

Crohn's disease: management in adults, children and young people – concise guidance

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ABSTRACT

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract. Individuals with CD present with acute inflammatory exacerbations as well as acute and chronic complications. Management requires specialist input from gastroenterologists, colorectal surgeons, nurse specialists and pharmacists as well as general and primary care physicians to allow appropriate selection of treatment options including surgery and rapid assessment and treatment of those with acute exacerbations. Monitoring of the individual and their medication is crucial in preventing and recognising complications including those associated with treatment. This concise guideline focuses on recommendations from National Institute for Health and Care Excellence (NICE) Clinical Guideline 152 (CG152) considered of key importance for implementation.

KEYWORDS: Treatment, Crohn's disease, inflammatory bowel disease

Introduction

Crohn's disease (CD) has a prevalence of 157/100,000 and affects around 115,000 people in the UK.¹ It is a chronic inflammatory condition and can affect any part of the gastrointestinal tract, with the terminal ileum and colon most frequently affected. Patients present with acute exacerbations followed by intervening periods of remission or less active disease. There is increasing recognition that clinical remission may not correlate with endoscopic or radiological remission.²

Treatment options include medication, nutritional support, smoking cessation and surgery, which is required in 50–80% of patients in their lifetime.¹ Treatment is aimed at inducing and maintaining remission, managing complications including fistula, strictures and perianal disease and monitoring of drug treatment. This requires an age-appropriate multidisciplinary team (MDT) with an important role for both primary and secondary care.

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Scope and purpose

This concise guideline highlights key recommendations of NICE CG152 *Crohn's disease management in adults, children and young people*¹ focusing on recommendations for adults and on those areas most relevant to the general physician. It incorporates recommendations from Technology Appraisal (TA)187 *Infliximab and adalimumab for the treatment of Crohn's disease*.³ TA456⁴ and TA352⁵ cover additional biological treatments – ustekinumab and vedolizumab – approved for use in moderate to severely active CD and are not incorporated in CG152 as they were licenced after its publication and are therefore not included in this concise guideline. However, they are likely to be incorporated in Clinical Commissioning Group (CCG) funded treatment pathways. Verbatim recommendations from CG152 are either italicised, included as a box or tabulated.

Recommendations

Patient education and information is essential. Issues to discuss with the person with CD and/or their parent or carer are shown in Box 1.

Box 1. Recommendations for patient education¹

- > Discuss treatment options and monitoring.
- > Give appropriate information, advice and support in line with published NICE guidance on: smoking cessation, patient experience, medicines adherence and fertility.
- > Discuss the possible nature, frequency and severity of side effects of drug treatment with people with CD, and/or their parents or carers if appropriate.
- > Give 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.
- > Offer 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.

Box 2. Recommendations for inducing remission in Crohn's disease: initial monotherapy¹

- > Offer monotherapy with a conventional glucocorticoid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of CD in a 12-month period.
- > In people with distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticoid is contraindicated, consider budesonide. Explain that budesonide is less effective than a conventional glucocorticoid but may have fewer side effects.
- > In people who decline, cannot tolerate or in whom glucocorticoid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticoid or budesonide but may have fewer side effects.
- > Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations.
- > Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission.

Induction of remission

Initial treatment

Choice of treatment is based on site of disease, severity of symptoms, previous treatments and patient and clinician preference. Recommendations are outlined in Box 2.

The choice between a conventional glucocorticoid (eg prednisolone) and budesonide for terminal ileal and right-sided colonic disease was debated by the Guideline Development Group (GDG) for CG152. Meta-analysis indicated that prednisolone was superior to budesonide for induction of clinical remission at week 8, particularly in severe disease. This was also the finding of a more recent Cochrane review, although budesonide was associated with fewer adverse events and was more effective than placebo.⁶ Given widespread concern about adverse effects of systemic steroids, a discussion with patients about the trade-off between efficacy and side effects of these two agents in this situation is important and is captured in the GDG recommendation.¹ Other guidelines have, however, suggested that budesonide should be first choice in mild active localised ileocaecal disease.⁷ Although aminosalicylates (5-ASA) are recommended as an option in those who decline, or do not tolerate conventional glucocorticoids or budesonide, the studies suggesting that 5-ASA were more effective than placebo were high in bias and of low quality.¹ Neither budesonide nor 5-ASA treatment should be used for severe presentations or exacerbations. Thiopurines as a monotherapy are not effective compared to placebo in inducing remission and not recommended as a monotherapy for induction of remission.⁸

Additional treatment

Additional treatment may be needed for disease that is severe, resistant to initial treatment or relapses rapidly on reducing initial treatment.

Anti-TNF agents: infliximab and adalimumab

Infliximab and adalimumab are recommended as treatment options for adults with severe active CD whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy. Severe active CD 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. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of ≥ 300 or more (Table 1), or a Harvey-Bradshaw Index (HBI) score of ≥ 8 (Table 2).

- > *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 to determine whether ongoing treatment is still clinically appropriate.*
- > *Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising CD 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.*
- > *Treatment with infliximab or adalimumab 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 whose disease relapses after treatment is stopped should have the option to start treatment again.*
- > *Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active CD whose disease has not responded to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.*

In recommending infliximab and adalimumab as treatment options in patients with severe active CD, NICE included CDAI and HBI thresholds. However, severe active CD may not always correspond to the specific threshold as defined by these scores. In particular, these clinical assessment tools may not be suitable in assessing patients who have had previous intestinal resection or who have a stoma.

Prior to starting treatment with an anti-TNF agent, infection should be excluded – including intra-abdominal and perianal sepsis and screening for latent tuberculosis.

Infliximab is administered as an intravenous infusion at 0, 2 and 6 weeks during induction and continued every 8 weeks for maintenance.¹¹ Adalimumab is administered by subcutaneous injection – 160 mg followed by 80 mg at week 2 and thereafter 40 mg every other week for maintenance.¹² Both infliximab and adalimumab are recommended as planned courses of treatment which is associated with fewer relapses, reduced immunogenicity³ and reduced need for surgery and hospitalisation.¹³ Dose escalation may be required for both infliximab and adalimumab. Although only adalimumab is licensed and NICE approved for dose escalation (up to 40 mg weekly), current practice is to increase infliximab dosing / reduce interval between infusions

in conjunction with published therapeutic drug monitoring algorithms if appropriate.¹⁴ Combination therapy with conventional immunosuppressants is associated with increased remission rates¹⁵ and reduced immunogenicity to infliximab.¹⁶ However, in using combination therapy, the risks of increased immunosuppression and adverse events including infection and the very low risk of lymphoma should be discussed with patients.¹⁵

- > When a person with CD is starting infliximab or adalimumab, discuss options of:
 - > monotherapy with one of these drugs, or
 - > combined therapy (either infliximab or adalimumab, combined with an immunosuppressant) and tell the person there is uncertainty about the comparative effectiveness and long-term adverse effects of monotherapy and combined therapy.¹⁵

Withdrawal of anti-TNF medications after 12 months can be considered in patients in stable clinical remission – and after reassessment. However, the optimum form of that assessment is not clear and there is a relapse rate of 36% 1 year after withdrawal.^{17–19} The impact of continued immunosuppression or evidence of endoscopic remission on rate of relapse after anti-TNF withdrawal has differed in published series,^{17–19} although raised faecal calprotectin is associated with an increased risk of relapse.^{18,19}

Maintenance of remission

- > Discuss the importance of not smoking.
- > Discuss with people with CD, 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.

Long-term use of medications requires patient education and monitoring for side effects. Immunomodulators routinely used in the management of Crohn's disease do not have a UK marketing authorisation for this indication and so the prescriber should follow relevant professional guidance and take full responsibility for the decision.

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.

Choice of medication to maintain remission

- > Consider adding azathioprine or mercaptopurine to a conventional glucocorticoid or budesonide to induce remission of CD if:
 - > there are two or more inflammatory exacerbations in a 12-month period, or
 - > the glucocorticoid dose cannot be tapered.

Prior to addition of thiopurines, assessment of thiopurine methyltransferase (TPMT) is essential to avoid toxicity.

- > 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.
- > Consider adding methotrexate to a conventional glucocorticoid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient.
- > Offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticoid or budesonide to induce remission.
- > Consider azathioprine or mercaptopurine 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, glucocorticoid use at presentation and severe presentations).
- > Consider methotrexate, 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).
- > Do not offer a conventional glucocorticoid or budesonide to maintain remission.

Monitoring of treatment

- > Monitor the effects of azathioprine, mercaptopurine and methotrexate, as advised in the current online version of the British National Formulary.²⁰ Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity.
- > 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.

Surgery for limited terminal ileal disease

Surgery should be considered as an alternative to medical treatment early in the course of the disease taking into account the following:

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

Since the publication of CG152, the LIRIC trial showed no difference between laparoscopic resection and infliximab in quality of life at 12 months in patients with limited terminal ileal disease (<40 cm) failing conventional therapy.²¹ There was a significant reduction in costs at 1 year in those undergoing surgery compared to infliximab,²¹ although the advent of biosimilar infliximab might affect the difference in cost as noted in the study.

Table 1. Crohn's Disease Activity Index⁹

Variable	Description	Score
Number of liquid stools	Sum of 7 days	x2
Abdominal pain	Sum of 7 days rating	x5
	None 0	
	Mild 1	
	Moderate 2	
	Severe 3	
General wellbeing	Sum of 7 days rating	x7
	Generally well 0	
	Slightly below par 1	
	Poor 2	
	Very poor 3	
	Terrible 4	
Extraintestinal complications	Score of 1 per complication in previous 7 days: Arthritis/arthralgia, iritis/uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess, fever >37.8°C	x20
Anti-diarrhoeal drugs	Use in previous 7 days	x30
	No 0	
	Yes 1	
Abdominal mass	No 0	x10
	Questionable 2	
	Yes 5	
Haematocrit	Expected–observed:	x6
	males: 47–observed, females: 42–observed	
Body weight	Ideal/observed ratio	x1
	1–(ideal/observed) x100	

Note: The score is based on a diary of symptoms for previous 7 days and clinical parameters. Remission <150, moderate disease ≥220 and severe disease ≥300.

Maintenance of remission after surgery

- > Consider azathioprine or mercaptopurine 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).
- > Consider 5-ASA treatment to maintain remission after surgery.
- > Do not offer budesonide or enteral nutrition to maintain remission after surgery.

Several important studies have been undertaken since publication of CG152. The use of mercaptopurine in smokers postoperatively

Table 2. Harvey Bradshaw Index¹⁰

Symptom	Severity	Score
General wellbeing	Very well	0
	Slightly poor	1
	Poor	2
	Very poor	3
Abdominal pain	Terrible	4
	None	0
	Mild	1
	Moderate	2
Number of liquid stool	Severe	3
		1 for each liquid stool per day
Abdominal mass	None	0
	Dubious	1
	Definite	2
	Definite with tenderness	3
Complications	Arthralgia	1 point each
	Uveitis	
	Erythema nodosum	
	Aphthous ulcers	
	Pyoderma gangrenosum	
	Anal fissure	
	New fistula	
Abscess		

Note: The first three items are scored for the previous day. Remission <5, active disease ≥5, severe disease ≥8.

significantly reduced the risk of relapse at 3 years compared to placebo (10% vs 46%).²² The POCER trial showed the benefit of an algorithmic approach to preventing postoperative recurrence based on risk stratification, with immunosuppression for those deemed to be at high risk (smokers, perforating disease, previous resection) and treatment escalation based on endoscopic appearances at colonoscopy, 6 months after surgery.²³ However, using these criteria, over 80% of patients would be deemed high risk and therefore receive more intensive treatment.

Management of strictures

Strictures can be managed endoscopically with balloon dilation or with surgical interventions.

- > Consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy.
- > Discuss the benefits and risks of balloon dilation and surgical interventions for managing strictures should involve the person with CD and/or their parent or carer, a surgeon and a gastroenterologist.
- > 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 and the person's preference.

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

Monitoring for osteopenia and assessing fracture risk

CD is a cause of secondary osteoporosis and patients should be assessed for fragility fracture risk as appropriate, in line with national and/or local guidance. Although routine monitoring for changes in bone mineral density in children and young people is not recommended:

- > 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 glucocorticoid use.

Limitations of the guideline

As with any guideline, new evidence alters guidance over time. Following the surveillance review in 2017, CG152 is currently being updated – with a focus on maintenance of remission after surgery.²⁴ The use of vedolizumab and ustekinumab in CD is evaluated in NICE Technology Appraisals^{4,5} and is not included in CG152.

Perianal disease was also excluded from CG152 other than the indication of infliximab for fistulating disease.²⁵ This is an important part of the management of CD, associated with significant debility, often under-reported by patients and often not fully addressed by clinicians. There are variations in management and combined multidisciplinary management is essential with measures in place to avoid delays during the care pathway.²⁶

However, perhaps most fundamental is the increased emphasis on and discussion of treatment strategies for CD that do not rely only on symptoms, which may not adequately represent ongoing tissue damage, and use markers of mucosal inflammation and damage as the 'target' of treatment – 'treat to target' strategies.²⁷ An increased number of studies examining different treatment strategies is expected. ■

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