indices with mean CDAI change 50 points used).
- Singleton 1994[255]: letter to editor; not fully published study.
- Saverymuttu 1986[238]: sulfasalazine plus placebo vs. sulfasalazine vs. glucocorticosteroid treatment; GDG criteria for assessment of remission not met (faecal granulocyte excretion used).
- Crohn's III 1997[124]: not fully published.
- Maier 1985[165] and Maier 1990[164]: comparison of two 5-ASA treatments and dose; not the question posed by the GDG.

After applying a methodologically rigorous approach to a *post-hoc* subgroup analysis (see full report in Appendix J:), a test for interaction between groups of different drug delivery mechanisms did not show an interaction with the outcome, induction of remission. On this basis the GDG agreed a 5-ASA class-effect for data analysis.

**Table 19: Evidence profile: 5-ASA treatment versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5-ASA | Placebo | Relative (95% CI) | Absolute | |
| **Remission (CDAI; Harvey Bradshaw Index) (follow-up 6-18 weeks);** Mahida 1990, Malchow 1984, Rasmussen 1987, Singleton 1993, Summers 1979, Tremaine 1994 | | | | | | | | | | | |
| 6 | randomised trials | serious[1] | serious[2] | no serious indirectness | serious imprecision[3] | none | 153/428 (35.7%) | 76/290 (26.2%) | RR 1.51 (1.20 to 1.92) | 134 more per 1000 (from 52 more to 241 more) | VERY LOW |
| **Adverse events (follow-up 16 weeks);** Rasmussen 1987, Singleton 1979, Tremaine 1994 | | | | | | | | | | | |
| 3 | randomised trials | serious[4] | serious[5] | no serious indirectness | serious imprecision[3] | none | 43/124 (34.7%) | 44/132 (33.3%) | RR 1.04 (0.8 to 1.36) | 13 fewer per 1000 (from 67 fewer to 120 more) | VERY LOW |
| **Withdrawal from study for any reason (follow-up 6-18 weeks);** Mahida 1990, Malchow 1984, Rasmussen 1987, Singleton 1993 | | | | | | | | | | | |
| 4 | randomised trials | serious[6] | very serious[7] | no serious indirectness | no serious imprecision | none | 180/397 (45.3%) | 113/247 (45.7%) | RR 0.92 (0.77 to 1.10) | 37 fewer per 1000 (from 105fewer to 46 more) | VERY LOW |
| **Quality of life 4 g controlled-release mesalazine (follow-up 16 weeks);** Singleton 1995 | | | | | | | | | | | |
| 1 | randomised trials | serious[8] | no serious inconsistency | no serious indirectness | not assessable | none | n = 75 4 g ASA | n = 80 | - | 7 QOL assess-ments statistic-ally significant p < 0.03 | VERY LOW |
| **Paediatric 5-ASA remission (follow-up 20 weeks) (Better indicated by lower values of CDAI) (follow-up eight weeks);** Griffiths 1993 | | | | | | | | | | | |
| 1 | randomised trials | serious [9] | no serious inconsistency | no serious indirectness | no serious imprecsion | none | n = 13 Mean CDAI = 152.3 ± | n = 13 Mean CDAI = 258.5 ± | - | MD -106.2 (-152.06,-60.34) | MODERATE |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 31.4 | 49.4 | | | |

*1 Randomisation and allocation concealment not described in three studies.*

*2 Variation in drug dose and composition: 3 g sulfasalazine (Malchow 1984), 1 g/15 kg sulfasalazine (Summers 1979),1500 mg slow release Pentasa (Rasmussen1987, Mahida 1990), 2400 g per day slow release (Tremaine 1994) and 4 g mesalazine daily (Singleton 1993).*

*3 Confidence interval crosses 1.25.*

*4 Randomisation and allocation concealment not described in two studies.*

*5 Variation in drug dose and composition: 1 g/15 kg sulfasalazine (Singleton 1979),1500 mg slow release Pentasa (Rasmussen1987 ), 2400 g per day slow release Asacol (Tremaine 1994). $I^2$ = 64%.*

*6 Randomisation and allocation concealment not described in two studies.*

*7 Variation in drug dose and composition: 3 g sulfasalazine (Malchow 1984), 1500 mg slow release Pentasa (Rasmussen1987, Mahida 1990), and 4 g mesalazine daily (Singleton 1993).*

*8 Method of randomisation and allocation concealment not described.*

*9 High drop-out rate.*

### 5.4.3 5-ASA treatment versus azathioprine/mercaptopurine

#### 5.4.3.1 Clinical evidence

There were no systematic reviews which met inclusion criteria for this review. Three RCTs were included.[173,258,270] The Singleton (1979) and Summers (1979) papers evaluated different outcomes for the same study. Patients recruited for the Singleton/Summers (1979) study had active Crohn's disease and were not receiving any other medications. All patients recruited for the Mate-Jimenez (2000) study had active disease and were glucocorticosteroid-dependent.

**Table 20: Evidence profile: 5-ASA treatment versus azathioprine/mercaptopurine**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5-ASA | AZA/MP | Relative (95% CI) | Absolute | |
| **Induction of remission (CDAI < 150 follow-up 16-30 weeks) [fixed effect];** Summers 1979, Mate-Jimenez 2000 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | serious inconsistency[2] | no serious indirectness | serious[3] | none | 29/81 (35.8%) | 36/75 (48%) | RR 0.81 (0.52 to 1.24) | 91 fewer per 1000 (from 230 fewer to 115 more) | VERY LOW |
| **Induction of remission (CDAI < 150 follow-up 16-30 weeks) [random effects];** Summers 1979, Mate-Jimenez 2000 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | serious inconsistency[2] | no serious indirectness | very serious[4] | none | 29/81 (35.8%) | 36/75 (48%) | RR 0.48 (0.07 to 3.53) | 250 fewer per 1000 (from 446 fewer to 1000 more) | VERY LOW |
| **Adverse events (follow-up 16 weeks);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 10/74 (13.5%) | 19/59 (32.2%) | RR 0.42 (0.21 to 0.83) | 187 fewer per 1000 (from 55 fewer to 254 fewer) | MODERATE |

*1 Randomisation and allocation concealment not described in Mate-Jimenez 2000.*
*2 $I^2$ > 50%.*
*3 Confidence interval crosses 0.75.*
*4 Confidence interval crosses 0.75 and 1.25.*

### 5.4.4 5-ASA treatment versus methotrexate

#### 5.4.4.1 Clinical evidence

There were no systematic reviews which met inclusion criteria for this review. One RCT was included.[173] The particular 5-ASA compound used in this investigation was not identified. All patients recruited for this study had active disease and were glucocorticosteroid -dependent.

**Table 21: Evidence profile: 5-ASA treatment versus methotrexate**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5-ASA | Methotrexate | Relative (95% CI) | Absolute | |
| **Induction of remission (CDAI < 150 follow-up 30 Weeks);** Mate-Jimenez 2000 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 1/7 (14.3%) | 12/15 (80%) | RR 0.18 (0.3 to 1.12) | 656 fewer per 1000 (from 560 fewer to 96 more) | LOW |

*1 Method of randomisation and allocation concealment not described.*
*2 Confidence interval crosses 0.75.*

### 5.4.5 Safety evidence

In addition to the data presented from RCTs, the GDG wanted observational data reviews of side effects to be available to clinicians and to people with Crohn's disease taking medication. A summary of this data is available in Appendix L:.

#### 5.4.5.1 Evidence statements– clinical

- In a meta-analysis of six RCTs (n = 718) (follow-up 6 to 18 weeks) 5-ASA treatment was more effective for induction of remission in adults than placebo (RR1.51 [95% CI 1.2 to 1.92]).[162,166,256,257,270,286] [VERY LOW QUALITY]
- In a meta-analysis of three RCTs (n = 256) (follow-up 16 weeks) there was no significant difference in adverse events between 5-ASAs and placebo (RR 1.04 [0.8 to 1.36]).[217,258,286] [VERY LOW QUALITY]
- In a meta-analysis of four RCTs (n = 644) (follow-up 6 to 18 weeks) there was no significant difference in all cause withdrawal from study between 5-ASA treatment and placebo (RR 0.92 [0.77 to 1.10]).[162,166,217,257] [VERY LOW QUALITY]
- In one RCT (n = 155) (follow-up 16 weeks) quality of life improved significantly on seven parameters ($p < 0.03$)with mesalazine compared with placebo.[256] [VERY LOW QUALITY]
- In one paediatric RCT (n = 13) (follow-up 20 weeks) there was more remission in the 5-ASA group than in the placebo group (MD 106.2 lower [152.06 lower to 60.34 lower]).[113][MODERATEQUALITY]
- In a meta-analysis of two RCTs (n = 156) (follow-up 16 to 30 weeks) there was no significant difference in remission between 5-ASA treatment and AZA/MP (RR 0.81 [0.52 to 1.24] fixed effect; RR 0.48 [0.68 to 1.67] random effects).[173,258] [VERY LOW QUALITY]
- In one RCT (n=133) (follow-up 16 weeks) there were fewer adverse events associated with 5-ASA treatment than AZA/MP (RR 0.42 [0.21 to 0.83]).[258] [MODERATE QUALITY]
- In one RCT (n = 22) (follow-up 30 weeks) there was no significant difference for induction of remission between 5-ASA treatment and methotrexate (RR 0.18 [0.3 to 1.12]).[173] [LOW QUALITY]

### 5.4.6 Economic evidence

No published data were found relating to the cost effectiveness of 5-ASA treatment for the induction of remission of Crohn's disease.

For primary health economic modelling, please see the health economic induction model summary, section 5.6 and Appendix H: for the full health economic report.

# 5.5 Immunosuppressives for induction of remission

## 5.5.1 Clinical questions

The clinical questions searched in the review of immunosuppressives for induction of remission in Crohn's disease included:

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for induction of remission compared with

- placebo?
- methotrexate?

In individuals diagnosed with Crohn's disease what is the incidence of serious adverse events for the following subgroups:

- normal blood TPMT activity, on a standard dose of azathioprine?
- low blood TPMT activity, on a low dose of azathioprine?
- blood TPMT is unknown, on a standard dose of azathioprine?

The objective of this review was to collect incidence data about serious adverse events in relation to TMPT levels and azathioprine dose (presented in tabular format below).

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for induction of remission

- compared with placebo?
- *plus* conventional glucocorticosteroid treatment compared with placebo *plus* conventional glucocorticosteroid treatment?

A further review of serious adverse events occurring in people with Crohn's disease was conducted to support discussion about treatment decisions between healthcare professional and the person with Crohn's disease, and also to provide clinical data for the economic analysis.

The review of TPMT monitoring included serious adverse events associated with normal TPMT activity, low TPMT activity and unknown TPMT activity.

The safety review for AZA/MP included the following adverse events:

- Death
- Malignancy, particularly lymphoma
- Neutropenia
- Agranulocytosis
- Pancreatitis
- Blood dyscrasias (methotrexate)
- Cirrhosis of the liver (methotrexate).

### 5.5.2 Azathioprine or mercaptopurine versus placebo

#### 5.5.2.1 Clinical evidence

There were no systematic reviews which met inclusion criteria for this review. Two RCTs were included in this review. These papers by Singleton[258] and Summers[270] evaluated different outcomes for the same study.

**Table 22: Evidence profile: azathioprine or mercaptopurine versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | AZA | placebo | Relative (95% CI) | Absolute | |
| **Remission (by CDAI follow-up 17 weeks);** Summers, 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 21/59 (35.6%) | 20/77 | RR 1.37 (0.82 to 2.28) | 96 more per 1000 (from 47 fewer to 332 more) | MODERATE |
| **Adverse events (follow-up 17 weeks);** Singleton, 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious | none | 19/59 (32.2%) | 5/77 (6.5%) | RR 4.96 (1.97 to 12.51) | 257 more per 1000 (from 63 more to 747 more) | HIGH |

*1 Confidence interval crosses 1.25.*

### 5.5.3 Azathioprine or mercaptopurine versus methotrexate

#### 5.5.3.1 Clinical evidence

Three studies met inclusion criteria for this review.[12,173,207] Meta-analysis was conducted for two outcomes.

**Table 23: Evidence profile: azathioprine or mercaptopurine versus methotrexate**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | AZA/MP | MTX | Relative (95% CI) | Absolute | |
| **Remission (CDAI ≤ 150 or HB ≤ 3, follow-up 24-36 weeks);** Ardizzone, 2003; Mate-Jimenez, 2000; Oren, 1997 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 37/75 (49.3%) | 34/68 (50%) | RR 0.99 (0.73 to 1.35) | 5 fewer per 1000 (from 135 fewer to 175 more) | VERY LOW |
| **Withdrawal due to adverse events (follow-up 24-36 weeks);** Ardizzone, 2003 ;Mate-Jimenez, 2000 ;Oren, 1997 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 5/75 (6.7%) | 6/68 (8.8%) | RR 0.79 (0.25 to 2.44) | 19 fewer per 1000 (from 66 fewer to 127 more) | VERY LOW |
| **Glucocorticosteroid-sparing (follow-up six months);** Ardizzone, 2003 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[3] | none | 17/27 (63%) | 15/27 (55.6%) | RR 1.13 (0.73 to 1.77) | 72 more per 1000 (from 150 fewer to 428 more) | LOW |

*1 Method of randomisation and allocation concealment not described in all three studies. Ardizzone 2003 not double blinded.*

*2 Confidence interval crosses 0.75 and 1.25.*

*3 Confidence interval crosses 0.75.*

### 5.5.4 Methotrexate versus placebo

#### 5.5.4.1 Clinical evidence

No RCTs comparing methotexate and placebo were identified. However a Cochrane systematic review[7] was identified which compared methotrexate as adjunctive therapy (a glucocorticosteroid *plus* methotrexate) to glucocorticosteroid treatment *plus* placebo. Please refer to section 5.2.5 for this review.

#### 5.5.4.2 Evidence statements – clinical

- In one RCT (n = 136)[270] there was no significant difference in induction of remission between AZA/MP and placebo (RR1.37 [0.82 to 2.28]).[MODERATE QUALITY]
- In one RCT (n = 136)[258] there were significantly more adverse events in the AZA/MP group compared with placebo (RR 4.96 [1.97 to 12.51]).[HIGH QUALITY]
- In three RCTs (n = 143)[12,173,207] there were no significant differences for induction of remission between AZA/MP and methotrexate (RR 0.99 [0.73 to 1.35]).[VERY LOW QUALITY]
- In three RCTs (n = 143)[12,173,207] there were no significant differences for withdrawal due to adverse events between AZA/MP and methotrexate (RR 0.79 [0.25 to 2.44]).[VERY LOW QUALITY]
- In one RCT (n = 54)[12] there was no significant difference for glucocorticosteroid-sparing between AZA/MP and methotrexate (RR 1.13 [0.73 to 1.77]).[LOW QUALITY]

### 5.5.5 Immunosuppressive safety data

Apart from the RCTs included above, additional side-effect data wereidentified.The GDG was keen to make available this observational data to clinicians and to people taking medication. It is important to be aware of the limitations of observational data. A summary of the data collated is available in Appendix N:.

## 5.5.6 Thiopurine methyltransferase (TPMT) activity

### 5.5.6.1 Clinical evidence

Azathioprine is an immunosuppressive prodrug rapidly converted to the active metabolite 6-MP via a non-enzymatic pathway. 6-MP is further metabolised by three competitive enzymes: xanthine oxidase (XO), thiopurine methyltransferase (TPMT), and hypoxanthine-guanine phosphoribosyl-transferase (HGRT). Only HGRT anabolises 6-MP into the active nucleotide responsible for therapeutic activity.

The role of TPMT was first recognised in 1987[151] and pre-treatment screening for TPMT was first suggested in 1992.[10]

Reduction in TPMT as a result of genetic variation may lead to bone marrow suppression because of preferential metabolism of 6-MP to 6-thioguanine. Most people (88%) have a genotype with two high (normal) metabolizing alleles. These people are homozygous with two wild type (normal) TPMT*1/TPMT*1 alleles corresponding to high enzyme activity. Heterozygosity occurs in 11% of patients who have one high and one low (mutant) allele. In 0.3% of patients a homozygous deficiency exists, characterised by two low metabolizing alleles.

For the purposes of this review, TPMT phenotyping reflects TPMT enzyme activity in red blood cells. Normal to high activity range is 24−80 units; intermediate enzyme activity is 14−23 units and TPMT deficiency is less than or equal to 13 units. However healthcare professionals should be familiar with local laboratory values when making prescribing decisions.

Patients may be tested either for TPMT genotype or TPMT activity (phenotype) or both. Correlation between genotype and phenotype is good, particularly in inflammatory bowel disease, but may not be complete, because factors other than genetic constitution can influence TPMT activity.

Normal dose: azathioprine 2−2.5 mg/kg; mercaptopurine 1−1.5 mg/kg/day.

The objective of this review was to collect incidence data about serious adverse events in relation to TPMT levels and azathioprine dose (presented in tabular format below).

This review includes only studies which reported serious adverse events in individuals with Crohn's disease. Specifically, these events include cytopenia and pancytopenia. Cytopenia refers to suppression of one of the major cell lines, for example thrombocytopenia, neutropenia, anaemia and leukopenia. Pancytopenia indicates a more global effect on bone marrow suppression. While these effects usually reverse on discontinuing treatment, the risk of fatality due pancytopenia or neutropenia is recognised.

Mixed IBD populations that were not able to be analysed separately as a Crohn's disease subgroup were excluded.

**Table 24: Serious adverse events in patients with different levels of TPMT activity**

| Reference | Study type<br>Sample size<br>Population characteristics | TPMT genotype<br>Wild type-homozygous:<br>Normal dose | TPMT genotype<br>Heterozygous:<br>Low dose | TPMT assay<br>High levels:<br>Normal dose | TPMT assay<br>Intermediate levels:<br>Low dose | Other reported results |
|---|---|---|---|---|---|---|
| | Prospective studies | | | | | |
| Jojic, 2003[140] | 35 people with IBD:<br>24 with CD<br>11 with UC | 23/24 people with Crohn's disease (1-2.5 mg/kg<br>1 patient with CD and pancytopenia | 1/24 people with Crohn's disease (125 mg/day)<br>WBC between 2600 and 3000/$mm^3$ | | | Low quality study |
| Regueiro, 2002[219] | 71 people with Crohn's disease | | | | | Low quality study<br><br>45 people with Crohn's disease with normal TPMT activity by genotype or phenotype on 2-2.5 mg/kg/day AZA<br>No acute leukopenia<br>2 pancreatitis<br>1 hepatitis<br>3 infection<br><br>7 people with Crohn's disease with normal TPMT activity by genotype or phenotype on 1-1.5 mg/kg/day AZA<br>No acute leukopenia<br>1 adverse reaction (not described) |

| Reference | Study type<br>Sample size<br>Population characteristics | TPMT genotype<br>Wild type-homozygous:<br>Normal dose | TPMT genotype<br>Heterozygous:<br>Low dose | TPMT assay<br>High levels:<br>Normal dose | TPMT assay<br>Intermediate levels:<br>Low dose | Other reported results |
|---|---|---|---|---|---|---|
| Reuther, 2003[221] | Cross- sectional study<br>71 people with Crohn's disease On maintenance AZA | 67 people with Crohn's disease on 1.57 mg/kg/day maintenance<br>No adverse events | | | | Low quality<br><br>4 heterozygous people with Crohn's disease on median dose of 1.81 mg/kg/day<br>No adverse events |
| | Retrospective studies | | | | | |
| Schwab 2002[247] | Retrospective study<br>77 people with Crohn's disease | 9 (12%) people with Crohn's disease on AZA doses ranging from 0.6-2.2 mg/kg/day with serious side effects:<br>3 pancreatitis (2 on low dose);<br>1 hepatotoxicity;<br>3 nausea, vomiting, abdominal pain;<br>1 cytopenia;<br>1 pancytopenia | | 9 (12%) people with Crohn's disease on AZA doses ranging from 0.6-2.2 mg/kg/day with serious side effects:<br>3 pancreatitis (2 on low dose);<br>1 hepatotoxicity;<br>3 nausea, vomiting, abdominal pain;<br>1 cytopenia;<br>1 pancytopenia | | Low quality<br><br>2 heterozygous people with Crohn's disease with intermediate TPMT activity on normal dose AZA of 2.5-3 mg/kg/day with serious side effects:<br>1cytopenia;<br>1 megaloblastic anaemia<br><br>(12 people with Crohn's disease experienced serious side effects, 1 person who was homozygous deficient experienced pancytopenia.<br>Low doses were notably associated with short treatment duration – ?effect of titration) |
| Colombel et al, 2000[43] | Retrospective case study | 13/30 (43%) wild type homozygous on AZA | | | | Low quality |

| Reference | Study type<br>Sample size<br>Population characteristics | TPMT genotype<br>Wild type-homozygous:<br>Normal dose | TPMT genotype<br>Heterozygous:<br>Low dose | TPMT assay<br>High levels:<br>Normal dose | TPMT assay<br>Intermediate levels:<br>Low dose | Other reported results |
|---|---|---|---|---|---|---|
| | 41 patients with Crohn's disease and with either: leukopenia, thrombocytopenia or both. | (median dose 125 mg/day) with severe leukopenia | | | | 2/7(29%) heterozygous on 100-200 mg/day AZA with severe leukopenia |

#### 5.5.6.2 Evidence statements - TPMT

- TPMT genotype or activity was not always associated with a pancytopenic event, (idiopathic pancytopenia occurred in the presence of normal TPMT activity) but heterozygosity was associated with leukopenia.[140][LOW QUALITY]
- Normal TPMT by genotype or phenotype on normal dose was not associated with leukopenia, but was associated with some other adverse events, but normal activity on low dose was associated with fewer adverse events.[219][LOW QUALITY]
- Low-dose azathioprine was associated with low numbers of adverse events in both normal and heterozygous people with Crohn's disease.[222][LOW QUALITY]
- 12% of people with Crohn's disease who had normal TPMT genotype and activity on a low- to normal- azathioprine dose experienced severe adverse events. Heterozygosity on a normal to high dose was associated with cytopenia.[247][LOW QUALITY]
- Of 41 people with Crohn's disease who retrospectively experienced serious adverse events, 40% with normal TPMT activity, and 30% who had low TPMT experienced adverse events. Intermediate or normal TPMT activity is not a good predictor of risk of serious adverse events.[43][LOW QUALITY]

### 5.5.7 Economic evidence

One study[71] was identified from the economic search. This is summarised in the economic evidence profile below. A full evidence table is also provided in Appendix F:.

**Table 25: Disease management strategies - economic study characteristics**

| Study | Comparators | Applicability | Limitations | Other Comments |
|---|---|---|---|---|
| Dubinsky et al 2005<br>USA | Azathioprine treatment with TPMT test[(a)] vs azathioprine treatment without TPMT test[(b)] | Partially applicable[(c)] | Potentially serious[(d)] | Population: Patients with moderate to severe chronically active Crohn's disease (CDAI 150-450)<br>One-year time horizon<br>The model was based on a decision tree structure where the difference in costs and outcomes for each strategy were driven by the response to different drug regimens and the number of cases identified with the TPMT monitoring strategy. The only adverse event considered was sepsis.<br>Costs: drugs, consultations, monitoring, treatment for sepsis and surgery.<br>Outcomes were reported as time to clinical response and time to sustained clinical response. |

a) *Patients in the TPMT arm were initially given 50 mg AZA, 100 mg AZA or MTX, depending on their TPMT levels. AZA doses could then be increased or decreased according to clinical response, with a minimum of 25 mg and a maximum of 250 mg. Patients not responding to MTX were switched to infliximab; no description was given for patients in this treatment arm not responding to the maximum dose of AZA, though based on the probability inputs quoted, this is likely to be a small number (~3%).*

b) *Patients in the no TPMT armwere initially treated with 50 mg AZA. The AZA dose was increased to 100 mg for patients who didn't respond to treatment after three months. Those who didn't respond to 100 mg AZA either underwent surgery (25%) or were given infliximab (75%) as well as continuing on 100 mg AZA.*

c) *A US perspective. QALYs were not reported.*

d) *Due to the lack of clinical data, a number of inputs for the model were taken from expert opinion. This was recognised as a limitation by the authors themselves. Due to the lack of published data identified by the literature review, no meta-analysis was conducted on model inputs and the authors did not conduct a probabilistic sensitivity analysis.*

**Table 26: Disease management strategies - economic summary of findings**

| Study | Comparators | Incremental cost (£) | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|
| Dubinsky et al 2005<br>USA | TPMT test vs azathioprine treatment without TPMT test | Reference-£2,075[(a)] | -3.31 weeks to response[(b)]<br>-2.45 weeks to sustained response[(c)] | TPMT dominates | Probabilities and costs were increased and decreased 50% from the base case and costs of azathioprine were increased three-fold.<br><br>The cost effectiveness rankings were not affected by the sensitivity analysis |

*(a) Converted from 2004 USD.*
*(b) 'Time to response in weeks' was defined as the elapsed time from the first administration of drug treatment until the first clinical response (CDAI < 150).*
*(c) 'Time to sustained response in weeks' was defined as the elapsed time from the first drug administration until the time a person was able to maintain CDAI < 150, and remain off glucocorticosteroid treatment for eight weeks.*

#### 5.5.7.1 Evidence statements – economic

- One partially-applicable cost-effectiveness analysis with potentially serious limitations found that TPMT screening and metabolite monitoring are associated with lower costs and better clinical outcomes.

## 5.6 Health economic induction model summary

### 5.6.1 Original economic analysis

The GDG considered the clinical evidence with regard to induction of remission and noted the superiority of

- conventional glucocorticosteroid treatment as first-line therapy
- and azathioprine plus conventional glucocorticosteroid combination therapy as second-line treatment.

The GDG noted that acquisition costs of these drugs are relatively inexpensive, however this does not account for costs of monitoring, consultations, treatment withdrawal or downstream costs due to treatment failure. Induction of remission was identified as high priority by the GDG in the early stages of guideline development, since this topic is relevant for everyone with Crohn's disease and no appropriate economic analyses in this area were identified in the literature. It was therefore decided that an original economic analysis would be conducted; a summary of the analysis is provided below and a full description can be found in Appendix H:.

### 5.6.2 Methods

#### 5.6.2.1 Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective. A decision tree was constructed in order to estimate costs and QALYs associated with different treatment strategies for medical induction of remission. Uncertainty was explored through probabilistic and univariate sensitivity analyses. The model time horizon was 30 weeks, chosen to reflect the length of the longest treatment sequence explored in the analysis.

#### 5.6.2.2 Population

The population entering the model comprises people with an acute inflammatory exacerbation of Crohn's disease, defined by a Crohn's Disease Activity Index (CDAI) score of > 150. Biologics are only recommended for people with severe Crohn's disease[198]; an assumption was made that people whose exacerbation failed to respond to two lines of treatment would be regarded as falling under the aegis of the technology appraisal, though it was noted that this may not always be the case. Strategy 9 in Table 27 is relevant for people in whom the Crohn's disease has progressed to being defined as severe before initiation of biologic treatment, despite only failing one line of treatment.

#### 5.6.2.3 Comparators

The comparators examined in the model were treatment sequences agreed by the GDG economic subgroup and ratified by the GDG. These are shown in Table 27. Due to the difference in costs and side-effect profile, the GDG decided to consider sulfasalasine and mesalazine separately within the economic model. The GDG also elected to consider the cost-effectiveness of one-off induction treatment strategies in the induction of remission model, to reflect the nature of the treatment and the data that could be extracted from the clinical trials. The GDG were satisfied that, having established the most cost-effective induction sequence, longer term costs and effects could be captured in the maintenance model, where relapses from maintenance treatment are then assumed to be treated with the most cost-effective one-off induction sequence found from this analysis.

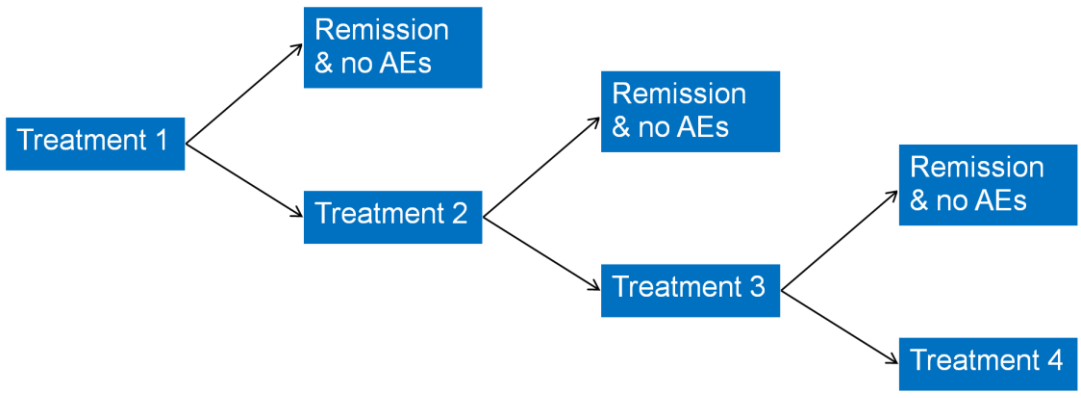
**Table 27: Treatment sequences in induction of remission model**

| Strategy | 1st line | 2nd line | 3rd line | 4th line |
|---|---|---|---|---|
| 1 | Sulfasalazine | Glucocorticosteroid | Azathioprine + a Glucocorticosteroid | Biologic |
| 2 | Sulfasalazine | Glucocorticosteroid | Methotrexate + a Glucocorticosteroid | Biologic |
| 3 | Mesalazine | Glucocorticosteroid | Azathioprine + a Glucocorticosteroid | Biologic |
| 4 | Mesalazine | Glucocorticosteroid | Methotrexate + a Glucocorticosteroid | Biologic |
| 5 | Glucocorticosteroid | Azathioprine + a Glucocorticosteroid | Biologic | - |
| 6 | Glucocorticosteroid | Methotrexate + a Glucocorticosteroid | Biologic | - |
| 7 | Budesonide | Glucocorticosteroid | Azathioprine + a Glucocorticosteroid | Biologic |
| 8 | Budesonide | Glucocorticosteroid | Methotrexate + a Glucocorticosteroid | Biologic |
| 9 | Glucocorticosteroid | Biologic | - | - |

### 5.6.2.4 Model structure and key assumptions

A decision tree was constructed, whereby the QALY gain was driven by the proportion of people in whom remission was successfully induced. Remission was defined as not withdrawing due to an adverse event and a CDAI score of ≤ 150. Although the GDG noted it was unlikely that all treatments would have the same side-effect profile, they accepted that the reporting of specific adverse events in the RCTs was not sufficient to model specific treatment-related adverse events. On that basis, they agreed that withdrawals from treatment could be used as a proxy for adverse events, and that costs and disutilities pertaining to adverse events for each treatment would be captured by both the additional cost of further treatment, and by patients still having the utility weight associated with active disease.

**Figure 4 Induction of remission model structure**




Key assumptions:

- Treatment continued to the end of the treatment cycle regardless of whether people entered remission.
- Utility was assumed to improve in the middle of the treatment cycle for those who entered remission.

- For time spent in active disease, people with Crohn's disease incurred more contacts with the health service than they would have had they been in remission.
- Withdrawals were assumed to occur at the end of a treatment cycle.
- All people who did not enter remission by the end of the time horizon were assumed to undergo surgery.

#### 5.6.2.5 Model inputs

Model inputs were based on RCT data, acquisition costs, PSSRU costs and NHS reference costs supplemented by additional data sources, including expert opinion provided by the GDG, as required. Model inputs were validated by the GDG.

To parameterise treatment effects in the model, a network meta-analysis (NMA) based on a conditional logistic regression was carried out. The aim of the NMA was to calculate treatment-specific odds ratios for withdrawal and remission conditional on not withdrawing. Separate analyses were carried out for first-line induction and second-line induction following failure of glucocorticosteroid treatment.

#### 5.6.2.6 Sensitivity analysis

In total, seven univariate sensitivity analyses were conducted, whereby, for each analysis one key model input was changed in order to explore the sensitivity of model results to changes in that parameter. The number one ranked strategy did not change in any univariate sensitivity analysis.

A probabilistic analysis was carried out whereby distributions were assigned to treatment effects, utilities and, where possible, costs in order to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.

Model outputs were very uncertain; this was in part due to the imprecision of estimates of withdrawal due to adverse events, which were highly imprecise due to low event rates.

### 5.6.3 Results

#### 5.6.3.1 Base case

The cost-effectiveness analysis found that glucocorticosteroid treatment followed by azathioprine plus a glucocorticosteroid then a biologic is the most cost-effective treatment strategy to induce remission of an inflammatory exacerbation of Crohn's disease. The base case results are shown in Table 28.

**Table 28: Base case cost-effectiveness results for induction of remission model**

| Ranking (95% CI)* | Strategy | Mean cost | Mean QALYs | Net monetary benefit* | Probability of being most cost-effective strategy* |
|---|---|---|---|---|---|
| 1 (1,6) | CS , AZA+CS , BIO | £1,099 | 0.463 | £8,169 | 72.7% |
| 2 (1,6) | BUD , CS , AZA+CS , BIO | £1,164 | 0.455 | £7,945 | 9.1% |
| 3 (2,7) | MES , CS , AZA+CS , BIO | £1,128 | 0.450 | £7,862 | 2.5% |
| 4 (1,8) | CS , MTX+CS , BIO | £1,398 | 0.461 | £7,823 | 11.1% |
| 5 (2,8) | BUD , CS , MTX+CS , BIO | £1,358 | 0.454 | £7,731 | 1.2% |
| 6 (1,8) | MES , CS , MTX+CS , BIO | £1,164 | 0.443 | £7,696 | 2.7% |
| 7 (3,8) | SUL , CS , AZA+CS , BIO | £1,318 | 0.448 | £7,652 | 0.2% |
| 8 (3,9) | SUL , CS , MTX+CS , BIO | £1,383 | 0.442 | £7,454 | 0.4% |

| Ranking (95% CI)* | Strategy | Mean cost | Mean QALYs | Net monetary benefit* | Probability of being most cost-effective strategy* |
|---|---|---|---|---|---|
| 9 (5,9) | CS , BIO | £2,068 | 0.457 | £7,079 | 0.1% |

* Based on a willingness-to-pay of £20,000 per QALY gained

CS-Glucocorticosteroid treatment AZA- Azathioprine MES- Mesalazine MTX- Methotrexate SUL- Sulfasalazine BUD- Budesonide BIO- Biologics

The analysis showed that in the base case, glucocorticosteroid treatment followed by azathioprine plus a glucocorticosteroid then a biologic was the dominant- most effective and least costly- strategy. The 95% confidence interval for the ranking ranged from one to six and it was the most cost-effective strategy in 73% of all simulations.

Following comments received during consultation regarding the lack of glucorticosteroid-related side effects considered in the model, a further sensitivity analysis was conducted, where the costs and disutilities of myocardial infarction (MI) and hip fracture were added in for patients receiving glucocorticosteroid therapy in the most cost-effective strategy (a glucocorticosteroid, azathioprine + a glucocorticosteroid, a biologic). This was based upon two publications[63,294] which explore the increased risks of fracture and MI in people having intermittent high-dose glucocorticosteroid therapy. The fact that these adverse events were only modelled for the most cost-effective strategy represents a conservative approach since glucocorticosteroid therapy is included in every other strategy and therefore including adverse events in other strategies would only weaken their cost effectiveness relative to the most cost-effective strategy. The adverse event specific risks, costs and utility weights associated with glucocorticosteroid monotherapy were applied to ***everyone*** in the most cost-effective strategy in the model receiving glucocorticosteroid monotherapy or azathioprine + a glucorticosteroid combination therapy and the model was run. The cost effectiveness ranking did not change.

### 5.6.4 Limitations and interpretation

This model was based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also applied to interpretation of the economic analysis. Limitations of the model include:

- The utility-loss and treatment-cost associated with adverse events was not explicitly incorporated.This is likely to mean the cost effectiveness of all the treatment strategies has been overestimated in the economic analysis, though since each treatment is likely to have a different side-effect profile, it is unlikely that ICERs have been underestimated by the same magnitude for all treatment strategies. For treatment strategies with more severe side effects, the overestimation of the ICER is likely to be higher than in treatment strategies with less severe side-effect profiles. However, the additional sensitivity analysis conducted on side effects associated with glucocorticosteroid monotherapy provides some extra assurance about conclusions related to the strategy ranked first in terms of cost effectiveness.
- No clinical review was conducted on the efficacy of biologic treatment as this was outside the Crohn's disease guideline remit. Efficacy data were derived from the two studies in the NICE Technology Appraisal 187[198].

### 5.6.5 Generalisability to other populations and settings

It should be noted that all of the findings from this cost-effectiveness-analysis relate to an adult population and the conclusions may not apply to paediatric treatment. It was not possible to conduct a separate model for children due to the paucity of both clinical and quality of life studies conducted in this area.

### 5.6.6 Conclusion evidence statement

The original cost-effectiveness analysis conducted for this guideline suggested that glucocorticosteroid treatment, followed by azathioprine plus a glucocorticosteroid then a biologic is the most cost-effective medical treatment strategy for a moderate to severe inflammatory exacerbation of Crohn's disease.

## 5.7 Linking evidence to recommendations

Given the complex and interrelated nature of the data reviewed for the induction chapters of the Crohn's guideline (and to avoid repetition) one 'linking evidence to recommendations' section is presented.

**Table 29: Linking evidence to recommendations – drug therapy for induction**

| | |
|---|---|
| **Clinical question** | **What is the most effective way to induce remission for people with an exacerbation of Crohn's disease? (Questions 1- 5)** |
| **Recommendations** | **1. Discuss treatment options and monitoring with the person with Crohn's disease, and/or their parent or carer if appropriate, and within the multidisciplinary team. Apply the principles outlined in 'Patient experience in adult NHS services' (NICE clinical guidance 138).**<br>**Monotherapy**<br>**2. Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.**<br>3. Enteral nutrition recommendation (see section 8.3).<br>**4. In people with one or more of distal ileal, ileocaecal or right-sided colonic disease[e] who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide[f] for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects.**<br>**5. In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment[g] for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid.**<br>**6. Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations.**<br>**7. Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission.**<br>**Add-on treatment**<br>**8. Consider adding azathioprine or mercaptopurine[a] to a conventional glucocorticosteroid or budesonide[f] to induce remission of Crohn's disease if:**<br>• **there are two or more inflammatory exacerbations in a 12-month period, or**<br>• **the glucocorticosteroid dose cannot be tapered.**<br>**9. Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine[a]. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).**<br>**10. Consider adding methotrexate[b,c] to a conventional glucocorticosteroid or budesonide[f] to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient if:**<br>• **there are two or more inflammatory exacerbations in a 12-month period, or**<br>• **the glucocorticosteroid dose cannot be tapered.**<br>**11. Monitor the effects of azathioprine, mercaptopurine[a] and methotrexate[b,c] as advised in the current online version of the 'British national formulary' (BNF)[d] or 'British national formulary for children' (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity.** |

| | |
|---|---|
| | **12. Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate.**<br>*a Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*<br>*b Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine, mercaptopurine and methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*<br>*c Follow BNF/BNFC cautions on prescribing methotrexate.*<br>*d Advice on monitoring of immunosuppressives can be found in the current online version of BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.*<br>*e See recommendations 1.5.1 and 1.5.2 for when to consider surgery early in the course of the disease for people whose disease is limited to the distal ileum.*<br>*f Although use is common in UK clinical practice, at the time of publication (October 2012), budesonide did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.*<br>*g Although use is common in UK clinical practice, at the time of publication (October 2012) mesalazine, olsalazine and balsalazide did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.* |
| **Relative values of different outcomes** | In relation to induction of remission and prior to evidence evaluation, the GDG identified objective measures of remission, such as CDAI or Harvey Bradshaw Index (HBI) for adults and PCDAI for children as being the most important measures of efficacy. The GDG discussed the difficulty of not having a standard definition of treatment response. The goal when treating active disease is to induce remission.<br><br>Of the accepted outcome measures, remission defined by a Crohn's disease activity index (CDAI) of ≤ 150 together with a CDAI fall of 70 was considered to be the most rigorous reflection of efficacy. Ideally both an endpoint and a fall would be taken into consideration because, for example, a person with a CDAI of 151 would be considered to be suffering active disease but a reduction in CDAI of 2 to an endpoint of 149 cannot be interpreted as a treatment success. Unfortunately not all studies report both parameters and the GDG did not feel otherwise well-conducted studies should be excluded on this basis. However, the GDG considered that "investigator-reported remission" without objective corroboration was inadequate and should be downgraded on quality grounds.<br><br>The group also debated the value of "endoscopic mucosal healing" as an index of response.[17,94] Whilst endoscopic appearances do not always correlate with clinical symptoms, the GDG were aware of evidence that certain endoscopic features – particularly deep ulceration - seen at endoscopy, carry an adverse prognostic significance. It was agreed that when studies reported it, the group would consider the parameter as valid. However this outcome was not reported in any of the studies relating to the drug therapies considered for induction in this guidance.<br><br>Quantification of the risk of specified adverse events when making decisions about prescribing drugs that are unlicensed for use in Crohn's disease (and for which informed and documented consent is required) is important. Some of these adverse events are uncommon but serious, and in order to assess specific risks, lower quality cohort studies and MHRA yellow card reporting scheme data were reviewed in addition RCT data for serious adverse events. The GDG considered the following adverse events |

| | |
|---|---|
| | to be particularly pertinent for specific drug categories:<br>• 5-ASAs – renal impairment and pancreatitis<br>• azathioprine and mercaptopurine – myelosuppression, pancreatitis and hepatotoxicity<br>• methotrexate – myelosuppression, hepatotoxicity, pulmonary fibrosis<br>• glucocorticosteroids – myocardial infarction, osteoporosis (refer to section 10.1 for monitoring of osteopenia and assessment of fracture risk), hip fracture.<br><br>Adverse events associated with some drugs are very relevant in the short term (i.e. for induction) while others are more of a consideration during maintenance therapy, for example, glucocorticosteroid effects on bone.<br><br>Glucocorticosteroid adverse-events were also noted between conventional glucocorticosteroid and budesonide treatment. |
| **Trade off between clinical benefits and harms** | The form of the disease (obstructive or inflammatory Crohn's disease) may have a bearing on the choice of treatment and associated benefits and harms. For example, a person with a Crohn's stricture presenting with obstructive symptoms may need different treatment (including surgery) from someone presenting with inflammatory Crohn's disease symptoms. There can be an element of both obstruction and inflammation in any presentation of the illness, but unless otherwise stated, recommendations refer to presentations in which inflammation is the predominant component and assumes that other causes of symptoms (for example, obstruction, bowel salt malabsorption, abscesses and infection) have been excluded as part of the diagnostic work-up. Please see section 9.4 for Crohn's disease stricture.<br><br>The GDG considered serious adverse events and withdrawals to be significant outcomes in determining the trade off between benefits and harms. They debated the difference between side effects, as reported in RCTs, and those serious, specific adverse events which are more likely to cause withdrawal from treatment and are hence a more important consideration for prescribing decisions.<br><br>Various drug treatment options for inducing remission have significantly different side-effect and safety profiles. In addition clinician and patient perceptions about these differ, and moreover, individual patients have varying views about the relative hazards of alternative treatment options for example, glucocorticosteroid vs. 5-ASA treatment.<br><br>The GDG was particularly interested in whether assessment of TPMT activity and monitoring of azathioprine or mercaptopurine in patients requiring these drugs would reduce the risks of serious side effects, and indeed death. The group unanimously agreed that patients known to have deficient (low or absent) TPMT activity should not be given azathioprine or mercaptopurine and should be offered alternative therapy.<br><br>Prospective and retrospective data from five studies of people with Crohn's disease assessed azathioprine dose-reduction on side effects in people with intermediate and normal TPMT activity. Lack of evidence for dosing decisions in people known to have intermediate TPMT activity and who might intuitively be at greater risk of side effects was noted and a "consider" recommendation about dose concerning patients with less than normal but not deficient TPMT levels was made. Intermediate and normal TPMT activity appeared to be poor predictors of some side effects - notably neutropenia - and idiosyncratic agranulocytic or pancytopenic reactions appeared to be independent of TPMT activity. The GDG also recommended that people on immunosuppressives should be monitored for neutropenia irrespective of their TPMT activity. |

| | |
|---|---|
| | The GDG debated at length the difficulties with explaining risk concepts. All agreed that quantification of specific risks (pictorially) would be more helpful in the course of an informed discussion with a patient than a qualitative indication similar to that reported in the BNF/BNFC and Summaries of Product Characteristics. The group acknowledged a number of challenges to a practical discussion about risk, including the low quality of data available to inform this quantification, the consideration that figures change over time, contextualizing treatment risk against background risk and quantifying the risk of not treating.<br><br>Of particular concern was the risk of lymphoproliferative disorders and cervical dysplasia. A 1.7-fold risk over an already relatively high background risk of cervical dysplasia prompted the GDG to emphasize that people with Crohn's disease should not be precluded from receiving human papilloma virus (HPV) vaccination. |
| **Economic considerations** | Glucocorticosteroid treatment, other than budesonide, is prescribed generically. Each 5-ASA is a different price - some are branded and some are generic.<br>The GDG questioned whether the low incidence of serious side-effects reflected in the safety review of 5-ASA treatment warranted regular monitoring of renal function. However, given the specific caution about monitoring of renal function in some Summaries of Product Characteristics, they did not consider the available evidence strong enough to make any recommendations to change monitoring practice. They agreed that clinicians should refer to the online version of the BNF/BNFC for standardised monitoring protocols, and that the monitoring protocols currently advised in the BNF/BNFC should be incorporated into the health economic model accordingly.<br><br>The GDG noted that, due to potential differences in costs and side effect profiles, 5-ASAs should be treated separately for economic analysis. The only 5-ASA studies included in the clinical review were in mesalazine and sulfasalazine, and therefore these were analysed separately within the economic model.<br><br>Induction of remission was identified as a high-priority area for original economic analysis, since it is an issue that affects most people with Crohn's disease, and no published economic evaluations were identified in this area which addressed the question. The cost-effectiveness of enteral nutrition could not be explored in the model since withdrawal (a key model input) was not reported by RCTs.<br><br>A decision-analytic model was developed with a 30-week time horizon, which was based on the results of two original network meta-analyses (one of first-line induction and one second line). The model compared alternative sequences of drugs for induction of remission.<br><br>The decision model showed that glucocorticosteroid treatment followed by azathioprine plus a glucocorticosteroid then a biologic was the most cost-effective treatment sequence for an inflammatory exacerbation of Crohn's disease. The strategies which started with budesonide and mesalazine, then moved on to the sequence described above were ranked second and third respectively in terms of cost effectiveness.<br><br>Due to paucity of evidence, specific costs and disutilities due to drug-related adverse events could not be captured in the economic model. This is likely to mean the cost effectiveness of all the treatment strategies has been over-estimated in the economic analysis, though since each treatment is likely to have a different side-effect profile, it is unlikely that ICERs have been underestimated by the same magnitude for all treatment strategies. For treatment strategies with more severe side-effects, the over estimation of the ICER is likely to be more pronounced than in treatment strategies |

| | |
|---|---|
| | with less severe side-effect profiles. Due to the lack of quality of life data reported in RCTs, different severities of inflammatory exacerbations could not be captured in the economic model.<br><br>Additional modelling was subsequently carried out which explored the effects of including drug-related adverse events for glucocorticosteroid monotherapy only; observational data was used to conduct this analysis. This was based upon two publications[63,294] which explore the increased risks of fracture and MI in people having intermittent high-dose glucocorticosteroid therapy. The analysis showed that when the additional risks of myocardial infarction and hip fracture associated with glucocorticosteroid monotherapy were accounted for in the model and the likely additional costs and reduction in quality of life quantified, the strategy that ranked top in terms of cost effectiveness did not change.<br><br>Further analysis of mild or transient glucocorticosteroid-related adverse events was undertaken comparing conventional glucocorticosteroids treatment with budesonide. Similar analyses of transient or non-life threatening adverse events have NOT been undertaken comparing conventional glucocorticosteroid treatment and budesonide with other interventions. For this reason costs associated with these mild or transient adverse events have not been incorporated into the health economic model.<br><br>Immunosuppressives are generic and cheap, but monitoring requirements and serious side effects have an impact on their cost effectiveness. The GDG considered the cost of a one-off assay to determine TPMT activity to be reasonable (around £26 at time of writing) to prevent potentially severe adverse events, such as neutropenia in people with low or no TPMT activity. The group referred to a partially-applicable US health economic analysis which found TPMT monitoring to be cost effective[71]. They also noted that the cost-effectiveness model incorporated the cost of a TPMT assay, and adjunctive azathioprine was considered to be the most cost-effective second-line therapy for inducing remission in people needing augmentation from conventional glucocorticosteroid treatment. For these reasons they agreed that the recommendation to assess TPMT activity in all patients prior to initiation of azathioprine or mercaptopurine did not require a formal health economic assessment. |
| **Quality of evidence** | **Induction of remission**<br><br>**Conventional glucocorticosteroid compared with placebo or 5-ASA**<br>The evidence for induction of remission with conventional glucocorticosteroid treatment included a Cochrane review.[22] This was composed mainly of moderate or high quality studies. Studies comparing conventional glucocorticosteroid and placebo did not exclude people with Crohn's disease occurring in any particular part of the gastrointestinal tract. Glucocorticosteroid treatment was of benefit versus placebo[166,270] and 5-ASA treatment[166,242] in Benchimol 2008[22] and this is in keeping with the clinical experience of the GDG. The GDG noted that the meta-analysis showed that conventional glucocorticosteroid treatment induced 65% more remissions than 5-ASA and at 95% confidence, this increase could be as high as 103% or as low as 33%. Significantly more side effects were reported with conventional glucocorticosteroid treatment than placebo or 5-ASA.<br><br>The GDG made an offer recommendation for conventional glucocorticosteroid treatment. To mitigate concerns about inappropriate repeat glucocorticosteroid prescribing, and maintain alignment with the add-on therapy with immunosuppressives below, the GDG limited the recommendation to "a first presentation or single exacerbation in a 12-month period." |

**Conventional glucocorticosteroid compared with budesonide**

The GDG agreed that from the meta-analysis of eight studies[19,35,75,117,153,232,290,293] conventional glucocorticosteroid treatment was shown to be more effective than budesonide for inducing remission at eight weeks, inducing 15% more remissions than budesonide. At 95% confidence, this increase in remissions ranged from 3% to 25%.

At 12 weeks the meta-analysis of three studies[35,75,153] showed little difference between the two treatments. In severe disease at eight weeks, meta analysis of two small trials (Campieri, 1997; Gross, 1996)[35,117]showed that conventional glucocorticosteroid treatment induced significantly more clinical remission than budesonide (RR 0.52 [0.28 to 0.95]).

For this reason, the GDG made a 'do not offer' recommendation to induce remission with budesonide in severe presentations or exacerbations. By extrapolation, they extended this 'do not offer' recommendation to 5-ASA treatment for severe Crohn's disease because budesonide was shown to be more effective than 5-ASA (although with uncertainty) and to have fewer side effects (see paragraph 'Budesonide compared with 5-ASA').

In addition, when only ileal/ileocolonic-specific sites were considered (meta-analysis of six RCTs[19,35,75,117,232,293]) conventional glucocorticosteroid treatment was more effective than budesonide for induction of remission (RR 0.86 (0.75 to 1.00), the GDG noted the confidence interval did include 1).

The GDG reviewed the data from the meta-analysis of five RCTs[19,75,117,232,290] of budesonide compared with glucocorticosteroid for treatment withdrawal. The analysis showed a numeric advantage for budesonide, but a high amount of imprecision (small numbers were noted) RR 0.57 (0.18 to 1.84).

The GDG noted that the outcomes were graded as low to very low quality.

Although budesonide demonstrated fewer side effects, withdrawal rates were similar and as this conformed to their clinical experience they agreed a 'consider' recommendation for budesonide in predominantly right-sided Crohn's disease.

To mitigate concerns about inappropriate repeat glucocorticosteroid prescribing, and maintain alignment with the add-on therapy with immunosuppressives below, the GDG limited the recommendation to "a first presentation or single exacerbation in a 12-month period."

**Budesonide compared with 5-ASA treatment**

At eight weeks, budesonide was originally shown in the Thomsen study[279] (which was included in the Seow Cochrane review[249]) to be more effective than mesalazine with a RR = 1.63. This was then updated with the larger Tromm study[288] and heterogeneity was noted (very low quality). The random effects meta-analysis was non-significant. However 12-week moderate-quality efficacy data based only on Thomsen favoured budesonide over 5-ASA (RR 1.59; 95% CI 1.17 to 2.15). Whilst the data for withdrawal due to adverse events was non-significant (RR 0.43; 95% CI 0.18 to 1.02), the GDG noted numerically more withdrawals in the 5-ASA group (2.8% vs 6.6%).

**5-ASA compared with placebo**

The GDG considered the meta-analysis of six trials[162,166,256,257,270,286] to be very low-quality evidence. The meta-analysis of 5-ASA (compared to placebo) induced 51% more remissions than placebo. At 95% confidence, this increase in remissions could be as high as 92% and as low as 20%. Whilst 5-ASA treatment demonstrated a significant result compared with placebo, the GDG noted the benefit of budesonide compared

with 5-ASA (see paragraph above). The GDG explored whether there was any data to support a recommendation for 5-ASA treatment in mild Crohn's disease, however severity was defined variously in the 5-ASA trials and it was not possible to subgroup data. When attempting to interpret the available evidence to draw conclusions about severity, the GDG felt it would have been necessary to know the level of the disease activity at the beginning and the end of the trial, and whether the level of severity of the disease at inclusion into the study affected outcomes. This level of detail was not available for most of the comparisons reviewed. TA187 suggests that people with severe Crohn's disease who have not responded to a glucocorticosteroid or immunosuppressive should be offered a biologic, and on this basis, the 'Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations recommendation was made.

Subsequent to the GDG review, publication of the Cochrane 5-ASA review in December 2010[154] precipitated GDG debate mainly for the following reasons:

The Cochrane review group included additional information (for example, letters to journal editors)

Differential licensing (only sulfasalazine is licensed for use for induction of remission in Crohn's disease)

Current perceptions about side-effect profile of sulfasalazine

Common prescribing practices (e.g. sulfasalazine is infrequently prescribed, mesalazine frequently prescribed)

The Cochrane review group analysed 5-ASA treatments separately based upon site of release (sulfasalazine, controlled-release and delayed-release preparations), whereas the Crohn's GDG ascribed a class effect to 5-ASA treatment.

For further information, please refer to Appendix J:.

The Cochrane review showed that only sulfasalazine was more effective than placebo in the induction of remission.

For methodological rigour, the GDG reviewed the per protocol subgroup analysis (severity, concurrent medication, age, site of disease) to determine if there was any heterogeneity that could have contradicted their assumption of a 5-ASA class effect. However, no interactions between subgroups were detected, and the GDG's original premise that 5-ASA treatment (as a class) was effective in the induction of remission of Crohn's disease was confirmed.

The GDG discussed the potential possibility of unpublished data being available [188] and initiated a call for evidence for 5-ASA efficacy and adverse events data. The GDG also noted concerns regarding the extent to which publication bias can impact on evidence-based practice and guideline development. No new data were submitted for review.

**Conventional glucocorticosteroid combined with azathioprine or mercaptopurine compared with placebo**

Moderate quality studies[38,80,148,170,207,213,224,227,302] in which azathioprine or mercaptopurine were added to glucocorticosteroid treatment suggest statistically significant benefit in achieving remission in comparison to placebo. The GDG noted that potentially serious side effects, a prolonged time for thiopurines to produce an effect, and inconvenience to patients as well as costs of monitoring make immunosuppressives less appealing as first-line treatment.

Having considered the above high-quality evidence that conventional glucocorticosteroid treatment is superior to 5-ASA treatment, and that addition of azathioprine or mercaptopurine to a conventional glucocorticosteroid may be beneficial when glucocorticosteroid alone does not suffice, the GDG agreed this

reflected their clinical experience.

The GDG made a 'consider' recommendation for the addition of azathioprine or mercaptopurine where conventional glucocorticosteroid treatment alone was not sufficient to induce remission. By GDG consensus this was agreed as two or more inflammatory exacerbations occurring in a 12-month period. In other words, "in those in whom the glucocorticosteroid dose cannot be tapered" or when the disease course is frequently relapsing or refractory to treatment, an immunosuppressive should be initiated early because of its prolonged time to produce an effect (three to four months).The GDG agreed that there should be no reason to avoid adjunctive thiopurine therapy with budesonide.

The GDG considered whether the available evidence provided information about *when* to start adjunctive therapy with an immunosuppressive. Because of the lack of relevant data the GDG agreed by consensus that this could either be immediately at the diagnosis of the second inflammatory exacerbation, or a few weeks later. This latter decision would be influenced by the person's history, disease course, preferences and whether there is prior knowledge of the person's TPMT activity.

**Azathioprine or mercaptopurine compared with placebo or methotrexate**

Conversely moderate quality studies[258,270] (two RCTs were included in this review. Singleton[258] and Summers[270] evaluated different outcomes for the same study) of azathioprine and mercaptopurine alone demonstrated no evidence of efficacy superior to placebo or compared with methotrexate (very low quality).[12,173,207] Mercaptopurine and its pro-drug azathioprine are for pragmatic and clinical purposes considered to be the same entity. The GDG made a negative recommendation that azathioprine or mercaptopurine monotherapy should not be used for induction of remission. The GDG agreed that only under rare circumstances in which people cannot tolerate both glucocorticosteroid treatment and 5-ASA treatment, should immunosuppressive monotherapy be used to induce remission.

Having considered all of the above, the GDG noted the immunosuppressive head to head data (azathioprine or mercaptopurine vs methotrexate) for which there was no evidence of a superiority favouring either drug. The group also agreed that no benefit was seen when methotrexate was added to conventional glucocorticosteroid (meta-analysis of three RCTs[14,85,207], low quality) and the GDG noted heterogeneity. (The random effects meta-analysis demonstrated a non-significant result with more withdrawals due to adverse events compared with glucocorticosteroid alone). The GDG was also aware of serious precautions associated with methotrexate in the BNF (for example, the need to avoid conception for three months after stopping the drug for both men and women because of its teratogenic effect). However, the GDG recognised that azathioprine or mercaptopurine are contraindicated for some patients, for example those with low or absent TPMT activity. For these circumstances, a 'consider' recommendation was made for methotrexate as an alternative immunosuppressive adjunctive therapy to conventional glucocorticosteroid treatment or budesonide should a person with Crohn's disease require augmented treatment to induce remission of an inflammatory exacerbation.

**Side effects**

Although there is clear evidence that conventional glucocorticosteroid treatment is the most effective option for inducing remission in Crohn's disease, the GDG reflected that in their clinical practice, side effects associated with glucocorticosteroid treatment generate concern for many people with Crohn's disease.

The GDG noted the predetermined review protocols for all interventions in which (for adults) efficacy, quality of life and pre-specified severe adverse events or withdrawals

due to adverse events (which were considered a surrogate for severe adverse events) would be outcomes considered: efficacy > withdrawal due to adverse events > overall adverse events.

For conventional glucocorticosteroid compared with budesonide, meta-analysis of adult's and children's adverse-event data from six low to moderate quality RCTs[19,35,75,117,153,232] was conducted (see Table 16). The glucocorticosteroid-related adverse events reported included: moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis. The GDG highlights that similar analyses of transient or non-life threatening adverse events have NOT been undertaken comparing conventional glucocorticosteroid treatment and budesonide with other interventions. This should be born in mind when comparing adverse events and withdrawals due to adverse events between conventional glucocorticosteroid treatment, or budesonide, with other interventions such as enteral nutrition, thiopurines and 5-ASA treatments.

Results for mild or transient glucocorticosteroid-related adverse events associated with conventional glucocorticosteroid treatment and budesonide showed statistically significant benefit for budesonide: random effects meta-analysis (RR 0.59 95% CI 0.46 – 0.77) and for adult data (RR 0.53; 95% CI 0.40 to 0.69) The GDG noted though that the results were highly heterogeneous.

While acknowledging this advantage for budesonide, the GDG noted that budesonide is not predominantly *without* glucocorticosteroid-related side effects.

The GDG considered the trade-off between the clinical benefits of conventional corticosteroids compared to budesonide and the harms from the glucocorticosteroid-related adverse events. The meta-analysis of six RCTs showed that conventional glucocorticosteroid treatment induced 15% more remissions than budesonide over eight weeks, and the GDG considered this to be clinically important in the face of the uncertainty associated with withdrawals due to adverse event data and the highly heterogeneous result for mild or transient glucocorticosteroid-related adverse events (less events with budesonide).

The GDG agreed that people with Crohn's disease and their advising healthcare professionals should discuss whether a reduced potential for mild or transient adverse events associated with budesonide is more clinically significant than greater efficacy together with a more rapid response by eight weeks associated with a conventional glucocorticosteroid (equivalence only achieved at 12 weeks).

People with Crohn's disease may have different views from healthcare professionals about the balance of risks, benefits and consequences of treatments. How an exacerbation of Crohn's disease affects the person, the person's circumstances and experiences all affect their condition and treatment. Rapid treatment with side-effects lasting for a short time balanced against the risk of the exacerbation remaining uncontrolled for a long period and patients experiencing side-effects for longer are important factors to consider.

The GDG agreed that the "offer" a conventional glucocorticosteroid recommendation accurately reflected both the clinical data for efficacy and withdrawal due to adverse events for conventional glucocorticosteroid treatment versus placebo, as well as the health economic analysis which determined first-line conventional glucocorticosteroid to be most cost-effective strategy for inducing remission. The GDG made a separate "consider" recommendation for budesonide to accommodate instances in which the

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|---|---|
| | person with Crohn's disease "declines" (or doesn't want) conventional glucocorticosteroid treatment or if there are tolerability issues or contraindications. The GDG limited the recommendation to right-sided disease because this reflected the Summary of product characteristics and the budesonide evidence base (see forest plot 24 in Appendix G:), whereas conventional glucocorticosteroid trials versus placebo[166,270] were undertaken in patients with Crohn's disease at any intestinal site.<br><br>Because a meta-analysis of six RCTs showed 5-ASA treatment to be more effective than placebo, the GDG made a separate recommendation that 5-ASA could be considered for people with glucocorticosteroid-related side-effect concerns and those who objected to glucocorticosteroid exposure of any kind. The recommendation acknowledges that 5-ASA treatment is less effective than budesonide.<br><br>The GDG also considered it important that people with Crohn's disease be made aware that budesonide and 5-ASA treatment are both less effective than conventional glucocorticosteroid treatment and this is noted in the recommendation.<br><br>Please see Appendix L: and Appendix M: for observational side-effect data pertaining to 5-ASA treatment and immunosuppressives respectively. The GDG noted that hepatotoxicity was not uniformly defined in the immunosuppressive safety studies. The GDG also noted that one study (Setshedi, 2011) showed non-melanoma skin cancer was significantly associated with thiopurine exposure – OR5.0 (95% CI 1.1-22.8), and that one study[169] demonstrated a different risk ratio (1.6) for lymphoproliferative disorders to the other three studies[20,82,143] RR 3-4. The GDG believed that this may have been because the Marehbian study[169] excluded patients who had less than one year of healthcare cover and suspected that patients with lymphoma may have been excluded on this basis. The study also included baseline comparisons showing a higher incidence of lymphoproliferative disorders in patients with Crohn's disease compared with the general population and proposed that this may have accounted for the lower RR in Crohn's patients exposed to immunosuppressives. The GDG concluded that when discussing risks with patients it should be highlighted that people with Crohn's disease may have a higher risk of these conditions and that azathioprine may increase that risk marginally.<br><br>The GDG commented that the frequency of serious adverse events reported in observational studies of 5-ASA treatment may tend to over-estimate the incidence of pancreatitis and renal dysfunction compared with clinical experience. They noted the limitations of the data because of the relatively small patient numbers and the fact that adverse events may not have been designated to be primary outcomes. They also noted the risks of under-reporting in the yellow card scheme (latest report 2008), but were reassured by the clear lack of large numbers of serious adverse events. |
| **Other considerations** | **Adjunctive therapy**<br>The GDG noted that most of the studies examining efficacy of drugs for induction of remission in Crohn's disease were complicated by varying levels of background therapy. Whilst evidence about which adjuvant therapy had been reviewed, data concerning when to add in adjunctive therapy had not. Furthermore, adjunctive therapy confounds analysis of adverse events, for example pancreatitis is associated with glucocorticosteroid treatment, 5-ASA treatment and azathioprine.<br><br>**Site of action**<br>The GDG also raised the issue of whether the purported site of action of various drugs was important.<br><br>In relation to 5-ASA compounds the studies considered to be of adequate quality for |

inclusion in the review were underpowered for subgroups of patients divided by site.

Site of disease was also considered by some members of the GDG to be a relevant factor when considering treatment with budesonide compared with conventional glucocorticosteroid treatment, although the evidence from the Cochrane Review[249] did not support the perception that budesonide may be more effective in the treatment of right-sided (distal ileal, ileocaecal, right colonic) Crohn's disease in adults - the evidence indicated that conventional glucocorticosteroid treatment was more effective in the treatment of right-sided Crohn's disease, and although budesonide was associated with fewer side effects, the rate of withdrawal (as a surrogate for serious adverse events) was not significantly different.

However, in children with right-sided disease, meta-analysis of two small studies[75,153], (80 patients) of budesonide vs. conventional glucocorticosteroid treatment demonstrated similar efficacy, with budesonide associated with fewer side effects and withdrawals. The data conformed to the clinical experience of the GDG. This led the GDG to propose that budesonide could be considered in adults and children with right-sided Crohn's disease and possibly children with isolated ileal disease.

**Licensing**

Of the 5-ASA compounds, only sulfasalazine is licensed for use in active Crohn's disease and some mesalazine compounds (Mesren MR and Asacol MR) are licensed for use in maintenance of remission of Crohn's ileocolitis and Octasa MR is licensed for maintenance of remission in Crohn's disease. The GDG noted the NICE requirement to indicate where recommendations include drugs that are used off label, but emphasizes that because use of 5-ASAs in Crohn's disease is common in the UK, these compounds have been grouped together for the purposes of this review.

**Legal**

The GDG noted that current law holds the prescriber rather than the drug company responsible for adverse events when drugs are prescribed off-licence. Most 5-ASA treatment and all of the immunosuppressives, are not licensed for inducing remission in Crohn's disease, therefore the need to obtain and document informed consent is emphasized. As informed consent requires an explanation of risks, the need to quantify safety data and clarify monitoring practice was highlighted. The GDG noted that readers might find it useful to refer to GMC guidance on prescribing medicines outside the terms of their licence.[101]

**Service provision**

The GDG highlighted the need for service providers to put in place a formal written structure to ensure that monitoring and safety results are followed up and managed appropriately and on time. They agreed that these structures may need to be different in primary and secondary care and determined locally. The GDG acknowledged that Crohn's disease may not be a national audit priority, but felt strongly that a specific person should be nominated to be accountable for acting on abnormal results and communicating with relevant healthcare professionals and the person with Crohn's disease.

**Infliximab**

It was noted that infliximab within its licensed indication, is recommended in TA 187 as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. The GDG considered that it would be prudent to exclude significant abscess prior to treating with infliximab.

**Children**

The GDG agreed to extrapolate and generalise data from adult populations to children and *vice versa* when there were no or little data for children and once they had given due consideration to the benefits and harms of such extrapolation.

The paediatric Crohn's disease inducing remission data were sparse and of moderate to very low in quality with small sample sizes. For a summary of the data for inducing remission in children, please see Appendix R.2.

Overall the paediatric trials looked at outcomes for glucocorticosteroid sparing and remission at one month, at eight and 12 weeks. The trials were old (dates ranged from 1975 (Rosenberg) through to 2004 (Escher).

Findings were non-significant for remission for glucocorticosteroid combined with mercaptopurine compared with glucocorticosteroid treatment alone at one month (Markowitz 2000) and for glucocorticosteroid compared with budesonide at eight and 12 weeks (Escher 2004, Levine 2003).

Whilst superiority was demonstrated for 5-ASA compared with placebo (Griffiths 1993) at eight weeks this was considered by the GDG to be low quality evidence (sample size n = 13 in total).

Both Rosenberg (1975) and Markowitz (2000), low and moderate quality studies respectively, demonstrated glucocorticosteroid sparing when azathioprine or mercaptopurine was added to glucocorticosteroid treatment.

Conventional glucocorticosteroid treatment, 5-ASA treatment and immunosuppressives are unlicensed for use in children with Crohn's disease. There may also be particular reluctance to use glucocorticosteroid treatment in children. In practice, concerns about potential glucocorticosteroid effects need to be balanced with the effects of active disease on growth.

Also of note, infliximab is recommended for people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy.

## 5.8 Recommendations

1. **Discuss treatment options and monitoring with the person with Crohn's disease, and/or their parent or carer if appropriate, and within the multidisciplinary team. Apply the principles outlined in 'Patient experience in adult NHS services' (NICE clinical guidance 138).**

2. **Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.**

3. Enteral nutrition recommendation (see section 8.3)

4. **In people with one or more of distal ileal, ileocaecal or right-sided colonic disease[e] who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide[f] for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects.**

5. **In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment[g] for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that a 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid.**

6. **Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations.**

7. **Do not offer azathioprine, mercaptopurineor methotrexate as monotherapy to induce remission.**

8. **Consider adding azathioprine or mercaptopurine[a] to a conventional glucocorticosteroid or budesonide[f] to induce remission of Crohn's disease if:**
   - **there are two or more inflammatory exacerbations in a 12-month period, or**
   - **the glucocorticosteroid dose cannot be tapered.**

9. **Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine[a]. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).**

10. **Consider adding methotrexate,[b,c] to a conventional glucocorticosteroid or budesonide[f] to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient if:**
    - **there are two or more inflammatory exacerbations in a 12-month period, or**
    - **the glucocorticosteroid dose cannot be tapered.**

11. **Monitor the effects of azathioprine, mercaptopurine[a] and methotrexate[b, c] as advised in the current online version of the 'British national formulary' (BNF)[d] or 'British national formulary for children' (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity.**

**12.Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, young people and children receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate.**

**Infliximab and adalimumab**

**The recommendations in the following section are from 'Infliximab and adalimumab for the treatment of Crohn's disease' (NICE technology appraisal guidance 187).**

**13.Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see recommendation 18) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 16) to determine whether ongoing treatment is still clinically appropriate.**

**14.Treatment as described in recommendation 13 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.**

**15.Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 16) to determine whether ongoing treatment is still clinically appropriate.**

**16.Treatment with infliximab or adalimumab (see recommendations 13 and 15) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.**

**17.Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.**

**18.For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the**

**disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.**

**19. When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate.**

**20. Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.**

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*a Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*b Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine, mercaptopurine and methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*c Follow BNF/BNFC cautions on prescribing methotrexate.*

*d Advice on monitoring of immunosuppressives can be found in the current online version of BNF/BNFC. The gastroenterology chapter and other relevant sections should be consulted.*

*e See recommendations 31 and 32 for when to consider surgery early in the course of the disease for people whose disease is limited to the distal ileum.*

*f Although use is common in UK clinical practice, at the time of publication (October 2012), budesonide did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.*

*g Although use is common in UK clinical practice, at the time of publication (October 2012) mesalazine, olsalazine and balsalazide did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

## 5.9 Research recommendations

1. **For patients with intestinal Crohn's disease, does the addition of azathioprine to glucocorticosteroid treatment at diagnosis, improve the long-term outcome compared with glucocorticosteroid treatment alone?**

Crohn's disease runs a relapsing and remitting course, with a significant inflammatory component during its early stages, compared with increasing degrees of fibrotic, stenosing or perforating disease later in its course. Earlier intervention, during this more inflammatory stage may affect disease progression and the associated debilitating effects of this, whilst avoiding the side-effects associated with systemic corticosteroids – which are the current mainstay of treatment for first flares of the disease. The question is applicable to adults and children and trials in both are therefore required. Patients with intestinal Crohn's disease in their first flare of the condition would be recruited and randomised to receive azathioprine or placebo, for prevention of relapse after an initial treatment with corticosteroids. Patients would be randomised once in remission. Co-primary end-points would be quality of life measures and maintenance of glucocorticosteroid-free remission measured by the Crohn's disease activity index (CDAI). Secondary end-points would be mucosal healing at endoscopy, hospitalisation, adverse events and surgery. Appropriate health-care costs would also need to be assessed to inform a cost-effectiveness model. Follow-up needs to be prolonged to at least two years, and ideally to five years.

# 6 Maintenance of remission

## 6.1 Clinical introduction

For many patients, Crohn's disease is characterized by periods of disease activity and remission. For others the course is one of unremitting ill health.[62] As time progresses there is a steady increase in risk of cancer, especially in patients with colonic disease.[37] The initial purpose of therapy is to induce resolution of symptoms as both the cause of the disease is unknown and at present there is no curative treatment. A significant clinical and therapeutic problem is how best to define remission, and measure long-term remission in Crohn's disease. While an emerging consensus[17,94] suggests that mucosal healing with an absence of inflammatory activity may become the gold standard by which other indicators may be measured[91], the patchy way in which the disease affects the intestines limits the application of histological sampling. Rather, surrogate markers have been used in many studies. In practice these have included measures of disease activity, such as the CDAI[26], serological indicators[97] and even patients' own assessment of their personal health status.[73,126] The lack of a uniform definition of what constitutes remission in Crohn's disease creates significant problems when interpreting clinical trials in this area. In addition there is the problem of deciding how long people need to be free of active disease to be considered in remission. Once in remission, is medication needed to maintain that remission and if so for how long must it be taken?

Adherence to medication is an important issue in maintenance therapy, and strong encouragement is required to maximise efficacy of drug therapy. There is evidence (not reviewed by this guideline) that 40 to 60% of patients do not take their 5-ASA treatment as prescribed.[144,251] None of the studies in the reviews for this guideline objectively tested for drug adherence.

Against this background patients and clinicians accept that recurrence of disease activity is almost inevitable.[36] Therefore, the purpose of maintenance treatment is to reduce both the severity and frequency of exacerbations and limit cancer risk.[37] Treatments that achieve these aims need to be considered in terms of side effects and potential adverse outcomes from long-term use. Added benefits which could arise from the use of such maintenance therapy include a general overall improvement in the feeling of well-being, reduced need for unplanned surgery and less aggressive surgery. Clearly the benefits of improved heath also allow patients to cope better with the demands of a working life[179] and for them to have greater involvement in day-to-day family activities.[90]

At present the main options open to clinicians and patients are either pharmacological or dietary in origin. For many years, glucocorticosteroid treatment, 5-ASA treatment and immunosuppressives were used with variable success. The introduction of biological treatments, such as infliximab and adalimumab has had a significant impact on the maintenance of clinical remission amongst patients in whom other therapies have failed.

There also appears to be clinical benefit from cessation of smoking with a reduction in the rate of recurrence of disease activity.[145,272] Readers are advised to emphasise the importance of smoking cessation to people with Crohn’s disease and should refer to NICE guidance: Smoking cessation services PH10 and Smoking cessation – Varenicline TA123.[193,195]

These considerations caused the GDG to ask the questions that would enable assessment of the most cost effective maintenance option.

Patient vignette 1

*The early days with Crohn's are like an unpleasant roller coaster ride – you just want to get off. Then it becomes a long-distance trek, with hills to climb and unexpected obstacles to negotiate. With a bit of luck, there should also be miles and miles of flat, boring plateau.*

Patient vignette 2

*The need to take daily maintenance treatment is obvious to a doctor. For most people, it doesn't make sense to take powerful drugs when you are well. It's a lesson that needs to be taught by the medical team, otherwise patients may learn the hard way.*

## 6.2 Conventional glucocorticosteroid treatment for maintenance of remission

### 6.2.1 Clinical questions

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for maintenance of remission for 12 months or longer

- compared with placebo?
- compared with 5-aminosalicylate (5-ASA) treatment?
- *plus* 5-ASA treatment with conventional glucocorticosteroid *plus* placebo ?
- compared with azathioprine or mercaptopurine (AZA/MP)?
- *plus* azathioprine or mercaptopurine compared with conventional glucocorticosteroid treatment *plus* placebo?
- compared with methotrexate?

### 6.2.2 Conventional glucocorticosteroid treatment for maintenance of remission

#### 6.2.2.1 Clinical evidence

A Cochrane review[264] of glucocorticosteroid treatment vs. placebo was identified for this review and was accepted and quality assessed.

As the question for this review also included a comparison of conventional glucocorticosteroid with 5-aminosalicylate or immunosuppressive treatment, a full comprehensive literature search was undertaken. No comparative studies of conventional glucocorticosteroid treatment vs. 5-ASA treatment, azathoprine or mercaptopurine or methotrexate for maintenance of remission were identified. No paediatric RCTs were identified.

Each of the studies included in the Cochrane review[166,258,260,270] was fully extracted including additional adverse event and study withdrawal data. It was not possible to analyse relapse + withdrawal data for the Steinhart 2000 meta-analysis, as full withdrawal data were not available for all three studies at one and two year intervals. This information is reported as individual study data.

Adverse events as described by Singleton 1979 included 'disastrous' defined as an event or condition which necessitated hospitalization and/or produced long-lasting (three-month) disability; 'severe' defined as side effects that caused withdrawal of the patient from the study or required specific treatment; 'moderate' side effects which required temporary or permanent reduction of study drug.

The minimal time for assessment of maintenance of remission was 12 months.

**Table 30: Evidence profile: conventional glucocorticosteroid treatment for maintenance of remission**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid | Placebo | Relative (95% CI) | Absolute | Quality |
| **Relapse or failure of remission glucocorticosteroid vs. placebo (CDAI, follow-up one year);** Malchow 1984, Smith 1978, Summers 1979 in Steinhardt Cochrane review 2000 | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 37/131 (28.2%) | 43/138 (31.2%) | RR 0.88 (0.62 to 1.25) | 37 fewer per 1000 (from 118 fewer to 78 more) | MODERATE |
| **Relapse or failure of remission glucocorticosteroid vs. placebo (CDAI, follow-up two years);** Malchow 1984, Smith 1978, Summers 1979 in Steinhardt Cochrane review 2000 | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 36/95 (37.9%) | 39/87 (44.8%) | RR 0.84 (0.61 to 1.17) | 72 fewer per 1000 (from 175 fewer to 76 more) | MODERATE |
| **Withdrawal due to side effects of drugs glucocorticosteroid vs. placebo (follow-up two years);** Malchow 1984 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22/66 (33.3%) | 13/52 (25%) | RR 0.16 (0.01 to 3.23) | 210 fewer per 1000 (from 248 fewer to 558 more) | LOW |
| **Withdrawal due to side effects of drugs glucocorticosteroid vs. sulfasalazine (follow-up two years);** Malchow 1984 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 13/63 (20.6%) | 13/52 (25%) | RR 0.19 (0.01 to 3.90) | 203 fewer per 1000 (from 248 fewer to 725 more) | LOW |
| **Adverse events: disaster glucocorticosteroid vs. placebo (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/61 (3.3%) | 1/101 (1%) | RR 3.31 (0.31 to 35.76) | 23 more per 1000 (from 7 | LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 344 more) | |
| **Adverse events: disasterous glucocorticosteroid vs. sulfasalazine (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/61 (3.3%) | 0/58 (0%) | RR 4.76 (0.23 to 97.05) | 0 more per 1000 (from 0 fewer to 0 more) | LOW |
| **Adverse events: disasterous glucocorticosteroid vs. azathioprine (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/61 (3.3%) | 2/54 (3.7%) | RR 0.89 (0.13 to 6.07) | 4 fewer per 1000 (from 32 fewer to 188 more) | LOW |
| **Adverse events: severe glucocorticosteroid vs. placebo (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no imprecision | none | 15/61 (24.6%) | 7/101 (6.9%) | RR 3.55 (1.53 to 8.21) | 177 more per 1000 (from 37 more to 500 more) | HIGH |
| **Adverse events: severe glucocorticosteroid vs. sulfasalazine (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no imprecision | none | 15/61 (24.6%) | 2/58 (3.4%) | RR 7.13 (1.70 to 29.83) | 211 more per 1000 (from 24 more to 994 more) | HIGH |
| **Adverse events: severe glucocorticosteroid vs. azathioprine (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious imprecision[3] | none | 15/61 (24.6%) | 8/54 (14.8%) | RR 1.66 (0.76 to 3.61) | 98 more per 1000 (from 36 fewer to 387 more) | MODERATE |
| **Withdrawal due to clinical relapse: glucocorticosteroid vs. placebo (follow-up three years);** Smith 1979 | | | | | | | | | | | |
| 1 | randomised | serious[4] | no serious | no serious | very serious[2] | none | 8/33 | 6/26 | RR 1.05 | 12 more | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | | | (24.2%) | (23.1%) | (0.42 to 2.65) | per 1000 (from 134 fewer to 381 more) | |

*1 Confidence interval crosses 0.75.*

*2 Confidence interval crosses 0.75 and 1.25.*

*3 Confidence interval crosses 1.25.*

*4 Method of ransomisation and allocation concealment not described.*

**Table 31: Evidence profile: conventional glucocorticosteroid plus sulfasalazine combination therapy versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Conventional glucocorticosteroid + 5-ASA | Placebo | Relative (95% CI) | Absolute | Quality |
| **Withdrawal due to side effects of drugs (follow-up two years);** Malchow 1984 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 24/56 (42.9%) | 13/52 (25%) | RR 0.46 (0.04 to 4.97) | 135 fewer per 1000 (from 240 fewer to 992 more) | LOW |

*1 Confidence interval crosses 0.75 and 1.25.*

#### 6.2.2.2 Evidence statements - clinical

- A well-conducted meta-analysis[265] of three studies[166,260,270] (n = 269) found that there was no significant difference in relapse or failure of remission between conventional glucocorticosteroid treatment and placebo at one year (RR 0.88 [0.62 to 1.25]) or at two years (RR 0.84 [0.61 to 1.17]) follow-up.[MODERATE QUALITY]
- One RCT[166] found that there was no significant difference in withdrawal due to drug side effects of:
  - conventional glucocorticosteroid treatment vs. placebo (n = 118) (RR 0.16 [0.01 to 3.23])
  - conventional glucocorticosteroid treatment + sulfasalazine versus placebo (n = 108) (RR 0.46 [0.04 to 4.97]) or
  - conventional glucocorticosteroid treatment versus sulfasalazine (n = 115) (RR 0.19 [0.01 to 3.90]) at two-year follow-up.[LOW QUALITY]
- One RCT[258] found that there was no significant difference in disastrous adverse events of:
  - conventional glucocorticosteroid treatment vs. placebo (n = 171)(RR 3.31 [0.31 to 35.76])
  - conventional glucocorticosteroid treatment vs. sulfasalazine (n = 119)(RR 4.76 (0.23 to 97.05)] or
  - conventional glucocorticosteroid treatment vs. AZA (n = 115)(RR 0.89 [0.13 to 6.07]) at two-year follow-up.[LOW QUALITY]
- One RCT[258] found that there were significantly more severe adverse events in the glucocorticosteroid arm when:
  - conventional glucocorticosteroid treatment was compared with placebo (n = 171)(RR 3.55 [1.53 to 8.21]) and when
  - conventional glucocorticosteroid treatment was compared with sulfasalazine (n = 119)(RR 7.13 [1.70 to 29.83]) at two-year follow-up.[HIGH QUALITY]
- There was no significant difference in severe adverse events when conventional glucocorticosteroid treatment was compared with AZA (n = 115)(RR 1.66 [0.76 to 3.61]) in the same two year study.[MODERATE QUALITY]
- One RCT (n = 59)[260] with a three-year follow-up found that there was no significant difference (RR 1.05 [0.42 to 2.65]) between conventional glucocorticosteroid treatment and placebo in withdrawals due to clinical relapse.[VERY LOW QUALITY]

### 6.2.3 Economic evidence

No published data were found relating to the cost effectiveness of conventional glucocorticosteroid treatment for the maintenance of remission of Crohn's disease.

For primary health economic modelling, please see the health economic induction model summary, section 6.7 and Appendix H: for the full health economic report.

## 6.2.4 Linking evidence to recommendations

**Table 32: Linking evidence to recommendations – glucocorticosteroid treatment**

| | |
|---|---|
| **Clinical question** | **6. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for maintenance of remission for 12 months or longer**<br>**6.1 compared with placebo?**<br>**6.2 compared with 5-aminosalicylate (5-ASA) treatment?**<br>**6.3 plus 5-ASA treatment with conventional glucocorticosteroid plus placebo ?**<br>**6.4 compared with azathioprine or mercaptopurine (AZA/MP)?**<br>**6.5 plus azathioprine or mercaptopurine compared with conventional glucocorticosteroid treatment plus placebo?**<br>**6.6 compared with methotrexate?** |
| **Recommendation** | **27. Do not offer a conventional glucocorticosteroid to maintain remission.** |
| **Relative values of different outcomes** | **Glucocorticosteroid treatment for maintenance of remission**<br>The GDG key outcome of interest agreed at the outset was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population.<br><br>The GDG also agreed that for glucocorticosteroid trials, adverse events and withdrawals (due to side effects) were both important outcomes.<br><br>The GDG debated at length the relative values of the different adverse events reported by the Summers and Singleton papers. Adverse events were classified by the authors as 'disastrous', 'serious' or 'moderate'. Of particular interest to the GDG were severe adverse events i.e. those considered by the authors of the relevant studies as disastrous and serious adverse event outcomes. These were defined as<br>o 'Disaster' in Singleton 1979 defined as '...an event or condition which necessitated hospitalization and/or produced long-lasting (three months) disability.'<br>o 'Serious' in Singleton 1979 defined as '...those that caused withdrawal of the patient from the study or required specific treatment.'<br><br>The GDG agreed that the disastrous adverse events reported were small in number. Severe adverse events of hypertension, fluid retention, infection, depression, gastric/duodenal ulcer and acne were all noted.<br><br>Data were also reported for this review if study withdrawal was noted to be due to drug effect (rather than non-compliance or other reasons for drop-out). |

| | |
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| | The GDG highlighted the absence of long-term reported outcomes for osteoporosis and osteopenia or bone fracture. The Summers and Singleton trials were published in 1979 and hence the GDG bore in mind the possible historical confounders from data that are now over 30 years old and the advent of biologic drugs that have subsequently changed the course of the treatment pathway.<br><br>Whilst the reported side effect and adverse event outcomes were noted to be small in number, clinically, the GDG confirmed that patients report that they find the side-effects of glucocorticosteroid treatment to be unpleasant.<br><br>Mucosal healing has been more recently emphasized as an end-point, and may not be described in older papers. The relative value of this outcome was felt to be less important than maintenance of remission data. This is because the patchy way in which the disease affects the intestines limits the application of histological sampling. The GDG noted that none of papers reported mucosal healing outcomes for glucocorticosteroid treatment and agreed that this outcome measure seemed to be more widely reported as an outcome for biological drugs. |
| **Trade off between clinical benefits and harms** | The GDG noted that the three trials comparing conventional glucocorticosteroid treatment to placebo (and combined into an new meta-analysis by the developers) reported non-significant results for maintenance of remission, side effects and withdrawals due to side effects at one- and two- year time points.<br><br>The trials reported both a lack of efficacy and evidence of serious side effects and for these reasons the GDG made a recommendation against using a conventional glucocorticosteroid for maintenance of remission in people with Crohn's disease.<br><br>The GDG debated not only statistical significance or non-significance but also the reported relative risk effect sizes. For outcomes reporting side effects and adverse events the GDG highlighted that there was probably an absence of evidence rather than evidence of absence. The numbers reported were small, confidence intervals wide and the trials were powered for efficacy outcomes rather than adverse events. Whilst some of the adverse event data demonstrated non-significant outcomes the GDG noted the importance of absolute numbers reporting a magnitude of effect for side effects that was greater in the glucocorticosteroid group than that of the comparator.<br><br>The GDG agreed that people should not be exposed to long-term treatment with a glucocorticosteroid.<br><br>The GDG concluded that for the glucocorticosteroid data reviewed there was no evidence of clear benefit and evidence of harm. |
| **Economic considerations** | A decision-analytic model was developed with a two-year time horizon, based on the results of the clinical review. The model compared different medical treatments for maintenance of medically-induced remission of Crohn's disease. The analysis was conducted in four different ways as described in the summary of the health economic model for maintenance of remission. Of the six treatments compared in |

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| | the model, prednisolone had the fifth and fourth highest mean QALYs in conservative and non-conservative analyses respectively. In the conservative analyses it had lower QALYs than no treatment. However, utility loss due to drug related adverse events was not explicitly incorporated in to the model due to lack of data.<br><br>Original economic analysis showed that prednisolone ranged from being the second most cost-effective treatment in the non-conservative analysis where azathioprine patients had a different induction sequence, to fifth in the conservative analysis where patients relapsing from all treatments had the same induction sequence.<br><br>Prednisolone was dominated by no treatment in the conservative analyses and in all four base case analyses it was less cost-effective than azathioprine. Utility loss due to drug-related adverse events was not explicitly incorporated in to the model due to lack of data. The GDG considered this a more serious omission for glucocorticosteroid maintenance treatment than for the other maintenance treatments being compared. And therefore the GDG concluded that glucocorticosteroid maintenance treatment was neither clinically effective nor cost effective. |
| **Quality of evidence** | Comparative monotherapy data were found for conventional glucocorticosteroid treatment vs. placebo, azathioprine and sulfasalazine.<br><br>Data were also found for conventional glucocorticosteroid treatment combined with sulfasalazine vs placebo.<br><br>There were no data for other monotherapy comparisons (for example glucocorticosteroid treatment vs. methotrexate) or combination therapies.<br><br>The GDG noted that the systematic literature review yielded no paediatric data.<br><br>The studies within a Cochrane review (Steinhart et al 2000) which answered the review question were assessed individually in order to obtain relative risk rather than odds ratios. The studies were also analysed to determine adverse event data and withdrawal due to adverse events.<br><br>The GDG agreed the 'moderate' quality rating applied to outcome of the relapse or failure of remission for the three studies reporting this outcome at one and two years.<br><br>The GDG commented on the general paucity of evidence (only three randomised controlled trials on maintenance of remission for the outcome of interest). The GDG agreed that these trials were well designed and powered in terms of efficacy but not powered to detect significant differences in adverse events or withdrawals. Wide confidence intervals and imprecision were noted.<br><br>Due to paucity of evidence, specific costs and disutilities due to drug- |

| | |
|---|---|
| | related adverse events could not be captured in the economic model. This may mean that the cost effectiveness of a glucocorticosteroid - and other treatments explored in the model- has been over-estimated (i.e. their ICERs have been under-estimated).<br><br>Due to lack of reporting in RCTs and quality of life literature, different severities of relapse could also not be captured in the economic model. |
| **Other considerations** | For glucocorticosteroid treatment, the GDG noted that three trials demonstrated no efficacy data for maintenance of remission. In addition the absolute numbers demonstrated more adverse events associated with their use. The adverse event data were statistically non-significant due to underpowering but given the lack of efficacy the GDG did not wish to recommend future research in this area.<br><br>The GDG noted that in clinical practice a small number of people with severe Crohn's disease may be refractory to other maintenance treatment. They debated at length inserting the word 'routinely' to the recommendation to take account of this small group – hence 'do not routinely offer'. However the GDG decided against this given the evidence they had seen. They also highlighted that TA187 indicates that "People whose disease relapses after [biologic] treatment is stopped should have the option to start treatment again."<br><br>**Children**<br>There were no studies on conventional glucocorticsteroid treatment for maintenance of remission in children. The GDG agreed that children should not be exposed to long-term treatment with a glucocorticosteroid for the same reasons as in adults, but in addition because of their potential to supress growth. |

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# 6.3 Budesonide for maintenance of remission

## 6.3.1 Clinical questions

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for maintenance of remission for 12 months or longer compared with

- placebo?
- conventional glucocorticosteroid treatment?
- 5-aminosalicylate (5-ASA) treatment?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

## 6.3.2 Clinical evidence

The review of budesonide for maintenance of remission in Crohn's disease assessed outcomes in patients who were randomised while in a quiescent phase of their disease.

A Cochrane review[23] was identified which assessed RCTs comparing budesonide with either placebo, mesalazine or prednisolone for maintenance of clinical remission in Crohn's disease for 12 months or longer. However, due to differences in inclusion criteria an independent review was undertaken. Specifically, the Cochrane review included post-surgical studies while the current review was limited to patients with medically-induced remission. Maintenance of remission in post-surgical patients is addressed in section 7.

No paediatric studies were identified.

Two analyses of relapse events were conducted. The primary analysis included all events defined as relapse by the trial protocol; a secondary analysis took account of dropouts/withdrawals and included these patients in the relapse events. Random effects models were run if heterogeneity ($I^2$) in any meta-analysis was greater than 50%.

The primary outcomes for this review were maintenance of remission and disease relapse.

### 6.3.2.1 Budesonide versus placebo

**Table 33: Evidence profile: budesonide versus placebo – relapse and withdrawal**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Placebo | Relative (95% CI) | Absolute | |
| **Relapse 6 mg budesonide (CDAI; follow-up 12 months);** Ferguson 1998, Greenberg 1996, Hanauer 2005, Lofberg 1996 | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 73/145 (50.3%) | 87/145 (60%) | RR 0.84 (0.68 to 1.03) | 96 fewer per 1000 (from 192 fewer to 18 more) | LOW |
| **Relapse 3 mg budesonide (CDAI; follow-up 12 months);** Ferguson 1998, Greenberg 1996, Gross 1998, Lofberg 1996 | | | | | | | | | | | |
| 4 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111/174 (63.8%) | 117/185 (63.2%) | RR 1.01 (0.86 to 1.18) | 6 more per 1000 (from 89 fewer to 114 more) | MODERATE |
| **Relapse + withdrawal 6 mg budesonide (CDAI; follow-up 12 months);** Ferguson 1998, Hanauer 2005, Lofberg 1996 | | | | | | | | | | | |
| 3* | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[2] | none | 61/109 (56%) | 69/109 (63.3%) | RR 0.88 (0.71 to 1.09) | 76 fewer per 1000 (from 184 fewer to 57 more) | LOW |
| **Relapse + withdrawal 3 mg budesonide (CDAI; follow-up 12 months);** Ferguson 1998, Gross 1998, Lofberg 1996 | | | | | | | | | | | |
| 3* | randomised trials | serious[5] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 98/141 (69.5%) | 110/149 (73.8%) | RR 0.95 (0.82 to 1.09) | 37 fewer per 1000 (from 133 fewer to 66 more) | MODERATE |

*1 Randomisation not described in Lofburg 1996; allocation concealment not described in Greenberg 1996, Hanauer 2005, Lofberg 1996.*
*2 Confidence interval crosses 0.75.*
*3 Randomisation not described in Lofbert 1996 and Gross 1998. Allocation concealment not described in Greenber 1996, Gross 1998 and Lofberg 1996.*
*4 Randomisation not described in Lofberg 1996. Allocation concealment not described in Hanauer 2005.*
*5 Randomisation and allocation concealment not described in Lofberg 1996.*
** The relapse (only) 6 mg analysis includes four studies – withdrawal information was only available in three of these. The same applies for the 3 mg data.*

**Table 34: Evidence profile: budesonide versus placebo – adverse events and withdrawal due to adverse events**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Placebo | Relative (95% CI) | Absolute | |
| **Withdrawal due to adverse events at one year budesonide 6 mg (follow-up 12 months);** Ferguson 1998, Hanauer 2005, Lofberg 1996 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 11/109 (10.1%) | 12/109 (11%) | RR 0.92 (0.45 to 1.88) | 9 fewer per 1000 (from 61 fewer to 97 more) | VERY LOW |
| **Withdrawal due to adverse event at one year budesonide 3 mg (follow-up 12 months);** Ferguson 1998, Gross 1998, Lofberg 1996 | | | | | | | | | | | |
| 3 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/141 (2.1%) | 6/149 (4%) | RR 0.60 (0.18 to 1.98) | 16 fewer per 1000 (from 33 fewer to 39 more) | VERY LOW |
| **Adverse events - suppressed adrenal function budesonide 6 mg (follow-up 12 months);** Ferguson 1998 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/17 (17.6%) | 3/18 (16.7%) | RR 1.06 (0.25 to 4.45) | 10 more per 1000 (from 125 fewer to 575 more) | LOW |
| **Adverse events - suppressed adrenal function budesonide 3 mg (follow-up 12 months);** Ferguson 1998 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/19 (10.5%) | 3/18 (16.7%) | RR 0.63 (0.12 to 3.35) | 62 fewer per 1000 (from 147 fewer to 392 more) | LOW |
| **Adverse events - cortisol level budesonide 6 mg (follow-up 12 months; Better indicated by lower values);** Greenberg 1996 | | | | | | | | | | | |
| 1 | randomised trials | serious | no serious inconsistency | no serious indirectness | serious[5] | none | 266 (272) 36 patients | 367 (200) 36 patients | - | MD 101.00 lower (211.29 lower to 9.29 higher) | LOW |
| **Adverse events - cortisol level budesonide 3 mg (follow-up 12 months; measured with: cortisol level; Better indicated by lower values);** Greenberg 1996 | | | | | | | | | | | |
| 1 | randomised | serious[4] | no serious | no serious | serious[5] | none | 367 (358) | 367 (200) | - | MD 0.00 | LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | | | 33 patients | 36 patients | | higher (138.52 lower to 138.52 higher) | |
| **Abnormal response to ACTH 6 mg budesonide (follow-up 12 months);** Lofberg 1996 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 5/23 (21.7%) | 0/13 (0%) | RR 6.42 (0.38 to 107.55) | - | VERY LOW |
| **Abnormal response to ACTH 3 mg budesonide (follow-up 12 months);** Lofberg 1996 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/21 (9.5%) | 0/13 (0%) | RR 3.13 (0.16 to 61.49) | - | VERY LOW |

*1 Randomisation not described in Lofberg 1996 Allocation concealment not described in Lofberg 1996 and Hanauer 2005.*

*2 Confidence interval crosses 0.75 and 1.25.*

*3 Randomisation and allocation concealment not described in Gross 1998 and Lofberg 1996.*

*4 Allocation concealment not described.*

*5 Confidence interval crosses -100.*

**Table 35: Evidence profile: budesonide versus placebo – quality of life**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Placebo | Relative (95% CI) | Absolute | |
| **IBDQ score budesonide 6 mg (follow-up 12 months; measured with: IBDQ; Better indicated by higher values);** Greenberg 1996 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 161 (36) 36 patients | 150 (38) 36 patients | - | MD 11 higher (6.1 lower to 28.1 higher) | LOW |
| **IBDQ score 3 mg budesonide (follow-up 12 months; measured with: IBDQ; Better indicated by higher values);** Greenberg 1996 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 156 (39) 33 patients | 150 (38) 36 patients | - | MD 6.00 higher (12.2 lower to 24.2 higher) | LOW |

*1 Allocation concealment not described.*
*2 Confidence interval crosses 19.*

### 6.3.2.2 Budesonide versus 5-ASA treatment

**Table 36: Evidence profile: budesonide versus mesalazine**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Mesalazine | Relative (95% CI) | Absolute | |
| **Relapse at one year (CDAI; follow-up 12 months);** Mantzaris 2003 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 16/29<br>55.20% | 23/28<br>82.10% | RR 0.67 (0.46 to 0.97) | 271 fewer per 1000 (from 25 fewer to 444 fewer) | VERY LOW |
| **Mean time to relapse (days : Better indicated by higher values; follow-up 12 months);** Mantzaris 2003 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 29 patients 241 + 114 days | 28 patients 147 + 117 days | - | MD 94.00 higher (34.00 to 154.00 higher) | VERY LOW |
| **IBDQ score (Better indicated by higher values; follow-up 12 months);** Mantzaris 2003 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 29 patients 150 [SD, 58.07] | 28 patients 113 [SD, 33] | - | MD 37 higher (16.85 to 57.15 higher) | LOW |

*1 Patients not blinded. Randomisation and allocation concealment not described.*

*2 Confidence interval crosses 0.75.*

*3 Confidence interval crosses 58.*

### 6.3.2.3 Budesonide versus conventional glucocorticosteroid treatment

**Table 37: Evidence profile: budesonide versus prednisolone**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Prednisone | Relative (95% CI) | Absolute | |
| **Relapse (follow-up 12 months);** Schoon 2005 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 19/46 (41.3%) | 11/44 (25%) | RR 1.65 (0.89 to 3.06) | 162 more per 1000 (from 28 fewer to 515 more) | VERY LOW |
| **Relapse + withdrawal (follow-up 12 months);** Schoon 2005 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 26/46 (56.5%) | 19/44 (43.2%) | RR 1.31 (0.86 to 2) | 134 more per 1000 (from 60 fewer to 432 more) | VERY LOW |
| **Withdrawal due to adverse events (follow-up 12 months);** Schoon 2005 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 4/46 (8.7%) | 0/44 (0%) | RR 8.62 (0.48 to 155.52) | - | VERY LOW |
| **Adrenal suppression (follow-up 12 months);** Schoon 2005 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 13/36 36.1%) | 20/33 (60.6%) | RR 0.60 (0.36 to 1) | 242 fewer per 1000 (from 388 fewer to 0 more) | VERY LOW |

*1 Unblinded study. Allocation concealment not done.*
*2 Confidence interval crosses 1.25.*
*3 Confidence interval crosses 0.75 and 1.25.*
*4 Confidence interval crosses 0.75.*

### 6.3.2.4 Evidence statements - clinical

- In a meta-analysis of four RCTs of budesonide 6 mg for maintenance of remission (n = 290; one year follow-up)[87,110,122,159] there was no significant difference (RR 0.84 [0.68 to 1.03] between budesonide and placebo.[LOW QUALITY]
- In a meta-analysis of four RCTs of budesonide 3 mg for maintenance of remission (n = 359; one year follow-up)[87,110,118,159] there was no significant difference (RR 1.01 [0.86 to 1.18) between budesonide and placebo.[MODERATE QUALITY]
- In a meta-analysis of three RCTs of budesonide 6 mg for maintenance of remission (n = 109; one year follow-up)[87,122,159] there was no significant difference (RR 0.88 [0.71 to 1.09] between budesonide 6 mg and placebo in relapse + withdrawal rates.[LOW QUALITY]
- In a meta-analysis of three RCTs of budesonide 3 mg for maintenance of remission (n = 287; one year follow-up)[87,118,159] there was no significant difference (RR 0.95 [0.82 to 1.09] between budesonide 3 mg and placebo in relapse + withdrawal rates.[MODERATE QUALITY]
- In a meta-analysis of three RCTs of budesonide 6 mg for maintenance of remission (n = 218; one year follow-up)[87,122,159] there was no significant difference (RR 0.92 [0.45 to 1.88]) between budesonide 6 mg vs. placebo in withdrawal due to adverse events.[VERY LOW QUALITY]
- In a meta-analysis of three RCTs of budesonide 3 mg for maintenance of remission (n = 290; one year follow-up) [87,118,159] there was no significant difference (RR 0.60 [0.18 to 1.98]) between budesonide 3 mg vs. placebo in withdrawal due to adverse events.[VERY LOW QUALITY]
- In one RCT of budesonide 6 mg (n = 35; one year follow-up) and budesonide 3 mg (n = 37; one year follow-up) for maintenance of remission[87] there was no significant difference in suppression of adrenal function between:
  - budesonide 6 mg vs. placebo (RR 1.06 [0.25 to 4.45])or
  - budesonide 3 mg vs. placebo ( RR 0.63 [0.12 to 3.35]).[LOW QUALITY]
- In one RCT of budesonide 6 mg (n = 72; one year follow-up) and budesonide 3 mg (n = 69; one year follow-up) for maintenance of remission[110] there was no significant difference in cortisol levels between:
  - budesonide 6 mg vs. placebo (MD 101.00 [-211.29 to 9.29]) or
  - budesonide 3 mg vs. placebo (MD 0.00 [-138.52 to 138.52]).[LOW QUALITY]
- In one RCT of 6 mg budesonide (n = 36; one year follow-up) and 3 mg budesonide (n = 34; one year follow-up) for maintenance of remission[159] there was no significant difference in abnormal response to ACTH hormone between:
  - budesonide 6 mg vs. placebo (RR 6.42 [0.38 to 107.55])or
  - budesonide 3 mg vs. placebo ( RR 3.13 [0.16 to 61.49]).[LOW QUALITY]
- In one RCT of budesonide 6 mg (n = 72; one year follow-up) and budesonide 3 mg (n = 69; one year follow-up) for maintenance of remission[110] there was no significant difference in IBDQ scores between:
  - budesonide 6 mg vs. placebo (MD 11.00 [-6.1 to 28.1])or
  - budesonide 3 mg vs. placebo (MD 6.00 [-12.2 to 24.2]).[VERY LOW QUALITY]
- In one RCT of budesonide 6 mg for maintenance of remission (n = 57; one year follow-up)[168] there were significantly fewer relapses with budesonide 6 mg than with mesalazine 3 mg (RR0.67 [0.46 to 0.97]).[VERY LOW QUALITY]
- In one RCT of budesonide 6 mg for maintenance of remission (n = 57; one year follow-up)[168] there was significantly more time to relapse with budesonide 6 mg than with mesalazine 3 mg (MD94.00 [34 to 154]).[VERY LOW QUALITY]

- In one RCT of budesonide 6 mg for maintenance of remission (n = 57; one year follow-up)[168] IBDQ scores were significantly higher with budesonide 6 mg than with mesalazine 3 mg (MD37.00 [16.85 to 57.15]).[LOW QUALITY]
- In one RCT of budesonide at variable doses for maintenance of remission[243] there was no significant difference between budesonide vs. prednisolone with regard to:
  - Relapse (RR 1.65 [0.89 to 3.06]) (n = 90; one year follow-up) [VERY LOW QUALITY]
  - Relapse + withdrawal (RR 1.31 [0.86 to 2]) (n = 90; one year follow-up) [VERY LOW QUALITY]
  - Withdrawal due to adverse events (RR 8.62 [0.48 to 155.52]) (n = 90; one year follow-up) [VERY LOW QUALITY]
  - Adrenal suppression (RR 0.60 [0.36 to 1]) (n = 69); one year follow-up).[VERY LOW QUALITY]

### 6.3.3 Economic evidence

Two studies were identified that included the relevant comparison. Budesonide was also included in an original economic analysis conducted for this guideline. Both published studies are summarised in the economic evidence profile below (Table 38 and Table 39). See also the full published study evidence tables in Appendix F: and summary of all results from the original economic analysis in section 6.7.

**Table 38: Economic study characteristics**

| Study | Limitations | Applicability | Other comments |
|---|---|---|---|
| Lofberg 1999 oral budesonide versus no maintenance therapy | Potentially serious limitations[a,b] | Partially applicable[c] | Study employed a Markov decision-analytic model with a one-year time horizon. |
| Noble 1998 budesonide CIR versus no maintenance therapy | Potentially serious limitations[a,b] | Partially applicable[d] | Study employed a Markov decision-analytic model with a one-year time horizon. |
| NCGC model (appendix H) oral budesonide versus no maintenance therapy[e] | Potentially serious limitations[b] | Directly applicable | Study employed a Markov decision-analytic model with a two-year time horizon. |

*(a) Modelling was undertaken over a short time horizon and no probabilistic sensitivity analysis was conducted.*
*(b) Specific costs and disutilities of drug-related adverse events could not be explicitly modelled. Adverse events were captured by modelling treatment-specific withdrawal rates. This may have overestimated the cost effectiveness of maintenance treatment.*
*(c) The cost-effectiveness model was designed to reflect the management of Crohn's disease in the Swedish healthcare setting. The value of health effects was not expressed in terms of QALYs.*
*(d) The cost-effectiveness model was designed to reflect the management of Crohn's disease in the Swedish healthcare setting. Although a cost per QALY estimate was reported, it was not based on health-related quality of life (HRQoL) values elicited from patients.*
*(e) The NCGC model compared a number of different maintenance treatments.*

**Table 39: Economic summary of findings**

| Study | Incremental cost vs no maintenance treatment (per patient) | Incremental effects vs no maintenance treatment (per patient) | ICER | Uncertainty |
|---|---|---|---|---|
| Lofberg 1999<br>oral budesonide versus no maintenance treatment | £131 | 17 days in remission | £2,920 per additional year in remission | Results are sensitive to cost of surgery |
| Noble 1998<br>budesonide CIR versus no maintenance treatment | £115 | 0.017 QALYs[a] | £6,981 per QALY gained | Results are sensitive to cost of surgery |
| NCGC model (appendix H)<br>oral budesonide versus no maintenance treatment[b] | £477[c]<br>£150[d]<br>£528[e]<br>£336[f] | 0.012[c]<br>0.012[d]<br>0.006[e]<br>0.005[f] | £40,392 per QALY gained[c]<br>£15,070 per QALY gained[d]<br>£87,610 per QALY gained[e]<br>£65,013 per QALY gained[f] | Results are sensitive to baseline risk of relapse.<br>In the PSA, the probability of budesonide being the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY gained ranged from 0[e] to 8%[c] |

*(a) Figures may differ due to rounding off.*
*(b) The NCGC model compared a number of different maintenance treatments.*
*(c) Conservative four-line model. Conservative treatment effects were used and people relapsing while on azathioprine maintenance treatment had a different induction sequence.*
*(d) Conservative three-line model. Conservative treatment effects were used and people were assumed to have the same induction sequence regardless of maintenance treatment.*
*(e) Non-conservative four-line model. Non-conservative treatment effects were used and people relapsing while on azathioprine maintenance treatment had a different induction sequence.*
*(f) Non-conservative three-line model. Conservative treatment effects were used and people were assumed to have the same induction sequence regardless of maintenance treatment.*

### 6.3.3.1 Evidence statements - economic

Please see section 6.7 for a summary of original economic analysis conducted for this guideline or Appendix H: for a full report.

1 ### 6.3.4 Linking evidence to recommendations

2 **Table 40: Linking evidence to recommendations – budesonide for maintenance**

| | |
|---|---|
| **Clinical question** | **7. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for maintenance of remission for 12 months or longer compared with**<br>**7.1 placebo?**<br>**7.2 conventional glucocorticosteroid treatment?**<br>**7.3 5-aminosalicylate (5-ASA) treatment?**<br>**7.4 azathioprine or mercaptopurine (AZA/MP)?**<br>**7.5 methotrexate?** |
| **Recommendation** | **27. Do not offer budesonide to maintain remission.** |
| **Relative values of different outcomes** | The key outcome of interest agreed prior to evidence evaluation was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when people were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population.<br><br>The GDG also agreed that for budesonide trials, adverse events and withdrawals (due to side effects) were both important outcomes. The GDG was particularly interested in the effect of budesonide compared with conventional glucocorticosteroid treatment on adrenal suppression.<br><br>Data were also reported for this review if study withdrawal was noted to be due to drug effect (rather than non-compliance or other reasons for drop-out).<br><br>Mucosal healing has been more recently emphasized as an end-point, and may not be described in older papers. The relative value of this outcome was felt to be less important than maintenance of remission data. This is because the patchy way in which the disease affects the intestines limits the application of histological sampling. The GDG noted that none of papers reported mucosal healing outcomes for budesonide and agreed that this outcome measure seemed to be more widely reported as an outcome for biologics. |
| **Trade off between clinical benefits and harms** | No statistically significant difference was demonstrated between budesonide 6 mg or 3 mg and placebo for any relapse outcomes, mean difference in CDAI scores or IBDQ scores. When the number of days in remission on budesonide was compared with mesalazine, budesonide was shown to be more effective.<br><br>Budesonide was shown to be no better than placebo, whilst mesalazine had a very small benefit over placebo and yet budesonide 6 mg was more effective than mesalazine with regard to relapse, mean time to relapse and IBDQ scores. This caused the GDG to look carefully at dosing. They decided that 3 mg budesonide was not effective but that 6 mg |

| | |
|---|---|
| | budesonide may have a modest efficacy of the same order of magnitude as 5-ASA.<br><br>When budesonide was compared with conventional glucocorticosteroid treatment, there was no statistically significant difference in relapse, [relapse + withdrawal], adrenal suppression and withdrawal due to adverse events. Adrenal function was maintained at a higher level than with conventional glucocorticosteroid treatment in one study, but the result was non-significant.<br><br>Conversely, no statistically significant difference in withdrawals due to adverse events at one year was demonstrated between placebo and budesonide. However the GDG expressed concern about people even on low dose budesonide being at risk for osteoporosis. Safety measures such as withdrawal, adrenal function and ACTH responses were not statistically significantly different between budesonide and mesalazine.<br><br>In summary, the efficacy data comparing budesonide, placebo and mesalazine were difficult to reconcile. In addition, there was no significant difference in adverse event rates between budesonide and conventional glucocorticosteroid treatment for maintenance of remission. On this basis the GDG agreed a 'do not offer' recommendation for budesonide in addition to 'do not offer' conventional glucocorticosteroid for maintenance of remission. |
| **Economic considerations** | A decision-analytic model with a two-year time horizon was developed, based on the results of the clinical review. The model compared different medical treatments for maintenance of medically-induced remission of Crohn's disease. The analysis was conducted in four different ways as described in the summary of the maintenance health economic model. Of the six treatments compared in the model, budesonide was associated with the 3rd most QALYs in all analyses. However, utility loss due to drug related adverse events was not explicitly incorporated in to the model due to lack of data.<br><br>Original economic analysis showed that budesonide ranged from being the third and fifth most cost-effective treatment out of six in the conservative and non-conservative analyses respectively.<br><br>The ICER for budesonide ranged from £15,070 per QALY gained in the conservative analysis where patients relapsing from all treatments had the same induction sequence, to £87,610 per QALY gained in the non-conservative analysis where patients relapsing from azathioprine had a different induction sequence.<br><br>The GDG noted that the two health economic studies[159,200] were both sponsored by a pharmaceutical company and that they were considered to be similar presentations of the same data, looking at slightly different budesonide preparations.<br><br>They noted that the limitations of the Lofberg study included a short time horizon and the lack of a probabilistic sensitivity analysis. It was also considered only partially applicable because it was conducted in Sweden and did not report QALYs. The Lofberg study showed budesonide to be not cost effective at £2900 per additional year in |

| | |
|---|---|
| | remission.<br><br>The other paper did look at QALYs however the investigators did not follow the NICE reference case (quality of life estimates were derived from expert opinion rather than patients). The Noble study showed budesonide to be cost effective at £7000 per QALY gained. However it predicted an extra seventeen days in remission per year for people on budesonide compared with no treatment, while the NCGC economic model predicted that budesonide would add, at most, an additional four days in remission over two years. The cost of relapse was also considerably higher in the Lofberg paper. This lead to lowerer estimates of the cost-effectiveness ratio in the published studies. The GDG were cautioned not to put too much importance on the published results as the health economic model presented (see Appendix H:) is more applicable to the UK. |
| **Quality of evidence** | All outcomes comparing budesonide with placebo were moderate, low, or very low quality and for budesonide compared with mesalazine very low quality. In particular, the GDG noted that while IBDQ score and time-to-relapse favoured budesonide over mesalazine, participants were aware of which treatment they were taking.<br><br>While adrenal function was recorded in many studies, the measures used to report adrenal function were all different, making it impossible to pool or interpret this data.<br><br>Due to paucity of evidence, specific costs and disutilities due to drug-related adverse events could not be captured in the economic model. This may mean that the cost-effectiveness of budesonide- and other treatments explored in the model- has been over-estimated (i.e. their ICERs have been under-estimated).<br><br>Due to lack of reporting in RCTs and quality of life literature, different severities of relapse could also not be captured in the economic model. |
| **Other considerations** | Prednisolone 7-20 mg/day was considered to be a high maintenance dose (compared with 30-40 mg/day for induction of remission) potentially biasing the study in favour of prednisolone.<br><br>Most of the studies comparing budesonide with placebo included patients with small bowel or right-sided colonic disease (the purported site of action of budesonide). Studying this population would ensure that the efficacy of budesonide was not 'diluted'. Only the Gross study included patients with Crohn's disease of all parts of the bowel.<br><br>**Children**<br>There were no studies on budesonide for maintenance of remission in children. The GDG agreed that it should not be offered to children for maintenance of remission for the same reasons as in adults. |

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# 6.4 5-ASA treatment for maintenance of remission

## 6.4.1 Clinical question

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA[o]) treatment for maintenance of remission compared with

- placebo?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

## 6.4.2 Clinical evidence

This review of 5-aminosalicylate treatment for maintenance of remission in Crohn's disease assessed outcomes in patients who were randomised while in a quiescent phase of their disease.

A Cochrane review[5] was identified which assessed RCTs comparing 5-ASA treatment with either placebo or sulfasalazine for maintenance of clinical remission in Crohn's disease for 12 months or longer. However, due to differences in the length of study specifications (12 months or longer) as well as the inclusion of comparisons with azathioprine, mercaptopurine and methotrexate in this review, a comprehensive literature search was undertaken. Nine studies[1,11,99,163,211,258,270,280,298] met the inclusion criteria for this review. No paediatric studies were identified.

Two analyses of relapse events were conducted. The primary analysis included all events defined as relapse by the trial protocol; a secondary analysis took account of dropouts/withdrawals and included these patients in the relapse events. Random effects models were run when heterogeneity was present. The primary outcomes for this review were maintenance of remission and disease relapse.

### 6.4.2.1 5-ASA treatment versus placebo

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*o 5-ASA treatment is used to denote plurality. It includes both 5-aminosalicylates: mesalazine (Mesren MR, Asacol MR and Octasa MR), olsalazine, balsalazide: and the aminosalicylates: sulfasalazine (Salazosulfapyridine). Reaers should be aware that not all 5-ASA tretments are licensed for maintenance of remission in Crohn's disease.*

**Table 41: Evidence profile: 5-ASA treatment versus placebo**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5-ASA | Placebo | Relative (95% CI) | Absolute | |
| **Relapse at 12 months (follow-up 12 months; assessed with: CDAI);** Arber 1995, IMSG 1990; Mahmud 2001; Prantera 1992; Thomson 1995; Wellman 1988 | | | | | | | | | | | |
| 6 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 152/553 27.5% | 202/559 36.1% | RR 0.76 (0.64 to 0.90) | 87 fewer per 1000 (from 36 fewer to 130 fewer) | MODERATE |
| **Relapse + withdrawal at 12 months (follow-up 12 months; assessed with: CDAI) [fixed effect];** Arber 1995, IMSG 1990; Mahmud 2001; Prantera 1992; Thomson 1995; Wellman 1988 | | | | | | | | | | | |
| 6 | randomised trials | no serious risk of bias | serious inconsistency[2] | no serious indirectness | no serious imprecision | none | 307/553 | 307/559 | RR 1.01 (0.91 to 1.12) | 5 more per 1000 (from 49 fewer to 66 more) | MODERATE |
| **Relapse + withdrawal at 12 months (follow-up 12 months; assessed with: CDAI) [random effects];** Arber 1995, IMSG 1990; Mahmud 2001; Prantera 1992; Thomson 1995; Wellman 1988 | | | | | | | | | | | |
| 6 | randomised trials | no serious risk of bias | serious inconsistency[2] | no serious indirectness | no serious imprecision | none | 307/553 (55.5%) | 307/559 (54.9%) | RR 0.96 (0.80 to 1.15) | 22 fewer per 1000 (from 110 fewer to 82 more) | MODERATE |
| **Relapse at two years (follow-up two years);** Gendre 1993 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | serious[1] | none | 30/80 (37.5%) | 36/81 (44.4%) | RR 0.84 (0.58 to 1.23) | 71 fewer per 1000 (from 187 fewer to 102 more) | LOW |
| **Maintenance of remission at one year (follow-up one year);** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 36/58 (62.1%) | 65/101 (64.4%) | RR 0.96 (0.75 to 1.24) | 26 fewer per 1000 (from 161 fewer to 219 more) | HIGH |
| **Maintenance of remission at two years (follow-up two years);** Summers 1979 | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious imprecision[5] | none | 12/39 (30.8%) | 23/57 (40.4%) | RR 0.76 (0.43 to 1.34) | 97 fewer per 1000 (from 230 fewer to 137 more) | LOW |
| **Withdrawal due to adverse events at two years (follow-up two years);** Gendre 1993 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious imprecision[4] | none | 7/80 (8.8%) | 10/81 (12.3%) | RR 0.71 (0.28 to 1.77) | 36 fewer per 1000 (from 89 fewer to 95 more) | VERY LOW |
| **Adverse events - disaster (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious imprecision[4] | none | 0/58 (0%) | 1/101 (1%) | RR 0.58 (0.02 to 13.92) | 4 fewer per 1000 (from 10 fewer to 128 more) | LOW |
| **Adverse events - severe: (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious imprecision[4] | none | 2/58 (3.4%) | 7/101 (6.9%) | RR 0.50 (0.11 to 2.32) | 35 fewer per 1000 (from 62 fewer to 91 more) | LOW |
| **Withdrawal due to adverse events 12 months (follow-up one year);** Arber 1995, IMSG 1990, Mahmud 2001, Prantera 1992, Thomson 1995 | | | | | | | | | | | |
| 5 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[5] | none | 78/520 (14.9%) | 49/524 (9.4%) | RR 1.62 (1.16 to 2.26) | 58 more per 1000 (from 15 more to 118 more) | MODERATE |

*1 Confidence interval crosses 0.75.*
*2 $I^2$ = 57%.*
*3 Randomisation not described.*
*4 Confidence interval crosses 0.75 and 1.25.*
*5 Confidence interval crosses 1.25.*

### 6.4.2.2 5-ASA treatment versus azathioprine

**Table 42: Evidence profile: 5-ASA versus azathioprine**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5-ASA | Azathioprine | Relative (95% CI) | Absolute | Quality |
| **Maintenance of remission at one year (follow-up one year);** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious imprecision[1] | none | 43/58 (74.1%) | 46/54 (85.2%) | RR 0.87 (0.72 to 1.05) | 111 fewer per 1000 (from 239 fewer to 43 more) | MODERATE |
| **Maintenance of remission at two years (follow-up two years);** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious imprecision[1] | none | 31/58 (53.4%) | 29/54 (53.7%) | RR 1.00 (0.70 to 1.41) | 0 fewer per 1000 (from 161 fewer to 220 more) | MODERATE |
| **Adverse events - disaster (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious imprecision[2] | none | 0/58 (0%) | 2/54 (3.7%) | RR 0.19 (0.01 to 3.80) | 30 fewer per 1000 (from 37 fewer to 104 more) | LOW |
| **Adverse events - severe (follow-up two years);** Singleton 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious imprecision[1] | none | 2/58 (3.4%) | 8/54 (14.8%) | RR 0.23 (0.05 to 1.05) | 114 fewer per 1000 (from 141 fewer to 7 more) | MODERATE |

*1 Confidence interval crosses 0.75.*
*2 Confidence interval crosses 0.75 and 1.25.*

#### 6.4.2.3 Evidence statements -clinical

- In a meta-analysis of six RCTs (n = 1112)[1,11,163,211,280,298] comparing 5-ASA to placebo for relapse (not including withdrawals) for a 12-month trial duration, patients taking 5-ASA were significantly less likely to relapse than those taking placebo (RR 0.76 [0.64 to 0.90]).[MODERATE QUALITY]
- In a meta-analysis of six RCTs (n = 1112)[1,11,163,211,280,298] comparing 5-ASA to placebo for relapse (including all withdrawals) for a 12-month trial duration, there was no significant difference in relapse between patients taking 5-ASA or placebo. (RR 1.01 [0.91 to 1.12] [fixed effect]; RR 0.96 [0.80 to 1.15] [random effects]).[MODERATE QUALITY]
- In one RCT (n = 161)[99] comparing 5-ASA to placebo for maintenance of remission for a two-year trial duration, there was no significant difference in relapse between patients taking 5-ASA vs. placebo (RR 0.84 [0.58 to 1.23]).[LOW QUALITY]
- In one RCT (n = 159)[270] there was no significant difference in maintenance of remission at one year or two years between patients taking sulfasalazine vs. placebo. (RR 0.96 [0.75 to 1.24] and RR 0.76 [0.43 to 1.34] respectively).[HIGH-LOW QUALITY]
- In a meta-analysis of five RCTs (n = 1044)[1,11,163,211,280] comparing 5-ASA with placebo for withdrawal due to adverse events during maintenance treatment for 12 months, there were significantly more withdrawals in the 5-ASA group (RR 1.62 [1.16 to 2.26]).[MODERATE QUALITY]
- In one RCT (n = 161)[99] comparing 5-ASA with placebo for withdrawal due to adverse events during maintenance treatment for two years, there was no significant difference in withdrawal between patients taking 5-ASA and placebo (RR 0.71 [0.28 to 1.77]).[VERY LOWQUALITY]
- In one RCT (n = 159)[258] there was no significant difference in disastrous or severe adverse events at two years between patients taking sulfasalazine and placebo (RR 0.58 [0.02 to 13.92] and RR 0.50 [0.11 to 2.32] respectively).[LOW QUALITY ]
- In one RCT (n = 112)[270] there was no significant difference in maintenance of remission at one year or two years between patients taking sulfasalazine vs. azathioprine (RR 0.87 [0.72 to 1.05] and RR 1.00 [0.70 to 1.41] respectively).[MODERATE QUALITY]
- In one RCT (n = 112)[258] there was no significant difference in disastrous or severe adverse events at one year or two years between patients taking sulfasalazine or azathioprine for maintenance of remission (RR 0.19 [0.01 to 3.80] and RR 0.23 [0.05 to 1.05] respectively).[LOW-MODERATE QUALITY ]

### 6.4.3 Economic evidence

One study was included. Mesalazine and olsalazine were also included in an original economic analysis conducted for this guideline. The study and original economic analysis for both drugs are summarised in the economic evidence profile below (Table 38 and Table 39). See also the full published study evidence tables in Appendix F: and summary of all results from the original economic analysis in section 6.7.

**Table 43: Economic study characteristics**

| Study | Limitations | Applicability | Other comments |
|---|---|---|---|
| Trallori and Messori 1997, mesalazine versus no maintenance therapy | Potentially serious limitations[a,b] | Partially applicable[c] | This study was a lifetime cost utility analysis of mesalazine as maintenance therapy for Crohn's disease. |
| NCGC model (appendix H), mesalazine vs no maintenance treatment[d] | Potentially serious limitations[b] | Directly applicable | Cost-utility analysis conducted from a UK perspective over a two-year time horizon. |
| NCGC model (appendix H), olsalazine vs no maintenance treatment[d] | Potentially serious limitations[b] | Directly applicable | Cost-utility analysis conducted from a UK perspective over a two-year time horizon. |

*(a) The choice of model (and its structural elements) is not clearly described. No probabilistic sensitivity analysis was conducted.*

*(b) Specific costs and disutilities of drug-related adverse events could not be explicitly modelled. Adverse events were captured by modelling treatment-specific withdrawal rates. This may have overestimated the cost effectiveness of maintenance treatment.*

*(c) The setting is the Italian healthcare system although cost-of-illness data were taken from a study conducted in the UK and the costs of mesalazine were those applicable in the UK as of the year 1994. HRQoL values were not elicited from patients but from an expert panel of gastroenterologists.*

*(d) The NCGC model compared a number of different maintenance treatments.*

**Table 44: Economic summary of findings**

| Study | Incremental cost vs no maintenance treatment (per patient) | Incremental QALYs vs no maintenance treatment (per patient) | ICER vs no maintenance treatment | Uncertainty |
|---|---|---|---|---|
| Trallori and Messori 1997<br>mesalazine vs no maintenance treatment | £607 | 0.19 | £3,197 per QALY gained | Results are sensitive to cost of illness (relapses, hospitalization and surgical interventions) |
| NCGC model (appendix H),<br>mesalazine vs no maintenance therapy[a] | £430[b]<br>-£17[c]<br>£355[d]<br>-£99[e] | 0.017[b]<br>0.015[c]<br>0.018[d]<br>0.015[e] | £25,133 per QALY gained[b]<br>Mesalazine dominates[c]<br>£20,319 per QALY gained[d]<br>Mesalazine dominates[e] | Results are sensitive to baseline risk of relapse.<br>In the non-conservative four line model, when the model was run for a ten-year time horizon mesalazine was the most cost-effective treatment.<br>In the PSA, the probability of mesalazine being the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY gained ranged from 1[e] to 7%[b] |
| NCGC model (appendix H),<br>olsalazine vs no maintenance treatment[a] | £933[b]<br>£1,340[c]<br>£415[d]<br>£425[e] | -0.023[b]<br>-0.018[c]<br>-0.00021[d]<br>-0.00017[e] | No treatment dominates[b]<br>No treatment Dominates[c]<br>No treatment dominates[d]<br>No treatment dominates[e] | In the PSA, the probability of olsalazine being the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY was 0% in all analyses[b,c,d,e]. |

*(a) The NCGC model compared a number of different maintenance treatments.*
*(b) Conservative four line model. Conservative treatment effects were used and people relapsing while on azathioprine maintenance treatment had a different induction sequence.*
*(c) Conservative three line model. Conservative treatment effects were used and people are assumed to have the same induction sequence regardless of maintenance treatment.*
*(d) Non conservative four line model. Non conservative treatment effects were used and people relapsing while on azathioprine maintenance treatment had a different induction sequence.*
*(e) Non conservative three line model. Conservative treatment effects were used and people are assumed to have the same induction sequence regardless of maintenance treatment.*

#### 6.4.3.1 Evidence statement – economic

Please see section 6.7 for a summary of original economic analysis conducted for this guideline or Appendix H: for a full report.

### 6.4.4 Linking evidence to recommendations

**Table 45: Linking evidence to recommendations – 5-ASA treatment for maintenance**

| | |
|---|---|
| **Clinical question** | **8. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for maintenance of remission compared with**<br>**8.1 placebo?**<br>**8.2 azathioprine or mercaptopurine (AZA/MP)?**<br>**8.3 methotrexate?** |
| **Recommendation** | **None made. See research recommendation section 6.9** |
| **Relative values of different outcomes** | The agreed key outcome of interest for the GDG was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>It was noted that maintenance of remission and relapse are two different disease states that are not necessarily the reverse of each other, since withdrawals can occur for many different reasons.<br><br>The GDG agreed that there were three categories:<br>• In remission<br>• Relapse<br>• Trial dropout with outcome unknown (person still in remission or relapsed)<br><br>The GDG also agreed that for 5-ASA trials, adverse events and withdrawals (due to side effects) were both important outcomes. They were particularly interested in severe adverse events defined as<br>o 'Disaster' in Singleton 1979 defined as '...an event or condition which necessitated hospitalization and/or produced long-lasting (three months) disability.'<br>o 'Serious' in Singleton 1979 defined as '...those that caused withdrawal of the patient from the study or required specific treatment.'<br><br>Data were also reported for this review if study withdrawal was noted to be due to drug effect (rather than non-compliance or other reasons for drop-out).<br><br>Mucosal healing has been more recently emphasized as an end-point, and may not be described in older papers. The relative value of this outcome was felt to be less important than maintenance of remission data. This is because the patchy way in which the disease affects the intestines limits the application of histological sampling. The GDG noted that none of papers reported mucosal healing outcomes for 5-ASA treatment and agreed that this outcome measure seemed to be more widely reported as an outcome for biological drugs.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission |

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| | were excluded as they were not considered comparable with a quiescent phase population.<br><br>The meta-analysis showed that when only confirmed relapse was considered (i.e. withdrawals were not assumed to be for adverse reasons) 5-ASA treatment compared with placebo was effective for maintaining remission. However when withdrawals were included as probable relapses there was no significant difference. The GDG felt that the true position was likely to be somewhere between the two. For relapse plus withdrawal the fixed effect meta-analysis demonstrated heterogeneity ($I^2$ of 57%) and hence random effects meta-analyses were run. Little difference was noted between the fixed and random effects meta-analyses for relapse and relapse + withdrawal.<br><br>Summers and Singleton looked at maintenance of remission (rather than relapse) and at one and two years there was a non-significant difference between the 5-ASA and placebo groups. The GDG also noted no significant differences for adverse events, disastrous adverse events and serious adverse events between the two groups in these two studies although event numbers were small. |
| **Trade off between clinical benefits and harms** | The GDG considered the 5-ASA efficacy data to be equivocal, with substantial differences in effect size and significance for relapse or relapse + withdrawal outcomes versus placebo and non-significant differences in relapse rates at one and two years compared with azathioprine.<br><br>The GDG noted significantly more withdrawals due to adverse events with 5-ASA treatment than placebo. They surmised that the large side effect-related withdrawals in the Mahmud study (which alone used olsalazine) were probably because of diarrhoea, a common side effect of this agent in their experience. They considered this to have skewed the results against 5-ASA treatment, even though there was no significant heterogeneity.<br><br>They also noted that 5-ASA treatment was associated with fewer serious and disastrous adverse events than azathioprine, although participant numbers were small and results were non-significant. |
| **Economic considerations** | Due to the lack of reporting of specific adverse events in the RCTs, costs and disutilities due to drug-related adverse events could not be captured in the economic model. This may mean that the cost-effectiveness of 5-ASAs- and other treatments explored in the model- has been over-estimated (i.e. their ICERs have been under-estimated).<br><br>Due to lack of reporting in RCTs and quality of life literature, different severities of relapse could also not be captured in the economic model.<br><br>A decision-analytic model was developed with a two-year time horizon, based on the results of the clinical review. The model compared different medical treatments for maintenance of medically-induced remission of Crohn's disease.<br><br>The GDG accepted that due to potential differences in costs and side-effect profiles, 5-ASAs should be treated separately for the purpose of |

economic analysis. The 5-ASA clinical review only included studies of mesalazine and olsalazine, and these were analysed separately within the economic model.

The analysis was conducted in four different ways as described in the summary of the health economic maintenance model.

Original economic analysis showed that of the six treatments compared in the model:

- mesalazine was associated with the second most QALYs in all analyses
- olsalazine was associated with the sixth most QALYs in all analyses (i.e. even less effective than no treatment).
-

However, utility loss due to drug-related adverse events was not explicitly incorporated in to the model due to lack of data.

- Mesalazine ranged from being the second most cost-effective treatment out of six in the non-conservative analysis where all treatments had the same induction sequence, to fourth in the non-conservative analysis where people treated with azathioprine had a different induction sequence.
- Olsalasine was the worst treatment in terms of cost effectiveness in all analyses.
- Mesalazine was dominant compared with no treatment in the analyses where only the azathioprine maintenance strategy had the short induction sequence, but was dominated by azathioprine. Mesalazine was associated with an ICER of £20,319 per QALY gained in the non-conservative analysis where only the azathioprine strategy had a short induction sequence, but was dominated by azathioprine.
- Mesalazine was associated with an ICER of £25,133 per QALY gained vs no treatment in the conservative analysis where all treatments had the short induction sequence, but the ICER for azathioprine vs mesalazine was £17,996 per QALY gained, showing that, at a willingness-to-pay threshold of £20,000 per QALY, azathioprine is still the preferred treatment.
- Olsalazine was dominated by no treatment in all analyses.

The GDG felt unable to recommend 5-ASA treatment as:

a) olsalazine maintenance was the least cost-effective option and worse than no maintenance treatment
b) mesalazine maintenance was less effective and less cost-effective than azathioprine
c) mesalazine maintenance cost more than £20,000 per QALY in the analyses with a four-line induction sequence.

The GDG was made aware of potentially serious limitations of the Trallori health economic study[284] because methods were not described and a probabilistic sensitivity analysis was not conducted. In addition, it was considered only partially applicable because the study was undertaken within the Italian healthcare system and HRQoL values were determined by gastroenterologists, not people with Crohn's disease. Most importantly the cost of relapse was considerably higher in the Trallori paper. This led to lower estimates of the cost-effectiveness ratio in the published study. The GDG concluded that a NCGC health

| | |
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| | economic model would be more relevant than this study. |
| **Quality of evidence** | No paediatric data and no comparisons of 5-ASA treatment vs. methotrexate were found.<br><br>For this review the Sutherland study was excluded as follow-up was for 48 weeks and not one year as per the agreed protocol.<br><br>The GDG noted the varying quality of the evidence for this review. They considered the 5-ASA (compared to placebo) efficacy data to be equivocal, with substantial differences in effect size and significance for relapse or relapse + withdrawal outcomes. The meta-analysis of six RCTs for relapse only at one year showed that 5-ASA reduced relapses by 24% and at 95% confidence this number ranged from 10 to 36%. When relapse and withdrawal were taken into account the meta-analysis showed no difference between 5-ASA and placebo in preventing relapse.<br><br>At two years a low-quality study (Gendre 1993) also demonstrated a non-significant relapse rate result.<br><br>In addition, the GDG was unable to draw any conclusions about the relative effectiveness of 5-ASA or azathioprine versus placebo, because of differences in study methodology (see section Linking evidence to recommendations 6.5.4).<br><br>The GDG noted issues of class effect and consistency of presenting the data in the guideline. The GDG agreed that the data should not be sub-grouped *post hoc* and that it would be inconsistent to specify one drug, olsalazine, in a 'do not consider' recommendation. In practice, the GDG believes that olsalazine is offered to very few people with Crohn's disease, and considered that such a recommendation would not make a substantial difference to current practice.<br><br>The GDG remarked that different 5-ASA preparations are purported to be effective in different parts of the bowel (see the current online version of the BNF) and commented on the lack of site-specific 5-ASA RCTs – hence no conclusions about this aspect of maintenance therapy could be drawn.<br><br>The GDG reflected that meta-analysis of 5-ASA as a class compared to placebo showed they may be effective, though not when withdrawals are factored in. The economic model showed, compared to no treatment, mesalazine may be cost-effective but olsalazine isn't, however neither were cost-effective compared to azathioprine.<br><br>The GDG concluded that there was too much uncertainty surrounding the 5-ASA clinical data and health economic analysis to make any recommendation for maintenance of medically-induced remission in Crohn's disease. The GDG acknowledged that further research in this field would be informative, and developed a research recommendation (see section 6.9). |
| **Other considerations** | The GDG noted that studies should ideally control for smoking, as a confounder and which is considered by some to have a larger effect |

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|---|---|
| | than drug therapy in maintenance of remission, however none of the studies reviewed reported this. The GDG agreed the importance of providing the necessary information about and support to patients to stop smoking in Chapter 11.<br><br>**Children**<br>There were no studies on 5-ASA treatment for maintenance of remission in children. The GDG did not make a recommendation for 5-ASA maintenance treatment in children in light of the paucity of paediatric evidence and uncertainty associated with adult data.<br><br>**Licensing**<br>Only three brands of 5-ASAs are licensed for maintenance of remission in Crohn's ileo-colitis (Asacol MR, Mesren MR and Octasa MR), but many are currently prescribed in clinical practice. |

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# 6.5 Immunosuppressives for maintenance of remission

## 6.5.1 Clinical questions: azathioprine or mercaptopurine

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for maintenance of remission for 12 months or longer

- compared with placebo?
- compared with methotrexate?
- *plus* conventional glucocorticosteroid or 5-ASA treatment compared with placebo *plus* conventional glucocorticosteroid or 5-ASA treatment?

## 6.5.2 Clinical evidence: azathioprine or mercaptopurine

Mercaptopurine and its pro-drug, azathioprine, are purine analogues that inhibit cell growth by directly interfering with nucleic acid synthesis. Azathioprine is non-enzymatically converted to mercaptopurine upon ingestion, and is for pragmatic and clinical purposes considered to be the same entity as mercaptopurine. Only RCTs were included in this review; cross-over studies were excluded. Studies in which patients were randomised when they had active disease were also excluded. Three RCTs[150,201,258,270,304] i.e. Summers, Singleton and Winship report different aspects of the same study were identified which addressed the review question and met inclusion criteria. No paediatric studies were identified. No studies comparing azathioprine or mercaptopurine to methotrexate were identified. A Cochrane review[212] was identified which compared azathioprine or mercaptopurine to placebo for maintenance of remission in Crohn's disease. However, due to inclusion of studies with a follow-up of less than 12 months[227,301], studies in which patients had active disease at randomisation[38,270], studies exclusively assessing post-surgical patients[58,123] and exclusion of studies comparing azathioprine or mercaptopurine to methotrexate, a full literature search and review were undertaken. For comparison of azathioprine or mercaptopurine with 5-ASA treatment, please see section 6.4.2.2.

### 6.5.2.1 Azathioprine versus placebo

**Table 46: Evidence profile: azathioprine versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Azathioprine | Placebo | Relative (95% CI) | Absolute | |
| **Relapse (defined by CDAI and clinical deterioration) at 12 months;** O'Donoghue 1978; Lémann 2005 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 3/64 (4.7%) | 16/70 (22.9%) | RR 0.21 (0.06 to 0.68) | 181 fewer per 1000 (from 73 fewer to 215 fewer) | MODERATE |
| **Relapse + withdrawal (defined by CDAI and clinical deterioration) at 12 months;** O'Donoghue 1978; Lémann 2005 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 10/64 (15.6%) | 19/70 (27.1%) | RR 0.58 (0.29 to 1.15) | 114 fewer per 1000 (from 193 fewer to 41 more | LOW |
| **Relapses at 18 months;** Lémann 2005 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 3/40 (7.5%) | 9/43 (20.9%) | RR 0.36 (0.1 to 1.23) | 134 fewer per 1000 (from 188 fewer to 48 more) | MODERATE |
| **Relapse + withdrawal (defined by CDAI and clinical deterioration) at 18 months;** Lémann 2005 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 17/40 (42.5%) | 16/43 (37.2%) | RR 1.14 (0.67 to 1.94) | 52 more per 1000 (from 123 fewer to 350 more) | LOW |
| **Maintenance of remission** at 12 months†;** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 37/54 (68.5%) | 65/101 (64.4%) | RR 1.06 (0.84 to 1.34) | 39 more per 1000 (from 103 fewer to 219 more) | MODERATE |
| **Maintenance of remission** at 24 months†;** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 10/54 (18.5%) | 23/101 (22.8%) | RR 0.81 (0.42 to 1.58) | 43 fewer per 1000 (from 132 fewer to 132 more) | LOW |
| **Maintenance of remission** at 24 months‡;** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 10/35 (28.6%) | 23/57 (40.4%) | RR 0.71 (0.38 to1.31) | 117 fewer per 1000 (from 250 fewer to 125 more) | LOW |
| **Withdrawal due to adverse events at 12 months;** O'Donoghue 1978; Lémann 2005 | | | | | | | | | | | |
| 2 | randomised | serious[1] | no serious | no serious | very serious[3] | none | 2/64 | 1/70 | RR 1.83 (0.25 to | 12 more per 1000 | VERY LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Azathioprine | Placebo | Relative (95% CI) | Absolute | |
| | trials | | inconsistency | indirectness | | | (3.1%) | (1.4%) | 13.38) | (from 11 fewer to 177 more) | |
| **Adverse events at 12 months;** O'Donoghue 1978; Lémann 2005 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 3/64 (4.7%) | 1/70 (1.4%) | RR 2.55 (0.39 to 16.72) | 22 more per 1000 (from 9 fewer to 225 more) | VERY LOW |
| **Adverse events at 24 months: severe;** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[4] | none | 8/54 (14.8%) | 7/101 (6.9%) | RR 2.14 (0.82 to 5.58) | 79 more per 1000 (from 13 fewer to 268 more) | MODERATE |
| **Adverse events at 24 months: disaster;** Summers 1979 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 2/54 (3.7%) | 1/101 (1%) | RR 3.74 (0.35 to 40.32) | 27 more per 1000 (from 6 fewer to 389 more) | LOW |

*1 1 of 2 studies: No details on allocation concealment or randomisation process (O'Donoghue 1978).*
*2 Confidence interval crosses 0.75.*
*3 Confidence interval crosses 0.75 and 1.25.*
*4 Confidence interval crosses 1.25.*
**Defined in O'Donoghue 1978 as significant deterioration in clinical state requiring treatment change .Defined in Lémann 2005 as CDAI score > 250, a CDAI score of 150 – 250 on 3 consecutive weeks with an increase of ≥ 75 points above the baseline value, or the need for surgery for Crohn's disease (except limited perianal surgery).*
*** Defined as no flare-up. Flare-up defined as CDAI > 150 and over 100 points greater than initial CDAI for two consecutive weeks, need for operation, development of new fistula other than simple anal fistula, persistence of daily fever > 38.9°C for > 14 consecutive days and interim barium x-rays worse than baseline X-rays.*
*†Maintenance of remission analysed on an ITT with imputation basis (Follow-up data were available for all patients at 12 months).*
*‡Maintenance of remission analysed according to censoring at 12 months; 92 patients entered the study at such a time that could be followed for 24 months.*

#### 6.5.2.2 Evidence statements – clinical: azathioprine or mercaptopurine

- In a meta-analysis of two RCTs comparing azathioprine vs. placebo for maintenance of remission (n = 134)[150,201] azathioprine therapy was significantly more effective than placebo for relapses at 12 months (RR 0.21 [0.06 to 0.68]).[MODERATE QUALITY]
- In a meta-analysis of two RCTs comparing azathioprine vs. placebo for maintenance of remission (n = 134)[150,201] there was no significant difference in relapse + withdrawal at 12 months (RR 0.58 [0.29 to 1.15]).[LOW QUALITY]
- In three RCTs ofazathioprine for maintenance of remission[150,201,270] there was no significant difference between azathioprine therapy and placebo for:
  - Maintenance of remission at 12 months (RR 1.06 [0.84 to 1.34])(n = 155).[270][MODERATE QUALITY]
  - Maintenance of remission at 24 months ITT with imputation analysis (RR 0.81 [0.42 to 1.58] (n = 155).[270][LOW QUALITY]
  - Maintenance of remission at 24 months (censoring at one year) (RR 0.71 [0.38 to 1.31]) (n = 92).[270][LOW QUALITY]
  - Relapses at 18 months (RR 0.36 [0.1 to 1.23]) (n = 83).[150][MODERATE QUALITY]
  - Relapse + withdrawal at 18 months (RR 1.14 [0.67 to 1.94]) (n = 83).[150][LOW QUALITY ]
  - Adverse events at 12 months (RR 2.55 [0.39 to 16.72]) (n = 134).[150,201][VERY LOW QUALITY]
  - Severe adverse events at 24 months (RR 2.14 [0.82 to 5.58]) (n = 155).[270][MODERATE QUALITY]
  - Disastrous adverse events at 24 months (RR 3.74 [0.35 to 40.32])(n = 155).[270][LOW QUALITY]
  - Withdrawal due to adverse events at 12 months (RR 1.83 [0.25 to 13.38] (n = 134).[150,201][VERY LOW QUALITY]

### 6.5.3 Economic evidence

No published data were found relating to the cost effectiveness of immunosuppressive treatment for the maintenance of remission of Crohn's disease.

Please see Health economic maintenance model summary section 6.7

## 6.5.4 Linking evidence to recommendations

**Table 47: Linking evidence to recommendations – azathioprine or mercaptopurine for maintenance**

| | |
|---|---|
| **Clinical question** | **9. In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for maintenance of remission for 12 months or longer**<br>**9.1 compared with placebo?**<br>**9.2 compared with methotrexate?**<br>**9.3 plus conventional glucocorticosteroid or 5-ASA treatment compared with placebo plus conventional glucocorticosteroid or 5-ASA treatment?** |
| **Recommendations** | **24. Offer azathioprine or mercaptopurine[h] as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission.**<br>**25. Consider azathioprine or mercaptopurineto maintain remission in people who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations).**<br>*h Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.* |
| **Relative values of different outcomes** | The agreed key outcome of interest was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population.<br><br>The GDG only considered studies in which maintenance therapy was both given, and outcome measures recorded, for 12 months or longer.<br><br>However, the GDG noted importantly that the Lémann and O'Donoghue trials were withdrawal trials, and hence intrinsically different to the trials reviewed for other interventions. Patients recruited to the trials were in remission and already on azathioprine treatment (i.e. randomised in quiescent phase to either continue with azathioprine or change to placebo). These trials were not designed to answer the question about the potential of azathioprine to maintain remission per se, because participants taking azathioprine for a long period of time are much more likely to be those in whom the drug has been both efficacious and well tolerated. This effect might falsely inflate the potential efficacy ascribed to azathioprine.<br><br>The GDG also agreed that for azathioprine or mercaptopurine maintenance trials, adverse events were important outcomes. They were predominantly interested in the incidence of lymphoproliferative disorders associated with long-term immunosuppressive drugs, as well as |

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| | pancreatitis and serious infections due to bone marrow suppression.<br><br>The GDG were also interested in withdrawal outcomes, specifically related to drug effect (rather than non-compliance or other reasons for drop-out which may be significant in number over long-term maintenance trials).<br><br>Mucosal healing has been more recently emphasized as an end-point, and may not be described in older papers. The relative value of this outcome was felt to be less important than maintenance of remission data. This is because the patchy way in which the disease affects the intestines limits the application of histological sampling. None of papers reported mucosal healing outcomes for azathioprine or mercaptopurine and agreed that this outcome measure seemed to be more widely reported as an outcome for biological drugs.<br><br>There was no evidence in children and no comparison between azathioprine/mercaptopurine and methotrexate. |
| **Trade off between clinical benefits and harms** | The GDG acknowledged that side effects associated with any long-term drug therapy are a major concern for people with Crohn's disease. Importantly, lymphoproliferative side effect data associated with long-term immunosuppressives are equivocal.<br><br>The studies show a benefit of azathioprine in maintaining remission at 12 months. However, the GDG noted that [relapse + withdrawals] resulted in a very large difference in the relative risk point estimate compared with confirmed relapse alone (RR 0.21 v RR 0.58). In the Lémann trial, the benefit of azathioprine [relapse + withdrawals] was also shown to disappear at 18 months.<br><br>No significant difference was demonstrated between azathioprine and placebo for serious or disastrous side effects<br>o 'Disaster' in Singleton 1979 defined as '...an event or condition which necessitated hospitalization and/or produced long-lasting (three months) disability.'<br>o 'Serious' in Singleton 1979 defined as '...those that caused withdrawal of the patient from the study or required specific treatment.'<br>or withdrawals at 12 or 24 months. However, the experience of the clinicians present contradicted this particularly as regards lymphoproliferative disorders over the long term. The GDG debated particular patient characteristics that might be associated with higher risk of relapse or severity of the course of the disease and which therefore may be traded off against potentially serious adverse events. In justifying the use of these treatments, the GDG listed a number of factors which they considered to imply an adverse prognosis. These include early age of onset, perianal disease, glucocorticosteroid treatment at presentation, severe presentations, and fistula formation. |
| **Economic considerations** | A decision-analytic model was developed with a two-year year time horizon, based on the results of the clinical review. The model compared different medical treatments for maintenance of medically induced remission of Crohn's disease. The analysis was conducted in four different ways as described in the health economic maintenance model summary. Of the six treatments compared in the model, azathioprine was |

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| | associated with the highest number of QALYs in all analyses. However, utility loss due to drug-related adverse events was not explicitly incorporated in to the model due to lack of data.<br><br>Original economic analysis showed that azathioprine was the most cost effective treatment in all analyses except the conservative analysis where azathioprine patients had a less cost-effective induction sequence than the other strategies where it was ranked second of six treatments.<br><br>Azathioprine was dominant compared with no treatment in all cases apart from the conservative analysis where patients relapsing from azathioprine had a different induction sequence to the other strategies. In this analysis azathioprine was associated with an ICER of £21,128 per QALY gained compared with no treatment. |
| **Quality of evidence** | There were only three studies meeting the protocol criteria. Two of these, the O'Donoghue and Lémann trials, were graded as low quality for the outcome of remission, with a combined sample size of 134 participants.<br><br>From the O'Donoghue and Lémann trials for relapse at one year a pooled statistically significant result favouring azathioprine (RR 0.21 CI 0.06 to 0.68). The trials however demonstrated non-significant results for relapse at 18 months, maintenance of remission both at 12 and 18 months, withdrawal due to adverse events at one year and adverse events at one and two years. When relapse + withdrawals at 12 months was considered, whilst the GDG noted a statistically non-significant result, the point estimate with a relative risk of 0.58 and absolute numbers of 114 fewer relapses and withdrawals in the AZA/MP group was considered to be potentially important.<br><br>The group debated the appropriateness of pooling two of the studies given their differences. There was no heterogeneity but the GDG found this unsurprising given that there were only two small trials.<br><br>The GDG discussed the differences between the two studies (O'Donoghue and Lémann). They noted that there were differences in remission definition, length of quiescence, background therapy and azathioprine dose difference (Lémann 1.7mg/kg vs. O'Donoghue 2mg/kg).<br><br>Of the O'Donoghue study participants (n = 51), 16 had been in remission for less than one year, 19 in remission for between one and two years, and 16 in remission for more than two years. Approximately 30% of participants were receiving additional sulfasalazine or low dose glucocorticosteroid treatment. It was also noted that this study was published in 1978 and pre dated the CDAI.<br><br>In the Lémann study (2005), the participants (n = 83) had been in remission on average for 57 months, receiving continuous azathioprine treatment for at least 42 months with an average of 64 months. They had received no treatment with oral prednisone > 10 mg/day. In this study relapse was defined as a CDAI of greater than 250 or score of 150-250 for three consecutive weeks with an increase of 75 points above baseline.<br><br>Hence the GDG noted that the Lémann study participants had been in established remission for a much longer period of time and the average |

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| | azathioprine dose was lower than normal. This may not relate directly to clinical practice in which azathioprine dose is calculated and prescribed bearing in mind the availability of 25 mg and 50 mg tablets.<br><br>The GDG discussed the difference in results between the two studies; one study was statistically significant and the other non-significant (at a low azathioprine dose) for reducing relapse at 12 months. The GDG was surprised by the fact that the Lémann participants were in remission for more than three years but that the trial still demonstrated a difference in relapse on a lower azathioprine dose. In light of this the GDG gave less credence to this study.<br><br>Whilst the GDG were aware of these differences they agreed that as there were only two trials available for the outcome of 'relapse' the studies should be pooled.<br><br>The Summers (1979) trial was also reviewed but not pooled with the two other studies as the outcome reported was maintenance of remission and not relapse. In this trial, the GDG noted non-significant differences between azathioprine and placebo in maintaining remission at 12 and 24 months.<br><br>The GDG discussed the differences between the results found for the Cochrane systematic review (Prefontaine 2009) compared with NCGC review. The GDG agreed it was difficult to compare the two as the Cochrane systematic review included eight studies whereas the NCGC included three studies. The Cochrane review looked at the outcome of maintenance of remission and the studies included people who had been randomised in active disease. In addition the Cochrane review included two studies that looked at outcomes at 24 and 26 weeks.<br><br>Due to paucity of evidence, specific costs and disutilities due to drug-related adverse events could not be captured in the economic model. This may mean that the cost-effectiveness of azathioprine- and other treatments explored in the model- has been over-estimated (i.e. their ICERs have been under-estimated).<br><br>Due to lack of reporting in RCTs and quality of life literature, different severities of relapse could also not be captured in the economic model. |
| **Other considerations** | Azathioprine is the prodrug of mercaptopurine. For pragmatic and clinical purposes they are considered to be the same pharmacological entity.<br><br>The GDG considered the length of time in remission prior to randomisation to be a significant issue influencing reported outcomes in the O'Donoghue and Lémann trials. People who have been in remission for a long time tend to have a lower risk of relapse. Therefore, a lower risk of relapse would be expected in the Lémann paper because of the 42-month quiescent phase prior to randomisation.<br><br>Conversely, the GDG also debated the impact of dose within these studies. They noted that the Lémann study used a lower (1.7mg/kg) than conventional dose (2 – 2.5mg/kg). The GDG commented that the non-significant Lémann results may be reflective of this low dose and hence a higher dose may add weight to supporting the efficacy of azathioprine. |

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| | The GDG agreed that azathioprine or mercaptopurine should be offered as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid to induce remission.<br><br>However the GDG felt that azathioprine or mercaptopurine maintenance of remission therapy should not be limited to people who had been induced with azathioprine or mercaptopurine in combination with a conventional glucocorticosteroid.<br><br>Given the clinical evidence, the health economic maintenance model findings and GDG consensus the GDG then went on to make a 'consider' recommendation. The GDG acknowledged that following discussion of the benefits and limitations of maintenance treatment, some people may decide against any form of medical maintenance treatment. For those who do decide to 'opt' for maintenance treatment, azathioprine or mercaptopurine should be 'considered'. The clinical consensus of the GDG was that some people are at higher risk of relapse and azathioprine or mercaptopurine should also be 'considered' for people with adverse prognostic factors. The examples listed in the recommendation are not intended to be exhaustive.<br><br>The GDG noted that although they had assessed the evidence in order to make a recommendation to offer azathioprine or mercaptopurine for maintenance of remission, this review did not enable them to draw any conclusions about how long maintenance treatment should be continued.<br><br>**Children**<br>There were no studies on azathioprine or mercaptopurine for maintenance of remission in children. The GDG agreed that because of the lack of any paediatric data it was acceptable to extrapolate from adult studies and to make the same recommendations as for adults. |

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### 6.5.5 Clinical question: methotrexate

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for maintenance of remission for 12 months or longer

- compared with placebo?
- *plus* conventional glucocorticosteroid treatment compared with placebo *plus* conventional glucocorticosteroid treatment?

### 6.5.6 Clinical evidence: methotrexate

A Cochrane review of methotrexate for maintenance in Crohn's disease was published in 2009[209]. The Cochrane review included three studies[84,173,207], but the review was excluded because the studies did not meet GDG inclusion criteria (Feagan followed up for 40 weeks, Mate-Jiminez meta-analysed for methotrexate vs. mercaptopurine with no placebo comparison and Oren randomised patients in active disease). However, one of these studies[84] (Feagan et al., 2000) met all GDG inclusion criteria other than length of follow-up and was included in preference to observational data to inform potential GDG decisions.

'Severe adverse events' in Feagan 2000 were not defined however patients had monthly serum aminotransferase levels and complete blood counts taken to monitor liver function and for leukopenia.

No paediatric RCTs were identified.

#### 6.5.6.1 Methotrexate versus placebo

**Table 48: Evidence profile: methotrexate versus placebo**

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality |
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Methotrexate | Placebo | Relative (95% CI) | Absolute | |
| **Maintenance of remission (follow-up 40 weeks),** Feagan 2000 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | none | 26/40 (65%) | 14/36 (38.9%) | RR 1.67 (1.05 to 2.67) | 261 more per 1000 (from 19 more to 649 more) | LOW |
| **Withdrawal due to adverse events (follow-up 40 weeks),** Feagan 2000 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 1/40 (2.5%) | 0/36 (0%) | RR 2.71 (0.11 to 64.43) | 0 more per 1000 (from 0 fewer to 0 more) | VERY LOW |
| **Severe adverse events (follow-up 40 weeks),** Feagan 2000 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 0/40 (0%) | 2/36 (5.6%) | RR 0.18 (0.01 to 3.64) | 46 fewer per 1000 (from 55 fewer to 147 more) | VERY LOW |

*1 Unclear allocation concealment.*
*2 Confidence interval crosses 1.25.*
*3 Confidence interval crosses 0.75 and 1.25.*

#### 6.5.6.2 Evidence statements - clinical

- In one RCT (n = 76)[84] of methotrexate for maintenance of remission of Crohn's disease, methotrexate was significantly more effective than placebo for maintenance of remission after 40 weeks (RR 1.67 [1.05 to 2.67]).[LOW QUALITY]
- In one RCT (n = 76)[84] of methotrexate for maintenance of remission of Crohn's disease, there was no significant difference in:
  - rates of severe adverse events (RR = 0.18 [0.01 to 3.64]).[VERY LOW QUALITY] or
  - withdrawals due to adverse events after 40 weeks (RR 2.71 [0.11 to 64.43]).[VERY LOW QUALITY]

### 6.5.7 Economic evidence

No published data were found relating to the cost effectiveness of methotrexate treatment for the maintenance of remission of Crohn's disease.

## 6.5.8 Linking evidence to recommendations

**Table 49: Linking evidence to recommendations – methotrexate for maintenance**

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| **Clinical question** | **In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for maintenance of remission for 12 months or longer**<br>• **compared with placebo?**<br>• **plus conventional glucocorticosteroid treatment compared with placebo plus conventional glucocorticosteroid treatment?** |
| **Recommendation** | **26. Consider methotrexate[i,c] to maintain remission only in people who:**<br>• **needed methotrexate to induce remission, or**<br>• **have tried but did not tolerate azathioprine or mercaptopurine for maintenance or**<br>• **have contraindications to azathioprine or mercaptopurine (for example, deficient TPMT activity or previous episodes of pancreatitis).**<br>*c Follow BNF/BNFC cautions on prescribing methotrexate.*<br>*i Although use is common in UK clinical practice, at the time of publication (October 2012) methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.* |
| **Relative values of different outcomes** | The key outcome of interest agreed prior to evidence evaluation was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population.<br><br>The GDG also agreed that for methotrexate trials, adverse events and withdrawals (due to side effects) were both important outcomes.<br><br>Data were also reported for this review if study withdrawal was noted to be due to drug effect (rather than non-compliance or other reasons for drop-out).<br><br>Mucosal healing has been more recently emphasized as an end-point, and may not be described in older papers. The relative value of this outcome was felt to be less important than maintenance of remission data. This is because the patchy way in which the disease affects the intestines limits the application of histological sampling. The GDG noted that none of papers reported mucosal healing outcomes for methotrexate and agreed that this outcome measure seemed to be more widely reported as an outcome for biological drugs.<br><br>No RCTs fulfilled the protocol inclusion criteria for methotrexate versus placebo maintenance of remission for 12 months or longer. For this reason the GDG accepted RCT data from the multicentre Feagan study of 40 weeks duration (rather than 12 months). |

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| | In addition, the GDG noted that no trials were found comparing methotrexate to glucocorticosteroid treatment or azathioprine (or mercaptopurine) for maintenance of remission of Crohn's disease. |
| **Trade off between clinical benefits and harms** | The GDG noted that for maintenance of remission at 40 weeks results favoured the methotrexate group over placebo (RR 1.67 CI 1.05 – 2.67). In relation to the trade off between clinical benefit and harms, there was no statistically significant difference between methotrexate and placebo for withdrawal due to adverse events and severe adverse events. The GDG noted that severe adverse events were noted in the placebo group (2/36) rather than the methotrexate group (0/40). |
| **Economic considerations** | Methotrexate was not included in the economic model due to the way the outcomes in the study were reported. Information on relapse and relapse plus withdrawal, which were used to parameterise treatment effects in the economic model could not be extracted from the Feagan study. |
| **Quality of evidence** | The GDG noted a Cochrane methotrexate systematic review however this was excluded (and used for quality assurance cross referencing purposes only) because the studies within it did not meet the GDG agreed protocol inclusion criteria. The studies within the Cochrane review were:<br>• Feagan (less than 12 months) – looked at separately see below<br>• Mate-Jiminez meta analysed for methotrexate versus mercaptopurine with no placebo comparison<br>• Oren (randomised in active disease)<br>• Feagan and Oren formally meta-analysed for methotrexate versus placebo.<br>In the absence of RCT evidence meeting the agreed protocol for methotrexate versus placebo, the GDG accepted the 40-week Feagan multicentre RCT of moderate quality with 76 participants. Whilst the trial result for maintenance of remission favoured methotrexate over placebo, the GDG noted that the trial used an intramuscular route of administration and without concomitant folic acid administration. The GDG considered the implications of different bioavailability and dose for different methods of administration, particularly where short bowel syndrome would significantly decrease oral bioavailability.<br><br>The GDG was also aware of the very low quality attributed to the adverse event outcome and very low quality withdrawal due to adverse events outcome (withdrawals due to adverse events methotrexate group 1/40 and nil in the placebo group). |
| **Other considerations** | The GDG recognised the limited evidence (one trial and hence no consistency of results) in favour of offering methotrexate, but noted the apparent value of the drug in other inflammatory conditions, particularly in the field of rheumatology.<br><br>Given the apparent efficacy of methotrexate in other conditions and lack of evidence for other drugs for maintenance of remission in Crohn's disease, the GDG debated why methotrexate was not more commonly prescribed. They thought in part that this was because of the known teratogenicity and side effects which were perceived by the GDG from clinical experience to be worse than other drugs. |

The GDG thought it unlikely that further research would be conducted in this area as methotrexate is considered to be an older, off-patent and unlicensed (for Crohn's disease) drug – it would be unlikely that anyone would sponsor further research in this field.

The GDG also discussed whether looking at lower levels of evidence would be of benefit in defining the eventual recommendation. The GDG were aware of descriptive case series that lacked controls and hence suffered from bias and problems with interpretation. The GDG agreed that on this basis they did not wish to explore lower evidence levels.

When thinking about a recommendation the GDG agreed that there is a limited amount of evidence that methotrexate maybe effective for preventing relapse in some groups of people. However, the GDG noted that the vast majority of patients in this single RCT were immunosuppressive naive (98%). On this basis as well as the clinical experience of the group, that the GDG concluded that this data could not justify a potential recommendation for methotrexate to be offered second-line in the event that azathioprine or mercaptopurine fails to maintain remission.

The GDG reflected upon current clinical practice and drug pathways. They agreed that methotrexate is currently offered for people who have not responded to glucocorticosteroid induction treatment *and* who have been intolerant of azathioprine. The GDG also acknowledged that methotrexate may have been commenced for active disease and then continued as maintenance treatment. Hence clinical experience of the GDG highlighted two potential areas where methotrexate fits a drug pathway. The GDG also noted that the drug is used when there is co-existing inflammatory arthropathy (an IBD associate arthritis or rheumatoid arthritis) as it treats both conditions, but they acknowledged that this fell outside the remit of the scope. Thus, the group made a 'consider' recommendation that methotrexate may be continued if it had been used successfully to induce remission, or when people had tried azathioprine or mercaptopurine for maintenance but it wasn't tolerated or if they have contraindications to treatment with azathioprine or mercaptopurine.

**Children**

There were no studies on methotrexate for maintenance of remission in children. The GDG agreed that ibecause of the lack of any paediatric data it was acceptable to extrapolate from adult studies and to make the same recommendations as for adults.

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## 6.6 Linking evidence to recommendations – maintaining remission summary

**Table 50: Linking evidence to recommendations –all people with Crohn's disease**

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| **Clinical question**<br><br>**Recommendations** | **After inducing remission of an inflammatory exacerbation of Crohn's disease, what is the most effective way to maintain remission? (Questions 6 - 10)**<br><br>**21. Discuss with people with Crohn's disease, and/or their parents or carers if appropriate, options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. Record the person's views in their notes.**<br>**22. Offer colonoscopic surveillance in line with 'Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas' (NICE clinical guideline 118).** |
| **Relative values of different outcomes** | The key outcome of interest agreed prior to evidence evaluation was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population. |
| **Trade off between clinical benefits and harms** | The GDG reflected upon the balance of effectiveness and safety of all the interventions reviewed and the economic model results.<br><br>The GDG concluded that 'no maintenance treatment' is a rational option for some people, particularly those in whom relapse risk is low, who are concerned about side effects of long-term drug treatment or whose disease tends to follow a mild to moderate course – please see<br><br>Table 51 for consensus recommendations and the GDG deliberations.<br><br>For theGDG debate about maintenance treatment for those who do choose this option, please see 'Linking evidence to recommendations' sections 6.2.4, 6.3.4, 6.4.4, 6.5.4 and 6.5.8. |
| **Economic considerations** | NICE clinical guideline 118 recommends a cost-effective strategy for colonoscopic screening, based on a person's risk of developing cancer. |
| **Quality of evidence** | The GDG made a consensus recommendation about follow-up and advice for people choosing no treatment after remission of an exacerbation is induced.<br><br>The GDG agreed that the following should be discussed with the person with Crohn's disease before deciding on a course of action:<br>• risks of relapse with and without active treatment<br>• risks of complications such as fistulae and strictures with and without active treatment, (although complications were not formally reviewed) as well as |

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| | • potential side effects of active treatment.<br>The group also agreed the importance of making people aware of the need for colonoscopic surveillance. |
| **Other considerations** | **Children**<br>The GDG agreed similar principles for decisions about maintenance treatment in children. However, they agreed that the considerations specific to paediatric practice may alter the balance of judgement in each child or young person, for example, growth and unknown long-term side effects. |

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**Table 51: Linking evidence to recommendations – maintaining remission for those who choose not to receive maintenance treatment**

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| **Clinical question**<br><br>**Recommendations** | **After inducing remission of an inflammatory exacerbation of Crohn's disease, what is the most effective way to maintain remission? (Questions 6 - 10)**<br><br>**Follow-up during remission for those people who choose not to receive maintenance treatment**<br>**23. When people choose not to receive maintenance treatment:**<br>**• discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see**<br>**• ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill health).**<br>**• ensure they know how to access the healthcare system if they experience a relapse**<br>**• discuss the importance of not smoking.** |
| **Relative values of different outcomes** | The key outcome of interest agreed prior to evidence evaluation was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population. |
| **Trade off between clinical benefits and harms** | The GDG reflected upon the balance of effectiveness and safety of all the interventions reviewed. They concluded that 'no maintenance treatment' is a rational option for some people, particularly those in whom relapse risk is low, who are concerned about side effects of long-term drug treatment or whose disease tends to follow a mild to moderate course. |
| **Economic considerations** | The clinical effectiveness evidence in support of maintenance drug therapy identified and analysed in the systematic review of this guideline was not that strong. For those patients who choose not to receive drug maintenance, lifestyle advice is likely to be cost effective. |
| **Quality of evidence** | The GDG made a consensus recommendation about follow-up and advice for people choosing no treatment after remission of an exacerbation is induced. |
| **Other considerations** | **Children**<br>The GDG agreed similar principles for decisions about maintenance treatment in children. However, they agreed that the considerations specific to paediatric practice may alter the balance of judgement in each child or young person, for example, growth and unknown long-term side effects. |

## 6.7 Health economic maintenance model summary

### 6.7.1 Original economic analysis

The GDG considered the clinical evidence with regard to maintenance of remission and noted the superiority of azathioprine. The GDG noted that acquisition cost of azathioprine is relatively low, however this does not account for costs of monitoring, consultations, treatment withdrawal or downstream costs due to treatment failure. Maintenance of remission was identified as high priority by the GDG in the early stages of guideline development, since this topic is potentially relevant for most patients with Crohn's disease. Some economic literature was identified, however no studies rated highly in terms of applicability or quality.

### 6.7.2 Methods

#### 6.7.2.1 Model overview

A cost-utility analysis was undertaken where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective. A Markov model was constructed in order to estimate costs and QALYs associated with different treatment strategies for medical maintenance of remission. Uncertainty was explored through probabilistic and univariate sensitivity analyses. A two year time horizon was considered in the base case to reflect the duration of the RCTs used to parameterise treatment effects.

#### 6.7.2.2 Population

The population entering the model comprised people with medically induced remission of Crohn's disease, defined by a Crohn's Disease Activity Index (CDAI) score of < 150.

#### 6.7.2.3 Comparators

The comparators examined in the model were the same as those compared in the clinical review:

- no treatment
- azathioprine
- mesalazine
- olsalazine
- budesonide
- glucocorticosteroid

It should be noted that although they were combined in the clinical review, mesalazine and olsalazine were separated in the economic analysis due to potential differences in costs and side-effect profiles.

#### 6.7.2.4 Model structure and key assumptions

A Markov model was constructed, whereby the QALY gain was driven by the amount of time people spend in remission and active disease. Active disease was defined as a CDAI score of > 150.

Due to the way withdrawals were reported in the RCTs, two separate analyses were conducted for the clinical review, a non-conservative analysis where only the 'relapse' outcome was analysed, and conservative analysis where 'relapse + withdrawals' was analysed. Treatment effects in the economic model were parameterised so as to account for these two different methods. For the non-conservative analysis in the economic model, withdrawals and relapses were treated separately so that people who withdrew from treatment were still assumed to be in remission (although from this

point their risk of relapse reverts back to the risk associated with no treatment). For the conservative analysis in the economic model, people who withdrew were assumed to be in relapse.

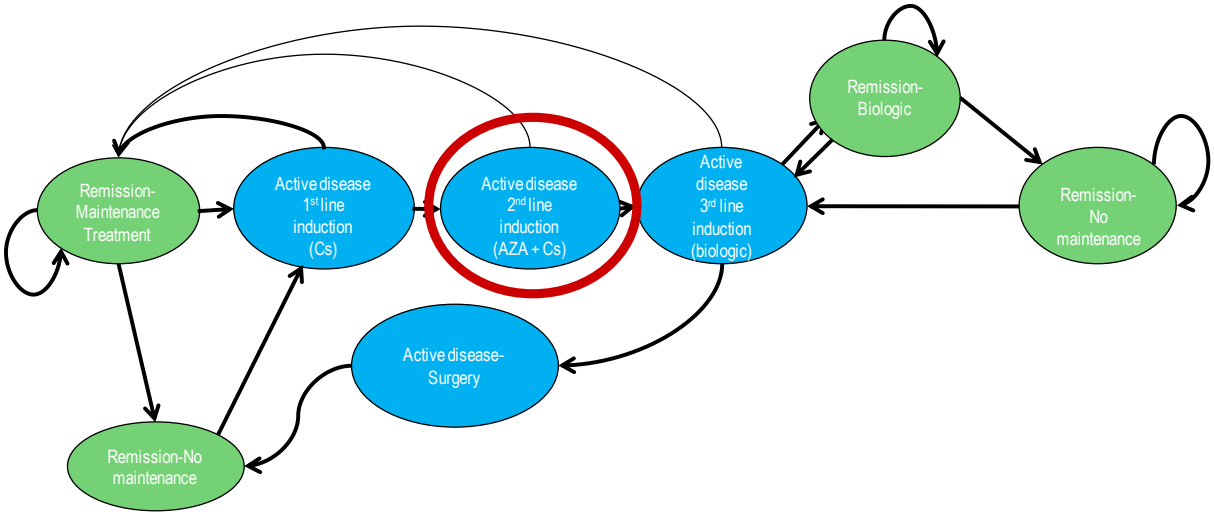
The GDG advised that people in relapse should be treated with the induction sequence that was found to be most cost-effective in the induction of remission model (a glucocorticosteroid, followed by azathioprine + a glucocorticosteroid then a biologic). The GDG were uncertain as to what the induction sequence should be for people who relapse while on azathioprine maintenance treatment. People who relapse on azathioprine treatment are likely to have a glucocorticosteroid or biologic induction therapy *added* to their azathioprine regimen, and therefore initiation of azathioprine induction therapy in these people is not relevant as they are already taking azathioprine. One plausible alternative was to assume a three-line induction sequence for azathioprine (a glucocorticoteroid – a biologic – surgery) but a four-line sequence (a glucocorticoteroid – azathioprine + a glucocorticosteroid- a biologic – surgery) for the other maintenance strategies but this three-line sequence is less cost-effective and this may potentially bias the assessment. This scenario was explored, but an analysis where there was a three-line induction sequence (a glucocorticoteroid – a biologic – surgery) for *all* maintenance strategies was also conducted in order to address this potential imbalance. In this analysis only the maintenance treatment varies between comparators and not the induction sequence but this is probably only a reasonable comparison for people who have had a recent history of severe disease and so would necessitate more urgent treatment.

The analysis was therefore conducted in four different ways:

- Conservative treatment effects -three lines of induction treatment (including surgery) for people relapsing on azathioprine, four lines of induction treatment for all other people (Cons 4L).
- Non-conservative treatment effects - three lines of induction treatment (including surgery) for people relapsing on azathioprine, four lines of induction treatment for all other people (Non-cons 4L).
- Conservative treatment effects - three lines of induction treatment (including surgery) for all people in relapse (Cons 3L).
- Non-conservative treatment effects- three lines of induction treatment (including surgery) for all people in relapse (Non-cons 3L).

The model structure is shown in Figure 5. Note that in the third and fourth analyses described above, the circled health state was omitted for people relapsing on azathioprine maintenance treatment. It was also omitted from the conservative three-line and non-conservative three-line models.

**Figure 5: Health states in the maintenance of remission economic model**




Key assumptions:

- People enter the model in the remission state on the maintenance treatment considered
- People who relapse enter the acute induction treatment sequence
- People in whom remission is successfully re-induced on first or second line induction treatment go back on their initial maintenance treatment
- People who fail induction on biologics undergo surgery
- If remission is successfully induced on biologics, people stay on biologics until either:
  - **Failure**: where they undergo dose escalation (equivalent to re-induction using biologics) and have then the probability of either :
    - responding and being put again on maintenance dose or
    - not responding and go to surgery
  - **Completion of 12 months**: where they are reassessed and
    - if in remission they go on to no maintenance treatment
    - if not they undergo dose escalation (i.e. re-induction) and go back to the start of the sequence.

### 6.7.2.5 Model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources, including expert opinion provided by the GDG, as required. Model inputs were validated by the GDG. All event numbers were taken from the guideline's clinical review. However, since relapse was modelled conditional on no withdrawal in the non-conservative analyses, in calculating non-conservative effect-sizes, any studies that reported relapse but not withdrawal were excluded.

### 6.7.3 Results

#### 6.7.3.1 Base case

The cost effectiveness analysis found that, in most cases azathioprine was the most cost-effective treatment for maintenance of remission of Crohn's disease. The incremental cost-effectiveness ratios (ICERs) for each treatment vs no treatment are shown inTable 52.

**Table 52: Incremental cost-effectiveness ratios in maintenance of remission model**

| Maintenance treatment | Cost per QALY gained compared with No treatment | | | |
|---|---|---|---|---|
| | Cons 3L | Non-cons 3L | Cons 4L | Non-cons 4L |
| No treatment | comparator | comparator | comparator | comparator |
| Azathioprine/ mercaptopurine | Dominates | Dominates | £21,128 | Dominates |
| Mesalazine | Dominates | Dominates | £25,133 | £20,319 |
| Budesonide | £15,070 | £65,013 | £40,392 | £87,610 |
| Glucocorticosteroid | Dominated | Dominates | Dominated | Dominates |
| Olsalazine | Dominated | Dominated | Dominated | Dominated |
| Optimal strategy at £20,000 per QALY | Azathioprine/ mercaptopurine | Azathioprine/ mercaptopurine | No treatment | Azathioprine/ mercaptopurine |

Table 53 shows the cost-effectiveness rankings in each analysis.

**Table 53: Cost-effectiveness rankings**

| Maintenance treatment | Cost-effectiveness rankings (95% CI) | | | |
|---|---|---|---|---|
| | Cons 3L | Non-cons 3L | Cons 4L | Non-cons 4L |
| No treatment | 4 (2,5) | 4 (2,6) | 1 (1,4) | 3 (2,5) |
| Azathioprine/ mercaptopurine | 1 (1,5) | 1 (1,1) | 2 (1,6) | 1 (1,5) |
| Mesalazine | 2 (1,5) | 2 (1,6) | 3 (1,5) | 4 (2,6) |
| Budesonide | 3 (1,5) | 5 (2,6) | 4 (1,5) | 5 (2,6) |
| Glucocorticosteroid | 5 (1,6) | 3 (2,6) | 5 (1,6) | 2 (1,6) |
| Olsalazine | 6 (5,6) | 6 (2,6) | 6 (4,6) | 6 (2,6) |

The analysis shows that in the base case:

- Azathioprine was dominant compared with no treatment and ranked as the most cost-effective treatment option in all cases apart from the conservative four-line induction analysis where it was associated with an ICER of £21,000 per QALY gained vs no treatment.
- The ICER for mesalazine compared with no treatment ranged from being dominant to £25,000 per QALY gained in the 3L and 4L analyses respectively. But in all four base case analyses, azathioprine was more cost-effective than mesalazine. In the case where mesalazine was dominant vs no treatment, mesalazine was dominated by azathioprine. In the case where mesalazine was associated with an ICER of £25,000 per QALY gained, the ICER for azathioprine vs mesalazine was £18,000 per QALY gained, showing that azathioprine was still the most cost-effective treatment at a willingness to pay threshold of £20,000 per QALY.
- The ICER for budesonide ranged from £15,000 to £88,000 per QALY gained in non-conservative and conservative analyses respectively.
- Prednisolone ranged from being dominant to dominated in conservative and non-conservative analyses respectively, showing there is a large amount of uncertainty in its cost-effectiveness.
- Olsalazine was dominated in all analyses.

#### 6.7.3.2 Univariate sensitivity analysis

In total, seven univariate sensitivity analyses were conducted, whereby, for each analysis one key model input was changed in order to explore the sensitivity of model results to changes in that parameter. Key changes in the cost-effectiveness ranking are summarised below according to the type of analysis:

- Conservative four-line: no treatment ranked first in all sensitivity analyses except:
    a. Ten-year time horizon: mesalazine ranked first
    b. Baseline relapse rate increased from 52% to 60% - mesalazine ranked first.
- Non-conservative four-line: azathioprine ranked first in all sensitivity analyses except:
    a. Baseline relapse rate decreased from 39% to 11% - no treatment ranked first.
- Conservative three-line: azathioprine ranked first in all sensitivity analyses except:
    a. Baseline relapse rate decreased from 52% to 11% - no treatment ranked first.
- Non-conservative three-line: azathioprine ranked first in all sensitivity analyses.

#### 6.7.3.3 Probabilistic sensitivity analysis

A probabilistic analysis was carried out whereby distributions were assigned to treatment effects, utilities and, where possible, costs in order to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.

Model outputs were very uncertain; this is in part due to the inclusion of the induction model treatment sequence and the associated uncertainty of the efficacy inputs.

The cost effectiveness of azathioprine was most certain in the non-conservative three-line model where, at a willingness-to-pay threshold of £20,000 per QALY the lower limit of the 95% confidence interval of the ranking of azathioprine was one and the probability of azathioprine being most cost-effective was 98%.

The cost-effectiveness of azathioprine was least certain in the conservative four-line model where, at a willingness-to-pay threshold of £20,000 per QALY, azathioprine was ranked second with 95% confidence interval ranging from first to sixth. In this analysis, the probability of azathioprine being the most cost-effective treatment was 41%.

### 6.7.4 Limitations and interpretation

This model was based on findings from RCTs included in the guideline's review and therefore any issues concerning interpretation in the clinical review also apply to interpretation of the economic analysis. Limitations of the model include:

- The utility loss and treatment cost associated with treatment-related adverse events were not explicitly incorporated. This is likely to mean the cost effectiveness of all the treatment strategies has been overestimated in the economic analysis, though since each treatment is likely to have a different side-effect profile, it is unlikely that ICERs have been underestimated by the same magnitude for all treatment strategies. For treatment strategies with more severe side effects, the over estimation of the ICER is likely to be higher than in treatment strategies with less severe side-effect profiles.
- No clinical review was conducted on the efficacy of biologic treatments as this was outside of the Crohn's disease guideline remit therefore efficacy data were derived from the two studies from within the NICE biologics Technology Appraisal[198].
- Efficacy for azathioprine in the model is based on withdrawal trials and thus any conclusions regarding its cost effectiveness should be made in this context. The participants in these trials were, by definition those who had already achieved a stable remission with azathioprine, and therefore more likely to experience continued remission if randomised to azathioprine than a patient who has not previously tried the drug.It is difficult to incorporate severity of disease with precision, since both the trial and utility evidence tends to dichotomise outcomes to active disease and remission, whereas in reality there is a blurred line between active disease and remission. Furthermore relapses vary in terms of their severity.
- The conclusions from this model relate to which maintenance treatment to use once it has been decided to put a patient on maintenance treatment. The model is not designed to answer the question of when exactly a patient should be put on maintenance treatment.

### 6.7.5 Generalisability to other populations and settings

It should be noted that all of the findings from this cost-effectiveness analysis relate to an adult population and the conclusions may not apply to paediatric treatment. It was not possible to conduct a separate model for children due to the paucity of both clinical and quality of life studies conducted in this area.

### 6.7.6 Conclusion evidence statement

The original cost-effectiveness analysis conducted for this guideline suggests that azathioprine is the most cost-effective treatment for maintenance of remission in Crohn's disease, although there was considerable uncertainty related to interpretation of withdrawals in the trials and the induction sequence assumed for people who relapse.

## 6.8 Recommendations for maintenance of remission

**21.Discuss with people with Crohn's disease, and/or their parents or carers if appropriate, options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. Record the person's views in their notes.**

**22.Offer colonoscopic surveillance in line with 'Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas' (NICE clinical guideline 118).**

**Follow-up during remission for those who choose not to receive maintenance treatment**

**23.When people choose not to receive maintenance treatment:**

- **discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see**
- **ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill health)**
- **ensure they know how to access the healthcare system if they experience a relapse**
- **discuss the importance of not smoking.**

**Maintenance treatment for those who choose this option**

**24.Offer azathioprine or mercaptopurine[h] as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission.**

**25.Consider azathioprine or mercaptopurine[h] to maintain remission in people who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations).**

**26.Consider methotrexate[c] to maintain remission only in people who:**

- **needed methotrexate to induce remission, or**
- **have tried but did not tolerate azathioprine or mercaptopurine for maintenance or**
- **have contraindications to azathioprine or mercaptopurine (for example, deficient TPMT activity or previous episodes of pancreatitis).**

**27.Do not offer a conventional glucocorticosteroid or budesonide to maintain remission.**

**See recommendations 11 and 12 for guidance on monitoring the effects of azathioprine, mercaptopurine and methotrexate.**

**See recommendation 16 for when to continue infliximab or adalimumab during remission.**

## 6.9 Research recommendation

**2. Following successful medical induction of remission of Crohn's disease of the colon, is mesalazine more clinically and cost effective than no treatment?**

The evidence for use of this group of drugs for maintenance of remission in Crohn's disease is not clear, and in particular, there is very limited reporting of disease site. It is possible that this might be a cost-effective treatment for maintenance of remission, with limited toxicity. Its use in this setting may therefore be associated with higher rates of successful maintenance of disease remission, reduced need for escalation of therapy, higher quality of life, and lower rates of hospital admissions and surgeries. The question is applicable to adults, children and young people, and trials in all are therefore required. A conventional glucocorticosteroid would be offered to induce remission in a first presentation of colonic Crohn's disease. Patients would be recruited once in remission and glucocorticosteroid-free and randomised to receive mesalazine or placebo, for maintenance of remission. Co-primary end-points would be quality of life measures and maintenance of glucocorticosteroid-free remission measured by the Crohn's disease activity index (CDAI). Secondary end-points would be mucosal healing at endoscopy, need for escalation of therapy to azathioprine or biological therapy, adverse events, hospitalisation and surgery. The time frame for follow-up should be at least 12 months, but ideally 24-36 months.

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*c Follow BNF/BNFC cautions on prescribing methotrexate.*

*h Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*i Although use is common in UK clinical practice, at the time of publication (October 2012) methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

# 7 Maintaining remission after surgery

## 7.1 Introduction

There is currently no treatment that cures Crohn's disease. Patients who require surgery are usually those with symptoms due to the development of a mechanical lesion such as a stricture causing obstruction or chronic perforation resulting in fistulation despite medical treatment. Despite medical treatment for severe Crohn's disease, continued ill-health is another indication for surgery.

Those patients who have surgery for Crohn's disease remain at risk of developing recurrent disease. Rates of second surgery were 33% at five years and 44% at ten years after the first intestinal resection.[24]

Following resection, inflammation can occur close to the anastomosis or develop in previously normal bowel. The severity of early endoscopic recurrence is related to the chance of developing subsequent symptoms and the need for further surgery.[205,230]

The question whether medical treatment is effective in helping to maintain remission after surgical resection of intestine involved by Crohn's disease is therefore important. A number of different drugs have been used with the aim of reducing the chance of recurrence after surgery including 5-ASA, glucocorticosteroid treatment and immunosuppressives.[93] Metronidazole has also been used after surgery to reduce post-surgical recurrence.

The effectiveness of maintenance medical treatment in reducing recurrence requires formal analysis.

Patient vignette

*Many patients do everything right; but the disease just keeps coming back. That's frustrating for the medical team, but completely devastating for the patient and their family.*

## 7.2 Clinical questions

In adults and children what is the clinical and cost effectiveness of post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer of

- conventional glucocorticosteroid treatment
- budesonide
- 5-aminosalicylate treatment
- azathioprine
- mercaptopurine
- methotrexate
- metronidazole or
- combinations thereof
- or nutritional treatment

compared with

- placebo
- no treatment?

## 7.3 Clinical evidence

Two Cochrane reviews[68,107] have addressed interventions for post-surgical recurrence of Crohn's disease. However, due to differences in inclusion criteria, an independent review was undertaken for this guideline.

Doherty et al[68] included studies which compared treatments outside the scope of this guideline and also reviewed trials of dose comparisons. Length of treatment protocols differed in some cases and finally, further differences were noted in the use of non-English studies and abstracts.

The Gordon et al[107] Cochrane review was based upon nine RCTs. Six of these trials[13,31,78,123,157,180] were included in both Cochrane reviews and also met the inclusion criteria for the guideline review. One study[299] was not included in Doherty et al but also met the guideline inclusion criteria. One study[79] was published in German. One study[271] included only per protocol data and was therefore excluded. The Cochrane reviews were utilised for quality assurance.

No studies comparing azathioprine with placebo were identified; however one study[123] compared mercaptopurine and placebo. There were no studies identified which compared methotrexate with placebo. There was no RCT evidence for enteral nutrition. As randomised placebo controlled trials are difficult to conduct for this nutritional intervention, it was agreed that observational data would be reviewed. There were no studies which assessed treatment in the paediatric population.

Two analyses of relapse events were conducted. The primary analysis included all events defined as relapse by the trial protocol; a secondary analysis took account of dropouts/withdrawals and included these patients in the relapse events. Random effects models were run if heterogeneity was present. A minimum treatment length of 12 months was specified with the exception of metronidazole as it was considered that long-term treatment with this antibacterial was not accepted medical practice.

## 7.4 5-ASA treatment

**Table 54: Evidence profile: 5-ASA versus placebo – maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Mesalazine | Placebo | Relative (95% CI) | Absolute | |
| **Relapse at one year (follow-up one year; assessed with: CDAI and control charts);** Wenkert 1977, Brignola 1995, Ewe 1989 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 29/187 (15.5%) | 51/198 (25.8%) | RR 0.6 (0.4 to 0.91) | 103 fewer per 1000 (from 23 fewer to 155 fewer) | LOW |
| **Relapse + withdrawal at one year (follow-up one year; assessed with: CDAI and control charts);** Wenkert 1977, Brignola 1995, Ewe 1989 | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 73/187 (39%) | 95/198 (48%) | RR 0.82 (0.65 to 1.03) | 86 fewer per 1000 (from 168 fewer to 14 more) | LOW |
| **Clinical remission one year (follow-up one year; assessed with: CDAI > 150);** Brignola 1995 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 31/44 (70.5%) | 29/43 (67.4%) | RR 1.04 (0.79 to 1.39) | 27 more per 1000 (from 142 fewer to 263 more) | MODERATE |
| **Withdrawal due to adverse events one year (follow-up one year);** Brignola 1995 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4] | none | 5/44 (11.4%) | 3/43 (7%) | RR 1.63 (0.41 to 6.4) | 44 more per 1000 (from 41 fewer to 377 more) | LOW |
| **Clinical relapse at 18 months (follow-up 18 months; assessed with: CDAI and control charts);** Lochs 2000, Wenkert 1977 | | | | | | | | | | | |
| 2 | randomised trials | serious[5] | no serious inconsistency | no serious indirectness | serious[2] | none | 40/184 (21.7%) | 59/200 (29.5%) | RR 0.74 (0.52 to 1.04) | 77 fewer per 1000 (from 142 fewer to 12 more) | LOW |
| **Clinical relapse + withdrawal at 18 months (follow-up 18 months; assessed with: CDAI);** Lochs 2000 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 45/152 (29.6%) | 55/166 (33.1%) | RR 0.89 (0.64 to 1.24) | 36 fewer per 1000 (from 119 fewer to 80 | MODERATE |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | more) | |
| **Endoscopic relapse at 18 months (follow-up 18 months; assessed with: CDAI);** Lochs 2000 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3,] | none | 40/61 (65.6%) | 36/72 (50%) | RR 1.31 (0.98 to 1.76) | 155 more per 1000 (from 10 fewer to 380 more) | MODERATE |
| **Maintenance of remission at 18 months (follow-up 18 months; assessed with: CDAI);** Lochs 2000 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 107/152 (70.4%) | 111/166 (66.9%) | RR 1.05 (0.91 to 1.22) | 33 more per 1000 (from 60 fewer to 147 more) | HIGH |
| **Serious adverse events at 18 months (follow-up 18 months; assessed with: CDAI);** Lochs 2000 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4] | none | 8/152 (5.3%) | 9/166 (5.4%) | RR 0.97 (0.38 to 2.45) | 2 fewer per 1000 (from 34 fewer to 79 more) | LOW |
| **Relapse at two years (follow-up two years; assessed with: CDAI and clinical grading scale);** Ewe 1989 Hanauer 2004 | | | | | | | | | | | |
| 2 | randomised trials | very serious[6,7] | no serious inconsistency | no serious indirectness | serious[2,] | none | 53/155 (34.2%) | 77/161 (47.8%) | RR 0.69 (0.53 to 0.9) | 148 fewer per 1000 (from 48 fewer to 225 fewer) | VERY LOW |
| **Relapse + withdrawal at two years (follow-up two years; assessed with: CDAI and clinical grading scale);** Ewe 1989 Hanauer 2004 | | | | | | | | | | | |
| 2 | randomised trials | very serious[6,7] | no serious inconsistency | no serious indirectness | serious[2,] | none | 94/155 (60.6%) | 115/161 (71.4%) | RR 0.84 (0.72 to 0.98) | 114 fewer per 1000 (from 14 fewer to 200 fewer) | VERY LOW |
| **Endoscopic recurrence at two years (follow-up two years; assessed with: Rutgeerts score);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4,] | none | 28/44 (63.6%) | 26/40 (65%) | RR 0.98 (0.71 to 1.35) | 13 fewer per 1000 (from 189 fewer to 228 more) | LOW |
| **Radiologic recurrence at two years (follow-up two years; assessed with: Radiographic grading scale);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4] | none | 20/44 (45.5%) | 20/40 (50%) | RR 0.91 (0.58 to 1.42) | 45 fewer per 1000 (from 210 fewer to 210 more) | LOW |
| **Withdrawal due to adverse events at two years (follow-up two years; assessed with: Clinical grading scale);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4] | none | 6/44 (13.6%) | 4/40 (10%) | RR 1.36 (0.41 to | 36 more per 1000 (from 59 | LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 4.48) | fewer to 348 more) | |
| **Relapse at three years (follow-up three years; assessed with: CDAI);** Ewe 1989 | | | | | | | | | | | |
| 1 | randomised trials | serious[8] | no serious inconsistency | no serious indirectness | serious[2] | none | 42/111 (37.8%) | 58/121 (47.9%) | RR 0.79 (0.58 to 1.07) | 101 fewer per 1000 (from 201 fewer to 34 more) | LOW |
| **Relapse + withdrawals at three years (assessed with: CDAI);** Ewe 1989 | | | | | | | | | | | |
| 1 | randomised trials | serious[8] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 89/111 (80.2%) | 99/121 (81.8%) | RR 0.98 (0.86 to 1.11) | 16 fewer per 1000 (from 115 fewer to 90 more) | MODERATE |
| **Recurrence rate up to 72 months (follow-up 72 months; assessed with: Symptomatic disease);** McLeod 1995 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 27/87 (31%) | 31/76 (40.8%) | RR 0.76 (0.5 to 1.15) | 98 fewer per 1000 (from 204 fewer to 61 more) | MODERATE |

*1 Randomisation not described in Ewe 1989; randomisation and allocation concealment not described in Ewe 1989 and Wenckert 1977.*
*2 Confidence interval crosses default MID at 0.75.*
*3 Confidence interval crosses default MID at 1.25.*
*4 Confidence interval crosses default MID at 0.75 and 1.25.*
*5 Randomisation and allocation concealment not described in Weckert 1977.*
*6 Validation of assessment tool not described in Hanauer 2004.*
*7 Method of randomisation not described in Ewe 1989.*
*8 Method of randomisation and allocation concealment not described.*

#### 7.4.1.1 Evidence statements – clinical

- In a meta-analysis of three studies of 5-ASA vs. placebo (n = 385)[31,78,299] for prevention of post-surgical clinical relapse, there were significantly fewer relapses in the 5-ASA group after one year of treatment (RR 0.6 [0.4 to 0.91]).[LOW QUALITY]
- In a meta-analysis of three studies of 5-ASA vs. placebo(n = 385)[31,78,299] for prevention of post-surgical clinical relapse including all withdrawals, there was no significant difference between the groups after one year of treatment (RR 0.82 [0.65 to 1.03]).[LOW QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 87)[31] for maintenance of clinical remission at one year, there was no significant difference between groups (RR 1.04 [0.79 to 1.39]).[MODERATE QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 87) [31] for withdrawal due to adverse events at one year, there was no significant difference between groups (RR 1.63 [0.41 to 6.4]).[LOW QUALITY]
- In a meta-analysis of two studies of 5-ASA vs. placebo (n = 384)[157,299] for prevention of post-surgical clinical relapse, there was no significant difference between groups after 18 months of treatment (RR 0.74 [95% CI 0.52 to 1.04]).[LOW QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 318)[157] for prevention of post-surgical clinical relapse including all withdrawals, there was no significant difference between groups (RR 0.89 [0.64 to 1.24]) after 18 months of treatment.[MODERATE QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 133)[157] for prevention of post-surgical endoscopic relapse there was no significant difference between groups (RR 1.31 [0.98 to 1.76]) at 18 months.[MODERATE QUALITY]
- In one study comparing 5-ASA vs. placebo(n = 318)[157] for maintaining remission after surgery there was no significant difference between groups (RR 1.05.[ [0.91 to 1.22]) at 18 months [HIGH QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 318)[157] for post-surgical serious adverse events there was no significant difference between groups (RR 0.97 [0.38 to 2.45]) at 18 months.[LOW QUALITY]
- In a meta-analysis of two studies of 5-ASA vs. placebo (n = 316)[78,123]for prevention of post-surgical clinical relapse, there were significantly fewer relapses in the 5-ASA group after two years of treatment (RR 0.69 [0.53 to 0.9]).[VERY LOW QUALITY]
- In a meta-analysis of two studies of 5-ASA vs. placebo(n = 316)[78,123] for prevention of post-surgical clinical relapse including all withdrawals, there were significantly fewer relapses in the 5-ASA group after two years of treatment (RR 0.84 [95% CI 0.72 to 0.98]).[VERY LOW QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 84)[123] for prevention of post-surgical endoscopic relapse there was no significant difference between groups (RR 0.98 [0.71 to 1.35]) at two years.[LOW QUALITY]
- In one study comparing 5-ASA vs. placebo(n = 84)[123] for prevention of post-surgical radiographic relapse there was no significant difference between groups (RR 0.91 [0.58 to 1.42]) at two years.[LOW QUALITY]
- In one study comparing 5-ASA vs. placebo (n = 84)[123] for study withdrawal due to adverse events there was no significant difference between groups (RR 1.36 [0.41 to 4.48]) at two years.[LOW QUALITY]
- In one study comparing 5-ASA vs. placebo(n = 232)[78] for prevention of clinical relapse there was no significant difference between groups (RR 0.79 [0.58 to 1.07]) at three years.[MODERATE QUALITY]

- In one study comparing 5-ASA vs. placebo (n = 232)[78] for clinical relapse including all withdrawals, there was no significant difference between groups (RR 0.98 [0.86 to 1.11]) at three years.[LOW QUALITY]
- In one study comparing 5-ASA vs. placebo(n = 163)[180] for clinical relapse there was no significant difference between groups (RR 0.76 [0.5 to 1.15]) at up to 72 months.[MODERATE QUALITY]

### 7.4.2 Economic evidence

No published health economic data were found and primary health economic modelling was not conducted.

## 7.5 Mercaptopurine

**Table 55: Evidence profile: mercaptopurine versus placebo – for maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | MP | Control | Relative (95% CI) | Absolute | |
| **Relapse at two years (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 24/47 (51.1%) | 31/40 (77.5%) | RR 0.66 (0.48 to 0.91) | 263 fewer per 1000 (from 70 fewer to 403 fewer) | LOW |
| **Relapse + withdrawal at two years (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 32/47 (68.1%) | 35/40 (87.5%) | RR 0.78 (0.62 to 0.98) | 193 fewer per 1000 (from 17 fewer to 332 fewer) | LOW |
| **Endoscopic recurrence at two years (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 20/47 (42.6%) | 26/40 (65%) | RR 0.65 (0.44 to 0.98) | 228 fewer per 1000 (from 13 fewer to 364 fewer) | MODERATE |
| **Radiographic recurrence at two years (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 16/47 (34%) | 20/40 (50%) | RR 0.68 (0.41 to 1.13) | 160 fewer per 1000 (from 295 fewer to 65 more) | MODERATE |
| **Withdrawal due to adverse events at two years (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 9/47 (19.1%) | 4/40 (10%) | RR 1.91 (0.64 to 5.75) | 91 more per 1000 (from 36 fewer to 475 more) | LOW |

*1 Validation of assessment tool not described.*

*2 MID crosses default 0.75.*

*3 MID crosses default 0.75 and 1.25.*

#### 7.5.1.1 Evidence statements – clinical

- In one study comparing MP vs. placebo (n = 87)[123] for prevention of clinical relapse there were significantly fewer relapses in the AZA/MP group (RR 0.66 [0.48 to 0.91]) at two years.[LOW QUALITY]
- In one study comparing MP vs. placebo (n = 87)[123] for prevention of clinical relapse including all withdrawals, there were significantly fewer relapses in the AZA/MP group (RR 0.78 [0.62 to 0.98]) at two years.[LOW QUALITY]
- In one study comparing MP vs. placebo (n = 87)[123] for prevention of endoscopic relapse there were significantly fewer relapses in the AZA/MP group (RR 0.65 [0.44 to 0.98]) at two years.[MODERATE QUALITY]
- In one study comparing MP vs. placebo (n = 87)[123] for prevention of radiographic relapse there was no significant difference between groups (RR 0.68 [0.41 to 1.13]) at two years.[MODERATE QUALITY]
- In one study comparing MP vs. placebo (n = 87)[123] for study withdrawals due to adverse events there was no significant difference between groups (RR 1.91 [0.64 to 5.75]) at two years.[LOW QUALITY]

### 7.5.2 Economic evidence

No published health economic data were found and primary health economic modelling was not conducted.

## 7.6 Azathioprine or mercaptopurine

**Table 56: Evidence profile: azathioprine or mercaptopurine versus 5-ASA – for maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 5-ASA | AZA | Relative (95% CI) | Absolute | |
| **Clinical relapse at 24 months (CDAI and clinical recurrence grading scale; follow-up two years);** Ardizzone 2004, Hanauer 2004 | | | | | | | | | | | |
| 2 | randomised trials | very serious[1,2] | no serious inconsistency | no serious indirectness | serious[3] | none | 46/115 (40%) | 36/116 (34.20%) | RR 1.32 (0.94 to 1.84) | 109 more per 1000 (from 21 fewer to 287 more) | VERY LOW |
| **Relapse + withdrawal at 24 months (CDAI and clinical recurrence grading scale; follow-up two years);** Ardizzone 2004, Hanauer 2004 | | | | | | | | | | | |
| 2 | randomised trials | very serious[1,2] | no serious inconsistency | no serious indirectness | serious[3] | none | 63/115 (54.8%) | 63/116 (56.50%) | RR 1.02 (0.81 to 1.28) | 11 more per 1000 (from 107 fewer to 158 more) | VERY LOW |
| **Surgical relapse at 24 months (Symptoms refractory to medical treatment; follow-up two years);** Ardizzone 2004 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[4] | none | 7/71 (9.9%) | 4/69 (5.80%) | RR 1.7 (0.52 to 5.55) | 41 more per 1000 (from 28 fewer to 264 more) | VERY LOW |
| **Withdrawal due to adverse events at 24 months (CDAI and clinical recurrence grading scale; follow-up two years);** Ardizzone 2004, Hanauer 2004 | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[5] | none | 12/115 (10.4%) | 24/116 (20.40%) | RR 0.51 (0.27 to 0.96) | 100 fewer per 1000 (from 8 fewer to 149 fewer) | LOW |
| **Endoscopic recurrence at 24 months (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 28/44 (63.6%) | 20/47 (42.60%) | RR 1.5 (1 to 2.23) | 213 more per 1000 (from 0 more to 524 more) | MODERATE |
| **Radiographic recurrence at 24 months (Clinical recurrence grading scale; follow-up two years);** Hanauer 2004 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 20/44 (45.5%) | 16/47 (34%) | RR 1.34 (0.8 to 2.23) | 116 more per 1000 (from 68 fewer to 418 more) | MODERATE |

*1 Allocation concealment not described in Ardizzone 2004; open label.*
*2 Validation of clinical outcome tool not described in Hanauer 2004.*
*3 Confidence interval crosses default MID at 1.25.*
*4 Confidence interval crosses default MID at 0.75 and 1.25.*
*5 Confidence interval crosses default MID at 0.75.*

#### 7.6.1.1 Evidence statements – clinical

- In a meta-analysis of two studies of 5-ASA vs. azathioprine/mercaptopurine (n = 231)[13,123] for prevention of post-surgical clinical relapse, there was no significant difference between groups after two years of treatment (RR 1.32 [0.94 to 1.84]).[VERY LOW QUALITY]
- In a meta-analysis of two studies of 5-ASA vs. azathioprine /mercaptpurine (n =231)[13,123] for prevention of post-surgical clinical relapse including all withdrawals, there was no significant difference between groups after two years of treatment (RR 1.02 [0.81 to 1.28]).[VERY LOW QUALITY]
- In a meta-analysis of two studies of 5-ASA vs. azathioprine /mercaptopurine (n = 231)[13,123] for study withdrawal due to adverse events, there were significantly fewer withdrawals in the 5-ASA group (RR 0.51 [0.27 to 0.96]) after two years of treatment.[LOW QUALITY]
- In one study comparing 5-ASA vs azathioprine (n = 140)[13] for prevention of surgical relapse there was no significant difference between groups (RR 1.7 [0.52 to 5.55]) at two years.[VERY LOW QUALITY]
- In one study comparing 5-ASA vs. mercaptopurine (n = 91)[123] for prevention of endoscopic recurrence there was no significant difference between groups (RR 1.5 [1 to 2.23]) at two years.[MODERATE QUALITY]
- In one study comparing 5-ASA vs.mercaptopurine (n = 91)[123] for prevention of radiographic recurrence there was no significant difference between groups (RR 1.34 [0.8 to 2.23]) at two years.[MODERATE QUALITY]

### 7.6.2 Economic evidence

Please see section 7.9.3 for details.

## 7.7 Budesonide

**Table 57: Evidence profile: budesonide versus placebo – for maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Budesonide | Placebo | Relative (95% CI) | Absolute | |
| **Recurrence based on CDAI at one year (CDAI follow-up one year);** Ewe 1999 Hellers 1999 | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 28/106 (26.4%) | 31/106 (28.9%) | RR 0.91 (0.59 to 1.4) | 26 fewer per 1000 (from 118 fewer to 116 more) | LOW |
| **Recurrence based on endoscopic findings at one year (Rutgeerts score; follow-up one year);** Ewe 1999 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 16/30 (53.3%) | 19/27 (70.4%) | RR 0.76 (0.5 to 1.15) | 169 fewer per 1000 (from 352 fewer to 106 more) | MODERATE |
| **Withdrawal due to treatment failure at one year (CDAI and Rutgeerts score; follow-up one year);** Ewe 1999 | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 3/43 (9.3%) | 7/40 (17.5%) | RR 0.53 (0.17 to 1.68) | 82 fewer per 1000 (from 145 fewer to 119 more) | LOW |
| **Withdrawal due to adverse events at one year (CDAI and Rutgeerts score; follow-up one year);** Ewe 1999, Hellers 1999 | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 6/106 (5.7%) | 6/106 (5.7%) | RR 1.03 (0.34 to 3.06) | 1 more per 1000 (from 33 fewer to 103 more) | LOW |
| **Withdrawal for any reason (CDAI and Rutgeerts score; follow-up one year) [fixed effect];** Ewe 1999, Hellers 1999 | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | serious inconsistency[5] | no serious indirectness | very serious[1] | none | 37/106 (34.9%) | 35/106 (34%) | RR 1.05 (0.72 to 1.53) | 17 more per 1000 (from 98 | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 185 more) | |
| **Withdrawal for any reason (CDAI and Rutgeerts score; follow-up one year) [random effects];** Ewe 1999, Hellers 1999 | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | serious inconsistency[5] | no serious indirectness | very serious[1] | none | 37/106 (34.9%) | 35/106 (34%) | RR 1.03 (0.59 to 1.77) | 10 fewer per 1000 (from 139 fewer to 254 more) | VERY LOW |
| **Endoscopic recurrence at new distal ileum at one year (Rutgeerts score; follow-up one year);** Hellers 1999 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 33/63 (52.4%) | 38/66 (57.6%) | RR 0.91 (0.66 to 1.24) | 52 fewer per 1000 (from 196 fewer to 138 more) | LOW |
| **Endoscopic recurrence at anastomosis at one year (Rutgeerts score; follow-up one year);** Hellers 1999 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[1] | none | 28/63 (44.4%) | 32/66 (48.5%) | RR 0.92 (0.63 to 1.33) | 39 fewer per 1000 (from 179 fewer to 160 more) | VERY LOW |

*1 MID crosses default at 0.75 and 1.25.*
*2 MID crosses default at 0.75.*
*3 Method of randomisation and allocation concealment not described in Heller 1999.*
*4 MID crosses default at 0.75.*
*5 $I^2$ 52%.*

#### 7.7.1.1 Evidence statements – clinical

- In a meta-analysis of two studies comparing budesonide vs. placebo (n = 212)[77,127] for clinical recurrence there was no significant difference between groups (RR 0.91 [0.59 to 1.4]) at one year.[LOW QUALITY]
- In one study comparing budesonide vs. placebo (n = 83)[77] for study withdrawal due to treatment failure, there was no significant difference between groups (RR 0.53 [0.17 to 1.68]) at one year.[LOW QUALITY]
- In a meta-analysis of two studies comparing budesonide vs. placebo (n = 212) [77,127] for study withdrawal due to adverse events, there was no significant difference between groups (RR 1.03 [0.34 to 3.06]) at one year.[VERY LOW QUALITY]
- In a meta-analysis of two studies comparing budesonide vs. placebo (n = 212)[77,127] for study withdrawal due to adverse events, there was no significant difference between groups (RR 1.05 [0.72 to 1.53] fixed effect; RR 1.03 [0.58, 1.77] random effects).[VERY LOW QUALITY]
- In one study comparing budesonide vs. placebo (n = 57)[77] for recurrence based on endoscopic findings at one year, there was no significant difference between groups (RR 0.76 [0.5 to 1.15]) at one year.[MODERATE QUALITY]
- In one study comparing budesonide vs. placebo (n = 129)[127] for endoscopic recurrence at new distal ileum there was no significant difference between groups (RR 0.91 [95% CI [0.66 to 1.24]) at one year.[LOW QUALITY]
- In one study comparing budesonide vs. placebo (n = 129)[127] for endoscopic recurrence at anastomosis there was no significant difference between groups (RR 0.92 [0.63 to 1.33]) at one year.[VERY LOW QUALITY]

### 7.7.2 Economic evidence

No published health economic data were found and primary health economic modelling was not conducted.

## 7.8 Enteral nutrition

**Table 58: Evidence profile: enteral nutrition versus placebo or normal diet - for maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Enteral nutrition | Non-EN | Relative (95% CI) | Absolute | |
| **Clinical recurrence (CDAI; follow-up one year);** Yamamoto 2007 | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 1/20 (5%) | 7/20 (35%) | RR 0.14 (0.02 to 1.06) | 301 fewer per 1000 (from 343 fewer to 21 more) | VERY LOW |
| **Endoscopic recurrence (Rutgeerts endoscopic score; follow-up one year);** Yamamoto 2007 | | | | | | | | | | | |
| 1 | observational studies | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 6/20 (30%) | 14/20 (70%) | RR 0.43 (0.21 to 0.89) | 399 fewer per 1000 (from 77 fewer to 553 fewer) | VERY LOW |

*1 Not randomised or blinded.*
*2 Confidence interval crosses default MID at 0.75.*

#### 7.8.1.1 Evidence statements- clinical

- In one prospective cohort study (n = 46)[309] comparing enteral nutrition with non-enteral nutrition, the clinical recurrence at one year was not significantly different (RR 0.14 [0.02 to 1.06]).[VERY LOW QUALITY]
- In one prospective cohort study (n = 40)[309] of endoscopic recurrence at one year, there were significantly fewer recurrences in the enteral nutrition group compared with the non-enteral nutrition group (RR 0.43 [0.21 to 0.89]).[VERY LOW QUALITY]

### 7.8.2 Economic evidence

No published health economic data were found and primary health economic modelling was not conducted.

## 7.9 Metronidazole

**Table 59: Evidence profile: metronidazole versus placebo (three months of treatment) - for maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Metronidazole | Placebo | Relative (95% CI) | Absolute | |
| **Clinical recurrence at one year (physician assessment; follow-up one year);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 2/29 (6.9%) | 7/28 (25%) | RR 0.28 (0.06 to 1.22) | 180 fewer per 1000 (from 235 fewer to 55 more) | VERY LOW |
| **Clinical recurrence at one year + withdrawals (physician assessment; follow-up one year);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 8/29 (27.6%) | 7/28 (25%) | RR 1.1 (0.46 to 2.64) | 25 more per 1000 (from 135 fewer to 410 more) | VERY LOW |
| **Clinical recurrence at two years (physician assessment; follow-up two years);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 7/29 (24.1%) | 12/28 (42.9%) | RR 0.56 (0.26 to 1.22) | 189 fewer per 1000 (from 317 fewer to 94 more) | VERY LOW |
| **Clinical recurrence + withdrawal (physician assessment; follow-up two years);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 13/29 (44.8%) | 12/28 (42.9%) | RR 1.05 (0.58 to 1.88) | 21 more per 1000 (from 180 fewer to 377 more) | VERY LOW |
| **Clinical recurrence at three years (physician assessment; follow-up three years);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/29 (31%) | 14/28 (50%) | RR 0.62 (0.32 to 1.2) | 190 fewer per 1000 (from 340 | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | fewer to 100 more) | |
| **Clinical recurrence at three years + withdrawals (physician assessment; follow-up three years);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 15/29 (51.7%) | 14/28 (50%) | RR 1.03 (0.62 to 1.72) | 15 more per 1000 (from 190 fewer to 360 more) | VERY LOW |
| **Endoscopic recurrence at three months (follow-up three months; Rutgeerts score);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[2] | none | 12/23 (52.2%) | 21/28 (75%) | RR 0.7 (0.45 to 1.09) | 225 fewer per 1000 (from 413 fewer to 68 more) | LOW |
| **Endoscopic recurrence at three years ( Rutgeerts score);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | no methodology chosen | serious[4] | no serious inconsistency | no serious indirectness | very serious[3] | none | 18/23 (78.3%) | 23/28 (82.1%) | RR 0.95 (0.72 to 1.26) | 41 fewer per 1000 (from 230 fewer to 214 more) | VERY LOW |
| **Withdrawal due to adverse events (physician/patient report; follow-up three years);** Rutgeerts 1995 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 5/29 (17.2%) | 0/28 (0%) | RR 10.63 (0.62 to 183.77) | - | VERY LOW |

*1 Method of randomisation and allocation concealment not described. Unvalidated clinical assessment.*
*2 Default MID crosses CI at 0.75.*
*3 Confidence interval crosses default MID at 0.75 and 1.25.*
*4 Method of randomisation and allocation concealment not described.*

#### 7.9.1.1 Evidence statements - clinical

- In one study comparing metronidazole vs. placebo (n = 57)[231] for prevention of clinical recurrence at one year (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 0.28 [0.06 to 1.22]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo + withdrawals (n = 57)[231] for clinical recurrence at one year (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 1.1 [0.46 to 2.64]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo (n = 57)[231] for clinical recurrence at two years (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 0.56 [0.26 to 1.22]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo + withdrawals (n = 57)[231] for prevention of clinical recurrence at two years (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 1.05 [0.58 to 1.88]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo (n = 57)[231] for prevention of clinical recurrence at three years (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 0.62 [0.32 to 1.2]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo + withdrawals (n = 57)[231] for prevention of clinical recurrence at three years (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 0.7 [0.45 to 1.09]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo (n=51)[231] for prevention of endoscopic recurrence at three months (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 0.7 [0.45 to 1.09]).[LOW QUALITY]
- In one study comparing metronidazole vs. placebo (n = 51)[231] for prevention of endoscopic recurrence at three years (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 0.95 [0.72to 1.26]).[VERY LOW QUALITY]
- In one study comparing metronidazole vs. placebo (n = 57)[231] for withdrawal due to adverse events at three years (after three months of treatment) there was no significant difference between metronidazole and placebo (RR 10.63 [0.62 to 183.77]).[VERY LOW QUALITY]

### 7.9.2 Economic evidence

One study was identified.[9] Please see section 7.9.3

**Table 60: Evidence profile: metronidazole plus azathioprine versus metronidazole plus placebo – for maintaining remission after surgery**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Metronidazole + AZA | Metronidazole + placebo | Relative (95% CI) | Absolute | |
| **Clinical recurrence at 12 months (CDAI; follow-up one year);** D'Haens 2008 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/40 (7.5%) | 7/41 (17.1%) | RR 0.44 (0.12 to 1.58) | 96 fewer per 1000 (from 150 fewer to 99 more) | VERY LOW |
| **Clinical recurrence + withdrawal at 12 months (CDAI; follow-up one year);** D'Haens 2008 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 11/40 (27.5%) | 19/41 (46.3%) | RR 0.59 (0.33 to 1.08) | 190 fewer per 1000 (from 310 fewer to 37 more) | LOW |
| **Endoscopic relapse at 12 months (Rutgeerts score; follow-up one year);** D'Haens 2008 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 14/40 (35%) | 20/41 (48.8%) | RR 0.72 (0.42 to 1.21) | 137 fewer per 1000 (from 283 fewer to 102 more) | LOW |
| **Endoscopic relapse + withdrawal at 12 months (Rutgeerts score; follow-up one year);** D'Haens 2008 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 22/40 (55%) | 32/41 (78%) | RR 0.7 (0.51 to 0.97) | 234 fewer per 1000 (from 23 fewer to 382 fewer) | LOW |
| **Withdrawal due to adverse events (CDAI; follow-up one year);** D'Haens 2008 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/40 (5%) | 2/41 (4.9%) | RR 1.02 (0.15 to | 1 more per 1000 | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 6.93) | (from 41 fewer to 289 more) | |

*1 Allocation concealment not described.*
*2 Confidence interval crosses default MID at 0.75 and 1.25.*
*3 Confidence interval crosses default MID at 0.75.*

#### 7.9.2.1 Evidence statements – clinical

- In one study comparing azathioprine + metronidazole vs. placebo + metronidazole (n = 81)[56] for prevention of clinical recurrence there was no significant difference between groups (RR 0.44 [0.12 to 1.58]) at one year.[VERY LOW QUALITY]
- In one study comparing azathioprine + metronidazole vs. placebo + metronidazole (n = 81)[56] for prevention of clinical recurrence including all withdrawals, there was no significant difference between groups (RR 0.59 [0.33 to 1.08]) at one year.[LOW QUALITY]
- In one study comparing azathioprine + metronidazole vs. placebo + metronidazole (n=81)[56] for prevention of endoscopic recurrence there was no significant difference between groups (RR 0.72 [0.42 to 1.21]) at one year.[LOW QUALITY]
- In one study comparing azathioprine + metronidazole vs. placebo + metronidazole (n = 81)[56] for prevention of endoscopic relapse including all withdrawals, there were significantly fewer relapses in the azathioprine + metronidazole group compared with the placebo + metronidazole group (RR 0.7 [0.51 to 0.97]) at one year.[LOW QUALITY]
- In one study comparing azathioprine + metronidazole vs. placebo + metronidazole (n = 81)[56] for prevention of clinical relapse there was no significant difference between groups (RR 1.02 [0.15 to 6.93]) at one year.[VERY LOW QUALITY]

### 7.9.3 Economic evidence

This is summarised in the economic evidence profile in Table 61 and Table 62. See also the full study evidence tables in Appendix F:. No studies were excluded.

**Table 61: Post-surgical medical maintenance of remission- economic study characteristics**

| Study | Limitations | Applicability | Other comments |
|---|---|---|---|
| Ananthakrishnan 2011 | Minor limitations [a] | Partially applicable [b] | Decision analysis based on meta analysis from Cochrane review |

*(a) Time horizon of one year reasonable given RCT data, and longer time horizon of three years explored in sensitivity analysis. Adverse events captured in terms of withdrawal from treatment, due to reporting from RCTs. Unclear if cost estimates come from the best source of data, but don't seem significantly different from UK equivalent. No probabilistic sensitivity analysis conducted, but model was run with upper and lower confidence intervals of treatment effect estimates. Deterministic sensitivity analysis conducted on baseline risk of relapse and low-high cost estimates.*

*(b) Addresses appropriate population and intervention. Health effect expressed in terms of Quality Adjusted Life Years. Conducted from US perspective; some drug costs reported are higher than in the current UK context. Discounting of costs and health outcomes not applicable in base case due to short time horizon; no mention of discounting of costs and outcomes in sensitivity analysis.*

**Table 62: Post-surgical medical maintenance of remission – economic summary of findings**

| Intervention | Total cost (base case)[(a)] | Total effects (base case) (QALYs) | Cost effectiveness base case | Uncertainty[(b)] |
|---|---|---|---|---|
| No treatment | £2,587 ($3,924) | 0.809 | Reference | Most cost-effective treatment in low risk patients<br>Dominated in the base case, and in high risk and very high risk patients. |
| Metronidazole | £1,872 ($2,840) | 0.821 | Dominant vs no treatment and azathioprine | Dominant vs azathioprine and no treatment in base case, high risk and very high risk patients.<br>ICER vs no treatment of £35,000 ($53,000) in low risk patients. |
| Azathioprine | £2,121 ($3,218) | 0.814 | Dominant vs no treatment, dominated by metronidazole | Dominant vs no treatment and dominated by metronidazole in base case, high risk and very high risk patients.<br>ICER vs no treatment of £24,000 ($37,000) in low risk patients. |

*(a)Costs converted from USA dollars to UK pounds using conversion factor of 0.66 taken from 2011 Purchasing power parity.*
*(b)Main sensitivity analysis conducted in the model was on baseline risk, where patients were classified as low risk, high risk and very high risk. Yearly relapse rates in the model for each sensitivity analysis were: Base case = 24%; low risk = 10%; high risk = 49%; very high risk = 78%.*

#### 7.9.3.1 Evidence statements - economic

- One partially applicable cost-effectiveness analysis with minor limitations found that for medical maintenance of post surgical remission in Crohn's disease:
  - azathioprine was dominant (i.e. less costly and more effective) compared with no treatment in moderate, high risk and very high risk patients
  - metronidazole maintenance was dominant (i.e. less costly and more effective) compared with azathioprine and no treatment in moderate, high risk and very high risk patients
  - azathioprine and metronidazole were associated with incremental cost-effectiveness ratios of £24,000 and £35,000 per QALY gained respectively in low risk patients.
- Costs and disutility associated with drug-specific adverse events were not explicitly incorporated into the analysis.

# 7.10 Linking evidence to recommendations

**Table 63: Linking evidence to recommendations – maintaining remission after surgery**

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| **Clinical question** | **In adults and children what is the clinical and cost effectiveness of post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer of**<br>• **conventional glucocorticosteroid treatment**<br>• **budesonide**<br>• **5-aminosalicylate treatment**<br>• **azathioprine**<br>• **mercaptopurine**<br>• **methotrexate**<br>• **metronidazole or**<br>• **combinations thereof**<br>• **or nutritional treatment**<br><br>**compared with**<br>• **placebo**<br>• **no treatment?** |
| **Recommendations** | **28. Consider azathioprine or mercaptopurine[h] to maintain remission after surgery in people with adverse prognostic factors such as:**<br>• **more than one resection, or**<br>• **previously complicated or debilitating disease (for example, abscess, involvement of adjacent structures, fistulising or penetrating disease).**<br>**29, Consider 5-ASA[k] treatment to maintain remission after surgery.**<br>**30. Do not offer budesonide or enteral nutrition to maintain remission after surgery.**<br>*h Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*<br>*k Although use is common in UK clinical practice, at the time of publication (October 2012) olsalazine, balsalazide and sulfasalazine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information. Some forms of mesalazine (Octasa MR, Mesren MR, Asacol MR) are licensed for maintaining remission in Crohn's ileo-colitis.* |
| **Relative values of different outcomes** | The value of these agents (with the exception of metronidazole) for maintaining remission has already been assessed in section 6. The question posed here for maintaining remission after surgery is clearly related, but not identical.<br><br>Firstly, although performing surgery will not alter the fundamental nature of Crohn's disease, there are additional factors which might be relevant to disease recurrence after surgery, for example bacterial overgrowth. More importantly, the question is not just about the ability of these treatments to prevent recurrence, but asks whether |

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| | maintenance therapy or one type in particular, should be started *routinely* after surgery.<br><br>Disease relapse, as assessed using clinical tools, was regarded by the GDG as the most important outcome, and their preferred tools were the CDAI or HBI as before. Unfortunately not all studies used the same cut-off points for disease relapse, and some studies used alternative measures. In addition, the studies reported relapse rates at different time points, for example one year, 18 months or two years. For these reasons pooling of data for meta-analysis was not possible in many instances. The GDG agreed relapse + withdrawals to be the conservative outcome measure for maintenance efficacy assessment and should therefore be the outcome measure informing recommendation decisions.<br><br>The GDG also felt that endoscopic evidence of relapse[17,94] should be given more weight in post-surgical studies than in those conducted in people with Crohn's disease under other circumstances. This is because some of the components of the CDAI can be affected by the surgical procedure itself. For example, following distal ileal resection it is common for people to develop bile acid diarrhoea. |
| **Trade off between clinical benefits and harms** | The GDG noted side effects where these were reported, but also referred to the work done in section 6 which considers the same agents outside the post-surgical setting. Metronidazole was not part of that review; the GDG noted that there is a significant risk of neurological toxicity with prolonged use of this agent.<br><br>Bearing in mind that none of the available agents are free from the potential to cause significant side effects, the GDG did not feel that the evidence supported a general recommendation in favour of routine maintenance treatment post-surgery. |
| **Economic considerations** | An economic evaluation of maintenance therapy specifically in post-surgery patients was not conducted. In the previous chapter, azathioprine appeared to be the most cost-effective maintenance strategy but there was high uncertainty in the estimates of cost-effectiveness. Furthermore, utility loss and treatment costs associated with adverse events were not captured in the model.<br><br>A partially applicable health economic analysis[8] with minor limitations was identified in this area. It was noted that this was an important paper for the GDG to consider, since original economic analysis was not conducted to address this question. The analysis was based on a decision model conducted from a US perspective and was rated as partially applicable since some of the costs used in the model were higher than the UK equivalent. The model compared azathioprine and metronidazole with no treatment. In the base case analysis, and in a sensitivity analysis for high-risk patients, metronidazole was the dominant strategy compared with both azathioprine and no maintenance. Azathioprine was dominant compared with no treatment in both these analyses, but dominated by metronidazole. Hence metronidazole was found to be associated with the highest increase in QALYs compared with both no treatment and aziothioprine. But utility loss due to drug-related side-effects of azathioprine and metronidazole were not explicitly modelled.. The GDG considered this to be a serious omission for metronidazole |

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| | given the neuropathy associated with it.<br><br>In people at low risk of relapse, neither metronidazole nor azathioprine was cost effective compared with no treatment at a cost-effectiveness threshold of £20,000 per QALY. |
| **Quality of evidence** | For most outcomes the quality was low or very low. The GDG concurred with this, noting that the studies were generally relatively small and many had other limitations including non-blinding (under normal circumstances such studies would not be considered, but for some comparisons there was no other available data). They also noted that the populations studied were heterogeneous in that some had experienced a first, whereas others had required multiple, resections.<br><br>**5-ASA treatment**<br>5-ASA treatment was the most extensively-studied (although even here the studies were relatively small, except for that by Ewe et al). The GDG agreed that as in sections 5 and 6, 5-ASA treatment was considered as a class and not assessed on the basis of different delivery mechanisms. In this review specifically, site of action is even less pertinent as the data include any intestinal surgery for Crohn's disease.<br><br>The NCGC meta-analyses of 3 RCTs (Brignola, Ewe and Wenckert) for 5-ASAs (sulfasalazine and mesalazine) vs placebo for relapse (only) at one year showed that 5-ASA reduced relapses by 40% compared to placebo. At 95% confidence this number ranged from 60 to 90% (RR 0.60 [0.40 to 0.91]). A meta analysis of two RCTs (Locks and Wenckert) at 18 months showed that 5-ASA reduced relapses by 26% compared to placebo. Of borderline significance at 95% confidence, this number ranged from a 48% decrease to a 4% increase. However at two years, meta analysis of two studies (Ewe and Hanauer) showed that 5-ASA reduced relapses by 31% compared to placebo and at 95% confidence this number ranged from 10 to 47%.<br><br>The GDG noted that when relapse and withdrawal were taken into account at one year, meta-analysis of the same three RCTs (Brignola, Ewe and Wenckert) demonstrated a non-significant trend favouring 5-ASA - relapses reduced by 18% compared with placebo and at 95% confidence, this number ranged from a 35% decrease to a 3% increase. By two years however a meta-analysis of two RCTs (Ewe and Hanauer) of sulfasalazine for relapse and withdrawal for maintaining remission after surgery showed a statistically-significant result - 5-ASA reduced relapses by 16% compared with placebo and at 95% confidence this number ranged from 28% to 2%.<br><br>The GDG were also aware of a Cochrane review[69] which pooled results of endoscopic relapse from four studies, and did not show benefit from 5-ASA treatment.<br><br>The GDG debated this evidence at length and ultimately agreed that overall, 5-ASAs were thought to be effective at preventing relapses from surgically-induced remission.<br><br>For these reasons the GDG made a "consider recommendation" for 5-ASAs to maintain remission after surgery. |

**Thiopurines**

In view of the paucity of RCTs, and the lack of any RCT comparing azathioprine and placebo, the GDG debated whether it was reasonable to pool results from studies of azathioprine + metronidazole versus placebo + metronidazole (D'Haens 2008) and mercaptopurine versus placebo (Hanauer 2004). The latter is regarded as being better-tolerated, but is not readily available in some localities, particularly some primary care settings. Mercaptopurine is usually only available under a shared care policy, and some GPs will also only prescribe azathioprine, under a shared care policy. The two have an identical mode of action. The GDG decided to consider the evidence from these two trials (D'Haens, Hanauer) together, and noted that some of the outcome measures were positive, including an intention-to-treat analysis of relapse rate at two years.

The GDG noted that despite the evidence supporting fewer relapses with mercaptopurine than placebo (Hanauer) there was only one study, and that this drug demonstrated more side effects. The GDG also noted that azathioprine did not demonstrate any greater effect than 5-ASA for clinical relapse or endoscopic relapse (which is thought to be predictive of clinical relapse). For these reasons, they did not recommend the use of mercaptopurine or azathioprine for all patients after surgery, but suggested azathioprine or mercaptopurine should be "considered" when poor prognostic factors increase the need to prevent relapse.

The group also noted that other ongoing trials may help to resolve uncertainty associated with mercaptopurine for maintaining remission after surgery. For this reason, the GDG did not prioritise azathioprine or mercaptopurine for maintaining remission after surgery as a question for future research.

In relation to 5-ASA (mesalazine only) compared with azathioprine for relapse only at the two-year time point the meta-analyses of two RCTs (Ardizzone and Hanauer) demonstrated statistical non-significance that azathioprine reduced relapses by 32% and at 95% conflidence this number ranged from a 6% increase to an 84% decrease. The result remained statistically non-significant when relapse and withdrawals at two years were taken into account in a meta-analysis of the same RCTs. This showed that azathioprine and 5-ASAs are approximately equivalent for preventing relapse for post-sugical maintenance of remission.

**Budesonide**

Studies of budesonide did not show any benefit for routine use and the GDG were aware of the side-effects associated with long-term glucocorticosteroid treatment.

**Enteral nutrition**

The available data for enteral nutrition were particularly disappointing; the GDG felt that the difficulty in adequate blinding of participants to the intervention did not excuse the absence of properly randomised trials with investigator blinding. The GDG noted that there was only one small very low-quality observational study (Yamamoto) demonstrating a non-significant trend towards enteral nutrition over placebo in maintaining remission after surgery. Given that there was no consistency of evidence the GDG agreed a 'do not offer' recommendation until such time that

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| | further data was available.<br><br>**Metronidazole**<br>Although some of the outcomes for metronidazole relapse compared with placebo, and metronidazole in combination with azathioprine, appeared encouraging, the GDG considered the numbers studied to be small and there to be substantial statistical uncertainty. The analysis included only two trials (not pooled) with low and very low quality outcome data and there were marked differences in effect sizes and significance when relapse, or relapse + withdrawal, were considered. The GDG also noted from the clinical review that benefit that might have been derived from metronidazole in the short-term, was lost at two- and three-year time points. For this reason the GDG felt unable to make a recommendation for metronidazole for maintaining remission after surgery for Crohn's disease. |
| **Other considerations** | As with the maintenance studies detailed in section 6, the GDG wished to consider only studies in which maintenance therapy was continued for at least 12 months. However, this criterion was not applied to metronidazole. The rationale for preventing relapse post-operatively with metronidazole may differ from other agents (all of which have, through varying mechanisms, some form of anti-inflammatory or immunomodulatory actions). Metronidazole has additional antibacterial actions, and because of side effects, administration for 12 months is not practical. However, although they considered studies in which metronidazole had been given for shorter periods of time, the GDG still required follow-up of at least 12 months in order to determine the effect of the treatment on maintenance of remission in the longer term.<br><br>The GDG noted the general limitations of the evidence base despite the common practice of prescribing azathioprine or mercaptopurine for people with a history of multiple resections or severe disease. The listed risk factors are based upon GDG consensus opinion derived from clinical experience.<br><br>When reflecting upon what characteristics might be considered to be "poor prognostic factors", the GDG confirmed that although fibrotic strictures are not the same as inflammatory strictures or exacerbations, both may be regarded as appropriate for azathioprine maintenance treatment after surgery. This would depend on the clinical picture, for example, the GDG did not consider first surgery for a fibrotic stricture to be an indication for azathioprine maintenance, but recurrent surgery was regarded as an indication for this.<br><br>Some people with Crohn's disease express a wish to continue prior maintenance treatment after surgery. While acknowledging that personal choice plays a part, the need for surgery while on azathioprine treatment, may prompt consideration of TA 187. One suggested management option was to establish if there is endoscopic recurrence six months after surgery and then to offer azathioprine. However the GDG recognised that this strategy is neither evidence-based nor universally available.<br><br>The GDG wished to highlight the importance of the difference between "complications" for example complicated by stricture or abscess, and "complex" i.e. difficult to treat or requiring many management |

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| | considerations.<br><br>They also stressed that in these situations, decisions about post-operative maintenance therapy should be made in partnership with people with Crohn's disease.<br><br>**Children**<br>There were no studies on maintenance of post-surgical remission in children. The GDG agreed that in the lack of any paediatric data it was acceptable to extrapolate from adult studies and to make the same recommendations as for adults. |

## 7.11 Recommendations

**28. Consider azathioprine or mercaptopurine[h] to maintain remission after surgery in people with adverse prognostic factors such as:**

- **more than one resection, or**
- **previously complicated or debilitating disease (for example, abscess, involvement of adjacent structures, fistulising or penetrating disease).**

**29. Consider 5-ASA[k] treatment to maintain remission after surgery.**

**30. Do not offer budesonide or enteral nutrition to maintain remission after surgery.**

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*h Although use is common in UK clinical practice, at the time of publication (October 2012) azathioprine and mercaptopurine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.*

*k Although use is common in UK clinical practice, at the time of publication (October 2012) olsalazine, balsalazide and sulfasalazine did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information. Some forms of mesalazine (Octasa MR, Mesren MR, Asacol MR) are licensed for maintaining remission in Crohn's ileo-colitis.*

## 7.12 Research recommendation

The GDG was aware of the TOPPIC trial (Randomised controlled trial of 6-Mercaptopurine versus placebo to prevent recurrence of Crohn's disease following surgical resection) which is expected to further inform treatment decisions in this area. This field was therefore not prioritised for future research.

# 8 Enteral nutrition

## 8.1 Clinical introduction: enteral nutrition for induction of remission

Many foods and food additives have been suggested as potential aetiological factors in the development of Crohn's disease and people with Crohn's disease (personal communication) have reported symptomatic relief by excluding specific foods. The role of diet in Crohn's disease has stimulated an interest in dietary modification as a treatment and the potential benefit of using diet as a method of avoiding glucocorticosteroid therapy was recognised early in the field of child health. However, the popularity of dietary therapy in adults has tended to follow a cyclical pattern.[300]

Nutritional therapy can be administered enterally (via the gastrointestinal tract) or parenterally (avoiding the gastrointestinal tract i.e. intravenously). A landmark study by Greenberg et al (1988)[111] showed that total parenteral nutrition, partial parenteral nutrition and enteral nutrition using a liquid feed were equally effective in achieving and maintaining remission. This showed that "bowel rest" was not necessary and as parenteral nutrition has a high complication rate it is now rarely used as the primary nutritional therapy for induction of remission. Therefore this review focuses on the role of exclusive enteral nutrition for induction of remission.

Enteral nutrition is provided in the form of a liquid feed which can be taken orally or may be administered via an enteral feeding tube (usually nasogastric). Route of delivery usually depends on patient preference. Tube feeding may increase compliance where oral palatability is an issue. Most units recommend that all solid food is stopped for up to eight weeks but there is variation in practice between adult and paediatric populations, across the UK and between countries. Enteral feeds can be polymeric - containing whole proteins, semi-elemental – containing oligopeptides, or elemental - containing amino acids, in addition to other essential nutrients. The optimal composition of enteral feeds is unknown. Several trials assessing the relative efficacy of the different types have been unable to demonstrate a difference[89,295] but lipid content may be important.[98,182] Cost, availability and palatability are relevant considerations when choosing a formula.

Enteral nutrition is widely used as first-line therapy in children and adolescents to facilitate growth and development.[237] Conversely, its use in adults is limited, commonly due to its association with poor compliance, lack of clinician experience in its administration and inadequate availability of dietetic services. Adult patients are often unaware of enteral nutrition as a treatment option.

The major arguments for the use of enteral nutrition are avoidance of the adverse effects associated with medications and improvement in nutritional status, bone health[202] and growth in children and young people.[21]

### 8.1.2 Clinical questions: enteral nutrition for induction of remission

The review questions asked, and upon which the literature was searched was:

In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) as a sole source of nutrition for induction of remission compared with

- usual diet?
- conventional glucocorticosteroid treatment?
- budesonide?
- a combination of conventional glucocorticosteroid treatment *plus* 5-ASA treatment?
- a combination of conventional glucocorticosteroid treatment *plus* azathioprine or mercaptopurine?
- a combination of conventional glucocorticosteroid treatment *plus* methotrexate?

In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness for induction of remission of enteral nutrition (elemental, semi-elemental and polymeric) plus medical therapy versus usual diet?

### 8.1.3 Clinical evidence: enteral nutrition for induction of remission

The literature search for trials of enteral nutrition did not identify any trials which compared enteral nutrition to immunosuppressives, trials which included a combination of enteral nutrition and a pharmacological agent, or trials which compared enteral nutrition to usual diet. The trials did not report glucocorticosteroid-sparing effects. The comparisons of interest for this review included enteral nutrition vs. conventional glucocorticosteroid and enteral nutrition vs. conventional glucocorticosteroid plus 5-ASA.

The Cochrane review of enteral nutrition for induction of remission[311] was quality assessed using the NICE systematic review assessment form and accepted for this review. Seven studies [98,105,156,158,167] are included in the Cochrane review.[311] The quality ratings allocated in the evidence profiles below pertain to the trials and not the Cochrane review. A subgroup analysis of the Cochrane data for adult and paediatric remission rates was conducted. A further four studies are reported in this review.[106,203,233,312] These studies have not been added to the Cochrane meta-analysis due to variations in outcome measures. The paediatric data has been reported in a separate table.

**Table 64: Evidence profile: enteral nutrition versus conventional glucocorticosteroid treatment**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Enteral nutrition | Conventional glucocorticosteroid | Relative(95% CI) | Absolute | |
| **Induction of remission adults and children (assessed with CDAI/PCDAI; follow-up four to ten weeks) [fixed effect];** Zachos, 2007 | | | | | | | | | | | |
| 7 | randomised trials | serious[1] | serious[2] | no serious indirectness | serious[3] | none | 95/192 (49.5%) | 120/160 (75%) | RR 0.68 (0.57 to 0.8) | 240 fewer per 1000 (from 150 fewer to 322 fewer) | VERY LOW |
| **Induction of remission adults and children (assessed with CDAI/PCDAI; follow-up four to ten weeks) [random effects];** Zachos, 2007 | | | | | | | | | | | |
| 7 | randomised trials | serious[1] | serious[2] | no serious indirectness | serious[3] | none | 95/192 (49.5%) | 120/160 (75%) | RR 0.70 (0.53 to 0.93) | 225 fewer per 1000 (from 52 fewer to 353 fewer) | VERY LOW |
| **Induction of remission adults only subgroup analysis of Cochrane data (assessed with: CDAI; follow-up four to ten weeks) [fixed effect];** Zachos, 2007 | | | | | | | | | | | |
| 5 | randomised trials | serious[4] | serious[5] | no serious indirectness | no serious imprecision | none | 80/173 (46.2%) | 108/142 (76.1%) | RR 0.62 (0.52 to 0.74) | 289 fewer per 1000 (from 198 fewer to 365 fewer) | LOW |
| **Induction of remission adults only subgroup analysis of Cochrane data (assessed with CDAI; follow-up four to ten weeks) [random effects];** Zachos, 2007 | | | | | | | | | | | |
| 5 | randomised trials | serious[4] | serious[5] | no serious indirectness | serious[3] | none | 80/173 (46.2%) | 108/142 (76.1%) | RR 0.64 (0.49 to 0.84) | 274 fewer per 1000 (from 122 fewer to 388 fewer) | VERY LOW |
| **Failure to achieve remission adults only (follow-up four weeks; assessed with: Disease Activity Index [DAI] );** Gorard, 1993 | | | | | | | | | | | |
| 1 | randomised trials | very serious[6] | no serious inconsistency | no serious indirectness | very serious[7] | none | 3/13 (23.1%) | 3/20 (15%) | RR 1.54 (0.36 to 6.49) | 81 more per 1000 (from 96 fewer to 823 more) | VERY LOW |
| **Premature termination adults only (follow-up four weeks);** Gorard, 1993 | | | | | | | | | | | |
| 1 | randomised trials | serious[6] | no serious inconsistency | no serious indirectness | very serious[7] | none | 2/22 (9.1%) | 1/20 (5%) | RR 1.82 (0.18 to 18.55) | 41 more per 1000 (from 41 fewer to 877 more) | VERY LOW |
| **Improvement adults only (assessed with clinical assessment; follow-up four weeks);** O'Morain, 1984 | | | | | | | | | | | |
| 1 | randomised trials | very serious[6] | no serious inconsistency | no serious indirectness | very serious[7] | none | 9/11 (81.8%) | 8/10 (80%) | RR 1.02 (0.67 to 1.55) | 16 more per 1000 (from 264 fewer to 440 more) | VERY LOW |
| **Improvement adults only (HBI; follow-up two weeks);** Zoli, 1997 | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[6] | no serious inconsistency | no serious indirectness | very serious[7] | none | 8/12 (66.7%) | 5/10 (50%) | RR 1.33 (0.64 to 2.79) | 165 more per 1000 (from 180 fewer to 895 more) | VERY LOW |

*1 Four studies not blinded; two studies randomisation method not described.*
*2 $I^2$ = 63%.*
*3 Confidence interval crosses default MID at 0.75.*
*4 Three studies not blinded; two studies randomisation method not described.*
*5 $I^2$ = 50%.*
*6 No blinding; method of randomisation not described; allocation concealment not described.*
*7 Confidence interval crosses default MID at 0.75 and 1.25.*

### 8.1.4 Enteral nutrition versus conventional glucocorticosteroid treatment in children

**Table 65: Evidence profile: enteral nutrition versus conventional glucocorticosteroid treatment in children**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Enteral nutrition | Conventional glucocorticosteroid | Relative (95% CI) | Absolute | |
| **Induction of remission in children subgroup analysis of Cochrane data (assessed with PCDAI; follow-up ten weeks);** Borelli 2006 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 15/19 (78.9%) | 12/18 (66.7%) | RR 1.18 (0.79 to 1.77) | 120 more per 1000 (from 140 fewer to 513 more) | LOW |
| **Adverse events children only (follow-up ten weeks);** Borelli 2006 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 4/17 (23.5%) | 11/15 (73.3%) | RR 0.32 (0.13 to 0.8) | 499 fewer per 1000 (from 147 fewer to 638 fewer) | LOW |
| **Change PCDAI score children only (measured with: PCDAI; follow-up two months);** Ruuska 1994 | | | | | | | | | | | |
| 1 | randomised trials | very serious[4] | no serious inconsistency | no serious indirectness | serious[5] | none | 10 | 9 | - | MD 2.40 lower (10.3 lower to 5.6 higher) | VERY LOW |
| **Adverse events children only (follow-up two months);** Ruuska 1994 | | | | | | | | | | | |
| 1 | randomised trials | very serious[4] | no serious inconsistency | no serious indirectness | very serious[6] | none | 1/10 (10%) | 1/9 (11.1%) | RR 0.9 (0.07 to 12.38) | 11 fewer per 1000 (from 103 fewer to 1000 more) | VERY LOW |
| **Endoscopic healing children only (follow-up ten weeks);** Borelli 2006 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 15/19 (78.9%) | 7/18 (38.9%) | RR 2.03 (1.09 to 3.79) | 401 more per 1000 (from 35 more to 1000 more) | LOW |
| **Histologic healing children only (follow-up ten weeks);** Borrelli 2006 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 14/19 (73.7%) | 6/18 (33.3%) | RR 2.21 (1.09 to 4.48) | 403 more per 1000 (from 30 more to 1000 more) | LOW |

*1 Open label - blinding not possible; allocation concealment not described.*
*2 MID crosses default 1.25.*
*3 MID crosses default 0.75.*
*4 No blinding; method of randomisation not described; allocation concealment not described.*
*5 Confidence intervall crosses -6.05.*
*6 MID crosses default 0.75 and 1.25.*

### 8.1.5 Economic evidence

No published data were identified and no primary health economic modelling was conducted due to the nature of the clinical evidence.

### 8.1.1 Enteral nutrition versus conventional glucocorticosteroid plus 5-ASA treatment

**Table 66: Evidence profile: enteral nutrition versus glucocorticosteroid plus 5-ASA treatment**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Enteral nutrition | Conventional glucocorticosteroid plus 5-ASA treatment | Relative (95% CI) | Absolute | |
| **Induction of remission mean change (measured with: Lloyd Still disease activity ; Better indicated by lower values; follow-up twelve weeks);** Sanderson 1987 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | not assessable[2] | none | 22 | 19 | - | MD 3.00 higher (0.62 lower to 6.62 higher) | VERY LOW |
| **Premature termination (follow-up twelve weeks);** Sanderson 1987 | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 1/9 (11.1%) | 1/8 (12.5%) | RR 0.89 (0.07 to 12.00) | 14 fewer per 1000 (from 116 fewer to 1375 more) | VERY LOW |

*1 Randomisation and allocation concealment not described. No blinding.*

*2 Standard deviations not reported.*

*3 MID crosses default 0.75 and 1.25.*

### 8.1.2 Enteral nutrition versus conventional glucocorticosteroid plus 5-ASA treatment in children

**Table 67: Evidence profile: enteral nutrition vs. conventional glucocorticosteroid plus 5-ASA treatment in children**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Enteral nutrition | Conventional glucocorticosteroid + 5-ASA | Relative (95% CI) | Absolute | |
| **Enteral nutrition vs. conventional glucocorticosteroid plus 5-ASA treatment in children (assessed with PCDAI; follow-up eight weeks);** Terrin 2002 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/10 (90%) | 5/10 50%) | RR 1.80 (0.94 to 3.46) | 400 more per 1000 (from 30 more to 1230 more) | LOW |
| **Growth - mean height velocity (Better indicated by higher values follow-up six months);** Thomas 1993 | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | not assessable[4] | none | + 3.2 12 patients | -3.1 12 patients | - | MD not estimable (SD not provided) p < 0.05 | VERY LOW |

*1 Allocation concealment not described.*
*2 MID crosses default 1.25.*
*3 Open label - blinding not possible; allocation concealment not described.*
*4 Standard deviations not reported.*

### 8.1.3 Evidence statements – clinical

- In a meta-analysis of seven RCTs (n = 352; follow-up 4-10 weeks)[311] in patients of all ages with active Crohn's disease, enteral nutrition was less effective than conventional glucocorticosteroid treatment for induction of remission (RR 0.68 [0.57 to 0.8] (fixed effect); RR 0.70 [0.53 to 0.93] (random effects)).[98,105,156,158,167][MODERATE QUALITY SYSTEMATIC REVIEW; VERY LOW QUALITY EVIDENCE]
- In a subgroup meta-analysis of five RCTs (n = 315; follow-up four to ten weeks) in adult patients with active Crohn's disease, enteral nutrition was less effective than conventional glucocorticosteroid treatment for induction of remission (RR 0.62 [0.52 to 0.74] (fixed effect); RR 0.64 [0.49 to 0.84] (random effects)).[98,105,156,158,167][MODERATE QUALITY SYSTEMATIC REVIEW; MODERATE-LOW QUALITY,VERY LOW QUALITY]
- In one RCT of paediatric patients (n = 37; follow-up ten weeks) there was no statistically significant difference in rates of induction of remission between those receiving enteral nutrition (79%) and those receiving conventional glucocorticosteroid treatment (67%) (RR1.18 [0.79 to 1.77]).[30][LOW QUALITY]
- In one RCT of paediatric patients (n = 37; follow-up ten weeks) there was significantly better endoscopic (RR 2.03 [1.09 to 3.79]) and histological healing (RR 2.21 [1.09 to 4.48]) with enteral nutrition compared with conventional glucocorticosteroid treatment.[30][LOW QUALITY]
- In one RCT of paediatric patients (n = 32; follow-up 10 weeks) there were significantly fewer adverse events with enteral nutrition compared with conventional glucocorticosteroid treatment (RR 0.32 [0.13 to 0.8]).[30][LOW QUALITY]
- In one RCT of adult patients (n = 33; follow-up four weeks) there was no significant difference in failure to achieve remission (RR 1.54 [0.36 to 6.49]) or in premature termination of the study (RR 1.82 [0.18 to 18.55]) between those receiving enteral nutrition and those receiving conventional glucocorticosteroid treatment.[106][VERY LOW QUALITY]
- In one RCT of adults patients (n = 21;follow-up four weeks) there was no significant difference in improvement of symptoms at four weeks between those receiving enteral nutrition and those receiving conventional glucocorticosteroid treatment (RR1.02 [0.67 to 1.55).[203][VERY LOW QUALITY]
- In one RCT of adult patients (n = 22; follow-up two weeks) study there was no significant difference in improvement measured by Harvey Bradshaw Index when enteral nutrition was compared with with conventional glucocorticosteroid treatment (RR 1.33 [0.64 to 2.79]).[312][VERY LOW QUALITY]
- In one RCT of paediatric patients (n = 37; follow-up two months) there was no significant difference in change in PCDAI scores (MD 2.40 lower [10.3 lower to 5.6 higher]) or in adverse events (RR 0.09 [0.07 to 12.38]) between patients on enteral nutrition therapy vs. conventional glucocorticosteroid treatment.[233][VERY LOW QUALITY]
- In one RCT of adult patients (n = 41; follow-up 12 weeks) which compared enteral nutrition to conventional glucocorticosteroid treatment plus 5-ASA, there was no significant difference in induction of remission by Lloyd Still score (MD 3.00 higher [0.62 lower to 6.62 higher]) or premature termination (RR 0.89 [0.07 to 12.00]).[236][VERY LOW]
- In one RCT study of paediatric patients (n = 20; follow-up eight weeks) which compared enteral nutrition with conventional glucocorticosteroid plus 5-ASA treatment, all study groups showed significant decreases in PCDAI scores but there was no significant difference between groups (1.80 [0.94 to 3.46]).[275][LOW QUALITY]
- In one RCT (n = 24; follow-up six months) of paediatric patients comparing enteral nutrition to conventional glucocorticosteroid plus 5-ASA treatment, height velocity was improved in the

enteral nutrition group (+3.2 in enteral nutrition group; -3.1 in conventional glucocorticosteroid plus 5-ASA group).[277][VERY LOW]

### 8.1.4 Economic evidence

No published data were found and original modelling was not undertaken for this question due to the nature of the clinical evidence.

## 8.2 Linking evidence to recommendations

**Table 68: Linking evidence to recommendations – enteral nutrition for induction**

| | |
|---|---|
| **Clinical question** | **What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for induction of remission compared with**<br>• **usual diet**<br>• **medical treatment**<br>• **conventional glucocorticosteroid treatment**<br>• **budesonide**<br>• **5-ASA treatment**<br>• **azathioprine or mercaptopurine**<br>• **methotrexate**<br><br>**In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness for induction of remission of enteral nutrition (elemental, semi-elemental and polymeric) plus medical therapy versus usual diet?** |
| **Recommendation** | **3. Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:**<br>• **children in whom there is concern about growth or side effects, and**<br>• **young people in whom there is concern about growth** |
| **Relative values of different outcomes** | The goal when treating active disease is to induce remission and hence this was agreed by the GDG as the primary outcome of interest. Remission defined by a Crohn's disease activity index (CDAI) of ≤ 150 together with a CDAI fall of 70 was considered to be the most rigorous reflection of efficacy. Ideally both an endpoint and a fall would be taken into consideration because, for example, a person with a CDAI of 151 would be considered to be suffering active disease but a reduction in CDAI of 2 to an endpoint of 149 cannot be taken as a treatment success. When the GDG was presented with the data it was apparent that not all studies report both of these CDAI parameters. Given the limited data available the GDG did not feel it could exclude studies on this basis.<br><br>For adults, in addition to the CDAI outcome measure, the Harvey Bradshaw Index (of < 3) was also accepted by the GDG as a recognised outcome measure for disease activity. Because of the paucity of data, the GDG agreed to consider the Disease Activity Index, but placed less importance on this outcome measure. The GDG considered that "investigator-reported remission" was subject to bias.<br><br>The GDG anticipated that there would be a paucity of paediatric literature for enteral nutrition and hence included remission measured by the PCDAI and the Lloyd Still Disease Activity Index.<br><br>For children, when assessing enteral nutrition in relation to other medical therapies, the outcomes of growth and height velocity were of particular interest to the GDG. |

| | |
|---|---|
| | Adverse event differences were also considered to be of importance.<br><br>The GDG debated the value of endoscopic healing[17,94] as a surrogate marker for an index of response. Deep ulceration is known to be linked to poor prognosis. It was agreed that when studies reported it, the group would wish to consider this information. The GDG noted that endoscopic healing was reported in some of the papers reviewed (in contrast to the studies considering drug therapy). |
| **Trade off between clinical benefits and harms** | The GDG debated the trade-offs between quantitative outcomes noted above and qualitative aspects pertaining to enteral nutrition, for example palatability, repeated insertion of a nasogastric tube and not being able to join in the social activity of meal times and eating. |
| **Economic considerations** | Costs are dependent on use in acute or community settings, type of feed used, route of delivery and duration of use.<br><br>Enteral nutrition was not included in the cost-effectiveness model looking at induction of remission since the trial evidence did not contain data on withdrawal rates. However, given the relatively low effectiveness observed in the guideline review, it is unlikely to be considered effective or cost effective compared with glucocorticosteroid treatment, in people who can tolerate both. |
| **Quality of evidence** | No data were identified comparing usual diet with combination enteral nutrition and drug therapy.<br><br>The enteral nutrition evidence compared with drug therapy generated extensive debate. GDG clinical experience is that enteral nutrition is used to induce remission as first-line therapy in children (and some adults particularly if it was effective when the patient was younger). However the data highlighted considerable methodological limitations and outcomes in adults that contradicted this clinical experience.<br><br>**Adults**<br>A moderate quality systematic review was conducted by Cochrane[311] however all the randomised controlled studies included within it were of moderate to very low quality. The studies were graded as low quality due to lack of clarity regarding methodology, small sample sizes and heterogeneity.<br><br>The methodological limitations and short-term follow-up (ranging from three to ten weeks) noted for the enteral nutrition studies contrasted with the higher quality of evidence seen for inducing remission with conventional glucocorticosteroid treatment compared with placebo [166,270] at 15 to 18 weeks.<br><br>In addition, from a quality perspective, the GDG considered that “investigator-reported remission” was subject to bias given that no objective measures were reported (such as CDAI).<br><br>The meta-analysis of seven studies comparing enteral nutrition to glucocorticosteroid treatment for inducing remission in adults and children measured by CDAI/PCDAI at four to ten weeks showed that |

conventional glucocorticosteroid treatment induced 30% more remissions than enteral nutrition and at 95% confidence, this increase in remissions ranged from 7% to 47%. The GDG noted the predominately low to very low quality and the methodological limitations.

Of note, the high dropout rate in the Gorard study is likely to impact upon the outcome (41% of the elemental diet group were withdrawn due to non-compliance).

The GDG agreed that further research was required and went on to make a research recommendation. The GDG agreed that there is value in repeating the investigation of effectiveness of enteral nutrition in adults, because the number of patients in the enteral nutrition meta-analysis was relatively small (350), and a large well-designed RCT would have the potential to either support or refute existing findings.

The GDG noted the ethical aspects of research in this area and not being able to compare enteral nutrition with placebo.

**Children and young people**

The GDG noted that for children and young people the picture was slightly different.

Five RCTs were identified which assessed the efficacy of enteral nutrition in children, but patient numbers were noted to be small in all the studies:

- Borelli 2006: enteral nutrition vs conventional corticosteroid
- Ruuska 1994: enteral nutrition vs conventional corticosteroid
- Terrin 2002: enteral nutrition vs conventional corticosteroid and 5-ASA
- Thomas 1993: enteral nutrition vs conventional corticosteroid and 5-ASA
- Sanderson 1987: enteral nutrition vs conventional corticosteroid and 5-ASA.

Borelli 2006 and Terrin 2002 suggested enteral nutrition was superior to conventional corticosteroid +/- 5-ASA for inducing remission and endoscopic (Borelli: RR 2.03 [1.09 – 3.79]) and histologic (Borelli: RR 2.21 [1.09 – 4.48]) healing but there was considerable uncertainty in the estimated effect size of these surrogate markers. Terrin 2002 and Sanderson 1987 suggested enteral nutrition was of benefit in children where there are growth concerns.

Also the Thomas and Sanderson studies[236,277] demonstrated outcomes that favoured enteral nutrition over glucocorticosteroid treatment for improved growth. (Mean height velocity for chronological age was significantly greater in the elemental group ($p < 0.05$) despite similar gain in weight in the Sanderson study, but further data were not provided).

Adverse events outcomes in paediatric studies were equivocal: significantly less in one trial at 10 weeks (Borelli) but not significantly less in another trial at two months (Ruuska). The GDG noted the very

| | |
|---|---|
| | small numbers and the low quality of the evidence.<br><br>In making their recommendation, the GDG considered that there may be reluctance to offer glucocorticosteroid treatment to children with Crohn's disease (given the side effects) and that none of the 5-ASAs, immunosuppressives or conventional glucocorticosteroids are licensed for use in children with Crohn's disease.<br><br>The evidence was low to very low quality but the GDG agreed that there were limited options available for children and there is known widespread paediatric use of enteral nutrition. On this basis, the GDG made a 'consider' recommendation for enteral nutrition for inducing remission in the presence of concerns about side effects or concerns about a child's or a young person's growth (and as an alternative to conventional glucocorticosteroid) appropriate.<br><br>The GDG commented on the paucity of high-quality paediatric data for a treatment that is generally accepted as standard clinical practice and this is why the GDG made a 'consider' rather than an 'offer' recommendation. This is also the reason for the extention of the research recommendation to encompass children and young people, as well as adults.<br><br>The GDG discussed transition care (children to adult services) and whether it would be appropriate for enteral nutrition to be prescribed for young people at a transition care stage. The GDG appreciated that because of pubertal delay, young people with Crohn's disease may still be growing until the age of 25. In summary the GDG agreed that enteral nutrition should be considered as an alternative to glucocorticosteroid treatment to induce remission in children and 'young people' (rather than stipulating an age cut off for which there is no direct evidence) in whom pubertal delay extended the potential for growth beyond the age of 18.<br><br>Whilst the GDG made a limited 'consider' recommendation they felt that future research in this area was a high priority. |
| **Other considerations** | Whilst the methodological limitations of the evidence led the GDG to make a research recommendation, the GDG acknowledged that enteral nutrition is currently offered to adults and anecdotally noted to be a preferred option for some people.<br><br>The GDG agreed the importance of encouraging patients to eat a varied, balanced diet when in disease remission. Whilst the GDG did not look at the evidence base pertaining to who should provide dietary advice (for example, dietitians) the group agreed that where appropriate, patients at risk of malnutrition or wishing to restrict their diet or avoid certain foods should be given healthcare professional advice.<br><br>The GDG emphasized that their enteral nutrition review was conducted on the basis of it being a treatment for inducing remission and not as a nutritional supplement. |

## 8.3 Recommendation

**3. Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:**

- **children in whom there is concern about growth or side effects, and**
- **young people in whom there is concern about growth.**

## 8.4 Research recommendation

**3. What are the benefits, risks and cost effectiveness of enteral nutrition compared with glucocorticosteroid treatment in adults, children and young people?**

Previous studies suggested that glucocorticosteroid treatment is more effective at inducing remission than enteral nutrition in adults with Crohn's disease, but some small paediatric studies suggested that growth and mucosal healing may be better following treatment with enteral nutrition. In clinical practice enteral nutrition is often used to avoid the side effects of glucocorticosteroid treatment in children and young people. There is little information about the relative effects on quality of life, bone density or cost effectiveness. Randomised controlled trials should be conducted in children, young people and adults with an inflammatory exacerbation of Crohn's disease to compare the effects of enteral nutrition and glucocorticosteroid treatment on these parameters and also growth in children and young people. Mucosal healing could also be assessed in a subgroup of participants. We do not believe that it is ethical or practical to conduct a randomised controlled trial of enteral nutrition versus placebo.

# 8.5 Clinical introduction: enteral nutrition for maintenance of remission

The effectiveness of longer-term enteral nutrition for maintenance of remission has been less well researched than for induction of remission. Long-term avoidance or minimisation of glucocorticosteroid and immunosuppressive agents reduces the potential for adverse events associated with these medications and may lead to improvements in bone health and growth in children and young people[303] and nutritional status in adults.[125] These considerations led the GDG to look for data that would inform the use of enteral nutrition therapy for maintaining remission in people with Crohn's disease.

## 8.5.1 Clinical questions: enteral nutrition for maintenance of remission

What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission compared with

- usual diet?
- medical treatment?
- conventional glucocorticosteroid treatment?
- budesonide?
- 5-ASA treatment?
- azathioprine or mercaptopurine?
- methotrexate?

What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission in combination with

- conventional glucocorticosteroid treatment?
- Budesonide?
- 5-ASA treatment?
- azathioprine or mercaptopurine?
- methotrexate?

compared with any of the above?

# 8.6 Clinical evidence: enteral nutrition for maintenance of remission

A Cochrane review[6] of enteral nutrition for maintaining remission in Crohn's disease was published in 2007. The Cochrane review included two studies.[274,295] Takagi 2006 met the inclusion criteria for this review. Verma 2001 compared an elemental formula with a polymeric formula and thus did not meet inclusion criteria. As there was no significant difference between the two enteral nutrition formulae investigated, the authors reported the overall effect of enteral nutrition for maintenance of remission.

Due to the paucity of RCT evidence on this topic, the literature was searched for observational studies to provide additional data to inform guideline development. A further four observational studies were identified and included in this review.[130,296,303,308]

The observational data includes three prospective non-randomised studies[130,296,308] and one retrospective chart review.[303]

**Table 69: Evidence profile: half enteral nutrition versus free diet**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Half enteral nutrition | Free diet | Relative (95% CI) | Absolute | |
| **Relapse rate (follow-up mean one year);** Takagi 2006 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/26 (34.6%) | 16/25 (64%) | HR 0.40 (0.18 to 0.98) | 305 fewer per 1000 (from 7 fewer to 472 fewer) | LOW |
| **Adverse events (follow-up mean one year);** Takagi 2006 | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | not assessable[3] | none | 0/26 (0%) | 0/25 (0%) | Not estimable | Not estimable | VERY LOW |

*1 Blinding not possible.*
*2 MID crosses default 0.75.*
*3 Standard deviations not reported.*

**Table 70: Evidence profile: enteral nutrition for maintenance of remission**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Enteral nutrition | Normal diet | Relative(95% CI) | Absolute | |
| **Maintenance of remission without conventional glucocorticosteroid treatment (assessed with CDAI; follow-up one year);** Verma 2001 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 14/33 (42.4%) | 19/33 (57.6%) | RR 0.74 (0.45 to 1.21) | 150 fewer per 1000 (from 317 fewer to 121 more) | LOW |
| **Remission, weaning prednisone and maintaining 5-ASA and AZA (assessed with: CDAI; follow-up one year);** Verma 2001 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 10/21 (47.6%) | 4/18 (22.2%) | RR 2.14 (0.81 to 5.67) | 253 more per 1000 (from 42 fewer to 1000 more) | VERY LOW |
| **Remission EN vs. no treatment (assessed with IOIBD score; follow-up one year);** Hirakawa 1993 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 24/25 (96%) | 3/6 (50%) | RR 1.92 (0.86 to 4.29) | 460 more per 1000 (from 70 fewer to 1000 more) | VERY LOW |
| **Remission EN + drugs vs. no treatment (assessed with IOIBD score; follow-up one year);** Hirakawa 1993 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 19/25 (76%) | 3/6 (50%) | RR 1.52 (0.66 to 3.49) | 260 more per 1000 (from 170 fewer to 1000 more) | VERY LOW |
| **Remission EN vs. no treatment (assessed with: CDAI; follow-up one year);** Yamamoto 2007 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | not assessable[4] | none | - | Not available Total n = 40 | Not available Total n = 40 | EN was significantly better than no treatment p = 0.01 | LOW |
| **Relapse EN in children vs. no treatment (assessed with PCDAI; follow-up one year);** Wilchanski 1996 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 12/28 (42.9%) | 15/19 (78.9%) | RR 0.54 (0.33 to 0.88) | 363 fewer per 1000 (from 95 fewer to 529 fewer) | VERY LOW |

*1 MID crosses default 0.75.*
*2 MID crosses 1.25 default.*
*3 MID crosses default 0.75 and 1.25.*
*4 Standard deviations not reported.*

### 8.6.1 Evidence statements - clinical

**Adult studies**

- In one RCT (n = 51)[274] of enteral nutrition supplements (half enteral nutrition for calories) plus mesalazine vs. normal diet plus mesalazine, patients receiving enteral nutrition supplements were significantly more likely to maintain remission after one year that those on normal diet. (HR 0.04 [0.18 to 0.98]).[LOW QUALITY]
- In one RCT (n = 51)[274] of enteral nutrition supplements (half enteral nutrition for calories) plus mesalazine vs. normal diet plus mesalazine, there were no adverse events in either study group.[LOW QUALITY]
- In one prospective cohort study (n = 66)[295] comparing enteral nutrition to normal diet, there was no significant difference in maintenance of remission between enteral nutrition and normal diet after complete withdrawal of glucocorticosteroid treatment and normal diet at one year (RR 0.74 [0.45 to 1.21]).[LOW QUALITY]
- In one observational study (n = 66)[296], there was no significant difference in treatment failure among patients using enteral nutrition supplements compared with normal diet (RR 2.14 [0.81 to 5.67]).[VERY LOW QUALITY]
- In one observational study (n = 31; one year)[130] in patients using enteral nutrition either alone (RR 1.92 [0.86 to 4.29]) or with drug therapy (RR 1.52 [0.66 to 3.49]) there was no significant different in maintenance of remission compared with patients with no treatment.[VERY LOW QUALITY]
- In one small observational study (n = 40; one year)[308] relapse rate was significantly lower in patients who received continuous nocturnal enteral nutrition compared with normal diet (enteral nutrition vs. no treatment by log rank test p = 0.01).[VERY LOW QUALITY]

**Paediatric studies**

- In one observational paediatric study (n = 47)[303] relapse rate was significantly lower in those who had enteral nutrition (RR 0.54 [0.33 to 0.88]) compared with normal diet.[VERY LOW QUALITY]

## 8.7 Economic evidence

One study was included, summarised in the economic evidence profile below (Table 38 and Table 39). See also the full study evidence table in Appendix F:.

**Table 71: Economic study characteristics**

| Study | Limitations | Applicability | Other comments |
|---|---|---|---|
| Takagi et al 2009: half-elemental diet versus free diet | Potentially serious limitations[a] | Partially applicable[b] | Based on the RCT by Takagi et al 2006 |

*(a) It is not clear whether all important and relevant costs were included in the study, and for the costs included, it is not clear as to whether these are real resource costs or charges. The trial was stopped early due to the observed treatment effect.*

*(b) The analysis was designed to reflect clinical management of Crohn's diseases in the Japanese healthcare system. HRQoL was assessed using disease-specific measurements rather than a generic instrument and QALYs were not calculated.*

**Table 72: Economic summary of findings**

| Study | Incremental cost (per patient) | Incremental effects (per patient) | ICER | Uncertainty |
|---|---|---|---|---|
| Takagi et al 2009: half-elemental diet versus free diet | £4512 | 0.29 relapses prevented[b] | £15,600 per relapse prevented[a] | Not reported |

*(a) Figures may differ due to rounding off.*

*(b) The study did not conduct an incremental analysis of costs and effects. Incremental costs and effects were calculated by the NCGC on the basis of data reported in the study.*

### 8.7.1 Evidence statements - economic

- On the basis of the one partially applicable economic study found (with potentially serious limitations):
  - It is unlikely that half-elemental diet compared with free-diet is cost-effective for maintenance of remission in Crohn's disease (at £15,600 per relapse prevented).

## 8.8 Enteral nutrition for maintaining remission after surgery

Please refer to section 7.8 for data pertaining to the use of enteral nutrition after surgery.

## 8.9 Linking evidence to recommendations

**Table 73: Linking evidence to recommendations – enteral nutrition for maintenance**

| | |
|---|---|
| **Clinical question** | **13.2 What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission in combination with**<br>• **conventional glucocorticosteroid treatment**<br>• **budesonide**<br>• **5-ASA treatment**<br>• **azathioprine or mercaptopurine**<br>• **methotrexate?**<br>**compared with any of the above?** |
| **Recommendation** | **None made. See research recommendation section 8.11** |
| **Relative values of different outcomes** | The key outcome of interest agreed prior to evidence evaluation was Crohn's disease remission maintained for 12 months or longer following medical treatment as measured by the CDAI.<br><br>Studies were only included in the review when patients were randomised during the quiescent phase of the disease. People with active Crohn's disease (active phase) and who then entered remission were excluded as they were not considered comparable with a quiescent phase population.<br><br>The GDG also agreed that for enteral nutrition trials, adverse events and withdrawals (due to palatability) were both important outcomes, although it is difficult to quantify some of the effects of ingesting a food supplement over a long-term period (e.g. lack of palatability) and then to draw a comparison with quantifiable effects ascribed to a drug.<br><br>Data were also reported for this review if study withdrawal was noted to be due to drug effect (rather than non-compliance or other reasons for drop-out).<br><br>Mucosal healing has been more recently emphasized as an end-point, and may not be described in older papers. The relative value of this outcome was felt to be less important than maintenance of remission data. This is because the patchy way in which the disease affects the intestines limits the application of histological sampling. When this evidence was available, it was reported. |
| **Trade off between clinical benefits and harms** | The GDG found it difficult to draw conclusions about the balance of adverse events versus efficacy when adverse event data were not well quantified and number and quality of studies reporting efficacy were low to very low. |
| **Economic considerations** | Enteral nutrition is considered to be a relatively costly option compared with normal diet or drug therapy with glucocorticosteroid, |

| | |
|---|---|
| | immunosuppressives and 5-ASAs. Cost is dependent on type, quantity and duration of enteral nutrition.<br><br>An economic evaluation from a Japanese perspective[274] found that half-elemental diet compared with free-diet cost about £15,600 per relapse prevented, which is unlikely to be cost-effective compared with a cost-effectiveness threshold of £20,000 per QALY gained.<br><br>Enteral nutrition was not included in the cost-effectiveness analysis because adverse event outcomes were poorly captured in the trial evidence. |
| **Quality of evidence** | **Induction of Remission**<br>The GDG noted that there was only one RCT considering maintenance of remission with enteral nutrition vs. normal diet in adults. The quality of this study was low due to large confidence intervals, small sample size and premature termination of the study. The GDG considered the other RCT included in the Cochrane review actually to be cohort observational data[295] as it compared two kinds of enteral nutrition and detected no difference between them.<br><br>Because of the paucity of data, observational studies were considered in the review – three prospective, and one retrospective chart study. The GDG commented in particular on the very low quality of the Yamamoto study for the following reasons: non-randomised, 40 consecutive patients, self-inserting nasogastric tube i.e. self selecting, no comparator group.<br><br>The GDG also noted that the enteral nutrition 'regimens' varied across studies e.g. enteral feeding via nasogastric tube, providing half-calorie requirements or oral nutritional supplements taken twice a day; thereby reducing consistency. |
| **Other considerations** | The GDG raised a number of points pertaining to the Japanese population studied (two of the total number of studies reviewed were in Japanese patients) and the application of the data to UK practice. Crohn's disease incidence, presentation, natural history and response to medication appear to be different in people of Japanese origin. The Japanese diet ("placebo arm") is very different from the UK Western diet. The formula, Elental, used in the Takagi study is currently unavailable in the UK. It is different in composition from the elemental formula currently available in the UK, particularly with regard to its lower fat content which may be important in Crohn's disease.<br><br>The GDG also made a number of observations about enteral nutrition in general. Costs of and commercial interests surrounding enteral nutrition are significant. The GDG highlighted the difference between enteral nutrition as a therapeutic agent for maintenance of remission and enteral nutrition as a nutritional supplement. Enteral nutrition is generally used as a food supplement to food (nutritional support) for people with malnutrition, growth failure or those following restricted diets, for example food reintroduction or exclusion diets following a period of exclusive enteral nutrition therapy, or for people who self-exclude foods they have identified to exacerbate symptoms and are unable to meet nutritional requirements once in remission (such as low |

| | |
|---|---|
| | fat food exclusion diet). In some cases, food exclusion diets are used to identify food intolerances with the aim of maintaining remission.<br>Nutrition support is not within the scope of this guideline, but readers are referred to Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition, published by the National Collaborating Centre for Acute Care; and available from www.rcseng.ac.uk/research/nccac.[192] Enteral nutrition can be used for nutritional support indefinitely, but it is preferable for people to return to a normal eating pattern and have a varied, balanced diet. Whilst acknowledging that dietetic advice and support is important, the GDG recognised that access to dietetic services is often limited.<br><br>There was some concern about long-term use of enteral nutrition for maintenance of remission (particularly regimens used in some studies which provide half-calorie needs), in people who are overweight or conversely who are able to meet their nutritional requirements with diet.<br><br>Given the overall consideration that the available data are poor (uncertainty, imprecision and indirect population), the GDG concluded that there is no evidence for the routine use of supplemental enteral nutrition for maintenance of remission in adults and children. The GDG was aware of a call for primary research into the effectiveness of enteral nutrition for maintenance of remission from the NIHR and agreed to await results of this research prior to making a recommendation. |

## 8.10 Recommendation

None made.

## 8.11 Research recommendation

The GDG was aware of a call for research initiated by the NIHR HTA programme in this area. For more information please visit: http://www.hta.ac.uk/funding/standardcalls/11_104cb.pdf.

# 9 Surgery

Surgery has a major role in the management of obstruction associated with Crohn's disease, as well as the removal of inflamed tissue which is unresponsive to medical therapy. Initial symptoms are due to local inflammation or to narrowing or stenosis causing obstruction. As time passes the disease can progress to a slow perforation of the intestinal wall which results in complications (such as local abscess formation[48,160]) that may require surgery.

Given the size of the topic in Crohn's disease, the GDG prioritised two areas for review considered to be both discreet clinical entities and for which data may exist that could pragmatically inform clinical practice – surgery compared with medical or nutritional management of disease limited to the distal ileum, and surgical management compared with balloon dilation of stricture in Crohn's disease.

# 9.1 Surgery versus medical management for disease limited to the distal ileum

## 9.1.1 Clinical introduction

Patients who present with disease limited to the distal ileum are usually treated by medication in the first instance, although practice varies widely. Evidence for thiopurine immunosuppression[49,216] and biological treatments compared with conventional medical therapy[55]) to reduce the need for surgery is equivocal. When medical treatment does not control the symptoms, surgery is then considered. A wide range of procedures can be performed, that involve removal of the diseased segment of intestine. Usually a surgical join (anastomosis) averts the necessity for a stoma.

Traditionally the operation has been carried out through an abdominal incision to enable open mobilisation and removal of the intestine. In the last ten years, laparoscopic surgery has been increasingly used so that by the end of 2009, just over 30% of abdominal colorectal procedures in the UK were carried out in this way[183,276], the rationale being that the reduced length of stay is offset by the cost of the instruments and the longer duration of the procedure.

Surgery results in a rapid restoration of the patient's health in most cases. Operative mortality is below 1% and anastomotic dehiscence below 5%.[41] A complication is more likely when perforating disease with local sepsis has occurred. Recurrent inflammation in the vicinity of the anastomosis occurs within one year in 70% of people with Crohn's disease[229] but this does not necessarily mean surgical resection will be required. Distal ileal Crohn's disease has a 90% likelihood of requiring surgery over a 15-year period.[24,81] Recurrence requiring resection has been reported to be about 30% at five years, and 50% at 10 years after the first resection[24,81] although lower rates of 17% at 10 years, and 56% at 20 years have been reported from a population-based study.[253] Long-term freedom from recurrence after surgical resection of up to 50% over 10 years has been reported.[54]

Early surgery has been advocated in patients with ileocolic Crohn's disease[133], with the reasoning that removal of the diseased segment is achieved before perforating disease develops. It is generally considered that a formal assessment of the relative benefits of surgery or non-surgical treatment would be of great practical value in a limited number of clinical situations, such as the management of distal ileal disease.[252]

It is argued that this strategy improves quality of life over time and is cost effective in avoiding long-term medical treatment. This is particularly relevant for children because timing of surgery in relation to closure of the epiphyses is a key consideration in terms of growth potential. The GDG were therefore interested to review any data that might inform surgery and medical management decisions in children.

Patient vignette 1

*The thought of surgery fills most Crohn's patients with overwhelming fear. After you've had it, you wonder where your symptoms have gone.*

Patient vignette 2

*A patient with Crohn's disease is more than an inflamed gut. Each one is a person with their own individual abilities, responsibilities, fears and hopes.*

### 9.1.2 Clinical question

In individuals diagnosed with Crohn's disease limited to the distal ileum, what is the clinical and cost-effectiveness of surgical resection for induction and maintenance of remission compared with medical or nutritional treatment?

### 9.1.3 Clinical evidence

No RCTs were identified which compared surgery and medical treatment or surgery and nutritional treatment for induction and maintenance of remission in Crohn's disease limited to the distal ileum. The data search was expanded to include observational studies of greater than 20 patients. It was decided that studies dating from the year 2000 would be separated out as a subgroup in order to take into account mainly the effect of biological treatments on the course of the disease but also changes in surgical techniques over the last decades including laparoscopic surgery. Two observational studies[240,254] (one paediatric) provided comparative data on the outcomes of patients managed either surgically or medically after 2000. Further details of the remaining studies are available in Appendix F:.

In view of the paucity of evidence for this question, it was considered that a summary of the data regarding the clinical, surgical and mucosal recurrence rates for elective surgery of the distal ileum would be useful when discussing options with people with Crohn's disease (Please refer to Appendix N:).

**Table 74: Evidence profile: medicine versus surgery: management for disease limited to the distal ileum – children**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Medicine | Surgery | Relative (95% CI) | Absolute | |
| **Height velocity (follow-up six months; Better indicated by lower values);** Singh Ranger et al, 2006 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 8 | | - | MD 0.39 higher (0.21 to 0.57 higher) | VERY LOW |
| **Weight velocity (follow-up six months; Better indicated by lower values);** Singh Ranger et al, 2006 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 8 | | - | mean 0.44 higher (0 to 0 higher) | VERY LOW |
| **Change HBI score (follow-up six months; measured with: HBI; Better indicated by lower values);** Singh Ranger et al, 2006 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 8 | | - | MD 1.16 lower (0.50 to 1.82 lower) | VERY LOW |

*1 Case series of eight patients.*

**Table 75: Evidence profile: medicine versus surgery: management for disease limited to the distal ileum – patients from age 14 onward**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Medicine | Surgery | Relative (95% CI) | Absolute | |
| **Hospital admissions (follow-up 16 months);** Sayfan et al 2000 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 5/22 (22.7%) | 1/12 (8.3%) | RR 9.17 (1.21 to 69.69) | 681 more per 1000 (from 18 more to 1000 more) | VERY LOW |
| **Weaned off glucocorticosteroid use (follow-up 16 months);** Sayfan et al 2000 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 0/8 (0%) | 10/16 (62.5%) | RR 0.09 (0.01 to 1.36) | 569 fewer per 1000 (from 619 fewer to 225 more) | VERY LOW |
| **Improved quality of life (follow-up 16 months; assessed with: questionnaire);** Sayfan et al 2000 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/12 (0%) | 22/22 (100%) | RR 0.04 (0.00 to 0.60) | 960 fewer per 1000 (from 400 fewer to 1000 fewer) | MODERATE |

*1 Crosses default MID 1.25.*

*2 Crosses default MIDs at 0.75 and 1.25.*

**Table 76: Time to recurrence – medical versus surgical management of disease of distal ileum**

| Study | Time to recurrence post medical treatment | Time to recurrence post surgery |
|---|---|---|
| Singh Ranger (2006)[254] | NA | Mean time to glucocorticosteroid-treated recurrence 20.1 months (5 to 61 months); mean surgery-free period 14.6 months (11 to 21 months) |
| Sayfan (2000)[240] | Not reported | Not reported |

**Table 77: Recurrence rates for elective surgery of disease of the distal ileum after first resection – from 2000 onwards**

| Author | Sample size | Site | Length of follow-up in years (median) | Overall recurrence rate (%) | Clinical recurrence rate (%) | Surgical recurrence rate (%) | Mucosal recurrence rate |
|---|---|---|---|---|---|---|---|
| Baldassano, 2001[18] | 39 | ileocaecal | 4.4 | 36 | NR | NR | NR |
| Cook, 2007[45] | 37 (32 with follow-up information) children | NR | 3.8 | NR | NR | 28 | NR |
| Eshuis, 2010[76] | 55 | ileocaecal | 6.8 | NR | 38 | 9 | NR |
| Ng, 2009[199] | 99 | ileocaecal | 1 | NR | 28 | 5 | NR |
| Stocchi, 2008[267] | 56 | NR | 10.5 | 52 | NR | 28.5 | NR |
| **Summary** | 247 | | | Range 36-52 % | Range 28-38% | Range 5-28.5% | NR |

*NR = not reported*

**Table 78: Time to recurrence – elective surgery of distal ileum - from 2000 onwards**

| Study | Time to recurrence | Time to reoperation |
|---|---|---|
| Baldassano (2001)[18] | Median recurrence free survival 3.94 years | NR |
| Cook (2007)[45] | NR | Median time to 2nd laparotomy 12 months (4 to 58 months) |
| Eshuis (2010)[76] | Kaplan Meir curve (follow-up time 84 months) presented but median recurrence of two types of surgery not estimable because there was more than 50% survival. | Kaplan Meir curve (follow-up time 84 months) presented but median recurrence of two types of surgery not estimable because there was more than 50% survival. |
| Ng (2009)[199] | Study population included patients with varying indications for surgery. At one year 28% of patients had clinical recurrence; 5% of patients had surgical recurrence. | Mean time to surgical relapse 11.8 months in 5% of patients with surgical recurrence. |
| Scarpa (2007)[241] | NR | NR |
| Stocchi (2008)[267] | NR | NR |

*NR = not reported*

#### 9.1.3.1 Evidence statements

- In one paediatric observational study of eight cases refractory to medical treatment, there was a significant increase in height velocity and a decrease in HBI scores after surgery. The mean weight velocity change was 0.44 kg/month (SD 0.88) and this was not significant (p = 0.19).[254] [VERY LOW QUALITY]
- In one observational study (n = 34), surgery was associated with:
  - A decrease in hospital admissions (RR 9.17 [1.21 to 69.69])
  - Weaning off glucocorticosteroid treatment (RR 0.09 [0.01 to 1.36])
  - Improvement in quality of life compared with no change in the medically-treated patients (RR 0.04 [0.00 to 0.60]).[240] [LOW - VERY LOW QUALITY]
- In four retrospective studies (n = 247) which followed patients from a median of 1 to 10 years, surgical recurrence rates for disease of the distal ileum ranged between 5% and 28.5%.[45,76,199,267][VERY LOW QUALITY]
- In one retrospective study (n = 39)[18] the overall median recurrence-free survival time was 3.94 years.[VERY LOW QUALITY]
- In one retrospective paediatric study of five children[66] all the children were weaned off glucocorticosteroid treatment following surgery and there was an average change in PCDAI score from baseline pre-operative score of -42.5 at six months.[VERY LOW QUALITY]

### 9.1.4 Economic evidence

No published data were found and original modelling was not undertaken for this question.

### 9.1.5 Linking evidence to recommendations

**Table 79: Linking evidence to recommendations – distal ileal surgery**

| | |
|---|---|
| **Clinical question** | **In adults and children diagnosed with Crohn's disease limited to the distal ileum what is the clinical and cost-effectiveness of surgical resection compared with medical or nutritional treatments for induction and maintenance of remission?** |
| **Recommendations** | **31. Consider surgery as an alternative to medical treatment early in the course of the disease for people whose disease is limited to the distal ileum, taking into account the following:**<br>**• benefits and risks of medical treatment and surgery**<br>**• risk of recurrence after surgery[l]**<br>**• individual preferences and any personal or cultural considerations.**<br>**Record the person's views in their notes.**<br>**32. Consider surgery early in the course of the disease or before or early in puberty for children and young people whose disease is limited to the distal ileum and who have:**<br>**• growth impairment despite optimal medical treatment and/or**<br>**• refractory disease.**<br>**Discuss treatment options within the multidisciplinary team and with the person's parent or carer and, if appropriate, the child or young person.**<br>*l Appendix N contains observational data on recurrence rates after surgery.* |
| **Relative values of different outcomes** | Surgery has the capacity both to induce and maintain remission (for an unpredictable length of time) via a single procedure.<br><br>In agreeing the key outcomes of interest prior to the evidence review, the GDG felt it was particularly important to consider a number of complications of surgery: for example, anastomotic dehiscence (which tends to occur early); wound herniation; adhesion, short bowel syndrome with multiple resections, obstruction; anaemia/B12 deficiency/bile salt malabsorption. Where these were found they were reported.<br><br>In other respects, such as for induction and maintenance of remission, the GDG considered similar parameters to those used to assess efficacy of drug treatment – namely objective measures of remission such as CDAI or HBI. The GDG noted a trend towards colonoscopy for determining mucosal healing or endoscopic recurrence, but acknowledged that this assessment of efficacy post surgery is not fully validated and is not universally available within England and Wales. |
| **Trade off between clinical benefits and harms** | Surgery can potentially provide many years of good health, but the complications which develop cannot be addressed as easily as is the case with medication, which can be stopped (although some of the hazards of medication are not reversible). The GDG debated increased risks associated with unplanned surgery and compared these with the benefits of less aggressive surgical interventions and cancer risk that may be ameliorated with surgery. However the evidence for these considerations was not formally reviewed as part of this question. |

| | |
|---|---|
| **Economic considerations** | Short-term costs are high with surgery (including in-patient stay, surgeon, anaesthetist and theatre costs) and complications can be expensive to treat. However, this needs to be weighed against relatively lower drug and monitoring costs. No formal comparison between surgery and medical treatment was found. |
| **Quality of evidence** | All the data presented were non-RCT observational.<br><br>There was considerable debate about possible effects of biologics on the course of Crohn's disease and patterns of surgery. High quality up-to-date data are not currently available – most data are case series – whereas the substantial recurrence rate following surgery will continue to stand despite changes in surgical techniques such as laparoscopy.<br><br>The GDG agreed that the studies included for review should be subgrouped into those that predated the introduction of biological treatments and those that might reflect any change in the course of Crohn's disease since their advent. For details of studies predating the year 2000, please see Appendix F:. Recurrence rate ranges for the two subgroups are reported in Appendix O:. The GDG noted that the range reported for the more recent analysis is narrower and considered a narrower range to be more useful when discussing risks and benefits with people with Crohn's disease. Recurrence rate ranges should be interpreted in the context of both background ranges of relapse rates with medical treatment and no treatment at all. These rates are not easily determined.<br><br>The GDG noted the small paediatric study which showed improved height velocity after surgery, and the prospective cohort study showing improved quality of life with surgery compared with a group managed conservatively. These data are consistent with the experience of the GDG. However, the absence of adequate control groups in these studies inevitably raises the possibility of bias in the outcome measures, and the GDG recognised the difficulty of drawing firm conclusions. |
| **Other considerations** | The GDG was aware of time commitments required to record in notes discussions about choices between surgery or medical treatment and resulting decisions, but felt this to be vital. The group agreed that decisions should be based upon discussion about risks of recurrence on medical treatment and with early surgery. The GDG felt that surgeons would be best placed to inform people with Crohn's disease about the benefits and risks of the surgery. The GDG was aware of the fear of surgery, and therefore considered "first-line" surgery (prior to a trial of medical treatment) to be unlikely from the patient's point of view.<br><br>**Children**<br>For surgery in children, the GDG agreed that timing of any surgery is critical, both in relation to timing of puberty and to key stages in education.<br><br>In generating the recommendation to consider surgery *early* in children with Crohn's disease limited to the distal ileum, the GDG wanted to be clear that surgery should not be delayed as the opportunity for remedial action for growth impairment may be lost when epiphyses fuse around puberty. (Of particular relevance to children with Crohn's |

| | |
|---|---|
| | disease, the GDG was aware of the association between glucocorticosteroid treatment and early fusion of the epiphyses.)<br><br>The group did not wish the recommendation to 'consider surgical intervention' early to be misinterpreted as an overly supportive stance for surgery in children, but the GDG debated the implications of growth impairment at length. The group acknowledged that failure to reach full height potential may result from long-term drug therapy which may not adequately have controlled the disease. They agreed that indications for surgery include:<br>• Crohn's disease-related growth impairment and failing medication or<br>• failing medication alone or<br>• growth impairment only, but as an indicator of refractory disease (i.e. occult disease activity demonstrated by further investigation of the child, for example, CRP or endoscopy)<br><br>When making a management decision, the GDG felt it important to consider the views of children and their parents/carers about potential adult height. A patient member of the GDG pointed out that people with Crohn's disease facing surgery find the risk of a resulting stoma to be challenging. These concerns should be balanced with the irreversibility of short stature.<br><br>**Multidisciplinary team**<br>If there is isolated distal ileal Crohn's disease a multidisciplinary approach was considered to be sensible, but the patient's wishes should be taken into account if they feel strongly either way and for any number of reasons. Even in the absence of a multidisciplinary team there should be discussion between gastroenterologist, surgeon and patient.<br><br>**Ongoing research**<br>The GDG was aware of an ongoing Dutch study in which ileocolic surgery is compared with infliximab therapy which may provide quality of life data over twelve months. The GDG agreed that it would be important to verify data from an UK effectiveness and cost perspective. A research recommendation comparing long-term quality of life outcomes with azathioprine maintenance, infliximab or surgery after a second presentation of Crohn's disease limited to the distal ileum was drafted. For more information please see Appendix O:. |

**Summary**

Based on the available evidence the GDG did not feel able to make a strong recommendation for surgical or medical/nutritional management of disease limited to the distal ileum, but considered that the best practice must include a patient-involved multidisciplinary approach.

## 9.2 Recommendations

**31. Consider surgery as an alternative to medical treatment early in the course of the disease for people whose disease is limited to the distal ileum, taking into account the following:**

- **benefits and risks of medical treatment and surgery**
- **risk of recurrence after surgery**[l]
- **individual preferences and any personal or cultural considerations.**

**Record the person's views in their notes.**

**32. Consider surgery early in the course of the disease or before or early in puberty for children and young people whose disease is limited to the distal ileum and who have:**

- **growth impairment despite optimal medical treatment and/or**
- **refractory disease.**

**Discuss treatment options within the multidisciplinary team and with the person's parent or carer and, if appropriate, the child or young person.**

## 9.3 Research recommendation

**4. What is the effect on quality of life of medical treatment (immunosuppressive or biological therapy) compared with early surgery for Crohn's disease limited to the distal ileum?**

Patients presenting for the first time with Crohn's disease limited to the distal ileum are usually treated with medical therapy. When relapse occurs there is the option of further medical treatment, including stepping up to a biological agent, or surgery in the form of a localised resection of the diseased segment of intestine. Comparative studies reporting the long-term outcome of each of these two management strategies are lacking. It is known that surgery is followed by recurrence in many cases, with rates for clinical and surgical recurrence of 30% to 50% and 20% to 30% respectively at five years. Reoperation rates rise to 30% to 60% at 10 years. Conversely, the majority of patients with Crohn's disease treated medically will require surgery at some time during their illness. During the period of continuing medical treatment, before a resection is performed, patients may have a reduced quality of life due to disease activity, or side effects of therapy. The relative merits of these two management strategies are unknown and there is a need to compare prospectively medical and surgical treatment for Crohn's disease limited to the distal ileum. A multicentre trial is currently in progress in Holland in which patients with Crohn's disease limited to the distal ileum are randomised to treatment with a biological agent or laparoscopic surgical resection at the point of failure of initial medical treatment. The study is asking an important question but whatever the results, it will require verification by other studies. It is recommended that a trial using a similar protocol be carried out in the UK, but that also considers the effectiveness of azathioprine as a medical treatment option. This would have the advantages of 1) comparing the results with those of the Dutch trial, 2) attempting to answer an important clinical question and 3) establishing multicentre trials in inflammatory bowel disease in the UK.

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*l Appendix N contains observational data on recurrence rates after surgery.*

# 9.4 Treatment of stricture in Crohn's disease: surgical management versus balloon dilation

## 9.4.1 Clinical introduction

Stricture formation is one of the pathological features of Crohn's disease and results in intestinal obstruction. This is a gradual process with acute obstruction being rare. Strictures may be long (over 5 cm) or short, they may be single or multiple and they may occur as part of the uninterrupted natural history of the disease or after an initial surgical resection when, usually, they are located on the proximal side of an anastomosis. The treatment of a symptomatic stricture is mechanical relief. This can be achieved by surgical resection or by surgical manipulation of the stricture by strictureplasty - transabdominal surgical intervention. The choice between these two options usually depends on various factors including the length of the stricture, the number, and extent of any previous resection(s), the rapidity with which recurrence had occurred and the possibility of further resection producing short bowel syndrome.

Endoscopic dilation of strictures has been carried out for some years. These have mostly been at a surgical anastomosis following an initial resection. Selected strictures amenable to possible dilation include those less than two to three centimetres in length without tortuosity. There is a risk of perforation of around 5% but, in selected cases, long-term surgery-free survival can be achieved in up to 50% of patients.[234] Improvements in instrumentation including the use of guide wires and better-adapted colonoscopes have been made. At the present time, a patient with an anastomotic stricture which may be suitable for dilation would reasonably have a trial of this treatment before surgery, provided the facility for immediate operation is available in case perforation occurs. The primary consideration for the GDG was what is the effectiveness of balloon dilation to either postpone or avoid surgery? The GDG were interested to review the recurrence rate of strictures amenable to dilation and which were considered to be successfully dilated at the time of surgery.

Developments in enteroscopy have rendered some strictures in the small intestine amenable to dilation.[65] However, this is an advancing field and more experience will be required before comparison with any other surgical treatment is possible. A review of stricture management in the small bowel is therefore not conducted within this guideline.

## 9.4.2 Clinical questions

In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of surgical treatment of stricture compared with

- balloon dilation?
- balloon dilation *plus* intralesional glucocorticosteroid injections?
- conservative management?

### 9.4.3 Clinical evidence

There were no RCTs which compared the efficacy, safety, quality of life and time to recurrence of balloon dilation for stricture to surgical procedures for stricture. Observational data for these two approaches to treating stricture in Crohn's disease were extracted into separate tables for comparison of outcomes. A minimum sample size of 20 was required for inclusion in this review. No time restriction was applied. Site-specific outcomes were not included in any of the balloon dilation study results reviewed. Only data from patients whose strictures were considered to have been successfully dilated were extracted as this presupposes appropriate patient selection for the procedure.

The summary results of 19 non-comparative observational studies of balloon dilation and 16 non-comparative observational studies of surgery for stricture are presented in the adapted GRADE tables below. Only one small paediatric study reporting change in PCDAI and weaning children off glucocorticosteroid treatment was found. As the data was non-comparative no statistical analysis could be conducted, and so a summary of the summed data is presented. Details of the individual studies can be found in evidence tables (Appendix F:) which contain the relevant data for each study.

**Table 80: Evidence profile: balloon dilation**

| Quality assessment | | | | | | | No of patients | Effect | Quality |
|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Balloon dilation | | |
| **Overall re-intervention for recurrence in successfully dilated patients versus re-operation (follow-up mean 6-107 months; assessed with endoscopy)** | | | | | | | | | |
| 7 | observational studies | no serious risk of bias | serious[1] | no serious indirectness | no serious imprecision | none | 278 | 137/278 (49.3%)[2] | VERY LOW |
| **Over all major complications (follow-up mean 6-107 months; clinically assessed)** | | | | | | | | | |
| 18 | observational studies | no serious risk of bias | serious[1] | no serious indirectness | no serious imprecision | none | 832 | 43/832 (5.2%)[2] | VERY LOW |

*1 Wide range of follow-up period.*

*2 Note the results presented are a summation from a number of studies without any statistical comparative analysis.*



**Table 81: Evidence profile: surgery for stricture**

| Quality assessment | | | | | | | No of patients | Effect | Quality |
|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | | |
| **Overall re-intervention for recurrence in successfully dilated patients versus re-operation (follow-up mean 6-107 months; assessed with endoscopy)** | | | | | | | | | |
| 16 | observational studies | no serious risk of bias | serious[1] | no serious indirectness | no serious imprecision | none | 1565 | 455/1565 (29.1%)[2] | VERY LOW |
| **Overall major complications (follow-up mean 6-107 months; clinically assessed)** | | | | | | | | | |
| 16 | observational studies | no serious risk of bias | serious[1] | no serious indirectness | no serious imprecision | none | 1565 | 210/1565 (13.4%)[2] | VERY LOW |

*1 Wide range of follow-up period.*

**Table 82: Surgery studies for stricture – in children**

| Study | Study period | No of patients | Median or mean age at surgery | Median* or mean follow-up (mo) | Site of surgery | | | | Early/late complications | Weaned from glucocortico-steroid treatment | Change in PCDAI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Jejunum/ Ileum | Previous anastomosis | Duodenum | Large bowel | | | |
| Oliva et al. (1994)[206] | 1987-1992 | 8 | Mean age 16 (10-19) | 19 (3-55) | Not reported | Not reported | Not reported | Not reported | 2 (haemorrhage) | 83% | NR |
| Di Abriola et al. (2003)[66] | N/A | 5 | Mean age 16 (14-20) | 22 (6-30) | 5 | 0 | 0 | 0 | 0 | 100% | -42.5 |

**Table 83: Evidence profile: surgery for stricture in children**

| Quality assessment | | | | | | | No of patients | Effect | Quality |
|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery | | |
| **Overall complications (early or late) (follow-up mean 19-22 months)** | | | | | | | | | |
| 2 | observational studies | no serious risk of bias | serious[1] | no serious indirectness | no serious imprecision | none | 13 | 2/13 (15.4%)[2] | VERY LOW |

*1 Very small sample size.*

#### 9.4.3.1 Evidence statements: balloon dilation versus surgery for treatment of stricture

**Efficacy and safety**

- In seven non-comparative observational studies of successful balloon dilation for treatment of stricture (n = 278)[4,88,95,131,174,184,234] the rate of re-intervention by balloon dilation or surgery for recurrencewas 49.7% (137/278).[VERY LOW QUALITY]
- In 16 non-comparative observational studies of surgery for stricture (n = 1565)[16,33,34,67,86,96,112,134,181,215,235,250,262,282,283,307], reoperation for recurrence occurred in 23.4% (455/1565) of patients.[VERY LOW QUALITY]
- In 18 non-comparative observational studies of successful balloon dilation for treatment of stricture (n = 832)[4,28,29,51,64,88,92,95,129,131,174,175,184,189,234,266,278,291] the rate of major complications was 5.2% (48/832).[VERY LOW QUALITY]
- In 16 non-comparative observational studies of surgery for stricture (n = 1565)[16,33,34,67,86,96,112,134,181,215,235,250,262,282,283,307], the overall rate of major complications was 13% (210/1565)).[VERY LOW QUALITY]
- The time to recurrence data were too disparate to permit summary statement.
- In one paediatric non-comparative observational study of eight children[206] there were two complications, one paediatric non-comparative observational study of five children[66] did not report any complications.[VERY LOW QUALITY]

### 9.4.4 Economic evidence

No published data were found and original modelling was not undertaken for this question.

### 9.4.5 Linking evidence to recommendations – management of stricture

**Table 84: Linking evidence to recommendations – management of stricture**

| | |
|---|---|
| **Clinical question** | **In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of surgical treatment of stricture compared with**<br>• **balloon dilation**<br>• **balloon dilation plus intralesional glucocorticosteroid injections,**<br>• **conservative management?** |
| **Recommendation** | **33. Consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy.**<br>**34. Discuss the benefits and risks of balloon dilation and surgical interventions for managing strictures[m] with:**<br>• **the person with Crohn's disease and/or their parent or carer, if appropriate, and**<br>• **a surgeon and**<br>• **a gastroenterologist.**<br>**35. Take into account the following factors when assessing options for managing a stricture:**<br>•**whether medical treatment has been optimised**<br>• **the number and extent of previous resections**<br>• **the rapidity of past recurrence (if appropriate)**<br>• **the potential for further resections**<br>• **the the consequence of short bowel syndrome**<br>• **the person's preference, and how their lifestyle and cultural background might affect management.**<br>**36. Ensure that abdominal surgery is available for managing complications or failure of balloon dilation.**<br>*m Appendix O contains observational data on stricturemanagement.* |
| **Relative values of different outcomes** | The GDG agreed that important outcomes when evaluating the effectiveness of balloon dilation compared with surgery for stricture were reoccurrence rates of symptomatic strictures necessitating repeat procedures (including subsequent surgery and / or second balloon dilation procedures) and time to reoccurrence. The GDG agreed these outcomes should be considered relative to quality of life and safety aspects including major complications such as perforation and severe haemorrhage requiring transfusion.<br><br>Sites of balloon dilation and site specific outcomes for this procedure were also of interest to the GDG – particularly whether there were more complications or better outcomes for certain sites. None of the papers found reported site specific outcomes for balloon dilation.<br><br>The GDG took account of trial data reporting surgery including resection or strictureplasty and not just strictureplasty.<br><br>The GDG were interested to know whether any of the papers reported stricture related malignancy. Again this was not reported in any of the papers found. |

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| **Trade off between benefits and harms** | The trade-offs between the success of either intervention (in terms of repeated procedures and time to reoccurrence) compared with the potential harms of perforation or major complications were of particular interest to the GDG.<br><br>The GDG debated when balloon dilation is likely to be used.<br>Anatomical site is also important in assessing suitability. Factors include whether the clinician can access the stricture, perceived risk of perforation, whether there has already been a high reoccurrence rate of stricture, subsequent need for surgery, and whether a single or multiple strictures. The consensus opinion of the GDG was that strictures generally regarded as being amenable to balloon dilation include those that are short, single, anastomotic, straight and inflammatory (as opposed to fibrotic/malignant).<br><br>The GDG noted the following rates based upon the observational data found:<br>Balloon dilation for strictures:<br>• 88% success<br>• 50% re-intervention in successfully dilated<br>• 5% major complications<br>• 1/4 end up needing surgery<br>• No reported deaths<br><br>Surgery for strictures:<br>• 23% re operation for recurrence<br>• 24% need for surgery<br>• Time to reoperation – variable<br>• 13% major complications<br>• 4/1565 x deaths.<br>For more information please see evidence tables in Appendix F:.<br><br>The GDG debated the different complication rates between the two interventions. They noted that the complication rate is dependent upon the time point at which is it reported. For surgery, approximately a third of people will have operations for reoccurrence and hence there is an added complication rate. For balloon dilation, if the complication rate is estimated immediately after the procedure the rate may appear lower than it actually is. The GDG noted the need to add the surgical complications rate to a third of those patients and that approximately half will have a re-balloon procedure and another quarter will have surgery.<br><br>Stricture population differences were discussed by the GDG. The consensus view was that most balloon interventions were on strictures at an anastomosis, whereas most strictureplasties were small bowel procedures. It was difficult for the GDG to make comparisons between two interventions when used in differing stricture populations. The group noted though that the reported data did not seem to support their clinical practice experience.<br><br>The GDG highlighted that 24% of people undergoing balloon dilation eventually required surgery. They also noted what they felt to be a fairly |

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| | high complication rate of 5% with each balloon procedure together with a 50% re-intervention in those with successfully dilated strictures.<br>This was traded off against the surgical complication rate of 13% (with each surgical stricture procedure) and 29% re-operation for recurrence.<br><br>There was no data available to allow the GDG to assess how many years of good quality life one could expect following each procedure.<br><br>The GDG also debated the possibility of carcinoma or lymphoma being associated with a long-standing stricture and that clinicians should be aware of this possibility as management for this would be substantially different. |
| **Economic considerations** | It is not possible to ascertain the relative cost-effectiveness of different treatments for stricture without better quality evidence of effectiveness. |
| **Quality of the evidence** | There were no RCTs which compared balloon dilation for stricture to surgical intervention for the outcomes of interest to the GDG. However 35 observational studies were available that reported outcomes for Crohn's disease stricture interventions; 19 papers reporting balloon dilation and 16 papers reporting surgery. The observation studies were graded as very low quality and only two of the papers were from a UK perspective. The GDG were aware that balloon dilation tends to be more commonly practised in the USA, Japan and some European countries.<br><br>The GDG noted the limitations in the evidence. The observational studies, whilst reporting differing types of stricture patients, did not provide comparative data. There were no truly comparative studies to enable the GDG to make a definitive recommendation about which intervention is better. The GDG debated the difficulties of comparative research in this area, for example, clinicians would not attempt to balloon dilate a long stricture.<br><br>There was one small paediatric study reporting change in HBI (Singh Ranger) and one adult study which looked at weaning people off glucocorticosteroid treatment (Sayfan). The GDG agreed that the long-term use of glucocorticosteroid treatment in children is unconventional.<br><br>The GDG noted one paper (Foster et al) reporting observational data (n = 24) for balloon dilation with adjunctive glucocorticosteroid intralesional injection at the time of the procedure. There was little evidence that this was of benefit.<br><br>The GDG noted one small observational (n = 27) Swiss study reporting that health related quality of life (HRQoL) was worse in the balloon dilation group. However the GDG highlighted that whilst significantly impaired in the balloon dilation patients this was versus both surgical controls and healthy subjects. The GDG gave little credence to this study given the limitations (Nguyen-Tang et al). |
| **Other considerations** | Balloon dilation was acknowledged by the GDG to be an advancing field. At present balloon dilation is not widely practised in the UK. The GDG |

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| | thought there was considerable variation across the UK in terms of current practice and availability of balloon dilation. Despite balloon dilation being available for some time and part of the armoury for treating Crohn's disease stricture it is more widely used on the Continent.<br><br>However, expert surgical UK advice indicated that if the stricture was amenable to balloon dilation this would generally be offered first in centres where available and already used before advising resection.<br><br>Overall with the observational data available the GDG agreed that it was not possible to compare the two interventions and to make a reasoned judgement for or against a particular intervention.<br><br>The GDG agreed that referrals for strictures varied across the UK and that combined multidisciplinary team decisions between the gastroenterologist, surgeon and patient should be facilitated.<br><br>The GDG agreed that in discussion with the person with Crohn's disease, individual patient factors should be taken into consideration by the surgeon and gastroenterology multidisciplinary team when deciding the best course of action.<br><br>The GDG considered that it would be helpful for healthcare professionals and people with Crohn's disease to be aware of the current observational data rates for intervention success, re-intervention and complications to enable informed decision-making. |

## 9.5 Recommendations

**33. Consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy.**

**34. Discuss the benefits and risks of balloon dilation and surgical interventions for managing strictures[m] with:**

- **the person with Crohn's disease and/or their parent or carer, if appropriate and**
- **a surgeon and**
- **a gastroenterologist .**

**35. Take into account the following factors when assessing options for managing a stricture:**

- **whether medical treatment has been optimised**
- **the number and extent of previous resections**
- **the rapidity of past recurrence (if appropriate)**
- **the potential for further resections**
- **the consequence of short bowel syndrome**
- **the person's preference, and how their lifestyle and cultural background might affect management.**

**36.Ensure that abdominal surgery is available for managing complications or failure of balloon dilation.**

## 9.6 Research recommendation

The GDG did not prioritise this area for future research.

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*m Appendix O contains observational data on stricture management.*

# 10 Monitoring

## 10.1 Monitoring for osteopenia and assessment of fracture risk

### 10.1.1 Clinical introduction

Osteopenia is the precursor to osteoporosis and the attendant risks associated with that condition. Its frequency has been reported as between 3% and 77%. However, in a population-based study from Limburg in the Netherlands male patients and those less than 18 years at diagnosis were more at risk of low bone mass at the lumbar spine. The prevalence of osteoporosis in postmenopausal women with Crohn's disease was 29% compared with 3% in premenopausal patients (odds ratio: 12).[244] In another study, bone mineral density was negatively correlated with lifetime glucocorticosteroid exposure, but not with previous bowel resection or current disease activity and fracture rate was not correlated with the bone mineral density or lifetime glucocorticosteroid dose.[268] In children, low bone mineral density has been associated with hypoalbuminemia, exposure to nasogastric tube feeds, total parenteral nutrition, mercaptopurine, and glucocorticosteroid treatment.[248]

The lack of clear causality between osteopenia and fracture in patients with Crohn's disease encouraged the GDG to focus on issues which were of practical concern to patients and impacted on daily life. Fractures are the clearest example of this. They do not need to be obviously symptomatic at the time of their occurrence. For example recurrent silent vertebral fractures can lead to long-term disability. However, in order to ensure early and effective treatment any predisposition to osteoporosis needs to be identified early and so the GDG elected to pose the question:

*"In adults and children diagnosed with Crohn's disease, what is the clinical and cost effectiveness of DEXA compared with no monitoring for changes in bone mineral density on patient outcomes (fracture rate)?"*

However, during the development of this guideline, the NICE clinical guideline on 'Osteoporosis: assessing the risk of fragility fracture' [190] in adults was developed. It identifies people at high risk of fragility fracture, and includes most people with Crohn's disease on the basis of glucocorticosteroid exposure, low body mass index (BMI), or both. This work supersedes the question originally posed by the GDG for people over 18 years. Readers are advised to refer to the NICE clinical guideline on osteoporosis. The GDG was nevertheless aware of the lack of guidance for children and young adults with Crohn's disease. They were interested to review any data that might indicate that children and young adults with Crohn's disease should be monitored in the same way as adults, as per the Osteoporosis Guideline. They therefore asked permission to change the question from the one originally posed.

### 10.1.2 Clinical question

In children and young people with Crohn's disease what is the risk of fracture?

### 10.1.3 Clinical evidence

This guidance cross refers to the NICE clinical guideline on 'Osteoporosis: assessing the risk of fragility fracture' (June 2012)[190]. However, the NICE guidance excludes young people under the age of 18. Therefore, a systematic review was undertaken to evaluate the literature on risk of fracture in children with Crohn's disease. One recent case-control study[147] was identified which assessed this outcome in a paediatric population.

**Table 85: Evidence profile: fracture risk in children with Crohn's disease**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Osteo monitoring** | **Control** | **Relative (95% CI)** | **Absolute** | |
| **Any fracture risk in children with Crohn's disease (follow-up two years);** Kappleman 2011 | | | | | | | | | | | |
| 1 | observational studies | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 60/737 8.10% | 200/1997 10% | OR 0.8 (0.6 to 1.1) | 18 fewer per 1000 (from 38 fewer to 9 more) | VERY LOW |

[1] *MID crosses default 0.75.*

#### 10.1.3.1 Evidence statement – clinical

- In one large paediatric case control study (n = 2734)[147] there was no significant difference in any fracture occurring in cases, versus controls (OR 0.8 [ 0.6 to 1.1]).[VERY LOW QUALITY].

### 10.1.4 Economic evidence

No published data were found and original modelling was not undertaken for this question.

### 10.1.5 Linking evidence to recommendations

**Table 86: Linking evidence to recommendations – monitoring for osteopenia in children and young people**

| | |
|---|---|
| **Clinical question** | **In children and young adults diagnosed with Crohn's disease, what is the risk of fracture?** |
| **Recommendations** | **Refer to 'Osteoporosis: assessing the risk of fragility fracture' (NICE clinical guideline 146) for recommendations on assessing the risk of fragility fracture in adults. Crohn's disease is a cause of secondary osteoporosis.**<br>**37. Do not routinely monitor for changes in bone mineral density in children and young people.**<br>**38. Consider monitoring for changes in bone mineral density in children and young people with risk factors, such as low body mass index (BMI), low trauma fracture or continued or repeated glucocorticosteroid use.** |
| **Relative values of different outcomes** | The GDG was aware that the Osteoporosis Guideline Update for *adults* would supersede any work done during development of this guideline. To support any recommendation for monitoring *children* with Crohn's disease for changes in bone mineral density, the GDG was keen to review the most stringent outcome measure - fracture risk. |
| **Trade off between benefits and harms** | Because no data were found indicating a best practice method for monitoring for bone density changes in children, the GDG felt that it could not specify a monitoring method. Hence an assessment of the balance of benefit and harm was not possible. |
| **Economic considerations** | To assess the cost-effectiveness of monitoring of bone mineral density would require the specification of a treatment protocol and estimates of effectiveness of treatment for specific population identified to be at risk, in addition to estimates of diagnostic accuracy. These are difficult to estimate for Crohn's disease. |
| **Quality of the evidence** | Only one case control study with 733 children matched to three controls, was identified, and critically appraised (Kappelman, 2008).[146] Participants were identified using US administrative database. Glucocorticosteroid exposure was measured using national drug codes and a sensitivity analysis conducted to determine the effect of glucocorticosteroid treatment on fracture risk in children. Children with Crohn's disease and ulcerative colitis were analysed separately.<br><br>Limitations to Kappelman data were noted:<br>• Fragility fracture and high impact fracture were not analysed separately (considering that well children participate in high impact sports and children who are unwell tend to be less exposed to trauma)<br>• Data relating to fractures in people on glucocorticosteroid treatment were not subdivided into Crohn's disease and ulcerative colitis (total IBD population)<br>• Children and young people were defined in the study as those less than 20 (Mean age in the study was 15) – not exactly in line with formal definition of less than 18 years, but the GDG did not consider this to be important.<br><br>Although the point estimate of the odds ratio (0.8) suggests that Crohn's |

| | |
|---|---|
| | disease appears to be protective against fracture, when confidence intervals are taken into account there is no statistically significant difference between children with Crohn's disease and n = 3287 controls i.e. children with Crohn's disease were not at greater risk of fracture. |
| **Other considerations** | In the absence of evidence the GDG were unable to make any paediatric recommendations specifically pertaining to the use of fracture risk assessment tools, monitoring or service provision implications.<br><br>Again in the absence of evidence the GDG agreed making a 'consider' recommendation for children based upon extrapolation from the adult Osteoporosis guideline indicating what factors might put children with Crohn's disease at high risk for fracture (for example low body mass index or repeated glucocorticosteroid use). The GDG agreed that decisions should be considered based on the clinical picture, but did not wish to specify either the method of monitoring or who would be best placed to manage the child should treatment be required. |

## 10.2 Recommendations

**Refer to 'Osteoporosis: assessing the risk of fragility fracture' (NICE clinical guideline 146) for recommendations on assessing the risk of fragility fracture in adults. Crohn's disease is a cause of secondary osteoporosis.**

**37. Do not routinely monitor for changes in bone mineral density in children and young people.**

**38. Consider monitoring for changes in bone mineral density in children and young people with risk factors, such as low body mass index (BMI), low trauma fracture or continued or repeated glucocorticosteroid use.**

## 10.3 Research recommendation

The GDG did not prioritise any future research in this area.

# 10.4 Early relapse

## 10.4.1 Clinical introduction

The concept that early detection of a relapse in Crohn's disease would lead to earlier treatment and therefore less severe and destructive disease is the basis for much of the long-term management of this condition. It appeals to both patient and clinician. It introduces the hope that effective treatment could alter the natural course of Crohn's disease. With this in mind there has been an ongoing search for indicators of an impending relapse. These have varied from a patient's own assessment of how they feel through to sophisticated monitoring of a range of inflammatory markers.

In order for such an approach to be effective it is essential that the marker changes significantly ahead of clinical deterioration. In other words changes in such markers need to be predictors of a clinical relapse rather than the consequence of it. For routine monitoring to be worthwhile these changes need to precede clinical deterioration by months rather than weeks. In addition there needs to be a clear level at which an abnormality is an effective predictor of disease relapse and there should not be significant overlap with levels that can be recorded during remission. Finally if such predictors of relapse can be identified they need to be of clinical value -they need to lead to interventions which can be shown objectively through randomised controlled trials to prevent or shorten disease relapse and to be reflected in a better quality of life for patients.

## 10.4.2 Clinical questions

Does predicting early relapse through monitoring

- Unintended weight loss
- CRP
- ESR
- MRI
- Calprotectin
- Colonoscopy/capsule endoscopy or
- Growth in children

compared with standard care, improve patient outcomes (quality of life, future surgery, hospitalization)?

## 10.4.3 Clinical evidence

There were no Cochrane reviews or RCTs identified for this prognostic review. A systematic review of the literature identified 11 cohort studies which met the inclusion criteria for this review. There were no studies which addressed the use of unintended weight loss, MRI, colonoscopy, endoscopy or growth in children for prediction of early relapse. Studies utilising faecal calprotectin (FC), CRP and ESR in adults[27,32,44,59,97,103,142,149,281,306] and children[297] for prediction of early relapse were reviewed. These studies were prognositic in design and assessed asymptomatic patients who were then followed to relapse.

The normal ranges for faecal calprotectin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are presented below. Measurement methods for faecal calprotectin in the included studies varied and all values are subject to laboratory specific variations.

| Faecal calprotectin µg/g | |
|---|---|
| Ages 2-9 years | < 166 |
| Ages 10-59 years | < 51 |
| Ages ≥ 60 | < 112 |
| | |
| **Faecal calprotectin mg/kg** | |
| Upper limit of normal | < 50 |
| | |
| **Faecal calprotectin mg/L** | |
| Upper limit of normal | < 10 |
| | |
| **CRP mg/L** | |
| Low risk IBD relapse (Normal) | < 10 |
| Average risk IBD relapse | 10 to 30 |
| High risk IBD relapse | > 30 |

| ESR mm/hour (upper limit of normal) | | | |
|---|---|---|---|
| Ages | 20 | 55 | 90 years |
| Men | 12 | 14 | 19 |
| Women | 18 | 21 | 23 |
| Neonatal to puberty | 3 to 13 | | |

For this prognostic review, time to event data, with multivariate analysis was extracted if possible. Cut-off values determined by ROC curves constructed to predict risk in individual studies are presented.

In this review the prognostic factor is a dichotomous variable and the outcome is time-to-event/dichotomous. The results (OR/RR/HR) describe the effect on the outcome of the presence compared with the absence of the prognostic factor. Presence versus absence means above versus below the threshold. The forest plots presented in Appendix G: show that when the odds ratio, relative risk or hazard ratio is greater than 1, values above the threshold predict relapse, and when below 1, values above the threshold predict protection against relapse.

**Table 87: Faecal calprotectin, CRP and ESR as predictors of early relapse – evidence profile**

| | Quality assessment | | | | | | Quality | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study design** | **Total number of patients** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other consideration** | **Study ID** | **Number of patients** | **Cut-off points** | **HR/OR/RR (95% CI)** | **Quality** |
| **Faecal calprotectin** | | | | | | | | | | | |
| 5 prospective cohort studies | 316 | High[1] | None | None | None | None | Dinca 2008 | 65 | > 130 mg/kg | OR 2.3 (0.21 to 25.68) | Low |
| | | | | | | | Garcia-Sanchez | 66 | > 200 mcg/kg | OR 4.35 (1.15 to 16.49) | |
| | | | | | | | Gisbert 2009 | 89 | > 150 mcg/kg | OR 4.22 (1.82 to 9.80) | |
| | | | | | | | Kallel 2010 | 53 | > 340 mcg/kg | OR 7.10 (1.22 to 41.43) | |
| | | | | | | | Tibble 2010 | 43 | > 500 mcg/kg | OR 10.80 (2.53 to 46.08) | |
| **CRP levels** | | | | | | | | | | | |
| 4 prospective cohort, 1 restrospective (Kurer 2007) | 388 | High[1] | None | None | None | None | Bitto 2008 | 101 | > 10 mg/L | HR 1.51 (1.15 to 1.98) | Low |
| | | | | | | | Kallel 2010 | 53 | > 6 mg/L | OR 5.10 (0.50 to 52.58) | |
| | | | | | | | Consigny 2006 | 71 | > 20 mg/L | RR 10.49 (0.33 to 330.15) | |
| | | | | | | | Dinca 2008 | 65 | > 6 mg/L | OR 0.64 (0.07 to 6.13) | |
| | | | | | | | Kurer 2007 | 98 | "Raised" vs "normal" | RR 0.84 (0.50 to 1.41) | |
| **ESR** | | | | | | | | | | | |
| Prospective cohort | 71 | High[1] | None | None | None | None | Consigny 2006 | 71 | > 15 mm/H | RR 6.1 (1.9 to18.9) | Low |

*1 All studies have high risk of bias, which include selection bias (not recruiting consecutive or random patients)27,44,149,297, high risk of bias for reporting of key confounders such as not considering all possible confounders, not stating clearly which confounders have been included, inadequate or unclear reporting confounder measurement, analysis method and covariates.*

#### 10.4.3.1 Evidence statements – clinical

- In a summary of five studies (n = 327)[97,103,142,281,297] faecal calprotectin appears to be effective for assessing risk of relapse in Crohn's disease. One study (n = 65)[59] showed no effect. Each study used different thresholds for prediction of relapse.[LOW QUALITY]
- In one study (n = 65)[59] CRP appears to be effective for assessing risk of relapse in Crohn's disease. A summary of three studies (n = 225)[27,44,142] showed no effect. Each study used different thresholds for prediction of relapse.[LOW QUALITY]
- In one study (n = 71)[44] ESR appears to be effective for assessing risk of relapse in Crohn's disease. One study (n = 65)[59] showed no effect. Each study used different thresholds for prediction of relapse.[LOW QUALITY]

### 10.4.4 Economic evidence

No published data were found and original modelling was not undertaken for this question.

## 10.4.6 Linking evidence to recommendations

**Table 88: Linking evidence to recommendations – monitoring for early relapse**

| | |
|---|---|
| **Clinical question** | **Does predicting early relapse through monitoring**<br>• **Unintended weight loss**<br>• **CRP**<br>• **ESR**<br>• **MRI**<br>• **Calprotectin**<br>• **Colonoscopy or capsule endoscopy**<br>• **Growth in children**<br>**compared with standard care, improve patient outcomes (quality of life, future surgery, hospitalization)?** |
| **Recommendation** | **None made.** |
| **Relative values of different outcomes** | The GDG wished to gather any evidence that might support the use of any of a list of alternative monitoring methods. The GDG felt that in order to be able to recommend monitoring for relapse, any test would need to demonstrate the ability to predict a relapse at a time period sufficiently early enough for action to be taken to avoid symptomatic relapse. Review of the literature revealed no studies pertaining to unintended weight loss, MRI, colonoscopy/capsule endoscopy or growth in children as predictors of relapse in Crohn's disease. In addition, thresholds associated with high relapse risk for any of the tests listed above, were not universally defined in the literature.<br><br>There was wide variation in threshold levels and the outcomes reported thereby making it very difficult for the GDG to compare data. The GDG made the following points:<br>• The timing of faecal calprotectin assay is important in interpreting the results. If faecal calprotectin was assessed immediately after an exacerbation, it would have different implications to if it was assessed at random time-points, for example at routine follow-ups. All patients in the studies reviewed were initially assessed in an asymptomatic state, after they had been in remission for at least one month.<br>• It is important to highlight that this question considers the potential of a test to *predict* relapse before people become symptomatic, rather than looking at the tests to assess their value in *confirming* a relapse, which is symptomatic.<br>• Even if there is a test that can predict relapse before symptoms occur, that the best course of action based upon this information is as yet undemonstrated i.e. to treat or not treat, and if so, with what? |
| **Trade off between benefits and harms** | The GDG did not consider the process of having a blood test to cause substantial harm. The GDG did consider whether a false positive test predictive of relapse might expose people to unnecessary harm should they be unnecessarily treated. As neither "accepted management" for this situation yet been agreed, nor was this the question posed, the GDG could not make an informed assessment of this issue. |
| **Economic considerations** | To assess the cost-effectiveness of monitoring of early relapse would require the specification of a treatment protocol and estimates of effectiveness of treatment for specific population identified to be at risk, in addition to estimates of diagnostic accuracy. The GDG was not aware of any trials that |

| | |
|---|---|
| | have evaluated the effects of early treatment.<br><br>If monitoring for early relapse is found to be effective then it is possible that monitoring could be a more cost-effective strategy than maintenance therapy. |
| **Quality of the evidence** | A prognostic approach using cohort studies was undertaken. Cox regression analysis is considered the best way to analyse prognostic data, but this was not always available in the studies identified.<br><br>Studies reviewed used ROC intersection of optimal specificity and sensitivity curves to determine the threshold of a given test to potentially indicate a high relapse risk. Studies were found reporting these thresholds for faecal calprotectin, ESR and CRP.<br><br>In order to compare the value of each heterogeneous test in predicting relapse, the standard error for each study was calculated. Each of these common measures of each statistic was put into a non-pooled forest plot.<br><br>Results:<br>• Faecal calprotectin appeared to predict potential relapse, but the data did not indicate when or how often the test should be done. The GDG felt this to significantly limit the value of this monitoring approach and acknowledged that future research in this area would be useful. They did not however prioritise it for a research recommendation.<br>• The GDG considered the CRP data to be less convincing, with two results crossing the line of no effect. The GDG considered CRP possibly to be helpful but on the basis of the above results and without more robust data it was difficult to draw a firm conclusion.<br>• Two studies looking at ESR had directly conflicting results. Therefore the GDG did not consider ESR to be helpful in predicting relapse.<br><br>The GDG looked for data which might provide evidence for the intervals at which patients should be assessed in order to predict relaps, prior to symptomatic presentation. This information could not be extracted from the available data. Given the paucity and low quality of the evidence, the GDG were unable to make a recommendation. Whilst the GDG acknowledged there was limited evidence currently available, the GDG did not give high priority to a future research recommendation in this area. |
| **Other considerations** | The GDG sought the views of the patient members of the GDG and noted the comment “If you can predict you are heading towards a flare-up, and something can be done to minimise or avert it, that would be a huge benefit” and, however, that “Colonoscopy is as bad as the disease”. They noted that patients may not accept frequent ongoing monitoring of this relatively invasive nature (as opposed to follow-up endoscopy/colonoscopy after surgery or biological treatments which are “once-off” investigations checking for endoscopic recurrence or mucosal healing respectively). In any event, the literature was searched, and no evidence found for the capsule endoscopy/colonoscopic monitoring element of the question.<br><br>The GDG felt it important to stress that even if a test could predict relapse before symptoms occur, best practice in responding to this information is as yet undetermined i.e. treat/do not treat, and if so, with what? Changes in |

| | |
|---|---|
| | outcomes have not yet been proven. |

## 10.5 Recommendation and research recommendation

Whilst the GDG did not feel there was enough evidence to make a recommendation they also did not designate high priority to future research in this area because they believed there to be ongoing commercial interests in the assessment of a range of biomarkers in this field.

# 11 Patient information and support

## 11.1 Clinical introduction

The effects of Crohn's disease on an individual are diverse. In addition to its physical impact there can be emotional, psychological, spiritual and social consequences. Information giving is one aspect of support that may help an individual address issues such as diagnosis, low mood, tiredness and coping skills, quality of life, effects on family and friends, relationships, education, work and social difficulties. In 1983 a study from South Wales had identified these needs.[218] It subsequently became clear that these concerns were common throughout much of Europe[141,171,186] and were also true for the parents of children with the condition.[61]Work from Leeds in the 1990s showed that more than 80% of patients wanted more information about their disease.[141] In a subsequent study from Austria low information levels about Crohn's disease were linked with greater concerns.[186] It is important that they are recognised and additional support is given.

The NICE document "Patient Experience in adult NHS Services (NICE clinical guidance 138)" highlights the need to treat people as individuals and to tailor their care accordingly.[191] Points emphasized include the person having timely and appropriate access to the relevant healthcare professional at point of need. People with Crohn's disease need ongoing access to a multidisciplinary team (MDT). Each member of the MDT plays an important role in the management and support of people with Crohn's disease. Regular team meetings can be used to identify people with complex needs and ensure the appropriate healthcare professionals become involved. This should also include radiologists and pathologists as well as physicians and surgeons.

The IBD Standards Group recommends rapid access to specialist advice and care which is generally provided by IBD Specialist Nurses[135]. This may include a telephone advice and support service, ensuring prompt and appropriate care.[102] Specialist Pharmacists are increasingly providing patient-centred care, particularly where immunosuppression and biological treatments are used. Dietitians are also important members of the MDT and provide nutritional assessment, advice and support for persons throughout their disease process.

Access to psychologists and counsellors is important for a range of problems and people with Crohn's disease may benefit from their input at various stages of their disease. Improved access to these services has been recommended by the IBD Standards Group and the British Society of Gastroenterology. The effectiveness of their role, however, awaits rigorous evaluation.

There is a particular aspect of information and support that requires special mention because of its unambiguous effect on people with Crohn's disease. In 1984 smoking was shown to increase the risk of developing Crohn's disease almost five-fold.[261] It soon became clear that heavy and prolonged smoking was associated with a worse outcome[155] and that it was an independent predictor of recurrence following surgery.[50] Counselling and smoking intervention programmes led to a more benign course for the disease[47]. However, despite these benefits, response rates can be disappointing - although in line with general smoking cessation programmes.[128] Nevertheless patients with Crohn's disease who smoke should be actively encouraged to give up the habit and be directed towards appropriate services and support as identified in other NICE guidance:

- Smoking cessation services. NICE public health guidance 10 (2008). www.nice.org.uk/guidance/PH10
- Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). www.nice.org.uk/guidance/TA123
- Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006). www.nice.org.uk/guidance/PH1

In addition to this information, however, the GDG wished to review any data that could help inform what information people with Crohn's disease actually want. The GDG was also interested to determine whether the information needs of children and young people (and their carers) differ from those of adults. To this end, a specific search for the population of children and young people was completed and results are presented separately.

Patient vignette 1

*Patients need good quality, well-written and reliable information – the right amount at the right time. And the opportunity to ask questions.*

Patient vignette 2

*If living with Crohn's is like a journey, then different forms of information and support will be needed at different points on the route. There's no point having a map of London when you're negotiating the Himalayas.*

Patient vignette 3

*Sometimes, all the emotional support a patient needs is to meet another person with Crohn's and realise that they are not alone; that life will go on.*

Patient vignette 4

*I find it incredible that smokers faced with this chronic incurable disease put a higher priority on the 'pleasure' of nicotine instead of the pleasures of enjoying life without Crohn's.*

## 11.2 Clinical questions

What are the primary information needs of adults with Crohn's disease in the UK?

What are the primary information needs of children and young people with Crohn's disease in the UK?

## 11.3 Clinical evidence

A literature search was conducted for studies that reported information needs identified by people with Crohn's disease. No study design filter, geographical location or time limit was placed on the literature search, and there were no limitations on sample size. Five patient surveys[40,171,177,204,218] were identified which addressed the question and were included in the review. Information from the studies was further synthesised into themes and has been summarised in a modified clinical evidence profile and evidence statements. The included studies were critically appraised using the appropriate checklist as specified in The Guidelines Manual.[197]

No paediatric papers were identified which addressed the question specifically. However a GDG member suggested that the group review two papers, Richardson et al 2001[225] and Griffiths 1999[116] to consider quality of life issues identified by children which might influence information-giving in this population.

1 **Table 89: Information needs of adults with Crohn's disease**

| No. of studies and study design | Study sample in the studies | Themes emerged<br>[Clarification: not all participants reported in the study sample had contributed to the themes] | Study limitations | Indirectness (Transferability) | Other considerations |
|---|---|---|---|---|---|
| Theme: Information needs | | | | | |
| 1 study<br>218<br>Questionnaire | n = 73 CD patients | The number of patients wanting more information about Crohn's disease in general: 64 (88%).<br>The top five information needs of CD patients (%):<br>Cause of CD (77%)<br>Treatment (53%)<br>Side effects of treatment (47%)<br>Diet (45%)<br>Systemic complications (44%) | Low quality – subjective data<br>No report of questionnaire development, testing for reliability and validity, data entry<br>Response rate not clearly stated (?100%)<br>Closed questions<br>Transferable to population | | |
| 1 study<br>177<br>Questionnaire | n = 175 CD patients and 93 nurses with CD | Inadequate information as assessed by Welsh patients (WP) and nurses (N) with CD:<br>Prognosis [72% WP; 68% N]<br>Risk to family members [54% WP; 30% N]<br>Complications of disease [47% WP; 21% N]<br>Drug treatment [28% WP; 21% N]<br>Surgical treatment [27% WP; 30% N]<br>Symptoms [25% WP; 26% N]<br>Investigations [23% WP; 15% N]<br>Medical examination of the patient [17% WP; 11% N]<br>Additional information requested by Welsh patients (WP) and nurses (N)with CD:<br>Risk of cancer [75% WP; 70% N]<br>Effect of disease on sexual activity and pregnancy [58% WP; 70% N]<br>Effect of disease on eligibility for life insurance [58% WP; 70% N]<br>Eligibility for disability allowances [63% WP; 60% N] | Overall comments<br>Low quality – subjective data<br>No report of questionnaire development, testing for reliability and validity, data entry.<br>Closed questions<br>Transferable to population | | |
| 1 study<br>171 | n = 50 | Information requested by patients with CD<br>High priority:<br>Causes of disease | Overall comments<br>Low quality – subjective data<br>No report of questionnaire development, testing for | | |

| No. of studies and study design | Study sample in the studies | Themes emerged<br>[Clarification: not all participants reported in the study sample had contributed to the themes] | Study limitations | Indirectness (Transferability) | Other considerations |
|---|---|---|---|---|---|
| Questionnaire | | Diet<br>Symptoms<br>Long-term evolution (prognosis)<br>New treatments and drugs<br>Therapy<br>Medium priority:<br>Psychology<br>Investigations<br>Surgery<br>Risks from therapy and investigations<br>Cancer<br>Consequences on work | reliability and validity, data entry. Arbitrary cut-off points applied.<br>Closed questions<br>Transferable to population | | |
| 1 study<br>204<br><br>Written response to an open-ended question | n = 60 CD patients | The top five information needs of CD patients (%):<br>Prognosis (17)<br>Cancer (17)<br>Medications (10)<br>Surgery (10)<br>Miscellaneous (10) | Overall comments<br>Low quality - subjective data<br>No report of data analysis<br>Transferable to population | | |
| 1 study<br>40<br><br>Questionnaire | n = 115 | Areas in which patients lacked information:<br>Causes of disease (65 patients)<br>Potential outcome of disease (60 patients)<br>Complications that may arise (58 patients)<br>Management of disease (24 patients)<br>Need for surgical procedure (19 patients)<br>Possibility of transmission to offspring or contagion (36 patients) | Overall comments<br>Low quality – subjective data<br>No report of questionnaire development, testing for reliability and validity, data entry<br>Closed questions<br>Transferable to population | | |

**Table 90: Concerns of children with IBD**

| No. of studies and study design | Study sample in the studies | Themes emerged<br>[Clarification: not all participants reported in the study sample had contributed to the themes] | Study limitations | Indirectness (Transferability) | Other considerations |
|---|---|---|---|---|---|
| Theme: Top ten concerns of children with IBD | | | | | |
| 1 study<br>Griffiths et al, 1999[116] | n = 87 CD patients; 30 UC patients<br>Ages 12 or less 20 CD, 6 UC. Ages 13 to 17 years 66 CD, 25 UC. | • Feeling bother by having to take medications<br>• Feeling worried about possible flare-up<br>• Feeling upset that IBD is a lifelong thing<br>• Being concerned about weight<br>• Feeling worried about health problems you might have in future<br>• Being bothered about height<br>• Feeling bothered about stomach pain or cramps<br>• Feeling you have to give up doing things because of IBD<br>• Feeling that you don't have energy to do the things you want<br>• Feeling that it is unfair that you have IBD | Low quality – subjective data<br>Questionnaire developed in conjunction with the adult IBDQ and paediatric interviews but not yet tested for reliability or validity<br>List of concerns represent a ranking by importance of interview results | | |
| 1 study<br>Richardson et al, 2001[225] | n = 47 CD patients and 6 patients with UC<br>Ages ≤ 12 1 UC and 13 CD; age ≥ 13 years 5 UC and 34 CD | Top ten concerns of children in UK with IBD CD:<br>• Feeling worried about the possibility of flare-up<br>• Feeling upset the IBD is life long<br>• Feeling that it is unfair that you have IBD<br>• Concern about weight<br>• Concern about way you look because of IBD<br>• Feeling worried about needing surgery<br>• Stomach pains or cramps<br>• Feeling worried about health problems you might have in the future<br>• Feeling angry that you have IBD<br>• Feeling bothered that there don't seem to be good treatments for IBD | Low quality – subjective data<br>No report of questionnaire development, testing for reliability and validity, data entry<br>Appears to be closed questions | | |

#### 11.3.1.1 Evidence statements - clinical

Information needs of patients based on five low quality surveys (n = 473)[40,171,177,204,218] of individuals with Crohn's disease:

- Therapy/management[40,171,177,204,218]
- Prognosis[40,171,177,204]
- Surgery[40,171,177,204]
- Cancer[171,177,204]
- Causes (aetiology)[40,171,218]
- Complications[40,177,218]
- Transmission[40,177]
- Symptoms[171,177]
- Investigation[171,177]
- Diet[171,218]
- New treatment and drugs[171]
- Medical examination[177]
- Effect on work[171]
- Sexual activity and pregnancy[177]
- Life insurance[177]
- Disability insurance[177]
- Side effects[218]

In two low-quality studies the concerns of children with IBD (n = 134 with CD and 36 with UC)[116,225] were identified:

- Feeling bother by having to take medications
- Feeling worried about possible flare-up
- Feeling upset that IBD is a lifelong thing
- Being concerned about weight
- Feeling worried about health problems you might have in future
- Being bothered about height
- Feeling bothered about stomach pain or cramps
- Feeling you have to give up doing things because of IBD
- Feeling that you don't have energy to do the things you want
- Feeling that it is unfair that you have IBD
- Concern about way you look because of IBD
- Feeling worried about needing surgery
- Feeling angry that you have IBD

## 11.4 Economic evidence

No published data were found and original modelling was not undertaken for this question.

## 11.5 Linking evidence to recommendations

**Table 91: Linking evidence to recommendations – patient information and support: adults**

| | |
|---|---|
| **Clinical question** | **What are the primary information needs of adults with Crohn's disease?** |
| **Recommendations** | **39. Ensure that information and advice about Crohn's disease:**<br>**• is age appropriate**<br>**• is of the appropriate cognitive and literacy level, and**<br>**• meets the cultural and linguistic needs of the local community.**<br>**40. Discuss the possible nature, frequency and severity of side effects of drug treatment[n] with people with Crohn's disease, and/or their parents or carers if appropriate.**<br>**41. Give all people with Crohn's disease, and/or their parents or carers if appropriate, information, advice and support in line with published NICE guidance on:**<br>**• smoking cessation**<br>**• patient experience**<br>**• medicines adherence**<br>**• fertility.**<br>**See 'Relationships between the guideline and other NICE guidance' section 2.6.**<br>**42. Give people with Crohn's disease, and/or their parents or caresr if appropriate, additional information on the following when appropriate:**<br>**• possible delay of growth and puberty in children**<br>**• diet and nutrition**<br>**• fertility and sexual relationships**<br>**• prognosis**<br>**• side effects of their treatment**<br>**• cancer risk**<br>**• surgery**<br>**• care of young people in transition between paediatric and adult services**<br>**• contact details for support groups.**<br>**43. Offer adults, children and young people, and/or their parents or carers if appropriate, age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education.**<br>[n] *Appendices L and M contain observational data on adverse events associated with 5-ASA treatment and immunosuppressives.* |
| **Relative values of different outcomes** | Much patient information is applicable to any patient. Moreover, much information relating to a chronic illness is applicable to many people with a different, but nevertheless long-term chronic conditions. The GDG was particularly interested to know what information people with Crohn's disease (specifically) requested. They gave more credibility to well-designed qualitative studies in a Crohn's disease population and which were methodologically rigorous.<br><br>They agreed that key information requirements specific to people with Crohn's disease included cancer risk, surgery, sexual issues and pregnancy. |
| **Trade off between benefits and harms** | The GDG was aware of some evidence that information may on occasion have a negative impact on outcomes. However this was not formally |

| | |
|---|---|
| | assessed as part of this review. Given this caution, the GDG felt that it was important for healthcare professionals to take into account their knowledge of the person with Crohn's disease and their preferences. |
| **Economic considerations** | The GDG commented that services would need to be configured taking account of the time and expertise required to collate and offer this information. |
| **Quality of the evidence** | A broad search was done to identify qualitative studies with no limitations on dates, study filters, population or sample size. Studies considering patients' requests for information were sifted and ordered. The GDG debated the following with relation to the quality of the data:<br>• differing comparisons were made between the studies – some stated what information patients wanted, and others stated what information they considered to be inadequate<br>• some studies considered what information patients needed, but did not specify what information these patients had had prior to the study (i.e. lacked historical information)<br>• questionnaires and surveys are tools and frequently employed closed question style i.e. patients choose from a list of topics (biased as the topics are pre-selected) rather than open-ended questions which are information generating. |
| **Other considerations** | In view of the applicability to all patients of certain information readers should refer to "Patient experience in adult NHS services (NICE clinical guidance 138)" and Medicines Adherence NICE clinical guideline 76). In addition the GDG discussed information available from local support groups and from other sources such as the Internet (NHS choices) as well as the need to make patients aware of members of the multidisciplinary team and relevant contact details. The GDG noted that these aspects were covered by Patient Experience CG138.<br>The patient representatives of the GDG noted that patients needed different information at different times, but that it is difficult to predict who needs what, when. They felt that information should be:<br>• action-based (that is, if this happens, do that, or call this person) and<br>• sign-posted to reliable and accurate information on a broad range of subjects (there was agreement that the list presented in review was considered to be comprehensive) and that this should be frequently reinforced.<br>The GDG noted that most of these points were covered by Patient Experience CG138.<br><br>The group agreed the need for a Crohn's disease research recommendation for information needs using a qualitative paradigm. The GDG noted the current evidence base in this area to be predominately surveys, interviews, questionnaires (e.g. tools).<br><br>The GDG debated the need for local protocols around patient information and concluded that this guideline and the resultant recommendations would meet this need. |

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**Table 92: Linking evidence to recommendations – patient information and support: children and young people**

| **Clinical question**<br><br>**Recommendations** | **What are the primary information needs of children and young people with Crohn's disease?**<br><br>**43. Offer adults, children and young people, and/or their parents or carers age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education.** |
|---|---|
| **Relative values of different outcomes** | The GDG noted focus group data pertaining to children's information needs.[116,225] In the absence of higher quality evidence, the GDG was interested in the qualitative results. |
| **Trade off between benefits and harms** | The GDG was aware of some evidence that information may on occasion have a negative impact on outcomes. However this was not formally assessed as part of this review. Given this caution, the GDG felt that it was important for healthcare professionals to take into account their knowledge of the person with Crohn's disease and their preferences. |
| **Economic considerations** | The GDG commented that services would need to be configured taking account of the time and expertise required to collate and offer this information. |
| **Quality of the evidence** | Two focus group reports of low quality, including both paediatric and adolescent populations with Crohn's disease were reviewed.<br><br>Children's concerns were found to be similar to those of adults, but perhaps were more focussed on body image. The data provided an indication of the support children and young people need. The GDG noted that although many children and young people have similar body issues, these concerns could be exacerbated by their Crohn's disease. |
| **Other considerations** | The GDG emphasized:<br>• the importance of a healthcare professional, for example an IBD nurse in liaising with schools and providing information regarding the non-infective nature of the diarrhoea associated with Crohn's disease<br>• that 'support' should not be interpreted within a narrow sense, for example only psychological support. Support should be broad-based and offered by those whom are best placed at the time to meet the needs of adults, children, and also the parents/carers of children with Crohn's disease<br>• that information and support, and indeed treatment, should be provided in an environment appropriate to the age of the person with Crohn's disease<br>• the existence of transition guidance for young people becoming adults: Transition: getting it right for young people: Improving the transition of young people with long term conditions (available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_4132944) considers the relevant principles.<br>• the challenge associated with balancing the rights of the child, confidentiality and acting within the best interests of the child. The reader is referred to the introductory section for children and young people, |

| | |
|---|---|
| | section 1.5. |

## 11.6 Recommendations

**39.Ensure that information and advice about Crohn's disease:**

- **is age appropriate**
- **is of the appropriate cognitive and literacy level, and**
- **meets the cultural and linguistic needs of the local community.**

**40.Discuss the possible nature, frequency and severity of side effects of drug treatment[n] with people with Crohn's disease, and/or their parents or carers if appropriate.**

**41.Give all people with Crohn's disease, and/or their parents or carers if appropriate, information, advice and support in line with published NICE guidance on:**

- **smoking cessation**
- **patient experience**
- **medicines adherence**
- **fertility.**

**See 'Relationships between the guideline and other NICE guidance' section 2.6.**

**42.Give people with Crohn's disease, and/or their parents or carers if appropriate, additional information on the following when appropriate:**

- **possible delay of growth and puberty in children and young people**
- **diet and nutrition**
- **fertility and sexual relationships**
- **prognosis**
- **side effects of their treatment**
- **cancer risk**
- **surgery**
- **care of young people in transition between paediatric and adult services**
- **contact details for support groups.**

**43.Offer adults, children and young people, and/or their parents or carers, age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education.**

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*n Appendices L and M contain observational data on adverse events associated with 5-ASA treatment and immunosuppressives*

## 11.7 Research recommendation

**5. What are the information needs of people with Crohn's disease, as defined by people with the condition, and can education and support based on these needs lead to better clinical and quality-of-life outcomes?**

Crohn's disease is a life-long condition which continues to have a significant impact on all aspects of life. The development of an educational and support program could lead to significant reductions in the cost of treatment and the social impact of the disease. Further research should be undertaken to determine the information and support needs of people with Crohn's disease. It should use qualitative techniques to identify the concerns of people with the condition and how they should be best addressed. Delphi techniques would ensure that the professional understanding of these needs was appropriate. From this work a randomised controlled trial would be designed to investigate the impact of a patient-originated program on health outcomes including frequency of relapse and need for surgery as well as quality of life issues.

# 12 Conception and pregnancy

## 12.1 Introduction

The scope remit included "Consideration will be given to specific needs, if any, in pregnancy and females of child-bearing potential." Therefore the specific needs of pregnant women and females of child-bearing potential were considered by the GDG. With the peak occurrence of Crohn's disease in people during reproductive years, 25% of people with Crohn's disease conceive after the diagnosis is made. Issues relating to fertility, pregnancy, delivery and breast-feeding are therefore important concerns for people with Crohn's disease and clinicians involved in their care. Advice and information may be required at a number of different times during an individual's course and evidence to support such discussions was felt to be important by the GDG. The inevitable lack of randomized-controlled trial data in women in pregnancy meant that the GDG had to make recommendations based on more descriptive systematic and narrative reviews.

The GDG felt it was important that clinicians are aware of the following special considerations relating to this population group:

- There is an acknowledged effect on fertility in women with Crohn's disease, which may be multifactorial.
- Prior to a planned pregnancy, advice may be offered to prospective mothers relating to timing of the pregnancy in relation to disease activity, nutrition, dietary or vitamin supplements, risks of the offspring developing Crohn's disease and the range of courses the condition may take during the pregnancy.
- The GDG also sought evidence that would help healthcare professionals advising women about potential benefits of the medication in terms of treating or preventing active disease, the effect of Crohn's disease and their medication on pregnancy outcomes, such as spontaneous abortion, stillbirths, occurrence of congenital abnormalities, low birth weight and preterm delivery.
- The effect of the disease on the choices for delivery available to women with Crohn's disease also needs consideration, especially in those with perianal Crohn's disease. This should be discussed with the obstetric team.
- Drug treatment is an important part of the management of Crohn's disease and the GDG specifically considered the implications of their recommendations for treatment during pregnancy and for breast-feeding mothers. The potential risks from medications need to be balanced with the consequences of continued active disease affecting pregnancy outcomes.
    - Aminosalicylates, conventional glucocorticosteroids, budesonide, azathioprine and mercaptopurine may all be considered during pregnancy and breast-feeding, but potential risks should be understood by clinicians and patients.
    - Methotrexate is of well documented teratogenicity. Methotrexate should be avoided and the BNF consulted. Advice may also be needed for potential fathers taking the drug.
    - Interpretation of studies estimating such risks needs care. Risks may be small and therefore not apparent in series of relatively small size, and apparent risks need to be set against the background population risk for adverse outcomes of pregnancy.

# 12.2 Clinical evidence

A full literature search was undertaken. Systematic and narrative reviews of fertility and pregnancy in Crohn's disease were identified and reviewed.

### 12.2.1 Fertility

Infertility rates in women with inactive CD are similar to those of the general population, 8% to 10% percent.[121] In Crohn's disease, women with active inflammation have reduced fertility by several mechanisms, depending on site of inflammation. Active inflammation or previous surgical intervention, especially in the distal ileum, causes scarring of fallopian tubes and ovaries.[132,178] Less direct effects, including poor nutrition and systemic inflammation could also play a more important role.[269] Pelvic surgery is negatively associated with fertility in women with Crohn's disease compared with those who had medical therapy only.[185]

Infertility rates in men were more difficult to assess. Sulfasalazine causes oligospermia. Increased disease activity and poor nutritional status (zinc deficiency in 70% of men with Crohn's disease) may also contribute to male infertility.

### 12.2.2 Effect of Crohn's disease on pregnancy outcome

One recent study by Cornish et al[46,114] showed that women with Crohn's disease are almost three times more likely than participants without Crohn's disease to have a low birth weight (LBW) infant (people with Crohn's disease vs. control (OR): LBW 2.82 [1.42 to 5.60]). They were twice as likely to deliver prematurely (1.97 [1.36 to 2.87]).

A population based cohort study by Dominitz et al (155 people with Crohn's disease and 1308 controls)[70] showed higher rates of preterm delivery, low birth weight and small for gestational age infants in women with Crohn's disease compared with controls.

With regard to disease state, during the past decade new findings have revealed that normal pregnancy outcomes can be achieved when a woman with Crohn's disease enters the pregnancy in remission.[121]

### 12.2.3 Effect of pregnancy on Crohn's disease

The risk of flaring during pregnancy is the same as if the person is not pregnant – approximately 34% at one year.[161]

### 12.2.4 Drugs in pregnancy

Drug use must be tempered by the knowledge that unforeseen long-term consequences of a medication, such as clear-cell vaginal or cervical cancer that developed in the daughters of women who were treated with diethylstilbesterol (DES) during pregnancy can rarely occur and require future monitoring of the offspring to detect.[305] Readers should refer to the latest version of the BNF for current advice on prescribing of drugs during pregnancy and breastfeeding, as well as prior to conception.

# 12.3 Economic evidence

No published data were found and original modelling was not undertaken for this question.

## 12.4 Linking evidence to recommendations

**Table 93: Linking evidence to recommendations – preconception and- pregnancy**

| | |
|---|---|
| **Scope special population** | **Consideration will be given to specific needs, if any, in pregnancy or females of child-bearing potential.** |
| **Recommendations** | **44. Give information about the possible effects of Crohn's disease on pregnancy, including the potential risks and benefits of medical treatment and the possible effects of the Crohn's disease on fertility.**<br>**45. Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gastroenterology) in the care of pregnant women with Crohn's disease.** |
| **Quality of the evidence** | The GDG questioned why fertility is reduced in women with Crohn's disease. Studies considering fertility before and after diagnosis of CD may be biased by a number of factors. Fertility is influenced by<br>• Disease itself<br>• Psychosexual factors<br>• Desire to have children when patient has a significant illness<br>• Desire to have (more) children<br><br>The GDG also questioned whether surgery *per se* is related to decreased fertility, and proposed that pelvic but not abdominal surgery is associated with diminished fecundability (combination of ability and desire to have children). This is because pelvic surgery is associated with potential for adhesions around the Fallopian tubes.<br><br>They also suggested that there is a higher rate of lower uterine segment Caesarean section because of a lower clinician threshold for surgical delivery when a woman has a co-morbid condition, for example Crohn's disease, and because women with perianal Crohn's disease have a high risk of perineal trauma (episiotomy/tears).<br><br>The GDG were aware of data[121] suggesting that perinatal morbidity e.g. small for gestational age (SFGA) is unlikely if a woman with Crohn's disease is in a quiescent phase throughout the pregnancy. The perinatal morbidity reported in the literature may be as a result of women with Crohn's disease having active Crohn's disease/flares during pregnancy, but these data were not separated out in the literature reviewed. Hence the GDG was not able to conclude whether it is the disease *activity* that is of importance, or just having Crohn's disease itself. |
| **Other considerations** | **Multidisciplinary care**<br>Gastroenterologists noted that they would tend to see a pregnant woman more frequently, liaise with the obstetricians and ensure documentation in their hand-held maternity notes. No data were identified comparing shared care and usual care of pregnant women with Crohn's disease and therefore the GDG had no evidence for whether outcomes are better with shared care. There is also no evidence to suggest that a person being looked after in primary care is being looked after any less satisfactorily than when the MDT is involved, but the GDG felt there are a surprising number of people with Crohn's disease who are not under the care of a gastroenterologist. |

The GDG agreed nevertheless, that pregnant women with Crohn's disease were at high risk regardless of whether the disease was in remission because

- a third of women with Crohn's disease are likely to flare during the pregnancy
- they are at high risk of low birth weight, preterm labour and having small for gestational age babies
- GPs cannot access biological treatments and many do not use azathioprine or mercaptopurine
- There may be risks associated with some of the drugs used. The benefits and potential risks need to be assessed and discussed.

They therefore deemed shared care to be an optimal strategy, including a gastroenterologist, obstetrician, GP and midwife.

Ultimately the GDG agreed that the important issue was around ensuring sound care coordination and communication links between healthcare professionals within different specialities, for example the maternity/obstetric team and the gastroenterology team. Preconception support and information should be given to women considering pregnancy.

**Drugs in pregnancy and the post-partum period**

The GDG noted that many drugs used to treat people with Crohn's disease are unlicensed, let alone not proven to be safe during pregnancy or breastfeeding. They generally thought that readers should be guided by the BNF which is frequently updated. Drugs should be used if their potential benefit outweighs their risk. Note: methotrexate should be avoided. The use of any medications in pregnancy should only follow a careful and documented discussion between the person with Crohn's disease and her doctor. It should balance the risk of disease flares against the potential known risks of the relevant medication in pregnancy. The discussion should acknowledge that there is always a risk of miscarriage and of birth abnormalities in all pregnancies.

**Male fertility and special drug precautions**

Male fertility was debated by the group but the guideline scope did not specify this as a population of interest and hence it is outside of remit. Nevertheless it was considered to be good practice to discuss the effects of drugs such as sulfasalazine in reducing male fertility as well as the teratogenic effects of methotrexate. Readers are advised to consult the BNF prior to prescribing these drugs.

In generating the recommendations, the GDG emphasised that information should be given to women who are of childbearing potential, not only those who are actively considering conception or those who are pregnant. People with Crohn's disease often don't go to see the obstetrician prior to conception, therefore it is important for the gastroenterologist to be able to provide this information. Enquiry about the impact of the Crohn's disease on future fertility and parental concern about the impact of the Crohn's disease on children (both boys and girls) are common.

A patient member of the GDG raised the point that when people want a child, they may go "all out" to achieve the pregnancy, irrespective of risks of the disease and medication. The GDG agreed that the person with Crohn's disease should make these decisions, but that these decisions should be informed.

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| | The GDG did acknowledge that not all gastroenterologists would currently be in a position to provide comprehensive advice, noting that US obstetricians specialise, for example, in managing women with IBD. However, the group felt that gastroenterologists could and should provide a minimal level of information relating to pregnancy issues, as defined in the recommendations. The GDG commented that gastroenterologists would also be well positioned to contribute to discussion about minimising obstetric injury with the obstetrician (for example third degree tear), even though the intention is not to interfere with obstetric management.<br><br>**Contraception**<br>The need for effective contraception applies to any sexually active person of child bearing age and for women with Crohn's disease. A Clinical Knowledge Summary (accredited by NHS Evidence) suggests that additional factors which need to be considered in women with Crohn's disease include malabsorption, surgical treatments, immobility, risk of venous thromboembolism, primary sclerosing cholangitis, and risk of osteoporosis.[42]<br>The GDG suggest that decisions about contraception are made with individual people with Crohn's disease based on their specific clinical and personal circumstances. |

## 12.5 Recommendations

**44. Give information about the possible effects of Crohn's disease on pregnancy, including the potential risks and benefits of medical treatment and the possible effects of the Crohn's disease on fertility.**

**45. Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gastroenterology) in the care of pregnant women with Crohn's disease.**

## 12.6 Research recommendation

The GDG did not prioritise a recommendation for future research in this area.

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# 14 Glossary

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| **5-ASA/s**<br>**5ASA/s**<br>**5-ASA compounds**<br>**5-ASA therapy**<br>**5-Aminosalicylates**<br>**5-Aminosalicylate compounds** | 5-aminosalicylate treatment including mesalazine, olsalazine and balsalazide as well as sulfasalazine. |
| **Abstract** | Summary of a study, which may be published alone or as an introduction to a full scientific paper. |
| **Active Crohn's disease** | A period when there is an exacerbation of symptoms including diarrhoea and abdominal pain. It is usually associated with abnormalities of inflammatory markers and deterioration in scoring measures such as the Harvey Bradshaw Index or the Crohn's Disease Activity Index (CDAI). |
| **Absolute risk difference** | The ARD is the difference in the risk of an event occurring between two groups of patients in a study. |
| **ACTH** | Adrenocorticotropic hormone. |
| **Adjunctive therapy** | One treatment associated with or assisting another treatment. |
| **Algorithm (in guidelines)** | A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows. |
| **Allocation concealment** | The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants. |
| **Anastomotic dehiscence** | Breakdown of tissue at a site of previous surgery |
| **Applicability** | The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting. |
| **Arm (of a clinical study)** | Sub-section of individuals within a study who receive one particular intervention, for example placebo arm. |
| **Association** | Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal. |
| **AZA** | Azathioprine (an immunosuppressive drug), prodrug of mercaptopurine. |
| **Baseline** | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are |

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| | compared. |
| **Bias** | Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted. |
| **Blinding** | Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study. |
| **BNF/BNFC** | British National Formulary/British National Formulary for Children |
| **Carer (caregiver)** | Someone other than a health professional who is involved in caring for a person with a medical condition. |
| **Case-control study** | Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause. |
| **Case-series** | Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients. |
| **CDAI** | Crohn's disease activity index. |
| **Cleveland Global Quality of Life** | A simplified quality of life index which consists of three items (current quality of life, current quality of health, and current energy level), each on a scale of 0 to 10 (0, worst; 10, best). |
| **Clinical effectiveness** | The extent to which an intervention produces an overall health benefit in routine clinical practice. |
| **Clinical efficacy** | The extent to which an intervention is active when studied under controlled research conditions. |
| **Clinician** | A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist. |
| **Cochrane Review** | The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). |
| **Cohort study** | A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest. |
| **Comparability** | Similarity of the groups in characteristics likely to affect the study results (such as health status or age). |
| **Concordance** | This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, |

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| | but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence. |
| **Confidence interval (CI)** | A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value. |
| **Confounding** | In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study. |
| **Consensus methods** | Techniques that aim to reach an agreement on a particular issue. Consensus methods may be used when there is a lack of strong evidence on a particular topic. |
| **Control group** | A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug. |
| **Conventional glucocorticosteroids** | "Steroids" without a hgh first pass metabolism. |
| **Cost-effectiveness analysis (CEA)** | An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness. |
| **Cost-effectiveness model** | An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes. |
| **Cost-utility analysis (CUA)** | A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs). |
| **C-Reactive Protein** | A plasma protein that circulates in increased amounts during inflammation and after tissue damage. |
| **Decision analysis** | An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes. |
| **Discounting** | Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs |

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| | reflects individual preference for costs to be experienced in the future rather than the present. |
| **Distal ileal disease** | Preferred term for "terminal" ileal disease, because of negative connotations of the word "terminal". |
| **Dominance** | An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective. |
| **Drop-out** | A participant who withdraws from a trial before the end. |
| **Economic evaluation** | Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences. |
| **Effect – relative and absolute** | Relative effect represents the *ratio* between two risks. Absolute effect represents the *difference* between two risks. |
| **Effect (as in effect measure, treatment effect, estimate of effect, effect size)** | The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association. |
| **Effectiveness** | See 'Clinical effectiveness'. |
| **Efficacy** | See 'Clinical efficacy'. |
| **Endoscopic healing** | Intestinal lumen appears normal when seen on endoscopy. |
| **EQ-5D (EuroQol-5D)** | A standardise instrument used to measure a health outcome. It provides a single index value for health status. |
| **Evidence** | Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients). |
| **Exclusion criteria (clinical study)** | Criteria that define who is ineligible to participate in a clinical study. |
| **Exclusion criteria (literature review)** | Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence. |
| **Extended dominance** | If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal. |
| **Extrapolation** | In data analysis, predicting the value of a parameter outside the range of observed values. |
| **Follow-up** | Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables. |
| **Food exclusion** | Avoidance of certain foods in an attempt to modify the presentation of the disease. |

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| **Forest plot** | A forest plot is a graphical representation of the results of a a meta-analysis. |
| **Generalisability** | The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country. |
| **Generic** | Not protected by trademark registration, non-proprietary. |
| **Glucocorticosteroid-dependent** | Refers to those patients in whom their Crohn's disease flares when glucocorticosteroid therapy is significantly reduced or stopped. |
| **GRADE/GRADE profile** | A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile. |
| **Harms** | Adverse effects of an intervention. |
| **HBI** | Harvey Bradshaw Index, used to measure activity and severity in Crohn's disease. |
| **Health economics** | The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health. |
| **Health-related quality of life (HRQoL)** | A combination of an individual's physical, mental and social well-being; not merely the absence of disease. |
| **Heterogeneity Or lack of homogeneity.** | The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up. |
| **Histological healing** | Histological healing refers to a pathological interpretation of intestinal biopsies in which samples no longer show signs of either acute or chronic inflammation. |
| **Histological sampling** | Biopsy for microscopic evaluation. |
| **IBDQ** | Inflammatory bowel disease questionnaire. |
| **Imprecision** | Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the |

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| | estimate of effect. |
| **Inclusion criteria (literature review)** | Explicit criteria used to decide which studies should be considered as potential sources of evidence. |
| **Incremental analysis** | The analysis of additional costs and additional clinical outcomes with different interventions. |
| **Incremental cost** | The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention. |
| **Incremental cost effectiveness ratio (ICER)** | The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. |
| **Incremental net benefit (INB)** | The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost. |
| **Indirectness** | The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome). |
| **IBD** | Inflammatory Bowel Disease (Chronic, non-specific disorders of unknown aetiology. Includes Crohn's disease and ulcerative colitis.) |
| **Intention to treat analysis (ITT)** | A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol. |
| **Intervention** | Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy. |
| **Kappa statistic** | A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance. |
| **Length of stay** | The total number of days a participant stays in hospital. |
| **Leukapheresis** | Leukapheresis involves extracorporeal removal of leukocytes from the blood, either by centrifugation or through an adsorptive system. |
| **Licence** | See 'Product licence'. |
| **Life-years gained** | Mean average years of life gained per person as a result of the intervention compared with an alternative intervention. |
| **Likelihood ratio** | The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The |

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| | likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity. |
| **Long-term care** | Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes. |
| **Markov model** | A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle). |
| **MDT** | Multidisciplinary team. |
| **Meta-analysis** | A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It generally has greater power to confirm or refute a hypothesis than the individual trials. |
| **MTX** | Methotrexate (an immunosuppressive drug). |
| **MP** | Mercaptopurine (an immunosuppressive drug). |
| **Mucosal healing** | An endoscopic appearance where the mucosa shows no visual evidence of inflammation. Ideally it should be supported by evidence of histological healing. |
| **Multivariate model** | A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable. |
| **Number needed to treat (NNT)** | The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest. |
| **Observational study** | Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies. |
| **Odds ratio** | A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events. |
| **Opportunity cost** | The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention. |
| **Outcome** | Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'. |
| **Padova Inflammatory Bowel Disease Quality of Life** | Italian version of the Cleveland Global Quality of Life (CGQL) instrument (see definition above). |

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| **Paediatric** | Pertaining to children or people less than 18 years of age. |
| **PCDAI** | Paediatric Crohn's disease activity index |
| **Per protocol** | Only the patients who adhered to their originally-assigned treatments (no switching) and who completed the trialare included in the analysis. |
| **Perioperative** | The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods. |
| **Photopheresis** | A process in which peripheral blood is exposed in an extracorporeal flow system to photoactivated 8-methoxypsoralen (METHOXSALEN) and ultraviolet light - a procedure known as PUVA THERAPY. |
| **PICO** | In order to define a review question, a number of essential aspects require specification. For the characteristics used to define intervention reviews, the mnemonic PICO is used: Population, Intervention, Comparison, Outcome). |
| **Placebo** | An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials. |
| **Polymeric** | Protein is present in its whole form.<br>Examples of currently available formulas for enteral nutrition: Fortisip (by Nutricia), Ensure (by Fresnius), Modulen IBD (by Nestle). |
| **Polypharmacy** | The use or prescription of multiple medications. |
| **Post-operative** | Pertaining to the period after patients leave the operating theatre, following surgery. |
| **Power (statistical)** | The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed. |
| **Pre-digested feed** | Elemental feed used in enteral nutrition. Protein is present in the form of free amino acids.<br>Example of currently available formula: Elemental 028 Extra (by SHS). |
| **Primary care** | Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals. |
| **Primary outcome** | The outcome of greatest importance, usually the one in a study upon which the power calculation is based. |
| **Product licence** | An authorisation from the MHRA to market a medicinal product. |
| **Prognosis** | A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor |

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| | prognosis is associated with a high rate of undesirable outcomes. |
| **Prospective study** | A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective. |
| **Publication bias** | Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found. |
| **P-value** | The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'. |
| **Quality of life** | See 'Health-related quality of life'. |
| **Quality-adjusted life year (QALY)** | An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment. |
| **Quiescent Crohn's disease** | A situation where the patient is symptom free and has no endoscopic or radiological evidence of disease activity. |
| **Randomisation** | Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias. |
| **Randomised controlled trial (RCT)** | A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups. |
| **RCT** | See 'Randomised controlled trial'. |
| **Receiver operated characteristic (ROC) curve** | A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal. |
| **Reference standard** | The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice. |

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| **Refractory Crohn's disease** | A situation where the condition does not respond to standard pharmacological treatments. |
| **Relapse** | The return of a sign, symptom, or disease after a remission. |
| **Relative risk (RR)/**<br><br>**Risk ratio** | The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B). |
| **Remission** | Remission is synonymous with quiescent disease and describes a situation where the patient is symptom free and has no endoscopic or radiological evidence of disease activity. |
| **Reporting bias** | See publication bias. |
| **Resource implication** | The likely impact in terms of finance, workforce or other NHS resources. |
| **Retrospective study** | A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective. |
| **Review question** | In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations. |
| **Secondary outcome** | An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes. |
| **Selection bias** | A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias. |
| **Semi-elemental** | Enteral nutrition formula in which protein is present in the form of peptide chains, made by protein hydrolysis. Usually these formulas have a mean peptide chain length of four or five amino acids.<br><br>Examples of currently available formulas: Peptisorb (by Nutricia), Pepdite (by SHS). |
| **Sensitivity** | Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects.<br><br>See the related term 'Specificity' |
| **Sensitivity analysis** | A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.<br><br>One-way simple sensitivity analysis (univariate analysis): each |

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| | parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.<br><br>Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.<br><br>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.<br><br>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation). |
| **Short bowel syndrome** | A malabsorption syndrome resulting from extensive operative resection of small bowel. |
| **Significance (statistical)** | A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20<br><br>($p < 0.05$). |
| **SPC** | Summary of Product Characteristics. |
| **Specificity** | The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases.<br><br>See related term 'Sensitivity'.<br><br>In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers. |
| **Stakeholder** | Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups. |
| **Symptomatic recurrence** | Subjective or objective assessment of symptoms that indicate a resurgence of the disease. |
| **Systematic review** | Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis. |
| **Time horizon** | The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation. |
| **TPMT** | Thiopurine methyl transferase. |
| **Treatment allocation** | Assigning a participant to a particular arm of the trial. |
| **TNF-α** | Tumour Necrosis Factor (TNF) alpha . |

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| **UNG** | Understanding NICE Guidance. |
| **Univariate** | Analysis which separately explores each variable in a data set. |
| **Utility** | A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value. |
| **Wireless capsule endoscopy** | A small capsule, consisting of a camera, light source and wireless circuit for the acquisition and transmission of images of the gastrointestinal tract. The capsule is swallowed and then passed in the patient's stool and is not used again. |

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# Appendices

# Appendix A: Scope

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# Appendix B: Declarations of interest

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# Appendix C: Review Protocols: clinical and health economic

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# Appendix D: Search strategies

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# Appendix E: Excluded studies

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# Appendix F: Evidence tables

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# Appendix G: Forest Plots

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# Appendix H: Full Health Economics report

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# Appendix I: Research recommendations

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# Appendix J: Review of Cochrane 5-ASA review for induction of remission in Crohn’s disease

See separate document

# Appendix K: Call for evidence

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# Appendix L: Observational data on adverse events associated with 5-ASA treatment

See separate document

# Appendix M: Observational data on adverse events associated with immunosuppressives

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# Appendix N: Observational data on recurrence rates in Crohn’s disease limited to the distal ileum – medication versus surgery

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# Appendix O: Observational data on stricture management – balloon dilation versus surgery

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# Appendix P: Patient information themes

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# Appendix Q: Sift audit

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# Appendix R: Summary of the evidence

## R.1 Summary of all interventional results

**Key**

VL = very low quality

L = low quality

M = moderate quality

H = high quality

| Drug comparisons and outcomes | Number of studies | Relative effect | Absolute effect | Favours | Comments |
|---|---|---|---|---|---|
| **Conventional glucocorticosteroid for induction of remission** | | | | | |
| **Conventional glucocorticosteroid compared with placebo** | | | | | |
| Induction of remission CDAI, follow-up at 15 weeks | 2 (H)<br>Malchow 1984<br>Summers 1979<br>(in Bechimol 2008) | RR 1.99 (1.51 – 2.64) | 308 more per 1000 (from 159 more to 510 more) | Favours conventional glucocorticosteroid | |
| Adverse events, follow-up at 17 weeks | 1 (H)<br>Singleton 1979 | RR 4.89 (1.98 – 12.07) | 253 more per 1000 (from 64 more to 719 more) | Favours placebo: more adverse events in conventional glucocorticosteroid group | |

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|---|---|---|---|---|---|
| Withdrawal due to adverse events, follow-up at 17-18 weeks | 2 (M)<br>Malchow 1984<br>Singleton 1979<br>(in Bechimol 2008) | RR 4.57 (0.75 – 27.83) | 26 more per 1000 (from 2 fewer to 199 more) | Non-significant | |
| **Conventional glucocorticosteroid compared with 5-ASA** | | | | | |
| Induction of remission CDAI, follow-up at 15 weeks | 3 (H)<br>Malchow 1984<br>Schomerich 1990<br>Summers 1979<br>(in Bechimol 2008) | RR 1.65 (1.33 – 2.03) | 272 more per 1000 (from 138 more to 430 more) | Favours conventional glucocorticosteroid | |

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|---|---|---|---|---|---|
| Withdrawal due to adverse events, follow-up at 15 weeks | 6 (L)<br>Gross 1995<br>Malchow 1984<br>Martin 1990<br>Prantera 1999<br>Scholmerich 1990<br>Singleton 1979<br>(in Bechimol 2008) | RR 1.18 (0.61 – 2.29) | 9 more per 1000 (from 21 fewer to 68 more) | Non-significant | |
| Adverse events, follow-up at 15 weeks | 5 (M) (L)<br>Gross 1995<br>Martin 1990<br>Pranera 1999<br>Schomerich 1990<br>Singleton 1979<br>(in Bechimol 2008) | Fixed effect: RR 2.53 (1.77 – 3.63)<br><br>Random effects: RR 3.13 (0.99 – 9.90) | Fixed effect: 210 more per 1000 (from 106 more to 361 more)<br><br>Random effects: 292 more per 1000 (from 1 fewer to 1222 more) | Fixed effect: more adverse events in conventional glucocorticosteroid group<br><br>Random effects: non-significant | Significant heterogeneity |
| **Conventional glucocorticosteroid plus sulfasalazine compared with conventional glucocorticosteroid plus placebo** | | | | | |

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|---|---|---|---|---|---|
| Induction of remission, follow-up at 8 -15 weeks | 2 (L)<br><br>Malchow 1984<br>Singleton 1979 | RR 0.88 (0.74 – 1.04) | 88 fewer per 1000 (from 192 fewer to 29 more) | Non-significant | |
| **Conventional glucocorticosteroid compared with AZA/MP**<br><br>**Conventional glucocorticosteroid plus AZA/MP compared with conventional glucocorticosteroid plus placebo** | | | | | |
| Induction CDAI, follow-up at 16 weeks | 8 (M) (L)<br><br>Prefontaine 2009 | Fixed effect: RR 1.57 (1.26 – 1.96)<br><br>Random effects: RR 1.59 (1.03 – 2.43) | Fixed effect: 190 more per 1000 (from 87 more to 320 more)<br><br>Random effects: 197 more per 1000 (from 10 more to 477 more) | Favours conventional glucocorticosteroid plus AZA | Significant heterogeneity |

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|---|---|---|---|---|---|
| Conventional glucocorticosteroid sparing effect, follow-up at 16 weeks | 5 (M) (L)<br>Prefontaine 2009 | Fixed effect: RR 1.81 (1.38 – 2.38)<br><br>Random effects: RR 1.80 (1.01 – 3.20) | 293 more per 1000 (from 132 more to 469 more)<br><br>286 more per 1000 (from 4 more to 787 more) | Favours conventional glucocorticosteroid plus AZA | |
| Fistula improvement, follow-up at 16 weeks | 3 (L)<br>Prefontaine 2009 | RR 2.0 (0.67 – 5.93) | 260 more per 1000 (from 134 fewer to 1694 more) | Non-significant | |
| Adverse events, follow-up at 16 weeks | 7 (H)<br>Prefontaine 2009 | RR 2.81 (1.28 – 6.17) | 169 fewer per 1000 (from 26 fewer to 483 more) | Favours conventional glucocorticosteroid plus placebo: more adverse events in conventional glucocorticosteroid plus AZA group | |
| **Conventional glucocorticosteroid plus AZA or MP compared with conventional glucocorticosteroid plus placebo in mixed age population** | | | | | |

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| Corticosteroid sparing reduction in dosage, follow-up at 26 weeks | 1 (VL)<br>Rosenberg 1975 | Corticosteroid plus AZA/MP = minus 15.5 mg<br><br>Corticosteroid plus placebo = minus 6.1 mg | Mean difference 9.4 mg higher p < 0.05 (confidence interval not given) | Steroid sparing for prednisone<br>Addition of AZA/MP to corticosteroid decreased need for prednisone | |
| **Conventional glucocorticosteroid plus MP compared with conventional glucocorticosteroid plus placebo in children** | | | | | |
| Conventional glucocorticosteroid sparing days on prednisone, follow-up at 18 months | 1 (VL)<br>Markowitz 2000 | Conventional glucocorticosteroid plus MP = 0.73 days<br><br>Conventional glucocorticosteroid plus placebo = 1.34 days | | 73 days on prednisone in the mercaptopurine plus conventional glucocorticosteroid arm compared with 1.34 days on prednisone in the conventional glucocorticosteroid arm alone | |
| Remission Harvey Bradshaw Index, follow-up at 1 month | 1 (M)<br>Markowitz 2000 | RR 1.18 (0.94 – 1.47) | 141 more per 1000 (from 47 fewer to 369 more) | Non-significant | |
| **Conventional glucocorticosteroid plus MTX compared with conventional glucocorticosteroid plus placebo** | | | | | |

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|---|---|---|---|---|---|
| Induction of remission CDAI or Harvey Bradshaw, follow-up at 16 weeks | 3 (VL)<br>Aurora 1999<br>Oren 1997<br>Feagan 1995 | Fixed effect: RR 1.25 (0.86 – 1.80)<br><br>Random effects: RR 1.09 (0.48 – 2.47) | Fixed effect: 85 more per 1000 (from 48 fewer to 237 more)<br><br>Random effects: 31 more per 1000 (from 177 fewer to 501 more) | Non-significant | Significant heterogeneity |
| Withdrawal due to adverse events, follow-up at 18 months | 3 (M)<br>Aurora 1999<br>Oren 1997<br>Feagan 1995<br>(in Alfadhli Ahmand 2004) | RR 6.97 (1.61 – 30.1) | 66 more per 1000 (from 7 more to 320 more) | Favours glucocorticosteroid plus placebo: more withdrawals in conventional glucocorticosteroid plus MTX group | |
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| **Budesonide for induction of remission** | | | | | |
| **Budesonide compared with placebo** | | | | | |

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|---|---|---|---|---|---|
| Induction of remission CDAI, follow-up at 8 weeks | 2 (L)<br>Greenberg 1994<br>Tremaine 2002<br>(in Seow 2008) | RR 1.96 (1.19 – 3.23) | 233 more per 1000 (from 46 more to 542 more) | Favours budesonide | |
| Withdrawal due to adverse events, follow-up at 8 – 10 weeks | 2 (VL)<br>Greenberg 1994<br>Termaine 2002<br>(in Seow 2008) | RR 1.16 (0.45 – 2.99) | 9 more per 1000 (from 31 fewer to 112 more) | Non-significant | |
| Change in IBDQ score (better indicated by lower values), follow-up at 8 – 10 weeks | 2 (VL)<br>Irvine 2000<br>Tremaine 2002<br>(in Seow 2008) | | Fixed effect: MD 17.84 higher (from 8.88 lower to 26.81 higher)<br><br>Random effects: MD 16.79 higher (from 6.34 lower to 39.91 higher) | Non-significant | Significant heterogeneity |
| **Budesonide compared with conventional glucocorticosteroid treatment** | | | | | |

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|---|---|---|---|---|---|
| Induction of remission CDAI, follow-up at 8 weeks | 8 (M)<br>Bar-Meir 1998<br>Campieri 1997<br>Escher 2004<br>Gross 1996<br>Levine 2003<br>Rutgeerts 1994<br>Van Ierssel 1995<br>(In Seow 2008) | RR 0.85 (0.75 – 0.97) | 92 fewer per 1000 (from 18 fewer to 153 fewer) | Favours conventional glucocorticosteroid | |
| Induction of remission CDAI, follow-up at 12 weeks | 3 (L)<br>Campieri 1997<br>Escher 2004<br>Levine 2003<br>(In Seow 2008) | RR 1.02 (0.81 – 1.3) | 11 more per 1000 (from 101 fewer to 159 more) | Non-significant | |
| Induction of remission in severe disease CDAI, follow-up at 8 weeks | 2 (L)<br>Campieri 1997<br>Gross 1996 | RR 0.52 (0.28 – 0.95) | 271 fewer per 1000 (from 28 fewer to 407 fewer) | Favours conventional glucocorticosteroid | |

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| Induction of clinical remission ileal or right sided ilecolonic disease, CDAI, follow-up at 8 weeks | 6 (L)<br>Bar-Meir19 98<br>Campieri 1997<br>Escher 2004<br>Gross 1996<br>Rutgeerts 1994<br>Van Ierssel 1995 | RR 0.86 (0.75 -1) | 86 fewer per 1000 (from 153 fewer to 0 more) | Favours conventional glucocorticosteroid | |
| Change in CDAI score (better indicated by lower values) | 6 (L)<br>Bar Meir 1998<br>D'Haens 1998<br>Escher 2004<br>Gross 1996<br>Rutgeerts 1994<br>Van Ierssel 1995<br>(In Seow 2008) | | Fixed effect: MD 33.83 lower (from 45.68 lower to 21.97 lower)<br><br>Random effects: MD 42.27 lower (from 69.67 lower to 14.86 lower) | Change lower in budesonide | Significant heterogeneity |

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|---|---|---|---|---|---|
| Withdrawal due to adverse events | 5 (VL)<br>Bar Meir 1998<br>Escher 2004<br>Gross 1996<br>Levine 2003<br>Rutgeerts 1994<br>Tursi 2006<br>(in Seow 2008) | RR 0.57 (0.18 – 1.84) | 21 fewer per 1000 (from 41 fewer to 42 more) | Non-significant | |
| Glucocorticosteroid-related adverse events in adults and children | 6 (L & VL)<br>Bar-Meir 1998<br>Campieri 1997<br>Escher 2004<br>Gross 1996<br>Levine 2003<br>Rutgeerts 1994<br>(In Seow 2008) | Fixed effect<br>RR 0.60 (0.53-0.67)<br><br>Random effects<br>RR 0.59 (0.46-0.77) | 251 fewer per 1000 (from 207 fewer to 294 fewer)<br><br>257 fewer per 1000 (from 144 fewer to 338 fewer) | Favours budesonide (fewer adverse events)<br><br>Favours budesonide (fewer adverse events) | Significant heterogeneity |

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|---|---|---|---|---|---|
| Glucocorticosteroid-related adverse events in adults only | 4 (L )<br>Bar-Meir 1998<br>Campieri 1997<br>Gross 1996<br>Rutgeerts 1994<br>(In Seow 2008) | Fixed effect RR 0.56 (0.49 – 0.64)<br><br>Random effects RR 0.53 (0.40 – 0.69) | 282 fewer per 1000 (from 231 fewer to 327 fewer)<br><br>301 fewer per 1000 (from 199 fewer to 384 fewer) | Favours budesonide (fewer adverse events)<br><br>Favours budesonide (fewer adverse events) | |
| **Budesonide compared with 5-ASA** | | | | | |
| Induction of remission CDAI, follow-up at 8 weeks (mesalazine) | 2(VL)<br>Thomsen 1998<br>(In Seow 2008)<br>Tromm 2010 | Fixed effect: RR 1.26 (1.10 – 1.46)<br><br>Random effects: RR 1.33 (0.91 – 1.92) | Fixed effect: 142 more per 1000 (from 55 more to 251 more)<br><br>Random effects: 180 more (from 49 fewer to 502 more) | Fixed effect: favours budesonide<br><br>Random effects: non-significant | Significant heterogeneity |
| Induction of remission CDAI, follow-up at 12 weeks (mesalazine) | 1 (L)<br>Thomsen 1998<br>(in Seow 2008) | RR 1.59 (1.17 – 2.15) | 232 more per 1000 (from 67 more to 452 more) | Favours budesonide | |

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|---|---|---|---|---|---|
| Withdrawal due to adverse events (mesalazine), follow-up at 5 weeks | 2 (L)<br>Thomsen 1998<br>(In Seow 2008)<br>Tromm 2010 | RR 0.43 (0.18 – 1.02) | 38 fewer per 1000 (from 54 fewer to 1 more) | Non-significant | |
| Change in CDAI score (better indicated by lower values), follow-up at 8 weeks (mesalazine) | 1 (M)<br>Tromm 2010 | | MD 19 lower (from 41.35 lower to 3.35 higher) | Non-significant | |
| Total adverse events, follow-up at 8 weeks (mesalazine) | 1 (M)<br>Tromm 2010 | RR 0.93 (0.89 – 0.98) | 69 fewer per 1000 (from 20 fewer to 109 fewer) | Favours 5-ASA: more adverse events in budesonide group | |
| **Budesonide compared with glucocorticosteroid treatment in children** | | | | | |
| Induction of remission PCDAI 8 weeks | 2 (VL)<br>Escher 2004<br>Levine 2003<br>(In Seow 2008) | RR 0.88 (0.58 – 1.33) | 69 fewer per 1000 (from 242 fewer to 190 more) | Non-significant | |
| Induction of remission PCDAI 12 weeks | 2 (VL)<br>Escher 2004<br>Levine 2003<br>(In Seow 2008) | RR 0.99 (0.65 – 1.50) | 1 fewer per 1000 (from 53 fewer to 75 more) | Non-significant | |

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|---|---|---|---|---|---|
| Change in PCDAI score (better indicated by higher values) | 1 (VL)<br>Escher 2004 | | MD 4.10 lower (from 12.77 lower to 4.57 higher) | Non-significant | |
| Induction of remission PCDAI 8 weeks; ileal or right-sided ileocolnic disease | 1 (VL)<br>Escher 2004 | RR 0.83 (0.52 – 1.34) | 111 fewer per 1000 (314 fewer to 222 more) | Non-significant | |
| Glucocorticosteroid-related adverse events in children | 2 (VL)<br>Escher 2004<br>Levine 2003<br>(In Seow 2008) | RR 0.57 (0.38 – 0.85) | 322 fewer per 1000 (112 fewer to 465 fewer) | Favours budesonide (fewer adverse events) | |
| Withdrawal due to adverse events 8 weeks | 1 (VL)<br>Escher 2004 | RR 0.17 (0.02 – 1.27) | 223 fewer per thousand (264 fewer to 73 more) | Non-significant | |
| **5-ASA induction** | | | | | |
| **5-ASA compared with placebo** | | | | | |

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|---|---|---|---|---|---|
| Remission CDAI or HB score, follow-up at 6 – 18 weeks | 6 (VL)<br>Mahida 1990<br>Malcholw 1984<br>Rasmussen 1987<br>Singleton 1993<br>Summers 1979<br>Tremaine 1994 | RR 1.51 (1.20 – 1.92) | 134 more per 1000 (from 52 more to 241 more) | Favours 5-ASA | |
| Adverse events, follow-up 16 weeks | 3 (VL)<br>Rasmussen 1987<br>Singleton 1979<br>Tremaine 1994 | RR 1.04 (0.8 – 1.36) | 13 fewer per 1000 (from 67 fewer to 120 more) | Non-significant | |
| Withdrawal for any reason, follow-up at 6-18 weeks | 4 (VL)<br>Mahida 1990<br>Malchow 1984<br>Rasmussen 1987<br>Singleton 1993 | RR 0.92 (0.77 – 1.10) | 37 fewer per 1000 (from 105 fewer to 46 more) | Non-significant | |
| QoL, 4 g controlled release mesalazine, follow-up at 16 weeks | 1 (VL)<br>Singleton 1995 | | 7 QoL assessments statistically significant | QoL improved with mesalazine | |

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|---|---|---|---|---|---|
| Paediatric remission CDAI, follow-up at 20 weeks children | 1(M)<br>Griffiths 1993 | | MD 106.2 lower (from minus 152.06 to 60.34) | More remission in 5-ASA group | |
| **5-ASA compared with AZA/MP** | | | | | |
| Remission CDAI, follow-up at 16-30 weeks | 2 (VL)<br>Summers 1979<br>Mate-Jimenez 2000 | Fixed effect: RR 0.81 (0.52 – 1.24)<br>Random effects: RR 0.48 (0.07 – 3.53) | Fixed effect: 91 fewer per 1000 (from 230 fewer to 115 more)<br>Random effects: 250 fewer per 1000 (from 446 fewer to 1000 more) | Non-significant | Significant heterogeneity |
| Adverse events, follow-up at 16 weeks | 1 (M)<br>Singleton 1979 | RR 0.42 (0.21 – 0.83) | 187 fewer per 1000 (from 55 fewer to 254 more) | Favours 5-ASA: more adverse events in AZA/MP group | |
| **5-ASA compared with MTX** | | | | | |

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|---|---|---|---|---|---|
| Remission CDAI, follow-up at 30 weeks | 1 (L)<br>Mate-Jimenez 2000 | RR 0.18 (0.3 – 1.12) | 656 fewer per 1000 (from 560 fewer to 96 more) | Non-significant | |
| | | | | | |
| **AZA for induction of remission** | | | | | |
| **AZA/MP compared with placebo**<br>**Immunosuppressive therapy = AZA/MP/MTX** | | | | | |
| Remission CDAI, follow-up at 17 weeks | 1 (M)<br>Summers 1979 | RR 1.37 (0.82 – 2.28) | 96 more per 1000 (from 47 fewer to 332 more) | Non-significant | |
| Adverse events, follow-up at 17 weeks | 1 (H)<br>Singleton 1979 | RR 4.96 (1.97 – 12 51) | 257 more per 1000 (from 63 more to 747 more) | Favours placebo: more adverse events in AZA/MP group | |
| **AZA/MP compared with MTX** | | | | | |
| Remission CDAI or HBI, follow-up at 24-36 weeks | 3 (VL)<br>Ardizzone 2003<br>Mate-Jimenez 2000<br>Oren 1997 | RR 0.99 (0.73 – 1.35) | 5 fewer per 1000 (from 135 fewer to 175 more) | Non-significant | |

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|---|---|---|---|---|---|
| Withdrawal due to adverse events, follow-up at 24-36 weeks | 3 (VL)<br>Ardizzone 2003<br>Mate-Jimenez 2000<br>Oren 1997 | RR 0.79 (0.25 – 2.44) | 19 fewer per 1000 (from 66 fewer to 127 more) | Non-significant | |
| Glucocorticosteroid sparing, follow-up at 6 months | 1 (L)<br>Ardizzone 2003 | RR 1.13 (0.73 – 1.77) | 72 more per 1000 (from 150 fewer to 428 more) | Non-significant | |
| | | | | | |
| **Maintenance** | | | | | |
| **Conventional glucocorticosteroid for maintenance of remission** | | | | | |
| **Conventional glucocorticosteroid vs placebo** | | | | | |
| Relapse or failure of remission CDAI, follow-up at 1 year | 3 (M)<br>Malchow 1984<br>Smith 1978<br>Summers 1979<br>(In Steinhardt 2000) | RR 0.88 (0.62 – 1.25) | 37 fewer per 1000 (from 118 fewer to 78 more) | Non-significant | |

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|---|---|---|---|---|---|
| Relapse or failure of remission CDAI, follow-up at 2 years | 3 (M)<br>Malchow 1984<br>Smith 1978<br>Summers 1979<br>(In Steinhardt 2000) | RR 0.84 (0.61 – 1.17) | 72 fewer per 1000 (from 175 fewer to 76 more) | Non-significant | |
| Withdrawal due to side effects of drugs, follow-up at 2 years | 1 (L)<br>Malchow 1984 | RR 0.16 (0.01 – 3.23) | 210 fewer per 1000 (from 248 fewer to 558 more) | Non-significant | |
| Adverse events disaster, follow-up at 2 years | 1 (L)<br>Singleton 1979 | RR 3.31 (0.31 – 35.76) | 23 more per 1000 (from 7 fewer to 344 more) | Non-significant | |
| Adverse events severe, follow-up at 2 years | 1 (H)<br>Singleton 1979 | RR 3.55 (1.53 – 8.21) | 177 more per 1000 (from 37 more to 500 more) | Favours placebo: more adverse events in conventional glucocorticosteroid group | |
| Withdrawal due to relapse, follow-up at 3 years | 1 (VL)<br>Smith 1979 | RR 1.05 (0.42 – 2.65) | 12 more per 1000 (from 134 fewer to 381 more) | Non-significant | |
| **Conventional glucocorticosteroid compared with 5-ASA (sulfasalazine)** | | | | | |

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|---|---|---|---|---|---|
| Withdrawal due to side effects of drugs, follow-up at 2 years | 1 (L)<br>Malchow 1984 | RR 0.19 (0.01 – 3.90) | 203 fewer per 1000 (from 248 fewer to 725 more) | Non-significant | |
| Adverse events disaster, follow-up at 2 years | 1 (L)<br>Singleton 1979 | RR 4.76 (0.23 – 97.05) | 0 more per 1000 (from 0 fewer to 0 more | Non-significant | |
| Adverse events severe, follow-up at 2 years | 1 (H)<br>Singleton 1979 | RR 7.13 (1.70 – 29.83) | 211 more per 1000 (from 24 more to 994 more) | Favours 5-ASA (sulfasalazine): more adverse events in conventional glucocorticosteroid group | |
| **Conventional glucocorticosteroid compared with AZA** | | | | | |
| Adverse events disaster, follow-up at 2 years | 1 (L)<br>Singleton 1979 | RR 0.89 (0.13 – 6.07) | 4 fewer per 1000 (from 32 fewer to 188 more) | Non-significant | |
| Adverse events severe, follow-up at 2 years | 1 (M)<br>Singleton 1979 | RR 1.66 (0.76 – 3.61) | 98 more per 1000 (from 36 fewer to 387 more) | Non-significant | |
| **Conventional glucocorticosteroid plus 5-ASA (sulfasalazine) compared with placebo** | | | | | |

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|---|---|---|---|---|---|
| Withdrawal due to side effects of drugs, follow-up at 2 years | 1 (L)<br>Malchow 1984 | RR 0.46 (0.04 – 4.97) | 135 fewer per 1000 (from 240 fewer to 992 more) | Non-significant | |
| | | | | | |
| **Budesonide for maintenance of remission** | | | | | |
| **Budesonide compared with placebo** | | | | | |
| Relapse, 6 mg budesonide, CDAI, follow-up at 12 months | 4 (L)<br>Ferguson 1998<br>Greenberg 1996<br>Hanauer 2005<br>Lofberg 1996 | RR 0.84 (0.68 to 1.03) | 96 fewer per 1000 (from 192 fewer to 18 more) | Non-significant | |
| Relapse, 3 mg budesonide, CDAI, follow-up at 12 months | 4 (M)<br>Ferguson 1998<br>Greenberg 1996<br>Gross 1998<br>Lofburg 1996 | RR 1.01 (0.86 to 1.18) | 6 more per 1000 (from 89 fewer to 114 more) | Non-significant | |

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|---|---|---|---|---|---|
| Relapse and withdrawal, 6 mg budesonide, CDAI, follow-up at 12 months | 3 (L)<br>Ferguson 1998<br>Hanauer 2005<br>Lofberg 1996 | RR 0.88 (0.71 to 1.09) | 76 fewer per 1000 (from 184 fewer to 57 more) | Non-significant | |
| Relapse and withdrawal, 3 mg budesonide, CDAI, follow-up at 12 months | 3 (M)<br>Ferguson 1998<br>Gross 1998<br>Lofberg 1996 | RR 0.95 (0.82 to 1.09) | 37 fewer per 1000 (from 133 fewer to 66 more) | Non-significant | |
| Withdrawal due to adverse events, budesonide 6 mg, follow-up at 12 months | 3 (VL)<br>Ferguson 1998<br>Hanauer 2005<br>Lofberg 1996 | RR 0.92 (0.45 to 1.88) | 9 fewer per 1000 (from 61 fewer to 97 more) | Non-significant | |
| Withdrawal due to adverse events, budesonide 3 mg, follow-up at 12 months | 3 (VL)<br>Ferguson 1998<br>Gross 1998<br>Lofberg 1996 | RR 0.60 (0.18 to 1.98) | 16 fewer per 1000 (from 33 fewer to 39 more) | Non-significant | |
| Adverse events - suppressed adrenal function, budesonide 6 mg, follow-up at 12 months | 1 (L)Ferguson 1998 | RR 1.06 (0.25 to 4.45) | 10 more per 1000 (from 125 fewer to 575 more) | Non-significant | |

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| Adverse events - suppressed adrenal function, budesonide 3 mg, follow-up at 12 months | 1 (L)<br>Ferguson 1998 | RR 0.63 (0.12 to 3.35) | 62 fewer per 1000 (from 147 fewer to 392 more) | Non-significant | |
| Adverse events - cortisol level, budesonide 6 mg, follow-up at 12 months | 1 (L)<br>Greenberg 1996 | | MD 101.00 lower (from 211.29 lower to 9.29 higher) | Non-significant | |
| Adverse events - cortisol level, budesonide 3 mg, follow-up at 12 months | 1 (L)<br>Greenberg 1996 | | MD 0.00 higher (from 138.52 lower to 138.52 higher) | Non-significant | |
| Abnormal response to ACTH hormone, 6 mg budesonide, follow-up at 12 months | 1 (VL)<br>Lofberg 1996 | RR 6.42 (0.38 to 107.55) | | Non-significant | |
| Abnormal response to ACTH hormone, 3 mg budesonide, follow-up at 12 months | 1 (VL)<br>Lofberg 1996 | RR 3.13 (0.16 to 61.49) | | Non-significant | |
| IBDQ Score, 6 mg budesonide, (better indicated by higher values), follow-up at 12 months | 1 (L)<br>Greenberg 1996 | | MD 11 higher (from 6.1 lower to 28.1 higher) | Non-significant | |

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| IBDQ Score, 3 mg budesonide, (better indicated by higher values), follow-up at 12 months | 1 (L)<br>Greenberg 1996 | | MD 6.00 higher (from 12.2 lower to 24.2 higher) | Non-significant | |
| **Budesonide compared with 5-ASA** | | | | | |
| Relapse at one year CDAI, follow-up at 12 months | 1 (VL)<br>Mantzaris 2003 | RR 0.67 (0.46 to 0.97) | 271 fewer per 1000 (from 25 fewer to 444 fewer) | Favours budesonide | |
| Mean time to relapse days (better indicated by higher values), follow-up at 12 months | 1 (VL)<br>Mantzaris 2003 | | MD 94.00 higher (from 34.00 to 154.00 higher) | Favours budesonide | |
| IBDQ score (better indicated by higher values), follow-up at 12 months | 1 (L)<br>Mantzaris 2003 | | MD 37 higher (from 16.85 to 57.15 higher) | Favours budesonide | |
| Budesonide compared with prednisolone | | | | | |
| Relapse, follow-up at 12 months | 1 (L)<br>Schoon 2005 | RR 1.65 (0.89 to 3.06) | 162 fewer per 1000 (from 28 fewer to 515 more) | Non-significant | |
| Relapse and withdrawal, follow-up at 12 months | 1 (VL)<br>Schoon 2005 | RR 1.31 (0.86 to 2) | 134 fewer per 1000 (from 60 fewer to 432 more) | Non-significant | |

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| Withdrawal due to adverse events, follow-up at 12 months | 1 (VL)<br>Schoon 2005 | RR 8.62 (0.48 to 155.52) | | Non-significant | |
| Adrenal suppression, follow-up at 12 months | 1 (VL)<br>Schoon 2005 | RR 0.60 (0.36 to 1) | 242 fewer per 1000 (from 388 fewer to 0 more) | Non-significant | |
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| **5-ASAs for maintenance of remission** | | | | | |
| **5-ASA compared with placebo** | | | | | |
| Relapse (5-ASA), follow-up at 12 months | 6 (M)<br>Arber 1995<br>IMSG 1990<br>Mahmud 2001<br>Prantera 1992<br>Thomson 1995<br>Wellman 1988 | RR 0.76 (0.64 – 0.90) | 87 fewer per 1000 (from 36 fewer to 130 more) | Favours 5-ASA | |

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| Relapse including withdrawal (5-ASA), follow-up at 1 year | 6 (M)<br>Arber 1995<br>IMSG 1990<br>Mahmud 2001<br>Prantera 1992<br>Thomson 1995<br>Wellman 1988 | Fixed effect: RR 1.01 (0.91 – 1.12)<br><br>Random effects: RR 0.96 (0.80 – 1.15) | Fixed effect: 5 more per 1000 (from 49 fewer to 66 more)<br><br>Random effects: 22 fewer per 1000 (from 110 fewer to 82 more) | Non-significant | Significant heterogeneity |
| Relapse (5-ASA), follow-up at 24 months | 1 (L)<br>Gendre 1993 | RR 0.84 (0.58 – 1.23) | 71 fewer per 1000 (from 187 fewer to 102 more) | Non-significant | |
| Maintenance of remission (sulfasalazine), follow-up at 12 months | 1 (H)<br>Summer 1979 | RR 0.96 (0.75 – 1.24) | 26 fewer per 1000 (from 161 fewer to 219 more) | Non-significant | |
| Maintenance of remission (sulfasalazine), follow-up at 24 months | 1 (L)<br>Summers 1979 | RR 0.76 (0.43 – 1.34) | 97 fewer per 1000 (from 230 fewer to 137 more) | Non-significant | |

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| Withdrawal due to adverse events (5-ASA), follow-up at 12 months | 5 (M)<br>Arber 1995<br>IMSG 1990<br>Mahmud 2001<br>Prantera 1992<br>Thomson 1995 | RR 1.61 (1.16 – 2.26) | 58 fewer per 1000 (from 15 more to 188 more) | Favours placebo: more withdrawals in 5-ASA group | |
| Withdrawal due to adverse events (5-ASA), follow-up at 24 months | 1 (VL)<br>Gendre 1993 | RR 0.71 (0.28 – 1.77) | 36 fewer per 1000 (from 89 fewer to 95 more) | Non-significant | |
| Adverse events disaster (sulfasalazine), follow-up 24 months | 1 (L)<br>Singleton 1979 | RR 0.58 (0.02 – 13.92) | 4 fewer per 1000 (from 10 fewer to 128 more) | Non-significant | |
| Adverse events severe (sulfasalazine), follow-up at 24 months | 1 (L)<br>Singleton 1979 | RR 0.50 (0.11 – 2.32) | 35 fewer per 1000 (from 62 fewer to 91 more) | Non-significant | |
| **5-ASA compared with AZA** | | | | | |
| Maintenance of remission, follow-up at 12 months | 1 (M)<br>Summers 1979 | RR 0.87 (0.72 – 1.05) | 111 fewer per 1000 (from 239 fewer to 43 more) | Non-significant | |

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| Maintenance of remission, follow-up at 24 months | 1 (M)<br>Summers 1979 | RR 1.0 (0.70 – 1.41) | 0 fewer per 1000 (from 161 fewer to 220 more) | Non-significant | |
| Adverse events disaster (sulfasalazine), follow-up at 24 months | 1 (L)<br>Singleton 1979 | RR 0.19 (0.01 – 3.80) | 30 fewer per 1000 (from 37 fewer to 104 more) | Non-significant | |
| Adverse events severe , follow-up at 24 months | 1 (M)<br>Singleton 1979 | RR 0.23 (0.05 – 1.05) | 114 fewer per 1000 (from 141 fewer to 7 more) | Non-significant | |
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| **AZA/MP (immunosuppressive) for maintenance of remission** | | | | | |
| **AZA compared with placebo** | | | | | |
| Relapse CDAI & clinical deterioration, follow-up at 12 months | 2 (M)<br>O'Donoghue 1978<br>Lémann 2005 | RR 0.21 (0.06 – 0.68) | 181 fewer per 1000 (from 73 fewer to 215 fewer) | Favours AZA | |
| Relapse and withdrawal (CDAI & clinical deterioration), follow-up at 12 months | 2 (L)<br>O'Donoghue 1978<br>Lémann 2005 | RR 0.58 (0.29 – 1.15) | 114 fewer per 1000 (from 193 fewer to 41 more) | Non-significant | |

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| Relapse (CDAI & clinical deterioration), follow-up at 18 months | 1 (M)<br>Lémann 2005 | RR 0.36 (0.1 – 1.23) | 134 fewer per 1000 (from 188 fewer to<br>48 more) | Non-significant | |
| Relapse and withdrawal (CDAI & clinical deterioration), follow-up at 18 months | 1 (L)<br>Lémann 2005 | RR 1.14 (0.67 – 1.94) | 52 more per 1000 (from 123 fewer to 350 more) | Non-significant | |
| Maintenance of remission, follow-up at 12 months | 1 (M)<br>Summers 1979 | RR 1.06 (0.84 – 1.34) | 39 more per 1000 (from 103 fewer to 219 more) | Non-significant | |
| Maintenance of remission, follow-up at 24 months | 1 (L)<br>Summers 1979 | RR 0.81 (0.42 – 1.58) | 43 fewer per 1000 (from 132 fewer to 132 more) | Non-significant | |
| Maintenance of remission (analysed censored 12/months) | 1 (L)<br>Summers 1979 | RR 0.71 (0.38 – 1.31) | 117 fewer per 1000 (from 250 fewer to 125 more) | Non-significant | |
| Withdrawal due to adverse events, follow-up at 12 months | 2 (VL)<br>O'Donoghue 1978<br>Lémann 2005 | RR 1.83 (0.25 – 13.38) | 12 more per 1000 (from 11 fewer to 177 more) | Non-significant | |

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| Adverse events, follow-up at 12 months | 2 (VL)<br>O'Donoghue 1978<br>Lémann 2005 | RR 2.55 (0.39 – 16.72) | 22 more per 1000 (from 9 fewer to 225 more) | Non-significant | |
| Adverse events severe at 2 years, follow-up at 24 months | 1 (M)<br>Summers 1979 | RR 2.14 (0.82 – 5.58) | 79 more per 1000 (from 13 fewer to 268 more) | Non-significant | |
| Adverse events disaster, follow-up at 24 months | 1 (L)<br>Summer 1979 | RR 3.74 (0.35 – 40.32) | 27 more per 1000 (from 6 fewer to 389 more) | Non-significant | |
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| **MTX vs placebo** | | | | | |
| Maintenance of remission, follow-up at 40 weeks | 1 (L)<br>Feagan 2000 | RR 1.67 (1.05 – 2.67) | 261 more per 1000 (from 19 more to 649 more) | Favours MXT | |
| Withdrawal due to adverse events, follow-up at 40 weeks | 1 (VL)<br>Feagan 2000 | RR 2.71 (0.11 – 64.43) | | Non-significant | |
| Adverse events severe, follow-up at 40 weeks | 1 (VL)<br>Feagan 2000 | RR 0.18 (0.01 – 3.64) | 46 fewer per 1000 (from 55 fewer to 147 more) | Non-significant | |

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| **Maintaining remission after surgery** | | | | | |
| **5-ASA compared with placebo** | | | | | |
| Relapse CDAI, follow-up 12 months | 3 (L)<br>Wenkert 1977<br>Brignola 1995<br>Ewe 1989 | RR 0.6 (0.4 – 0.91) | 103 fewer per 1000 (from 23 fewer to 155 fewer) | Favours 5-ASA: fewer relapses in 5-ASA group | |
| Relapse and withdrawal CDAI, follow-up at 12 months | 3 (L)<br>Wenkert 1977<br>Brignola 1995<br>Ewe 1989 | RR 0.82 (0.65 – 1.03) | 86 fewer per 1000 (from 168 fewer to 14 more) | Non-significant | |
| Remission CDAI, follow-up at 12 months | 1 (M)<br>Brignola 1995 | RR 1.04 (0.79 – 1.39) | 27 more per 1000 (from 142 fewer to 263 more) | Non-significant | |
| Withdrawal dues to adverse events, follow-up at 12 months | 1 (L)<br>Brignola 1995 | RR 1.63 (0.41 – 6.4) | 44 more per 1000 (from 41 fewer to 377 more) | Non-significant | |

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| Relapse CDAI, follow-up at 18 months | 2 (L)<br>Lochs 2000<br>Wenkert 1977 | RR 0.74 (0.52 – 1.04) | 77 fewer per 1000 (from 142 fewer to 12 more) | Non-significant | |
| Relapse and withdrawal, follow-up at 18 months | 1 (M)<br>Lochs 2000 | RR 0.89 (0.64 – 1.24) | 36 fewer per 1000 (from 119 fewer to 80 more) | Non-significant | |
| Endoscopic relapse, follow-up at 18 months | 1 (M)<br>Lochs 2000 | RR 1.31 (0.98 – 1.76) | 155 more per 1000 (from 10 fewer to 380 more) | Non-significant | |
| Maintenance of remission CDAI, follow-up at 18 months | 1 (H)<br>Lochs 2000 | RR 1.05 (0.91 – 1.22) | 33 more per 1000 (from 60 fewer to 147 more) | Non-significant | |
| Adverse events serious, follow-up at 18 montha | 1 (L)<br>Lochs 2000 | RR 0.97 (0.38 – 2.45) | 2 fewer per 1000 (from 34 fewer to 79 more) | Non-significant | |
| Relapse CDAI, follow-up at 24 months | 2 (VL)<br>Ewe 1989<br>Hanauer 2004 | RR 0.69 (0.53 – 0.9) | 148 fewer per 1000 (from 48 fewer to 225 fewer) | Favours 5-ASA: fewer relapses in 5-ASA group | |

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| Relapse and withdrawal, follow-up at 24 months | 2 (VL)<br>Ewe 1989<br>Hanauer 2004 | RR 0.84 (0.72 – 0.98) | 114 fewer per 1000 (from 14 fewer to 200 fewer) | Favours 5-ASA: fewer relapses in 5-ASA group | |
| Endoscopic recurrence, follow-up at 24 months | 1 (L)<br>Hanauer 2004 | RR 0.98 (0.71 – 1.35) | 13 fewer per 1000 (from 189 fewer to 228 more) | Non-significant | |
| Radiological recurrence, follow-up at 24 months | 1 (L)<br>Hanauer 2004 | RR 0.91 (0.58 – 1.42) | 45 fewer per 1000 (from 210 fewer to 210 more) | Non-significant | |
| Withdrawal due to adverse events, follow-up at 24 months | 1 (L)<br>Hanauer 2004 | RR 1.36 (0.41 – 4.48) | 36 more per 1000 (from 59 fewer to 348 more) | Non-significant | |
| Relapse, follow-up at 36 months | 1 (L)<br>Ewe 1989 | RR 0.79 (0.58 – 1.07) | 101 fewer per 1000 (from 201 fewer to 34 more) | Non-significant | |
| Relapse and withdrawal at 3 years, follow-up at 36 months | 1 (M)<br>Ewe 1989 | RR 0.98 (0.86 – 1.11) | 16 fewer per 1000 (from 115 fewer to 90 more) | Non-significant | |

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| Recurrence rate, follow-up at 72 months | 1(M)<br>McLeod 1995 | RR 0.76 (0.5 – 1.15) | 98 fewer per 1000 (from 204 fewer to 61 more) | Non-significant | |
| **Mercaptopurine compared with placebo** | | | | | |
| Relapse, clinical grading scale, follow-up at 24 months | 1 (L)<br>Hanauer 2004 | RR 0.66 (0.48 – 0.91) | 263 fewer per 1000 (from 70 fewer to 403 more) | Favours AZA/MP | |
| Relapse and withdrawal, clinical grading scale, follow-up at 24 months | 1 (L)<br>Hanauer 2004 | RR 0.78 (0.62 – 0.98) | 193 fewer per 1000 (from 17 fewer to 332 fewer) | Favours AZA/MP: fewer relapses AZA/ MP group | |
| Endoscopic recurrence, clinical grading scale, follow-up at 24 months | 1 (M)<br>Hanauer 2004 | RR 0.65 (0.44 – 0.98) | 228 fewer per 1000 (from 13 fewer to 364 fewer) | Favours AZA/MP group | |
| Radiographic recurrence, clinical grading scale, follow-up at 24 months | 1 (M)<br>Hanauer 2004 | RR 0.68 (0.41 – 1.13) | 160 fewer per 1000 (from 295 fewer to 65 more) | Non-significant | |
| Withdrawal due to adverse events, follow-up at 24 months | 1 (L)<br>Hanauer 2004 | RR 1.91 (0.64 – 5.75) | 91 more per 1000 (from 36 fewer to 473 more) | Non-significant | |
| **AZA compared with 5-ASA** | | | | | |

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| Relapse, CDAI, follow-up at 24 months | 2 (VL)<br>Ardizzone 2004<br>Hanauer 2004 | RR 1.32 (0.94 – 1.84) | 109 more per 1000 (from 21 fewer to 287 more) | Non-significant | |
| Relpase and withdrawal, CDAI, follow-up at 24 months | 2 (VL)<br>Ardizzone 2004<br>Hanauer 2004 | RR 1.02 (0.81 – 1.28) | 11 more per 1000 (from 107 fewer to 158 more) | Non-significant | |
| Surgical relapse, follow-up at 24 months | 1 (VL)<br>Ardizzone 2004 | RR 1.7 (0.52 – 5.55) | 41 more per 1000 (from 28 fewer to 264 more) | Non-significant | |
| Withdrawal due to adverse events, follow-up at 24 months | 2 (L)<br>Ardizzone 2004<br>Hanauer 2004 | RR 0.51 (0.27 – 0.96) | 100 fewer per 1000 (from 8 fewer to 149 fewer) | Favours 5-ASA: more adverse events in AZA group | |
| Endoscopic recurrence , follow-up at 24 months | 1 (M)<br>Hanauer 2004 | RR 1.5 (1 to 2.23) | 213 more per 1000 (from 0 more to 524 more) | Non-significant | |
| Radiographic recurrence, follow-up at 24 months | 1 (M)<br>Hanauer 2004 | RR 1.34 (0.8 – 2.23) | 116 more per 1000 (from 68 fewer to 418 more) | Non-significant | |
| **Budesonide compared with placebo** | | | | | |

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| Recurrence, CDAI, follow-up at 12 months | 2 (L)<br>Ewe 1999<br>Hellers 1999 | RR 0.91 (0.59 – 1.4) | 26 fewer per 1000 (from 118 fewer to 116 more) | Non-significant | |
| Endoscopic recurrence, follow-up at 12 months | 1 (M)<br>Ewe 1999 | RR 0.76 (0.5 – 1.15) | 169 fewer per 1000 (from 352 fewer to 106 more) | Non-significant | |
| Withdrawal due treatment failure, follow-up at 12 months | 1 (L)<br>Ewe 1999 | RR 0.53 (0.17 – 1.68) | 82 fewer per 1000 (from 145 fewer to 119 more) | Non-significant | |
| Withdrawal due to adverse events, follow-up at 12 months | 2 (L)<br>Ewe 1999<br>Hellers 1999 | RR 1.03 (0.34 – 3.06) | 1 more per 1000 (from 33 fewer to 103 more) | Non-significant | |

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| Withdrawal due to any reason, follow-up at 12 months | 2 (VL)<br>Ewe 1999<br>Hellers 1999 | Fixed effect: RR 1.05 (0.72 – 1.53)<br><br>Random effects: RR 1.03 (0.59 – 1.77) | Fixed effect: 17 more per 1000 (from 98 fewer to 185 more)<br><br>Random effects: 10 more per 1000 (from 139 fewer to 254 more) | Non-significant | Significant heterogeneity |
| Endosocpic recurrence at anastomosis, follow-up at 12 months | 1 (VL)<br>Hellers 1999 | RR 0.92 (0.63 – 1.33) | 39 fewer per 1000 (from 179 fewer to 160 more) | Non-significant | |
| Endoscopic recurrence at new distal ileum, follow-up at 12 months | 1 (L)<br>Hellers 1999 | RR 0.91 (0.66 – 1.24) | 52 fewer per 1000 (from 196 fewer to 138 more) | Non-significant | |
| **Enteral nutrition compared with placebo/normal diet** | | | | | |
| Clinical recurrence, CDAI, follow-up at 12 months | 1 (VL)<br>Yamamoto 2005 | RR 0.14 (0.02 – 1.06) | 301 fewer per 1000 (from 343 fewer to 21 more) | Non-significant | |

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| Endoscopic recurrence, follow-up at 12 months | 1 (VL)<br>Yamamoto 2007 | RR 0.43 (0.21 – 0.89) | 399 fewer per 1000 (from 77 fewer to 553 fewer) | Favours enteral nutrition | |
| **Metronidazole compared with placebo after 3-month treatment** | | | | | |
| Clinical recurrence, follow-up at 12 months | 1 (VL)<br>Rutgeerts 1995 | RR 0.28 (0.06 – 1.22) | 180 fewer per 1000 (from 235 fewer to 55 more) | Non-significant | |
| Clinical recurrence and withdrawal, follow-up at 12 months | 1 (VL)<br>Rutgeerts 1995 | RR 1.1 (0.46 – 2.64) | 25 more per 1000 (from 135 fewer to 410 more) | Non-significant | |
| Clinical recurrence, follow-up at 24 months | 1 (VL)<br>Rutgeerts 1995 | RR 0.56 (0.26 – 1.22) | 189 fewer per 1000 (from 317 fewer to 94 more) | Non-significant | |
| Clinical recurrence and withdrawal, follow-up at 24 months | 1 (VL)<br>Rutgeerts 1995 | RR 1.05 (0.58 – 1.88) | 21 more per 1000 (from 180 fewer to 377 more) | Non-significant | |
| Clinical recurrence, follow-up at 36 months | 1 (VL)<br>Rutgeerts 1995 | RR 0.62 (0.32 – 1.2) | 190 fewer per 1000 (from 340 fewer to 100 more) | Non-significant | |

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| Clinical recurrence and withdrawal, follow-up at 36 months | 1 (VL)<br>Rutgeerts 1995 | RR 1.03 (0.62 – 1.72) | 15 more per 1000 (from 190 fewer to 360 more) | Non-significant | |
| Endoscopic recurrence, follow-up at 3 months | 1 (L)<br>Rutgeerts 1995 | RR 0.7 (0.45 – 1.09) | 225 fewer per 1000 (from 413 fewer to 68 more) | Non-significant | |
| Endoscopic recurrence, follow-up at 36 months | 1 (VL)<br>Rutgeerts 1995 | RR 0.95 (0.72 – 1.26) | 41 fewer per 1000 (from 230 fewer to 214 more) | Non-significant | |
| Withdrawal due to adverse events, follow-up at 36 months | 1 (VL)<br>Rutgeerts 1995 | RR 10.63 (0.62 – 183.77) | | Non-significant | |
| **Metronidazole plus AZA compared with metronidazole plus placebo** | | | | | |
| Recurrence, CDAI, follow-up at 12 months | 1 (VL)<br>D'Haens 2008 | RR 0.44 (0.12 – 1.58) | 96 fewer per 1000 (from 150 fewer to 99 more) | Non-significant | |
| Recurrence and withdrawal, CDAI, follow-up at12 months | 1 (L)<br>D'Haens 2008 | RR 0.59 (0.33 – 1.08) | 190 fewer per 1000 (from 310 fewer to 37 more) | Non-significant | |

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| Endoscopic relapse, follow-up at 12 months | 1 (L)<br>D'Haens 2008 | RR 0.72 (0.42 – 1.21) | 137 fewer per 1000 (from 283 fewer to 102 more) | Non-significant | |
| Endoscopic relapse and withdrawal , follow-up at 12 months | 1 (L)<br>D'Haens 2008 | RR 0.7 (0.51 – 0.97) | 234 fewer per 1000 (from 23 fewer to 382 fewer) | Favours metronidazole plus AZA: more relapse and withdrawal in metronidazole plus placebo group | |
| Withdrawal due to adverse events, follow-up at 12 months | 1 (VL)<br>D'Haens 2008 | RR 1.02 (0.15 – 6.93) | 1 more per 1000 (from 41 fewer to 289 more) | Non-significant | |
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| **Enteral nutrition for induction of remission** | | | | | |
| **Enteral nutrition compared with conventional glucocorticosteroid** | | | | | |

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| Induction of remission in adults and children CDAI / PCDAI, follow-up at 4-10 weeks | 7 (VL)<br>Zachos 2007 | Fixed effect: RR 0.68 (0.57 – 0.8)<br><br>Random effects: 0.70 (0.53 – 0.93) | Fixed effect:<br>240 fewer per 1000 (from 150 fewer to 322 fewer)<br><br>Random effects: 225 fewer per 1000 (from 52 fewer to 353 fewer) | Favours conventional glucocorticosteroid | Significant heterogeneity |
| Induction of remission in adults (subgroup of Cochrane) CDAI, follow-up at 3 – 10 weeks | 5 (L & VL)<br>Zachos 2007 | Fixed effect: RR 0.62 (0.52 – 0.74)<br><br>Random effects: 0.64 (0.49 – 0.84) | Fixed effect: 289 fewer per 100 (from 198 fewer to 365 fewer)<br><br>Random effects: 274 fewer per 100 (from 122 fewer to 388 fewer) | Favours conventional glucocorticosteroid | Significant heterogeneity |

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| Failure to achieve remission in adults (DAI), follow-up at 4 weeks | 1 (VL)<br>Gorard 1993 | RR 1.54 (0.36 – 6.49) | 81 more per 1000 (from 96 fewer to 823 more) | Non-significant | |
| Premature termination in adults, follow-up at 4weeks | 1 (VL)<br>Gorard 1993 | RR 1.82 (0.18 – 18.55) | 41 more per 1000 (from 41 fewer to 877 more) | Non-significant | |
| Improvement clinical assessment in adults, follow-up at 4 weeks | 1 (VL)<br>O'Morain 198484 | RR 1.02 (0.67 – 1.55) | 16 more per 1000 (from 264 fewer to 440 more) | Non-significant | |
| Induction of remission Harvey Bradshaw in adults, follow-up at 2 weeks | 1 (VL)<br>Zoli 1997 | RR 1.33 (0.64 – 2.79) | 165 more per 1000 (from 180 fewer to 895 more) | Non-significant | |
| **Enteral nutrition compared with conventional glucocorticosteroid in children** | | | | | |
| Induction of remission(subgroup of Cochrane) PCDAI, follow-up at 10 weeks | 1 (L)<br>Borrelli 2006 | RR 1.18 (0.79 – 1.77) | 120 more per 1000 (from 140 fewer to 513 more) | Non-significant | |
| Adverse events, follow-up at 10 weeks | 1 (L)<br>Borrelli 2006 | RR 0.32 (0.13 – 0.8) | 499 fewer per 1000 (from 147 fewer to 638 more) | Favours enteral nutrition | |

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| Change in PCDAI (better indicated by lower values), follow-up at 2 months | 1 (VL)<br>Ruuska 1994 | | MD 2.40 lower (10.3 lower to 5.6 higher) | Non-significant | |
| Adverse events at 2 months, follow-up at 2 months | 1 (VL)<br>Ruuska 1994 | RR 0.9 (0.07 – 12.38) | 11 fewer per 1000 (from 103 fewer to 1264 more) | Non-significant | |
| Endoscopic healing, follow-up at 10 weeks | 1 (L)<br>Borrelli 2006 | RR 2.03 (1.09 – 3.79) | 401 more per 1000 (from 35 more to 1000 more) | Favours enteral nutrition | |
| Histologic healing, follow-up at 10 weeks | 1 (L)<br>Borrelli 2006 | RR 2.21 (1.09 – 4.48) | 403 more per 1000 (from 30 more to 1000 more) | Favours enteral nutrition | |
| **Enteral nutrition compared with conventional glucocorticosteroid plus 5-ASA (mesalazine)** | | | | | |
| Remission (mean change in Lloyd Still disease activity: better indicated by lower values), follow-up at 12 weeks | 1 (VL)<br>Sanderson 1987 | | MD 3.00 higher (from 0.62 lower to 6.62 higher) | Non-significant | |
| Premature termination, follow-up at 12 weeks | 1 (VL)<br>Sanderson 1987 | RR 0.89 (0.07 – 12.00) | 14 fewer per 1000 (from 116 fewer to 1375 more) | Non-significant | |

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| **Enteral nutrition compared with conventional glucocorticosteroid plus 5-ASA in children** | | | | | |
| Induction of remission PCDAI, follow-up at 8 weeks | 1 (L)<br>Terrin 2002 | RR 1.80 (0.94 – 3.46) | 400 more per 1000 (from 30 fewer to 1230 more) | Non-significant | |
| Growth mean height velocity (better indicated by higher values), follow-up at 6 months | 1 (VL)<br>Thomas 1993 | | MD not estimable (SD not provided) $p < 0.5$ | Favours enteral nutrition | |
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| **Enteral nutritional for maintenance of remission** | | | | | |
| **Half enteral nutrition compared with free diet** | | | | | |
| Relapse, follow-up at 1 year | 1 (L)<br>Takagi 2006 | HR 0.40 (0.18 – 0.98) | 305 fewer per 1000 (from 7 fewer to 472 fewer) | Favours enteral nutrition | |
| Adverse events, follow-up at 1 year | 1 (VL)<br>Takagi 2006 | No events in either groups | No events in either group | No differnece | |
| **Enteral nutrition compared with normal diet** | | | | | |

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|---|---|---|---|---|---|
| Maitenance of remission without conventional glucocosteroid treatment, follow-up at 1 year | 1 (L)<br>Verma 2001 | RR 0.74 (0.45 – 1.21) | 150 fewer per 1000 (from 317 fewer to 121 more | Non-significant | Observational data |
| Remission, weaning prednisone and maintaining 5-ASA and AZA, follow-up at 1 year | 1 (VL)<br>Verma 2001 | RR 2.14 (0.81 – 5.67) | 253 more per 1000 (from 42 fewer to 1000 more) | Non-significant | Observational data |
| **Enteral nutrition compared with no treatment** | | | | | |
| Remission, IOIBD score, follow-up at 1 year | 1 (VL)<br>Hirakawa 1993 | RR 1.92 (0.86 – 4.29) | 460 more per 1000 (from 70 fewer to 1000 more) | Non-significant | Observational data |
| Remission, CDAI, follow-up at 1 year | 1 (L)<br>Yamamoto 2007 | | P = 0.01 | Favours enteral nutrition | Observational data |
| **Enteral nutrition plus drugs compared with no treatment** | | | | | |
| Remission, IOIBD score, follow-up at 1 year | 1 (VL)<br>Hirakawa 1993 | RR 1.52 (0.66 – 3.49) | 260 more per 1000 (from 170 fewer to 1000 more) | Non-significant | Observational data |
| **Half enteral nutrition compared with no treatment in children** | | | | | |

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|---|---|---|---|---|---|
| Relapse, PCDAI, follow-up at 1 year | 1 (VL)<br>Wilschanski 1996 | RR 0.54 (0.33 – 0.88) | 363 fewer per 1000 (from 95 fewer to 529 fewer) | Favours enteral nutrition | Observational data |

## R.2 Summary of studies for inducing remission in children

| Comparison | Study | Quality | Outcome and time point | Results | Sample size | Summary |
|---|---|---|---|---|---|---|
| GCCS + AZA V GCCS + placebo | Rosenberg 1975 | Very low | GCCS-sparing: reduction in GCCS dosage; 26 weeks | -15.5 mg in GCCS + AZA compared with -6.1 mg in GCCS + placebo | 9 in GCCS + AZA group; 10 in GCCS + placebo group | Mean Difference 9.4mg higher<br>$p < 0.05$ |
| GCCS + MP V GCCS + placebo | Markowitz 2000 | Very low | GCCS-sparing: days on prednisone; 18 months | 0.73 days in GCCS + MP group; 1.34 days in GCCS + placebo | 21 in GCCS + MP group; 11 in GCCS + placebo group | $p < 0.001$ |
| | Markowitz 2000 | Moderate | Remission (HBI); 1 month | 1.18 (0.94-1.47) | 27 in GCCS + MP group; 28 in GCCS + placebo | NS difference |
| Budesonide V GCCS | Escher 2004;Levine 2003 in Seow 2008 | Very low | Induction of remission; 8 weeks | RR 0.88 (0.58 to 1.33) | 41 in budesonide group; 40 in GCCS group | NS difference |
| | Escher 2004;Levine 2003 in Seow 2008 | Very low | Induction of remission; 12 weeks | RR 0.99 (0.65 to 1.50) | 41 in budesonide group; 40 in GCCS group | NS difference |
| | Escher 2004 | Very low | Change in PCDAI; 8 weeks | Mean Difference 4.10 lower (12.77 lower to 4.57 higher ) | 22 in budesonide group; 26 in GCCS group | NS difference |
| 5-ASA V placebo | Griffiths 1993 | Moderate | Paediatric 5-ASA remission (CDAI); | Mean Difference 106.2 lower | 13 in total | more remission in the 5-ASA group than |

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|---|---|---|---|---|---|---|
| | | | | | | in the placebo group |
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| | | | | | (152.06 lower to 60.34 lower) | |
| | | | | 20 weeks | | |
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