Crohn’s disease: management

NICE guideline
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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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This guideline replaces CG152.

This guideline is the basis of QS81.

Overview

This guideline covers the management of Crohn's disease in children, young people and adults. It aims to reduce people's symptoms and maintain or improve their quality of life.

We have also produced a NICE guideline on colonoscopic surveillance for adults with Crohn's disease, ulcerative colitis or adenomas.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- People with Crohn's disease and their families and carers
Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Providing information and support

1.1.1 Ensure that information and advice about Crohn's disease:

- is age appropriate
- is of the appropriate cognitive and literacy level
- meets the cultural and linguistic needs of the local community. [2012]

1.1.2 Discuss treatment options and monitoring with the person with Crohn's disease, with their family members or carers (as appropriate), and within the multidisciplinary team. Apply the principles in the NICE guideline on patient experience in adult NHS services. [2012]

1.1.3 Discuss the possible nature, frequency and severity of side effects of drug treatment with people with Crohn's disease and their family members or carers (as appropriate). Appendices L and M of the full guideline contain observational data on adverse events associated with aminosalicylate treatment and immunosuppressives. [2012]

1.1.4 Give all people with Crohn's disease and their family members or carers (as appropriate) information, advice and support in line with published NICE guidance on:
• smoking cessation
• patient experience
• medicines adherence
• fertility. [2012]

1.1.5 Give people with Crohn's disease and their family members or carers 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
• transition between paediatric and adult services
• contact details for support groups. [2012]

1.1.6 Offer people with Crohn's disease and their family members or carers (as 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. [2012]
1.2 Inducing remission in Crohn's disease

Monotherapy

In May 2019, the use of some medicines was off label:

- 1.2.3: budesonide in children and young people
- 1.2.4: mesalazine, olsalazine and balsalazide.

See NICE's information on prescribing medicines.

1.2.1 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. [2012]

1.2.2 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
- young people in whom there is concern about growth. [2012]

1.2.3 Consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period for people:

- who have one or more of distal ileal, ileocaecal or right-sided colonic disease (see the recommendations on when to consider surgery early in the course of the disease in the section on Crohn's disease limited to the distal ileum) and
- if conventional glucocorticosteroids are contraindicated, or if the person declines or cannot tolerate them.

Explain that budesonide is less effective than a conventional glucocorticosteroid, but may have fewer side effects. [2012]
1.2.4 Consider aminosalicylate treatment for a first presentation or a single inflammatory exacerbation in a 12-month period if conventional glucocorticosteroids are contraindicated, or if the person declines or cannot tolerate them. Explain that aminosalicylates are less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]

1.2.5 Do not offer budesonide or aminosalicylate treatment for severe presentations or exacerbations. [2012]

1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

Add-on treatment

In May 2019, the use of some medicines was off label:

- 1.2.7: budesonide (in children and young people), mercaptopurine, and most preparations of azathioprine
- 1.2.8: mercaptopurine and most preparations of azathioprine
- 1.2.9: some formulations of methotrexate (in adults), all formulations of methotrexate (in children and young people), and budesonide (in children and young people)
- 1.2.10: some formulations of methotrexate (in adults), all formulations of methotrexate (in children and young people), mercaptopurine, and most preparations of azathioprine.

See NICE’s information on prescribing medicines.

1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn’s disease if:

- there are 2 or more inflammatory exacerbations in a 12-month period or
• the glucocorticosteroid dose cannot be tapered. [2012]

1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. 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). [2012]

1.2.9 Consider adding methotrexate (follow British national formulary [BNF]/British national formulary for children [BNFC] cautions) to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:

• there are 2 or more inflammatory exacerbations in a 12-month period or
• the glucocorticosteroid dose cannot be tapered. [2012]

1.2.10 Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the BNF or BNFC. Consult the monographs of individual drugs for advice on monitoring immunosuppressives. Monitor for neutropenia in people taking azathioprine or mercaptopurine even if they have normal TPMT activity. [2012]

1.2.11 Ensure that there are documented local safety monitoring policies and procedures (including audit) for people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs, people with Crohn's disease and their family members or carers (as appropriate). [2012]

**Infliximab and adalimumab**

The recommendations in the following section (except for the recommendation on discussing the options of monotherapy or combined therapy) are from the NICE technology appraisal guidance on infliximab and adalimumab for the treatment of Crohn's disease.

1.2.12 Infliximab and adalimumab, within their licensed indications, are recommended as
treatment options for adults with severe active Crohn's disease (see recommendation 1.2.18) 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 1.2.16) to determine whether ongoing treatment is still clinically appropriate. [2010]

1.2.13 Treatment as described in recommendation 1.2.12 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 individuals because of differences in the method of administration and treatment schedules. [2010]

1.2.14 When a person with Crohn's disease is starting infliximab or adalimumab (in line with recommendations 1.2.12, 1.2.15, 1.2.17 and 1.2.20), discuss options of:

- monotherapy with one of these drugs or
- combined therapy (either infliximab or adalimumab, combined with an immunosuppressant).

Tell the person there is uncertainty about the comparative effectiveness and long-term adverse effects of monotherapy and combined therapy. [2016]

1.2.15 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 1.2.16) to determine whether ongoing treatment is still clinically appropriate. [2010]

1.2.16 Treatment with infliximab or adalimumab (see recommendations 1.2.12 and 1.2.15)
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. [2010]

1.2.17 Infliximab, within its licensed indication, is recommended for the treatment of people aged 6 to 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. [2010]

1.2.18 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 to 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. [2010]

1.2.19 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. [2010]

1.2.20 Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease. [2010]
Ustekinumab and vedolizumab

1.2.21 For guidance on using ustekinumab, see the NICE technology appraisal guidance on ustekinumab for moderately to severely active Crohn's disease after previous treatment. [2019]

1.2.22 For guidance on using vedolizumab, see the NICE technology appraisal guidance on vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. [2019]

1.3 Maintaining remission in Crohn's disease

1.3.1 Discuss with people with Crohn's disease and their family members or carers (as 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. [2012]

1.3.2 Offer colonoscopic surveillance in line with the NICE guideline on colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas. [2012]

Follow-up during remission for people who choose not to have maintenance treatment

1.3.3 When people choose not to receive maintenance treatment:

- discuss and agree with them and their family members or carers (as 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. [2012]

Maintenance treatment for people who choose this option

In May 2019, the use of some medicines was off label:

• 1.3.4 and 1.3.5: mercaptopurine and most preparations of azathioprine
• 1.3.6: some formulations of methotrexate (in adults), all formulations of methotrexate (in children and young people).

See NICE’s information on prescribing medicines.

1.3.4 Offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission. [2012]

1.3.5 Consider azathioprine or mercaptopurine to maintain remission in people who have not previously received these drugs (particularly people with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations). [2012]

1.3.6 Consider methotrexate (follow BNF/BNFC cautions) 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 thiopurine methyltransferase [TPMT] activity or previous episodes of pancreatitis). [2012]
1.3.7 Do not offer a conventional glucocorticosteroid or budesonide to maintain remission. [2012]

See recommendations 1.2.10 and 1.2.11 for guidance on monitoring the effects of azathioprine, mercaptopurine and methotrexate.

See recommendation 1.2.16 for when to continue infliximab or adalimumab during remission.

1.4 Maintaining remission in Crohn's disease after surgery

In May 2019, the use of some medicines was off label:

- 1.4.1 and 1.4.3: some preparations of azathioprine, and of the combination of azathioprine and metronidazole
- 1.4.2: some preparations of azathioprine.

See NICE's information on prescribing medicines.

1.4.1 To maintain remission in people with ileocolonic Crohn's disease who have had complete macroscopic resection within the last 3 months, consider azathioprine in combination with up to 3 months' postoperative metronidazole. [2019]

1.4.2 Consider azathioprine alone for people who cannot tolerate metronidazole. [2019]

1.4.3 Monitor the effects of azathioprine and metronidazole as advised in the BNF or BNFC. Monitor for neutropenia in people taking azathioprine even if they have normal thiopurine methyltransferase (TPMT) activity (see also recommendation 1.2.11 for ensuring that there are documented local safety monitoring policies and procedures in place). [2019]

1.4.4 Do not offer biologics to maintain remission after complete macroscopic resection of ileocolonic Crohn's disease. [2019]
1.4.5 For people who have had surgery and started taking biologics before this guideline was published (May 2019), continue with their current treatment until both they and their NHS healthcare professional agree it is appropriate to change. [2019]

1.4.6 Do not offer budesonide to maintain remission in people with ileocolonic Crohn's disease who have had complete macroscopic resection. [2019]

To find out why the committee made the 2019 recommendations and how they might affect practice, see the rationale and impact section on maintaining remission in Crohn's disease after surgery.

Full details of the evidence and the committee's discussion are in the evidence review: Crohn's disease management – post surgical maintenance of remission.

1.5 Surgery

Crohn's disease limited to the distal ileum

1.5.1 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 (appendix N of the full guideline contains observational data on recurrence rates after surgery)
- individual preferences and any personal or cultural considerations.

Record the person's views in their notes. [2012]

1.5.2 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 with the child or young person and their family members or carers (as appropriate), and within the multidisciplinary team. [2012]

Managing strictures

1.5.3 Consider balloon dilation, particularly for people with a single stricture that is short, straight and accessible by colonoscopy. [2012]

1.5.4 Discuss the benefits and risks of balloon dilation and surgical interventions for managing strictures with:

• the person with Crohn's disease and their family members or carers (as appropriate) and
• a surgeon and
• a gastroenterologist.

Appendix O of the full guideline contains observational data on efficacy, safety, quality of life and time to recurrence for balloon dilation and surgery for stricture. [2012]

1.5.5 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. [2012]

1.5.6 Ensure that abdominal surgery is available for managing complications or failure of balloon dilation. [2012]

1.6 Monitoring for osteopenia and assessing fracture risk

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

1.6.1 Do not routinely monitor for changes in bone mineral density in children and young people. [2012]

1.6.2 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. [2012]

1.7 Conception and pregnancy

1.7.1 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. [2012]

1.7.2 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. [2012]
Terms used in this guideline

Complete macroscopic resection

The surgical removal of the section of bowel with visible (rather than microscopic) disease.
Recommendations for research

The 2019 guideline committee has made the following recommendation for research.

Recommendations for research from the 2019 guideline

1 Enteral nutrition after surgery

What are the benefits, risk and cost effectiveness of enteral nutrition in maintaining remission in the post-surgical period of Crohn's disease?

For a short explanation of why the committee made the recommendation for research, see the rationale on maintaining remission in Crohn's disease after surgery.

Full details of the evidence and the committee's discussion are in the evidence review: Crohn's disease management – post surgical maintenance of remission.

Other recommendations for research from the 2012 guideline

2 Azathioprine

Does the addition of azathioprine to systemic glucocorticosteroid treatment at diagnosis improve the long-term outcome compared with glucocorticosteroid treatment alone for patients with intestinal Crohn's disease?

3 Mesalazine

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

What is the effect on quality of life of medical treatment compared with early surgery for Crohn's disease limited to the distal ileum?

5 Enteral nutrition compared to glucocorticosteroid treatment

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

6 Information needs

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?
Rationale and impact

This section briefly explains why the committee made the recommendations and how they might affect practice. It links to details of the evidence and a full description of the committee's discussion.

Maintaining remission in Crohn's disease after surgery

Recommendations 1.4.1 to 1.4.6

Why the committee made the recommendations

The recommendations apply to people with ileocolonic Crohn's disease who have had complete macroscopic resection and who have no residual active disease. This is the population covered in the studies the committee reviewed. The committee was aware that a proportion of people could still have residual active disease after surgery. It agreed that in these people, their disease is not in remission and the recommendations in the section on inducing remission in Crohn's disease would apply.

The evidence showed that azathioprine in combination with up to 3 months' metronidazole was effective in maintaining endoscopic remission. While there was some evidence of clinical benefit with azathioprine on its own, the effect was less certain. However, the committee included it as an option because some people have trouble tolerating metronidazole. The committee did not recommend metronidazole alone because, based on the evidence and their clinical experience, the potential benefits did not outweigh the potential harms (or adverse effects). Azathioprine can also be difficult to tolerate, and can cause adverse effects, so the committee looked at mercaptopurine as an alternative. However, mercaptopurine is not cost effective for maintaining remission because it has a high cost relative to the limited benefits it provides. The committee also reviewed the evidence for aminosalicylates (such as mesalazine). The evidence on relapse rates (assessed endoscopically) showed that aminosalicylates were not clinically or cost effective. Because of this, the 2012 recommendation on aminosalicylates was removed.

The committee made a recommendation on monitoring because of the tolerability issues...
and potential adverse effects of azathioprine and metronidazole. This is based on the 2012 recommendation on monitoring azathioprine when using it to induce remission.

There was limited evidence available for biologics, and a lot of uncertainty around how much benefit they provide. Biologics are also expensive, and all these factors together mean that they are not currently cost effective when compared with the other options for maintaining remission. To avoid unnecessarily changing treatments for people who started taking biologics before this guideline was published, the committee made a recommendation to cover this group.

The committee made a recommendation against offering budesonide because evidence shows that it is not beneficial in maintaining remission after surgery.

None of the included studies looked specifically at maintaining remission for children and young people after surgery, so the committee did not make separate recommendations for this population. In their experience children and young people are offered the same post-surgery treatment as adults.

There was no randomised controlled trial evidence on enteral nutrition. The committee made a recommendation for research on enteral nutrition after surgery because it is sometimes used alone or with other maintenance therapy for maintaining remission after surgery.

How the recommendations might affect practice

The committee noted that the recommendations made are in line with current practice. There is variation across the UK in whether people receive 3 months of metronidazole after surgery.

The committee believe that the recommendation to not start biologics after surgery could potentially result in cost savings and maintain consistency in clinical practice.
Context

Crohn's disease is a chronic inflammatory disease that mainly affects the gastrointestinal tract. The disease may be progressive in some people, and a proportion may develop extra-intestinal manifestations. Crohn's & Colitis UK estimate there are at least 115,000 people in the UK with Crohn's disease. The causes of Crohn's disease are widely debated. Smoking and genetic predisposition are 2 important factors that are likely to play a role.

Typically people with Crohn's disease have recurrent relapses, with acute exacerbations interspersed with periods of remission or less active disease. 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. Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission).

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

The aims of drug treatment are to reduce symptoms, promote mucosal healing, and maintain or improve quality of life, while minimising toxicity related to drugs over both the short- and long-term. Glucocorticosteroid treatment, aminosalicylate treatment, antibiotics, immunosuppressants and tumour necrosis factor (TNF)-alpha inhibitors are currently considered to be options for treating Crohn's disease. Enteral nutrition has also been used widely as first-line therapy in children and young people to facilitate growth and development, but its use in adults is less common. Between 50 and 80% of people with Crohn's disease will eventually need surgery for strictures causing symptoms of obstruction, other complications such as fistula formation, perforation or failure of medical therapy.

The 2015 routine surveillance review of the guideline highlighted evidence on the combined use of TNF-alpha inhibitor and immunosuppressant medications for inducing remission in people with severe active Crohn's disease. The recommendations were updated in May 2016, to provide guidance on the combined use of TNF-alpha inhibitor biologics (infliximab or adalimumab) together with an immunosuppressant medication, compared with biologic medication given alone. An update in May 2019 made new recommendations on maintaining remission after surgery.
Finding more information and resources

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on inflammatory bowel disease.

For full details of the evidence and the guideline committee's discussions, see the evidence review and full guideline. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.
Update information

May 2019: This guideline is an update of NICE guideline CG152 (published October 2012, last updated May 2016) and replaces it.

We have reviewed the evidence on maintaining remission in Crohn's disease after surgery. These recommendations are marked [2019].

We have also rewritten recommendation 1.2.3 to make it easier to follow. However, no change in meaning is intended.

Recommendations marked [2010] or [2012] last had an evidence review in 2010 or 2012. In some cases minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

May 2016: A new recommendation has been added on inducing remission in people with Crohn's disease. This is marked as [2016].

Minor changes since publication

July 2019: The recommendations for research from the 2012 guideline were added.

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