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# British Society of Gastroenterology guidelines on inflammatory bowel disease in adults: 2025

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## ABSTRACT

In response to recent advancements in inflammatory bowel disease (IBD) management, the British Society of Gastroenterology (BSG) Clinical Services and Standards Committee (CSSC) has commissioned the BSG IBD section to update its guidelines, last revised in 2019. These updated guidelines aim to complement the IBD standards and promote the use of the national primary care diagnostic pathway for lower gastrointestinal symptoms to enhance diagnostic accuracy and timeliness. Formulated through a systematic and transparent process, this document reflects a consensus of best practices based on current evidence. The guideline, while developed primarily for the UK, is structured to support IBD management internationally. It is endorsed by the BSG executive board and CSSC without external commercial funding, with involvement primarily supported through professional roles in public institutions and the National Health Service (NHS). Methodological revisions since the prior guidelines have enhanced rigor in technical review and development, with methodology details published independently following peer review. In developing the recommendations, 89 clinical experts and stakeholders participated in an online survey, identifying primary outcomes, such as clinical and endoscopic remission, as well as adverse event metrics, all stratified by clinically relevant effect sizes. These guidelines are intended to support clinical decision-making but are not prescriptive, recognizing that individual clinical scenarios may warrant tailored approaches. Further research may inform future revisions as new evidence emerges.

## EXECUTIVE SUMMARY

### CROSS IBD

#### General principles

- The Montreal phenotypic classification system should be used in adults.
- Ileocolonoscopy is necessary for reliable diagnosis and assessment of inflammatory bowel disease, particularly at initial presentation. The endoscopist should take at least two biopsy samples, each from the terminal ileum, at least four different colonic segments and the rectum, and identify the sites of origin clearly. Biopsies for the diagnosis of suspected new inflammatory bowel disease (IBD) should be accompanied by full clinical details.
- All patients with IBD to be started on immunomodulators or advanced therapies should receive written information. Prior to starting advanced therapies, safety checks are required, including screening for risk of serious and opportunistic infections, and provision of vaccinations where required. An interferon-γ release assay (IGRA) and a chest X-ray examination are the minimum tests for low-risk patients.
- Vaccination history should be obtained, and vaccinations updated for all patients. Live vaccinations may be given at least 4 weeks before starting, and at least 3 months after stopping, immunomodulators or advanced therapies. Live vaccinations should not be given to people with IBD receiving immunosuppressive therapy.
- Patients with IBD receiving immunomodulators or advanced therapies should receive influenza vaccination each autumn, pneumococcal vaccination with a booster after 5 years and 6 monthly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination or in accordance with the most recent best practice. All female patients with IBD should be encouraged to take part in national cervical screening and HPV vaccination programme. Live vaccines are contraindicated if a patient is on immunosuppression or has significant protein calorie malnutrition.
- Recombinant zoster vaccination (Shingrix) is recommended for all patients receiving

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immunomodulators or advanced therapies who are aged ≥50 years, and in patients ≥18 years starting Janus kinase (JAK) inhibitors.

### Drug monitoring

- In people receiving purine analogues, therapeutic drug monitoring (TDM) of purine analogue metabolites is recommended to optimise their dosing, alongside routine blood monitoring.
- Consider initiation of a concomitant immunomodulator, with or before initiation of anti tumour necrosis factor (anti-TNF) therapy, to reduce the risk of antidrug antibody development.
- There remains uncertainty about the benefit of TDM for anti-TNF therapies. When people receiving anti-TNF therapy experience loss of response, TDM can be beneficial to guide optimisation strategies, such as concomitant immunomodulator introduction and anti-TNF dose adjustment.
- There is currently no role for TDM in people receiving non-anti-TNF advanced therapies.

### Surgery in IBD

- All patients with IBD admitted to hospital for any reason should receive pharmacological venous thromboembolism (VTE) prophylaxis unless contraindicated.
- Patients undergoing IBD surgery need support of the wider multidisciplinary team (MDT), including IBD physicians, surgeons, radiologists, clinical nurse specialists, dietitians, psychologists, and peer support.
- Prior to elective IBD surgery, corticosteroids should ideally be stopped, or the dose reduced, to reduce risk of postoperative complications.
- Postoperatively, the IBD medical team should actively review the plan for ongoing medical therapy with the patient. Ideally, this should be undertaken prior to discharge. Patients with IBD who have been receiving oral corticosteroids for more than 4 weeks prior to surgery should receive an equivalent intravenous dose of hydrocortisone, and nil by mouth in the perioperative period.
- Immunomodulators and advanced therapies can be continued in the perioperative period in patients requiring surgery for IBD.
- Malnutrition screening, nutritional assessment and correction of nutritional status should be part of preoperative optimisation of all patients who require abdominal surgery for IBD. Nutritional support (oral nutritional supplements or enteral or parenteral nutrition) should be provided as required.

### Superinfection in IBD relapse

- Patients with new or worsening symptoms of IBD should have stool cultures for enteroinvasive bacterial infections and stool *Clostridioides difficile* assay. Careful review of travel and contact history should be taken, with appropriate testing for amoebic or *Shigella* dysentery in patients with relevant travel history.
- Patients with IBD flare requiring hospitalisation, and outpatients with moderate to severe refractory IBD not responding to immunosuppressive therapies, should have colonic tissue sent for cytomegalovirus (CMV) immunohistochemistry or PCR.

### Anaemia in IBD

- Iron deficiency anaemia is very common in patients with active IBD.
- As systemic inflammation inhibits absorption of iron, iron tablets should not be used in those with active disease.
- In patients with inactive disease, no more than 100 mg elemental iron should be taken daily.
- Ferritin levels up to 100 µg/L in the presence of inflammation may still reflect iron deficiency. Measurement of iron indices, such as transferrin saturation, is therefore recommended.
- Other causes of anaemia, such as vitamin B12 and folate deficiency, marrow suppression due to anaemia of chronic disease, and overt blood loss, should be considered and managed accordingly.
- Treatment of iron deficiency anaemia should be with one tablet per day of iron. If not tolerated, a reduced dose of one tablet every other day, alternative oral preparations or parenteral iron should be considered.

## Pregnancy in IBD

### Pre-conception

- Patient education includes the importance of keeping well and the potential adverse foetal outcomes of uncontrolled IBD.
- Patient concerns should be explored, including risk of IBD inheritance.
- General health measures include daily vitamin D, daily folic acid (400 $\mu$g/day for everyone and 5 mg/day for those taking sulfasalazine, those with significant small bowel resections or active small bowel disease), nutritional optimisation, engagement with cervical screening, smoking cessation and up to date vaccinations.
- Current IBD activity should be assessed and medical therapy optimised, to enhance efficacy and safety.
- If possible, a 3-month period of remission before conception is advisable.
- Methotrexate, JAK inhibitors and sphyngosine-1-P modulators should be stopped for at least 3 months before conception, to reduce the risk of teratogenicity.
- Individualised IBD management plans for disease monitoring and management during pregnancy are recommended.

### During pregnancy

- Approach to IBD maintenance, IBD relapses and indications for surgery in pregnant women are the same for non-pregnant patients. An MDT approach is recommended.
- Therapies with the best evidence base for safety in pregnancy should be prioritised.
- Cross-sectional imaging should be performed as required, with emphasis on minimising radiation exposure and preference for ultrasound and MRI. Avoid the use of gadolinium as part of MR enterography during pregnancy.
- Outpatients with active IBD should receive VTE prophylaxis during the third trimester, unless contraindicated.
- All IBD patients should be assessed at least once in a consultant-led obstetric clinic. Joint IBD antenatal clinics may offer optimal care.
- Given the increased burden of mental health disease in people with IBD, mental health screening should be performed with onward referral to appropriate services before, during and after pregnancy.



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### Delivery and post partum

- Mode of delivery should be determined by obstetric considerations and patient preference, except in people with active peri-anal disease, ileoanal pouch or ileorectal anastomosis, where caesarean section is often preferred.
- VTE prophylaxis is important after caesarean section.
- Medicines that are low risk in pregnancy are also low risk in breast feeding and should be continued.
- Breast feeding is the preferred method of feeding and does not affect the course of IBD.
- For patients with IBD receiving appropriate advanced therapy, we suggest that the drug is continued throughout pregnancy to minimise the risk of relapse and the adverse outcomes associated with active disease.
- Tofacitinib, filgotinib, upadacitinib, ozanimod and etrasimod are contraindicated during conception, pregnancy and lactation due to serious malformations found in animal studies.
- Overall data from several studies have suggested that continuation of vedolizumab or ustekinumab is not associated with adverse maternal or foetal outcomes.
- Where advanced therapy continues during pregnancy, live vaccinations (including BCG) should be postponed for the infant for the first 12 months.
- Non-live vaccinations should be given according to standard vaccination schedule. Breast feeding while on biological therapy is not likely to confer an additional risk and vaccination decisions should be based on in utero exposure only.

### Patient education

- Patient education interventions may be offered to patients with IBD as an adjuvant to routine clinical practice, with the aim of improving patient engagement, medication adherence and reducing hospital attendances.
- All patients with IBD should be advised to stop smoking, and national guidance on smoking cessation should be followed.
- The use of digital health technology should be offered to patients with IBD as an adjunct to face to face interactions, particularly aimed at improving patient engagement and medication adherence. Care must be taken not to disadvantage those affected by digital poverty, and alternative inclusive parallel strategies must be developed.

## Ulcerative colitis

### General principles

- A multimodal approach to monitoring of remission in patients with ulcerative colitis is advised, including clinical, biochemical, imaging and endoscopic modalities, supported by histology.
- Histological remission could be used as an adjunct to endoscopic remission to indicate a deeper level of healing but is not a mandatory treatment target for ulcerative colitis.
- Patients with ulcerative colitis who have achieved prolonged remission and mucosal healing with immunomodulators and/or advanced therapies can discontinue their 5-aminosalicylic acid (5-ASA).
- In patients with ulcerative colitis, withdrawal of purine analogues, or anti-TNF therapy, when used as monotherapy or combination therapy, is associated with a significant risk of relapse. Shared decision-making should be undertaken before withdrawal.

### Proctitis

- Mild or moderately active ulcerative proctitis should be treated with 5-ASA suppositories/enemas.
- Oral 5-ASA or rectal corticosteroid can be considered as second line in patients with ulcerative proctitis. Refractory ulcerative proctitis may require treatment with oral corticosteroids, topical tacrolimus and/or advanced therapies.

### Acute severe ulcerative colitis

- Adult patients with acute severe ulcerative colitis (ASUC) defined by Truelove and Witts' criteria should be admitted to hospital for assessment and intensive management.
- Hospitalised patients with ASUC should have urgent assessment of blood tests (full blood count (FBC), C-reactive protein (CRP), urea and electrolytes (U&E) and liver function tests (LFTs) including albumin), stool culture, *Clostridioides* screen, non-invasive imaging and flexible sigmoidoscopy.
- Hospitalised patients with ASUC should be treated with high-dose intravenous corticosteroids, such as methylprednisolone 30 mg every 12 hours or hydrocortisone 100 mg 6-hourly.
- Patients responding to IV corticosteroids should be treated with a purine analogue or suitable maintenance advanced medical therapy.
- Patients with ASUC not responding to at least 3 days of IV corticosteroids, as judged by a suitable scoring system, should be treated with rescue therapy in the form of intravenous infliximab or ciclosporin. Ciclosporin can be bridged to purine analogues (if naive) or a suitable advanced therapy according to local practice.
- In ASUC, delay in surgery is associated with an increased risk of surgical complications. Early referral and communication with specialist colorectal surgical and stoma care teams is advised.
- Patients with ASUC who have not responded within 7 days of rescue therapy with infliximab or ciclosporin, or those with complications (including toxic megacolon, severe haemorrhage or perforation), require subtotal colectomy and ileostomy.
- For patients who do not respond to initial IV corticosteroids, an intensified dosing regimen of infliximab should be considered in a select group of patients, especially if serum albumin levels are low.
- Oral JAK inhibitors may be considered in selected patients with ASUC who are corticosteroid-refractory and, after careful consideration and counselling of benefits and risks, via an MDT approach.
- Patients with ulcerative colitis should not undergo pouch surgery while taking corticosteroids.
- A subtotal colectomy and ileostomy with preservation of the rectum should be offered to patients who have not responded to medical therapy, at least by day 7 of treatment for acute severe ulcerative colitis.
- Surgical resection of the colon and rectum should be offered to patients who have chronic, active ulcerative colitis despite optimised medical therapy.
- Ileoanal anal pouch formation or end ileostomy provide equivalent levels of quality of life, and selection should be guided by patient preferences and choice (Table 1).

### Pouchitis

- Patients with ongoing symptoms after pouch surgery should have a pelvic MRI scan, stool culture and *Clostridioides*



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*difficile* assay. Pouchoscopy should be performed to assess the pouchitis, the pre-pouch ileum and the mucosa at the anal transition zone.

- A 2-week course of ciprofloxacin or metronidazole is the first-line treatment of acute pouchitis. Chronic pouchitis may be treated with a combination of antibiotics (ciprofloxacin, metronidazole, tinidazole, rifaximin), oral budesonide or oral beclometasone.
- In the absence of other causes, patients with chronic refractory pouchitis not responding to antibiotics or locally acting corticosteroids may be offered advanced therapy. Vedolizumab is suggested as first-line therapy.

## CROHN'S DISEASE

### General principles

- A multimodal approach to monitoring of remission in patients with Crohn's disease is advised, including clinical, biochemical, imaging and endoscopic modalities with histology. The specific combination of modalities and frequency of monitoring appointments depends on disease phenotype, therapy and duration of remission.
- Faecal calprotectin should be used to monitor disease in patients with Crohn's disease in a known location, where there is a baseline faecal calprotectin.

**Table 1** Individual therapies for ulcerative colitis

| Ulcerative colitis | | | |
|---|---|---|---|
| **GRADE recommendation** | **Strength of recommendation** | **Certainty of evidence** | **Magnitude of effect** |
| Prednisolone is recommended for induction of remission in moderate to severe ulcerative colitis. | Strong | Very low | *Not available* |
| Beclomethasone dipropionate is suggested for induction of remission in patients with ulcerative colitis where 5-ASA therapy fails or is not tolerated, and who wish to avoid systemic corticosteroids. | Conditional | Moderate | Small |
| Budesonide MMX is suggested for the induction of remission in mild to moderate ulcerative colitis for patients in whom 5-ASA induction therapy fails or is not tolerated, and who wish to avoid systemic corticosteroids. | Conditional | Moderate | Trivial |
| 5-ASAs are recommended for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Strong | High | Moderate |
| Methotrexate is not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Trivial |
| Purine analogues (azathioprine/mercaptopurine) are not suggested for induction of remission, but are suggested for maintenance or remission for patients with moderate to severe ulcerative colitis, once remission is achieved. | Conditional | Low | Trivial in ulcerative colitis, Moderate for maintenance |
| Infliximab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis | Conditional | Moderate | Small |
| Adalimumab is not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis | Conditional | Low | Trivial |
| Golimumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Small |
| Etrasimod is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Moderate | Small |
| Ozanimod is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Moderate | Moderate |
| Filgotinib 200 mg is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Moderate |
| Upadacitinib is recommended for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | High | Large |
| Tofacitinib is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Moderate | Large |
| Mirikizumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Small |
| Risankizumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Moderate | Moderate |
| Ustekinumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Small |
| Vedolizumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Moderate | Small |
| Antibiotics are not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Trivial |
| FMT is not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. | Conditional | Low | Trivial |
| Probiotics are not suggested for induction or maintenance of remission in patients with ulcerative colitis. | Conditional | Low | Small |

5-ASA, 5-aminosalicylic acid ; FMT, faecal microbial transplantation.



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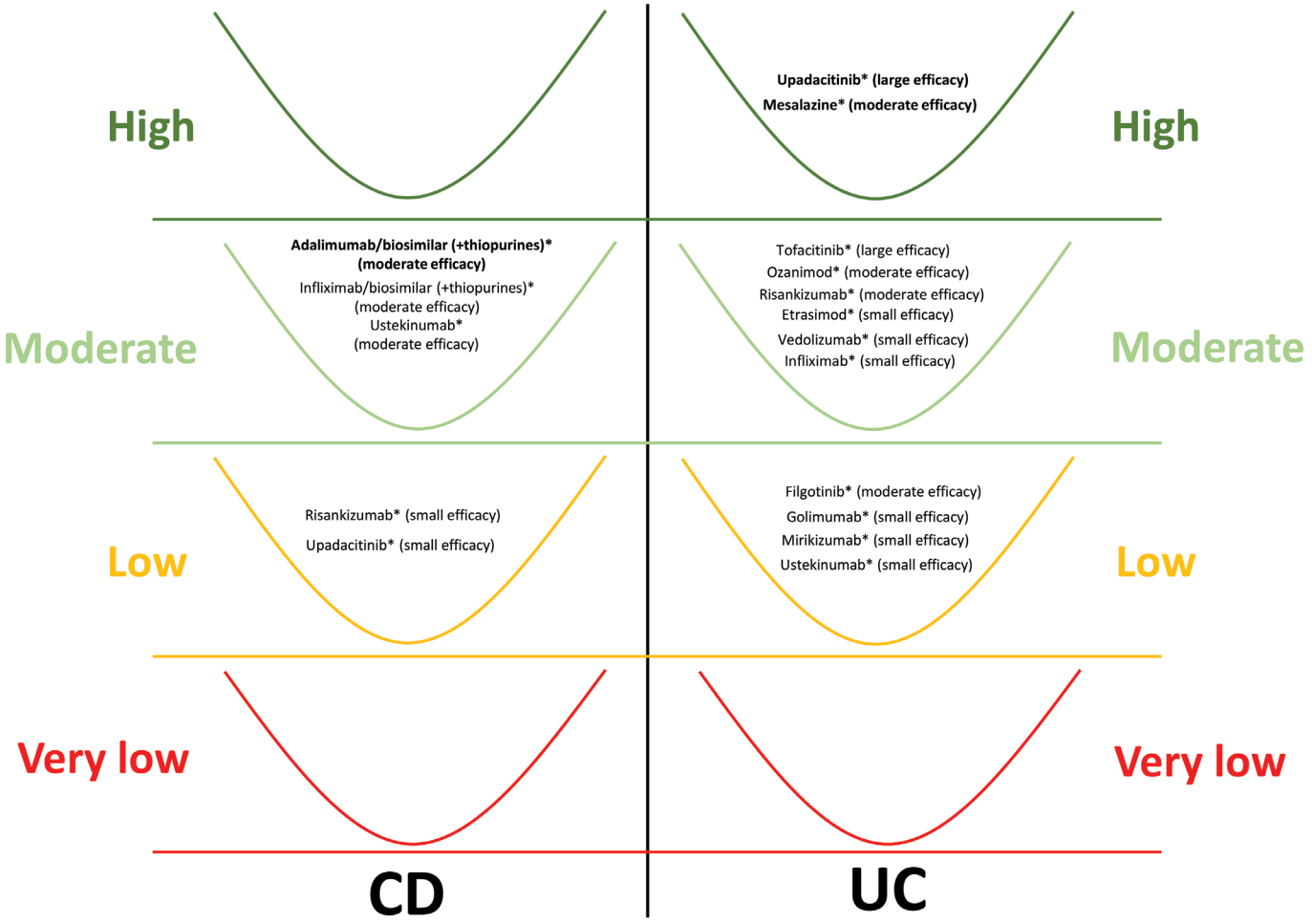



**Figure 1** Medical therapies for the induction and maintenance of remission in ulcerative colitis (UC) and Crohn's disease (CD).

- We suggest performing small bowel capsule endoscopy when small bowel Crohn's disease is suspected despite normal or inconclusive investigations. A patency capsule should be considered.
- Cross-sectional imaging, specifically MRI and CT, and intestinal ultrasound (IUS) may be used to evaluate both luminal and extraluminal disease. Emphasis should be placed on MR enterography (MRE) and IUS, depending on local availability and expertise, as they do not expose patients to ionising radiation. For diagnosis and determining disease extent, MRI is preferred as first line. The use of cross-sectional abdominal imaging and IUS should be prioritised in the diagnosis and assessment of strictures, as well as the use of ileocolonoscopy in colonic and anastomotic strictures when clinically safe to perform, with biopsies to exclude dysplasia and aid distinction of fibrotic from inflammatory strictures.
- An oesophagogastroduodenoscopy may be warranted in patients experiencing upper gastrointestinal symptoms, but it is otherwise not routinely needed for assessment of Crohn's disease.
- In patients with Crohn's disease, withdrawal of purine analogues, or anti-TNF therapy, when used as monotherapy or combination therapy, is associated with a significant risk of relapse. Shared decision-making should be undertaken before withdrawal.
- There is currently insufficient evidence to recommend routine use of exclusive enteral nutrition (EEN) in Crohn's disease. Preoperative EEN can be considered in undernourished patients with fibrotic or penetrating Crohn's disease (Table 2).

### Perianal Crohn's disease

- Modalities for assessment of perianal Crohn's disease include clinical assessment, pelvic MRI scan and examination under anaesthesia, by a colorectal surgeon experienced in evaluation of fistulising perianal Crohn's disease. Depending on local availability and expertise, endoanal ultrasound may have a role.
- Endoscopic assessment of the rectal mucosa should be undertaken.
- Patients with perianal Crohn's disease should be managed via the IBD MDT.
- Setons should be placed to prevent sepsis in fistulising perianal Crohn's disease. The optimal timing of seton removal is uncertain, factoring patient preferences, and complexity of the fistulae.
- Surgical repair, such as advancement flap, and ligation of intersphincteric fistula tract (LIFT), may be considered for selected patients in a multidisciplinary setting.
- Patients with severe perianal Crohn's disease refractory to medical therapy and affecting quality of life should be offered faecal stream diversion surgery. Patients should



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be counselled and informed that the rates of subsequent successful reversal are low, and proctectomy may ultimately be required.
- Medical therapies should be started promptly after adequate surgical drainage of perianal abscesses.
- Infliximab is recommended as first-line advanced therapy for perianal Crohn's disease.
- Patients with inadequate response to infliximab may be offered other advanced therapies.

### Surgical considerations for luminal Crohn's disease

- A laparoscopic resection should be considered in localised ileocaecal Crohn's disease in patients not responding to, or relapsing after, initial medical therapy, or in those preferring surgery rather than initiation or continuation of drug therapy.
- Following ileocaecal resection, early maintenance medical therapy should be considered in people with high-risk features, or those with a personal preference for early maintenance therapy, as part of shared decision-making.
- Assessment of Crohn's disease activity to guide medical therapy should be performed 6 months after surgery, preferably with ileocolonoscopy.
- Patients with stricturing small bowel Crohn's disease should have joint medical and surgical assessment to optimise medical therapy and plan requirement for surgical resection or strictureplasty.

**Table 2** Individual therapies Crohn's disease

| Crohn's disease | | | |
|---|---|---|---|
| **GRADE recommendation** | **Strength of recommendation** | **Certainty of evidence** | **Magnitude of effect** |
| Conventional corticosteroids are suggested for induction of remission in patients with moderate to severe Crohn's disease, for not more than 8 weeks. (moderate certainty, moderate effect size). | Conditional | Moderate | Small |
| Budesonide is suggested for the induction of remission in patients with mild ileocaecal Crohn's disease, with treatment for not more than 8 weeks. | Conditional | Moderate | Small |
| Corticosteroids are not recommended for maintenance of remission in patients with Crohn's disease. | Conditional | Moderate | Small |
| 5-ASA use is not suggested for induction and maintenance of remission for patients with Crohn's disease. | Conditional | Low | Trivial |
| Methotrexate is not suggested for use as monotherapy treatment for induction and maintenance of remission for patients with moderate to severe Crohn's disease. | Conditional | Very low | *Uncertain* |
| Purine analogues (azathioprine and 6-MP) are not suggested for use as monotherapy in induction and maintenance of remission for patients with moderate to severe Crohn's disease. | Conditional | Low | Small |
| Advanced therapies should be suggested for induction and maintenance of remission in moderate to severe Crohn's disease. | Conditional | Low | Moderate |
| Adalimumab (including biosimilar) is recommended for induction and maintenance of remission for patients with moderate to severe Crohn's disease. | Conditional | Moderate | Moderate |
| When adalimumab (including biosimilar) is used for induction and maintenance of remission for Crohn's disease, it is recommended this is done in combination with purine analogues. | Conditional | Moderate | Moderate |
| Infliximab (including biosimilar) is suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease. | Conditional | Moderate | Moderate |
| When infliximab is used for induction and maintenance of remission for Crohn's disease, it is recommended this is done in combination with purine analogues. | Conditional | Moderate | Moderate |
| Routine withdrawal of Infliximab therapy is not suggested after 1 year of stable remission in Crohn's disease. | Conditional | Moderate | Moderate |
| Risankizumab is suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease. | Conditional | Low | Small |
| Ustekinumab (including biosimilar) is suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease. | Conditional | Moderate | Moderate |
| Upadacitinib is suggested for induction and maintenance therapy in patients with moderate to severe Crohn's disease. | Conditional | Low | Small |
| Vedolizumab is not suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease. | Conditional | Low | Moderate |
| Antibiotics are not suggested for induction and maintenance or remission in patients with moderate to severe Crohn's disease. | Conditional | High | Trivial |
| Probiotics are not suggested for induction and maintenance of remission in patients with Crohn's disease. | Conditional | Very Low | *Uncertain* |
| Anti-TNF therapy (infliximab or adalimumab) or vedolizumab are suggested after ileocolonic resection for patients with Crohn's disease if there are significant risk factors for disease recurrence, or patient preference for early treatment through shared decision-making, or endoscopic evidence of recurrent disease 6 months after surgery. | Conditional | Low | Large |
| 5-ASA and Purine analogues are not suggested for post-surgical maintenance of remission of Crohn's disease. | Conditional | Low | Trivial |
| It is suggested that no other treatments are currently used for maintenance of post-surgical remission in Crohn's disease. | Conditional | Low | Trivial |

5-ASA, 5-aminosalicylic acid ; 6-MP, 6-mercaptopurine; TNF, tumour necrosis factor.



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- A strictureplasty is an alternative to resection in patients with small bowel Crohn's disease strictures shorter than 10 cm, and is useful where there are multiple strictures or a need to preserve gut length. Longer strictures can be treated using non-standard strictureplasty techniques.
- Endoscopic balloon dilatation is an appropriate treatment for ileocolonic anastomotic strictures less than 4 cm in length, without sharp angulation, and with non-penetrating disease. Repeated dilatation is often required. Endoscopically accessible ileal strictures are also amenable to balloon dilatation, but complication rates and recurrence rates are higher. There is no role for intralesional corticosteroid injection at the time of stricture dilatation. Long-term data on the impact of dilatation on surgical resections are lacking.
- Intra-abdominal abscesses should be treated by antibiotics and, if possible, radiologically guided percutaneous drainage should be performed.
- Following treatment of an abdominal abscess in the setting of non-perianal fistulising Crohn's disease, joint medical and surgical discussion is required, but interval surgical resection is not always necessary.

## INTRODUCTION

In the past 5 years, there have been several advancements in the management of inflammatory bowel disease (IBD). To this effect, the British Society of Gastroenterology (BSG) Clinical Services and Standards Committee (CSSC) have commissioned the BSG IBD section to develop a new guideline for the management of IBD. The aim of this document is to update the most recent guideline published in 2019. This guideline should be used in conjunction with the IBD standards in a complementary fashion.[1] We would also encourage the use of the national primary care diagnostic pathway for lower gastrointestinal symptoms to improve diagnosis in a timely manner (https://www.whatsupwithmygut.org.uk) for IBD.

This guideline contains the official recommendations of the BSG on all aspects of IBD care. This set of procedures has been approved by the CSSC and the BSG executive board. No funding has been received from any outside organisation, commercial or otherwise, for the production of this document, with some support provided for members' time as part of their employment at public higher educational institutions or within their roles as National Health Service (NHS) funded health professionals.

While primarily designed for use within the UK, the guideline will be useful for professionals and patients in many areas worldwide and therefore is presented in a full systematic and transparent fashion. The prospective publishing of this document is part of that process of systematic guideline production.

These BSG guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations, but we suggest that reasons for this are documented in the medical record. BSG guidelines are intended to be an educational device to provide information that may assist in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring or discouraging any particular treatment.

## METHODS

The methods have been changed substantially since the previously published guideline to reflect current best practice in all aspects of technical review and guideline production. The methodology and operating procedures for this guideline were developed and prospectively agreed, then published independently in full after peer review.[2] All the approaches followed are in line with best practice but may represent a substantial shift in approach and presentation for stakeholders using the guideline. While it is outside of the scope of this guideline to review the previously published operating procedures and methods,[2] there are a few key points that will be of use to the user:

- This is an update guideline and so the focus on searches for evidence was for new output in the last 7 years since the last guideline searches were completed and, where appropriate, combining these with existing evidence from the previous guideline.
- Systematic reviews of randomised trials (updated and meeting high methods standards) and randomised controlled trials were included for efficacy outcomes. Observational studies were included for safety outcomes, although these were also appraised using appropriate tools.
- Network meta-analyses were completed for this guideline for key induction and remission areas of study. These findings were not used to supersede individual or meta-analysis findings, but to triangulate them with another source of evidence. The most up to date methods were used for Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis of networks and, as such, these were created exclusively for the guideline as no published equivalent existed.
- GRADE methods were used, and this encompasses two separate but symbiotically linked elements: (1) assessing the certainty of evidence for each outcome in a comparison, (2) defining the strength of recommendations made on the overall evidence base.
- These two elements inform each other but are not directly correlated. There are numerous examples where the certainty of evidence is low, because of other factors (cost, acceptability, strong clinician practical experience, safety), but a strong recommendation can still be made. The opposite is also true, especially in the context of juxtaposed outcomes, such as when a therapy may be effective, but safety concerns prevent a recommendation for its use.
- The magnitude of effects in absolute terms are used throughout the decision-making process. They supported judgements on precision of estimates and therefore their certainty. They were also used to judge the significance of the outcomes seen against pre-agreed thresholds. Such thresholds have been used before in IBD guidelines but often with a single dichotomous level (eg, less than 10% is trivial, more is a significant difference).[3] In this guideline, an ordinal scale of magnitudes was used as this supports more nuanced understanding of precision and comparison of therapies. Further details surrounding this have been published in full.[3] Of particular note from this recent publication[3] is the triangulation of the thresholds of the UK based guidelines development group (GDG) with international colleagues, and this found little difference, suggesting face validity of these judgements.
- GRADE recommendations should be considered in the context of table 3, which clarifies the prespecified and standardised GRADE language. This may be particularly novel



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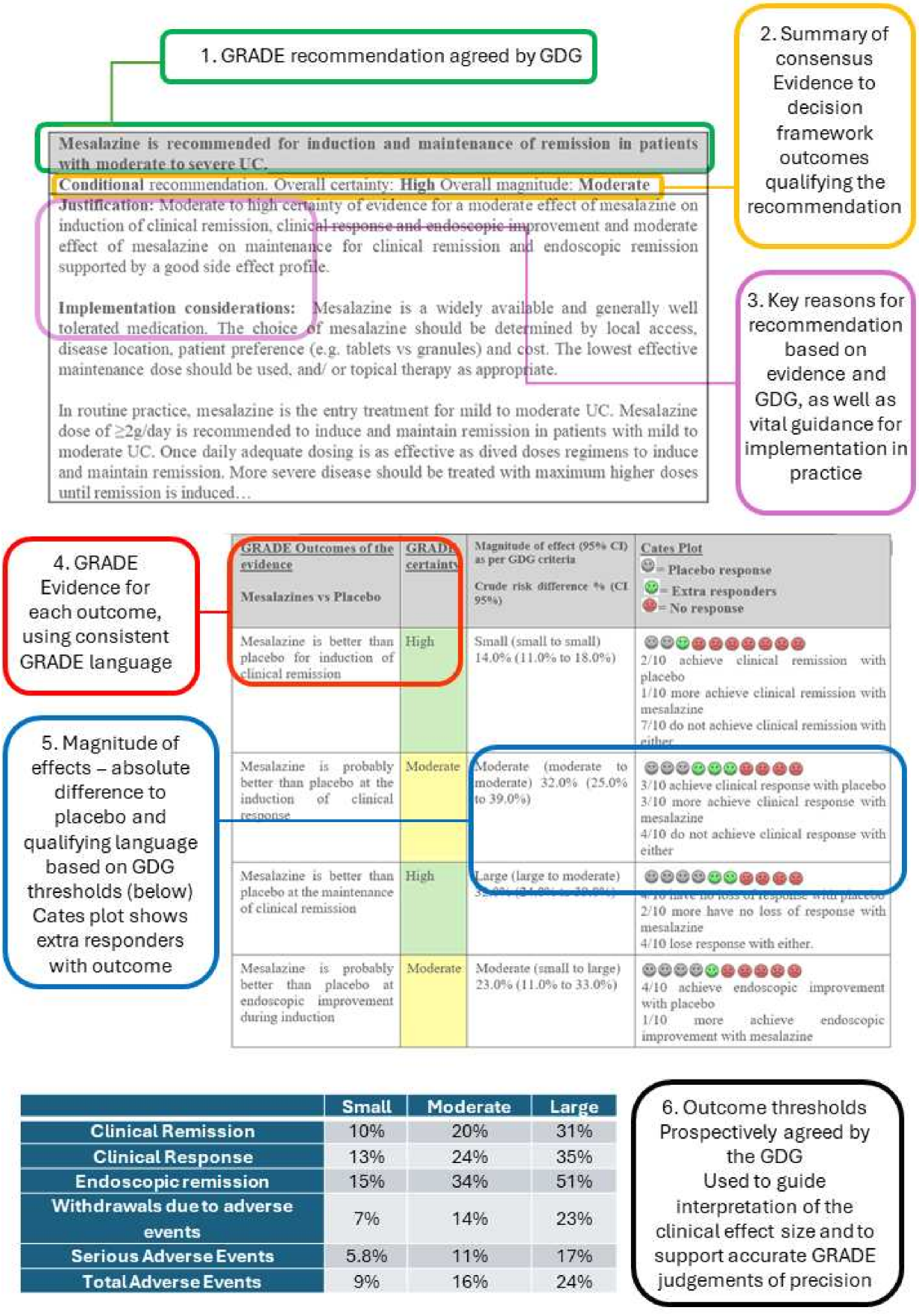



**Figure 2** Annotated model of the GRADE approach.



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to the reader as this has not been applied in such a fashion within previous IBD guidelines. It is therefore important to remember that the language used has not been devised ad hoc and is informed by the key factors—namely, the effectiveness and safety of interventions, the certainty of these findings and the magnitude of effects seen—in an objective manner. There are clearly opportunities where borderline or complex decisions on such recommendations could be challenged, but the use of language is consistent with these decisions.

- It may be initially unusual to see key therapies recommended 'conditionally'. This does not mean they are ineffective or should not be used. In line with the GRADE approach and language guidance discussed, this is a reflection of the likelihood that future research may change the current findings. A change does not mean that an effective treatment is ineffective (or vice versa), instead, it may simply mean that the certainty of evidence may change with further research, owing to increased quality, reduced inconsistency and increased precision. From this perspective, it is clear that many (if not most) therapies have the potential to be conditional as we constantly evolve the evidence base and increase the quality and precision of findings.
- GRADE recommendations are supplemented by Good Practice Statements (GPS). In line with best international practice, such statements are only made when there are strong sources of non-traditional evidence (expert knowledge and eminent experience, patient voices, observational bodies of evidence) or when standard studies would simply not be feasible. GPS must be of a substantial net benefit to the user. As such, the GDG does not suggest that GRADE recommendations are more truthful or important than GPS statements. The novel approach of this guideline is to present both, transparently displaying the rationale for the different approaches, but acknowledging the importance of both groups of guidance to the field.

It is suggested that for more information the detailed supplementary appendices and published methods[2] are consulted, but it is hoped this summary will orientate readers.

## RESULTS

A total of 89 clinical experts/stakeholders participated in this online survey. Clinical remission, clinical response, endoscopic remission, withdrawal due to adverse events and serious adverse events were considered critical (primary) outcomes. Trivial to small, small to moderate and moderate to large thresholds were agreed[3] and are presented in figure 1.

### Presentation of statements

Three categories of statement are presented in this guideline.

GRADE recommendations are presented where evidence was sufficient and the GDG were able to make such recommendations for practice. A standardised approach to presentation has been developed. This adopts clear and consistent GRADE language, includes core data from the evidence to decision frameworks that present the balance of risks and benefits, displays all individual and overall GRADE certainty levels of evidence, and finally, presents magnitude in relative, absolute and visual terms (with the use of Cates plots). The approach is described in full in our published protocol,[2] but a summary citing the grade handbook[4] can be seen in table 3.

Figure 1 presents an annotated model of this approach, as well as a summary of the agreed thresholds used and GRADE explanation. This should guide interpretation and use of the GRADE recommendations for readers. The details of the agreed thresholds for magnitude of effects are included for quick reference.[3] For practical and readability reasons, these have been split in the final manuscript. The main GRADE recommendation and explanation are included in the text. Tables summarising the findings are included in the supplementary material.

Readers will note the inclusion of Cates plots within the supplementary appendices to visually show the impact of therapies. These were reported over 20 years ago,[5] but have been refined, and for this manuscript were produced using an online resource with specific amendments to aid and support interpretation of the Cates plots. A red face indicates that there is no change in risk. So, in the context of a treatment, this will mean no change in clinical state (not necessarily any worsening, but no response). The pale grey/green faces demonstrate therapeutic successes that would occur with a placebo intervention (without active treatment). The bright green faces are additional successes that would occur if treatment was used.

Good practice statements (GPS) are clear and actionable and made when they are necessary to include in IBD practice. The presentation and wider use of the statements must be likely to lead to large net consequences. They are informed by several bodies of linked indirect evidence.

**GPS 1**

We continue to support the use of the Montreal phenotypic classification system in adults, and the Paris phenotypic classification system in children.

**GPS 2**

Where ulcerative colitis is diagnosed by sigmoidoscopy, we recommend a full ileo-colonoscopy to delineate disease extent, severity of inflammation and to exclude Crohn's disease.

The final form of statement is expert opinion. These are presented within the wider narrative of the review and all guidance, information and discussion within the guideline that does not fall into the first two categories should be considered as expert opinion. These are reflective of the consensus view of the GDG (online supplemental appendix 1).

### Decision-making

The approach to decision-making is aligned with the various methods cited and represents a shift from previous and other international guideline approaches. A cyclical process was followed.

Individual authors gathered the evidence, including that within evidence to decision frameworks, where appropriate. Initial draft recommendations or statements were made. GPS were reviewed by the GDG subgroup of relevant stakeholder and content experts, and then the wider group. Formal voting was not performed and instead changes made in an iterative fashion based on feedback.

For GRADE recommendations, the same approach was taken. The final recommendations were discussed at a 2-day face to face summit attended by over 75% of the GDG in November 2023. Two additional statements were discussed and voted on later (14 August 2024); these are appropriately marked in the table.



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**Table 3** GRADE language for recommendations – the advised language for a statement in the guideline

| Statement strength | Language used in statement | Explanation | Exception consideration |
|---|---|---|---|
| Strong | Recommended | A strong recommendation is one for which the guideline panel is *confident* that the desirable effects of an intervention outweigh its undesirable effects or that the undesirable effects of an intervention outweigh its desirable effects | No clinical practice guideline or recommendation can take into account all of the often-compelling unique features of individual patients and clinical circumstances. Thus, strong recommendations may not be applicable for some patients |
| Conditional | Suggested | A conditional recommendation is one for which the desirable effects *probably* outweigh the undesirable effects, or undesirable effects *probably* outweigh the desirable effects, but appreciable *uncertainty exists*. The justification and implementation considerations will give details | Given the element of doubt within such statements, reflecting the primary evidence and magnitude data, considerable latitude exists (whether supporting or refuting use of therapy) and individual patient, resource and other contextual factors must be considered Clinicians, patients, third-party payers, institutional review committees, other stakeholders or the courts should **not interpret these recommendations as mandatory** |
| GRADE certainty of outcome – the rating of the primary evidence as a whole for a given outcome and then for all outcomes combined | | | |
| **Certainty** | **Pivotal language example** | **Explanation** | **Example** |
| HIGH | Is more/or less/better/worse | The available evidence provides a high level of confidence in the estimate of the effect, whatever the magnitude | Tofacitinib **is better** than placebo at the maintenance of clinical remission in ulcerative colitis (high certainty) |
| Moderate | Probably is more/or less/better/worse | The available evidence is sufficient to support a conclusion, but further research may still affect confidence in the result or the result itself | Tofacitinib **is probably better** than placebo for the induction of clinical response in ulcerative colitis (moderate certainty) |
| Low | May be more/or less/better/worse | The available evidence is limited, and the true effect may be substantially different from the estimate so may change in the future | Infliximab **may be more** effective than placebo at week 4 for the induction of clinical remission (NNTB 3, low certainty) |
| Very low | No conclusions can be drawn / very uncertain | The available evidence is insufficient to support any firm conclusions and any result seen should not be employed and the true effect treated as unclear | The evidence **is very uncertain** for induction of clinical remission using methotrexate in Crohn's disease (very low certainty) |

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Members were presented with all the core data and the final statements. After discussion an online anonymous voting tool was used for live voting on agreement or disagreement with the statement. All members with conflict of interest to the given intervention abstained. Any item with agreement below 75% was not passed, and a further discussion held with any amendment and further voting. Details of agreement are included in online supplemental file 2 and online supplemental file 3.

## DIAGNOSIS AND MONITORING

### Investigations to assess ulcerative colitis

#### Diagnosis and classification

Diagnosis of ulcerative colitis relies on a combination of clinical history, non-invasive biomarkers of inflammation and colonoscopy with histology. Clinical history and non-invasive biomarkers such as CRP and faecal calprotectin are useful adjuncts to colonoscopy in diagnosing ulcerative colitis. Patients presenting to primary or secondary care with a suggestive history should be initially assessed with a full panel of blood tests, including a full blood count, CRP, albumin and stool samples, to exclude infection and for faecal calprotectin. Faecal biomarkers, in particular calprotectin and lactoferrin, are released by gut neutrophils and have excellent sensitivity in diagnosing IBD but have poor specificity.[6] However, infections and drugs are other common causes of raised faecal biomarkers, which should be considered.[7] Ultimately, the diagnosis rests on endoscopic evaluation and histological assessment.

In patients presenting with acute severe colitis as their first manifestation of ulcerative colitis, an unprepared flexible sigmoidoscopy during the acute phase, with a subsequent planned colonoscopy for assessment of disease extent, is recommended. Non-invasive imaging, like an abdominal X-ray, CT or ultrasound examination, could be used to define disease extent and complications.

The Montreal classification[8] in adults, and the Paris classification[9] in children, are useful in ascribing phenotypes to patients both for treatment and to assist with service delivery and research.[10] Children developing IBD generally have more extensive disease than adults.[11] Establishing the extent of the inflammation in a patient with ulcerative colitis is important for prognosis as the likelihood of colectomy is dependent on disease extent. A systematic review showed for those with extensive colitis, a 19% 10-year colectomy rate , 8% for left-sided colitis and 5% for proctitis; backwash ileitis is also associated with more aggressive disease, and with primary sclerosing cholangitis.[12]

Those with extensive colitis also have the highest risk of developing colorectal cancer.[13 14] Disease extent can change after diagnosis.[15] Up to half with proctitis or proctosigmoiditis will develop more extensive disease.[16–18] Of patients with proctitis initially, 10% will ultimately have extensive colitis.[19] However, over time the extent of inflammation can also regress, and classification should always remain as the maximal extent.[15]

Endoscopic appearance may significantly underestimate the true extent (particularly in quiescent ulcerative colitis), and this should be confirmed by segmental biopsies. The Mayo Score for ulcerative colitis is widely used in clinical trials and may be applied to clinical practice as a composite clinical and endoscopic tool.[20] The score of 0–12 includes a measure of stool frequency,



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rectal bleeding, a physician's global assessment and a measure of mucosal inflammation at endoscopy. The partial Mayo score uses the non-invasive components of the full score and correlates well with patient perceptions of response to therapy.[21] There is wide variation in interpretation of disease activity endoscopically.[22] The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) has been developed to improve reliability.[23 24] The Modified Mayo Endoscopic Score (MES) is another simple measure of endoscopic activity that correlates well with clinical and biological activity (table 4).[25] Although both have been extensively validated, interobserver variation remains a significant limitation of these visual scores.[26 27]

Symptomatic and endoscopic scores may be limited by their ability to quantify accurately the impact of disease on quality of life, including fatigue and psychosocial function; however, if made more complex the indices may be difficult to apply to clinical practice.[28 29] An increasing emphasis on patient-reported outcome measures (PROMs: standardised questionnaires filled out by patients without clinician involvement) in clinical trials may translate to routine clinical practice.[30]

## Monitoring remission in ulcerative colitis

**GPS 3**

We recommend a multimodal approach to monitoring of remission in patients with ulcerative colitis. Patients should be assessed with a clinical index, such as the partial Mayo or Simple Clinical Colitis Activity Index, in addition to haemoglobin, C-reactive protein, faecal calprotectin or, if available, intestinal ultrasound and ideally colonoscopy or sigmoidoscopy with histology. The combination of modalities and frequency of monitoring appointments depends on therapy, duration of remission and local availability of resources.

Clear monitoring strategies in ulcerative colitis are essential, not only to confirm remission, but also to detect complications of therapy. Monitoring appointments also provide opportunity to confirm adherence to cancer prevention surveillance programmes reference the surveillance guidelines and to evaluate extraintestinal manifestations and vaccination uptake.

Treatment targets in ulcerative colitis have evolved from traditional clinical remission to include endoscopic and laboratory-assessed remission. While there is evidence to support an association between mucosal healing and long-term clinical remission, confirmation of these parameters with colonoscopy is typically expensive and less accepted by patients than alternatives, such as blood or stool-based biomarkers, or intestinal ultrasound.[7] Resource availability may also shape[781] preferred strategy, with the increasing ultrasound availability making this a possible strategy in the UK. Furthermore, monitoring strategies in IBD run alongside colorectal cancer surveillance programmes, such that, all patients with IBD affecting the colon should have a colonoscopy 8 years after symptoms, and those with pancolitis will undergo regular colonoscopy (for specific details of IBD surveillance please see related BSG guidance). While the primary aim is dysplasia detection, it also serves as opportunity to confirm endoscopic remission and disease extent. Colorectal cancer surveillance should be undertaken when the patient is in remission.

The risk of relapse or treatment complication varies considerably between patients, requiring different monitoring strategies depending on disease phenotype, duration of remission, age, frailty and current therapy. Although there is evidence to support multimodal disease assessment in ulcerative colitis, there is a lack of direct comparisons between modalities. Below, we outline clinical scoring systems in ulcerative colitis, then discuss the correlation of faecal calprotectin, CRP, anaemia and intestinal ultrasound with endoscopic and histological scoring systems. Thereafter, we propose a multimodal approach to monitoring of patients in clinical remission.

### *Clinical scoring systems to monitor remission in ulcerative colitis*

Clinical scoring systems in ulcerative colitis are useful for systematically assessing disease activity, although they are still open to a degree of subjectivity. The partial Mayo score and Simple Clinical Colitis Activity Index are commonly used instruments,[31] although there is no validated comparison between these. Within the many PROMs, PRO-2 is widely used in clinical trials, and yet not widely adopted in clinical practice. Clinical indices do not always correlate with active inflammation.[32] However, they serve to guide clinicians in providing a degree of standardisation in the assessment and documentation of symptoms.

### *Faecal calprotectin in monitoring of remission in ulcerative colitis*

Faecal calprotectin correlates well with clinical, endoscopic and histological disease activity in ulcerative colitis,[33] and is thereby of value for monitoring the clinically stable patient. However, determining a specific target to trigger further disease assessment is more challenging, with variability regarding patient treatment targets and change from baseline.

Cortesi *et al* identified that a faecal calprotectin target of <100 μg/g was associated with a lower probability of clinical relapse.[33] Indeed, several studies have associated faecal calprotectin with endoscopic activity, although cut-off values and definitions of endoscopic remission or healing vary. Dulai *et al* established faecal calprotectin of <250 μg/g (compared with >250 μg/g) to be associated with endoscopic and histological remission, and protective against hospital admission or colectomy.[34] Likewise, Walsh *et al* demonstrated a tight correlation between faecal calprotectin and endoscopic activity as measured by UCEIS, with a threshold of 187 μg/g predictive of active disease.[35] Others showed faecal calprotectin thresholds predictive of endoscopic remission to be dependent on the scoring index used, with cut off values of 112, 148 and 161 μg/g predictive of activity using Mayo endoscopic score, UCEIS and modified PICaSSO, respectively.[36] Similarly, values correlating with histological remission also vary between studies and scoring systems, with cut-off values between 75 μg/g and 100 μg/g identified within the literature.[35–37]

Taking this information into account, a pragmatic approach may be to consider patients with faecal calprotectin <100 μg/g likely to be in endoscopic remission, faecal calprotectin 100–200 μg/g to have intermediate probability of endoscopic remission, and those with faecal calprotectin of >200 μg/g to have a low likelihood of endoscopic remission. Subsequent action depends on the patient disease phenotype and treatment history, with a general principle of advocating endoscopic evaluation before significant changes to therapy are made wherever the clinical setting and service capacity allow.

We advocate that faecal calprotectin >200 μg/g should trigger a discussion about lower gastrointestinal endoscopy. Values of 100–200 μg/g in an otherwise well patient, should prompt a test within a reasonable time frame (with further increase indicative



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of impending clinical relapse, and triggering discussion of endoscopic assessment).

### *Interpretation of blood parameters in monitoring of remission in ulcerative colitis*

Monitoring blood tests assess the safety of medications, especially in patients who have achieved remission with advanced therapies or immunomodulators. However, acute phase reactants may also serve as surrogate markers of subclinical disease activity, with blood tests as a convenient option in the outpatient setting. CRP is a marker of disease activity in ulcerative colitis, although one which correlates less tightly with activity than faecal calprotectin.[38] Indeed, it is recognised patients may have completely normal CRP even during a disease flare, thus rendering the negative predictive value low.[38] However, an elevated CRP, above that of laboratory reference range, may be suggestive of active disease. As faecal calprotectin is a more sensitive and specific biomarker, we suggest that patients with an unexpectedly raised CRP and no localising symptoms or signs to suggest an alternative cause, should have faecal calprotectin measured to validate biochemical disease activity before arranging endoscopic evaluation, in the absence of clinical symptoms.

### *Iron deficiency anaemia sectio*

Anaemia in IBD is covered in section 8.4.3. The two most common causes of anaemia in IBD are iron deficiency and anaemia of chronic disease, both of which may reflect subclinical disease activity in patients in clinical remission.[39] In the absence of an alternative cause for anaemia, such as menorrhagia or coeliac disease, disease activity should be further assessed. As with interpretation of CRP, when managing anaemic patients in clinical remission it would be reasonable to consider faecal calprotectin as a surrogate of endoscopic activity in the first instance, deferring endoscopic evaluation for those with refractory anaemia or those with raised faecal calprotectin.

### *Colonic ultrasound in monitoring of remission in ulcerative colitis*

Intestinal ultrasound (IUS) is increasingly recognised as a useful tool for monitoring disease activity in ulcerative colitis.[40] In the era of 'treat to target', endoscopic remission and response are frequently selected targets due to their association with long-term clinical response. However, colonoscopy is invasive and not always well tolerated by patients. By contrast, intestinal ultrasound is well tolerated, requires no bowel preparation and has the potential to provide real time information about disease extent and severity in the outpatient setting.[7 41]

There are currently two scoring systems used to quantify and standardise results of IUS of the colon; the Milan Ultrasound Criteria (MUC)[7] and the Ulcerative Colitis Intestinal Ultrasound Index (UC-IUS).[42] Both show strong correlation with endoscopic disease activity. The UC-IUS integrates the parameters of bowel wall thickness, Doppler signal, abnormal haustrations and fat wrapping, and demonstrates strong correlation with both the endoscopic Mayo sore ($\rho = 0.830$; $p < 0.001$),[40] and the UCEIS index ($\rho = 0.759$; $p < 0.001$).[42] The MUC is calculated from bowel wall thickness (BWT) and bowel wall flow. MUC also correlates highly with endoscopic improvement, with MUC<6.2 predictive of endoscopic response and MUC<4.3 predictive of endoscopic remission.[40] MUC with faecal calprotectin also correlates with the Nancy Histological Index, thus demonstrating preliminary evidence that the two modalities may be used to infer histological response or remission.[43]

Point of care ultrasound is not often available in the gastroenterology outpatient setting in the UK, and there is currently patchy provision of IUS by radiology departments.[44] However, it is included in this section on monitoring, as we felt that it was important to provide guidance based on evidence, as opposed to current resource availability.

## Clinical diagnosis of Crohn's disease

### *Classification of Crohn's disease*

The first classification for Crohn's disease issued in 1991 by the International Working Party, was based on anatomical distribution, surgical history and clinical behaviour, including inflammatory, fistulising or stenotic disease.[45] This was refined as the Vienna classification in 1998 to include age of onset (A), disease location (L) and disease behaviour (B) as the predominant phenotypic elements.[46] The Montreal revision of the Vienna classification further refined each of the three subclassifications (table 4).[15] Specifically, the Montreal classification added early onset of disease with age of diagnosis at 16 years or younger. The major limitation of the Vienna classification was the mutual exclusivity between upper gastrointestinal disease and more distal disease, whereas in the Montreal classification upper gastrointestinal disease can coexist with more distal disease. The last modification was to include perianal disease as a separate entity from intestinal fistulising disease. The Montreal Working Party addressed these aspects of clinical definition and classification, for the purposes of adoption in clinical practice, and to support future genetic and serological studies.

The Crohn's Disease Activity Index (CDAI) was developed and validated in 1976[47 48] as a tool to assess the severity of inflammatory disease. A multivariable regression analysis was used to develop an equation that best predicted the investigators' overall rating for each patient, with eight variables that determine the final score: number of liquid stools, the extent of abdominal pain, general well-being, the occurrence of extraintestinal symptoms, the need for antidiarrhoeal drugs, the presence of abdominal masses, haematocrit and body

**Table 4** Vienna and Montreal classification for Crohn's disease

| | Vienna classification | Montreal classification |
|---|---|---|
| Age at diagnosis (B) | A1: < 40 years<br>A2: ≥ 40 years | A1: ≤16 years<br>A2: between 17 and 40 years of age<br>A3: >40 years |
| Location (L) | L1: ileal<br>L2: colonic<br>L3: ileocolonic<br>L4: upper GI disease | L1: ileal<br>L2: colonic<br>L3: ileocolonic<br>L4: upper GI disease* |
| Behaviour (B) | B1: non-stricturing, non-penetrating disease<br>B2: stricturing disease<br>B3: penetrating disease | B1: non-stricturing, non-penetrating disease<br>B2: stricturing disease<br>B3: penetrating disease<br>p: perianal disease† |

*L4 is added to L1–L3 when concomitant upper gastrointestinal disease is present with distal disease.
†'p' is added to B1–B3 when concomitant perianal disease is present.



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weight. Scores range from 0 to 600, with quiescent disease demonstrating a score of <150, mildly active disease between 150 and 219, moderately active disease between 220 and 450 and very severe disease of >450 points. The CDAI (table 5) is the most widely used measure of disease activity in clinical trials, allowing for standardised approaches to data collection, patient inclusion criteria, trial management decisions, and is a principal response measure.[49] However, the use of the CDAI in routine clinical practice is limited by interoperator variability, cumbersome calculation, the subjective perception of 'general well-being' and 'abdominal pain', the heavily weighted diarrhoeal symptoms and the difficulty in maintaining a 7-day symptom diary.[50] Moreover, this index is not applicable for patients with stomas, is not validated for postoperative use and may underestimate symptoms and effects of fistulising disease.[51]

The Harvey-Bradshaw Index (HBI) was created to simplify the CDAI by using only a single day's reading for diary entries and excluding three variables—namely, the use of anti-diarrhoeal medications, haematocrit and body weight[47] (table 6). It is also more operator friendly by summing values of variables rather than applying weighted coefficients. Some studies have demonstrated the precision of HBI to be less than CDAI in correlating with objective markers of inflammation.[52 53] Thus, while the HBI is considered adequate for the use in routine clinical practice, the CDAI is still recommended for the continued use in prospective clinical trials. It should be noted that neither the CDAI nor HBI use laboratory values, such as CRP, endoscopic or histological parameters to indicate active inflammation, and neither incorporates faecal calprotectin.

In recent years, several questionnaires have been developed, recognising that patient-reported outcomes (PROs) represent an important endpoint and major therapeutic goal of IBD. To improve objectivity and performance, studies conducted in Crohn's disease investigated a two-item PRO (PRO-2), with stool frequency and abdominal pain as the main objective measures of disease activity. Further review of all PROs is beyond the scope of this guideline.

**Table 5** Crohn's disease activity index

| Variable | Description | Multiplier | Score |
|---|---|---|---|
| 1 | Number of liquid or soft stools (each day for 7 days) | ×2 | |
| 2 | Abdominal pain, sum of 7 daily ratings<br>0=none<br>1=mild<br>2=moderate<br>3=severe | ×5 | Clinical remission <150 |
| 3 | General well-being, sum of 7 daily ratings<br>0=generally well<br>1=slightly under par<br>2=poor<br>3=very poor<br>4=terrible | ×7 | Mildly active disease 150–219 |
| 4 | Number of listed complications<br>Arthritis/arthralgia<br>Iritis/uveitis<br>Erythema nodosum or pyoderma gangrenosum or aphthous stomatitis<br>Anal fissure or fistula or abscess<br>Other fistula<br>Fever over 37.8°C | ×20 | Moderately active disease 220–450 |
| 5 | Use of antidiarrhoeal medications<br>0=no<br>1=yes | ×30 | |
| 6 | Abdominal pain<br>0=no<br>2=questionable<br>5=definite | ×10 | Severely active disease >450 |
| 7 | Haematocrit<br>Men, 47-Hct (%)<br>Women, 42-Hct (%) | ×6 | |
| 8 | Body weight<br>(1 wt/standard weight) x100 | ×1 | |

**Table 6** Harvey-Bradshaw Index

| Variable | Description | Score |
|---|---|---|
| 1 | General well-being<br>0=very well<br>1=slightly below par<br>2=poor<br>3=very poor<br>4=terrible | Clinical remission ≤4 |
| 2 | Abdominal pain<br>0=none<br>1=mild<br>2=moderate<br>3=severe | Mildly active disease 5–7 |
| 3 | Number of liquid stools per day | |
| 4 | Abdominal mass<br>0=none<br>1=dubious<br>2=definite<br>3=definite and tender | Moderately active disease 8–16 |
| 5 | Complications (one score per item)<br>Arthralgia<br>Uveitis<br>Erythema nodosum<br>Aphthous ulcer<br>Pyoderma gangrenosum<br>Anal fissure<br>New fistula<br>Abscess | Severely active disease >16 |

## Clinical assessments in Crohn's disease

**GPS 4**

We recommend assessment of disease activity when a relapse of Crohn's disease is suspected using clinical, biochemical, cross-sectional abdominal imaging, intestinal ultrasound, capsule endoscopy and/or ileo-colonoscopy, personalised to the individual's disease phenotype and location, taking into account the urgency, availability and tolerability of tests.



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Several imaging modalities can be used in the diagnosis and monitoring of Crohn's disease, each with strengths and drawbacks. Previous BSG guidance addressed the decline in use of luminal barium fluoroscopic techniques for diagnosis and their replacement with cross-sectional imaging such as CT enterography (CTE) and magnetic resonance enterography (MRE), as well as IUS.

Primary considerations in the choice of imaging modality are diagnostic accuracy, sensitivity, and specificity, as well as minimising exposure to ionising radiation and acceptability to patients. In addition, imaging choice will largely be determined by the local expertise and availability of tests, the specific clinical question, as well as patient presentation (stable outpatient setting vs emergency admission), which may also be a significant factor in the initial imaging modality.

### *Faecal calprotectin*

**GPS 5**

Faecal calprotectin should be used to monitor disease in patients with known Crohn's disease in a known location, where there is a baseline faecal calprotectin value.

Faecal calprotectin is a reliable indicator of remission in Crohn's disease, indicated by mucosal healing,[54] and is sensitive enough to distinguish between mild, moderate and severe disease activity.[55] However, there is considerable disagreement in the cut-off values in Crohn's disease,[56–58] which may also be dependent on disease location.[57] The sensitivities and specificities of faecal calprotectin to accurately measure disease activity in Crohn's disease at different disease locations are diverse, and no firm conclusion can be drawn[59]; however, it may be less reliable in small bowel disease than in colonic Crohn's disease.[60 61] Changes in an individual's faecal calprotectin over time may be more meaningful than absolute numbers.[62 63]

### *Ileo-colonoscopy*

**GPS 6**

We recommend that ileo-colonoscopy, when Crohn's disease is suspected and the procedure is clinically safe to perform, should include ileo-colonic biopsies and standardised endoscopic scoring systems to assist in defining the severity and aetiology of macroscopic and microscopic inflammation.

Ileo-colonoscopy remains the first-line investigation to diagnose Crohn's disease since it allows for an assessment of disease extent, and importantly, the collection of biopsy specimens for a histological diagnosis.[64] This is particularly important at the index presentation prior to the initiation of medical therapy and is supported by the ECCO-ESGAR guidelines of 2019[65] and by the European Society of Gastrointestinal Endoscopy (ESGE) guidelines for the diagnosis of small bowel disorders.[66] The importance of histology to diagnose Crohn's disease should not be underestimated even in the era of advancing imaging modalities, such as cross-sectional imaging, IUS and capsule endoscopy, especially to differentiate Crohn's disease from infective, drug-induced, ischaemic aetiologies of enterocolitis and small bowel lymphoma.

### *Small bowel capsule endoscopy*

**GPS 7**

We suggest performing small bowel capsule endoscopy when small bowel Crohn's disease is suspected despite normal or inconclusive investigations.

Video capsule endoscopy provides endoluminal images of the GI tract, most valuable to examine the small bowel, where conventional endoscopy access is limited. Presently, neither upper GI endoscopy nor colon capsule endoscopy are recommended for the routine diagnosis of Crohn's disease, although pan-enteric capsules have shown equivalent diagnostic yield compared with ileo-colonoscopy and MRE.[67] The ESGE recommends ileo-colonoscopy as first-line investigation for suspected Crohn's disease, and small bowel capsule endoscopy (SBCE) is recommended as the initial investigation of the small bowel after a negative ileo-colonoscopy.[66]

**GPS 8**

We suggest the use of a patency capsule prior to capsule endoscopy in those with suspected Crohn's disease who have obstructive symptoms.

In two published meta-analyses, SBCE was diagnostically superior to barium follow-through, but similar to CT and MRE.[68 69] Both meta-analyses noted SBCE to be superior to MRE for more proximal and superficial lesions. The capsule retention rates have reduced with successive meta-analysis over time, with higher retention rates in patients with established versus suspected Crohn's disease,[70] an outcome that can be further reduced by prior use of patency capsules. Balloon-assisted enteroscopy permits the entry of endoscopes beyond the limits of conventional gastroscopy, push enteroscopy and ileo-colonoscopy relying on balloons attached to the enteroscopy devices. Previously published systematic reviews suggest similar diagnostic yields to SBCE[71] and greater sensitivity than MRE[72] with a perforation risk of 0.15% for diagnostic procedures.[73] ESGE recommends consideration of balloon-assisted enteroscopy to obtain biopsy specimens where there is diagnostic uncertainty of Crohn's disease, and where it might alter the therapeutic approach.[66]

### *Cross-sectional imaging*

**GPS 9**

Cross-sectional imaging, specifically MRI and CT, and IUS may be used to evaluate both luminal and extraluminal Crohn's disease. Emphasis should be placed on MRE and IUS as they do not expose patients to ionising radiation. For diagnosis and determining disease extent, MRI is preferred as first line. As MRE and IUS appear to be of similar value for monitoring transmural healing in Crohn's disease during treatment, the choice of imaging modality depends on local availability and expertise.



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A combined approach with a supportive clinical history, raised faecal calprotectin, together with locally available small bowel imaging (CT, MRE, IUS or capsule endoscopy) and ileocolonoscopy with histological sampling, will provide the necessary information to diagnose Crohn's disease. Confirming a Crohn's disease diagnosis is critically important at the start of treatment.

The advantage of MRE and US over CTE is the lack of exposure to radiation. CT scanning exposes patients with Crohn's disease to ionising radiation, which may increase their lifetime risk of cancer,[74–76] and this risk is particularly important for children and young adults. Patients with Crohn's disease have more than twice the radiation exposure of patients with ulcerative colitis. A study of 409 patients from a tertiary hospital showed that 15.5% had a cumulative exposure dose in excess of 75 mSv[75] (this dose is considered to increase the risk of cancer mortality by 7.3%). Factors associated with excessive diagnostic radiation exposure included age under 17 at diagnosis, upper gastrointestinal disease location, penetrating disease, need for intravenous corticosteroids and more than one surgical operation for Crohn's disease . Therefore, MRE and US are generally preferred over CT for monitoring of Crohn's disease to limit repeated patient exposure to ionising radiation. Generally, the role of CT is usually limited to acute presentations.

MRI is, however, not without limitations and considerations, including time, availability, patient experience, cost and available expertise in reporting.[77] Some validated and reproducible Crohn's disease activity scoring systems have been developed to standardise MRI assessment in Crohn's disease, and STRIDE II suggest using the Magnetic Resonance Index of Activity (MaRIA) score to help define resolution of inflammation on MR imaging. A simplified MaRIA score has also been developed and validated in 2019 for easier and more time efficient assessment of Crohn's disease activity and severity.[78] Radiological signs of disease activity include increases in bowel wall thickness, vascularity and contrast enhancement, T2 and diffusion weighted imaging signal (for MRE), reduced bowel motility and identification of ulceration and acute extraluminal complications.

With respect to diagnostic accuracy, multiple meta-analyses[79–81] failed to show any significant differences between MRE and IUS. METRIC, a prospective multicentre UK-based trial in 2018,[82] compared MRE with US in 284 patients and found that both modalities were highly accurate for detecting small bowel Crohn's disease, achieving 97% sensitivity for MRE and 92% sensitivity for US. MRE had significantly higher sensitivity for small bowel disease presence and location than US (80% vs 70%, respectively), and greater specificity (95% vs 81%, respectively). It is worth noting that US had superior sensitivity to that of MRE for colonic disease presence in newly diagnosed patients (67% vs 47%, respectively). Diagnostic accuracy for abscess, fistulae and stenosis were largely equivalent between techniques, although MRE numerically found more fistulae and abscesses than US. US may lack accuracy to diagnose deep pelvic pathology.

**GPS 10**

Cross-sectional imaging, specifically MRI and CT, and US may be used to evaluate both luminal and extraluminal Crohn's disease. Emphasis should be placed on MRE and US as they do not expose patients to ionising radiation. For diagnosis and determining disease extent, MRI is preferred as first line. As MRE and US appear to be of similar value for monitoring transmural healing in Crohn's disease during treatment, the choice of modality depends on local availability and expertise.

Intestinal US is increasingly recognised as a useful tool for monitoring disease activity in IBD.[83] However, the application of US remains limited in comparison with other modalities owing to lack of expertise and availability, and absence of validated indices, which needs to be addressed.[84] The TRUST study confirmed the utility of bowel US for monitoring disease activity and response to treatment in Crohn's disease. US, performed at treatment initiation and at fixed time intervals showed improvement of ultrasonographic parameters, including BWT, presence of mesenteric lymph nodes, mesenteric hypertrophy and strictures.[78] There may be a role for fluoroscopy on a case-by-case basis for assessing complex anatomy, enteric fistulae and for presurgical planning or defining complex postsurgical anatomy and bowel length due to the dynamic nature of the study.

**GPS 11**

We suggest prioritising the use of cross-sectional abdominal imaging and intestinal ultrasound in the diagnosis and assessment of strictures, and recognising the role of ileocolonoscopy in colonic and anastomotic strictures when clinically safe to perform, with biopsies to exclude dysplasia and aid distinction of fibrotic from inflammatory strictures.

### *Monitoring remission in Crohn's disease*

**GPS 12**

We recommend a multimodal approach to monitoring of remission in patients with Crohn's disease. Patients should be regularly assessed with a clinical index, such as PRO-2, in addition to blood monitoring, CRP, faecal calprotectin, ileocolonoscopy and non-invasive imaging. The combination of modalities and frequency of monitoring appointments depends on disease phenotype, therapy and duration of remission.

Regular disease monitoring for Crohn's disease in remission aims to confirm the state of remission, ensure adherence to, and tolerance of, treatments, review nutritional status, extraintestinal manifestations and vaccination uptake.

In 2015, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative, defined a treat-to-target approach for Crohn's disease, with the aim of extending beyond clinical response to both clinical and endoscopic remission.[6] The following targets were identified as most important: clinical response and remission, endoscopic healing (EH), normalisation of CRP/erythrocyte sedimentation rate and faecal calprotectin. Long-term targets included clinical remission, EH, absence of disability and restoration of quality of life, and short-term targets were symptomatic relief and normalisation of biochemical markers. Transmural healing in Crohn's disease did not emerge as a formal target from STRIDE II, although the panel still recommended its assessment through imaging as a measure of the remission depth.[6]

The approach to monitoring Crohn's disease in remission will inevitably depend on local resources. Moreover, frequency and type of monitoring will depend on disease phenotype, management and duration of remission.

#### *Clinical scoring systems*

The potential mismatch between objective measures of inflammation and clinical symptoms, alongside the possibility of other



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differential diagnoses (eg, irritable bowel syndrome (IBS), bile salt malabsorption, small bowel bacterial overgrowth) in IBD,[85] makes clinical indices alone insufficient to confirm disease activity.

Patient-reported outcomes (PROs) are increasingly becoming a standard tool for disease monitoring. The most used PRO in adult Crohn's disease is PRO-2—that is, the average daily stool frequency and abdominal pain subscores from the CDAI.[6] Clinical remission in Crohn's disease is defined as PRO-2 (abdominal pain≤1 and stool frequency≤3) or HBI≤4.

### *Biochemical markers*

Faecal calprotectin correlates with clinical, endoscopic and histological disease activity in Crohn's disease,[86] and its non-invasive attribute positions it within a key role in monitoring patients in remission. However, determining a specific target to trigger further disease assessment is more challenging due to variability among patients' phenotypes; faecal calprotectin in patients with isolated small bowel Crohn's disease shows weaker correlation with endoscopic activity than in patients with colonic disease. Faecal calprotectin should therefore be used as an adjunct to endoscopic and radiological investigations and be calibrated to each individual patient and phenotype.[6]

Figure 3 outlines a suggested approach to interpreting faecal calprotectin for monitoring of Crohn's disease clinical remission. Subsequent actions will depend on disease phenotype and treatment history, with a general principle of advocating endoscopic and/or radiological evaluation before deciding on significant changes to therapy.

### *Endoscopy*

Endoscopic healing (EH) is a core STRIDE-II treatment target in IBD and has been shown to correlate with improved long-term outcomes.[6] EH is defined by a simple endoscopic score for Crohn's disease of <3 points, or absence of ulcerations.[6] The limitations of endoscopies in assessing patients with Crohn's disease include its invasiveness, costs, partial access to the small bowel and inability to assess the intestinal tract wall beyond the mucosa. A Lewis score of <135 in SBCE is consistent with EH.[87]

The emergent concept of deep remission refers to the presence of both clinical remission *and* mucosal healing, with the absence of corticosteroid therapy for ≥8 weeks. Its clinical impact stems from the CALM study, which demonstrated a reduced risk of disease progression in patients meeting the criteria for deep remission.[88]

SBCE is useful as a non-invasive method of mucosal assessment in cases where there is disease involvement in the proximal small bowel inaccessible by conventional ileocolonoscopy.

### *Histology*

Despite progressive debates in recent years on the topic of histological healing as a treatment target, histological remission is not currently recommended as a treatment target by STRIDE II for Crohn's disease.[6] This might partly be explained by the lack of consensus on the definition of histological remission, and the limited effectiveness of available therapies in achieving histological remission.

### *Non-invasive imaging and assessment of transmural healing*

In recognition of the transmural nature of Crohn's disease, transmural healing (TH), defined as the normalisation of BWT, has been suggested as a treatment goal. Patients with Crohn's disease with TH after 2 years of biological therapy, showed a lower risk of clinical relapse, hospitalisation and surgery in the following year, compared with patients with mucosal healing alone.[89] However, because of the limited ability of current available treatments to achieve TH, STRIDE II recommends TH assessment with imaging as an adjunct to endoscopic remission, rather than a formal isolated treatment target.[6]

Intestinal imaging is a valuable, non-invasive, complementary option to endoscopy, as well as allowing evaluation for disease complications, such as stricturing or penetrating disease, and assessment of perianal disease. MRE and US have the benefits of limiting patient exposure to radiation, unlike CT imaging. Additionally, as for IUS, three main scores have now increasingly been validated.[90] Details of the relative accuracy of different modalities areis covered in the diagnostic section above.

### *Quality of life*

Quality of life is a more holistic measurement of overall well-being. The LIR!C trial is an excellent example of the increasing relevance of well-being as an outcome. The study compared surgical resection with anti-TNF therapy in terminal ileal Crohn's disease not responding to at least 3 months of conventional therapy with corticosteroids, purine analogues or methotrexate, by assessing patients' quality of life (QoL) using the IBD Questionnaire as the primary outcome.[91] Similarly, a randomised controlled trial (RCT) by Sands *et al* demonstrated the positive effect of ustekinumab on health-related QoL in an adult Crohn's disease cohort,[92] whereas Herrera-deGuise *et al* demonstrated that restoration of QoL at 14 weeks after initiation of anti-TNF therapy was associated with 1 year sustained remission.[93]

The STRIDE II panel voted to include restoration of QoL and reduction in disability as formal long-term treatment targets, irrespective of other objective markers of inflammation.[6]

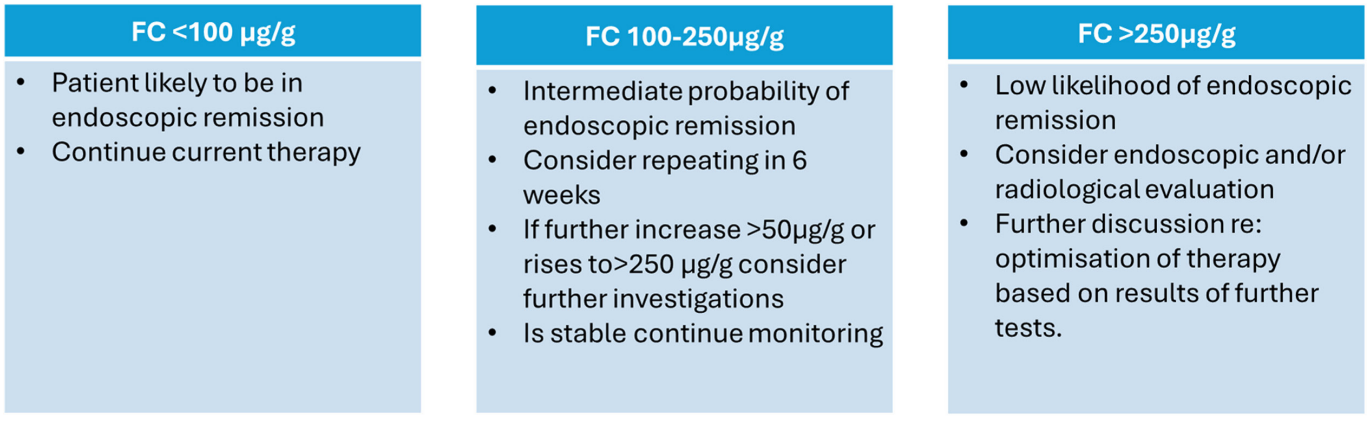



**Figure 3** Suggested approach to interpreting faecal calprotectin (FC) in a patient with Crohn's disease.



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*Upper GI Crohn's disease*

GPS 13

We recommend routine clinical assessment for upper gastrointestinal symptoms in patients with Crohn's disease to determine if an oesophagogastroduodenoscopy is warranted in patients experiencing upper gastrointestinal symptoms, but it is otherwise not routinely needed.

The prevalence of upper gastrointestinal Crohn's disease is reported as between 3% and 16% in some studies,[94–96] although prevalences of up to 75% have been quoted.[97] It is hypothesised that the presence of upper GI Crohn's disease suggests a more aggressive phenotype. It is widely accepted that the younger age of diagnosis of Crohn's disease suggests a more aggressive phenotype, and therefore gastroscopy is recommended alongside ileocolonoscopy in the paediatric population, <17 years.[98] However, upper GI Crohn's disease may be less common in adults, and routine gastroscopy at diagnosis is not indicated. The present recommendation remains to request gastroscopies only in adult patients with Crohn's disease who have upper GI symptoms.

*Histopathology of IBD*

Recent comprehensive reviews and guidance documents on the histological assessment of IBD are available, especially from ECCO.[99–103] The following text presents good practice statements and commentary for the most common and clinically relevant aspects of histopathology, especially those directly relevant to other sections of this guideline document.

In the setting of IBD, histopathology has three main functions—namely, to diagnose IBD (and exclude differential or additional diagnoses); to determine activity; and to assess for neoplasia. The histopathology of IBD-related neoplasia is covered in the complementary IBD colorectal cancer surveillance guideline.[104]

*Endoscopy biopsy sampling of a patient with suspected new IBD*

Therapy for IBD can alter the anatomical distribution and/or histological features of IBD.[105 106] Therefore, histological diagnosis and subtyping of IBD is best performed on biopsy specimens from a patient with suspected new IBD who has not received treatment. Histological abnormalities can be present in endoscopically normal mucosa in patients with IBD.[107] For example, the terminal ileum and/or right colon may show histological changes in a patient who only appears to have left-sided disease at colonoscopy. Therefore, ileocolonoscopy permits optimal tissue sampling for suspected new IBD, and such sampling should comprise at least two biopsy specimens, each from the terminal ileum, from at least four different colonic segments (these segments being caecum, ascending colon, transverse colon, descending colon and sigmoid colon) and from the rectum.[99] Biopsy specimens should be taken from abnormal, non-ulcerated areas or from normal areas if there is no mucosal abnormality in that bowel segment.[99] The biopsy specimens from different segments should be clearly separated and labelled with their respective anatomical site of origin.

There is little evidence to guide how many biopsy specimens should be taken and from what anatomical sites during endoscopic follow-up of patients with an established diagnosis of Crohn's disease or ulcerative colitis. However, as discussed further below and elsewhere in this guideline document, histological remission is not considered a treatment target for Crohn's disease, and in ulcerative colitis may have a supplementary role but is also not a mandatory treatment target.

GPS 14

Ileocolonoscopy is necessary for reliable diagnosis and assessment of IBD, particularly at initial presentation. The endoscopist should take at least two biopsy specimens each from the terminal ileum, at least four different colonic segments, and the rectum, and identify the sites of origin clearly. The same thorough sampling protocol should be followed at any subsequent endoscopy should a diagnosis of IBD, or designation of subtype, remain uncertain.

*Clinical information required for IBD biopsy assessment*

Several other causes of ileitis and colitis can mimic the histological features of IBD, including certain drugs, a variety of infections and diverticular colitis.[100] Therefore, any clinical history which could point to one of these differential diagnoses[100] should accompany the biopsies to aid histological assessment. Diagnostic interpretation of biopsies is based not just on histological features, but also on knowing the nature and duration of symptoms, the endoscopic appearance of the area sampled, and the overall distribution of macroscopic disease along the bowel segments. Clinical details must indicate either new or treated IBD, because therapy can alter the anatomical distribution and histological features considerably.[105 106]

GPS 15

Biopsies for the diagnosis of suspected new IBD should be accompanied by full clinical details, including the nature and duration of symptoms, current endoscopic findings, any past history of IBD, past history of any other relevant conditions and details of any systemic or topical therapies applied.

*Histological features requiring assessment in biopsies*

Inflammatory bowel disease typically shows chronic histological changes in addition to acute inflammation. The chronic changes include architectural distortion, crypt atrophy, an increase in lamina propria chronic inflammatory cells, and Paneth cell metaplasia.[108 109]

The microscopic features which help to distinguish IBD from its histological differential diagnoses are outlined in detail elsewhere.[100] In general, crypt architectural disturbances and basal plasmacytosis are the most reliable features favouring IBD over acute infectious colitis and other non-IBD colitides.[108 109]

The features that most reliably distinguish ulcerative colitis from Crohn's disease include granulomas and distribution of changes. Non-cryptolytic granulomas are not necessary for a diagnosis of Crohn's disease and are present in only a minority of samples, but strongly favour Crohn's disease over ulcerative colitis if present.[110] In ulcerative colitis and other colitides, cryptolytic granulomas may form in reaction to ruptured crypts.[111] They are less useful than non-cryptolytic granulomas for distinguishing Crohn's disease from ulcerative colitis. Regarding



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distribution, ulcerative colitis almost always involves the rectum at presentation and often extends continuously from the rectum into the colon for a variable distance. Continuity between sites and diffuse chronic changes within sites favour ulcerative colitis over Crohn's disease. In contrast, Crohn's disease is typically discontinuous between anatomical sites and the architectural and inflammatory changes vary in intensity within and between biopsies. Rectal sparing favours Crohn's disease over ulcerative colitis in the untreated patient. However, even at presentation, there are exceptions to this pattern.

In both forms of IBD there is usually at least some degree of histological activity—that is, acute inflammatory changes superimposed on chronic changes (see below), prior to initial treatment. Evidence of activity includes neutrophils in the lamina propria, cryptitis, crypt abscesses, erosion and ulceration. Histological activity is not synonymous with endoscopic activity.

Atypical epithelial changes in IBD biopsies may be due to regenerative change or dysplasia. For the reasons outlined above, the histological diagnosis of IBD-related dysplasia is not covered here.

In children, new ulcerative colitis may demonstrate less crypt distortion and atypical features, such as rectal sparing and skip lesions.[112 113] Granulomas are more common among paediatric than adult patients with Crohn's disease. There are further differences between children and adults in the histological features and anatomical distributions of ulcerative colitis and Crohn's disease, and these are described in more detail elsewhere.[99]

Certain clinical settings of IBD require assessment of endoscopic tissue for cytomegalovirus infection. Some suggest this is best performed by PCR and/or immunohistochemistry, but the ideal approach to sampling, testing and interpretation is uncertain. Further details on cytomegalovirus assessment of tissue from patients with IBD are available elsewhere.[114]

**GPS 16**

To help diagnose and subtype IBD histologically, biopsy pathology reports should mention basal lamina propria chronic inflammatory cell distribution, crypt architecture, crypt atrophy, lamina propria neutrophils, neutrophils in the surface and crypt epithelium (cryptitis), crypt abscesses, erosions, ulcers, granulomas and atypical epithelial changes.

### *Histological features of activity in IBD*

It is generally agreed that neither the lamina propria nor epithelium of normal large bowel mucosa should contain neutrophils. Some have suggested that the presence of one, two, or even three neutrophils, particularly in the lamina propria, is not indicative of acute inflammation, but the topic remains controversial.[108 115] Bowel preparation could explain some instances of small numbers of neutrophils. Neutrophils lying solely within a capillary lumen do not define acute inflammation. There is also no universal agreement on the minimum number of neutrophils required to define a crypt abscess.[116] Some definitions refer to a 'cluster' or 'chain' of neutrophils, whereas general definitions of 'abscess' usually require the presence of more than one neutrophil.

An ECCO consensus panel agreed that one intraepithelial neutrophil is sufficient to define cryptitis.[101] The panel also agreed that at least two neutrophils should be present within a crypt lumen to define a crypt abscess.[101]

The convention is to interpret the terms 'cryptitis' and 'crypt abscesses' as referring to neutrophil cryptitis and neutrophil crypt abscesses. Cryptitis or a crypt abscess can include other inflammatory cells in addition to the neutrophil. However, cryptitis or crypt abscesses which contain eosinophils without neutrophils are not regarded as markers of IBD activity.

In the GI tract, an erosion is defined as a mucosal defect which does not extend deep to muscularis mucosae, whereas an ulcer extends at least into submucosa.[117] However, distinguishing between erosions and ulcers may be difficult or impossible when assessing biopsies, especially if they are superficial and lack muscularis mucosae and submucosa. Both erosions and ulcers can show granulation tissue, surface fibrin and/or neutrophils and, for ulcers, proliferating fibroblasts in the submucosa.[117] The mucosa adjacent to erosions and ulcers may show evidence of re-epithelialisation, and this regenerative epithelium can show cytological atypia.

**GPS 17**

Histological activity in IBD is defined by at least one intraepithelial neutrophil or a crypt abscess with at least two neutrophils or at least two neutrophils in the lamina propria or erosion or ulceration or a combination of these features. Eosinophils are not a marker of activity.

### *Histological scoring systems for ulcerative colitis*

The past seven decades has seen the proposal of more than 30 scoring systems for histological inflammation and/or histological activity in IBD.[102] These systems variably include assessments of mucosal architecture, mononuclear cell infiltrate, eosinophils, neutrophils (in the lamina propria or epithelium), crypt destruction and erosions/ulcers.[102] They vary considerably in the number and range of histological features assessed, the terminology and the approach to categorising severity, making direct comparisons difficult.

Among the older systems, the Gupta, Geboes, Truelove and Riley systems[118–121] are well known. The Geboes score is widely used, although only partially validated.[102] Two more recent and better validated systems are the Nancy Histological Index and the Robarts Histopathology Index (RHI).[122–124]

Compared with the RHI, the Nancy Index presents fewer grade options for each parameter assessed. Further, a final Nancy Index is derived through a stepwise process rather than through the more complex calculation that is required for a final RHI score. Therefore, the Nancy Index may be more appropriate for clinical applications.

**GPS 18**

The Robarts Histopathology Index and Nancy Index are fully validated scores for assessing histological inflammation in ulcerative colitis. The Nancy Index is most appropriate for clinical applications. The Geboes score is widely used, but less well validated.

### *Histological remission in ulcerative colitis*

There are numerous definitions of histological remission or histological mucosal healing. These vary from completely normal mucosa to an absence of various histological abnormalities to



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scores in various systems that lie below certain thresholds. For example, histological remission could be defined as a Geboes score ≤2.0, 125, a Nancy Index=0[123] or RHI≤3 (with subscores of 0 for lamina propria neutrophils and neutrophils in the epithelium and without ulcers or erosions).[124]

Despite increasing debate in recent years regarding histological healing as a treatment target, histologic remission is not recommended by STRIDE II as a treatment target in ulcerative colitis.[94] There is no currently accepted consensus on the definition of histologic remission, and current available therapies have limited effectiveness for achieving histologic remission. However, histologic remission could be used as an adjunct to endoscopic remission to represent a deeper level of healing.[94]

'Histological response' has a different definition from histological remission. The need to formally define and quantify histological response is less relevant to the recommendations of this guideline. Definitions of histological response are not outlined here, but may be found elsewhere.[102]

**GPS 19**

Definitions of histological remission in ulcerative colitis are numerous and include: histological normalisation; absence of inflammation: absence of neutrophils/erosion/ulceration; absence of intraepithelial neutrophils/erosions/ulceration; RHI≤3; Nancy Index=0; Geboes score ≤2.0.

*Biopsy assessment of disease activity in Crohn's disease*

Crohn's disease usually manifests as discontinuous bowel disease and also has the potential to involve any part of the GI tract.[125–127] This increases the possibility of non-representative biopsy sampling and hampers or prevents endoscopic access to abnormal and clinically relevant foci. Furthermore, because Crohn's disease is typically transmural, endoscopic and biopsy findings may fail to represent clinically relevant changes occurring in bowel layers deep to the mucosa.[128 129]

**GPS 20**

In Crohn' s disease, biopsy appearances may not accurately reflect disease activity.

*Histological scoring systems for Crohn's disease*

More than 14 histological indexes have been proposed for Crohn's disease,[103] but none is fully validated, and none is widely accepted for use in clinical trials or in clinical practice.[126 130–132] An ideal histological scoring system for Crohn's disease should quantify disease activity separately at different anatomical sites. The Global Histological Activity Score (GHAS) was designed to do so,[133] and remains a widely used scoring system for Crohn's disease. However, this system has not been fully validated, and its inclusion of granulomas has been questioned.[103] Furthermore, compared with colonic disease, GHAS scoring of ileal disease shows lower interobserver consistency[134] and less correlation with faecal calprotectin and lactoferrin levels.[125]

Several attempts have been made to apply ulcerative colitis histological scoring systems (especially the Geboes score, the Nancy Index and the RHI) to Crohn's disease.[135–138] The results have been conflicting. For example, Almradi and colleagues reported that both the Geboes score and the RHI are appropriate for use in Crohn's disease, but were less certain about the applicability of the Nancy Index.[131] By contrast, Villanacci and colleagues scored ulcerative colitis and Crohn's disease cases with these three systems as well as the Extension, Chronicity, Activity, Plus (ECAP) system and their own novel scoring system, and reported that the Nancy Index had the highest interobserver agreement.[137] However, all ulcerative colitis scoring systems have limitations for Crohn's disease because they were designed to assess large bowel mucosa alone.

**GPS 21**

The Global Histological Activity Score is the most commonly used histological scoring system specific to Crohn's disease, but it lacks validation. No well-validated system for Crohn's disease exists. Histological scoring systems for ulcerative colitis—including the Geboes score, RHI and Nancy Index—have been used to assess intestinal biopsies from patients with Crohn's disease, but are designed for assessing large bowel disease only.

*Predictive value of histology in ulcerative colitis*

Histological activity may be present in the absence of endoscopic activity.[107] In patients with endoscopically quiescent ulcerative colitis, absence of histological activity predicts a lower likelihood of relapse or exacerbation of disease in some reports.[139] Furthermore, the presence of histological remission predicts a lower risk of hospitalisation,[140] corticosteroid use[140] and colectomy.[141] Histological examination may therefore supplement the ability of endoscopic examination to predict long-term remission.[107 142 143]

However, while certain ulcerative colitis histological features may be associated with failure of medical therapy,[144 145] there are limited data addressing whether histological activity is an independent predictor of the need to escalate to biologic and/or immunomodulator therapy in ulcerative colitis. Furthermore, there has been recent international agreement that histological remission is a difficult target to achieve, especially when balanced against the risks and costs of therapies required.[6] The STRIDE II group did not recommend histological remission as an independent treatment target, but did acknowledge that it may supplement endoscopic remission as a marker of a deeper level of healing.[6]

**GPS 22**

Microscopic activity may be present in endoscopically quiescent ulcerative colitis. The absence of histological activity in this setting is associated with a better clinical outcome. Histological remission could be used as an adjunct to endoscopic remission to indicate a deeper level of healing, but is not a mandatory treatment target for ulcerative colitis.

*Predictive value of histology in Crohn's disease*

Certain histological features of Crohn's disease may predict poorer disease course and worse prognosis.[146] Furthermore, histological remission of Crohn's disease appears to have some predictive value. Among patients with only ileal disease, such remission was associated with a lower risk of clinical relapse, escalation of medication and corticosteroid use.[147] In a study



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of 215 patients with Crohn's disease who achieved clinical and endoscopic remission through treatment optimisation, histological remission was associated with a lower risk of relapse.[148]

However, there is no universal acceptance that histological activity and histological remission have independent prognostic value in Crohn's disease. Some of this uncertainty may result from the use by previous studies of different definitions of histological activity and remission. Because of the latter and the fact that current therapies have limited efficacy in attaining histological remission in Crohn's disease, there has been recent international consensus that remission should not represent a treatment target for Crohn's disease.[6] This consensus recommendation is further supported by the fact that biopsy histology may not be representative of disease activity in Crohn's disease.

**GPS 23**

In Crohn's disease, histological remission may predict a better clinical outcome. However, histological remission is not a mandatory treatment target for Crohn 's disease.

*Preassessment required before biologics/immunosuppressants*

The rates of serious and opportunistic infections are higher in patients with IBD with moderate to severe disease taking purine analogues, biologics and/or small molecules. In a study involving 38 850 patients receiving purine analogues and/or anti TNFs, the incident rate for serious infections was 9.4 per 1000 person years. These included chest, GI, skin, urothelial, ENT, central nervous system and musculoskeletal infections.[149] The risk of serious infections is lower with ustekinumab, p19 antibodies and vedolizumab There is higher incidence of herpes zoster infection with JAK inhibitors compared with biological therapies, evident as a class effect. Yet filgotinib, a highly selective JAK1 inhibitor, has a lower risk of herpes zoster than tofacitinib.[150 151]

When disease status is reviewed or prior to changing biological/small molecules therapy, we advise re-evaluating the risk factors for serious and opportunistic infections.

### Tuberculosis

The incidence of new TB and latent TB reactivation in patients receving biological agents is significantly higher than that of the general population. Rheumatological data demonstrated that the risk of TB reactivation has fallen from 50-fold to a 90-fold increase prior to routine pre-biologics testing, with an incidence risk ratio of 19 (95% CI 11 to 32) to 1.8 (95% CI 0.28 to 7.1)) following implementation of screening.[152] Although there is a paucity of data for newer drugs, emerging data suggest a lower risk with ustekinumab and vedolizumab than with infliximab and adalimumab. Purine analogues, methotrexate and 5-ASA confer a lower risk than other agents.

Cumulative doses of corticosteroids also confer a higher risk of reactivation.[153] Immunosuppressive therapies and corticosteroids affect the sensitivity of biochemical and skin diagnostic tests for TB,[154–160] therefore we recommend clinical risk stratification and testing of all patients with IBD at the point diagnosis and/or prior to starting any IBD therapy. Should risk factors change, repeat of TB tests during therapy should be considered. We recommend an interferon-λ release assay (IGRA) and a chest X-ray examination as minimum tests.[161] Any indeterminate IGRA should also be discussed with the TB team for consideration of further tests such as tuberculin skin test or induced sputum culture. Patients whose risk factors, such as contact or exposure history, change while receiving immunosuppressive therapy should also be discussed with the local TB team. Although there is moderate to good concordance between IGRA and the tuberculin skin test, the latter is affected by BCG vaccination and the former is more cost-effective.[153 162]

**GPS 24**

All patients with IBD in whom advanced therapies are initiated should receive written information about the benefits, risks, side effects of treatment and their monitoring schedules.

Prior to starting advanced therapies, the following are recommended:

Pre-assessment history:
- ⇒ Infections: relevant symptoms, exposure and contact history for TB, history of HSV (oral, genital) and VZV (χ, shingles);
- ⇒ Thromboembolic and cardiac risk factors: hypertension, high cholesterol, smoking status, previous arrhythmias and ischaemic heart disease;
- ⇒ Previous history of cervical and/or anal dysplasia;
- ⇒ Previous history of all cancers, including skin;
- ⇒ Other immune disorders, such as multiple sclerosis.

Specialist investigations:
Blood:
- ⇒ TPMT (all patients);
- ⇒ NUDT15 (East and South Asian patients), where available;
- ⇒ IGRA for TB (please use locally available assay), EBV, HBV, HCV, HIV and, if no previous history, VZV.

Imaging:
- ⇒ Chest X-ray;
- ⇒ ECG, if ozanimod or etrasimod are considered.

Optical coherence tomography
- ⇒ If ozanimod or etrasimod are considered.

Screening:
- ⇒ Encourage cervical screening in all females;
- ⇒ Advise all patients to take part in national cancer screening programmes.

Surveillance:
- ⇒ Skin mapping by GP with special interest or dermatology team for patients who are at increased risk of skin cancers above and beyond the risk conveyed by advanced immunosuppressive therapies (for example, those with a previous history of non-melanoma skin cancer).

**GPS 25**

An interferon-λ release assay (IGRA) and a chest X-ray examination are the minimum tests for low-risk patients.

### Epstein-Barr virus

The role of serological screening for Epstein-Barr virus (EBV) before starting advanced therapy in adult patients lacks consensus among gastroenterologists.

Primary EBV infection in immunocompromised patients has been associated with viral colitis, chronic active EBV



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infection, haemophagocytic lymphohistiocytosis, B- or T/NK-cell lymphomas, other malignancies, including nasopharyngeal carcinoma, post-transplant lymphoproliferative disease, gastric adenocarcinoma and autoimmune diseases.

One study reported that 29% of patients between the ages of 18–25 years are seronegative for EBV and at risk of primary EBV infection, which may result in adverse outcomes such as haemophagocytic lymphohistiocytosis.[15] In another large study involving 1582 adult patients, an overall seroprevalence rate of 97.4% dropped to 90.8% in patients younger than 30.[163] Reported risk of lymphoma with use of purine analogues in IBD varies between studies, and one of the large cohorts, CESAME, quoted multivariate HR as 5.28 (95% CI 2.01 to 13.9).[164] That study found that older age, male gender and longer duration positively correlated with lymphoma. In a study involving 17 834 patients with IBD, 92% of patients who developed EBV-positive lymphoma were exposed to purine analogues compared with 19% of patients with EBV-negative lymphomas.[165] Although infliximab and adalimumab have lower risks as monotherapies, combination with purine analogues confers greater risk than purine analogue monotherapy (0.69 and 0.28 per 1000 person-years respectively).[166] Data are limited for newer drugs.

We suggest screening for EBV in patients before starting purine analogues, biologics and small molecule therapies. It should be noted that there is poor concordance between blood and tissue EBV DNA counts.[165] Diagnostic methodologies may change in the future. There is a level of uncertainty relating to what to do with EBV status, so a risk/benefit discussion should be had with individual patients relating to the efficacy of purine analogues especially in ulcerative colitis, anti-TNF therapy in both Crohn's disease and ulcerative colitis, and their perceived risk.

**GPS 26**

We suggest screening for EBV in all patients before starting purine analogues and anti-TNF therapy. In seronegative patients, discussion should be had about choosing other advanced therapies rather than purine analogues and anti-TNF therapy. Patients who are seronegative and in whom purine analogues/anti-TNF therapy is started should be closely monitored should they develop acute EBV infection while receiving this treatment.

### Varicella

In a study involving 108 604 patients with IBD, the incident risk ratio of herpes zoster (HZ) was 1.68 (95% CI 1.60 to 1.76) compared with patients without IBD. Subgroup analysis showed elevated risk with anti-TNF therapy (1.81, 95% CI 1.48 to 2.21), corticosteroids (1.73, 95% CI 1.51 to 1.99), purine analogues (1.85, 95% CI 1.61 to 2.13) and combination therapy (3.29, 95% CI 2.33 to 4.65), which were all independently associated with HZ.[167]

In a post hoc analysis of HZ incidence from the entire tofacitinib ulcerative colitis clinical programme, an overall incident rate (IR) of 3.62 (95% CI 1.33 to 7.88) was shown in the induction cohort vsersu placebo (IR=1.98 95% CI 0.05 to 11.05). In the maintenance cohort, both 10 mg BD (two times a day) and 5 mg BD were associated with increased HZ risk.[168] Elevated risk of HZ have also been shown with newer JAK inhibitors, upadacitinib[169] and filgotinib,[170] although data are limited. HZ reactivation is independent of previous exposure to varicella zoster virus or vaccination.

All patients with IBD should have a thorough history taken about their past medical history of varicella zoster virus and vaccinations.

We recommend serological testing for varicella zoster IgG in patients who do not recollect previous history of varicella before starting any immunosuppressive therapy. Please refer to vaccinations section for seronegative patients.

**GPS 27**

We recommend serological testing for varicella zoster IgG in patients with no previous history of χ before starting any immunosuppressive therapy.

### Hepatitis B and C

In a systematic review and meta-analysis of the prevalence of hepatitis B and C in patients with IBD globally, the overall pooled prevalence of hepatitis B surface antigen was 3.3% (95% CI 2.5 to 4.0) across Europe and Asia, similar to that of the general population. The prevalence of hepatitis B core antibody was 14.2% (95% CI 10.6% to 17.8%), which was higher in patients with IBD than in the general population. Only 35.6% (95% CI 28.7 % to 42.4%) of patients with IBD had effective immunisation against hepatitis B. The prevalence of anti-hepatitis C antibody was 1.8% (95% CI 1.2% to 2.4%), which was not different from that of the general population. Untreated, hepatitis B and C can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma.[171 172] Immunosuppressive therapies carry a risk of reactivation of chronic hepatitis B and C infections; therefore, we recommend screening for both viruses before starting any immunosuppressive therapy, and discussion with hepatology about all patients who are positive for hepatitis B surface antigen and/or hepatitis C antibody.

**GPS 28**

All patients should be screened for hepatitis B and C, before starting any immunosuppressive therapy, and patients who are positive for hepatitis B surface antigen/core antibody and/or hepatitis C antibody should be discussed with the local hepatology team.

### HIV

**GPS 29**

We recommend offering an HIV test to all patients with IBD as a public health measure, and mandating screening for HIV before starting any advance therapy, including corticosteroids. All positive results should be discussed with a dedicated HIV team.

The prevalence of HIV is similar in patients with IBD to that of the general population. Patients with HIV and stable CD4 counts are able to receive immunosuppressive therapies without an increase in opportunistic infections. Data on biologics and HIV have been limited.[173 174]



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### Cervical and anal cancer screening

Incidence of cervical high-grade neoplasia is higher in patients with IBD than in the general population (OR=1.34; 95% CI 1.34 to 1.46),[175] therefore we recommend regular cervical screening for all female patients.

Although the overall incidence of anal cancer is low (0.01–0.02 per 1000 patient years), risk factors have been identified: men who have sex with men, women with cervical dysplasia, and fistula in established (>10 years) perianal Crohn's disease. The incidence can be as high as 0.38 per 1000 years in the last group.[176 177] Although most anal cancers are of squamous cell origin and related to HPV, adenocarcinoma related to anal fistula also develops. In patients with high risk factors, we encourage consideration of referral to a local anal cancer screening programme.

**GPS 30**

All female patients with IBD should be encouraged to take part in national cervical screening and HPV vaccination programme.

### Other drugspecific considerations

#### *Skin cancer*

The use of purine analogues, methotrexate and anti-TNF therapy in patients with IBD has been associated with skin cancers.[178–180] We advise counselling about skin cancer in all patients, and use of sun block when exposed to direct sunlight. Patients who are at increased risk of skin cancers, above and beyond that conveyed by advanced immunosuppressive therapy, such as those who have had previous non-melanoma skin cancers, should have formal skin mapping by a GP or dermatologist.[181]

#### *Cholesterol*

All JAK inhibitors increase both HDL and LDL cholesterol levels. A study looking at tofacitinib has shown that this stabilises after week 8 during 4.4 years of follow-up.[182] This is not associated with any adverse outcome and the clinical significance is still uncertain. We recommend measurement of cholesterol at baseline and after initiation of JAK inhibitors and consideration of statin therapy by primary care clinicians in accordance with best practice.

#### *Venous thromboembolism and major adverse cardiovascular events*

In the ORAL surveillance study, a large cohort of patients with rheumatoid arthritis aged more than 50, and with one risk factor for a cardiovascular event were reported to have higher incidence rates of major adverse cardiovascular events (MACE), deep vein thrombosis (DVT), pulmonary embolism (PE) and venous thromboembolism (VTE) with tofacitinib than TNF inhibitors, with rates for 10 mg bd higher than 5 mg bd.[183] In ulcerative colitis, a post hoc analysis of an ulcerative colitis programme, including one phase 2 and phase 3 OCTAVE trial with open label extension, reported 0.04 events/100 patient-years of exposure (95% CI 0.00 to 0.23) for DVT and 0.16/100 patient-years (95% CI 0.04 to 0.41) for PE with tofacitinib 10 mg bd dose.[184] A subsequent post hoc analysis of the ORAL surveillance study reported differential risks for MACE, DVT, PE and VTE between two groups for tofacitinib compared with anti-TNFs: 'age >65 years and ever smoker' (high-risk group) and 'age <65 years and never smoked' (low-risk group), where the DVT, PE and VTE events were associated with the high-risk groups only.[185] The European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) have therefore advised caution when using JAK inhibitors in patients who are above the age or 65 and/or have one or more cardiovascular risk factor.[186]

#### *Sphingosine-1-phosphate receptor modulators*

Sphingosine-1-phosphate (S1P) receptor modulators have been associated with an increased risk of cardiac arrhythmias, chronic cardiac failure, coronary artery disease, pericarditis and elevated blood pressure. Retrospective analysis from True North, SUNBEAM and RADIANCE trials for ulcerative colitis and multiple sclerosis have shown that cardiac adverse events were low: 1.3% of the total patients experienced bradycardia; other cardiac events occurred in 0.4%; 2 of 882 patients with multiple sclerosis experienced serious cardiac events. We recommend comprehensive history should be taken about cardiovascular risk factors and past medical cardiac problems. S1P receptor modulators are contraindicated in a number of cardiac conditions. An ECG should be taken before starting S1P receptor modulators and should be reviewed for arrhythmias, QT interval and atrioventricular conduction problems. Patients with ECG abnormalities beyond first-degree atrioventricular block or with significant cardiac comorbidities should be discussed with a cardiologist prior to starting S1P receptor modulator modulators. Patients with risk factors or a history of macular oedema should have a baseline ophthalmic examination before, or within a specific time frame of, initiating therapy.

### Vaccinations prior to immunosuppressants

**GPS 31**

Vaccination history should be obtained, and vaccinations updated at diagnosis for all patients with Crohn's disease and patients with moderate to severe ulcerative colitis, and before starting immunomodulator or advanced therapy in all patients. Live vaccines may be administered at least 4 weeks before starting and at a minimum of 3 months after stopping, but not while receiving immunosuppressive therapy.

#### *Non-live vaccines*

Patients with IBD have a greater risk of contracting influenza than non-IBD populations (IR=1.58; 95% CI 1.49 to 1.68) and are more likely to require admission to hospital.[187] Annual influenza vaccination is recommended for all immunosuppressed patients,[188–190] although vaccine efficacy may be reduced, particularly in those receiving anti-TNF therapy and JAK inhibitors.[191] The oral influenza vaccine formulation contains live virus and should be avoided; the non-live injection is favoured instead. Immunosuppressed patients harbour a theoretical risk tof acquiring influenza from household contacts who receive the live attenuated influenza vaccine. However, no cases of transmission have been reported after 10 million doses administered in the UK, and the risk to patients on IBD therapies is therefore likely to be extremely low.[190]

Assessment of hepatitis B serology followed by vaccination for all seronegative patients at diagnosis is recommended in ECCO guidelines. The value of this approach in low prevalence countries has been questioned. In the UK it may be more appropriate to offer vaccines to high-risk groups based on lifestyle, occupation or other high-risk factors.[192] Efficacy of vaccination may be impaired in two situations: during active IBD[193] and during exposure to immunosuppressive drugs.[194 195] Following hepatitis B vaccination, anti-HBs response should be measured



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GPS 32

Patients with IBD receiving immunomodulators or advanced therapies should receive influenza vaccination each autumn, pneumococcal vaccination with a booster after 5 years, and 6month-ly SARS-CoV-2 vaccination adjusted according to the most recent best practice. General advice about vaccination is given below.

⇒ Live vaccines are contraindicated in patients receiving immunosuppressive therapy or with significant protein calorie malnutrition. Live vaccines include BCG, attenuated (oral) influenza, measles, mumps and rubella, oral polio (no longer in routine use in the UK),[767] rotavirus, oral typhoid Ty21a, varicella zoster, yellow fever, live shingles (Zostavax). Immunosuppressive therapies include: corticosteroids (prednisolone ≥20 mg/day or equivalent for 2 weeks or more), purine analogues, methotrexate, biologic and other advanced therapies.

⇒ Immunomodulators should be withheld for 4 weeks after live vaccine administration.

⇒ Live vaccines should be avoided for at least 3 months after discontinuing treatment with the immunosuppressive therapies above.

⇒ Infants exposed to biologics in utero should not receive live vaccines for 12 months after birth (see also 0: Infant vaccinations after exposure to biologics). Live rotavirus vaccine may be provided on schedule to children within utero exposure to anti-TNF.

⇒ Patients with IBD on immunosuppressant therapy should receive pneumococcal vaccine and annual influenza vaccination (before starting treatment if possible) with a single pneumococcal booster at 5 years.

⇒ Recombinant zoster vaccination (Shingrix) should be considered in all patients aged 50 or over receiving any immunomodulators or advanced therapies, and patients aged 18 and over starting JAK inhibitors. All adults aged 50 years and over (regardless of therapy) are now eligible for recombinant zoster vaccination.

⇒ Live varicella vaccination can be considered in patients with IBD with no known history of chickenpox who are varicella antibody negative. Where it is not possible to identify a window of opportunity to administer the vaccine without ongoing immune-modifying therapies, patients should be advised to seek guidance on post-exposure prophylaxis if exposed to active chickenpox or herpes zoster.

as higher doses may be required. Accelerated double-dose vaccination in IBD has been shown to improve response, with double-dose Engerix-B vaccine at 0, 1 and 2 months.[196]Pneumococcal vaccination may also be affected by immunosuppression and should ideally be administered at least 2 weeks before starting immunosuppressive therapy. Three pneumococcal vaccines are licensed in the UK: pneumococcal polysaccharide vaccine (PPV23, containing polysaccharide from 23 capsular types of pneumococcus) and two variants of pneumococcal conjugate vaccine (PCV13 and PCV10, containing polysaccharide from 13 and 10 capsular types of pneumococcus).[197] The current recommendation for adults on immunosuppression is a single dose of PCV13 followed by PPV23 at least 2 months later; however, we recommend reviewing the Green Book for further details. Booster pneumococcal vaccination with PPV23 is recommended after 5 years in patients who are asplenic, hyposplenic or have chronic renal disease. It also seems reasonable to give boosters to patients on long-term immunomodulator and advanced therapy, although there is little evidence in this group.

During earlier phases of the COVID-19 pandemic, the UK government and the BSG recommended that patients on immune-modifying therapies receive three primary doses of SARS-CoV-2 vaccination.[198] These patients continue to be recommended 6-monthly booster doses in seasonal spring and autumn campaigns. Household contacts aged 12 to 64 of immunosuppressed patients have also been eligible for the autumn booster. If a patient who is unvaccinated starts immune-modifying therapies, they should be offered two doses of a SARS-CoV-2 vaccine, 3 months apart, before receiving their regular boosters via the seasonal campaign.[199] These recommendations reflect the impact of immune-modifying therapies, particularly anti-TNFs and JAK inhibitors, on both serological and clinical responses to SARS-CoV-2 vaccines.[200 201]

Herpes zoster can cause serious complications as well as long-term sequelae. In a meta-analysis, JAK inhibitors, in particular, seemed to increase the risk of zoster.[202] The Green Book recommends vaccination with the recombinant zoster vaccine (Shingrix) at age 60 for all adults, as well as from 50 for those on immunosuppressive therapies.[199] There is no current UK recommendation for vaccination in most patients under the age of 50, although the ECCO guidelines recommend recombinant zoster vaccine in all patients receiving immunosuppressive therapy.[203] The UK Joint Committee on Vaccination and Immunisation has broadened the eligibility for the vaccination programme for the Shingrix recombinant herpes zoster vaccine (GlaxoSmithKline, London, UK) to include all severely immunosuppressed adults aged 18 years and older in the UK.[204]

Clinicians may wish to discuss recombinant zoster vaccine in patients aged between 18 and 49 who have started or are planning to start JAK inhibitors or S1P modulators, in view of the particular increased risk with this class of therapy.[202]

### *Live vaccines*

The UK Department of Health currently recommends a 4week-window between live vaccination and starting immunosuppressive or biologics therapy to allow establishment of an immune response.[205] Live vaccination should be avoided during biologics therapy and for a minimum of 3 months after stopping,[206–208] although the evidence to support the 3-month period is lacking; drug blood levels will be minimal by at the early stage of therapy, but this may still alter white cell populations, with persistent subtle effects on immunity.

Live varicella vaccination can be considered for patients without a history of chickenpox and who are varicella antibody negative. In practice the timing of this can be difficult in view of the need to avoid use of immune-modifying therapies (including corticosteroids) on either side of the course of two doses. If a suitable window of time cannot be identified for vaccination, patients with IBD starting immune-modifying therapies should be advised to avoid contact with people with active chickenpox or herpes zoster and to seek guidance on post-exposure prophylaxis if exposed to active chickenpox or herpes zoster in accordance with the Green Book chapter 34.[209] Current UK guidelines recommend aciclovir in this situation rather than varicella immunoglobulin, with a 7-day course starting 7 days after the exposure.[205]



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## ULCERATIVE COLITIS

The treatment of ulcerative colitis is guided mainly by disease location and severity.

Ulcerative proctitis is treated with topical 5-ASA therapy. For patients who do not respond, or if treatment is not tolerated, oral 5-ASA or topical corticosteroids are added or substituted. Refractory proctitis might require oral corticosteroids, topical tacrolimus, JAK inhibitors, S1P agonists or biologic therapy.

Mild to moderate ulcerative colitis extending beyond the rectum is treated with oral 5-ASA, which can be combined with topical 5-ASA therapy. If a response to treatment is not achieved within 2–4 weeks, oral corticosteroids should be initiated. If response is achieved, maintenance therapy with 5-ASA should be continued.

Prednisolone is recommended for induction of remission in moderate to severe ulcerative colitis and should be combined with 5-ASA. High-dose 5-ASA alone can be considered, but corticosteroids should be initiated if there is no response within 2 weeks.

Advanced therapy (biologic and small molecule drugs) should be started if there is no adequate response to oral corticosteroids within 2 weeks, if the corticosteroid taper is unsuccessful, or to avoid repeated courses of corticosteroids. To avoid long-term disease complications, the overall treatment goal in ulcerative colitis has shifted from achieving clinical response to achieving remission and should be assessed biochemically or endoscopically and histologically. Maintenance therapy should be continued with the agent successful in achieving induction, with the important exception that corticosteroids are not recommended for long-term maintenance. For maintenance, purine analogues can be used, but usually require induction with another agent, often a corticosteroid. They are also suggested alongside infliximab therapy.

The increasing number of effective ulcerative colitis treatments has complicated treatment selection, and the choice of advanced therapy requires consideration of patient and disease factors and prior treatment history. It is also dependent on local availability and reimbursement pathways.

### Use of steroids in ulcerative colitis

Grade statement: Prednisolone

**Summary of evidence:** This study comprised 210 patients with active disease or relapse randomised to cortisone or placebo. The cortisone doses were as follows: 100 mg a day for 6 weeks in 38 patients, 100 mg a day for 2–3 weeks followed by smaller doses of 50–75 mg a day in 38 patients, doses exceeding 100 mg a day in 17 patients. All patients had treatment for a total of 6 weeks, with 16 patients receiving cortisone for less than 6 weeks. 25 mg of cortisone acetate is equivalent to 5 mg of prednisolone.[210] The primary outcome was clinical remission defined as one or two stools per day with no rectal bleeding.

**Efficacy induction:** At the end of the induction period, 41.3% of patients randomised to cortisone were in remission, 27.5% improved and 31.2% showed no improvement. Treatment was effective in initial presentations and relapses of existing disease. Please see table 7 for estimated time to treatment goals for oral corticosteroids.

**Certainty and rationale:** In a meta-analysis of five randomised controlled trials, corticosteroids were superior to placebo for inducing remission in ulcerative colitis (RR of no remission 0.65; 95% CI 0.45 to 0.93).[211] Although uncertainty exists regarding the optimal dose and regimen for systemic corticosteroids in ulcerative colitis, a 40 mg/day dose of prednisolone was found to be more effective than a 20 mg/day dose. Evidence suggests no additional benefit with doses higher than 40–60 mg/day, with potential for increased adverse effects. The regimen should be tailored based on individual patient factors, with careful

**Prednisolone is recommended for induction of remission in moderate to severe ulcerative colitis**

Recommendation: **strong**. Overall certainty: **very low**. Overall magnitude: **not available**.

**Justification**: Despite the relative lack of robust trial evidence, with just two RCTs,[290 287 768] prednisolone has been extensively used in the clinical management of ulcerative colitis flares. Its efficacy in inducing remission and ameliorating symptoms is well-documented in clinical practice. Prednisolone may be used as a step-down therapy following response to initial intravenous corticosteroids, or as an addition to current ulcerative colitis therapy in the presence of inflammation. The GDG therefore made a strong recommendation in the absence of these RCT data using the expert consensus approach.

Owing to a lack of trial data, the optimal prednisolone dosing regimen is not validated, but a commonly uses regimen is a starting dose of 40 mg daily followed by dose reduction of ulcerative colitis 5 mg per week to 0 mg.

**Implementation considerations:** Systemic corticosteroid treatment is associated with adverse effects, including immunosuppression, osteoporosis, glucose intolerance and mood disturbances. Tailored prednisolone weaning protocols may be required depending on comorbidities (such as diabetes, mental health issues, adrenal suppression) and experienced adverse effects (such as glucose intolerance, mood changes, sleep disturbances). Once-daily prednisolone dosing is recommended, preferably in the morning and with food to prevent sleep disturbances and mitigate dyspepsia. Calcium and vitamin D supplementation are recommended for bone protection unless contraindicated, and in those over 65 years risk of fracture should be estimated and oral bisphosphonate considered.[769] For dyspepsia, concomitant supportive therapies can be started, such as proton pump inhibitors (PPIs) unless contraindicated.

**Beclomethasone dipropionate is suggested for induction of remission in patients with ulcerative colitis where 5-ASA therapy fails or is not tolerated, and who wish to avoid more potent systemic corticosteroids.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Small**.

**Justification:** The use of beclomethasone dipropionate (BDP) in the clinical management of mild to moderate ulcerative colitis, is based on the evidence from five RCTs. Beclomethasone has potent topical effect, with high first-pass metabolism, therefore, considered low risk compared with conventional corticosteroids. Its efficacy in inducing remission and ameliorating symptoms is modest compared with placebo, and similar to 5-ASA.

**Implementation considerations:** 5 mg/day prolonged release tablet once a day for 4 weeks was most commonly assessed dosing schedule in clinical trial GRADE statements, and there was no difference between 5 mg/day and 10 mg/day doses. Therefore 5 mg/day dosing schedule is recommended.



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consideration given to minimising adverse effects and ensuring a gradual tapering schedule to optimise outcomes.

### GRADE statement: Beclomethasone dipropionate

**Summary of evidence**: There are four RCTs comparing BDP with placebo or 5-ASAs available, and one RCT comparing BDP and prednisone in mild to moderate ulcerative colitis for induction of clinical and endoscopic outcomes. A recent meta-analysis summarised available evidence on efficacy and safety of BDP compared with placebo or 5-ASAs.[212]

**Efficacy induction**: On analysis, both BDP 5 mg (OR2.36, 95% CI 1.37 to 4.08) and BDP 10 mg (OR=2.23, 95% CI 1.02 to 4.87) were more effective than placebo for inducing clinical remission or improvement. One trial compared BDP 5 mg with placebo, demonstrating the superiority of the intervention arm (OR=2.70, 95% CI 1.28 to 5.67) in inducing endoscopic remission. No differences were found between 5-ASA and BDP 5 mg (OR=0.90, 95% CI 0.51 to 1.57) or BDP 10 mg (OR=1.54, 95% CI 0.42 to 5.64). On analysis of safety outcomes, BDP 5 mg was not associated with increased adverse events compared with placebo (OR=0.51, 95% CI 0.21 to 1.24). Similarly, BDP 5 mg was not associated with increased withdrawals compared with placebo or budesonide MMX or 5-ASA. One RCT compared efficacy of BDP 5 mg and prednisone in mild to moderate ulcerative colitis, in which 64.6% of patients receiving BDP achieved response compared with 66.2% with prednisone (p=0.78) at week 4, demonstrating non-inferiority.[213] Similar rates of adverse events were observed with both interventions (38.7% vs 46.9%, p=0.17).

**Efficacy maintenance**: No data are available for maintenance of clinical remission.

**Certainty and rationale**: Meta-analysis of four RCTs showed BDP 5 mg is superior to placebo but as effective as 5-ASAs and there was no difference between 5 mg and 10 mg doses. All studies assessed in mild to moderate ulcerative colitis for a duration of 4 weeks. BDP is associated with high first-pass metabolism and considered low risk. Available evidence suggests that BDP 5 mg has similar efficacy to 5-ASA or prednisolone in mild to moderate ulcerative colitis. Therefore, can be considered in the short term to induce clinical remission.

Budesonide MMX is suggested for the induction of remission in mild to moderate ulcerative colitis in patients for whom 5-ASA induction therapy fails or is not tolerated, and who wish to avoid more potent systemic corticosteroids.

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Trivial**.

**Justification:** The overall certainty is moderate for trivial effect on inducing remission with budesonide MMX versus placebo, with in subgroup analysis showing higher efficacy in patients with left-sided disease. The certainty is low for no difference in efficacy between budesonide MMX and oral 5-ASA. Considering the favourable adverse effect profile, budesonide MMX is suggested for induction of remission in patients with mild to moderate ulcerative colitis, where oral 5-ASA has failed or is not tolerated, or when more potent systemic corticosteroids should be avoided.

**Implementation considerations:** In subgroup analysis, the efficacy was highest in patients with left-sided disease. The cost is higher than for 5-ASA, while the efficacy of the two agents is equal (low certainty). In the UK, access to the treatment varies by region, with some commissioning groups excluding budesonide MMX owing to expense and lack of greater efficacy data. Alternatively, beclomethasone dipropionate can be used, which has also been shown to be more effective than placebo.[213 770 771]

### GRADE statement: Budesonide MMX

**Summary of evidence**: Included in the Cochrane systematic review are two RCTs comparing budesonide MMX 9 mg vs 5-ASA, and six RCTs comparing budesonide MMX 9 mg vs placebo. In terms of achieving clinical remission or improvement, budesonide MMX 9 mg was more effective than placebo; Budesonide MMX 9 mg daily was superior to placebo for inducing remission at 8 weeks. Fifteen per cent (71/462) of patients in the budesonide MMX 9 mg group achieved remission compared with 7% (30/438) placebo patients (RR2.25, 95% CI 1.50 to 3.39). Overall, budesonide MMX was considered safe and well tolerated. The GRADE summary of findings is in online supplemental appendix 4, table 1.

**Efficacy induction**: The evidence showed, with moderate certainty, that budesonide MMX has a trivial magnitude of effect compared with placebo in induction of remission (combined clinical and endoscopic). However, there were no differences in effect when compared with oral 5-ASA therapy.

**Efficacy maintenance**: No evidence is available.

**Certainty and rationale**: For induction of clinical remission, there is low certainty for no difference in efficacy compared with oral 5-ASA therapy and moderate certainty that budesonide MMX has a trivial magnitude of effect compared with placebo. In subgroup analysis the efficacy was highest in patients with left-sided disease. Budesonide MMX has a good safety profile and is well tolerated. Budesonide MMX is therefore suggested for induction of remission in patients with mild to moderate ulcerative colitis where 5-ASA therapy is ineffective or not tolerated, or when systemic corticosteroids are to be avoided.

## 5-ASA in ulcerative colitis

5-AsaSAs are recommended for induction and maintenance of remission in patients with mild to moderate ulcerative colitis.

Recommendation: **Strong**. Overall certainty: **High**. Overall magnitude: **High**.

**Justification:** 5-ASAs are a widely available and generally well tolerated medication. The choice of 5-ASA should be determined by local access, disease location, patient preference (eg, tablets vs granules) and cost. The lowest effective maintenance dose should be used, and/or topical therapy as appropriate.

In routine practice, 5-ASAs are the entry treatment for mild to moderate ulcerative colitis. A 5-ASA dose of ≥2 g/day is recommended to induce and maintain remission in patients with mild to moderate ulcerative colitis. Once-daily adequate dosing is as effective as divided dose regimens to induce and maintain remission. Although there is no prospective RCT evidence for use of high-dose 5-ASA from outset, for patients with more severe disease or for patients not responding to conventional doses of 5-ASA (1.5–2.4 g/day depending on formulation) higher doses (3–4.8 g/day) might be used until remission is induced. Combining oral and topical 5-ASA to induce remission for active disease may have better efficacy than monotherapy with oral 5-ASA alone.



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GRADE statement: 5-ASAs

**Summary of evidence**: A Cochrane review[214] of induction remission included 54 randomised trials with a total of 9612 people taking part. Most studies were rated at low risk of bias. A Cochrane review[215] of maintenance identified 44 studies (9967 participants). Most studies were at low risk of bias. Both studies included only patients with mild to moderate disease (as defined by Truelove and Witt criteria). The GRADE summary of findings is in online supplemental appendix 4, table 2.

**Efficacy induction**: The Cochrane review found 71% (1107/1550) of 5-ASA-exposed participants did not enter clinical remission compared with 83% (695/837) of placebo participants (RR0.86, 95% CI 0.82 to 0.89; 2387 participants, 11 studies; high-certainty evidence). There was no evidence of a difference in the incidence of adverse events and serious adverse events between 5-ASA and placebo, once-daily and conventional doses of 5-ASA, and 5-ASA and comparator 5-ASA formulation studies. Common adverse events included flatulence, abdominal pain, nausea, diarrhoea, headache and worsening ulcerative colitis. The Cochrane review suggested that once-daily dosing was as effective as conventional dosing (two or three times per day). Please see table 7 for estimated time to treatment goals for 5ASAs.

**Efficacy maintenance**: 5-ASAs were found to be more effective than placebo for maintenance of clinical or endoscopic remission. About 37% (335/907) of 5-ASA participants relapsed at 6 to 12 months compared with 55% (355/648) of placebo participants (RR=0.68, 95% CI 0.61 to 0.76; eight studies, 1555 participants; high-certainty evidence). The Cochrane review suggested that once-daily dosing was as effective as conventional dosing (two or three times per day)

It was noted 3% (41/1587) of participants in the once-daily group experienced a serious adverse effect (SAE) compared with 2% (35/1609) of participants in the conventional-dose group at 6 to 12 months (RR=1.20, 95% CI 0.77 to 1.87; moderate-certainty evidence).

**Certainty and rationale**: Moderate to high certainty of evidence that the magnitude of effect of induction with 5-ASAs is moderate for clinical response, clinical remission and endoscopic improvement, while the magnitude of effect of maintenance with 5-ASAs is moderate for clinical remission and endoscopic remission. The targeted population receiving this therapy were patients with mild to moderate ulcerative colitis.

## WITHDRAWAL OF 5-ASAS IN ULCERATIVE COLITIS

**GPS 33**

We suggest that patients with ulcerative colitis who have achieved prolonged remission and mucosal healing with biologic agents and/or immunomodulators or JAK inhibitors can discontinue their 5-ASAs.

**GPS 34**

We suggest that when monotherapy mesalazine is prescribed as treatment for ulcerative colitis it may also have a chemo preventative effect. It is not clear whether there is an additional chemo preventative effect with mesalazine for patients with ulcerative colitis receiving advanced therapies, where the mesalazine is not needed for control of inflammation.

5-ASA medications are typically used as a first-line treatment for mild to moderate ulcerative colitis. More severe disease is treated with biologic agents, immunomodulators and JAK inhibitors. Several arguments support withdrawal of 5-ASAs when mucosal healing is achieved with these agents. First, mucosal healing suggests effective resolution of underlying inflammation, mitigating the need for the additional anti-inflammatory effects of 5-ASA. Second, 5-ASA medications can cause adverse effects such as gastrointestinal symptoms, allergic reactions and interstitial nephritis. By discontinuing 5-ASAs, risks of side effects and overall medication burden is reduced for patients. A prospective randomised observer-blind 2-year-trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis found that the relapse rate in the patients receiving azathioprine alone was 19%, whereas the combination therapy group showed a relapse rate of 18%, which was not statistically significant. There were no significant differences between groups in time to relapse or discontinuation of treatment, clinical activity and quality of life score. However, the number of adverse events and the treatment costs were significantly higher, with poorer treatment compliance in the combination therapy.[216]

A pooled analysis of individual participant data from clinical trials found no benefit of concomitant 5-ASA in patients with moderate to severe ulcerative colitis escalated to biologic therapy. A total of 2183 patients were treated with infliximab or golimumab. Concomitant use of 5-ASA was not associated with odds of achieving clinical remission (adjusted OR=0.67 (95% CI 0.45 to 1.01), p=0.06), clinical response (aOR=0.89 (95% CI 0.60 to 1.33), p=0.58) or mucosal healing (aOR=1.12 (95% CI 0.82 to 1.51), p=0.48).[217]

An analysis of two nationwide population-based cohorts compared clinical outcomes in 3589 patients with ulcerative colitis already receiving 5-ASA, who started anti-TNF and then either stopped or continued 5-ASA. The authors found that stopping 5-ASA after initiating anti-TNF was not associated with an increased risk of adverse clinical events (aHR=1.04 (95% CI 0.90 to 1.21), p=0.57) in the US population and aHR=1.09 (95% CI 0.80 to 1.49), p=0.60).[218] Similarly, a further nationwide population-based study of 2963 patients with ulcerative colitis from Korea demonstrated that discontinuation of 5-ASA after initiating anti TNF was not associated with adverse clinical events, including intestinal surgery, hospitalisation and new corticosteroid use (aHR=0.996 (95% CI 0.85 to 1.16)).[219] The IBD CRC Surveillance Guidelines present GPS on chemo prevention.[104]

## IMMUNOMODULATORS IN ULCERATIVE COLITIS

GRADE statement: Methotrexate

**Summary of evidence**: Two studies (n=101 patients) were included in the most recent Cochrane review.[220] One study (n=67) compared oral methotrexate (12.5 mg/week) with placebo. The other study (n=32) compared oral methotrexate (15 mg/week) with mercaptopurine (1.5 mg/kg/day) and 5-ASA (3 g/day). The placebo-controlled study was judged to be at low risk of bias. The other study was judged to be at high risk of bias due to an open-label design.[221] The GRADE summary of findings is in online supplemental appendix 4, GRADE table 3.

**Efficacy induction**: There was no statistically significant difference in clinical remission rates between patients receiving methotrexate and those receiving a placebo (RR=1.19, 95% CI 0.72 to 1.96). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was low due to very sparse data (32 events).



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Methotrexate is not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Trivial**.

**Justification**: Although methotrexate was tolerated, the studies showed no benefit for methotrexate over placebo for induction of remission in ulcerative colitis. The results for efficacy outcomes between methotrexate and placebo are of low certainty.[220]

**Implementation considerations**: For patients already receiving methotrexate as monotherapy in this context, a discussion should be held to reach a shared decision before any change in therapy is made. Methotrexate may continue to have a role in combination with an anti-TNFα monoclonal antibody in reducing immunogenicity in those patients who have contraindications or are intolerant to a purine analogue. Female patients of childbearing age should be advised about the risk of teratogenicity when prescribed methotrexate and advised to use suitable contraception.[220]

**Efficacy maintenance**: There was no statistically significant difference in the proportion of patients who maintained remission (RR=1.06; 95% CI 0.79 to 1.43). A GRADE analysis indicated that the quality of evidence is low due to very sparse data.

**Certainty and rationale**: There may be no difference between methotrexate and placebo in the induction and maintenance of remission of ulcerative colitis (low certainty), so its use as monotherapy in ulcerative colitis is not recommended. As a cost-effective, widely available drug, and generally well tolerated, particularly when used in subcutaneous form, methotrexate (10–12.5 mg/week)[222] may have a role as an immunomodulator to reduce immunogenicity of anti-TNF therapies. There are even fewer data sources to assess this, as purine analogues are more widely used as first-line immunomodulator therapy, with a switch to methotrexate if appropriate when purine analogues are not tolerated or contraindicated. Methotrexate is contraindicated for women who are actively family planning due to the very high risk of miscarriage and teratogenicity.

The GDG supports individualised patient discussion for patients currently established on methotrexate, and consideration of planned withdrawal as remission may be spontaneously maintained with 5-ASA monotherapy.

## GRADE STATEMENT: PURINE ANALOGUES

**Summary of evidence**: The evidence for induction is limited with a review including four RCT,s all more than 20 years old. A Cochrane review for maintenance included seven RCTs with 302 patients with risk of bias high in three studies.[223] The GRADE summary of findings is in online supplemental appendix 4, GRADE table 4.

**Efficacy induction**: Meta-analysis[224] did not allow any conclusions to be drawn (RR1.59, 95% CI 0.59 to 4.29, very low certainty, downgraded owing to very serious concerns with imprecision, heterogeneity and risk of bias).

**Efficacy maintenance**: Purine analogues may be more effective at maintaining remission, with 51/115 patients exposed to purine analogues failing to maintain remission compared with 76/117 placebo patients (four studies, 232 patients; RR=0.68, 95% CI 0.54 to 0.86, low due to risk of bias and imprecision (sparse data)). Adverse events related to study medication included acute pancreatitis (three cases, plus one case on ciclosporin) and significant bone marrow suppression (five cases). Please see table 7 for estimated time to treatment goals for purine analogues.

Purine analogues are not suggested for induction of remission but are suggested for maintenance of remission for patients with moderate to severe ulcerative colitis, once remission is achieved

⇒ Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Trivial induction, moderate**. **maintenance**.

⇒ **Justification**: The overall certainty is low, for no benefit in induction and a moderate magnitude benefit for maintenance of remission. Purine analogues are inexpensive, widely available, once established can be prescribed by general practice and generally well tolerated, with extensive real-world experience 0f their use.

⇒ **Implementation consideration**: Purine analogues have slow onset of action and require a bridging agent, usually corticosteroids. There is a significant intolerance rate, including pancreatitis. There is also significant risk of myelosuppression, and frequent blood test monitoring including for individualised dose optimisation, is required. Increased risk of malignancy with long-term use requires shared decision-making regarding duration of use, and clearly this must consider the risks with alternative therapies in a balanced fashion. Purine analogues may play a role as concomitant medication with anti-TNFs to prevent immunogenicity and may be given with allopurinol in cases of toxicity.[541]225

**Certainty and rationale**: There is low certainty that purine analogues are no better than placebo at induction of remission in ulcerative colitis. There is low certainty with a trivial to moderate magnitude that purine analogues may be better than placebo at maintenance of clinical remission, where a bridging agent has induced remission.

Purine analogues are cost-effective, widely available, once established may be prescribed by general practice and generally well tolerated, with extensive real-world experience. Despite attempts to reduce risk by pre-emptive TPMT±NUDT15 testing, when they occur, significant side effects, although rare, may cause significant morbidity, such as pancreatitis and increased risk of malignancy, which are pertinent to our ageing and comorbid patient populations.

Monitoring for purine analogues should be continued throughout use, as the risk of hepatotoxicity and myelosuppression persists, particularly in patients with polypharmacy. The use of purine analogue metabolite monitoring for individualised dose optimisation is encouraged, particularly when co-prescribed with allopurinol.

The duration of a clinical trial follow-up is not sufficient to capture longer-term risks associated with purine analogues, including malignancy. For this reason, real-world data have been evaluated to assess the long-term safety of thiopurine use.

A meta-analysis of two prospective and two retrospective large observational cohorts, comprising 61 794 patients who received purine analogues compared with 165 867 unexposed, demonstrated pooled incident rate ratio (IRR) (per 1000 patient-years) of lymphoma to be 2.23 (95% CI 1.79 to 2.79; p<0.001) with purine analogue exposure.[225] A French nationwide cohort study, including 50 405 patients exposed to purine analogues, with a median follow-up of 6.7 years, yielded an adjusted hazard ratio



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(aHR) for lymphoma of 2.60 (95% CI 1.96 to 3.44; p<0.001).[166] A second meta-analysis identified 18 relevant studies and calculated a standardised incidence ratio (SIR) of lymphoma to be 2.80 (95% CI 1.82 to 4.32) in eight population studies and 9.24 (95% CI 4.69 to 18.2) in 10 referral studies.[226] This study also demonstrated the highest relative risk in men under 30 (SIR=6.99; 95% CI 2.99 to 16.4), but the highest absolute risk in patients over 50 years of age (1:354 cases per patient-year, with a relative risk of 4.78). In addition to lymphoproliferative disorders, purine analogues have been associated with increased incidence of urinary tract cancer and non-melanomatous skin cancer.[179 227–229] Meta-analysis and systematic review of 13 studies and 149 198 participants revealed relative risk (RR) of non-melanoma skin cancer associated with purine analogue use to be 1.88 (95% CI 1.48 to 2.38, p<0.001).[230]

The slow onset of action and risks of side effects are reflected by common practice, where it is used as dual therapy as an exit strategy for maintenance after induction of remission with corticosteroids or other agents, or maintenance of remission in those with a high risk of relapse. The duration of use of purine analogues needs to be determined by individualised shared decision-making to ensure benefits continue to outweigh cumulative risks. The role for purine analogues to reduce immunogenicity risk when used in combination therapy with biologics is considered in other sections.

### Withdrawal of purine analogue therapy in ulcerative colitis

GPS 35

Withdrawal of purine analogues as monotherapy or combination therapy in ulcerative colitis is associated with a risk of relapse. Shared decision-making should be undertaken in the light of the long-term risks of continuing purine analogues, including elevated risk of lymphoproliferative disorders, non-melanoma skin cancers, myeloid disorders and urinary tract cancers.

A historical RCT study in 1992[231] assessed withdrawal of azathioprine monotherapy in ulcerative colitis, wherein 79 patients with ulcerative colitis treated with azathioprine for at least 6 months were randomised to placebo or azathioprine. Patients in remission for 2 months or more and patients with chronic or steroid-dependent disease were randomised separately. In the remission group (n=67), 35% of the azathioprine group relapsed at 1 year versus 59% in the placebo group, (p=0.01). Subgroup analysis of patients (n=54) who had been in more prolonged remission (> 6 months) identified 31% relapse in the azathioprine group versus 61% in the placebo group at 1 year, demonstrating that continuing treatment in those in remission has benefit. Within the smaller chronic or steroid- dependent group (n=12), no benefit was found in continuing azathioprine treatment.

A 2015 systematic review[232] summarised the published data on purine analogues withdrawal for patients in clinical remission. Relapse rates were higher among patients randomised to withdrawal at 12 months; relapse rates ranged from 11% to 77%.

An open-label,[233] prospective and randomised clinical trial in a population of 81 patients receiving azathioprine combination therapy for ulcerative colitis or Crohn's disease compared the effects of azathioprine withdrawal on durable remission of at least 6 months (36 with ulcerative colitis). Three groups were randomised to steady-dose azathioprine versus half-dose azathioprine versus azathioprine withdrawal. At 1 year the ulcerative colitis subgroup showed no significant difference between the groups with regard to clinical outcome, with a Mayo subscore equivalent across the three groups (p=0.25). However, the azathioprine half-dose group had higher infliximab trough levels and lower antibody formation rates than the azathioprine withdrawal group, suggesting some benefit from combination therapy.

## ADVANCED THERAPIES IN ULCERATIVE COLITIS

### GRADE statement: Infliximab

**Summary of evidence**: The two RCTs[236] are subject to concerns over the outcome measurement timing. Maintenance data could not be included in the network meta-analyses (NMA) because week 30 and 54 study phases were treat-through design, whereas the datasets for the maintenance NMA were acquired from re-randomised maintenance studies.[236] The average proportion of patients receiving concomitant immunomodulators was 46% (42–55% in the different study arms). The GRADE summary of findings is in online supplemental appendix 4, GRADE table 5.

**Efficacy induction**: The two RCTs included a total of 728 participants receiving infliximab 5 mg/kg (n=242), infliximab 10 mg/kg (n=242), or placebo (n=124).[236] All patients were biologic-naive. At week 8, clinical remission rates in patients receiving infliximab 5 mg/kg and 10 mg/kg were 39% and 34% (vs 15% and 6% for placebo, respectively). Clinical response in patients receiving infliximab 5 mg/kg and 10 mg/kg was 69% and 64% (vs 37% and 29% placebo, respectively; p<0.001 for both comparisons). Endoscopic remission rates for infliximab 5 mg/kg and 10 mg/kg were 62% and 60% (vs 34% and 31% placebo), respectively. Please see table 7 for estimated time to treatment goals for infliximab.

**Infliximab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Small**.

**Justification**: The recommendation is made based on the NMA for induction, RCT data and extensive clinician experience from widespread use. Maintenance NMA data are lacking, as the ACT2 treat-through trial could not be included in our analyses, but this is a widely used biologic agent with extensive clinician experience from widespread use.

**Implementation considerations**: Most data are derived from dosing at 5 mg/kg. Evidence is of very low and low certainty for 10 mg/kg due to imprecision, but the magnitude is similar. RCT data of escalation of dosing are not available, but this is common practice. As such, this can be considered as part of shared decision-making when considering response to 5 mg/kg is ineffective or in cases of severe disease. It is common practice to concomitantly treat with an immunomodulator. at least until remission has been achieved.

Subcutaneous infliximab for maintenance can be used instead of intravenous infusions. In an open-label, randomised study the efficacy, safety, and immunogenicity outcomes did not differ between patients with IBD patients receiving intravenous versus subcutaneous biosimilar infliximab.[234] Subcutaneous injections are well accepted by patients and have resource advantages.[235]



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In the NMA, the certainty was moderate for a small benefit in clinical remission, the certainty was high for a moderate benefit for clinic response and the certainty was moderate for a moderate benefit for endoscopic improvement with infliximab 5 mg/kg over placebo.

**Efficacy maintenance**: The ACT 1 study randomised 364 patients to receive placebo (n=121), 5 mg/kg of infliximab (n=121) or 10 mg/kg of infliximab (n=122). For the 5 mg/kg dose, the week 54 sustained response rate was 39% (14% placebo) and sustained remission rate 20% (6% placebo).[236]

**Certainty and rationale**: The NMA data show, with moderate certainty, that infliximab has small efficacy for induction of remission in ulcerative colitis. After considering maintenance data from RCTs and extensive clinical experience, infliximab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. Superiority of infliximab 10 mg/kg over 5 mg/kg in the two RCTs and the NMA was not demonstrated. However, in these studies, patient selection for the 10 mg/kg was random, unlike in clinical practice where decision-making for dose escalation is guided by a lack of optimal response and/or therapeutic drug monitoring. This approach is embedded in routine clinical practice and thus is supported by the GDG.

As with purine analogues, risks of infliximab monotherapy may extend beyond the trial study period, with systematic review and meta-analysis of real world data largely combining anti-TNF therapy for analysis. The systematic review with meta-analysis of Chupin *et al*, which included 261 689 patients with IBD from four high-quality observational studies, demonstrated that the pooled IRR (per 1000 patient-years) of lymphoma in patients receiving anti-TNF monotherapy was 2.23 (95% CI 1.79 to 2.79; p<0.001), statistically comparable with those exposed to thiopurine (pooled IRR of 0.72 (95% CI 0.48 to 1.07; p=0.107).[225] These findings were consistent with an earlier meta-analysis of 26 studies, comprising over 21 178 years of patient follow-up.[237] A French National cohort study also found an increased risk of lymphoma with exposure to anti-TNF monotherapy, aHR=2.41 (95% CI 1.60 to 3.64).[166] However, interpretation of magnitude of risk from real-world data is challenging, as many patients included within the meta-analyses were exposed to thiopurines prior to receiving anti-TNF.

Associations between anti-TNF therapy and melanoma from real-world data have been identified, but are inconsistent. A large case-control study of 10 879 patients with IBD receiving either anti-TNF or natalizumab demonstrated an association with melanoma in Crohn's disease (OR=1.94 (95% CI 1.03 to 3.68), but this did not reach significance in ulcerative colitis.[180] However, this finding has not been replicated in other studies, with a meta-analyses published in 2020, including 7901 patients receiving anti-TNF, failing to demonstrate a significant association, pooled RR (pRR) 1.20 (95% CI 0.60 to 2.40).[238]

## GRADE STATEMENT: GOLIMUMAB

**Summary of evidence**: Only one study was included in the NMA for the induction of remission in ulcerative colitis.[239] There are some concerns with the reporting of this study in relation to the measurement of outcomes. There are no further concerns with risk of bias. Two studies were included in the NMA for the maintenance of remission of ulcerative colitis. One enrolled treatment-responders from the induction study[240]; the second, was a maintenance study in Japan following open-label induction.[241] There are some concerns regarding the risk of bias due to measurement of outcomes, for both maintenance studies. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 6.

**Golimumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Small**.

**Justification**: The overall certainty is low, for small magnitude of effects in induction and maintenance over placebo. There are no unfavourable safety outcomes.

**Implementation considerations**: The NMA evidence is very uncertain regarding the safety outcomes for golimumab compared with placebo, but other medications are widely available, low safety risk and used frequently in real-world practice, provided that best practice baseline screening procedures are undertaken.

**Efficacy induction**: This study included a total of 516 participants, 258 participants were randomised to golimumab therapy while 258 were randomised to placebo. Nearly a third (29.5%) of participants were co-prescribed immunomodulator therapy.

**Efficacy maintenance**: There were data from 527 participants in total, with up to 31%[240] and 50%[241] of participants taking concurrent immunomodulator therapy in the two studies.

**Certainty and rationale**: Based on one study included in the NMA for induction and two studies for maintenance, the overall certainty of the efficacy outcomes for induction and maintenance were low. The overall magnitude of effect was small. Although of very low certainty, the favourable safety outcomes (no difference compared with placebo) and clinician experience from use of anti-TNFs, make golimumab a suitable option for moderate to severe ulcerative colitis. However, lack of long-term studies to demonstrate efficacy and safety should be considered when deciding on this therapy.

## GRADE STATEMENT: ADALIMUMAB

**Summary of evidence**: Four RCTs were included in the NMA, with a total of 1917 participants. The average proportion of patients receiving concomitant immunomodulators was 40.7% (24–59%). There were some concerns over measurement of the outcomes in one study[242] and over missing outcomes data in a second study.[242] No maintenance data could be included in the NMA because the maintenance studies ULTRA 2[243] maintenance arm and a separate phase II/III Japanese study[242] were treat-through studies, whereas the datasets for the maintenance NMA were acquired from re-randomised maintenance studies The SERENE ulcerative colitis study[244] compared higher versus standard induction and did not have a placebo arm. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 7.

**Efficacy induction**: In NMA the certainty was low for a trivial benefit for clinical remission, clinical response and endoscopic improvement with induction with standard dosing adalimumab (160/80 mg at week 0 and 2 then 40 mg every other week) over placebo. For the higher induction dosing of 160 mg at weeks 0, 1, 2, and 3; then 40 mg at weeks 4 and 6, the certainty was low for a small benefit for clinical response at week 8. The other outcomes were no different from standard dosing. Please see table 7 for estimated time to treatment goals for adalimumab.



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**Adalimumab is not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Trivial**.

**Justification**: The magnitude of effect of induction with standard dose adalimumab is trivial for clinical response, clinical remission and endoscopic improvement. Because treatments with higher magnitude of effect are available, adalimumab is not suggested as standard treatment for induction of remission in moderate to severe ulcerative colitis.

**Implementation considerations**: Adalimumab has a low-risk safety profile, is easily available and has been widely used by clinicians. Patients already receiving adalimumab should not have their treatment stopped, but a discussion with shared decision-making should be undertaken before any changes are made. Additionally, there may be situations where adalimumab may be considered, such as access issues, patient choice, mixed disease phenotype, including extraintestinal manifestations, or multiple immune-mediated diseases necessitating adalimumab treatment.

**Efficacy maintenance**: In the ULTRA 2 study,[243] adalimumab 40 mg every other week after standard induction, was assessed at weeks 8 and 52. The efficacy for clinical remission was trivial (17.5% vs 8.5% for placebo, delta 8.8%); this was slightly higher in anti-TNF naive participants (22% vs 12% for placebo, delta 10%) and lower in anti-TNF exposed patients (week 52 clinical remission 10.2% vs 3% for placebo, delta 7.2%). In the VARSITY study[245]; vedolizumab 300 mg at weeks 0, 2 and 6 and then every 8 weeks versus adalimumab subcutaneously 160 mg at week 0, 80 mg at week 2 and then 40 mg fortnightly, was assessed. At 52 weeks, clinical remission rates were 31.3% for vedolizumab versus 22.5% for adalimumab-treated participants.

**Certainty and rationale**: The NMA data show with low certainty that adalimumab has trivial efficacy for induction of remission in ulcerative colitis. RCT data show this is not improved by higher than standard dosing.[244] Given that there are other agents available with higher efficacy, adalimumab is not suggested as standard treatment for induction of remission in ulcerative colitis, yet may be appropriate in selected patients, such as those with extraintestinal manifestations and or multiple immune-mediated diseases necessitating adalimumab treatment.

## WITHDRAWAL OF ANTI-TNF IN ULCERATIVE COLITIS

GPS 36

Patients with ulcerative colitis considering withdrawal of anti-TNF therapy should be counselled that even with at least 6 months corticosteroid-free clinical remission and mucosal healing (defined as a MES 0–1), anti-TNF withdrawal is associated with an increased risk of relapse in approximately one in two patients in the first year.

Patients with ulcerative colitis receiving anti-TNF therapy, should not be considered for therapy withdrawal, as there is an elevated risk of relapse of approximately one in two patients in the first year. One RCT compared patient outcomes between infliximab maintenance and infliximab discontinuation in ulcerative colitis (Koyabashi *et al*).[246] In tht study, patients in corticosteroid-free remission for more than 6 months, with a Mayo Endoscopic Subscore of 0 or 1 were randomised to either continuing or discontinuing infliximab. At week 48, 37 of 46 (80% (95% CI 66·1% to 90·6%)) in the group continuing infliximab compared with 25 of 46 patients (54% (95% CI 39·0% to 69·1%)) in the group discontinuing infliximab were in remission, p=0·0059. In the group discontinuing infliximab who were re-treated with infliximab after relapsing, 67% (8 of 12 patients) were in remission within 8 weeks of re-treatment with no infusion reactions. Subgroup analysis identified that baseline immunomodulator and 5-ASA therapy did not provide protection from a relapse following infliximab discontinuation.

There is limited evidence on clinical predictors of relapse after withdrawal, although histological evidence of inflammation (defined as a Nancy score of >1) and a raised CRP at the time of infliximab withdrawal are associated with an increased risk of relapse.

## GRADE STATEMENT: OZANIMOD

**Summary of evidence**: One phase III study of ozanimod for induction and maintenance therapy was included for analyses in the NMA,[247] with a total of 645 patients randomised versus placebo for the induction study, and 457 ozanimod responders randomised versus placebo for the maintenance study. No patients were receiving concomitant immunomodulator therapy. Low risk of bias was observed for both studies. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 8.

**Efficacy induction**: There were two cohorts in the induction study. In the first cohort patients were assigned to receive oral ozanimod hydrochloride at a dose of 1 mg (equivalent to 0.92 mg of ozanimod) (n=429) or placebo (n=216) once daily. Participants in a second cohort received open-label ozanimod at the same daily dose (n=367).

**Efficacy maintenance**: Patients experiencing clinical response to ozanimod at 10 weeks in either induction cohort underwent re-randomization to receive double-blind ozanimod (n=230) or placebo (n=227) for the maintenance period through to week 52.

**Certainty and rationale**: Based on a single phase III study included in the NMA, the overall certainty of the efficacy outcomes for induction and maintenance were moderate. The overall magnitude of effect was moderate. Low-quality

**Ozanimod is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Moderate**.

**Justification**: The evidence is of moderate certainty, with a moderate magnitude of effect. No unfavourable outcomes

**Implementation considerations**: This is a newly licensed medication with limited long-term safety data. At the time of writing, NICE guidance limits it use to cases where previous exposure to anti-TNF therapy has failed to induce remission, or if anti-TNF therapy is clinically contraindicated. Long-term safety monitoring is proposed.



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evidence suggested no evidence of differences in safety outcomes from placebo, apart from treatment adverse event (TAE) during the maintenance phase, which showed a large effect of ozanimod. The favourable efficacy outcomes, combined with safety outcomes, make ozanimod a suitable option for moderate to severe ulcerative colitis.

### GRADE STATEMENT: ETRASIMOD

**Summary of evidence**: Two phase III RCTs, including 787 participants contributed to the NMA. In both the ELEVATE ulcerative colitis 52 studies and ELEVATE ulcerative colitis 12 studies, patients were randomised to etrasimod versus placebo.[248] In ELEVATE ulcerative colitis 52, 289 patients were assigned to etrasimod and 144 to placebo, while in ELEVATE ulcerative colitis 12, 238 patients were assigned to etrasimod and 116 to placebo. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 9.

**Efficacy induction:** Clinical remission at week 12 was achieved in 27% of etrasimod-treated patients in ELEVATE ulcerative colitis 52, vs 7% placebo, and in 25% patients of etrasimod-treated patients vs 15% placebo in ELEVATE ulcerative colitis 12. Please see table 7 for estimated time to treatment goals for etrasimod.

Adverse events were reported in 71% of etrasimod patients and 56% of placebo patients in ELEVATE ulcerative colitis 52, and in 47% of etrasimod patients and 47% of placebo patients in ELEVATE ulcerative colitis 12. In the NMA, the certainty was low for a trivial benefit for clinical remission with etrasimod over placebo. The certainty was moderate for both a small benefit for clinical response and a moderate benefit for endoscopic improvement.

**Efficacy maintenance:** In ELEVATE ulcerative colitis 52, patients were treated from randomisation through to week 52. Clinical remission was 32% in etrasimod-treated patients versus 7% placebo. This study was not included in the NMA owing to the treat-through design.

**Certainty and rationale:** Based on two phase III studies included in the NMA, the overall certainty of the efficacy outcomes was moderate. The overall magnitude of effect was small. Low to moderate quality evidence suggested no evidence of differences in safety from placebo. The favourable efficacy outcomes, combined with safety outcomes make etrasimod a suitable option for moderate to severe ulcerative colitis.

**Etrasimod is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Small**.

**Justification**: There is moderate quality of evidence for induction and only direct maintenance data available.

**Implementation considerations**: No published maintenance data could be included in the NMA as the RCT was treat-through, but given the results from maintenance data, the GDG would support its use for maintenance in induction responders. Long-term safety monitoring is proposed. NICE application for approval is also currently ongoing at the time of writing this guideline.

### GRADE STATEMENT: TOFACITINIB

**Summary of evidence:** Three phase III RCTs contributed data to our NMA.[250] The OCTAVE Induction 1 and 2 induction trials included 598 and 541 patients, respectively. The OCTAVE sustain study included 593 responders from the induction studies.[249] The GRADE summary of findings is in online supplemental appendix 4, GRADE table 10.

**Efficacy induction:** Participants were randomly allocated to receive either tofacitinib 10 mg twice daily (OCTAVE 1 n=476, OCTAVE 2 n=429) or placebo (OCTAVE 1 n=122, OCTAVE 2 n=112). There are no significant concerns with risk of bias. Please see table 7 for estimated time to treatment goals for tofacitinib.

**Efficacy maintenance:** In OCTAVE Sustain trial, patients were allocated to tofacitinib 10 mg twice daily (n=198), tofacitinib 5 mg twice daily (n=197) or placebo (n=198). There were some concerns with missing outcome data reporting; there are no further concerns in relation to risk of bias.

**Certainty and rationale:** There is low to moderate certainty for a small to moderate benefit for inducing remission with tofacitinib over placebo. There is high certainty for a large benefit for maintaining remission with tofacitinib 5 mg and tofacitinib 10 mg, over placebo. Data from its use in rheumatoid arthritis raised safety concerns regarding VTE particularly PE, MACE and malignancy and tofacitinib should only be used in these patients if no further options are available. It should be avoided during pregnancy and lactation.

**Tofacitinib is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Large**.

**Justification**: In the NMA there is moderate to high certainty overall, for large effect in re-randomised responders. The safety data from the NMA for the use of tofacitinib in ulcerative colitis does not corroborate safety data from tofacitinib in rheumatoid arthritis, which showed increased risk of serious side effects.

**Implementation considerations**: The ORAL surveillance study[183] randomised patients with rheumatoid arthritis, aged over 50 and with at least one cardiovascular risk factor, to receive tofacitinib versus anti-TNF therapy and found that several adverse events, including major adverse cardiac events (MACE) and cancer, were more common with tofacitinib. The European Medicines Agency (EMA) cautions that JAK inhibitors should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer. JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE), other than those listed above. Furthermore, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.[249]



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### GRADE STATEMENT: UPADACITINIB

**Summary of evidence:** Data were included from a multicentre, randomised, double-blind, placebo-controlled clinical programme that consisted of two induction studies (U-ACHIEVE induction and U-ACCOMPLISH) and a single maintenance study (U-ACHIEVE maintenance).[251] There were no significant concerns with risk of bias for any of the included studies. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 11.

**Efficacy induction:** In U-ACHIEVE, 474 patients were randomly assigned to upadacitinib 45 mg once daily (n=319) or placebo (n=155). In U-ACCOMPLISH, 522 patients were randomly assigned to upadacitinib 45 mg once daily (n=345) or placebo (n=177). Please see table 7 for estimated time to treatment goals for upadacitinib.

**Efficacy maintenance:** In the U-ACHIEVE maintenance study a total of 451 patients (21 from the phase IIb study, 278 from U-ACHIEVE induction, and 152 from U-ACCOMPLISH), who achieved a clinical response after 8 weeks of upadacitinib induction treatment, were randomly assigned to upadacitinib 15 mg (n=148), upadacitinib 30 mg (n=154), or placebo (n=149) in the primary analysis population.

**Certainty and rationale:** The overall certainty is high for a large benefit for induction and maintenance of remission of moderate to severe ulcerative colitis with upadacitinib over placebo. The benefit extended to patients with previous biologic exposure. Data regarding side effects are of low certainty, showing no difference from placebo. There is a lack of long-term safety data, and general precautions regarding JAK inhibitors should be applied regarding risk of hyperlipidaemia, pregnancy, lactation, infections, cardio-vascular and thrombotic events.

**Upadacitinib is recommended for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.**

Recommendation: **Conditional**. Overall certainty: **High**. Overall magnitude: **Large**.

**Justification**: The NMA evidence supports this recommendation with high certainty. There is a large magnitude of effect in induction, and for both maintenance doses, including in patients with previous biologic exposure. Direct and indirect analysis clearly demonstrated large magnitude effects with high certainty using multiple outcome rankings. Sensitivity analysis on naivety status did not reveal a major difference to the main network.

**Implementation considerations**: This is a relatively newly licensed agent with limited long-term safety data. There is a generic warning for all JAK inhibitors that medications of this class should be avoided in pregnancy and lactation and unless there are no other options available, is not recommended in patients aged 65 and older, those with an elevated risk of major cardiovascular issues, smokers or former smokers with a long history of smoking, and those at a heightened risk of cancer. Additionally, JAK inhibitors should be used carefully in patients with risk factors for blood clots in the lungs and deep veins (VTE), not limited to the mentioned groups. In the NMA there were no differences in adverse outcomes versus placebo, but long-term safety monitoring is proposed.

### GRADE STATEMENT: FILGOTINIB

**Summary of evidence:** There was one phase IIb/3 RCT investigating the efficacy of filgotinib for induction and maintenance treatment in ulcerative colitis[170] included in our NMA. There were no identified concerns about risk of bias for this study. The induction study included 1348 participants, including those biologic naive (n=659) and biologic exposed (n=689). Participants were randomised to receive either filgotinib 100 mg (n=562), filgotinib 200 mg (n=507) or placebo (n=279). Concomitant use of immunosuppressants was 12–24% across the study groups. During the maintenance study, patients with a clinical response at 10 weeks in either inducion study underwent randomization to receive filgotinib at their induction regimen of 100 mg (n=179) or filgotinib 200 mg (n=202) or placebo (n=190). Responders from the induction placebo arm continued placebo (n=93) through to week 58. 24–27% of participants were taking concurrent immunomodulator therapy. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 12.

**Efficacy induction:** In the RCT, clinical remission at week 10 was achieved in 26% of patients receiving filgotinib 200 mg vs 15% placebo in cohort A and 11% of patients receiving filgotinib 200 mg vs 4% placebo in cohort B. There was no difference between filgotinib 100 mg and placebo.

In the NMA the certainty was low for a trivial benefit for clinical remission; the certainty was low for a moderate benefit for clinical response; and the certainty was moderate for a moderate benefit for endoscopic improvement with filgotinib 200 mg over placebo.

**Efficacy maintenance:** In the RCT, 37.0% of patients treated with filgotinib 200 mg achieved clinical remission at week 58 versus 11.0% for placebo. For filgotinib 100 mg, 23.8% of patients achieved clinical remission versus 13.5% for placebo. In NMA the certainty was high for a large benefit for the maintenance clinical remission; the certainty was moderate for a moderate benefit for a reduction in loss of response; and the

**Filgotinib 200 mg is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: M**oderate**.

**Justification**: Filgotinib 200 mg has low-certainty evidence of trivial magnitude for the induction of clinical remission, low-certainty evidence of moderate magnitude for induction of clinical response and high-certainty evidence of a large magnitude for maintenance of remission.

**Implementation considerations**: Filgotinib 100 mg is not effective for induction of remission, but has low-certainty evidence for small effect size for maintenance of remission. There may be situations when filgotinib 100 mg for maintenance is appropriate, such as in patients with renal disease. This medication should be avoided in pregnancy and lactation, and unless there are no other options available is not recommended in patients aged 65 and older, those with an elevated risk of major cardiovascular issues, smokers or former smokers with a long history of smoking and those at a heightened risk of cancer. Additionally, JAK inhibitors should be used carefully in patients with risk factors for blood clots in the lungs and deep veins (VTE), not limited to the mentioned groups. Long-term safety monitoring is proposed.



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certainty was high for a large benefit for endoscopic improvement with filgotinib 200 mg over placebo.

**Certainty and rationale:** Overall certainty is low that filgotinib 200 mg is better than placebo, with a moderate magnitude, for induction of remission in moderate to severe ulcerative colitis, while the evidence for maintenance of remission is of moderate certainty with a moderate magnitude. Compared with placebo, filgotinib 100 mg had low-certainty evidence for a trivial effect for induction of clinical remission and low-certainty evidence for a small effect at induction of clinical response. Compared with placebo, filgotinib 100 mg had low-certainty evidence of a small effect at the maintenance of clinical remission and low-certainty evidence of a small effect at reduction in loss of response. In certain high-risk populations, the 100 mg dose could be considered appropriate for maintenance (kidney failure/liver failure). There is low-certainty evidence regarding adverse events, with no difference seen between filgotinib and placebo.

### GRADE STATEMENT: MIRIKIZUMAB

**Summary of evidence:** One phase III study contributed data to our NMA.[252] A total of 1281 patients underwent randomization in the induction trial, 544 patients with a response to mirikizumab undergoing randomization to the maintenance study. Across both studies there are significant concerns with risk of bias due to attrition being considerably higher in the placebo group than in the mirikizumab group. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 13.

**Efficacy induction:** During the induction trial, participants were randomised to receive either mirikizumab (n=958) or placebo (n=321). The use of concurrent immunomodulator therapies was 23–24%. At week 12, rates of clinical remission were 24.2% in mirikizumab-treated patients versus 13.3% in placebo. Please see table 7 for estimated time to treatment goals for mirikizumab.

**Efficacy maintenance:** During the maintenance study, only patients who responded to mirikizumab induction therapy were randomised to receive either mirikizumab (n=389) or placebo (n=192). The use of concurrent immunomodulator therapies was 21.6%. At week 52, 49.9% 0f patients treated with mirikizumab were in clinical remission versus 25.1% treated with placebo.

**Certainty and rationale:** Based on phase III data included in the NMA, the overall certainty of the efficacy outcomes for induction and maintenance was low. The overall magnitude of effect was small. Although of low certainty, the favourable safety outcomes make mirikizumab a suitable option for moderate to severe ulcerative colitis.

Mirikizumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Small**.

**Justification**:The overall certainty is low with a small magnitude of effect. No unfavourable outcomes have been demonstrated.

**Implementation considerations**: This is a newly licensed medication with limited safety data. At the time of writing, the NICE guidance is for use only if previous exposure to anti-TNF therapy has failed to induce remission or is clinically contraindicated. Long-term safety monitoring is proposed.

Risankizumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Moderate**.

**Justification**: The certainty is moderate for a moderate benefit for induction of remission with risankizumab over placebo. No maintenance RCT data were available for this guideline and hence no formal suggestion or recommendation can be issued. At this time, the GDG would support its use in maintenance in induction responders.

**Implementation considerations**: No published maintenance data were available when the NMA was performed, and long-term efficacy and safety data are lacking. Long-term safety monitoring is proposed.

### GRADE STATEMENT: RISANKIZUMAB

**Summary of evidence:** One phase III induction study, INSPIRE, contributed to the NMA.[253] A total of 975 patients underwent randomization to receive risankizumab 1200 mg intravenously at weeks 0, 4 and 8, (n=650) or placebo (n=325). The study enrolled patients who demonstrated intolerance or inadequate response to conventional therapies and/or advanced therapies (biologics, JAK inhibitors and S1P receptor modulators). The use of concurrent immunomodulator therapies was not reported. The risk of bias was unclear as this study was only available in abstract format at the time of performing the NMA. The GRADE summary offindings is in online supplemental appendix 4, GRADE table 14.

**Efficacy induction:** In the RCT, clinical remission at week 12 was achieved in 20.3% of patients receiving risankizumab compared with 6.2% of patients receiving placebo. Clinical response at week 12 was 64.3% in risankizumab treated patients versus 35.7% with placebo, and endoscopic improvement for risankizumab was 36.5% versus 12.1% placebo. In the NMA, the certainty was low for a moderate benefit for clinical remission; moderate for a moderate benefit for clinical response; and moderate for a large benefit for endoscopic improvement with risankizumab over placebo.

**Efficacy maintenance:** Responders from the INSPIRE study have been re-randomised to a risankizumab maintenance study (COMMAND).[253] The results from this study are expected.

**Certainty and rationale:** This is a new agent for which only the induction data have been published at the time of writing, and the results from the maintenance study are awaited. The certainty is moderate for a moderate benefit for induction of remission with risankizumab over placebo. Safety outcomes from the induction study are favourable. The GDG supports the use of risankizumab, conditional to further availability of maintenance data.

### GRADE STATEMENT: USTEKINUMAB

**Summary of evidence:** Data were included from two RCTs which evaluated ustekinumab as 8-week induction therapy and 44week-maintenance therapy.[254] A total of 961 patients were randomised to receive an intravenous induction with ustekinumab 130 mg (n=320 patients), 6 mg/kg (n=322), or placebo (n=319). Patients who had a response to induction therapy were randomised to receive subcutaneous maintenance injections of 90 mg of ustekinumab every 12 weeks (n=172 patients), or every 8 weeks (n=176) or placebo (n=175). 26–28% of participants



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**Ustekinumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis**

Recommendation: **Conditional.** Overall certainty: **Low**. Overall magnitude: **Small**.

**Justification**: The overall certainty is low, for a small benefit in induction and maintenance, with ustekinumab over placebo, and there are no unfavourable safety outcomes.

**Implementation considerations**: At the time of writing, the NICE guidance is for use only if previous exposure to anti-TNF therapy has failed to induce remission or is clinically contraindicated. Long-term safety monitoring is proposed.

were taking concomitant immunomodulator therapy. There were no significant concerns in relation to risk of bias. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 15.

**Efficacy induction:** Clinical remission at week 8 was achieved in 15.6% of patients receiving ustekinumab 130 mg and in 15.5% of those receiving induction with 6 mg/kg, versus 5.3% placebo ($p<0.001$ for both comparisons). In NMA the certainty was low for a small benefit for clinical remission; high for a moderate benefit for clinical response; and low for a moderate benefit for endoscopic improvement with ustekinumab 6 mg/kg over placebo.

**Efficacy maintenance:** The percentage of patients who had clinical remission at week 44 was 38.4% in patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks, 43.8% for 90 mg subcutaneously every 8 weeks and 24.0% for placebo. In NMA the certainty was low for a trivial benefit with ustekinumab 90 mg every 12 weeks over placebo and a small benefit for ustekinumab 90 mg every 8 weeks for clinical remission. For clinical response, 90 mg every 12 weeks and every 8 weeks, both had a small benefit over placebo, with low and moderate certainty, respectively. For endoscopic improvement, the benefit of 90 mg every 12 weeks over placebo was trivial and 90 mg every 8 weeks was small, both with low certainty.

**Certainty and rationale:** The overall certainty is low for a small benefit for inducing and maintaining remission of moderate to severe ulcerative colitis with ustekinumab over placebo. NMA and RCT data showed that in responders to induction, maintenance with 90 mg eight-weekly subcutaneous injections achieved higher rates of clinical remission than 12-weekly dosing. NMA and RCT data included studies of patients who were either biologic naïve or biologic exposed (anti-TNF therapy or vedolizumab). There was moderate certainty that ustekinumab had no unfavourable safety concerns compared with placebo.

## GRADE STATEMENT: VEDOLIZUMAB

**Summary of evidence:** Four RCTs were included in the NMA with a total of 1368 participants. In three studies, patients were randomised to vedolizumab versus placebo.[255 256] In the VARSITY study, patients were randomised to vedolizumab versus adalimumab.[245] A mean of 24% (range 22–52%) were receiving concurrent immunomodulator therapies. There were no significant concerns in relation to risk of bias. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 16.

**Efficacy induction:** The induction studies included study arms for treatment with vedolizumab (n=761), adalimumab (n=386) or placebo (n=221). In NMA the certainty was low for a trivial

**Vedolizumab is suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Small**.

**Justification**: There is moderate certainty for a small benefit for inducing and maintaining remission with vedolizumab over placebo. In safety analysis there was moderate and low certainty for trivial or no differences compared with placebo.

**Implementation considerations**: It should be noted that the treatment effect is small in patients with prior anti-TNF therapy exposure. Considering the trivial effect of adalimumab in the treatment of ulcerative colitis, it is suggested that caution is used in patients with prior infliximab failure. This is based on NMA sensitivity analyses.

In NMA there is no difference or a trivial difference between 4-weekly and 8-weekly dosing, for the outcomes assessed. Owing to its gut-specific action, vedolizumab avoids systemic immunosuppression, making it a suitable treatment option for patients at higher risk of complications from broad immunosuppressive treatments. This includes the elderly and those with comorbidities that might impair their immune response.

benefit for clinical remission with vedolizumab over placebo. The certainty was high for a moderate benefit for clinical response, and the certainty was low for a small benefit for endoscopic improvement with vedolizumab over placebo. Please see table 7 for estimated time to treatment goals for vedolizumab.

**Efficacy maintenance:** In the placebo-controlled maintenance studies, 428 responders to induction treatment, were randomised to receive vedolizumab 300 mg 8-weekly (n=156); or 4-weekly (n=155), versus placebo (n=117). The VARSITY study was a treat-through design and was excluded from the maintenance NMA. In NMA the certainty was high for a moderate benefit for clinical remission with vedolizumab 8-weekly, and the certainty was moderate for a moderate benefit for clinical remission with vedolizumab 4-weekly, over placebo. For clinical response, the certainty was high for a large benefit for vedolizumab 8-weekly, and the certainty was moderate for a moderate benefit for vedolizumab 4-weekly, over placebo. The certainty was moderate for a large benefit for endoscopic improvement with vedolizumab 8-weekly, and the certainty was moderate for a large benefit for endoscopic improvement with vedolizumab 4-weekly, over placebo.

**Certainty and rationale:** Based on four RCTs, the NMA demonstrates no demonstrable difference between 4-weekly (q4) and 8-weekly (q8) dosing. There is a trivial effect on induction of remission (low certainty), but a moderate effect on sustained remission when used at 300 mg q8 dosing or 300 mg q4 dosing (high and moderate certainty, respectively). Vedolizumab had a moderate effect on clinical response (high certainty) with sustained clinical response seen in both 300 mg 8-weekly dosing (large effect; high certainty) and 300 mg 4-weekly dosing (moderate effect; moderate certainty). There was a small effect on endoscopic improvement (low certainty) during induction, but sustained endoscopic improvement during maintenance remission was demonstrated in both 300 mg q8 dosing (large effect; moderate certainty) and 300 mg q4 dosing (large effect; high certainty). There were no significant safety concerns regarding vedolizumab induction or maintenance highlighted in the NMA (low to moderate certainty).



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Antibiotics are not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis

Recommendation: **Conditional**. Overall certainty: **Low.** Overall magnitude: **Trivial**.

**Justification**: The quality of evidence is low, and the magnitude of effect is trivial.

**Implementation considerations**: While the overall certainty is low, the certainty that antibiotics show no difference in achieving clinical remission compared with placebo is high. Together with safety concerns about the use of antibiotics, such as antibiotics resistance, leads the GDG to recommend not using antibiotics for ulcerative colitis.

FMT is not suggested for induction and maintenance of remission in patients with moderate to severe ulcerative colitis.

Recommendation: **Conditional.** Overall certainty: **Low**. Overall magnitude: **Trivial**.

**Justification**: Ongoing research indicates the potential usefulness of FMT for ulcerative colitis treatment, but current magnitude of effect is trivial to small, with low certainty.

**Implementation considerations**: There may be a role for clinical use of FMT for the induction of remission in ulcerative colitis in rare circumstances, such as when there are no remaining licensed medical therapies available. However, such cases need to be discussed at an individual level, both with the patient and with consensus from an expert panel, with decisions on the FMT administration regimen, timing for early assessment of response/failure and risks compared with other options, such as a colectomy. There is a need for more high-quality, controlled studies to establish its efficacy and safety in ulcerative colitis.

## OTHER THERAPIES IN ULCERATIVE COLITIS

### GRADE statement: Antibiotics

**Summary of evidence:** In a Cochrane systematic review, 12 RCTs involving 847 participants were included. One study focused on maintenance of remission, comparing sole antibiotic therapy with 5-ASAs. The remaining trials examined induction of remission by investigating concurrent medications or standard of care regimens with antibiotics as adjunct therapy, or by comparing antibiotics with other adjunct therapies.[257] The GRADE summary of findings is in online supplemental appendix 4, GRADE table 17.

**Efficacy induction:** High-certainty evidence shows no difference in clinical remission between antibiotics and placebo (RR=0.88, 95% CI 0.74 to 1.06). There is low-certainty evidence that antibiotics may be no different from placebo (RR=0.75, 95% CI 0.47 to 1.22) for induction of clinical response. There is low-certainty evidence that antibiotics show no difference from placebo for serious adverse events. The data related to withdrawal due to adverse events are very uncertain. It is unclear if there is any difference between antibiotics and 5-ASAs in failure to achieve clinical remission (RR=2.20, 95% CI 1.17 to 4.14).

**Efficacy maintenance:** It is unclear if there is any difference between antibiotics and 5-ASAs for decreasing relapses during maintenance (RR=0.71, 95% CI 0.47 to 1.06). The certainty of the evidence is very low.

**Certainty and rationale:** The overall certainly is low, with a trivial magnitude of effect compared with placebo, based on the evidence. While no safety concerns have been raised, there is insufficient evidence available to be able to make a recommendation for induction or maintenance of remission.

### GRADE STATEMENT: FMT

**Summary of evidence:** A Cochrane review included 10 studies with 468 participants, of which nine studies focused on adults and one focused on children. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 18.

**Efficacy induction:** FMT may increase rates of induction of clinical remission in ulcerative colitis compared with control (RR=1.79, 95% CI 1.13 to 2.84; low-certainty evidence). Five studies showed that FMT may increase rates of induction of endoscopic remission in ulcerative colitis at longest follow-up (range 8 to 12 weeks); however, the findings were non-significant (RR=1.45, 95% CI 0.64 to 3.29; low-certainty evidence). Nine studies with 417 participants showed that FMT may result in no difference in rates of any adverse events (RR=0.99, 95% CI 0.85 to 1.16; low-certainty evidence). The evidence was very uncertain and non-significant for risk of serious adverse events (RR=1.77, 95% CI 0.88 to 3.55; very low-certainty evidence) and improvement in quality of life (mean difference (MD) 15.34, 95% CI −3.84 to 34.52; very low-certainty evidence) when FMT was used to induce remission in ulcerative colitis.[258]

**Efficacy maintenance:** The evidence exploring FMT for maintenance of remission in ulcerative colitis is highly uncertain and comprises only one RCT. Patients with ulcerative colitis who had achieved clinical remission through multiple sessions of FMT were randomly assigned to receive maintenance FMT or placebo colonic delivery every 8 weeks for 48 weeks. Of patients assigned to FMT, 27/31 (87.1%) achieved steroid-free remission, compared with 20/30 (66.7%) in the placebo group.

**Certainty and rationale:** The overall certainty for induction of remission is low with a small effect. There is low certainty of evidence that demonstrates no difference in adverse events between FMT and placebo. This current evidence base is insufficient to make recommendations for its use in routine practice. FMT may, however, be considered on a case-by-case basis for treatment of patients with ulcerative colitis in whom licensed treatment options have failed or for those who are not suitable for currently available treatments. There is insufficient evidence on efficacy or safety to be able to make a recommendation for use of FMT for maintenance of remission.

### GRADE STATEMENT: PROBIOTICS

**Summary of evidence:** A Cochrane review included 14 induction studies (865 randomised participants) that met the inclusion criteria.[259] Twelve of the studies looked at adult participants. The studies ranged from 2 weeks to 52 weeks in follow-up. The risk of bias was high for all except two studies due to allocation concealment, blinding of participants, incomplete reports of outcome data and selective reporting. This led to GRADE ratings of the evidence ranging from moderate to very low. A Cochrane review included 12 maintenance studies (1473 randomised participants) that met the inclusion criteria.[260] Participants were mostly adults. The risk of bias was high in all except three studies due to selective reporting, incomplete outcome data and lack of blinding. This resulted in low-certainty to very low-certainty of evidence. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 19.



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Probiotics are not suggested for induction or maintenance of remission in patients with ulcerative colitis.

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Small**.

**Justification**: There is low-certainty evidence of small magnitude effect from probiotics, for induction versus placebo. There is only very low-certainty evidence for maintenance. However, the nature of probiotics (type, number of strains, dosing frequency) remains unclear. The GDG therefore do not recommend its use for the induction or maintenance of remission in ulcerative colitis. There is no evidence to support subgroup analysis and therefore species-specific recommendations are not possible.

**Implementation considerations**: The optimum type and number of bacterial strains along with dosing frequency of the probiotic remains uncertain.

**Efficacy induction:** The Cochrane review found that probiotics may induce clinical remission when compared with placebo (RR=1.73, 95% CI 1.19 to 2.54; nine studies, 594 participants; low-certainty evidence; downgraded owing to imprecision and risk of bias, number needed to treat for an additional beneficial outcome (NNTB) 5). Low-certainty evidence from a single study shows that when combined with 5-ASA, probiotics may slightly improve the induction of remission (based on the Sunderland disease activity index) compared with 5-ASA alone (RR=1.22 CI 1.01 to 1.47; one study, 84 participants; low-certainty evidence; downgraded due to unclear risk of bias and imprecision).[259]

**Efficacy maintenance:** Reported data related to maintenance and safety are very low certainty.

**Certainty and rationale:** The overall certainty is low, with an overall small magnitude of effect compared with placebo in induction of clinical remission, based on the evidence. The effect size varies from small to large between induction studies. However, there is no evidence to support subgroup analysis and the type and number of bacterial strains together with dosing frequency of the probiotic remains uncertain, and species-specific recommendations are not possible. There is insufficient evidence to support probiotics in general for the induction or maintenance of remission in ulcerative colitis.

Table 7 outlines suggested rough estimates of time to achieve treatment goals after initiation of ulcerative colitis therapies, as advised by the STRIDE consensus.[6] Thus, these times could be used as a guide when deciding on time intervals to monitor for remission in ulcerative colitis after initiating a new treatment for this disease. Data on timelines have been obtained from the relevant licensing trials.

**Table 7** Estimated time (weeks) to treatment goals in ulcerative colitis

| Colitis | Clinical remission | Norm of CRP/ESR | Decrease in FC | EH |
|---|---|---|---|---|
| **Ulcerative colitis** | | | | |
| Oral 5-ASA | 8 | 8 | 10 | 13 |
| Oral steroids | 2 | 5 | 8 | 11 |
| Locally active steroids | 8 | 8 | 9 | 13 |
| Purine analogues | 15 | 15 | 15 | 20 |
| Adalimumab | 11 | 10 | 12 | 14 |
| Infliximab | 10 | 9 | 11 | 13 |
| Vedolizumab | 14 | 14 | 15 | 18 |
| Tofacitinib | 11 | 9 | 11 | 14 |
| Upadacitinib | 8 | 8 | 8 | 8 |
| Etrasimod | 12 | 12 | 12 | 12 |
| Mirikizumab | 12 | 12 | 12 | 12 |

CRP, C-reactive protein; EH, endoscopic healing; ESR, erythrocyte sedimentation rate; FC, faecal calprotectin .

## MANAGEMENT OF ULCERATIVE PROCTITIS

GPS 37

We recommend that mild or moderately active ulcerative proctitis should be treated with 5-ASA suppositories/ foam enemas (evidence is of moderate certainty for induction and low certainty for maintenance).

One-third of patients with ulcerative colitis have inflammation limited to rectum at the time of diagnosis known as ulcerative proctitis (UP). From a clinical perspective, this is inflammation in the rectum, usually up to a maximum of 15 cm, and not beyond 20 cm from the anal verge. Topical 5-ASAs are effective for induction and maintenance of clinical remission and have remained the first-line treatment of choice for UP. However, a significant proportion of patients do not respond to 5-ASAs. Active UP, for which rectal and oral therapy with 5-ASA and corticosteroids fails, is termed as refractory UP. Refractory UP is generally treated in line with the management principles for left-sided or extensive colitis.

For the treatment of mild to moderate UP, first-line therapy should be either 5-ASA suppositories or enemas. These medications achieve higher mucosal concentrations, up to 200-fold greater, when treating disease limited to the rectum compared with oral agents.[261] A systematic review identified 10 studies assessing the efficacy of topical therapy compared with placebo and found that topical therapy is significantly superior to placebo for induction of clinical remission (RR=2.72, 95% CI 1.94 to 3.82, GRADE moderate-certainty evidence) without any statistically significant difference in the rate of adverse events (RR=1.27, 95% CI 0.24 to 6.57, GRADE very low-certainty evidence).[262] Four studies[263–266] have investigated the efficacy of topical therapy for maintenance treatment and were included in a systematic review that demonstrated superiority to placebo (RR=2.09, 95% CI 1.26 to 3.46, GRADE very low-certainty evidence).[262] For maintenance treatment there is also no statistically significant difference in adverse events compared with placebo (RR=1.38, 95% CI 0.68 to 2.81, GRADE low-certainty evidence).

Suppositories have been shown to be better tolerated than enemas[267] and there is no statistically significant difference in efficacy outcomes[268]; we suggest individual patient preference and tolerability should be taken into account. Once-daily dosing is more convenient for patients, and a pooled analysis of three studies[269–271] found that there is no difference between once-daily or increased dosing regimens of two to three times daily (RR=1.00, 95% CI 0.92 to 1.08, GRADE moderate certainty).[262] Administering this once-daily dose at bedtime is convenient and allows maximal time for the therapy to be retained. There are limited data with regards to dose-ranging, but one double-blind study found no statistically significant difference between those



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receiving a 1 g dose of topical treatment (suppository) and 1.5 g.[272] There is minimal evidence comparing different formulations of topical therapy,[262] but one study showed that acetyl-containing 5-ASA preparations may be less effective than 5-ASA preparations (RR=3.26, 95% CI 1.10 to 9.64) for induction of remission.[273] The GDG suggest that suppositories should be considered first-line treatment where the maximum extent of microscopic and macroscopic disease activity is within 15 cm of the anal verge.

### MAINTENANCE THERAPY FOR ULCERATIVE PROCTITIS

Many patients rapidly respond to initial treatment with topical 5-ASAs and remain in clinical remission without the need for maintenance therapy. In this setting, many patients prefer to start treatment when they develop symptoms. However, for some, regular preventative treatment is required. Moreover, adherence to topical therapy can be a challenge, particularly when patients are in remission as they lose the motivation to administer their treatment. Given this, it should be noted that alternate or every third night suppository treatment does not appear to substantially reduce the rate of remission.[274]

**GPS 38**

We suggest that patients with ulcerative proctitis who do not respond or are intolerant to 5-ASA suppositories/enema or wish to avoid systemic 5-ASA may be switched to corticosteroid suppositories/foam/ enema (evidence is of moderate certainty). There is no difference in efficacy between suppositories, foam or enemas.

**GPS 39**

We suggest that refractory UP may require treatment with corticosteroids, topical tacrolimus, JAK-1, S1P agonists and/or biological therapy.

Topical corticosteroids can be used to induce remission in UP, and both topical corticosteroids (RR=2.83, 95% CI 1.62 to 4.92, GRADE moderate-certainty evidence) and topical budesonide (RR=2.34, 95% CI 14.2 to 3.81, GRADE moderate certainty) were shown to be superior to placebo in a systematic review ,which pooled data from five studies.[262] Overall, in this meta-analysis there was no difference in significant adverse events compared with placebo. These studies also included suppositories, foam and enema preparations and found no difference among them. When different doses were compared, 2 mg budesonide suppository may be marginally inferior to 4 mg dose in inducing clinical remission (RR=0.74, 95% CI 0.57 to 0.96) with no difference in adverse events.[275] Kruis *et al* have also demonstrated that the 4 mg budesonide suppository is non-inferior to 2 mg budesonide foam enema when inducing remission, but the 4 mg suppository group were more likely to experience an adverse event (RR=1.21, 95% CI 1.01 to 1.45).[276] There are data suggesting that patients may prefer budesonide foam compared with budesonide enemas owing to better tolerability and improved retention.[277]

When comparing topical corticosteroids with topical 5-ASAs, pooled data from three trials[267 275 278 279] show that there was no statistically significant difference in clinical response (RR=0.99, 95% CI 0.65 to 1.51, GRADE very low-certainty evidence).[262] Please see table 7 for estimated time to treatment goals for locally active steroids. However, pooled analysis from these studies did show that histological response is inferior for topical corticosteroids compared with topical 5-ASA (RR=0.77, 95% CI 0.62 to 0.95, GRADE low-certainty evidence). Moreover, Kruis *et al* found that endoscopic remission rates were inferior compared with topical 5-ASAs (RR=0.78, 95% CI 0.65 to 0.93). There was no difference in adverse events between topical corticosteroids and topical 5-ASA.

For those patients who do not respond to topical 5-ASA monotherapy, the addition of a topical corticosteroid has been shown to be superior in inducing clinical response (RR=1.41, 95% CI 1.05 to 1.9).[278] For those being treated with topical corticosteroid alone, the addition of topical 5-ASA has also been shown to be superior to monotherapy for induction of endoscopic remission (RR=1.28, 95% CI 1.08 to 1.53).[275] Combination therapy of topical and oral 5-ASA has also been shown to be superior to topical monotherapy in inducing clinical response.[280]

For those patients not responding to topical 5-ASA monotherapy, there is no high-quality evidence comparing whether addition of oral 5-ASA or topical corticosteroid improves outcomes. We advise this should be a shared decision, with patient preference and history taken into account.

In severe or refractory UP, it should be ensured that the diagnosis is correct, and that topical therapy has been optimised and adhered to. Concurrent diagnoses, such as irritable bowel syndrome or proximal constipation, can contribute to symptoms. Differential diagnoses that need to be excluded include infection (lymphogranuloma venereum, *Neisseria gonorrhoeae*, herpes simplex virus, syphilis, *Giardia duodenalis*, amoebiasis), solitary rectal ulcer, Crohn's colitis, psoriatic colitis, chemical colitis and rectal prolapse. When appropriate, endoscopic re-evaluation may be required to rule out proximal extension of the disease.

If the diagnosis has been confirmed initial treatment with a course of oral corticosteroids is recommended, and there are no data to suggest that either budesonide MMX or prednisolone is more effective than the other for UP. If there is an adequate response to corticosteroids or a need for maintenance therapy, then biologics, topical tacrolimus or small molecule therapy can be considered. Pivotal randomised trials assessing efficacy and safety of advanced therapies, including biologics and oral small molecules, in ulcerative colitis generally exclude patients with proctitis. As a result, the available evidence to inform the management of refractory ulcerative proctitis is limited to very few studies, the majority of which are observational studies.

A French nationwide retrospective cohort study by Pineton de Chambrun *et al* investigated 104 patients with UP treated with anti-TNF therapy (either infliximab, adalimumab or golimumab). At 3 months, 50% of those treated with anti-TNF had achieved clinical remission and 60% had achieved mucosal healing.[281] A further retrospective study by Dubois *et al* looked at long-term outcomes for UP over a 21-year period.[282] In their study, 31% required treatment for refractory UP and were either treated with azathioprine monotherapy, anti-TNF therapy or vedolizumab. Of these, 50% (13/26) treated with anti-TNF therapy achieved clinical remission with median follow-up of 21 months, compared with 67% (10/15) patients with vedolizumab with median follow-up of 11 months; clinical response



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rates were significantly higher compared with those treated with azathioprine monotherapy (p=0.001). Seven patients treated with anti-TNF developed adverse events that required treatment to be stopped, although it should be noted that neither of these studies used therapeutic drug monitoring.

Topical tacrolimus, a calcineurin inhibitor, has been shown to be effective for refractory UP. A study by Lawrance *et al* showed that topical tacrolimus, administered as twice-daily enemas, was superior to placebo for induction of clinical response (RR=7.27, 95% CI 1.09 to 48.35) and endoscopic remission (R= 7.27, 95% CI 1.09 to 48.35).[283] A systematic review that included five studies reported no concerning systemic adverse events.[284] Serum tacrolimus levels were generally low, but there was heterogeneity in the dosing regimen in these studies and so monitoring of trough serum levels is advisable with appropriate dose adjustment if indicated.

Data from ELEVATE ulcerative colitis 12 and ELEVATE ulcerative colitis 52 have shown that etrasimod, a sphingosine-1-phosphate receptor modulator, is superior to placebo for induction of clinical remission (RR=4.71, 95% CI 1.2 to 18.49) and maintenance of remission in quiescent UP (RR=2.08, 95% CI 1.31 to 3.32).[248 262] Safety data for the UP cohort were not specifically reported.

Data for other small molecules is very limited, but a prospective real-world cohort study from India found that tofacitinib-induced clinical remission in 47% (15/32) of patients at week 8.[285] Adverse events were comparable to previously published data.

Overall, there are limited data from RCTs as historically, isolated UP has often been an exclusion criterion for trials in ulcerative colitis. There are also no data comparing different advanced therapies in the treatment of UP to inform which is superior.

There is insufficient evidence at present to recommend topical acetarsol or appendicectomy as treatment for UP. In refractory cases, these interventions may be considered in specialist units with experience in these treatments.

## ACUTE SEVERE COLITIS

### Medical management in ASUC

**GPS 40**

We suggest that adult patients with acute severe ulcerative colitis (ASUC) defined by Truelove and Witts' criteria should be admitted to hospital for assessment and intensive management.

Approximately 25% of patients with ulcerative colitis will require hospitalisation for an acute severe flare of disease at some stage in the natural history of their disease, often as the index presentation.[286] Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition and initial risk stratification of patients with ASUC is based on criteria proposed by Truelove and Witts.[287] According to the Truelove and Witts definition, ASUC is characterised by the presence of six or more bloody stools per day and at least one of the following signs of systemic toxicity: tachycardia (mean pulse rate >90 beats per minute), fever (>37.8°C), anaemia (haemoglobin <105 g/L) and/or a raised ESR (>30 mm/h). These criteria were later modified to include elevated CRP. ASUC is the most severe form of ulcerative colitis and is a medical emergency, with overall mortality of 1%, and relatively high mortality in elderly patients compared with younger patients.[288] Around one-fifth of patients hospitalised with ASUC require subtotal colectomy during same admission, and risk of colectomy further increases after subsequent episodes of ASUC.[289]

**GPS 41**

We suggest that patients hospitalised with ASUC should have urgent assessment of blood tests (FBC, CRP, U&E and LFTs, including albumin), stool culture, *Clostridioides* screen, non-invasive imaging and flexible sigmoidoscopy.

**GPS 42**

We suggest that patients with ASUC should be treated with high-dose intravenous corticosteroids, such as methylprednisolone 30 mg every 12 hours or hydrocortisone 100 mg every 6 hours.

### INITIAL MANAGEMENT

All patients admitted with ASUC should have baseline bloods (FBC, CRP, U&E, LFTs, including albumin, lipid profile and magnesium, stool culture and *Clostridium difficile* assay, radiological imaging (abdominal X-ray scan, intestinal US or CT scans) and flexible sigmoidoscopy, with close monitoring after admission. CT is the preferred modality when perforation or intra-abdominal collection is suspected. The results of these tests will also assist in determining the prognosis for that admission (particularly to predict corticosteroid failure and the need for colectomy).[286 290] Early flexible sigmoidoscopy is important to confirm diagnosis, assess severity for prognostication, to obtain tissue samples for histological evaluation for cytomegalovirus and to exclude important differential diagnoses, like malignancy. Stool culture and microscopic examination should be performed routinely, as soon as practicable, to exclude pathogenic bacteria, including testing for *C. difficile* toxin. *C. difficile* infection has been associated with a worse outcome in hospitalised patients with IBD.[291 292] If *C. difficile* is detected (or strongly suspected), treatment with oral vancomycin should be initiated.[293] However, routine use of antibiotics has not proved to be beneficial.[294] Patients with ASUC are at increased risk of venous thrombosis, therefore appropriate anticoagulant prophylaxis should be administered; this does not precipitate or exacerbate colonic bleeding.[295]

### INPATIENT TREATMENT

**GPS 43**

We suggest that patients with ASUC responding to IV corticosteroids should be treated with a purine analogue or receive suitable maintenance advanced medical therapy.

Intravenous corticosteroids, such as hydrocortisone 100 mg four times daily or methylprednisolone 30 mg every 12 hours, are the cornerstone in the management of ASUC.[296] Methylprednisolone has less mineralocorticoid effect than hydrocortisone at these doses and so causes significantly less hypokalaemia.[297] Higher doses of corticosteroids do not offer any additional advantage and are associated with adverse events.[298] Moreover, prolonged intravenous courses beyond 7–10 days carry no additional benefit and increase toxicity.[299] In corticosteroid responders, intravenous corticosteroids should be switched to oral corticosteroids when clinically appropriate, usually within 7 days of initiation, and then tailed as per local protocols.



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Approximately two-thirds of patients with ASUC respond to IV corticosteroids. A systematic review of 32 trials of steroid therapy for ASUC involving 1991 patients reported an overall response to steroids of 67%, with 29% (95% CI 28% to 31%) having colectomy. Mortality was 1% (n=22/1991; 95% CI 0.7% to 1.6%), and none of these outcomes changed between 1974 and 2006 (R2=0.07, p=0.8).[296] Patients should be assessed for a clinical and biochemical, and radiological response after 3–5 days of intravenous corticosteroid steroid therapy to determine the need for salvage medical or surgical therapy.[296 300]

The risk of relapse and need for colectomy increases following an episode of ASUC, and increases further after subsequent episodes.[301] In the absence of advanced maintenance therapy, the incidence of 1-year relapse is approximately 50% despite purine analogues maintenance therapy.[302] In this clinical setting accelerated progression to a suitable advanced therapy is reasonable.

Optimal maintenance therapy in immunosuppressant naïve patients presenting with ASUC who responded to IV corticosteroids following discharge is debatable. Although patients who responded to IV corticosteroids appear to have lower risk of hospitalisation and colectomy than patients who needed medical rescue therapy, the prognosis remains unfavourable.[303 304] In a retrospective study of 142 patients with ASUC who responded to IV corticosteroids, the probabilities of relapse-free survival were 58%, 48% and 40% at 1, 2 and 5 years, respectively, and the probabilities of colectomy-free survival were 96%, 95% and 91% at 1, 2 and 5 years, respectively.[305]

There are limited studies that have compared outcomes following maintenance therapy with different agents in this setting. A retrospective study of 141 patients showed that there was no difference between 5-ASA or azathioprine or infliximab.[305] However, in this study only limited numbers of patients were in the infliximab group (n=18). In another retrospective study, patients who received anti-TNF therapy as maintenance following response to IV corticosteroids were at low risk of relapse.[305] A recent open-label RCT showed that patients who responded to steroids and were maintained on azathioprine had a higher frequency of composite outcome compared with those maintained on infliximab and azathioprine combination.[302] In that study treatment failure at week 52 was observed in 81.5% in the azathioprine arm versus 53.3% in the infliximab and azathioprine arm (OR=3.85, 95% CI 1.15 to 12.88, p=0.03). Treatment failure was defined as absence of steroid-free clinical remission (MCS≤2 with no individual subscore >1), absence of endoscopic response (endoscopic subscore ≤1), use of a prohibited treatment, adverse event leading to interruption of allocated treatment, colectomy or death. Therefore, advanced therapy can be considered for maintenance therapy (biologics or JAK inhibitors) for patients who responded to IV corticosteroids during an episode of ASUC. However, local availability of advanced therapies and patient preference should be considered.

**GPS 44**

We suggest that patients with ASUC failing to respond to at least 3 days of IV corticosteroids, as judged by a suitable scoring system, should be treated with rescue therapy in the form of intravenous infliximab or ciclosporin. Ciclosporin can be bridged to purine analogues (if naïve) or a suitable advanced therapy in accordance with local practice.

### Inpatient treatment of corticosteroid-refractory disease

Head-to-head comparisons between ciclosporin and infliximab have demonstrated equivalent efficacy. In the open-label CySIF trial, 115 patients previously naïve to infliximab and ciclosporin, who had a Lichtiger score >10 points (range 0–21) and colitis refractory to at least 5 days of intravenous steroids, were randomised in a 1:1 ratio to receive intravenous ciclosporin (2 mg/kg per day for 1 week followed by oral drug until day 98) or infliximab (5 mg/kg on days 0, 14 and 42).[306] In both groups, azathioprine was started at day 7 in patients with a clinical response. The primary endpoint was treatment failure defined by absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, a severe adverse event leading to treatment interruption, colectomy or death. There was no statistically significant difference between treatment failure in patients given ciclosporin (60%) and infliximab (54%). Nine (16%) patients in the ciclosporin group and 14 (25%) in the infliximab group had severe adverse events, which was also not statistically different. Similar mucosal healing rates (47% ciclosporin, 45% infliximab) and colectomy rates (17% ciclosporin, 21% infliximab) were achieved in both groups. There was no difference in colectomy-free survival at 1 and 5 years in patients treated with either ciclosporin or infliximab.[307]

The CONSTRUCT trial was an open-label pragmatic randomised trial in 270 patients, who were randomly allocated (1:1) to receive either infliximab (5 mg/kg intravenous infusion given over 2 hours at baseline and again at 2 weeks and 6 weeks after the first infusion) or ciclosporin (2 mg/kg per day by continuous infusion for up to 7 days, followed by twice-daily tablets delivering 5.5 mg/kg per day for 12 weeks). The primary outcome was quality-adjusted survival; the area under the curve of scores from the Crohn's and Ulcerative Colitis Questionnaire was completed by participants at baseline, 3 months and 6 months, then every 6 months from 1 year to 3 years.[308] There was no statistically significant difference between the two groups for the primary endpoint as well as the secondary endpoints of colectomy rates, time to colectomy, serious adverse events or death. Colectomy rates were 29% for infliximab and 30% for ciclosporin at 3 months, and 35% and 45%, respectively, at 1 year, with no significant difference between the treatments.[308] However, treatment with infliximab was associated with a greater cost thanwith ciclosporin.

A meta-analysis of infliximab and ciclosporin RCTs shows no difference in response up to 1 year.[309] For those treated with infliximab, either continuing repeat infusions, combination therapy with azathioprine, or azathioprine only, the 5-year colectomy rate was similar at 26.2%.[310] Mortality from infliximab trials is comparable to data on ciclosporin (0–2%).[286 300 310] The most significant risk for both infliximab and ciclosporin relates to those receiving either of these drugs combined with high-dose corticosteroids, for whom medical treatment fails, and who go on to colectomy with deteriorating physical condition (anaemia, hypoalbuminaemia and oedema) where surgical complications are a significant concern.

Generally, purine analogues are considered for maintenance therapy following induction of remission with intravenous ciclosporin in patients with ASUC. However, in patients for whom purine analogues have already failed, ciclosporin can be considered as bridge therapy to advanced therapies such as vedolizumab or ustekinumab. However, the available evidence supporting this approach is very limited.



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### GPS 45

In acute severe ulcerative colitis, delay in surgery is associated with an increased risk of surgical complications, mandating early referral and direct involvement of specialist colorectal surgical and stoma care teams.

### GPS 46

We suggest that patients with ASUC who have not responded within 7 days of rescue therapy with infliximab or ciclosporin, or those with a deterioration or complications before that time (including toxic megacolon, severe haemorrhage or perforation) require subtotal colectomy and ileostomy.

Despite effective medical rescue therapy, a significant proportion of patients still require surgery. Delay in decision to surgery has been shown to be associated with worse clinical outcomes. Therefore, timely decision-making is crucial to prevent delays or prolongation of time to medical therapy, as those patients not responding to medical therapy and undergoing colectomy have higher postoperative complication rates after delayed surgery[299]; as prolonged admission prior to surgery is a significant predictor of postoperative complications.[311]

Multidisciplinary team involvement with gastroenterologists, colorectal surgeons and stoma therapists enables better management.[286 312] Surgical input at an early stage helps patients to understand that colectomy is an important treatment option and is not an outcome to be avoided at any cost. Prompt joint decision-making is essential to avoid unnecessary delays. Please see figure 4.

## INFLIXIMAB DOSING

### GPS 47

For patients who do not respond to initial IV corticosteroids, we suggest consideration of an intensified dosing regimen of infliximab in a select group of patients, especially if serum albumin levels are low.

Several studies have demonstrated an association between higher serum levels of anti-TNF and better outcomes in moderate to severe ulcerative colitis.[313] A post hoc analysis of ACT 1 and 2 clinical trials noted that patients in the lowest quartile of infliximab serum concentration were less likely to achieve clinical response, remission and mucosal healing, independent of randomised dose (5 mg/kg or 10 mg/kg).[314] In ASUC, various factors, including a high TNF burden, proteolytic degradation of anti-TNF associated with increased drug clearance and faecal losses from increased gut permeability due to severe inflammation, support the need for dose optimisation of infliximab in this setting.[315] One study showed a relationship between serum and non-inflamed tissue anti-TNF drug levels, but for inflamed tissues, serum and tissue drug levels showed no association.[316] This suggests that high mucosal cytokine levels during inflammation act as a 'sink' for the drug, and thus a higher serum level of the drug may be required to neutralise tissue TNF.

In another study, a high baseline CRP (>50 mg/L) and a low serum albumin (<35 g/L), as surrogates for severe inflammation and extensive colitis, independently correlated with lower infliximab concentrations from weeks 0–6.[317] Consequently, several observational studies were conducted to investigate benefits of an accelerated or intensified dose of infliximab in patients with steroid-refractory ASUC. So far, the results have been conflicting. In a retrospective study, three doses of accelerated infliximab dosing at 5 mg/kg, administered over a median 24 days to steroid-refractory patients, demonstrated a colectomy rate of 6.7% compared with 40% (standard 5 mg/kg induction at 0, 2 and 6 weeks).[318] However, longer-term colectomy rates were similar between standard and accelerated dosing regimens.[318]

A review suggested that dose intensification may benefit half of patients with ASUC treated with infliximab, with case–control studies showing that 1–2 extra infusions in the first 3 weeks can dramatically reduce colectomy rates.[315] Conversely, a systematic review that included 10 observational studies assessing a pooled population of 705 patients found no difference between accelerated and standard induction regimens associated with either short-term (17% vs 14.5%) or long-term (25% vs 30.7%) colectomy rates, and no significant difference in complication rates.[319] In a recent open-label randomised trial (NCT02770040) conducted in 13 Australian centres, 138 patients with steroid-refractory ASUC were randomised to receive a first dose of 10 mg/kg or 5 mg/kg infliximab in a 1:2 ratio.[320] Patients in the 5 mg/kg group were re-randomised 1:1 to standard or accelerated induction groups. Patients in the 10 mg/kg group received a second dose at day 7 or earlier at time of non-response. There was no difference in day 7 clinical response between 10 mg/kg and 5 mg/kg groups (65% (30/46) vs 61% (56/92), p=0.76). In the 5 mg/kg group, the rate of day 7 response was numerically lower in those with albumin <25 g/L vs ≥25 g/L (47% (15/32) vs 68% (41/60), p=0.07). However, no difference in clinical response was observed in the 10 mg/kg group when stratified by albumin (64% (9/14) vs 66% (21/32) p>0.99). Patients receiving intensified or accelerated induction achieved clinical and biochemical remission earlier than with standard induction, but there was no difference in outcomes at 3 months.

### GPS 48

Oral Janus kinase inhibitors may be considered in selected patients with ASUC who are corticosteroid-refractory and, after careful consideration and counselling of benefits and risks.

Oral JAK inhibitors, tofacitinib and upadacitinib, have been approved by medical regulatory authorities for the treatment of moderate to severe ulcerative colitis. The OCTAVE clinical programme demonstrated the superior efficacy and safety of tofacitinib in moderate to severe ulcerative colitis.[250] Subsequently, upadacitinib also demonstrated superior efficacy and similar safety to placebo for induction and maintenance of moderate to severe ulcerative colitis. There have been several reports of successful off-label use of these oral small molecules for the management of steroid-refractory ASUC. A short half-life with rapid symptomatic improvement by as early as day 3 in moderate to severe ulcerative colitis and less susceptibility to intestinal loss than infliximab make these agents attractive options for the management of ASUC. However, there are concerns regarding an increased risk of major adverse cardiac events and thrombotic events in patients exposed to



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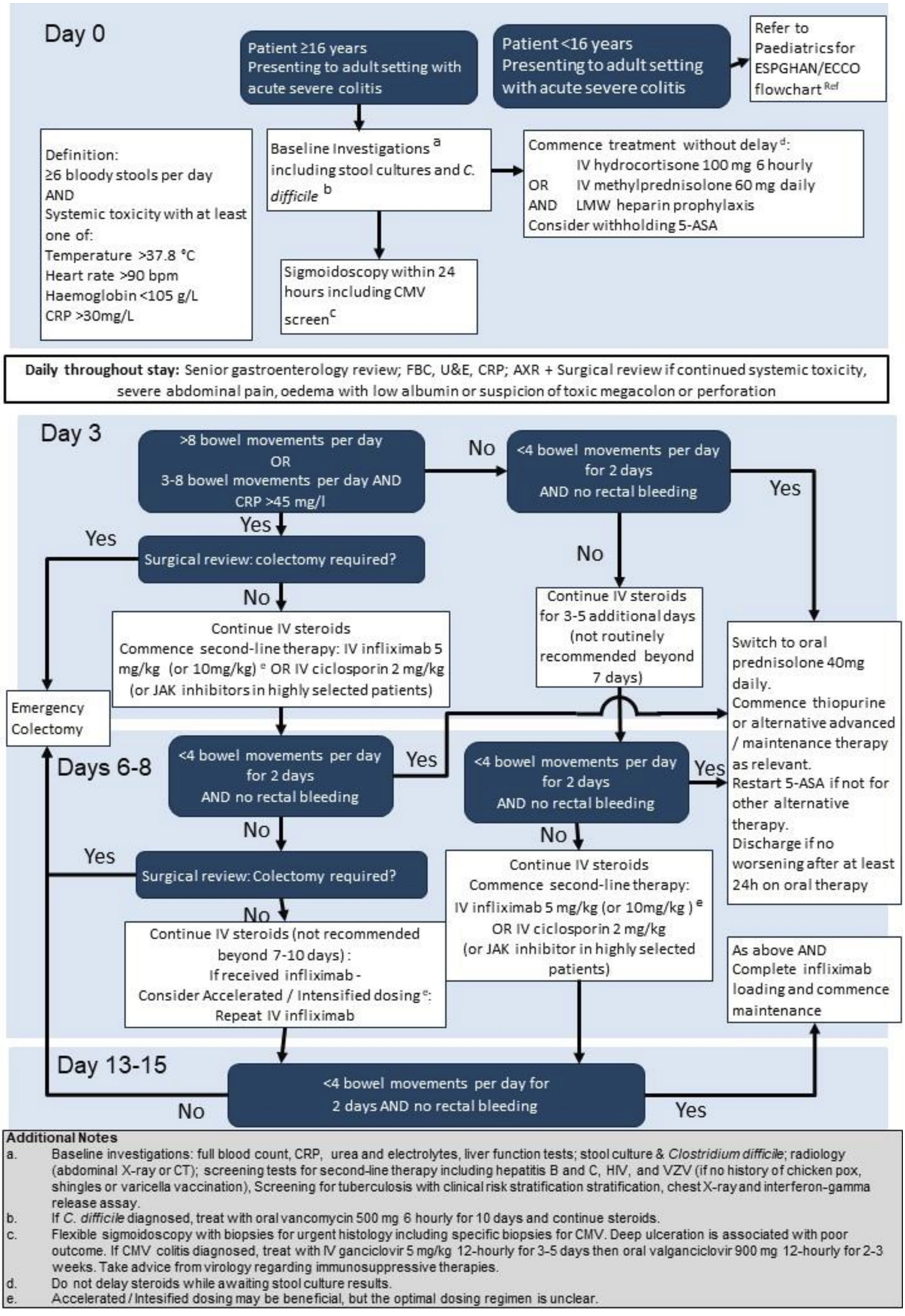



**Figure 4** Management of acute severe colitis. 5-ASA, 5-aminosalicylic acid; AXR, abdominal X-ray; CMV, cytomegalovirus.



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tofacitinib.[183] Consequently, the FDA issued a black box warning for all currently approved JAK inhibitors, and guidelines now recommend tofacitinib as a second-line agent after failure of anti-TNF therapy in the USA. Therefore, these drugs should be used with caution in patients with ASUC, which is itself considered an additional risk factor for thrombosis.

A retrospective cohort study of tofacitinib in hospitalised paediatric patients with ulcerative colitis for whom corticosteroids and infliximab had failed , demonstrated that 8 out of 11 (73%) patients were free of colectomy at 90 days and 6 (54%) were free of colectomy at 6 months.[321] In another retrospective cohort study, hospitalised patients with ASUC who received tofacitinib (n=40) were matched to controls with ASUC according to sex and date of admission (n=113).[322] The 90-day colectomy rate was significantly lower in patients managed with tofacitinib induction therapy in addition to intravenous corticosteroids (HR=0.28; 95% CI 0.10 to 0.81; p=0.018) compared with patients in the control group, when adjusted for disease severity covariables. Subgroup analyses showed that this benefit was statistically significant with tofacitinib doses of 10 mg three times daily, but not with twice-daily dosing. Although these data are interesting, they are largely limited to retrospective case series and should not be used to inform routine clinical practice.

In an interim analysis from a recent phase IV prospective interventional trial, conducted across five Canadian hospitals (NCT04925973), which recruited patients with ASUC refractory to 3 days of IV corticosteroids, 24 patients with ASUC received tofacitinib 10 mg twice daily. Day 7 clinical response was achieved in 58.3% (14/24) patients, and at 6 months, 45.8% (11/24) patients remained on tofacitinib.[323] In another recent pilot RCT, 104 patients with ASUC were randomised to receive tofacitinib 10 mg three times daily for 7 days while continuing IV corticosteroids. At day 7, a statistically significant proportion of patients receiving tofacitinib achieved response (83.0% (44/53) vs 58.8% (30/51), p=0.007) compared with patients receiving placebo. Notably, one patient receiving tofacitinib developed dural venous sinus thrombosis. There are a few reported case series of patients with steroid-refractory ASUC whose disease was successfully managed by upadacitinib.[324 325] The use of JAK inhibitors in ASUC is currently supported by only limited evidence and should therefore be restricted to corticosteroidrefractory patients in whom conventional rescue therapy is contraindicated or has historically failed. Therefore, efficacy and safety of these agents for ASUC should be assessed rigorously in well-designed RCTs. There is insufficient evidence to make any recommendation on sequential ASUC treatments required within the same admission.

## PREOPERATIVE CORTICOSTEROIDS

**GPS 49**

We recommend that prior to elective surgery for ulcerative colitis, corticosteroids should be stopped, or the dose minimised wherever possible to reduce risk of postoperative complications.

**GPS 50**

We recommend that patients with ulcerative colitis should not undergo pouch surgery while taking corticosteroids.

**GPS 51**

We recommend that patients with IBD who have been taking oral corticosteroids for more than 4 weeks prior to surgery should receive an equivalent intravenous dose of hydrocortisone while nil by mouth in the perioperative period.

While the data from the ulcerative colitis population are fewer, patients with ulcerative colitis taking corticosteroids have a higher risk of postoperative infectious complications after IBD surgery,[326] reflecting the studies of mixed IBD or Crohn's disease populations.[327–330] This is further borne out by studies from cohorts of patients with Crohn's disease. There is some evidence from studies of a mixed group of patients with IBD and Crohn's disease that risks are greater for those taking high-dose corticosteroids (40 mg prednisolone or more).[328 330] A comparison of prednisolone doses greater than 20 mg vs 20 mg or less did not show a significant difference in risk of infections.[327] Use of ≥15 mg oral corticosteroid in patients with ulcerative colitis within 30 days of ileal pouch-anal anastomosis (IPAA) surgery, or ≥20 mg in the setting of proctocolectomy, is associated with an increased risk of complications.[331 332] Patients with IBD having elective surgery should have their corticosteroids stopped if possible or brought to the lowest dose that can be managed without deterioration. Patients who are taking corticosteroids at the time of their IBD surgery should be given IV hydrocortisone in equivalent dose until they can resume oral prednisolone.[329] Prednisolone 5 mg is equivalent to hydrocortisone 20 mg or methylprednisolone 4 mg. There is no additional advantage in increasing steroid dosage to cover stress in the perioperative period, as shown in a randomised trial in IBD surgery[333] and case series.[334] Anaesthesiologists generally consider a single dose of corticosteroid prior to induction (such as dexamethasone 4 mg intravenously or intramuscularly) for those taking more than 5 mg prednisolone.[335] Patients who are taking physiological corticosteroid replacement because of disorders of the hypothalamic pituitary axis (such as oral hydrocortisone 20 mg in the morning, 10 mg at night) should receive supplemental doses in the perioperative period.[336] For patients who have had complete resection of active disease, it is important to avoid inappropriate prolongation of steroids after surgery, and there is virtue in standardised steroid-tapering protocols in the postoperative period, dependent on the dose and duration of steroids preoperatively.

## PREOPERATIVE 5-AMINOSALICYLIC ACIDS (5-ASAS)

A meta-analysis of 5-ASA therapy leading up to surgery does not report an association with an increased risk of postoperative complications, although only one study of patients with ulcerative colitis was included.[326]

## PREOPERATIVE PURINE ANALOGUES

The literature on the use of immunosuppressive therapy (purine analogues and methotrexate) leading up to surgery does not describe an association with an increased risk of postoperative complications in patients with ulcerative colitis .[326 328]

## PREOPERATIVE ANTI-TNF THERAPY

For preoperative anti-TNF exposure in patients with ulcerative colitis, three meta-analyses concluded that the risk of postoperative infectious complications after IBD surgery was not



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**GPS 52**

We recommend that anti-TNF therapy can be continued in the preoperative period for patients undergoing surgery for ulcerative colitis.

increased overall (although data are fewer than for Crohn's disease).[326 337 338] A recent prospective observational study of a pooled IBD population showed no increased risk of infective complications in patients with IBD exposed to anti-TNF within 12 weeks of surgery and/or with detectable anti-TNF trough levels.[339]

### PREOPERATIVE ANTI-INTEGRIN THERAPY

**GPS 53**

We recommend that anti-integrin therapy can be continued in the preoperative period for patients undergoing surgery for ulcerative colitis.

One study of vedolizumab exposure in a pooled IBD population showed an increased risk of infectious and non-infectious postoperative complications compared with those who had received recent anti-TNF.[340] However, two more recent meta-analyses, comparing vedolizumab with anti-TNF or no biologic exposure, and vedolizumab with no vedolizumab, concluded that there were no significant differences in infectious or non-infectious postoperative complications of abdominal surgery in patients with IBD.[326 341] Relevant data for other advanced therapies are lacking.

### SURGERY IN ULCERATIVE COLITIS

#### Surgical management of ASUC

**GPS 54**

We recommend that subtotal colectomy and ileostomy with preservation of the rectum should be offered to patients who have not responded to medical therapy at least by day 7 of treatment for acute severe ulcerative colitis, and that surgical resection of the colon and rectum should be offered to patients who have chronic, active ulcerative colitis despite optimised medical therapy. Ileoanal pouch reconstruction or end ileostomy provide equivalent levels of quality of life, and selection should be guided by patient preferences and choice.

Surgery in ASUC is indicated when the disease is non-responsive to medical therapy, when there are intolerable side-effects of medication options, or when there is life-threatening haemorrhage, toxic megacolon or perforation.[8] For acute severe ulcerative colitis, the preferred operation is a subtotal colectomy and end ileostomy with long rectal stump.[342–344] Surgical input at an early stage helps patients to understand that colectomy is an important treatment option and is not an outcome to be avoided at any cost. While the guideline suggests that surgery should be offered at least by day 7, it is recommended that surgical involvement and engagement in discussions with the patient about the potential for surgical options will often take place prior to this. Early surgical involvement and joint decision-making is essential to avoid unnecessary delays.[8] The procedure itself can be performed either laparoscopically or open depending on local expertise, although a laparoscopic approach is likely to result in shorter length of stay and reduced risk of infectious complications.[345–347]

In addition, surgical resection of the colon and rectum in ulcerative colitis is a treatment option for patients who have chronic, active symptoms despite optimised medical therapy. Proctocolectomy followed by IPAA is a well-established management option for ulcerative colitis. This procedure has been associated with good outcomes for quality of life, with a majority of patients indicating they would undertake the same procedure again.[348–351] IPAA should not be undertaken in the acute setting, given the significant risk of complications. Timing of pouch surgery should be an individualised decision with multidisciplinary input, with a minimum of 3 months and preferably 6 months from the initial subtotal colectomy in order that adhesions may be safely managed, and the patient allowed time to generally recover from the initial procedure.[8] Pouch surgery discussions should ideally take place with a surgical team that has experience of performing pouch surgery in a high-volume centre. If local expertise is not available in pouch surgery, then patients should be referred onwards for discussion at a high-volume pouch centre. At the time of ileoanal pouch surgery, a temporary loop ileostomy will reduce the clinical anastomotic leak rate as well as the septic sequelae of a leak. Creation of an ileoanal pouch without creation of an initial temporary loop ileostomy is uncommon and should be considered only in optimal circumstances.[347] Any subsequent anastomotic leak from an ileal pouch anal anastomosis would generally require defunctioning.[8] The occurrence of complications following IPAA surgery in patients with coexistent ulcerative colitis and primary sclerosing cholangitis (PSC) are higher, with pouchitis rates as high as 64% reported.[352 353] In a more recent study comparing PSC-pouchitis (n=182) with matched non-PSC-ulcerative colitis-pouchitis (n=182), patients with PSC-pouchitis were more likely to develop chronic pouchitis (68.1% vs 34.1%; p<0.001), have moderate-to-severe pouch inflammation (54.9% vs 32.4%; p<0.001) and prepouch ileitis (34.1% vs 11.5%; p<0.001) compared with ulcerative colitis-pouchitis.[354] However, patients can still be offered pouch formation if they have PSC so long as they have had detailed counselling and understand the potential implications and risks of such a procedure.

### POUCHITIS

**GPS 55**

Patients with ongoing symptoms after pouch surgery should have pelvic MRI scan, stool culture and *Clostridioidies difficile* assay. Pouchoscopy should be performed to assess the pouch, the pre-pouch ileum and the mucosa at the anal transition zone.

Complications following IPAA are relatively common, and can include infective, inflammatory or functional pouch disorders. Pouchitis is the most common complication. Acute pouchitis, also known as intermittent pouchitis, is defined as pouchitis of less than 4 weeks' duration which resolves fully with between 2–4 weeks antibiotic therapy. Chronic antibiotic-dependent pouchitis describes frequent episodes of pouchitis that are initially antibiotic responsive, but reccur days to weeks after



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completion of antibiotic therapy. Chronic antibiotic refractory pouchitis describes inadequate or incomplete response to antibiotic therapy with continuous or relapsing-remitting symptoms. Cuffitis describes inflammation of the pouch localised to the rectal cuff. Additionally patients with IPAA may suffer from Crohn's-like disease of the pouch, whereby disease phenotypes more akin to Crohn's disease appear; these include fistula arising greater than 12 months after surgery, stricture of the pouch body or pre-pouch ileum or pre-pouch ileitis.

Acute and chronic pouchitis are the most common complications after IPAA formation following subtotal colectomy for ulcerative colitis. Patients suffer from diarrhoea, rectal bleeding, pain, faecal urgency and reduced quality of life. In a large retrospective study from the USA, 48% of patients experienced pouchitis within 2 years of surgery, increasing to 80% within 30 years, reported in a longitudinal prospective study.[355 356] In a separate single-centre study, approximately 17% of patients had either chronic antibiotic-dependent pouchitis or antibiotic-refractory pouchitis, with symptoms lasting more than 4 weeks, for which the frequency of relapse can vary significantly between patients.[350]

Consideration of pouchitis should prompt evaluation of the severity with biochemical markers, such as faecal calprotectin and blood tests, and endoscopic assessment to include examination of the pre-pouch ileum, pouch body and mucosa at the anal transition zone (the rectal cuff).[357] Other conditions, such as pelvic sepsis, specific infections such as *C. difficile*, mechanical obstruction, pre-pouch or anal stenoses, pelvic floor dysfunction or non-pouchrelated conditions, should be considered.

### Efficacy of treatments for the induction of clinical remission of pouchitis in adults

**GPS 56**

We recommend a 2 week course of ciprofloxacin or metronidazole as the first-line treatment of acute pouchitis. We suggest that ciprofloxacin is better-tolerated and may be more effective than metronidazole. We suggest that chronic pouchitis may be treated with a combination of antibiotics (ciprofloxacin, metronidazole, tinidazole, rifaximin), oral budesonide or oral beclometasone.

**GPS 57**

Acute treatments for pouchitis are normally well-tolerated yet patients should be counselled about possible side-effects and advised to seek medical advice should they experience adverse events. Antibiotics should be prescribed at the lowest dose and for the shortest duration possible to achieve the intended clinical benefit.

**GPS 58**

Chronic refractory pouchitis not responding to antibiotics or locally-acting corticosteroids should be reassessed to consider other factors and, if excluded, we suggest that patients may be offered advanced immunosuppressive therapies. Vedolizumab is suggested as first-line therapy.

Infrequent episodes of acute pouchitis may be treated with a short course of antibiotics. A small, randomised study testing the efficacy of ciprofloxacin 1 g/day against metronidazol 0 mg/kg/day, reported that both groups achieved remission after 2 weeks of treatment (7/7 vs 6/9, RR=1.44, 95% CI 0.88 to 2.35), although ciprofloxacin produced better reduction in the Pouch Disease Activity Index, symptom scores and endoscopic outcomes.[358] A 2–4-week course can be considered where sufficient benefit is not derived from a 2-week course. Budesonide enemas (2 mg/100 ml at night) are an option, with comparable clinical remission and response rates to metronidazole (500 mg twice daily) after 6 weeks of treatment.[359] High-quality studies to support the use of probiotics or faecal microbiota transplantation to treat acute pouchitis are lacking.

The advanced therapy with the most data to support use in chronic pouchitis is vedolizumab; the EARNEST study, a phase IV multicentre double-blind placebo controlled RCT, demonstrated efficacy of vedolizumab in management of chronic antibiotic-dependent or antibiotic-refractory pouchitis.[350] In total, 102 patients were recruited and prescribed a 4week-course of 500 mg twice-daily ciprofloxacin at enrolment, alongside vedolizumab or placebo infusions (both n=51) at the standard induction and maintenance intervals. Clinical remission was higher in the vedolizumab group at week 14 (16/51, 31% vs 5/51, 10%) and at week 34 (18/51, 35% vs 9/51, 18%). In contrast, a small, randomised trial comparing adalimumab with placebo for chronic pouchitis showed no benefit.[360] The effectiveness of other therapies in chronic pouchitis, has only been reported in observational cohort studies. Pooled data from these studies indicate clinical response rates of 54% for anti-TNF medications, 72.3% for ustekinumab, 52.0% for vedolizumab and 30.9% for tofacitinib, although though confidence levels are wide across the drugs.[357]

In the study comparing ciprofloxacin and metronidazole to treat acute pouchitis, ciprofloxacin was better tolerated. No patients receiving ciprofloxacin experienced adverse events, while 33% of the metronidazole group had side-effects such as vomiting, dysgeusia and transient peripheral neuropathy.[358] A study comparing metronidazole with budesonide enemas, reported withdrawal owing to adverse events in 14% in the metronidazole group, compared with 0% in the budesonide group, with symptoms such as metallic taste, headache and anorexia.[359]

## CROHN'S DISEASE

The treatment of Crohn's disease is commonly approached in two phases: initially aiming for control of active disease (induction of remission), followed by ongoing treatment to maintain remission. While traditionally corticosteroids have been used for the induction of remission, with exclusive enteral nutrition (EEN) and surgery also used in some situations, the available evidence supports the initiation of early, effective treatment in the form of an advanced therapy (biologic and small molecule drugs), particularly for those patients with moderate and severe disease activity.[361]

Early effective treatment has the potential to modify disease behaviour and prevent complications, including a need for surgery. Besides proving a safer approach than an 'accelerated step-up' strategy (steroids, followed by thiopurine and then anti-TNF), it also require less use of healthcare resources.[362]

The recent expansion in therapeutic classes has made treatment selection an increasingly complex decision, particularly when first-line therapy has failed. Consideration of factors such



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as previous treatment experience, disease trajectory, expected efficacy, speed of onset and durability of effect, adverse effect profile, and patient factors, including choice of route of delivery, comorbid conditions, local availability, resources and cost is necessary. The optimal preferred treatment may differ markedly between patients, and typically a multidisciplinary meeting approach can assist in providing the optimal next steps for the individual patient's management.[362]

While there may be less certainty around the management of mild disease, frequent monitoring including an array of markers for gut inflammation (faecal calprotectin, intestinal ultrasound, MRE, ileocolonoscopy) is key to identifying those patients with ongoing inflammation who may benefit from therapy optimisation. Regular disease monitoring is also essential for patients established on advanced therapies as ongoing disease activity or progression of bowel damage might suggest that a change in medical therapy or a surgical approach is indicated.[361]

## STEROIDS IN CROHN'S DISEASE

### GRADE statement: Corticosteroids

**Systemic corticosteroids are suggested for induction of remission in patients with moderate to severe Crohn's Budesonide is suggested for the induction of remission in patients with mild ileocaecal Crohn's disease with treatment for not more than 12 weeks with mild ileocaecal Crohn's disease with treatment for not more than 12 weeks.disease, for not more than 8 weeks (moderate certainty, moderate effect size). Corticosteroids are not recommended for maintenance of remission in patients with Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Small**.

**Justification**: Systemic corticosteroids are effective for induction of remission, but not maintenance therapy, in Crohn's disease, and may be associated with increased risk of adverse events. We suggest offering systemic corticosteroids for no longer than 8 weeks. Controlled ileal release budesonide is as effective as systemic corticosteroids for induction of clinical remission, but not for maintenance in mild to moderate ileal or right-sided ileocolonic Crohn's disease

**Implementation considerations**: Corticosteroids are easily accessible, but systemic corticosteroids may be associated with significant side effects, both when patients receive recurrent induction courses, or when the corticosteroids are continued long term. The relatively arbitrary duration of up to 8 weeks was set considering that early effective treatment is important for the long-term management of Crohn's disease. The consideration of early clinical and/or biomarker (ie, fCAL) assessment (ie, 2 weeks after commencement) may be useful in order to achieve timely escalation to an effective treatment, if required.[361] It is vital to consider best practice related to side-effects due to corticosteroid use, including good patient education and use of tools, such as giving patients a 'steroid alert card'.

In view of increasing evidence for early advanced therapy in moderate to severe Crohn's disease,[361 363] we advocate consideration of whether initiation or change of advanced therapy is required whenever a course of systemic corticosteroids is prescribed.

**Systemic corticosteroids for induction**: In a Cochrane review published in 2008,[364] two studies compared systemic corticosteroids with placebo and six studies compared systemic corticosteroids with 5-ASA.[364] Corticosteroids were found to be significantly more effective than placebo at inducing remission in Crohn's disease (RR=1.99; 95% CI 1.51 to 2.64; p<0.00001) with absolute risk reduction of 30% (95% CI 20% to 41%) and the number needed to treat (NNT) was 3.33 (95% CI 2.4 to 5.0). Corticosteroid induced adverse events in a higher proportion of patients than placebo (RR=4.89; 95% CI 1.98 to 12.07; p=0.0006), or low-dose 5-ASA (RR=2.38; 95% CI 1.34 to 4.25; p=0.003). The GRADE summary of findings is in online supplemental appendix 4, GRADE tables 20 and 21. Please see table 9 for estimated time to treatment goals for oral corticosteroids.

**Systemic corticosteroids for maintenance**: A Cochrane review performed in 2003[365] evaluated the effectiveness and safety of conventional systemic corticosteroid therapy in maintaining clinical remission in Crohn's disease. Three studies were included in the analysis. The ORs for relapse on active treatment and the corresponding 95% confidence intervals were 0.71 (0.39 to 1.31), 0.82 (0.47 to 1.43) and 0.72 (0.38 to 1.35) at 6, 12 and 24 months , respectively. The use of conventional systemic corticosteroids in patients with clinically quiescent Crohn's disease does not appear to reduce the risk of relapse over a 24-month period of follow-up. An updated literature search performed in July 2008 by the same authors did not identify any new trials.

**Budesonide for induction**: Thirteen induction trials were included in another meta-analysis.[366] Budesonide 9 mg/day was more effective than placebo (RR=1.93; 95% CI 1.37 to 2.73; GRADE: moderate) but less effective than conventional steroids (R=0.85; 95% C, 0.75 to 0.97; GRADE: moderate) for inducing clinical remission. At 8 weeks, 47% (115 of 246) of those receiving a daily dose of budesonide 9 mg/day achieved remission compared with 22% (29/133) of those receiving placebo. Please see table 9 for estimated time to treatment goals for budesonide.

Budesonide was inferior to conventional steroids (pooled RR=0.85; 95% CI 0.75 to 0.97; p=0.012; $I^2$=0%; eight studies; 750 participants). Conventional steroids were no longer superior to budesonide in those with mild to moderate disease as defined by CDAI<300 (pooled RR=1.00; 95% CI 0.65 to 1.56; p=0.99; $I^2$=67%; two studies; 175 participants) or those with ileal or right-sided ileocolonic disease (pooled RR=0.86; 95% CI 0.75 to 1.00, p=0.05; $I^2$=0%; six studies; 561 participants).

Corticosteroid-related AEs occurred less often with induction doses of budesonide than steroids (RR=0.64; 95% CI 0.54 to 0.76; GRADE: moderate); budesonide did not increase AEs relative to placebo (RR=0.97; 95% CI 0.76 to 1.23; GRADE: moderate). The evidence comparing budesonide with conventional steroids was of moderate quality.

**Budesonide for maintenance**: Budesonide 6 mg/day was not different from placebo for maintaining remission (RR=1.13; 95% CI 0.94 to 1.35; GRADE: moderate). Both induction (GRADE: low for 3 mg/day, moderate for 9 mg/day) and maintenance budesonide treatment (GRADE: very low for 3 mg/day, low for 6 mg/day) increased the risk of an abnormal adrenocorticotropic hormone test compared with placebo, but less than conventional steroids (GRADE: very low for both induction and maintenance). We suggest that the specific phenotype, disease activity, chronicity and burden are all considered as part of shared decision-making when deciding whether or not to use corticosteroids.

We suggest that repeated courses of steroids are avoided unless futility of other effective therapies has been established, and surgical options are not available. Importantly the GDG aims to encourage early assessment (ie, 2 weeks) of clinical and/



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or biochemical (ie, fCAL) response hoping to encourage early initiation of effective treatment, which has been shown to associated with sustained, corticosteroid-free clinical remission and avoidance of surgical interventions.[361] We propose that the clinical team review the response to an induction course of corticosteroids and in cases of limited or poor response, consider the appropriateness of other treatments.

Conventional corticosteroids are effective for induction of remission but not maintenance therapy in Crohn's disease but may be associated with an increased risk of adverse events. The efficacy is of low certainty from trials, and there is no head-to-head comparison of safety in RCTs between short and long courses of corticosteroids (8 vs 12 weeks), but eminent expert opinion for safety has been considered and has led to the statement of 8 weeks.

## 5-ASAS IN CROHN'S DISEASE

### GRADE statement: 5-ASAs

**Summary of evidence:** A Cochrane review 2016[367] addressed induction therapy for mild to moderate active Crohn's disease, compared with placebo or active treatment, including steroids.[367] Included trials were of highly variable quality, with half rated as low quality. A separate Cochrane review[368] addressed maintenance therapy. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 22.

**Efficacy induction:** The Cochrane review included 20 studies (n=2367) of variable quality. A non-significant trend for benefit of sulphasalazine over placebo was seen, mainly within patients with Crohn's colitis (63/141 vs 43/148 remission at weeks 17–18 (RR=1.38 (1 to–1.89). Safety profiles were similar. Compared with corticosteroids, sulphasalazine was inferior (for remission RR=0.68). 5-ASA preparations are not more effective than placebo in induction of remission at various doses studied, including 4–4.5 g/day.

**Efficacy maintenance:** A Cochrane review of maintenance of medically induced remission analysed 12 studies (2146 participants) compared 5-ASA with placebo. No difference was seen between 5-ASA (526/998) and placebo (544/1016) in remission rates at 12 months (RR=0/98, 0.9 to 1.07), for doses 1.6–4 g/day. Safety profiles were similar.

**Certainty and rationale:** There is overall low-certainty evidence of no therapeutic effect of 5-ASA for induction or maintenance treatment of Crohn's disease. Numerous specific regimens, doses and subgroups have been assessed, although variable quality studies. Safety profiles are equivalent. Based on this the GDG does not support the use of 5-ASAs in the induction and maintenance of remission in Crohn's disease. For patients already receiving such therapy, a discussion should be held to reach a shared decision before any change in therapy is made.

**5-ASA use is not suggested for induction and maintenance of remission for patients with Crohn's disease.**

Recommendation: **Conditional**. Overall certainty. **Low**. Overall magnitude: **Trivial.**

**Justification**: 5-ASAs are not effective in induction and maintenance of remission, with efficacy assessed through direct pairwise meta-analysis.

**Implementation recommendations**: This recommendation is unchanged from the 2019 guideline as there are no new studies to include in analysis. For patients already established on 5-ASAs for Crohn's disease, we would suggest confirmation of biochemical remission with a faecal calprotectin. When deciding whether to continue in patients established on 5-ASA and in remission, we advocate shared decision-making with the patient. Because the safety profile is similar to that of placebo, when patients are keen to continue established therapy, this should be respected.

**Methotrexate is not suggested for use as monotherapy treatment for induction and maintenance of remission for patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty. **Very low**. Overall magnitude: **Small.**

**Justification**: GRADE evaluation did not show evidence of a beneficial effect of methotrexate monotherapy in Crohn's disease beyond the value determined to be a trivial effect. Cochrane review results of pairwise analysis for induction are of moderate certainty for a trivial effect size for efficacy, and of moderate and low certainty for no difference for safety outcomes. The maintenance of remission Cochrane review showed with low certainty a small effect size for efficacy and low certainty for trivially more total adverse events.

In the NMA, certainty was very low for induction and maintenance. The RCT data for safety were all of very low certainty.

**Implementation considerations**: For patients already in remission on methotrexate, a discussion should be held to reach a shared decision before any change in therapy is made

## IMMUNOMODULATORS IN CROHN'S DISEASE

### GRADE statement: Methotrexate

**Summary of evidence:** A 2014 Cochrane review of induction of remission with a total of seven RCTs,[369] and a 2014 review of maintenance of remission, including five RCTs,[370] were undertaken. Data from these RCTs were also included in our technical review network meta-analyses. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 23.

**Efficacy induction:** GRADE analyses indicated that the quality of evidence was very low to low for most outcomes. The network meta-analysis demonstrated very low certainty data for induction of remission and, as well as for WAEs and TAEs. Please see table 9 for estimated time to treatment goals for methotrexate.

**Efficacy maintenance:** The maintenance Cochrane review concluded that methotrexate is probably better than placebo at the maintenance of clinical remission to 36–40 weeks (RR=1.57, 95% CI 1.1 to 2.23; 98 patients; moderate-certainty evidence, moderate effect size). However, this conclusion is based on very imprecise data, while inconsistency has not been taken into account. The network meta-analysis demonstrated very low certainty data for maintenance of remission.

**Certainty and rationale:** The evidence for methotrexate for induction, maintenance and safety outcomes is very uncertain. No advanced therapy trials had concomitant methotrexate use of more than 50%, limiting the data to a small set of old and predominately prebiologic populations.

## GRADE STATEMENT: PURINE ANALOGUES

**Summary of evidence:** In a 2016 Cochrane review of induction of remission, a total of 13 RCTs with 1211 adult participants for induction of remission were included.[371] They were conducted



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**Purine analogues (azathioprine and mercaptopurine) are not suggested for use as monotherapy in induction and maintenance of remission for patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Small.**

**Justification**: Purine analogues (azathioprine and mercaptopurine) have only trivial efficacy in induction of remission and small effect size for efficacy in maintenance of remission; they are therefore not routinely suggested for the management of Crohn's disease.

Cochrane review results of pairwise analysis for induction are of moderate certainty for a trivial effect size for efficacy, and of moderate and low certainty for no difference for safety outcomes. The maintenance of remission Cochrane review showed with low certainty a small effect size for efficacy and low certainty for trivially more total adverse events.

In the NMA, certainty was very low for induction and maintenance. The RCT data for safety were all of very low certainty.

**Implementation considerations**: For patients already in established remission on these agents, we would suggest a consultation to encourage shared decisionmaking, and do not suggest routinely stopping this therapy. Long-term safety outcomes that are not captured within the RCT study period should also be considered in clinical practice, when considering continuation of purine analogues for longer periods.

between 1971 and 2010. In a 2015 Cochrane review of maintenance of remission, 11 RCTs with 881 adult participants were included.[372] They were conducted between 1971 and 2013 The studies included in both reviews ranged in terms of previous medication use, and allowed concomitant medication during the trials, but no advanced therapies were permitted. The data from these RCTs were also included in our technical review network meta-analyses. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 24.

**Efficacy induction:** Based on the induction Cochrane review purine analogues are probably not more effective than placebo for clinical remission (95/197 vs 68/183 achieved remission; RR=1.23, 95% CI 0.97 to 1.55; and clinical response (107/225 vs 75/209; RR=1.26, 95% CI 0.98 to 1.62). The evidence was moderate certainty. The safety outcomes of the review were low and moderate in GRADE certainty for no difference with placebo. The network meta-analysis demonstrated very low-certainty data for induction of remission and clinical response, as well as for all safety outcomes.

**Efficacy maintenance:** In the Cochrane review, 73% of participants treated with purine analogues maintained clinical remission over a 6- to 18-month period, compared with 62% of participants receiving placebo (RR=1.19, 95% CI 1.05 to 1.34; five studies, 489 participants; low-certainty evidence, small effect size). There was low-certainty evidence that purine analogues may lead to more total adverse events than placebo (RR=2.45, 95% CI 1.02 to 1.64, trivial effect size). The other safety outcomes were of very low certainty. The network meta-analysis demonstrated very low-certainty data for maintenance of remission, as well as for all safety outcomes. A review of all RCTs in Crohn's disease found there is probably a higher occurrence of pancreatitis of 3.8% in patients exposed to purine analogues compared with those in 0.2% in placebo groups (moderate certainty).[373] Most were non-clinically relevant pancreatitis, but they did necessitate cessation of the purine analogues. As this was within the stringent monitoring of the trial environment, awareness in wider clinical use of this risk is important. For a wider consideration of the long-term safety profile of purine analogues please review section 5.3.2. Please see table 9 for estimated time to treatment goals for purine analogues.

**Certainty and rationale:** There is very uncertain evidence of any effect for purine analogues in the induction, and uncertain evidence for maintenance of remission in Crohn's disease. Moreover, despite attempts to reduce risk by pre-emptive TPMT±NUDT15 testing, when they occur, side effects may associate with significant morbidity (ie, pancreatitis). Consideration of this may be taken by starting low-dose azathioprine in combination with allopurinol, as the side-effect profile and tolerability may be improved with combination treatment.[374 375]

The PROFILE study demonstrated that top-down therapy with an infliximab and immunomodulator combination was superior at 1 year than with accelerated step-up therapy, starting with corticosteroid weaning and escalating sequentially to immunomodulator monotherapy at first relapse, followed by anti-TNF at second relapse, in the treatment of newly diagnosed Crohn's disease. This reinforces the importance of early, effective treatment with advanced therapies in achieving clinically relevant endpoints.[361]

## WITHDRAWAL OF MONOTHERAPY AZATHIOPRINE IN CROHN'S DISEASE

**GPS 59**

Patients with Crohn's disease considering withdrawal of immunomodulator monotherapy should be counselled that even with at least 6 months clinical remission after >2 years of therapy, withdrawal is associated with an elevated risk of relapse of one in three patients in the first 1 to 2 years and new Crohn's disease related complications.

The effects of withdrawal of immunosuppressant monotherapy in people with Crohn's disease in remission are uncertain. Low-quality evidence suggests that continuing azathioprine monotherapy may be superior to withdrawal of azathioprine for avoiding clinical relapse in people with Crohn's disease in remission.[376]

A Cochrane review[376] identified four RCTs where azathioprine monotherapy was stopped in patients with Crohn's disease in clinical remission. Thirty-two per cent (36/111) of participants withdrawing from azathioprine relapsed, compared with 13% (14/104) of participants who continued with azathioprine therapy (RR=0.42, 95% CI 0.24 to 0.72, GRADE low-quality evidence). The trials included patients in clinical remission, but there was no assessment of biochemical or endoscopic remission at the point of inclusion. Even so, these studies are likely to have selected a subgroup of patients whose Crohn's disease is responsive to azathioprine, by virtue of the fact they were in clinical remission while on azathioprine maintenance, and at elevated risk of relapse after azathioprine withdrawal. This reflects the real-world situation of many patients who are in clinical remission on long-term azathioprine monotherapy, where the risk of withdrawing azathioprine should be balanced against the risks of



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continuing treatment, such as the increased incidence of lymphoproliferative disorders in patients over the age of 50.[164]

In clinical practice, at the time of withdrawal of an immunomodulator, direct replacement with an advanced therapy without waiting for disease flare should also be considered.

## ADVANCED THERAPIES IN CROHN'S DISEASE

### GRADE statement: Advanced therapies

Certainty and rationale: While concerns about the safety of advanced therapies and cost associated with the use of this class of medication for the induction and maintenance of Crohn's disease have previously led to their positioning after corticosteroid and purine analogues or methotrexate use, accumulating evidence now supports that early, effective treatment is key for beneficial long-term outcomes for patients with Crohn's disease. The advent of biosimilars and availability of oral, subcutaneous and infusion options allows for a wider choice of agents, and modes of action that may facilitate a personalised approach taking into account each individual patient's needs when managing their Crohn's disease.

**Advanced therapies are suggested for induction and maintenance of remission in moderate to severe Crohn's disease.**

Recommendation: **Conditional**. recommendation, Overall certainty-**Low**. Overall magnitude – **Moderate**

**Justification**: Based on the available body of evidence (direct and network meta-analysis performed as part of this guideline), the efficacy and safety of advanced medical therapies (either biologics or JAK inhibitors), in comparison with no treatment or treatment with a purine analogue or methotrexate, is clear and summarised here. Three large, prospective studies have compared 'top-down' versus 'step-up' approaches and have shown superiority in both efficacy and safety with a 'top down' approach, including improvement in clinical activity, corticosteroid use, endoscopic remission and reduced need for surgery or hospitalisation.

PROFILE supports that early effective treatment in moderate/severe Crohn's disease can lead to sustained, corticosteroid-free remission, with lower risk for hospitalisations and surgery. Importantly, it provided further reassurance on the safety of this approach highlighting, as other phase III and IV studies have shown before, that the risks associated with active disease outweigh the risks of effective treatment.[361 377 378]

A suggestion, as opposed to a recommendation, is made due to the low certainty and moderate magnitude of evidence.

**Implementation considerations**: While this guideline does not aim to provide a 'one size fits all' approach or therapy by algorithm, this overarching principle is presented based on available data to encourage joint decision-making with patients at the heart of the MDT. It is likely that the decision on the appropriate therapeutic strategy will not just include consideration of the wider individual GRADE recommendations but depend on mode of action related to individual patient disease activity, mode of delivery, experience with particular agents and circumstances (ie, patient preference, family planning, pregnancy, frailty, presence of comorbidities including other immune-mediated inflammatory diseases, previous exposure to other treatments) and on local availability. It is important to highlight that surgery is a potential option that should be contemplated whenever an initiation or switching of medical therapy due to lack of efficacy is considered.

### GRADE STATEMENT: ADALIMUMAB (INCLUDES BIOSIMILAR)

**Summary of evidence:** In a 2019 Cochrane review of induction of remission, three RCTs with 714 adult participants for induction of remission were included. They were conducted between 2006 and 2012, with a mix of biologically naïve and exposed patients. In a 2020 Cochrane review of maintenance of remission, six RCTs, with 1158 adult participants, were included. They were conducted between 2007 and 2015; on a mix of advanced therapy naive and experienced patients. One study included patients in remission, three studies included patients who had shown response to a biologic, and two studies included those who had had ileocolonic resection. The data from these RCTs were also included in our network meta-analysis, apart from the studies on patients with ileocolonic resection, which are considered in a different section. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 25.

**Efficacy induction:** Based on the induction Cochrane review, adalimumab is more effective than placebo at week 4 for clinical remission (197/451 vs 173/263 failed to achieve remission; RR=0.85, 95% CI 0.79 to 0.9; and response (257/451 vs 199/263 failure to achieve 100-point response; RR=0.77, 95% CI 0.69 to 0.86). The evidence was high certainty. The safety outcomes of the review were low and moderate in GRADE certainty for no difference with placebo. The network meta-analysis demonstrated moderate certainty data for induction of remission and clinical response, with a moderate and a large magnitude effect, respectively. Safety outcomes ranged

**Adalimumab (including biosimilar) is recommended for induction and maintenance of remission for patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Moderate.**

**Justification**: Cochrane review results of pairwise analysis for induction and maintenance of remission are of high certainty, with a moderate effect size for efficacy and moderate/low certainty of no major differences from placebo for safety, for adalimumab alone (instead of combination). There are similar data for the use of biosimilar agents. In the NMA, certainty was moderate for induction of remission and response, with a similar magnitude effect size of moderate/large. For maintenance, the clinical picture is similar. The RCT data for safety ranged in certainty, but there was no indication of differences from placebo.

**Implementation considerations:** Adalimumab is widely available and used frequently in real-world practice, therefore on balance we suggest offering this option for induction and maintenance of remission in Crohn's disease. Risks of serious adverse events are trivial to small, meaning that in those who have achieved remission, continuing treatment can be suggested to maintain remission. Systems are in place to deliver this medication to patients, and monitoring of the safety and efficacy is assisted by the availability of drug and antibody titres. Decision as to whether to use the originator or biosimilar must be considered within the local clinical commissioning context, with no evidence to suggest inferiority of biosimilars.



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in their GRADE ratings. For all safety outcome with GRADE certainty between low and high, the differences from placebo were trivial. Please see table 9 for estimated time to treatment goals for anti-TNFs.

Efficacy maintenance: In the Cochrane review, 59% (252/430) of participants treated with adalimumab failed to maintain clinical remission at 52 to 56 weeks, compared with 86% (217/253) of participants receiving placebo (RR=0.70, 95% CI 0.64 to 0.77; three studies, 683 participants; high-certainty evidence). Among those who received prior TNF-α antagonist therapy, 69% (129/186) of adalimumab participants failed to maintain clinical or endoscopic response at 52 to 56 weeks, compared with 93% (108/116) of participants who received placebo (RR=0.76, 95% CI 0.68 to 0.85; two studies, 302 participants; moderate-certainty evidence).

The network meta-analysis demonstrated moderate-certainty data that adalimumab may lead to a large effect size increase in the maintenance of clinical remission. There were moderate-certainty data that adalimumab may lead to a small effect size increase in the maintenance of clinical response. The difference in magnitude between response and remission could be attributed to the inclusion criteria of clinical response at trial commencement, while the number of people in clinical remission at trial commencement is unclear.

*Certainty and rationale:* Adalimumab is one of the most widely used therapies for induction and remission for Crohn's disease. Based on literature review and synthesis the magnitude of effect is moderate with moderate certainty. The risks of adalimumab monotherapy may extend beyond the trial study period. The majority of systematic reviews/meta-analyses of observational data combine anti-TNF therapy for analysis, with further details discussed beneath the GRADE statement for infliximab. Real-world data supports an association between anti-TNF and lymphoproliferative disorders.

## GRADE STATEMENT: ADALIMUMAB WITH PURINE ANALOGUES (INCLUDES BIOSIMILARS)

**Summary of evidence:** There are no direct RCT data that compare adalimumab combined with purine analogues with placebo, but there are indirect data from an open-label RCT (DIAMOND) from 2016, which compared adalimumab combined with purine analogues with monotherapy adalimumab in 176 patients who were naïve to biologics and purine analogues.[380] Another study compared adalimumab combined with purine analogues with monotherapy adalimumab in 205 patients[381]; and one final study nominally compared adalimumab with placebo; however, more than 50% of the 325 included patients were receiving concomitant purines.[382] Specific evidence for dosing is lacking, as the trials do not report this. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 26.

**Efficacy induction:** The induction RCT data were included in the network meta-analysis we performed for induction of remission in Crohn's disease. Adalimumab with purine analogues is probably better than placebo, with a large effect, which can range from small to large. It may be better than placebo for clinical response, with a large effect, which can range from small to large. All safety outcomes for adalimumab with purine analogues were all of very low certainty, and no conclusions can be drawn.

**Efficacy maintenance:** There is no randomised evidence on maintenance. The data are lacking as the RCTs do not stretch to more than 12 months and did not perform re-randomisation of participants for a maintenance phase. Maintenance suggestions are though made based on the induction data.

**When Adalimumab is used for induction and maintenance of remission for Crohn's disease, it is recommended this is done in combination with purine analogues.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Moderate**.

**Justification**: The evidence suggests that adalimumab in combination with purine analogues is probably effective for induction of remission and response in Crohn's disease (the evidence is of moderate certainty). Of particular relevance is the magnitude of effect, which is 12% larger than adalimumab alone for remission and 7% larger for response, and the NNT doubles from 4 to 2.

The maintenance data are lacking for the network owing to lack of re-randomisation, but data from the DIAMOND[379] Trial only stretch to 12 months. Specific evidence for dosing is lacking, as the trial data do not report. If the choice is made to use this option, the GDG notes the recommendation for adalimumab combination with purine analogues, and this is also considered here.

Decision as to whether to use the originator or biosimilar must be considered within the local clinical commissioning context.

**Implementation considerations:** Individual patient-centred decision-making should guide the length of dual therapy, and consideration as to if or when purine analogues are started and stopped should be based on response and adverse event experience.

**Certainty and rationale:** While adalimumab has traditionally been seen predominantly as a medication that can be used as monotherapy, the network meta-analyses performed as part of this guideline suggest that in combination with a purine analogue there may be a therapeutic benefit, which is captured by the reduction in NNT from 4 to 2. There are no data to suggest that this may also be true for combination with methotrexate. Considering also the risk of immunogenicity, as demonstrated in a large, prospective, observational study with adalimumab monotherapy, the GDG decided that the combination of adalimumab with a purine analogue is recommended.[383] The appropriateness and length of combination therapy will need to be tailored to the individual patient's needs. The longer-term risks of adalimumab combination therapy may extend beyond trial follow-up, with the majority of real-world data including all anti-TNFs in analysis. This is covered within the infliximab combination therapy GRADE statement.

## GRADE STATEMENT: INFLIXIMAB (INCLUDES BIOSIMILARS)

**Summary of evidence:** In a Cochrane review of induction of remission, a total of 10 RCTs with 1101 participants for induction of remission were included.[384] They were conducted between 1999 and 2019, and seven RCTs included biologically naive participants. The age of the participants ranged from 26 to 65 years. In a Cochrane review of maintenance of remission, 9 RCTs with 1257 participants were included.[385] They were conducted between 1999 and 2022; seven RCTs included biologically naïve patients, and the remaining two included a mix of naïve/not naïve patients. Three studies included patients in clinical remission, five included patients with a mix of activity scores, and one study included biologic responders with active



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**Infliximab is suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty **Moderate**. Overall magnitude: **Moderate**.

**Justification**: Cochrane review results of pairwise analysis for induction of remission are low/moderate certainty for both efficacy and safety for infliximab alone (instead of combination), with moderate-effect size. In the network meta-analyses, certainty was low/moderate for remission and response, respectively, but with similar magnitude effect size of moderate. For maintenance, the clinical picture is similar. There are limited RCT safety data but significant expert experiential use of the drug. The magnitude is similar to that of the originator, infliximab, but the overall certainty is low for induction.

Maintenance data are of low to moderate certainty but of large effect size.

**Implementation considerations**: The recommendations regarding combination therapy with infliximab and purine analogues should be considered. Additionally, evidence from both pairwise and network analysis suggests similar efficacy for biosimilar preparations, both as primary therapy and if switched to these therapies and so this should be considered in the context of local commissioning; data concerning subcutaneous preparations were also of very low certainty, but given the impacts on feasibility and acceptability, this also represents an option to be considered if such factors are relevant on a case-by-case basis. Decision as to whether to use the originator or biosimilar must be considered within the local clinical commissioning context.

disease at baseline. All studies allowed some form of concomitant medication during their duration. The age of the participants ranged from 18 to 69 years old. The data from all the RCTs were also included in our network meta-analysis. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 27.

**Efficacy induction:** Infliximab may be more effective than placebo at week 4 for the induction of clinical remission (30/55 vs 3/25; RR=4.55, 95% CI 1.53 to 13.50; number needed to treat for an additional beneficial outcome (NNTB) 3) and response (36/55 vs 4/25; R=4.09, 95% CI 1.63 to 10.25, NNTB 3). The evidence was low certainty but is from just one small trial. This is because most trials are either against other comparators or in combination with other treatments (see below). The network meta-analysis demonstrated very low-certainty data for induction of remission, but clinical response probably (moderate certainty) demonstrated a large magnitude effect. There were no studies of endoscopic induction of remission. All safety outcomes were of very low-certainty evidence of no difference between infliximab and placebo. Please see table 9 for estimated time to treatment goals for anti-TNFs.

**Efficacy maintenance:** Infliximab is probably superior to placebo in preventing clinical relapse in patients who have mixed levels of clinical disease activity at baseline and are biologically naïve (56% vs 75%, RR=0.73, 95% CI 0.63 to 0.84, NNTB=5, moderate-certainty evidence). We cannot draw any conclusions on loss of clinical response, withdrawals due to adverse events or serious adverse events, because the evidence is very low certainty. Infliximab may be equivalent to biosimilar for clinical relapse (47% vs 40% RR=1.18, 95% CI 0.82 to 1.69), and may be slightly less effective in averting loss of clinical response (49% vs 32%, RR=1.50, 95% CI 1.01 to 2.23, low-certainty evidence), for a population with mixed/low disease activity at baseline. We cannot draw any conclusions on the effects of a subcutaneous biosimilar compared with an intravenous biosimilar due to very low-certainty evidence for all outcomes.

The network meta-analysis demonstrated low-certainty data that infliximab may lead to a moderate effect size increase in the maintenance of clinical remission. Although, it was noted that as this outcome was defined as loss of response from those who had only achieved response, not all the patient cohort could be expected to be included in this outcome and the actual effect was relatively larger. Endoscopic outcome data were not available.

**Certainty and rationale:** The overall certainty of the efficacy outcomes from the pairwise analysis was moderate. The network data were of lower certainty due to the impact of concomitant purine analogues that were very common across the cohort of RCTs and as such has left the evidence base much smaller for infliximab alone. Therefore, the pairwise data weres considered in detail by the GDG in the ETDs and led to this overall moderate judgement, mostly related to issues of risk of bias. The safety outcomes were all of very low certainty. For further detail on the safety of long-term infliximab please review section 5.4.1.

The GDG made a conditional recommendation as the sum of evidence for infliximab alone is relatively limited in certainty and magnitude data are capricious. Further consideration of biosimilars demonstrated no difference in efficacy as either primary therapy or when switched from infliximab in a state of remission. The GDG considered that biosimilars share properties so they should be considered under the single category of infliximab. Data for subcutaneous preparations were limited owing to significant imprecision and risk of bias concerns, but within the single study with 53 participants the rates of relapse were similar (17/28 SC vs 15/25 IV). The GDG noted that for some patients the advantages for acceptability and other pragmatic considerations may outweigh the evidence limitations, and as such, this remains an option.

## GRADE STATEMENT: INFLIXIMAB WITH PURINE ANALOGUES (INCLUDING CT-P13 BIOSIMILAR)

**Summary of evidence:** A recent Cochrane review considered the evidence base and in particular, the role of direct purine analogues study and its proxy study as a significant concomitant therapy.[384] There are no direct RCT data that compare infliximab combined with purine analogues with placebo, but there are indirect data from the SONIC trial,[386] which compared infliximab combined with purine analogues with infliximab alone and with purine analogues (three groups, 508 patients); the study of D'Haens 2008[387] compared infliximab combied nwith purine analogues with corticosteroids in 133 patients[388]; compared infliximab combined with purine analogues with infliximab alone and with purine analogues alone (three groups, 24 patients)[389]; compared infliximab combined with purine analogues with purine analogues alone in 115 patients[216]; compared infliximab combined with purine analogues with infliximab alone in 50 patients[390]; and[391] compared infliximab with natalizumab in 79 patients and infliximab with a biosimilar in 220 patients; however, more than 50% of their participants were receiving more than 50% concomitant purine analogues. The STOP-IT RCT compared infliximab with Purine analogues to Purine analogues for maintenance of remission in 115 participants.[392] Specific evidence for dosing is lacking, as the trials do not report this, or report it capriciously.



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**When infliximab is used for induction and maintenance of remission for Crohn's disease, it is recommended this is done in combination with purine analogues.**

Recommendation: **Conditional recommendation,** overall certainty **moderate,** overall magnitude **moderate.**

**Justification**: There is widespread availability and real-world application of the use of infliximab for induction and maintenance lone and in combination, including a recent Cochrane review. The evidence does exist for combination of moderate certainty for both induction and maintenance, but the larger magnitude in maintenance must be highlighted as this is close to 20% higher for combination therapy.

The evidence on safety is of very low-certainty, so no conclusions can be drawn. No data on the potential benefits of increasing longevity of infliximab through effects on immunogenicity are available in clinical trials. Expert eminence suggests the use of combination therapy.

**Implementation considerations**: Individual decisionmaking should guide the length of dual therapy and consideration as to if and when purine analogues are started and stopped (based on response and adverse event experience).

The GRADE summary of findings is in online supplemental appendix 4, GRADE table 28.

**Efficacy induction:** The induction RCT data were included in the network meta-analysis we performed for induction of remission in Crohn's disease. Infliximab with purine analogues is probably better than placebo, with a moderate effec,t which can range from small to large. They are probably better than placebo for clinical response, with a large effect, which can range from small to large. Endoscopic remission and response were of very low certainty, and no conclusions can be drawn. All safety outcomes for infliximab with purine analogues were all of very low certainty, and no conclusions can be drawn.

**Efficacy maintenance:** The maintenance data from the network meta-analysis for clinical relapse and withdrawals due to adverse effects and serious adverse events are of very low certainty, and no conclusion can be drawn. For all other outcomes, no maintenance RCT exists, or a network meta-analysis could not be performed.

The risks of infliximab combination therapy may extend beyond trial follow-up. Therefore, real-world data have been considered when describing safety outcomes, with the majority of data from pooled analysis of all anti-TNFs used in combination with purine analogues for management of IBD. Chupin *et al*'s meta-analyses of four observational studies, comprising 261 689 patients, demonstrate a pooled IRR (per 1000 patient-years) of lymphoma of 3.71 (95% CI 2.30 to 6.00; p≤0.01) with combination therapy, which is significantly greater than either purine analogue or anti-TNF monotherapy; pooled IRR=1.70 (95% CI 1.03 to 2.81; p=0.039) and 2.49 (95% CI 1.39 to 4.47; p=0.002) respectively.[225] A French national database cohort study of 189 289 patients also confirmed increased risk compared with both anti-TNF and purine analogue monotherapy, aHR=2.35 (95% CI 1.31 to 4.22; p<0.001) and 2.53 (95% CI: 1.35 to 4.77; p<0.001), respectively.[166] However, an earlier meta-analysis, while consistent with findings concerning relative risk, demonstrated the absolute risk of lymphoproliferative disorders with anti-TNF use to be relatively modest (6.1 per 10 000 patient years vs 1.9 per 10 000 as population expected) in a group who were largely also exposed to purine analogues[237].

Certainty and rationale: The data related to induction of clinical remission and response are of moderate certainty and moderate/large magnitude. Considering also the risk of immunogenicity, as demonstrated in a large, prospective, observational study with infliximab monotherapy, the GDG decided that the combination of infliximab with a purine analogue is recommended.[383] The appropriateness and length of combination therapy will need to be tailored to the individual patient's needs. Moreover, the superiority of top-down therapy with infliximab and purine analogues over accelerated step-up therapy should be once again highlighted.[361]

## THERAPEUTIC DRUG MONITORING

### The use of therapeutic drug monitoring for purine analogues

Purine analogues are pro-drugs that exert their action through metabolism into their active metabolites, thioguanine nucleotides (6-TGN) and the methylated metabolite (methylmercaptopurine (MMP)), implicated in adverse effects.[393] 6-TGN exert their anti-inflammatory action in IBD by incorporating into leucocyte DNA and inhibiting DNA synthesis and by inducing apoptosis of activated T lymphocytes.[394]

## PURINE ANALOGUES S-METHYLTRANSFERASE (TPMT)

Purine analogues S-methyltransferase (TPMT) enzymatic activity is a major determinant of purine analogues metabolism and is used as a guide for the initial dosing of purine analogues. Reduced TPMT enzymatic activity results in lower MMP levels, higher 6-TGN metabolites and an increased risk of severe and potentially life-threatening myelosuppression. Normal or high activity is most common (89%) in the general population with intermediate (11%) and low/absent activity (0.3%) relatively rare.[393 395]

For purine analogues monotherapy, a meta-analysis demonstrated that therapeutic levels of 6-TGN between 235 and 450 pmol/8×$10^8$ red blood cells (RBCs) were associated with an improvement in rates of clinical remission in IBD.[396–398] Table 1 describes the interpretation of purine analogues metabolites. In hypermethylators, purine analogues metabolism is skewed away from 6-TGN and towards MMP, which can lead to subtherapeutic 6-TGN (<235 pmol/8×$10^8$ erythrocytes) resulting in lower purine analogues efficacy, and elevated MMP levels (>5700 pmol/8×$10^8$ erythrocytes) increasing the risk of hepatotoxicity.[393] To detect hypermethylation, defined by a ratio of MMP to 6-TGN>11,[399] purine analogues metabolites can be checked as early as 4 weeks after initiation of purine analogues. Hypermethylation, and subsequent risk of hepatotoxicity can be reduced by switching patients to low-dose purine analogues (a reduction to 25–33% of the dose) in combination with allopurinol at a once daily dose of 100 mg.[375 400]

Use and interpretation of purine analogues metabolites are shown in table 8. Adapted from Goel *et al*.[401]

## NUDT 15

The higher prevalence of Nudix hydrolase 15 (NUDT15) enzyme variants in Asian populations has been recognised.[402] Genetic polymorphism results in a decreased function of the NUDT15 enzyme and increased levels of active purine analogue metabolites.[403]

Similar to patients with TPMT polymorphisms, patients with a genetic variant in only one NUDT15 allele (heterozygous) are



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**Table 8** Use and interpretation of purine analogues metabolites

| 6-TGN (pmol/8×10$^8$ RBCs | MMP (pmol/8×10$^8$ RBCs | Interpretation | Potential modification to treatment |
|---|---|---|---|
| Undetectable | Undetectable | Poor adherence | Explore factors contributing to adherence with patient. Rarely poor absorption |
| Low (<235) | Low/normal (<5700) | Subtherapeutic dosing/variable adherence | Increase dose by 25–33% and repeat metabolites in 4 weeks |
| Low (<235) | High (>5700 or MMP:TGN>11) | Purine analogues hypermethylator | Reduce purine analogues dose to 25–33% and start allopurinol 100 mg/day, then repeat metabolites after 4 weeks |
| Therapeutic[170 183 227–286 288–440] | Normal (<5700) | Correct dose of purine analogues | If clinically responding, continue current dose. If not responding, change drug category |
| Therapeutic[170 183 227–286 288–440] | High (>5700) | Possible supratherapeutic dosing | Reduce dose and repeat metabolites in 4 weeks. If MMP remains high, or if 6-TGN falls <235, consider adding allopurinol as above |
| High (>450) | High (>5700) | Supratherapeutic dosing | Reduce dose and repeat metabolites in 4 weeks |

MMP, methyl mercaptopurine nucleotides; RBCs, red blood cells; 6-TGN, thioguanine nucleotides.

recommended to start with a purine analogue dose between 30 and 80% of their normal dose, while patients with homozygous NUDT15-variant genotypes should not start purine analogues; however, NUDT15 testing is not currently widely available.[402 404] At time of publication NUDT15 testing is not widely available in the UK.

**Purine analogue monitoring in combination with anti-TNF therapies**

A recent retrospective review of patients ith IBD treated with purine analogues and infliximab combination therapy found sevenfold lower odds of developing antibodies to infliximab, with 6-TGN levels between 235 and 450 pmol/8×10$^8$ RBCs, compared with 6-TGN levels of <235 pmol/8×10$^8$ RBCs.[405] Several studies suggest targeting a 6-TGN level of >125 pmol/8×10$^8$ as this is associated with lower odds of infliximab anti-drug-antibody formation.[233 406–408] This suggests that targeting lower 6-TGN levels may be sufficient to optimise infliximab therapy in patients with IBD treated with purine analogues and infliximab combination therapy, with possible benefits including decreased immunosuppressive burden and reduced purine analogues toxicity. However, the PANTS extension study found that individuals in the highest baseline purine analogues dose quartile (azathioprine 2.20–4.15 mg/kg, mercaptopurine 1.06–2.95 mg/kg) were least likely to lose response to combination therapy, suggesting that full doses of purine analogues may be more efficacious in combination with anti-TNF therapy.[383]

**GPS 60**

For thiopurine monotherapy, we suggest thiopurine metabolites are used to optimisedrug dosing, aiming for 6-TGN levels 235-450 pmol/8x 10 8 RBCs and MMP levels < 5700 pmol/8x 10 8 RBCs, alongside routine blood monitoring. We suggest consideration of initiating a concomitant immunomodulator with or before initiation of an anti-TNF therapy to reduce the risk of anti-drug antibody development. We suggest monitoring thiopurine metabolites in combination therapy with anti-TNFtherapy; however, target levels are less clearly defined. We suggest aiming for 6- TGN levels of at least 125 pmol/8x 10 8 RBCs but 235-450 pmol/8x 10 8 RBCs may be needed to prevent immunogenicity to anti-TNF therapy. We suggest monitoring FBC, U&E and LFT at weeks 2, 4, 8, and 12, after initiating thiopurines and then at least 3-monthly to check for myelotoxicity and hepatoxicity.

## THE USE OF THERAPEUTIC DRUG MONITORING IN ANTI-TNF THERAPIES

Therapeutic drug monitoring (TDM) can be either proactive, where dosing is adjusted based on planned measurements of serum drug levels; or reactive, where measurements of drug levels are taken in response to some clinical change.[409]

A systematic review and meta-analysis of nine prospective RCTs comparing proactive TDM with conventional management did not demonstrate a benefit with proactive TDM for maintaining clinical remission in IBD.[410] A subsequent systematic review and meta-analysis, examining both reactive and proactive TDM, found proactive TDM to be associated with a decreased risk of treatment failure, relative to standard care (RR=0.64, 95% CI 0.48 to 0.86, p<0.01), and a reduced risk of hospitalisation relative to reactive TDM (R= 0.33, 95% CI 0.21 to 0.54, p<0.01).[411] While the earlier meta-analysis was more selective by only including RCTs, with hindsight the study designs may explain why they did not demonstrate any benefit from proactive TDM. In the TAXIT trial, patients with IBD were randomised to infliximab dosing based on either serum infliximab levels or clinical judgement alone, and similar proportions of each arm achieved clinical remission at 1 year.[412] However, at the time of study enrolment, 29% of patients were considered to have subtherapeutic infliximab levels (<3 μg/mL) and all patients had initial infliximab dose optimisation (levels of 3–7 μg/mL) prior to randomisation. Other studies only escalated the dose when infliximab and adalimumab levels were <3 μg/mL and<5 μg/mL, respectively.[412–416] Retrospective data now suggest that higher levels of >4.1 μg/mL and>6.2 μg/mL, respectively, are associated with clinical remission.[417 418] The PANTS extension study measured serum drug levels at week 14 after initiating anti-TNF and found that the optimal levels to predict remission at later time points over the 3-year study were 6.1–10.0 mg/L for infliximab and 10.1–12.0 mg/L for adalimumab.[383] The study also demonstrated that drug levels were associated with multiple factors, including dose, weight, immunogenicity and disease severity. Currently, however, there is insufficient evidence to recommend targeting such high levels.

While trough levels for intravenous (IV) infliximab are necessary, there is little variation of subcutaneous (SC) adalimumab throughout the cycle,[419] and this has also been found for SC infliximab.[420] IV and SC infliximab levels are not equivalent as was demonstrated in a study where 80 patients were switched from IV to SC infliximab with a resultant rise in mean trough concentration from 8.2±4.5 μg/mL to 14.5±5.9 μg/



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mL (p<0.001).[421] While optimal dosing levels have not yet been established, a recent RCT from the USA demonstrated that biweekly dosing of SC CT-P13 provided consistent serum infliximab concentrations above 13 µg/mL (range 13.2–16.3 µg/mL) for botu Ulcerative colitis and Crohn's disease, which was maintained from week 14 to week 54.[420] Another recent study demonstrated that higher concentrations of SC infliximab were associated with higher rates of favourable therapeutic outcomes, with serum concentrations >20 µg/mL significantly associated with patients with IBD in deep remission.[422]

Detecting and interpreting anti-drug-antibody levels is dependent on the type of laboratory assay, the dilution accuracy and the positivity thresholds.[423–426] For example, drug-sensitive assays have limited ability to detect anti-drug antibodies in the presence of circulating drug, due to the formation of anti-drug antibody–drug complexes whereas drug-tolerant assays detect anti-drug antibodies in the presence of detectable drug. Thus, it is important to interpret immunogenicity data in the context of the laboratory methods used. Furthermore, anti-drug antibodies have been shown to return to normal in a minority of patients when repeated 4 weeks later.[383] The PANTS extension study demonstrated that patients with loss of response associated with anti-drug antibodies had the lowest persistence of anti-TNF therapies. The use of TDM could therefore aid early decisions to switch therapy if anti-drug antibodies are detected.[383] Several small retrospective studies have consistently observed that anti-drug antibodies may be suppressed with the addition of an immunomodulator,[427] and a recent meta-analysis found this strategy resulted in an 87% reduction in anti-drug antibody levels, a 6.7-fold increase in infliximab trough levels, and recapture of clinical remission in 76%, although the total number of patients studied was small.[428] A subsequent study of 102 individuals on anti-TNF who developed anti-drug antibodies found dose escalation of anti-TNF therapy *plus* dose optimisation of an immunomodulator was the most effective strategy for suppression of anti-drug antibodies, which occurred in 65% of patients within a year, roughly twice that achieved with either strategy in isolation.[429]

**GPS 61**

Whilst there remains uncertainty about the benefit of therapeutic drug monitoring for anti-TNF therapies, strategies that lead to dose escalation, whether guided by TDM or not, tend to result in better clinical outcomes. Anti-TNF therapy dose escalation alone is less likely to be effective in the presence of anti-drug-antibodies andtherefore testing for these, when loss of response occurs, may guide treatment decisions, favouring either dose escalation plus the addition of an immunomodulator or a switch to another.

## THERAPEUTIC DRUG MONITORING IN NON-ANTI-TNF THERAPIES

Data for the exposure–efficacy relationships for vedolizumab (VDZ) and ustekinumab (UST) are inconsistent, and evidence for applying TDM in non-anti-TNF regimens are relatively scarce.

### VEDOLIZUMAB

As with anti-TNF therapy, low albumin and high body weight are predictors of accelerated VDZ clearance.[430] Post-hoc analyses of the GEMINI programme showed that week 6 VDZ serum levels <17 mg/mL (ulcerative colitis) and <16 mg/mL (Crohn's disease) were associated with clinical remission rates comparable to those of placebo.[431] Higher trough concentrations of VDZ in ulcerative colitis (>38.3 µg/mL) at week 6 were associated with clinical remission at week 14.[431] Furthermore, higher median trough concentrations of VDZ at weeks 2 (>35.6 µg/mL) and 4 (>59.4 µg/mL) were also associated with higher clinical remission rates at week 14, compared with patients not in clinical remission.[431] Dose escalation by increasing dosing frequency from 8-weekly to 4-weekly (GEMINI long-term study) in patients on maintenance therapy with secondary LOR, who had withdrawn early from the GEMINI-2 trial, was reported to have increased rates of clinical remission (32% vs 4% remission before dose increase).[432] The concomitant use of immunomodulators does not appear to affect the clearance of VDZ, the development of anti-vedolizumab antibodies, or enhance the efficacy of VDZ.[433 434] The available evidence suggests that for IV administration, VDZ concentrations of 33–37 µg/mL at week 6, 15–20 µg/mL at week 14 and 10–15 µg/mL during maintenance is associated with improved outcomes. Dose optimisation may improve clinical outcomes, in those with partial response or LOR. Further studies are needed to optimise the utility of TDM with VDZ.

### USTEKINUMAB

Available data on the correlation between trough serum UST drug concentrations and clinical outcomes are limited and mixed, making the role of therapeutic drug monitoring less clear. In the UNITI-1 and 2 studies in Crohn's disease, a median concentration of UST of 2.1 and 6.4 µg/mL respectively, for the 130 mg and 6 mg/kg dose groups and serum concentrations of the drug correlated with clinical remission at week 8.[435 436] In the maintenance (IM-UNITI) study, median steady-state serum trough UST concentrations at week 26 in the group receiving the drug every 8 weeks (1.97–2.24 µg/mL) were approximately threefold higher than in the group receiving the drug every 12 weeks (0.61–0.76 µg/mL), with a trend towards higher rate of clinical remission in the 8-weekly group. The recently published STARDUST trial reported that a trough serum UST concentration of 0.8 to 1.4 µg/mL or greater was associated with clinical remission at weeks 8 and 16.[437 438] Further studies have demonstrated that escalating the dose from 12-weekly to 8- or 4-weekly allowed response to be recaptured in >50% of patients.[436 439–441] Further studies are needed to optimise the use of TDM with UST.

**GPS 62**

Data for the exposure-efficacy relationships for vedolizumab (VDZ) and Ustekinumab (UST) are inconsistent, and evidence for applying TDM in non-anti- TNF regimens are relatively scarce. Dose escalation may improve clinical outcomes in those with partial response or LOR however there is insufficient evidence to support testing for vedolizumab or ustekinumab levels.

## GRADE STATEMENT: WITHDRAWAL OF INFLIXIMAB

**Summary of evidence:** The SPARE trial,[442] randomly assigned adult patients with Crohn's disease on combination therapy of infliximab and immunosuppressant therapy for at least 8 months and in corticosteroid-free clinical remission for more than 6 months, to one of three arms; continue combination therapy, withdrawal of infliximab or immunosuppressant therapy.



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**Routine withdrawal of Infliximab therapy is not suggested after 1 year of stable remission in Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Moderate**.

**Justification**: There have been two RCTs, and both have demonstrated an elevated risk of relapse in those discontinuing infliximab therapy, even with at least 6 months steroid-free remission and/or in full endoscopic, clinical, and biochemical remission.

**Implementation considerations**: Joint decisions regarding drug withdrawal should be taken in the context of the individual patient, their disease history, estimated risk of and predicted consequences of, relapse. Patient preference, disease history, severity and extent are key factors to guide shared decision-making.

Before withdrawal of any maintenance IBD therapy is considered, assessment of disease activity and confirmation of clinical remission using a combination of clinical, biochemical, endoscopic/histological, and/or radiological investigations should be considered to inform the risks and benefits of stopping, while accepting that even complete remission is associated with a sizeable risk of relapse.[392]

Patients with Crohn's disease should be counselled that even with at least 6 months corticosteroid-free clinical remission and with biochemical and endoscopic remission, anti-TNF withdrawal is associated with an elevated risk of relapse of approximately one in three patients in the first 1 to 2 years. Re-treatment with infliximab in the event of relapse is usually successful, but treatment failure may be higher in patients who smoke (HR=14 (1.5 o to 100)).

We suggest that patients in whom therapy is withdrawn, should be monitored for evidence of relapse. The optimal monitoring strategy following withdrawal of maintenance treatment has not been defined. Monitoring of clinical symptoms, objective markers of inflammation, such as C-reactive protein/faecal calprotectin and/or endoscopy and/or non-invasive imaging for reassessment, seems reasonable.

Relapse was defined by a CDAI of ≥250 at any visit or a CDAI between 150 and 250 with an increase of at least 70 points, over two consecutive visits, and a CRP >5 mg/L or a faecal calprotectin >250 μg/g. Overall, 207 patients were included in the final analysis; 67 in the combination group, 71 in the infliximab withdrawal group and 69 in the immunosuppressant withdrawal group. After 2 years, 39 patients had a relapse; 8 (12%) of 67 in the combination group, 25 (35%) of 71 in the infliximab withdrawal group, 6 (9%) of 69 in the immunosuppressant withdrawal group. At 2 years the HR for relapse was 3·45 (95% CI 1·56 to 7·69), p=0·003, for infliximab withdrawal versus combination, and 4·76 (95% CI 1·92 to 11·11), p=0·0004, for infliximab withdrawal versus immunosuppressant withdrawal. Of note, 22 of 23 patients in the infliximab withdrawal group who were re-treated with infliximab achieved remission. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 29.

Factors associated with time to relapse in multivariable analysis were: infliximab withdrawal group (HR=6·67 (95% CI 2·17 to 20), p=0·001 versus the combination group; HR=6·25 (95% CI 2 to 20), p=0·002 versus the immunosuppressant withdrawal group), young age at diagnosis <17 years (HR=3·34 (95% CI 1·43 to 7·82), p=0·005), high-sensitivity CRP at baseline as a continuous variable (1·0 mg/L of high sensitivity CRP inducing a 0·1 increment of HR; HR=1·10 (95% CI 1·00 to 1·20), p=0·039), faecal calprotectin >300 μg/g at baseline (HR=2·62 (95% CI 1·11 to 6·18), p=0·028), CDEIS at baseline as a continuous variable (1·0 point of CDEIS inducing a 0·1 increment of HR; HR=1·20 (95% CI 1·02 to 1·42), p=0·029). In patients who discontinued infliximab; only a 6-TGN at baseline >300 pmol per 8 × $10^8$ red blood cells was associated with a reduced risk of relapse (HR 0·23 (95% CI 0·07 to 0·69) p=0·009).

Treatment failure was associated with clinically significant stricture at the time of infliximab induction or during infliximab treatment (HR=3·68 (95% CI 1·41 to 9·61), p=0·008), and high sensitivity CRP at baseline as a continuous variable (1·0 mg/L of high sensitivity CRP inducing a 0·1 increment of HR; HR=1·14 (95% CI 1·0 to –1·21), p<0·0001). In patients who discontinued infliximab, the only factor associated with failure in multivariable analysis was active smoking (HR=14·28 (1·47 to 100·00), p=0·022).

The STOP-IT Trial (Discontinuation of Infliximab Therapy in Patients with Crohn's Disease)[392] was a multicentre randomised double-blind placebo-controlled trial investigating withdrawal of infliximab in patients in clinical (CDAI<150), biochemical (normal CRP, WBC, haemoglobin and albumin) and endoscopic (simple endoscopic score for Crohn's disease of ≤2) or imaging/capsule endoscopy remission.[443] Patients had been on infliximab infusions for at least 1 year. Overall, 115 patients were randomised to infliximab continuation or discontinuation for a total of 48 weeks. The primary endpoint was time to relapse defined as CDAI of 150 or greater, with an increase in at least 70 points over baseline. Overall, no relapses were seen among the 59 patients continuing infliximab, compared with 23 relapses in the 56 patients discontinuing infliximab (time to relapse was significantly shorter in those stopping infliximab (HR=0.08 (95% CI 0.035 to 0.187), p<0.001). By week 48 relapse-free survival was 51% in the discontinuation group.

*Safety*: Withdrawing infliximab from combination with immunomodulator may lead to no difference in adverse events than continuing infliximab, except the risk of relapse of Crohn's disease.

## WITHDRAWAL OF AZATHIOPRINE IN ANTI-TNF COMBINATION CROHN'S DISEASE

**GPS 63**

Crohn's disease patients on a combination of anti-TNF and immunomodulator therapy should be counselled that withdrawal of immunomodulator therapy is not associated with a significant risk of relapse at 2 years if the withdrawal is attempted after >2 years of anti-TNF therapy and if in corticosteroid-free remission for > 6 months.

Low-quality evidence suggests that stopping the immunomodulator after combination therapy does not seem to have an impact on relapse risk. In a systematic review of data from three RCTs, which examined relapse rate after discontinuation of immunomodulator,[233 444 445] Dohos *et al* pooled data on 186 patients in stable remission on combination therapy with either infliximab or adalimumab.[446] Stopping the immunomodulator did not show a significant elevation in risk of relapse compared with continuation of both drugs (RR=1.30, 95% CI 0.81 to 2.08,



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p=0.641). Sensitivity analysis showed that removal of any one study did not change the direction of the association. Nevertheless, the quality of the pooled evidence was judged to be low, and the authors concluded that scarcity of data meant there was insufficient power. The authors further cited data from two retrospective cohort studies examining this question,[447 448] which showed no significant differences between those who did, or did not remain on the immunomodulator component. Taken together, these data on outcomes observed over 1–2 years favour considering withdrawal of the immunomodulator from combination therapy in those who have achieved longstanding stable remission of their Crohn's disease.

It is uncertain whether removal of the immunomodulator might result in an increased risk of relapse or adverse events in the longer term. Given the potential advantages of combination therapy on immunogenicity, and the pharmacokinetics of anti-TNFs, it is conceivable that long-continued immunomodulator therapy might mitigate the loss of response or specific immune-mediated adverse events.[446] However, there is no current evidence of downstream benefits that would justify remaining on long-term combination therapy in someone with well-established, stable remission, and this also needs to be balanced against the increased risk of malignancies in certain cohorts.[449]

## GRADE STATEMENT: USTEKINUMAB

**Summary of evidence:** A 2016 Cochrane review on induction of remission included a total of four RCTs with 2324 adult participants.[450] They were conducted between 2008 and 2016, with a mix of biologically naïve and exposed patients. A 2019 Cochrane review on maintenance of remission included two RCTs, with 542 adult patients, who had responded to a previous induction phase.[451] The data from these RCTs were also included in our network meta-analysis. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 30.

**Efficacy induction:** The induction Cochrane review concluded that ustekinumab was shown to lead to fewer cases of failing to achieve clinical remission at week 6 (RR=0.92, 95% CI 0.88 to 0.96; high-certainty evidence). The raw numbers of participants failing to achieve clinical remission at week 6 were 84% (764/914) and 90% (367/406) in the ustekinumab and the placebo groups, respectively. Ustekinumab was shown to lead to less failure to achieve clinical response at week 6 (RR=0.78, 95% CI 0.71 to 0.85; high-certainty evidence). In raw numbers, failure to achieve clinical response by 70-point decline in CDAI at week 6 was 55% (502/914) of participants in the ustekinumab and 71% (287/406) in the placebo groups, respectively. Ustekinumab was found to be no different from placebo for TAEs with high certainty, while there was moderate certainty there was no difference for SAEs, and low certainty for no difference in WAEs. Please see table 9 for estimated time to treatment goals for ustekinumab.

The network meta-analysis demonstrated moderate-certainty evidence for a small difference favouring ustekinumab to placebo for induction of remission, and moderate-certainty evidence for a moderate difference favouring ustekinumab to placebo for clinical response. The RCT evidence for the safety outcomes was high and moderate certainty for trivial or no differences from placebo.

**Efficacy maintenance:** In the Cochrane review, the proportion of participants who failed to maintain clinical remission at week 22 was 58% (42/72) in the ustekinumab group compared with 73% (53/73) in the placebo group (RR=0.8, 95% CI 0.63 to 1.02, moderate certainty), and in week 44, 49% (126/257) compared with 64% (84/131) (RR=0.76, 95% CI 0.64 to 0.91, moderate certainty). The proportion of participants who failed to maintain clinical response at week 22 was 31% (22/72) in the ustekinumab group compared with 58% (42/73) in the placebo group (RR=0.53, 95% CI 0.36 to 0.79, moderate certainty) and in week 44, 41% (106/257) compared with 56% (73/131) (RR 0.74, 95% CI 0.6 to 0.91, moderate certainty). Ustekinumab was found to be no different from placebo for TAEs with high certainty, while there was moderate certainty there was no difference from SAEs, and low certainty for no difference from WAEs. The network meta-analysis showed that ustekinumab may not be better than placebo at maintenance of clinical remission (low-certainty evidence) and probably leads to less loss of response than with placebo (moderate-quality evidence). The safety outcomes were all of low certainty and showed there may be no differences from placebo.

**Certainty and rationale:** Overall certainty is moderate, with a moderate magnitude, that ustekinumab is better than placebo for induction and maintenance of remission in patients with moderate to severe Crohn's disease. This is based on the data from the network meta-analyses, which suggests a small effect for induction and moderate effect for maintenance. The trials reviewed included biologic naïve and biologic-exposed patients which is why ustekinumab can be used after failure of immunomodulator therapy and/or anti-TNF.

Evidence of moderate certainty suggests that there are trivially fewer withdrawal adverse events with ustekinumab compared with placebo during the induction period and high certainty that there are no differences in SAEs and TAEs in comparison with placebo during the induction period. Evidence for adverse events during the maintenance phase are of lower certainty, but real-world experience suggests that ustekinumab is generally well tolerated.

**Ustekinumab is suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Moderate**. Overall magnitude: **Moderate**.

**Justification**: A Cochrane review of pairwise analysis for induction of remission concluded with moderate certainty on a trivial effect size for clinical induction of remission and small size for response. No major differences from placebo for safety outcomes with low to high certainty. A Cochrane review for maintenance concluded with moderate certainty that ustekinumab probably leads to fewer cases of failure to maintain clinical remission, with a small effect size, and it probably leads to less failure of clinical response with a small effect size. In the NMA, certainty was moderate for induction of remission for a small effect in favour of ustekinumab compared with placebo, and a moderate effect for clinical response. For maintenance of clinical remission the certainty was low that there may be no difference, while for clinical response there was moderate-certainty evidence for a small effect size of less loss of response compared with placebo. The RCT data for safety during induction were of high and moderate certainty for no or trivial difference, while for maintenance the safety evidence was of low certainty for no difference.

**Implementation considerations**: Real-world experience suggests that ustekinumab is well tolerated. It can be used after failure of purine analogues therapy and/or anti-TNF failure



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### GRADE STATEMENT: RISANKIZUMAB

**Summary of evidence:** There are four RCTs available (one phase II and three phase III) assessing efficacy and safety of risankizumab. In the phase II study, 121 patients were randomised 1:1:1 ratio to 200 mg, 600 mg of risankizumab and placebo. In this study, 93% of the included patients were previously treated with at least one TNF antagonist. Subsequently, two phase III RCTs (ADVANCE (intolerant or non-response to conventional therapy or biologics) and MOTIVATE (intolerant or non-response to biologics)) assessed efficacy in the induction phase, and one RCT (FORTIFY (participants who had clinical response in ADVANCE AND MOTIVATE studies)) in maintenance. In the ADVANCE study, 931 patients were assigned to risankizumab 600 mg (n=373), risankizumab 1200 mg (n=372) or placebo (n=186). In MOTIVATE, 618 patients were assigned to risankizumab 600 mg (n=206), risankizumab 1200 mg (n=205) or placebo (n=207). In FORTIFY study, 542 patients were randomised 1:1:1 to subcutaneous risankizumab 180 mg or 360 mg or placebo every 8 weeks. We included all of these studies in our network meta-analysis. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 31.

**Risankizumab is suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Small**.

**Justification:** The evidence for induction is of moderate certainty on direct comparison and very low certainty on the network, with a small to moderate magnitude of effect size. The data for maintenance did not demonstrate higher efficacy of risankizumab for maintenance of clinical remission. The data are of moderate certainty on direct comparison, and very low certainty on network meta-analysis. Although the evidence is uncertain about the efficacy and safety of rizankizumab in maintenance of Crohn's disease, well conducted RCT data suggest that risankizumab was associated with higher maintenance of clinical and endoscopic remission rates than placebo. Higher than expected clinical remission rates in the placebo group were believed to be secondary to a carry-over effect from risankizumab that was received during induction phase. We feel it is still a valuable option for maintenance following induction. The GDG believed the direct data as well as inducion data supported the recommendation.

**Implementation considerations**: Risankizumab has recently been approved for use in moderate to severe Crohn's disease with a history of inadequate response or loss of response to a previous advanced therapy, intolerance to other advanced therapies or where an anti-TNF is not considered suitable. While long-term safety data are still collected, the expectation for low side-effect profile, in keeping with its mode of action and its efficacy in both naive and refractory disease, will need to be considered for its positioning. The recently published data of a head-to-head, open label RCT comparing risankizumab to ustekinumab in anti-TNF treated patients (SEQUENCE study),[452] showing non-inferiority for clinical remission at week 24 and superiority in endoscopic remission at week 48 should be taken into consideration when a decision between the two drugs is made.

**Efficacy induction:** At week 12, 25 (30%) of 82 risankizumab patients (pooled 41 patients in 200 mg and 41 patients in 600 mg arms) achieved clinical remission vs six (15%) of 39 placebo patients (difference vs placebo 15·0%, 95% CI 0·1 to 30·1; p=0·0489). In ADVANCE, CDAI clinical remission rate was 45% (adjusted difference 21%, 95% CI 12 to 29; 152/336) with risankizumab 600 mg and 42% (17%, 8–25; 141/339) with risankizumab 1200 mg vs 25% (43/175) with placebo. In MOTIVATE, CDAI clinical remission rate was 42% (22%, 13% to 31%; 80/191) with risankizumab 600 mg and 40% (21%, 12% to 29%; 77/191) with risankizumab 1200 mg versus 20% (37/187) with placebo. The overall incidence of treatment-emergent adverse events was similar among the treatment groups in both trials. In our network meta-analysis, the evidence was uncertain for induction of clinical remission and the effect was small. Whereas for the induction of clinical response, risankizumab was superior to placebo with moderate effect; however, the certainty of evidence was low. Please see table 9 for estimated time to treatment goals for risankizumab.

**Efficacy maintenance:** In the FORTIFY study, at week 52, clinical remission was reached in 52% with risankizumab 360 mg compared with 41% with placebo, adjusted difference 15% (95% CI 5% to 24%) (p=0.005). Similarly, clinical remission with risankizumab 180 mg was 55% with adjusted difference of 15% (95% CI 5% to 24%) when compared with placebo (p=0.003). At week 52, risankizumab was associated with statistically superior endoscopic remission rates compared with placebo (180 mg vs 360 mg vs placebo: 30% vs 39% vs 13%; p<0.0001 for both comparisons). Adverse event rates were similar among groups. In our network meta-analysis, the evidence was uncertain for clinical relapse outcome. On analysis of safety outcomes, there was no difference between risankizumab and placebo. However, the certainty of evidence was low to very low.

**Certainty and rationale:** The evidence for induction is of moderate certainty on direct comparison and very low certainty on network, with a small to moderate magnitude of effect size. The data for maintenance did not demonstrate higher efficacy of risankizumab for maintenance of clinical remission. The data are of moderate certainty on direct comparison and very low certainty on network meta-analysis. Although evidence is uncertain about the efficacy and safety of rizankisumab in maintenance of Crohn's disease, well-conducted RCT data suggest that risankizumab was associated with higher maintenance of clinical and endoscopic remission rates than placebo. Higher than expected clinical remission rates in the placebo group were believed to be secondary to a carry-over effect from risankizumab that was received during induction phase. The GDG feels it is still a valuable option for maintenance following induction. The GDG believed the direct evidence as well as induction data support the recommendation. The SEQUENCE study showed non-inferiority of risankizumab versus ustekinumab, in an open-label run-through RCT, in clinical remission at week 24 and superiority in endoscopic remission at week 48.[453] All patients had failed or not tolerated anti-TNF.

### GRADE STATEMENT: UPADACITINIB

**Summary of evidence:** There are four RCTs available (one phase II and three phase III) assessing efficacy and safety of upadacitinib.[454 455] In the double blind, phase II, dose-ranging study (CELEST), 220 patients were randomised in 1:1:1:1:1 ratio to received 3 mg, 6 mg, 12 mg, or 24 mg upadacitinib twice daily; or 24 mg upadacitinib once daily, or placebo.[455] Subsequently, two phase III RCTs (U-EXCEL (intolerant or non-response to



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**Upadacitinib is suggested for induction and maintenance therapy in patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Small**.

**Justification**: Overall certainty is low. Upadacitinib is suggested for induction and maintenance of Crohn's disease.

**Implementation considerations**: Upadacitinib is currently recommended where anti-TNF have failed or are not tolerated or contraindicated. With regard to choice of dosing for maintenance, there is a lack of good evidence to guide specific choice or ability to escalate/de-escalate. Upadacitinib is the first oral agent which has been shown to have efficacy in inducing and maintaining remission in Crohn's disease and can facilitate timely commencement of an early effective therapy. Black box warning for VTE and MACE in higher-risk patients, although emerging experience may clarify this risk further. Risk of other events such as acne/varicella zoster virus (VZV) continue to be defined and will influence use in Crohn's disease.

conventional therapy or biologics) and U-EXCEED (intolerant or non-response to one or more biologics)) assessed efficacy in the induction, phase and one RCT (U-ENDURE (participants who had clinical response in U-EXCEL and U-EXCEED studies))[454] assessed efficacy during maintenance. In U-EXCEL, 526 patients (2:1) were assigned to either upadacitinib 45 mg or placebo. Whereas, in U-EXCEED, 495 patients (2:1) were assigned to upadacitinib 45 mg, or placebo for 12 weeks. In U-ENDURE study, 502 patient responders were randomised 1:1:1 to upadacitinib 15 mg or 30 mg or placebo once daily for 52 weeks. We included all of these studies in our network meta-analysis. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 32.

**Efficacy induction:** In the phase III trials, a significantly higher percentage of patients who received 45 mg upadacitinib than those who received placebo had clinical remission (in U-EXCEL, 49.5% vs 29.1%; in U-EXCEED, 38.9% vs 21.1%) and an endoscopic response (in U-EXCEL, 45.5% vs 13.1%; in U-EXCEED, 34.6% vs 3.5%) ($p<0.001$ for all comparisons). In our network meta-analysis, upadacitinib was superior to placebo for induction of clinical remission and clinical response with a small magnitude of effect with low-certainty evidence. Please see table 9 for estimated time to treatment goals for upadacitinib.

**Efficacy maintenance:** In the U-ENDURE study, at week 52, a higher percentage of patients had clinical remission with 15 mg upadacitinib (37.3%) or 30 mg upadacitinib (47.6%) than with placebo (15.1%), and a higher percentage had an endoscopic response with 15 mg upadacitinib (27.6%) or 30 mg upadacitinib (40.1%) than with placebo (7.3%) ($p<0.001$ for all comparisons). Herpes zoster reactivation occurred more frequently in the 45 mg and 30 mg upadacitinib groups than in the respective placebo groups, and hepatic disorders and neutropenia were more frequent in the 30 mg upadacitinib group than in the other maintenance groups. Gastrointestinal perforations developed in four patients who received 45 mg upadacitinib and in one patient each who received 30 mg or 15 mg upadacitinib. There was low-certainty evidence to suggest that there was no difference between upadacitinib and placebo for clinical relapse outcome in the maintenance phase but, there was high-certainty evidence for loss of clinical response with moderate-effect size. On analysis of safety outcomes, there was no difference between upadacitinib and placebo.

**Certainty and rationale:** Overall certainty is low, suggesting that upadacitinib may be better than placebo for induction and maintenance of clinical remission. It is important to highlight, that this is the first oral agent shown to be effective and safe in both inducing and maintaining remission in Crohn's disease. Initiation and maintenance will depend on the individual patient's needs, taking into consideration their background risk for major cardiovascular events, VTE and family planning.

## GRADE STATEMENT: VEDOLIZUMAB

**Summary of evidence:** In a 2023 Cochrane review of induction and maintenance of remission, a total of four RCTs with 1025 adult participants for induction and three RCTs with 895 participants for maintenance were included.[452] They were conducted between 2008 and 2021, with a mix of biologically naïve and exposed patients. The induction studies included participants with active disease, while the maintenance studies included participants with both active and inactive disease, who had shown clinical response in the preceding induction trial phases. All studies allowed some form of concomitant medication. The data from these RCTs were also included in our network meta-analysis. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 33.

**Efficacy induction:** Based on the induction Cochrane review, vedolizumab is more effective than placebo at week 6 to 10 for clinical remission, with a trivial effect (71 more per 1000 with clinical remission; RR=1.61, 95% CI 1.2 to 2.17, NNT for additional benefit 13, high certainty; and clinical response at weeks 52–60 (105 more per 1000 with clinical response; RR=1.43, 95% CI 1.19 to 1.71). The evidence was high certainty. The safety outcomes of the review were low and moderate in GRADE certainty for no difference with placebo. The network

**Vedolizumab is not suggested for indulcerative colitistion and maintenance of remission in patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional.** Overall certainty: **Low**. Overall magnitude: **Trivial**.

**Justification**:A Cochrane review of pairwise analysis for induction and maintenance of remission concluded with high-certainty evidence of a trivial effect size for induction and small effect size for maintenance of remission. No major differences from placebo were observed for safety outcomes (moderate certainty). In the network meta-analyses, certainty was low for induction of remission and response, with trivial magnitude of effect size. For maintenance, the clinical picture is similar. The RCT data for safety ranged in certainty, but there was no indication of differences from placebo.

**Implementation considerations:** The trivial effect size is seen on all direct evidence, whether biologic naïve or not. However, a better effect was seen in naïve patients. This therapy may have a role in targeted patients when other options are not appropriate or when induction is achieved through other modalities, but the low effect size must be discussed with patients as part of shared decision-making. The recommendation is based on the magnitude thresholds used to guide decision-making for the BSG guideline and does not preclude the use of the drug for the management of Crohn's disease where this has been agreed with the patient and the wider IBD MDT.



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meta-analysis demonstrated low-certainty data for induction of remission and clinical response, with a trivial magnitude effect. A range of GRADE ratings were applied to safety outcomes. There was moderate certainty for WAEs and high certainty for SAEs and TAEs for no difference from placebo. Please see table 9 for estimated time to treatment goals for vedolizumab.

**Efficacy maintenance:** In the Cochrane review, vedolizumab was superior to placebo for maintenance of remission, with a small effect size (141 more per 1000 with maintenance of clinical remission, RR=1.52, 95% CI 1.24 to 1.87, NNTB 7, high certainty). The safety outcomes of the review were low and moderate in GRADE certainty for no difference with placebo. In the network meta-analysis, vedolizumab may not be superior to placebo for maintenance of clinical remission with moderate-certainty evidence. There was low-certainty evidence that vedolizumab may lead to a trivial effect on maintenance of clinical response. There was moderate certainty for WAEs and low certainty for SAEs and TAEs for no difference from placebo.

**Certainty and rationale:** Overall certainty is low with a trivial magnitude that vedolizumab is better than placebo for induction, and small magnitude for maintenance of remission in patients with moderate to severe Crohn's disease. This is based on the data from the network and Cochrane review. The trivial effect size was irrespective of whether biologic naive or exposed. The trivial effect size must be discussed with patients as part of shared decision-making.

Evidence of moderate certainty suggests that there are fewer withdrawal adverse events with vedolizumab, compared with placebo during the induction period and high certainty that there are no difference in SAEs and TAEs in comparison with placebo during the induction period. Evidence for adverse events during the maintenance phase is of lower certainty, but real-world experience suggests that vedolizumab is generally well tolerated with a low incidence of adverse events.

There are clinical scenarios where individual patient factors may still indicate a role for this therapy, but it is vital to clearly discuss and communicate the magnitude of effect data with patients. This should clarify that the existing data do not indicate a smaller effect in individuals, rather that fewer individuals will experience a successful outcome overall. If patients do experience such a remission, this will be no different from the result with other therapies. The practising clinician should take into consideration the findings from the LOVE-CD prospective study. This study was not used in our evidence synthesis owing to its lack of randomisation. Nevertheless, anti-TNFs had previously failed for 88% of recruited patients. Corticosteroid-free clinical remission was observed in 29% and 31% of patients following 26 and 52 weeks of vedolizumab therapy, respectively, and clinical response was present in 38% and 35% at these time points. Endoscopic remission was achieved by 33% and 36% of patients at weeks 26 and 52, respectively. Vedolizumab levels >10 mg/L at week 22 were associated with endoscopic remission at week 26.[136]

The recommendation is based on the magnitude thresholds used to guide decision-making for the BSG guideline and does not preclude the use of these drugs in combination for the management of Crohn's disease, presuming agreement with the patient and the wider IBD MDT.

**GPS 64**

Recommendation cannot be made regarding the use of Vedolizumab with concurrent purine analogues in Crohn's disease due to lack of evidence.

## OTHER THERAPIES IN CROHN'S DISEASE

### GRADE statement: Antibiotics

**Summary of evidence:** Thirteen RCTs (n=1303 participants) were included in the analyses.[456] Two trials were rated as high risk of bias (no blinding). Seven trials were rated as unclear risk of bias, and four trials were rated as low risk of bias. Comparisons included ciprofloxacin (500 mg twice daily) versus placebo, rifaximin (800 to 2400 mg daily) versus placebo, metronidazole (400 mg to 500 mg twice daily) versus placebo, clarithromycin (1 g/day) versus placebo, cotrimoxazole (960 mg twice daily) versus placebo, ciprofloxacin (500 mg daily), metronidazole (500 mg daily) and budesonide (9 mg daily) versus placebo with budesonide (9 mg daily), ciprofloxacin (500 mg twice daily) versus 5-ASA (2 g twice daily), ciprofloxacin (500 mg twice daily) with infliximab versus placebo with infliximab, clarithromycin (750 mg daily) and antimycobacterial versus placebo, and metronidazole (400 mg twice daily) and cotrimoxazole (960 mg twice daily) versus placebo. The effect of individual antibiotics on Crohn's disease was generally uncertain due to imprecision. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 34.

Thirty-eight per cent (214/568) of participants exposed to antibiotics had at least one adverse event compared with 45% (128/284) of placebo-exposed participants (RR=0.87, 95% CI 0.75 to 1.02; nine studies; high-certainty evidence). The effect of antibiotics on SAEs and withdrawal due to AEs was uncertain. Two per cent (6/377) of antibiotic participants had at least one adverse event compared with 0.7% (1/143) of placebo participants (RR=1.70, 95% CI 0.29 to 10.01; three studies; low-certainty evidence). Nine per cent (53/569) of antibiotic participants withdrew due to AEs compared with 12% (36/289) of placebo participants (R= 0.86, 95% CI 0.57 to 1.29; nine studies; low-certainty evidence). The GRADE summary of findings is in online supplemental appendix 4, GRADE table 34.

**Antibiotics are not suggested for induction and maintenance of remission in patients with moderate to severe Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **High**. Overall magnitude: **Trivial**.

**Justification**: Assessment of efficacy is challenging due to the sheer number of antibiotics investigated, in various combinations and doses, within predominantly small studies. No individual antibiotic or combination agent has been sufficiently studied to robustly assess. As a therapeutic class, the evidence is of high certainty that overall antibiotics show a small effect as induction treatment, but there is no evidence to assess their efficacy in maintenance. As such, we cannot support their use as induction or maintenance treatment in moderate to severe Crohn's disease.

**Implementation considerations**: Antibiotics are widely available but are not recommended. Notably, this assessment does not address the use of antibiotics in special situations such as intra-abdominal or perianal sepsis.



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**Efficacy induction:** 55% (289/524) of antibiotic-exposed participants failed to achieve remission at 6 to 10 weeks compared with 65% (149/231) of placebo-exposed participants (RR=0.86, 95% CI 0.76 to 0.98; seven studies; high-certainty evidence). At 10 to 14 weeks, 41% (174/428) of antibiotic participants failed to achieve a clinical response compared with 49% (93/189) of placebo participants (RR=0.77, 95% CI 0.64 to 0.93; five studies; moderate-certainty evidence).

**Efficacy maintenance:** The effect of antibiotics on relapse in uncertain. Forty-five per cent (37/83) of participants exposed to antibiotics relapsed at 52 weeks compared with 57% (41/72) of placebo-exposed participants (RR=0.87, 95% CI 0.52 to 1.47; two studies; low-certainty evidence). Relapse of endoscopic remission was not reported in the included studies.

**Certainty and rationale:** Moderate- to high-quality evidence suggests that any benefit provided by antibiotics in active Crohn's disease is likely to be small or trivial. High-quality evidence suggests that there is no increased risk of side effects with antibiotics compared with placebo. The effect of antibiotics on the risk of serious side effects is uncertain. The effect of antibiotics on preventing relapse in Crohn's disease is uncertain. Thus, no firm conclusions regarding the benefits and harms of antibiotics for maintenance of remission in Crohn's disease can be drawn. More research is needed to determine the harms and benefits of antibiotic therapy in Crohn's disease.

## GRADE STATEMENT: PROBIOTICS

**Summary of evidence:** There were two studies that met criteria for inclusion for assessment for the induction of remission.[457 458] One study from Germany had 11 adult participants with mild-to-moderate Crohn's disease, who were treated with a 1week-course of corticosteroids and antibiotics (ciprofloxacin 500 mg twice daily and metronidazole 250 mg three times a day), followed by randomised assignment to *Lactobacillus rhamnosus* strain GG (two billion colony-forming units per day) or corn starch placebo. The other study from the UK had 35 adult participants with active Crohn's disease (CDAI 150 to 450) randomised to receive a symbiotic treatment (comprised of freeze-dried *Bifidobacterium longum* and a commercial probiotic) or placebo. The overall risk of bias was low in one study, whereas the other study had unclear risk of bias in relation to random sequence generation, allocation concealment and blinding. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 35.

Seven small studies were identified and included in the Cochrane review investigating clinical remission in Crohn's disease. Studies varied according to probiotics tested, methodological quality and medication regimen. No studies were pooled for statistical analysis.

**Efficacy induction:** There was no evidence of a difference between probiotics and placebo for induction of remission in Crohn's disease (RR=1.06; 95% CI 0.65 to 1.71; two studies, 46 participants) at 6 months. There was no difference in adverse events between probiotics and placebo (RR=2.55; 95% CI 0.11 to 58.60; two studies, 46 participants). The evidence for both outcomes was of very low certainty due to risk of bias and imprecision.[459]

**Efficacy maintenance:** There was no statistically significant benefit of *Escherichia coli* Nissle for reducing the risk of relapse compared with placebo (RR=0.43, 95% CI 0.15 to 1.20), or *Lactobacillus GG* after remission which was surgicallyinduced (RR=1.58, 95% CI 0.30 to 8.40) or medically induced (RR=0.83, 95% CI 0.25 to 2.80). There was no statistically significant benefit of probiotics for reducing the risk of relapse compared with maintenance therapy employing 5-ASA or azathioprine (RR=0.67, 95% CI 0.13 to 3.30). In this study the probiotic *Lactobacillus GG* was associated with adverse events. A small study using the yeast *Saccharomyces boulardii* demonstrated a difference that was not statistically significant in favour of probiotic combined with a reduced level of maintenance therapy over standard maintenance treatment alone (RR=0.17, 95% CI 0.02 to 1.23).[460]

**Certainty and rationale:** There is no evidence to suggest that probiotics are beneficial for the maintenance of remission in Crohn's disease. All of the included studies enrolled small numbers of patients and might have lacked statistical power to show differences, should they exist. There is no evidence to suggest that probiotics are beneficial for the maintenance of remission in Crohn's disease. Larger trials are required to determine if probiotics are of benefit in Crohn's disease.

Table 9 outlines suggested rough estimates of time to achieve treatment goals after initiation of Crohn's disease therapies, as advised by the STRIDE consensus.[6] These times could be used as a guide when deciding on time intervals to monitor for remission in Crohn's disease after initiating a new treatment.

**Table 9** Estimates of time (weeks) to achieve treatment goals after initiation of Crohn's disease therapies

| Therapies | Clinical remission | Norm of CRP/ESR | Decrease of FC[a] | EH |
|---|---|---|---|---|
| **Crohn's disease** | | | | |
| Oral steroids/EEN | 4 | 5 | 8 | 13 |
| Budesonide | 6 | 8 | 10 | 15 |
| Purine analogues | 15 | 15 | 17 | 24 |
| Methotrexate | 14 | 14 | 15 | 24 |
| Anti-TNF | 4–6 | 9 | 11 | 17 |
| Vedolizumab | 17 | 15 | 17 | 24 |
| Ustekinumab | 13 | 11 | 14 | 19 |
| Upadacitinib | 12 | 12 | 12 | 12 |
| Risankizumab | 12 | 12 | 12 | 12 |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, faecal calprotectin; EH, endoscopic healing; EEN, exclusive enteral nutrition; anti-TNF, anti-tumour necrosis factor.

**Probiotics are not suggested for induction and maintenance of remission in patients with Crohn's disease.**

Recommendation: **Conditional**. Overall certainty **Very low**
Overall magnitude: **Unknown.**

**Justification:** The evidence is of very low certainty therefore we are unable to make an informed recommendation.

**Implementation considerations:** Probiotics are not recommended in Crohn's disease.

## USE OF EXCLUSIVE ENTERAL NUTRITION IN CROHN'S DISEASE

Exclusive enteral nutrition (EEN) is the term used when a patient receives an exclusively liquid diet for a defined period, and is used routinely in paediatric Crohn's disease to induce remission (73% remission rates on an intention-to-treat basis), but not currently in adults.[461–463]

A Cochrane review,[452] including 27 trials, examining EEN for inducing remission in Crohn's disease, found no difference in



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efficacy against steroids, but no conclusions can be drawn due to very low-certainty evidence.

There are different types of enteral nutrition (elemental, semi-elemental (peptide based) and polymeric (whole protein)) but the efficacy of EEN in Crohn's disease is not affected by the type of formula used or to the route of administration (oral vs nasogastric tube).[464–466]

In the preoperative setting, a retrospective UK case–control study showed that patients given preoperative EEN (6 weeks) had lower rates of postoperative abscesses and anastomotic leaks, lower CRP and voided surgery in 25% of cases (13/51).[467] A prospective single-centre French study of 35 patients with Crohn's disease at high risk of surgical complications (with obstructive symptoms, and/or steroid treatment, and/or preoperative weight loss >10%, and/or perforating Crohn's disease) were treated with preoperative EEN for a mean of 3 weeks before surgery.[468] Postoperative outcomes were compared for 21 patients with Crohn's disease at low surgical risk. Preoperative EEN resulted in similar postoperative complication rates in the high-risk (23.8%) and low-risk (22.9%) patients, suggesting that preoperative EEN is protective for high surgical risk patients who require resection. Discontinuation of steroids was also possible in 10/16 patients (62.5%) receiving EEN.

A small case-matched prospective Chinese study compared 24 patients on EEN for at least 2 weeks before surgery with a control group of 24 patients who underwent surgery without receiving preoperative EN or parenteral nutrition. The incidence of postoperative septic complications was significantly lower in the EN group (4% vs 25%, p=0.04).[469]

A systematic review, which included seven studies, also suggested that preoperative EEN may reduce the infectious complications of surgery, with a trend towards fewer patients requiring stoma formation. Please see table 9 for estimated time to treatment goals for EEN.[470]

## PERIANAL CROHN'S DISEASE

Perianal Crohn's disease is a distinct phenotype characterised by the presence of at least one fistula tract between the epithelial surfaces of the anal canal, and the perineal skin and/or the vagina.[471] The prevalence of perianal Crohn's disease has been reported to range between 20% and 40% and is associated with significant morbidity—namely, debilitating symptoms affecting psychosocial well-being and sexual health.[472 473]

There is an increased risk of more aggressive rectal and anal cancer in patients with chronic perianal fistulising Crohn's disease. The need for surveillance has not been defined in current guidelines,[474] and the optimal intervals and modalities are unknown.[449 475 476] In the absence of dedicated consensus or guidelines, we would suggest careful assessment at regular intervals, and especially when symptoms change, with standard techniques, including endoscopy, imaging and direct examination under anaesthesia with biopsy of the fistulous tracts to detect cancer early and discuss treatment options with the wider MDT.[475] Please refer to IBD CRC surveillance guidelines for additional context.[104]

The complexity of perianal Crohn's disease therefore justifies multidisciplinary working to optimise patient outcomes.[477] Prompt multimodal assessment followed by the initiation of early advanced therapies is associated with favourable outcomes.[472]

**GPS 66: A practical guide for exclusive enteral nutrition (EEN) to induce remission in Crohn's disease.**

- ⇒ Counsel patients on the risks and benefits of all available treatment options including EEN.
- ⇒ EEN is provided as a prescribed liquid diet, excluding all food and drink except still water. Some units allow limited optional intake beyond this, but there is little evidence supporting what foods or drinks can be added without affecting efficacy.
- ⇒ Whole protein (polymeric), peptide, semi-elemental or elemental diets are equally efficacious, but whole protein feeds are more palatable and are more likely to be tolerated.
- ⇒ EEN is nutritionally complete with all relevant micronutrients and trace elements included.
- ⇒ Limited palatability and tolerance are often reasons for failure, so encouragement from the whole MDT is important for success. This is best achieved with a formalised MDT pathway for EEN management and specific points of contact to assess progress.
- ⇒ A starter regimen, increasing the prescribed daily volume gradually over a few days while reducing food intake, is important to build up tolerance and prevent the risk of refeeding, especially in patients where dietary intake has been suboptimal beforehand, or weight loss has been significant.
- ⇒ Bloods for refeeding syndrome include urea and electrolytes (for potassium), phosphate and magnesium, and should be monitored daily while calorie intake is increased to maximum in at-risk patients.
- ⇒ A standard target regimen should be based on requirements for energy: 25–30 kcal/kg/day and protein: 1 g/kg/day. Non-standard regimens may be used where refeeding syndrome is a risk (with lower calories), or where catch-up nutrition is required.
- ⇒ Once the target regimen is met, EEN should be continued for 6–8 weeks to induce mucosal healing.
- ⇒ Once EEN is established, the vast majority of patients can continue with their usual daily activities.
- ⇒ Most adult patients can tolerate EEN orally; however, nasogastric feeding may be required if target volumes cannot be met orally or where feed tolerance is limited with boluses.
- ⇒ Regular monitoring via email or telephone will help to maintain adherence.

## INVESTIGATIONS

**GPS 65**

Malnutrition screening, nutritional assessment and correction of nutritional status should be part of preoperative optimisation of all patients who require abdominal surgery for IBD. Nutritional support (oral nutritional supplements or enteral or parenteral nutrition) should be provided as required.

**GPS 67**

We recommend pelvic MRI as an important adjunct to clinical assessment and examination under anaesthesia, by an experienced colorectal surgeon, in evaluation of fistulising perianal Crohn's disease. Depending on local availability and expertise, endoanal ultrasound may have a role.



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**GPS 68**

We recommend that examination under anaesthesia should include an assessment of the rectal mucosa, as the presence of proctitis is associated with lower rates of fistula healing in perianal Crohn's disease.

The assessment of perianal disease includes pelvic MRI, examination under anaesthesia (EUA), and endoanal ultrasound (EAUS). Poor sonographic tissue penetration and pain associated with perianal disease may limit the use of EAUS for deep-seated abscesses and complex fistulae.[478 479] Furthermore, EAUS may not be available in all IBD treatment centres. MRI is the standard imaging modality in perianal disease in the UK. Radiological reporting may be enhanced with validated radiological scoring e.g. MAGNIFI-CD score, among others.[480]

Multimodal assessment with an EUA and radiological investigations increases the diagnostic accuracy, as indolent abscesses may be missed at EUA.[473 481] Imaging allows for accurate follow-up, as the closure of an external fistula opening does not always equate to remission of inflammation of the fistula tract.[482 483] An EUA undertaken by an experienced colorectal surgeon, carries a sensitivity of 90% in classifying fistulae, sinus tracks and abscesses, and allows for initiation of early surgical treatment.[477] The presence of proctitis is associated with poorer surgical outcomes (OR=2.85, 95% CI 1.65 to 4.89, p=0.0001), underscoring the need for an early endoscopic assessment of the rectal lumen.**484**

There are no new studies to alter recommendation since the publication of the last BSG guidelines.[8]

## MEDICAL AND SURGICAL TREATMENTS FOR PERIANAL CROHN'S DISEASE

**GPS 69**

Multidisciplinary decision making should be the standard of care for patients with perianal Crohn's disease.

The management of perianal disease warrants a flexible therapeutic approach, to reflect the multidimensional and changing nature of the disease, preference-sensitive patient goals and differential healthcare professional expertise, as specified in a novel classification (see figure 1).[475] Uncertainties and deficiencies in the evidence relating to perianal disease, were addressed in a recent consensus from leading experts, with a high agreement for collaborative multidisciplinary working as a platform for shared decision-making in this setting.[475 485] Other guidelines support this approach.[474 477]

## SETON INSERTION

**GPS 70**

We suggest that setons should be placed to prevent sepsis in fistulising perianal Crohn's disease. The optimal timing of seton removal is uncertain and should be based on patient preferences and complexity of the fistulae.

There is no additional evidence to support placement and timing of seton removal since the last guidelines.[8] The placement of a seton depends on the complexity of the fistula (eg, high fistula, rectovaginal fistula), and the presence of proctitis.[484]

In the PISA study, participants with a single high internal opening fistula were randomised to chronic seton drainage (removal of seton at 1 year), or anti-TNF therapy alone or in conjunction with definitive surgical closure (surgical closure is discussed further below). This study was terminated early owing to the high prevalence of re-intervention in the chronic seton drainage group (74% compared with 42% for infliximab monotherapy, and 23% with combined anti-TNF and surgery).[486] This implies that benefits of setons drainage are greater in conjunction with additional advanced medical therapy. The subsequent PISA-II study showed a clinical closure rate of 76% for the combined anti-TNF therapy and reparative surgery, where all participants had seton placement at inclusion.[487] An observational study of 156 patients treated with infliximab following seton placement found a higher likelihood of sustained fistula closure in those patients who started anti-TNF therapy within 6 weeks of surgery.[488]

## ROLE OF REPARATIVE SURGICAL THERAPIES IN PERIANAL CROHN'S DISEASE

**GPS 71**

Reparative surgical options, such as advancement flap, and ligation of intersphincteric fistula tract (LIFT), may be considered for selected patients in a multidisciplinary setting.

Reparative surgical therapies aim to provide definitive surgical closure of the perianal fistula. The surgical options include: fistulotomy, mucosal advancement flaps, video-assisted anal fistula treatment, fistula plug, ligation of intersphincteric fistula tract (LIFT) and fistula glue.

The PISA-II study was the only published surgical RCT for perianal Crohn's disease since the last BSG guidelines. The study was designed to incorporate the learnings and limitation of the initial PISA-I study.[486] Patient without preferences were randomised to surgery (advancement flap or LIFT procedure) or anti-TNF therapy (infliximab or adalimumab, with dose escalation permitted). Preference-sensitive patients were allowed to choose their treatment arm. All participates had seton placement at study entry with time intervals to study intervention of 8–12 weeks in the surgical arm and 2 weeks in the anti-TNF therapy group. Seton removal was during the surgical closure procedure and 6 weeks after insertion for anti-TNF therapy, respectively. MRI-assessed fistula closure was higher for the surgery group (12% compared with 9%, p=0.005).[487] There is insufficient evidence to support the use of other surgical interventions which may be considered in the setting of future clinical trials.

Mesenchymal stem cell therapy showed promising initial results in achieving fistula closure, especially when combined with fibrin glue.[489] A phase III, randomised, double-blind, parallel group, placebo-controlled, international, multicentre study (ADMIRE-CD II) was designed to assess the efficacy and safety of Cx601, adult allogeneic expanded adipose-derived stem cells (darvadstrocel) for the treatment of complex perianal fistulae in Crohn's disease. This study failed to meet its primary endpoint of combined remission at 24 weeks.[490]



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**GPS 72**

We suggest that patients with severe perianal Crohn's disease refractory to medical therapy and affecting quality of life should be offered faecal stream diversion surgery. Patients should be counselled that the rates of subsequent successful reversal are low, and proctectomy may ultimately be required.

Refractory perianal Crohn's disease may present as early and rapidly progressive destructive disease or as gradually debilitating symptomatic fistula(s) unsuitable for surgical repair.[475] Both presentations may cause severe symptoms and profoundly affect quality of life. Early intervention with a defunctioning ostomy, and sometimes early proctectomy, is required.[475] The risk of proctectomy following defunctioning stoma has been reported to be as high as 68% on long-term follow-up of up to 103 months.[491] although, a recent meta-analysis found that the early use of medical therapies post-faecal diversion, and the absence of proctitis were associated with a higher likelihood of restoring bowel continuity.[492] Post-proctectomy, poor wound healing may continue to impact quality of life, with limited evidence on the risk of this or on efficacious therapies to avoid this eventuality.

### Medical therapies in perianal Crohn's disease

**GPS 73**

We recommend that medical therapies should be started promptly after adequate surgical drainage of perianal abscesses.

In a systematic review of published RCTs, 19 studies reported outcomes for fistulising Crohn's disease, summarised in meta-analyses. Both enterocutaneous and perianal fistulae were included in a few studies,[51 493] and for others, outcomes were reported from subgroup analysis or post-hoc analysis.[494] The quality of evidence and uncertainty of outcomes precluded adoption of the GRADE approach to the following recommendations.

#### Antibiotics

Ciprofloxacin and/or metronidazole showed no benefit in fistula response or remission in perianal Crohn's disease, yet they may play a role in the acute setting to manage sepsis, or in conjunction with advanced medical therapy.[495]

#### *Anti-TNF therapies*

**GPS 74**

We suggest infliximab as first-line biologic therapy for perianal Crohn's disease, to be started as soon as adequate drainage of sepsis is achieved.

In a sensitivity analysis restricted to studies where the primary outcomes were fistula-related, pooled data for anti-TNFs (infliximab, adalimumab, certolizumab and humanised infliximab CDP571) showed superiority to placebo for fistula induction of remission (RR=1.94 95% CI 1.10 to 3.41) and maintenance of remission (RR=1.79, 95% CI 1.10 to 2.92), supporting a role for anti-TNFs in the management of perianal Crohn's disease.[494] For individual anti-TNFs, complete fistula closure rates for infliximab induction were up to 55% for cutaneous and perianal fistulae.[51] The ACCENT II trial explored maintenance therapy with infliximab compared with placebo for week 14 responders (69% responded at week 14). The RR ratio for induction of response was 1.32 (0.54 to 3.22), without corresponding results for induction of remission. For maintenance of response and remission, the RR ratio was 1.88 (1.23 to 2.88) and 1.79 (1.10 to 2.92), respectively.[493]

In contrast, a subgroup analysis from two adalimumab studies reported a RR for induction of response of 0.69 (0.18 to 2.62) and 0.75 (0.2,2.77), and induction of remission of 0.69 (0.09 to 5.55) and 0.63 (0.06 to 6.41).[496 497] The benefits of adalimumab for induction of response/remission in perianal Crohn's disease are uncertain, with wide variations in the magnitude and direction of the effects. There are no corresponding data for maintenance of response, yet a study ny Colombel *et al*[498] reported maintenance of remission with a RR ratio of 2.57 (1.13 to 5.84), suggesting superiority over placebo.[498]

The efficacy of anti-TNF therapy may be related to drug levels, which were not considered in RCTs. Nevertheless, observational studies suggest that higher serum trough infliximab levels are associated with better outcomes, with a suggested target of >10 µg/mL in one study.[499] This may be achieved with escalated dosing at 10 mg/kg, notwithstanding the possibility of higher risk of infections.[500]

#### *Other biologics and small molecules*

**GPS 75**

Patients with inadequate response to anti-TNF therapies may be offered other advanced therapies; upadacitinib, ustekinumab or vedolizumab may be considered.

Post-hoc pooled analysis of the ustekinumab clinical trials (UNITI-1, UNITI-2 and IM-UNITI, CERTIFI-M) showed superiority compared with placebo for fistula response (RR=1.80, 95% CI 1.04 to 3.11).[494] Vedolizumab, when compared with placebo, showed evidence of efficacy for induction of fistula remission (28% compared with 13%) in a post-hoc subgroup analysis of the GEMINI-2 trials, although though this did not reach statistical significance.[501]

Induction of response and remission with filgotinib from subgroup analysis of DIVERGENCE-2 trial reported a RR ratio of 1.79 (0.60, 5.31) and 2.50 (0.64, 9.73), respectively. The post-hoc analysis of data from upadacitinib U-EXCEL and U-EXCEED trials, included 96 treated patients with different types of fistulae compared with 47 in the placebo group (including 19 who had fistulae at other sites). Upadacitinib showed superiority for induction of response and remission with a RR of 3.67 (91.23 to 10.93) and 3.26 (1.02 to 10.43), respectively.[502]

Pooled outcomes for JAK inhibitors (upadacitinib and filgotinib) for induction of response and remission showed a RR ratio of 2.56 (95% CI 1.18 to 5.53) and 2.92 (95% CI 1.21 to 7.05) respectively.[494]

U-ENDURE maintenance data suggest that upadacitinib is not as effective for maintenance, but the population was much smaller (36 for response and 79 for remission).[454]



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## WITHDRAWAL OF THERAPY IN CROHN'S DISEASE

### GPS 76

Joint decisions regarding drug withdrawal should be taken in the context of the individual patient, their disease history, estimated risk of, and predicted consequences of relapse. Patient preference, disease history, severity and extent are key factors to guide shared decisio-making.

Once disease remission has been achieved, it is uncertain if long-term immunomodulation is necessary in all patients. Long-term immunomodulation is associated with high drug costs and therapy-related adverse events, such as skin reactions, infections and cancers. Some patients may also want to consider treatment cessation/holidays for a variety of reasons, such as medication burden/compliance and personal risk of cancer and infections. The risk of withdrawing effective therapies include disease relapse, poor quality of life and the consequence of relapse. Re-treatment following withdrawal may also lead to adverse events, such as an increased risk of developing antibodies to infliximab and hypersensitivity reactions.

Before withdrawal of any maintenance IBD therapy is considered, assessment of disease activity and confirmation of clinical remission using a combination of clinical, biochemical, endoscopic/histological and/or radiological investigations should be considered to inform the risks and benefits of stopping, while accepting that even complete remission is associated with sizeable relapse risk. Nevertheless, several factors have been reported as being associated with an increased risk of relapse after stepping down or withdrawing therapy, although there is inconsistency between studies. For example, raised CRP and calprotectin, persistent inflammation on radiological imaging[503] and endoscopic inflammation at the time of drug withdrawal have all been reported to be associated with an increased relapse risk.[442]

We suggest that patients, in whom therapy is withdrawn, should be monitored for evidence of relapse. The optimal monitoring strategy following withdrawal of maintenance treatment has not been defined. Monitoring of clinical symptoms, objective markers of inflammation, such as CRP/faecal calprotectin, and/or endoscopy and/or radiology for reassessment seems reasonable.

There are good practice statements regarding withdrawal of therapy within the specific text, where there is evidence to support a statement.

## MODIFICATIONS AND ADDITIONAL THERAPIES PRIOR TO SURGICAL INTERVENTIONS FOR CROHN'S DISEASE

It is estimated that intestinal resection surgery is required in 18–31% of patients with Crohn's disease within 5 years of diagnosis and 25–40% within 10 years.[504] Surgery is most commonly performed for complications of Crohn's disease—for example, stricture formation, fistulising disease; however, it can also be considered as an early treatment option for patients with isolated terminal ileal disease.[91] Acute emergency abdominal surgery in Crohn's disease should be avoided unless there is peritonism or ischaemia.[99]

Deferred surgery when the patient is optimised for surgery results in lower complication rates and lower rates of stoma formation.[505] There is sufficient evidence to propose delaying surgery, when possible, to allow a multimodal approach to management, including nutrition, corticosteroid weaning and management of any abscesses.

Please see further information on management of corticosteroids, advanced therapies and immunomodulator agents in the preoperative period in section 8.31 and 8.32.

Radiologically guided drainage of abscess or collection is recommended where possible. It is suggested that surgery should be avoided for at least 2 weeks after percutaneous drainage.[506]

Poor preoperative nutritional status has been identified as an independent risk factor for postoperative intra-abdominal septic complications (OR=6.23, 95% CI 1.75 to 22.52) in multivariate analysis, with malnutrition and nutrient deficiencies being common in IBD.[127 507]

Malnutrition screening and nutritional assessment and correction of nutritional status should be part of preoperative optimisation of all patients who require abdominal surgery for Crohn's disease. Those with a low BMI or recent weight loss of >10% body weight are at increased risk of surgical complications, particularly intra-abdominal sepsis and increased mortality. Obesity is also an independent risk factor for surgical site infection, readmission and postoperative complication both in adults and children.[508–510] Assessment should be ideally performed by a dietitian. Albumin level is not a reliable marker of nutritional status as levels physiologically decrease in the presence of active disease or infection.[99]

There are few prospective studies of preoperative nutrition support and no prospective randomised trials with a non-nutrition control group. A meta-analysis of preoperative nutritional support in gastrointestinal surgery patients found that the provision of 500–1000 kcal of an immune-enhancing oral nutritional supplement plus usual food significantly reduced postoperative complications.[511] The rate of postoperative complications in the group receiving preoperative nutrition (enteral nutrition or total parenteral nutrition) support was 20.0% compared with 61.3% in the group who had standard care without nutrition support (OR=0.26, 95% CI 0.07 to 0.99, p<0.001).[512]

The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends preoperative nutritional support for 7–10 days in patients who are undergoing major gastrointestinal surgery and are mildly malnourished.[513] A longer duration is recommended for severely malnourished patients, even if it delays surgery.[513] If oral nutritional supplements are not tolerated, then enteral nutrition should be considered, and parenteral nutrition should only be used when nutritional targets cannot be delivered by the enteral route.[513]

## SURGICAL MANAGEMENT OF CROHN'S DISEASE

### GPS 77

We suggest that laparoscopic resection should be considered in localised ileocaecal Crohn's disease for those not responding to, or relapsing after, initial medical therapy, or in those preferring surgery to initiation or continuation of drug therapy.

## MANAGING STRICTURES

### GPS 78

Patients with symptomatic stricturing small bowel Crohn's disease should have joint medical and surgical assessment to optimise medical therapy and plan requirement for surgical resection or strictureplasty.



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**GPS 79**

We recommend that strictureplasty is an alternative to resection in patients with small bowel Crohn's disease strictures shorter than 10 cm and is useful where there are multiple strictures or a need to preserve gut length. Longer strictures can be treated using non-standard strictureplasty techniques.

**GPS 80**

If there are multiple strictures close to each other in a segment of bowel and there is adequate remaining healthy bowel, a single resection may be preferable to multiple strictureplasties.

**GPS 81**

We suggest prioritising the use of cross-sectional abdominal imaging and intestinal ultrasound in the diagnosis and assessment of strictures as well as the use of ileocolonoscopy in colonic and anastomotic strictures when clinically safe to perform, with biopsies to exclude dysplasia and aid distinction of fibrotic from inflammatory strictures.

Strictureplasty, a technique for surgical treatment of small bowel strictures without loss of bowel length, is indicated with single or multiple strictures, impending short gut or previous extensive small bowel resection. The presence of fistulae, fistula-associated abscesses or possible carcinoma are contraindications. The presence of active inflammation at the stricture site does not prevent successful strictureplasty. Strictureplasty is not associated with increased reoperation rates. There is evidence that reoperation rates may be lower at strictureplasty than resection sites. Although a systematic review and meta-analysis of 12 studies (1026 patients) from 2020, showed an increased likelihood of disease recurrence and significantly reduced recurrence-free survival with strictureplasty than for those with bowel resection.[514] If multiple small bowel strictures can be dealt with by a single resection in a patient with adequate bowel length elsewhere, then this is preferable to avoid a complex multiple strictureplasty procedure. Such decisions have to be individualised, considering the patient's condition at the time of surgery (corticosteroid and immunosuppressive drug use, serum albumin, anaemia, nutritional status), potential for postoperative complications from complex surgery and the risk of future malabsorption and malnutrition due to short gut.

## ASPECTS RELATED TO SURGICAL INTERVENTIONS IN CROHN'S DISEASE

### Non-surgical management of strictures

The CREOLE study evaluated patients with Crohn's disease (n=97) with symptomatic ileal strictures and assessed response to adalimumab treatment.[515] Treatment was successful at week 24 in 64% of patients, defined as an absence of escalation to steroid therapy, no endoscopic dilatation and no surgery. A prognostic score was constructed. This comprised clinical features (use of immunosuppressive drugs at baseline, obstructive symptoms, severity and duration) and magnetic resonance enterography features (length of stricture <12 cm, an intermediated proximal small bowel dilatation (18–29 mm), marked enhancement on delayed T1-weighted sequence and absence of fistula). A higher score was associated with greater likelihood of response to adalimumab therapy. The authors emphasised the complexity of assessing inflammation and fibrotic stricturing, which nearly always occur together, and the value of both clinical and MRI features in deciding the value of using drug therapy rather than surgery for small bowel strictures.[516 517]

A systematic review of intralesional medical therapy identified six studies reporting outcomes in 134 patients after intralesional administration of corticosteroids. Case series have described administration of intralesional infliximab in patients with primary (n=3) and anastomotic (n=3) strictures).[518] All patients had an improvement in obstructive symptoms and no patients required surgery over a short 6month- follow-up period, but there is insufficient evidence to recommend the use of intralesional anti-TNF therapy in current practice.

**GPS 82**

We suggest that endoscopic balloon dilatation is an appropriate treatment for ileocolonic anastomotic strictures less than 4 cm in length, without sharp angulation and with non-penetrating disease, although the majority will require repeated dilatation. Endoscopically accessible ileal strictures are also amenable to balloon dilatation, but complication rates and recurrence rates are higher. There is no role for intralesional corticosteroid injection at the time of dilatation. Long-term data on the impact of dilatation on surgical resections is lacking. The GDG suggests a detailed discussion between the clinical teams and patients before embarking on this therapy.

**GPS 83**

Intra-abdominal abscesses should be treated by antibiotics and, if possible, radiologically guided percutaneous drainage.

**GPS 84**

Following treatment of an abdominal abscess in the setting of non-perianal fistulising Crohn's disease, joint medical and surgical discussion is required, but interval surgical resection is not always necessary.

## POST-SURGICAL CROHN'S DISEASE

Post-surgical Crohn's disease recurrence can be defined as endoscopic recurrence, clinical recurrence and surgical recurrence (ie, need for further surgery). Endoscopic recurrence is most commonly described using the Rutgeert's scoring system. Lack of agreed definitions of recurrence in research studies make comparisons between studies difficult. It is widely seen that Crohn's recurrence occurs with high frequency after surgical resection of diseased bowel. The post[519] , stratified participants by risk factors (multiple prior surgeries, resection for penetrating Crohn's disease, history of perianal disease or active smoker) to postoperative[514] It is now best practice for an assessment of mucosal inflammation to be performed by ileocolonoscopy at 6 months after surgical resection.[520] [521 522] MRE and IUS may be used with sensitivities of 89% to 100% and specificities of 69% to 86%.



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## GRADE STATEMENT: ADVANCED THERAPY FOR POST-SURGICAL CROHN' DISEASE

**Summary of evidence:** A 2019 Cochrane NMA for maintenance of surgically induced remission in Crohn's disease,[524] which included 35 RCTs with 3249 participants, was updated as part of these guidelines. Vedolizumab data are only included in the updated version. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 36.

**Efficacy:** The 2019 NMA estimated with low certainty that adalimumab and infliximab may be more effective than placebo at preventing clinical relapse (adalimumab HR=0.1, 0.02 to 0.33; infliximab: HR=0.36, 0.02 to 1.74) and endoscopic relapse (adalimumab HR=0.1, 0.01 to 0.32; infliximab: HR=0.24, 0.01 to 1.2). The updated NMA results showed with low certainty that adalimumab may have a large effect in preventing clinical and endoscopic relapses, and infliximab may have a moderate effect in preventing endoscopic relapse. It also showed with moderate certainty that vedolizumab probably has a large effect in preventing endoscopic relapse.

In an open label study, patients with Crohn's disease post-ileocolonic resection with primary anastomosis, who were considered high risk for recurrence due to two or more risk factors (young age at diagnosis, penetrating disease, active smoking, perianal disease, less than 3 years from previous surgery), were randomised to infliximab (n=10) or adalimumab (n=10).[525] There was no difference in rate of endoscopic, histologic or clinical recurrence at 12 months. A very similar trial compared infliximab (n=11) with azathioprine (n=11) monotherapy using the same inclusion criteria for postoperative patients with Crohn's disease deemed high risk.[526] At 12 months, there was no significant difference in endoscopic ((IFX 9% vs azathioprine 40%, p=NS) or clinical recurrence (IFX 9% vs azathioprine 10%), but histological recurrence was significantly reduced in the infliximab arm (18% vs 80%, p=0.008).

Four papers included in the NMA compared infliximab with placebo in patients with Crohn's disease who had undergone ileocolonic resection. In the USA, endoscopic recurrence at 1 year was lower in patients with Crohn's disease recruited within 4 weeks of resection and randomised to infliximab compared with placebo, (1/11 (9%) vs 11/13 (85%), p=0.0006), despite significantly more active smokers in the infliximab arm.[527] In a Japanese cohort of patients with Crohn's disease randomised within 4 weeks of ileocolonic resection, the primary outcomes of 12 month and 36 month clinical remission, defined by CDAI<150, were significantly higher in patients receiving infliximab compared with placebo (100% and 93% vs 69% and 56%, respectively, p<0.03).[528] The PREVENT trial included patients post-ileocolonic resection at high risk of recurrence, including multiple prior surgeries, resection for penetrating Crohn's disease, history of perianal disease or active smoker.[529] There was no significant difference in the primary endpoint of clinical recurrence at 76 weeks, but endoscopic recurrence up to week 76 was significantly reduced in the infliximab arm (17% had concomitant immunomodulators) compared with placebo (45/147 (31%) vs 90/150 (60%), p<0.001). In Japan, a multicentre trial randomised patients within 4 weeks of ileocolonic resection to infliximab monotherapy or placebo. The primary outcome of composite endoscopic or clinical recurrence at 2 years was significantly reduced in the infliximab arm compared with placebo (10/19 (53%) vs 18/19 (95%), p=0.0032).[529]

Data on the use of vedolizumab to reduce postoperative recurrence are beginning to emerge. A retrospective multicentre study evaluated the effectiveness of early prophylaxis (within 6 months since surgery) with biological therapy, comparing anti-TNF therapy with vedolizumab and ustekinumab in a real-world setting. Among 297 patients there was no significant difference in endoscopic postoperative recurrence rates within 1 year (anti-TNF 40.2%, vedolizumab 33% and ustekinumab 61.8%). Patients treated with vedolizumab and ustekinumab were more biologic-experienced with higher rates of previous surgery. After controlling for confounders, no differences in the endoscopic post-operative recurrence risk were seen between anti-TNF prophylaxis and other groups, and combining immunomodulators was not associated with a lower endoscopic postoperative recurrence.[530] A retrospective ENEIDA cohort study involving 40 patients treated with ustekinumab and 25 with vedolizumab for the prevention of postoperative recurrence also showed that within 18 months of surgery, the incidence of endoscopic postoperative recurrence was similar at 40% for vedolizumab and 42% for ustekinumab.[531]

The REPREVIO trial is the first prospective, multicentre RCT evaluating vedolizumab in the prevention of endoscopic post-operative recurrence after ileocolonic resection. Patients who underwent surgery and had ≥1 risk factor (active smoking, prior surgery, surgery for a perforating complication, previous exposure to anti-TNFs) were randomised to receive vedolizumab (n=43) or placebo (n=37) at weeks 0, 8, 16 and 24 after surgery. Nearly half (49%) of patients were anti-TNF exposed. Patients on vedolizumab had a greater chance of endoscopic remission (77% vedolizumab vs 38% placebo, p=0.0004) and had lower

**Anti-TNF therapy (infliximab or adalimumab) or vedolizumab are suggested after ileocolonic resection for patients with Crohn's disease if there are significant risk factors for disease recurrence, or patient preference for early treatment through shared decision-making, or endoscopic evidence of recurrent disease 6 months post-surgery.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Large.**

**Justification**: The studies within this context are unique in Crohn's disease trials. The NMA enrolled nearly all patients within the first 90 days post-surgery. Given the significant relapse rate in placebo or comparator groups, this calls into question the need to wait for 6 months before starting biologic therapy to reduce risk of clinical relapse in non-smokers with no high-risk factors (or motivated patients as part of shared decisionmaking). Recently, it has been recommended that regulatory trials assessing effectiveness of therapy for postoperative recurrence recruit patients within 30 days of ileocolonic resection,[523] further highlighting the discrepancy between clinical practice assessing disease recurrence at 6 months, and emerging trial data.

**Implementation considerations**: The GDG has included patient preference as an indication for initiating early biologic therapy prior to 6-month surgical anastomotic endoscopic assessment, as well as risk factors (eg, multiple prior surgeries, resection for penetrating Crohn's disease, history of perianal disease or active smoker). This will need an early clinical consultation after surgery to discuss and make a decision on potential maintenance therapy. The choice of agent must be made on an individual patient basis, with shared decision-making, taking into account prior experience and exposure. The GDG recommends post-surgical advanced therapy should be started within 90 days of surgery where indicated.



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Rutgeert's scores than those on placebo, despite similar rates of clinical recurrence.[532]

**Certainty and rationale:** There is low certainty of a large magnitude of effect for adalimumab, infliximab and vedolizumab in maintenance of postoperative remission in patients with Crohn's disease. These data arise from trials recruiting patients within the first 90 days after surgery, highlighting the role for early initiation of advanced therapy postoperatively, with individualised shared decision-making taking into account risk factors for disease recurrence, patient preference and previous medication history,

### GRADE STATEMENT: 5-ASAS AND PURINE ANALOGUES FOR POST-SURGICAL CROHN'S DISEASE

**Summary of evidence:** Two 2019 Cochrane reviews studied 5-ASAs and purine analogues for maintenance of surgically induced remission in Crohn's disease.[533 534] Fourteen 5-ASA RCTs with 1867 participants, and 10 purine RCTs with 928 were included. They were also included in the updated NMA for these guidelines. The GRADE summary of findings is in online supplemental appendix 4, GRADE table 37.

**Efficacy:** The 5-ASA Cochrane review found low-certainty results that 5-ASAs may be no different from placebo for prevention of clinical relapse (RR=0.71, 0.46 to 1.1). The review found moderate-certainty results that purine analogues may lead to fewer clinical relapses than placebo (RR=0.79, 0.67 to 0.92), and low-certainty evidence that there may be no difference from placebo for endoscopic relapse. The results of the updated NMA showed with low certainty that 5-ASA and purine analogues may only be trivially effective compared with placebo for clinical relapse, and the data on endoscopic relapse was very uncertain.

**Certainty and rationale:** There is low-certainty evidence that purine analogues or 5-ASA monotherapy may be effective in maintenance of postoperative remission in Crohn's disease;, however, the magnitude of effect is trivial. Therefore, purine analogues or 5-ASA monotherapy is not recommended. We recommend individualised shared decision-making to consider the need to convert patients already on 5-ASA or purine analogues to anti-TNF or ustekinumab or vedolizumab.

**5-ASA and purine analogues are not suggested for post-surgical maintenance of remission of Crohn's disease**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Trivial**.

**Justification**: While 5-ASA and purine analogues data reached statistical significance in the maintenance of surgically induced remission with low-certainty evidence, both treatments were of very trivial magnitude, equating to NNT of 13 and 14, respectively. Neither had evidence of effect for endoscopic relapse prevention (due to lack of evidence and very low-certainty outcomes). The GDG has recommended against the use of purine analogues monotherapy, or 5-ASA monotherapy or combination therapy in the prevention of postoperative disease recurrence. To be clear, there is no evidence to support or refute this at present, but this reflects the GDG commitment for clarity, and until such evidence exits, these treatments are not recommended. The NMA and direct evidence from clinical practice has also been considered. In clinical practice, 5-ASAs have little to no role in management of Crohn's disease, supported by subgroup expert opinion. The NMA data are not compelling enough to suggest use of 5-ASAs in post-surgical maintenance of remission.

This statement represents a move away from purine analogues for first line post-surgical monotherapy, supported by NMA results and direct meta-analysis, which suggests that the magnitude of effect is trivial-to-small for both clinical and endoscopic outcomes. While 5-ASA monotherapy was also significantly better than placebo at reducing risk of clinical relapse, the subgroup did not support a recommendation for its routine use in post-surgical prophylaxis due to the precise estimate at trivial for clinical outcomes and the lack of supporting data on endoscopic remission.

**Implementation consideration**: For patients already on either therapy in this context, a discussion should be held to reach a shared decision before any change in therapy is made.

### GRADE STATEMENT: OTHER TREATMENTS FOR POST-SURGICAL CROHN' DISEASE

**It is suggested that no other treatments are currently used for maintenance of post-surgical remission in Crohn's disease.**

Recommendation: **Conditional**. Overall certainty: **Low**. Overall magnitude: **Trivial**.

**Justification**: Curcumin evidence is of low certainty for both clinical and endoscopic relapse showing no difference from placebo and so this is reflected in the statement.

Other treatments studied (including probiotics, sulfasalazine (with or without prednisolone), budesonide, antibiotics, vitamin D) gave low-/very low-certainty outcomes; no statements for or against can be made.

**Implementation considerations**: While antibiotics collectively did not demonstrate statistically significant benefit in NMA for prevention of postoperative recurrence, expert consensus supported the use of nitroimidazole antibiotics such as metronidazole, for 3 months postoperatively, in conjunction with available evidence.[535] In one study, patients within 1 week of ileocolonic resection were randomised to metronidazole 20 mg/kg (n=30) or placebo (n=30).[536] Colonoscopy after 12 weeks of treatment showed a trend towards a lower rate of ileal lesions in patients receiving metronidazole (12/23 (52%) vs 21/28 (75%), p=0.09) and a significantly lower rate of severe disease (i3–i4) in those receiving metronidazole (3/23 (13%) vs 12/28 (43%), p=0.02). A similar study design was employed to test ornidazole, demonstrating a statistically significant reduction in the primary endpoint of clinical recurrence after 54 weeks (3/38 (7.9%) vs placebo 15/40 (37.5%), p=0.0046).[537] However, the risk of poor compliance related to the high rate of side effects, including taste disturbance and gastrointestinal upset, should be noted.

Many patients enquire about the use of over the counter (OTC) treatments, such as probiotics. The network meta-analyses demonstrated no magnitude of effect for these therapies. Equally, the network did not demonstrate adverse safety signals related to OTC preparations, such as probiotics, curcumin and vitamin D. These treatments cannot be recommended by the GDG and should not replace our evidence-based recommendations above. However, it is unlikely that patient preference-driven use of these OTC preparation is harmful, alongside evidence-based advanced therapies.



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**Table 10** Drug monitoring in inflammatory bowel disease

| Drug class | Particular side-effects/concerns | Prior screening | Blood monitoring | Relevant sources |
|---|---|---|---|---|
| **Steroids (systemic)** | Mood swings<br>Psychological symptoms<br>Headache<br>Weakness<br>Moon face<br>Abnormal fat deposits<br>Fluid retention<br>Excessive appetite<br>Weight gain<br>Hypertrichosis<br>Acne<br>Striae<br>Ecchymosis<br>Increased sweating<br>Pigmentation<br>Dry scaly skin<br>Thinning scalp hair<br>Increased blood pressure<br>Tachycardia<br>Thrombophlebitis<br>Opportunistic infections<br>Delayed bone and wound healing<br>Fractures<br>Osteoporosis<br>Menstrual disorders<br>Accentuated menopausal symptoms<br>Neuropathy<br>Peptic ulcer<br>Hypokalemia<br>Adrenal insufficiency | Blood pressure<br>Body weight, BMI<br>Diabetes (HbA1c)<br>Dyslipidaemia<br>Bone health<br>Deep venous thrombosis | Urea and electrolytes Glucose level<br>Triglycerides –<br>frequency depends on individual response and risk factors, generally 2 weeks following the start of a weaning course of oral prednisolone, and on completion of the weaning course | 772<br>8<br>773 |
| **5-aminosalicylates (5-ASA)** | Muscle or joint pain, aching, tightness or stiffness<br>Back pain<br>Fever or flu-like symptoms<br>Headache<br>Nausea, vomiting, heartburn, burping<br>Decreased appetite<br>Constipation, bloating<br>Diarrhoea with blood<br>Mouth sores or blisters, dry mouth<br>Rash, hives, itching or peeling or blistering skin<br>Dizziness, sweating<br>Acne, hair loss<br>Chest tightness, shortness of breath, cough<br>Pancreatitis<br>Interstitial nephritis<br>Liver toxicity | Full blood count<br>U&Es<br>Liver function tests | 3 months after starting treatment, then annually:<br>FBC<br>LFTs<br>Creatinine (or estimated glomerular filtration rate)<br>Us&Es<br>Urine analysis | 774<br>8<br>773 |
| **Purine analogues (azathioprine and mercaptopurine)** | Nausea, vomiting, abdominal pain<br>Loss of appetite<br>Mouth sores and ulcers<br>Flu-like symptoms (sweat, chills, headache, fatigue)<br>Skin rash, tenderness, swelling<br>Hair loss<br>Bone marrow suppressions (leukopenia, thrombocytopenia)<br>Pancreatitis<br>Liver toxicity<br>Kidney damage<br>Increased risk of non-melanoma skin cancer and lymphoma | Calculated glomerular filtration rate or serum creatinine (for creatinine clearance)<br>Cervical screening · check this is up to date<br>FBC<br>LFTs<br>TPMT assay<br>Serology for hepatitis C (HCV), hepatitis B (HBV), HIV<br>Vaccination status (BCG, diphtheria, tetanus, pertussis, Haemophilus influenzae type B, polio, meningococcus, measles, mumps, rubella, pneumococcus, HPV, rotavirus, influenza, varicella zoster virus<br>VZV Immunity<br>If available, test NUDT15 genotype (especially in East and South Asian patients) | Weeks 2-4-8-12, then 3 monthly:<br>FBC<br>Albumin<br>Serum creatinine (for creatinine clearance) or Calculated glomerular filtration rate<br>LFTs<br>Consider yearly: azathioprine metabolite levels (6-TGN) | 775<br>8<br>773 |

Continued



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**Table 10** Continued

| Drug class | Particular side-effects/concerns | Prior screening | Blood monitoring | Relevant sources |
|---|---|---|---|---|
| **Anti-TNF (infliximab, adalimumab, golimumab)** | Opportunistic reactions<br>Malignancies<br>Congestive heart failure<br>Drug-induced lupus<br>Demyelinating disorders<br>Skin rashes (psoriasis-like)<br>Allergic reactions<br>Liver toxicity<br>Headache<br>Dizziness | FBC<br>U&Es<br>LFTs<br>HBV, HCV and HIV serology<br>EBV serology<br>TB screen IGRAs<br>VZV IgG | Four monthly:<br>FBC<br>U&Es<br>LFTs | 8 773 776 |
| **Methotrexate** | Nausea, vomiting<br>Loss of appetite<br>Swollen, tender gums<br>Abdominal pain<br>Diarrhoea<br>Headaches<br>Tiredness<br>Drowsiness<br>Skin sensitivity to sunlight<br>Hair loss<br>Liver toxicity<br>Conjunctivitis<br>Blurred vision | FBC<br>Albumin<br>LFTs<br>Serum creatinine (for creatinine clearance) or estimated glomerular filtration rate<br>HBV, HCV, HIV serology<br>TB screen (IGRAs)<br>VZV IgG<br>Vaccination status (BCG, diphtheria, tetanus, pertussis, Haemophilus influenzae type B, polio, meningococcus, measles, mumps, rubella, pneumococcus, HPV, rotavirus, influenza, VZV/shingles) | Weeks 2-4-8-12, then 3 monthly:<br>FBC<br>Albumin<br>Serum creatinine (for creatinine clearance) or Calculated glomerular filtration rate<br>LFTs | 777<br>8<br>773 |
| **Anti-integrins (vedolizumab)** | The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection, bronchitis, influenza and sinusitis), headache, nausea, fever, fatigue, cough, arthralgia. Infusion-related reactions (with symptoms sulcerative colitish as dyspnoea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) have also been reported in patients treated with vedolizumab.<br>Healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms as outlined in physician edulcerative colitisation materials and consider neurological referral if they occur. If PML is suspected, treatment with vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued. | FBC<br>U&Es<br>LFTs<br>HBV, HCV and HIV serology<br>TB screen IGRAs<br>VZV IgG | Four monthly:<br>FBC<br>U&Es<br>LFTs | |
| **Anti-IL-23/IL-12 (ustekinumab)** | Common side effects (may affect up to 1 in 10 people): Diarrhoea, nausea, vomiting,feeling tired, feeling dizzy, headache, itching ('pruritus') back, muscle or joint pain, sore throat, redness and pain where the injection is given, sinus infection.<br>Uncommon side effects (may affect up to 1 in 100 people): tooth infections, vaginal yeast infection, depression, blocked or stuffy nose, bleeding, bruising, hardness, swelling and itching where the injection is given, feeling weak, drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary. A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis). Peeling of the skin (skin exfoliation), acne.<br>Rare side effects (may affect up to 1 in 1000 people): redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a type of psoriasis symptoms (erythrodermic psoriasis). Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis).<br>Very rare side effects (may affect up to 1 in 10 000 people): blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid), skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains). | FBC<br>U&Es<br>LFTs<br>HBV, HCV and HIV serology<br>TB screen<br>IGRAs<br>VZV IgG | Four monthly:<br>FBC<br>U&Es<br>LFTs | |

Continued



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**Table 10** Continued

| Drug class | Particular side-effects/concerns | Prior screening | Blood monitoring | Relevant sources |
|---|---|---|---|---|
| **Anti-IL-23/p19 (mirikizumab, risankizumab)** | Common (may affect up to 1 in 10 people): upper respiratory tract infections (nose and throat infections), joint pain, headache, rash, injection site reactions (eg, red skin, pain). Uncommon (may affect up to 1 in 100 people): shingles, infusion-related allergic reaction (eg, itch, hives), increase in the level of liver enzymes in your blood | FBC<br>U&Es<br>LFTs<br>HBV, HCV and HIV serology<br>TB screen<br>IGRAs<br>VZV IgG | Four monthly:<br>FBC<br>U&Es<br>LFTs | 778 |
| **Pan-JAK inhibitors (tofacitinib)** | VZV infection<br>Infections<br>Nasopharyngitis<br>Headache<br>VTE<br>Arthralgia | FBC, LFTs<br>Lipid profile<br>Hepatitis B, C, HIV status<br>VZV status<br>TB quantiferon test<br>Chest x-ray<br>Zoster vaccination<br>Non-live vaccine (Shingrix) preferable. Ideally administer before starting treatment.<br>If unavailable, live vaccine to be given ideally >4 weeks before treatment) | After 4–8 weeks:<br>FBC<br>Lipid profile<br>LFTs<br>Ensure second dose of Shingrix given within 2 months.<br>3 monthly:<br>FBC<br>U&Es<br>LFT<br>Serum CK | 778 |
| **JAK1 inhibitors (upadacitinib, filgotinib)** | HZV infection<br>Nasopharyngitis<br>Infections<br>Headache<br>Nausea<br>Lymphopenia (filgotinib), neutropenia (upadacitinib)<br>Acne (upadacitinib)<br>Hepatic dysfunction | | | |
| **S1P receptor modulators (ozanimod, etrasimod)** | Lymphopenia<br>Increased ALT<br>Headaches<br>Nasopharyngitis<br>Arthralgia.<br>Rare cases of bradycardia, heart block and macular oedema | FBC<br>LFTs<br>ECG<br>VZV status<br>Ophthalmic assessment if history of uveitis or macular oedema<br>Zoster vaccination<br>Medication review to assess for potential drug–drug interactions. | LFTs: at month 1, then 3-monthly intervals.<br>FBC 3 monthly.<br>Regular blood pressure monitoring: at 3 months then every 6 months. If pre-existing hypertension, weekly for first month.<br>Ophthalmic- monitor for changes in vision, light sensitivity. Patients with diabetes, uveitis or macular oedema should have regular ophthalmic assessment. | |

ALT, alanaine transaminase; BCG, Bacillus Calmette-Guerin ; CK, creatine kinase; EBV, Epstein-Barr virus; FBC, full blood count; IGRAs, interferon-gamma release assays; IL, interleukin; LFTs, liver function tests; S1P, sphingosine-1-phosphate; 6-TGN, thioguanine nucleotides; TPMT, thiopurine methyltranferase; UCEIS, ulcerative colitis index of severity; U&Es, urea and electrolytes; VZV, varicella zoster virus.

## CROSS IBD SECTION

### Drug monitoring in inflammatory bowel disease

A myriad of drug therapies are now in routine use in IBD, mostly immunosuppressant in nature. Each of these medications has specific recommendations in terms of monitoring for safety, which often include blood monitoring. We have attempted to summarise these recommendations in a single table for ease of use but would reiterate that these are not newly generated recommendations from this guideline but adapted recommendations from elsewhere (table 10).

### Managing side effects of immunomodulators and advanced therapy

No high-quality evidence is available on recommendations about managing side effects of immunotherapy and biological therapy for IBD, or their management/therapy withdrawal. One recently published review suggests that de novo cutaneous lesions (either psoriasiform, eczematous or lupus-like) occurring in people affected by IBD while on TNFα inhibitors require topical management (in cases of eczema or mild psoriasiform pathology); or discontinuation (in cases of lupus); or switch to another TNFα inhibitor; or change of biologic class (in cases of moderate/severe psoriasiform pathology).[538] Au *et al* also suggest that assessment of de novo cutaneous lesions arising in patients on TNFα inhibitor treatment should be multidisciplinary.[538] Paradoxical articular inflammatory manifestations may arise in 5.2% of patients with IBD treated with TNFα inhibitors, without specific predictive factors. Most cases are transient and do not require therapy discontinuation, although in a small proportion (1.8%) paradoxical articular manifestations represent the onset of de novo spondyloarthopathies (SpA).[539] In one retrospective study,[540] vedolizumab was associated with 46% lower risk (HR=0.54; 95% CI 0.35 to 0.83) of serious infections in comparison with TNFα inhibitors. However, this was restricted to ulcerative colitis, and the authors observed no significant differences when they analysed cases of Crohn's disease. One review performed in 2023[540] confirmed such findings. The review by Solitano *et al* also found that ustekinumab was associated with lower risk of serious infections in comparison with TNFα inhibitors (OR, 0.49; 95% CI, 0.25 to 0.93; I2=16%) and when compared with vedolizumab (OR=0.40; 95% CI 0.17 to 0.93; $I^2$=67%). Another retrospective study[541] found that methotrexate (either oral or subcutaneous injection formulations) was less well tolerated than purine analogues, though no comparisons with other drugs were performed. Notably, patients with IBD on methotrexate were older, had had longer disease duration and were more likely to be refractory to previous immunemodulatory treatments. The results of another retrospective study[542] suggest that patients with IBD on treatment with azathioprine or methotrexate are less likely to experience infusion reactions to infliximab. Our group would like to highlight that no high-quality studies were available to retrieve evidence to address this topic. The scarcity of medical literature on this specific matter brings to the attention of the gastroenterology community one scientific unmet need.



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### 5-ASA therapy

5-ASAs are a widely available and generally well-tolerated medication. The choice of 5-ASA should be determined by local access, disease location, patient preference (eg, tablets vs granules) and cost. Once established on oral medication, brand-specific prescribing should continue. Brand specificity is not required for rectal products, but preferences can be considered for ease of use. The lowest effective maintenance dose should be used, and/ or topical therapy as appropriate.

**GPS 85**

Monitoring of patients on oral 5-ASA should include baseline full blood count; renal and hepatic function testing which should be used with caution in mild to moderate impairment and avoided in severe impairment. Blood test monitoring for full blood count, renal and liver function should be repeated at 3 months, then annually, but adjusted for individual patient factors, such as baseline results, polypharmacy and comorbidity.

### Corticosteroids and bone density

No new evidence is available on recommendations about the timing of appropriate BMD evaluation, and how to manage low BMD, in patients affected by IBD. Guidance on management of osteoporosis in the UK is available from the National Osteoporosis Guideline Group (NOGG) website. Diet and nutritional status both contribute to low BMD as risk factors and are relevant to its management. The scarcity of new medical literature on this specific matter–and the lack of IBD-specific references in regards with the suggested timings of assessment of BMD/ management of low BMD–- brings to the attention of the gastroenterology community one underinvestigated field where new research will be welcome. Our group felt that cross-referencing to the NICE clinical guideline CG146, published in August 2012 (and last updated in February 2017) would be useful to the readership.

## Efficacy and safety of thromboprophylaxis during and after hospitalisation

The risk of venous thromboembolism (VTE) in patients with IBD appears to be two times greater (95% CI 1.72 to 2.39) than in patients without IBD.[543] In patients with IBD admitted to hospital for any reason the risk is approximately 1.5 times greater than for inpatients without IBD.[544–546]

The risk of VTE increases significantly in patients with IBD with active inflammation.[547] VTE risk in these patients is increased compared with healthy controls (HR=8.4, 95% CI 5.5 to 12.8, p<0.0001). When considering only the subgroup of patients admitted to hospital, the additional risk of VTE conferred by active IBD was lower (HR=3.2, 95% CI 1.7 to 6.3, p=0.0006), probably because of VTE prophylaxis.[548] Prophylactic use of subcutaneous low molecular weight heparin is therefore recommended during hospital admissions. It is important to note that this does not precipitate or exacerbate colonic bleeding and patients with ASUC should all receive VTE prophylaxis.[39 549]

The risk of VTE does not resolve on hospital discharge. Patients admitted with active inflammation have a persistently increased risk for 60–90 days. Key risk factors include prolonged length of stay, advancing age, emergency admission type, ulcerative colitis and multiple previous admissions for IBD in the preceding 3month-period. Risk prediction scoring systems have been proposed but require further investigation.[550–552] Despite this, the evidence is currently insufficient to recommend continuing VTE prophylaxis post discharge. Patients admitted for elective surgery are at an increased risk of VTE during their admission and following discharge.[553] It is routine practice in UK to extend VTE prophylaxis post discharge after major abdominal luminal surgery.

**GPS 86**

All patients with inflammatory bowel disease admitted for acute medical illness or surgery should receive pharmacological VTE prophylaxis unless contraindicated.

## Surgery in IBD

**GPS 87**

Patients undergoing IBD surgery need support of the wider MDT. This should include, where possible, IBD physicians, surgeons, radiologists, dietitians, psychologists and peer support.

In elective surgery, patients with IBD should have their condition assessed and optimised prior to surgery. This should include assessment of comorbidities, imaging or endoscopy to document disease extent, drainage of abscesses and treatment of sepsis, assessment and correction of nutritional deficiencies, and stopping corticosteroids and biologics, where possible. All patients with IBD undergoing surgery should follow an enhanced recovery protocol.[91 504]

**GPS 88: IBD operative checklist**

**Preadmission**

Surgeons to notify medical team and patient of planned surgical date for elective surgery.

⇒ Co-ordination between medical and surgical team with clear plan regarding optimisation of medical therapy before and after surgery.
⇒ Minimise steroid use.
⇒ Surgeons to notify IBD physicians regarding emergency admissions and dates of planned admissions.
⇒ Dietitian assessment with optimisation of nutritional status in the weeks prior to elective surgery
⇒ Psychological and peer support.
⇒ Stoma counselling (if required).
⇒ Smoking cessation education and support, including from general practitioner and community support services.

**Inpatient and postoperative care.**

⇒ Involvement of the IBD team to ensure medication appropriately managed and clear plan agreed with patient on decision to stop, change or continue IBD medications as appropriate for each individual.
⇒ Consider medical prophylaxis in patients at high risk of disease re-occurrence.
⇒ Holistic care, including dietitians, psychologists and peer support.
⇒ Taper prednisolone.
⇒ Dietary assessment and nutritional plan.



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### Corticosteroids in the perioperative period

Patients undergoing IBD surgery while on corticosteroids have an increased risk of postoperative infectious complications, VTE and anastomotic leak.[554] There is some evidence that risks are greater for those taking high-dose steroids (≥40 mg prednisolone).[328 330] A comparison of prednisolone doses >20 mg vs ≤20 mg did not show a significant difference in risk of infections.[327] In the setting of proctocolectomy, the use of use of ≥20 mg prednisolone is associated with increased risk of complications.[331 332] Patients with IBD having elective surgery should have corticosteroids stopped, if possible, or brought to as low a dose as can be managed without deterioration. This advice does not pertain to patients who are being managed for ASUC – please see section 5.6 for additional information.

Patients who are on corticosteroids at the time of IBD surgery should be given the equivalent dose of intravenous hydrocortisone until they can resume oral prednisolone.[329] Prednisolone 5 mg is equivalent to hydrocortisone 20 mg or methylprednisolone 4 mg. There is no value increasing steroid dosage to cover stress in the perioperative period, as shown in a randomised trial in IBD surgery[333] and a case series.[334] Anaesthetists will generally give a single steroid dose prior to induction (such as dexamethasone 4 mg intravenously or intramuscularly) for those taking more than 5 mg prednisolone.[335] Patients who are on physiological corticosteroid replacement because of disorders of the hypothalamic pituitary axis (such as oral hydrocortisone 20 mg in the morning, 10 mg mid-day) should receive supplementary doses in the perioperative period.[336] For patients who have had complete resection of active disease, it is important to avoid inappropriate prolongation of steroids after surgery, and there is virtue in standardised steroid-taper protocols in the postoperative period, dependent on the dose and duration of steroids preoperatively, with clear communication between patient, medical and surgical teams about postoperative medication plans.

**GPS 89**

Patients with IBD who have been on oral corticosteroids for more than 4 weeks prior to surgery should receive an equivalent intravenous dose of hydrocortisone while nil by mouth in the perioperative period.

**GPS 90**

For non-emergency surgery in Crohn's disease or ulcerative colitis, corticosteroids should be stopped preoperatively, or dose minimised, wherever possible, to reduce risk of postoperative complications.

### Immunosuppressive agents in the perioperative period

**GPS 91**

Immunosuppressive agents (purine analogues and methotrexate) and biological agents can be continued in the perioperative period in patients requiring IBD surgery.

With one exception, the literature on the use of immunosuppressive therapy (purine analogues and methotrexate) leading up to surgery does not describe an association with an increased risk of postoperative complications.[328 330] Anti-TNF impairs neutrophil chemotaxis, which raises concern about the impact it might have on infection rates post-surgery.[555]

Numerous single-centre retrospective studies and meta-analyses of predominately Crohn's disease observational cohorts have been published, with conflicting results, with some suggesting an increased risk of postoperative complications (surgical site infection and postoperative infection) in patients receiving anti-TNF therapy and other studies showing no association.[556 557]

Two large prospective studies are reassuring. In PUCCINI, a prospective multicentre observational US study of 947 patients with IBD (640 Crohn's disease, 382 anti-TNF exposed) the rates of any infection, including surgical site infection, were similar in both anti-TNF exposed and unexposed patients irrespective of anti-TNF drug concentration.[339]

The French Remind Study of 209 patients with Crohn's disease undergoing ileocaecal resection found that preoperative anti-TNF therapy (regardless of the serum level or the time interval between last administration and surgery) was not associated with postoperative complications.[439]

Some early reports raised concerns that vedolizumab use in the perioperative period may increase the risk of surgical site infections.[355 558] However, larger more recent studies, which have taken into account disease severity and type of surgery, are reassuring, showing no increased risk of postoperative or infectious complications in patients exposed to vedolizumab in the preoperative period.[559–561]Although prospective studies are lacking regarding the safety of ustekinumab in the perioperative period, the two largest retrospective studies,[562 563] including 44 and 66 patients on ustekinumab, respectively, did not show an increased risk of surgical complications. A meta-analysis of 172 patients with Crohn's disease whose last dose of ustekinumab was at most 16 weeks prior to surgery found similar complication rates (including surgical site infection, intra-abdominal sepsis and readmission) to those of patients exposed to anti-TNF agents.[564]

In a further meta-analysis of 3225 patients with Crohn's disease, 332 of whom received ustekinumab preoperatively, there was no evidence of difference in the overall complications (OR=0.84, 95% CI 0.57 to 1.23), p=0.37, I2=40%) between Crohn's disease patients who had ustekinumab preoperatively and those who had no ustekinumab. There was also no difference in infectious complications (OR=1.15, 95% CI 0.86 to 1.53), p=o.35, $I^2$=2%).[565] These studies support continuation of biologics and immunosuppressants in the perioperative period.

Regarding the safety of JAK inhibitors in the operative setting, there is one retrospective review of 53 patients exposed to tofacitinib within 4 weeks of total colectomy for refractory ulcerative colitis. 13.2% of patients had a VTE, and it was suggested that prolonged VTE prophylaxis should be used in these patients.[562 563] There are no available data on other JAK inhibitors or small molecules at present, and this is an area where future research is required.

## SCREENING AND TREATMENT FOR SUPERADDED INFECTIOUS COLITIS

New onset or worsening of symptoms in IBD should be scrutinised to discern disease relapse from superinfections, which should be promptly identified and treated prior to initiation or alterations of any immunosuppressive therapies.

Moderate to severe activity in IBD, immunosuppressive medications, poor nutrition, comorbidities, including congenital and acquired immunodeficiencies, and age can be risk factors



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for infections.[203] A thorough history, including travel, recent courses of antibiotics, changes in immunosuppressive therapies, contact history and social history including diet and sexual practice, should be sought. All patients presenting with worsening of symptoms or refractory disease should have stool cultures sent for microscopy and culture. Testing for ova, cysts and parasites is recommended according to local policies and travel history. Details of appropriate returning travellers should be discussed with the local infectious diseases team. In those with relevant sexual history, rectal swabs for sexually transmitted diseases and repeat HIV testing or referral to genitourinary medicine clinics should be considered.

**GPS 92**

Patients with new or worsening symptoms of IBD should have stool cultures for enteroinvasive bacterial infections and stool *Clostridioides difficile* assay. Careful review of travel and contact history should be taken, with microscopy culture and microscopy for amoebic and/or *Shigella* dysentery sent in patients with relevant travel history.

## CYTOMEGALOVIRUS

Cytomegalovirus (CMV) can be present in up to 10–30% of patients with steroid refractory IBD[566] and is associated with poor outcomes, such as recurrent flares, toxic megacolon and need for surgery. Purine analogues are an independent risk factor for CMV reactivation.

Patients requiring hospitalisation for active IBD, and outpatients with moderate to severe disease refractory IBD not responding to immunosuppressive therapy, should be investigated for CMV. Diagnosing active CMV can be challenging. Serum antigen and PCR tests do not correlate with colonic infection; therefore, we recommend gastrointestinal tissue immunohistochemistry or PCR.[567] Haematoxylin and eosin staining (H&E) for inclusion bodies has poor sensitivity when compared with these techniques.

**GPS 93**

Patients with IBD flare requiring hospitalisation and outpatients with moderate to severe refractory IBD not responding to immunosuppressive therapies should have colonic tissue sent for CMV immunohistochemistry or PCR.

Site and number of biopsies influence the yield of CMV. Sampling from actively inflamed areas and from multiple segments of colon will increase the likelihood of capture. A minimum of 11 and 16 samples from the left colon in ulcerative colitis and Crohn's disease, respectively, was recommended by one study.[568]

The decision to treat CMV reactivation should consider patient history, serological findings (antigen/DNA titre, leucopenia, low platelet count and elevated liver enzymes) and tissue viral load. Low-level serological reactivation of CMV in patients on immunosuppressive therapy often does not need treatment. There is no clear threshold as to when to treat CMV reactivation; however, steroid refractoriness, high tissue viral load and systemic illness warrant treatment. Discussion with the local microbiology team may also aid decision to treat.

CMV infection in patients who are hospitalised with flares in ulcerative colitis or Crohn's disease should be treated with intravenous ganciclovir 5 mg/kg twice daily for 5–10 days, followed by valganciclovir 900 mg daily until completion of a 2–3 week course.[203] Unless there is evidence of disseminated CMV reactivation illness, immunosuppressive therapies for IBD should be continued to minimise relapse of IBD. Full blood count and renal function should be closely monitored as neutropenia, thrombocytopenia and acute kidney injuries are associated with antiviral therapy. Evidence of disseminated systemic CMV reactivation (fever, meningoencephalitis, pneumonitis, oesophagitis or hepatitis) requires cessation of all immunosuppressive therapies, prompt initiation of intravenous ganciclovir and discussion with local infectious diseases team.

**GPS 94**

Where a decision has been made to treat CMV, intravenous ganciclovir 5 mg/kg twice daily for 5–10 days should be given, followed by valganciclovir 900 mg daily until completion of a 2–3 week course.

## *Clostridioides difficile* infection associated with IBD

A diagnosis of IBD is an independent risk factor for *C. difficile* infection, independent of co-prescription of PPI or antibiotics.[5] The incidence of *C. difficile* is significantly higher in patients with active disease than in those in remission.[569] *C. difficile* infection in IBD contributes to higher rates of colectomy, postoperative complications and higher mortality.[570 571] Colonic involvement and use of biologics and antibiotics are risk factors for developing *C. difficile* in patients with IBD.[571]

There are a number of different assays available when screening for *C. difficile* infection. Glutamate degydrogenase (GDH) antigen is used to detect *C. difficile* organism, and molecular methods such as nucleic acid amplification technology tests detect the presence of toxin genes.[572] Enzyme immunoassays (EIA) and cytotoxicity neutralisation assay are used to detect *C. difficile* toxin. Given the cost of highly sensitive assays, most laboratories carry out two-step procedures, such as GDH antigen testing (highly sensitive) followed by toxin A/B EIA (highly specific). Please liaise with local laboratories to understand which assays are used.

As part of the disease activity assessment in IBD, stool samples should be sent for *C. difficile* infection. Vancomycin or fidaxomicin are recommended for 10 days for treating non severe *C. difficile* infection. Intravenous metronidazole should be added for 10 days in severe cases.[203] Faecal microbiota transplantation should be considered as a treatment option in cases of recurrent *C. difficile* infection. A systematic review containing nine cohort studies, comprising a total of 346 patients with IBD and *C. difficile* patients who were treated with, FMT concluded that there is no difference in cure rate between the IBD and non-IBD population.[573] Another systematic review containing 457 patients with *C. difficile* and IBD reported overall pooled cure rate of 88% compared with IBD flare after FMT in 26.8%.[574] Other systematic reviews have reported similar success rates with low adverse events.[574 575]

Decisions surrounding continuing immunosuppressive therapies should take into consideration the severity of the C. *difficile* infection and IBD activity.



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**GPS 95**

*C. difficile* infection should be treated with vancomycin or fidaxomicin for 10 days in non-severe cases in accordance with local trust guidelines. Addition of intravenous metronidazole should be considered in hospitalised patients with severe infection with microbiologist guidance.

**GPS 96**

FMT should be considered for treatment refractory or recurrent *C. difficile* on an individual basis in patients with IBD.

**GPS 97**

Patients with IBD who have travelled for long periods or lived in endemic areas may be at increased risk of parasitic infections and should have Strongyloides serology and eosinophil count checked before starting anti-TNF therapy.

## IRON DEFICIENCY ANAEMIA

**Summary of evidence:** A Cochrane review of treatment of iron deficiency anaemia in IBD included 11 studies (1670 randomised participants).[576] The studies compared intravenous iron sucrose versus oral iron sulphate (two studies); oral iron sulphate versus oral iron hydroxide polymaltose complex (one study); oral iron fumarate versus intravenous iron sucrose (one study); intravenous ferric carboxymaltose versus intravenous iron sucrose (one study); erythropoietin injection+intravenous iron sucrose versus intravenous iron sucrose+injection placebo (one study); oral ferric maltol versus oral placebo (one study); oral ferric maltol versus intravenous ferric carboxymaltose (one study); intravenous ferric carboxymaltose versus oral iron sulphate (one study); intravenous iron isomaltoside versus oral iron sulphate (one study); erythropoietin injection versus oral placebo (one study). The GRADE summary of findings is in online supplemental appendix 4, GRADE table 38.

All studies compared participants with Crohn's disease and ulcerative colitis together, as well as considering a range of disease activity states. The primary outcome of number of responders, was defined as those with an increase in haemoglobin of 20 g/L in all but two studies, in which an increase of 10 g/L was used.

An analysis of all intravenous iron preparations versus all oral iron preparations showed that intravenous administration may lead to more responders (368/554 vs 205/373, RR=1.17, 95% CI 1.05 to 1.31, NNTB=11, low certainty due to risk of bias and inconsistency). Withdrawals due to adverse events may be greater in oral iron preparations versus intravenous (15/554 vs 31/373, RR=0.39, 95% CI 0.20 to 0.74, low certainty due to risk of bias, inconsistency and imprecision).

**Certainty and rationale:** Oral iron as ferric maltol may lead to more people having resolution of iron deficiency than placebo treatment. It is unclear whether there is any difference between any of the other treatments studied for treating iron deficiency anaemia. It is unclear whether there is any difference in any adverse events between all the therapies tested.GPS

**GPS 98 Recommendations for managing iron deficiency anaemia in IBD.**

- ⇒ Iron deficiency anaemia is very common in patients with active IBD – often resulting in significant morbidity
- ⇒ As systemic inflammation inhibits absorption of iron, iron tablets should not be used in those with active disease and, in patients with inactive disease, no more than 100 mg elemental iron should be taken daily.
- ⇒ Ferritin levels up to 100 µg/L in the presence of inflammation may still reflect iron deficiency. Measurement of transferrin saturation may therefore be helpful.
- ⇒ Other causes of anaemia, such as vitamin B12 and folate deficiency, marrow suppression due to anaemia of chronic disease and overt blood loss, should be considered and managed accordingly.
- ⇒ Treatment of IDA should be with one tablet per day of iron. If not tolerated, a reduced dose of one tablet every other day, alternative oral preparations or parenteral iron should be considered.

*What treatments can be used for iron deficiency anaemia in adult patients with IBD, independently of treatments to achieve or maintain remission?*

Iron deficiency anaemia is a common systemic complication of IBD—particularly with active IBD—causing significant morbidity with consequential impacts on quality of life. Other causes of anaemia, such as vitamin B12 and folate deficiency, bone marrow suppression due to anaemia of chronic disease, and overt blood loss may contribute to the anaemic state. These should be considered and managed accordingly.[577]

The ECCO guidelines on the diagnosis and management of iron deficiency and anaemia in IBD recommend that iron tablets should not be used in patients with active disease, as systemic inflammation inhibits the absorption of iron. For patients with inactive disease, no more than 100 mg elemental iron should be taken daily. Ferritin levels up to 100 µg/L in the presence of inflammation may still reflect iron deficiency, therefore measurement of transferrin saturation may still be helpful.[577]

**We suggest treatment of IDA in patients in remission should be with one tablet per day of iron. If not tolerated or effective, consider either reducing to one tablet every other day, alternative oral preparations or, if required, parental iron.**

Recommendation: **Conditional**. Overall certainty: **Low.** Overall magnitude: **Trivial difference comparing intravenous and oral for success**.

**Justification**: The overall certainty of evidence is low, although certainty of evidence for the safety data is very low due to sparse events. There was only a trivial difference between intravenous and oral preparations of iron for response. Therefore, given the practical, feasibility and cost advantages of oral iron supplementation, it is proposed as the suggested treatment. Data on tolerability is of very low certainty so no recommendations may be made.

**Implementation considerations**: We suggest initial treatment with oral iron if this is tolerated. If this is not tolerated intravenous iron should be supplemented.



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Oral iron tablet therapy should be limited to one tablet to be taken once daily/alternate days to improve absorption and tolerance. If oral iron is not tolerated and patients with IBD have moderate to severe iron deficiency anaemia (Hb<100 g/L), then intravenous iron should be used.[577]

In a review[576] of interventions for treating iron deficiency anaemia in IBD, various intravenous and oral iron preparations were evaluated. An updated review is summarised in the findings table. Overall, the data were limited owing to a low number of suitable studies. Intravenous iron was found to be better than oral iron in terms of the number of responders; 9.3% more (2.2%–17%, GRADE: certainty of evidence is low, effect range trivial to small), with trivially (5.1%) fewer withdrawals from therapy due to adverse events (2.1%–6.6%, GRADE: certainty of evidence is very low). However, serious adverse events with intravenous iron were worse (3.5% more) than with oral iron (0.6%–10.4%, GRADE: certainty of evidence is low, effect range trivially more to moderately more). The data for change in haemoglobin (with treatment), compliance, and tolerability was very uncertain (GRADE: certainty of evidence is very low).[576]

Fatigue as a stand-alone symptom in patients with IBD is a challenging symptom to manage when reversible causes such as anaemia, hypothyroidism, and active IBD inflammation have been addressed. In a 2020 Cochrane review, interventions such as cognitive behavioural therapy, physical activity, and pharmacological therapies such as iron were evaluated. Owing to insufficient data, no firm conclusions regarding the efficacy and safety of interventions could be drawn.[578]

## Pre-conception, pregnancy and post-partum IBD

### Pre-conception counselling

In counselling patients aiming to get pregnant and delivering a healthy baby, the key message is “healthy mum, healthy baby”. An early discussion about conception and pregnancy should occur in all women of childbearing age with IBD to reduce the risk of voluntary childlessness. The consultation should focus on addressing the patient’s concerns, patient education and a review of general health with the aim of disease remission prior to conception. It is well known that medication adherence, smoking cessation and pregnancy outcomes are improved in those who receive pre-conception counselling.[579]

Patients with IBD worry about passing on their disease to their children, and these concerns should be explored. In a Danish population study, the familial risk was higher in first-degree relatives of patients with Crohn’s disease, almost an eightfold increased risk, compared with ulcerative colitis, which had a fourfold increased risk.[580] Offspring of one affected parent have a 10% risk of inheriting IBD, which increases to 30% when both parents are affected.[581] Patient education is key as many women continue to proceed with voluntary childlessness, affecting 17% of 1324 women in a UK study, which in part was due to poor disease knowledge.[582] Counselling should also be provided to male patients with IBD and they should be advised to continue their medication when indicated. However, patients on sulfasalazine affected by subfertility should switch this therapy to 5-ASA if possible. Similar to non-IBD patients, cases of subfertility should be referred to the appropriate specialist services at a suitable time.

### Disease activity

A 2013 meta-analysis of 14 studies showed that both patients with ulcerative colitis (10 studies, n=1130) and Crohn’s disease (six studies, n=519) who conceived with clinically active disease

**GPS 99: General guidance on pregnancy in patients with IBD.**

**Pre-conception:**

⇒ Education: Importance of keeping well (‘you need to be well for your baby to be well’). Discuss potential adverse foetal outcomes of uncontrolled IBD (eg, pre-term birth and low birth weight), the risk of disease relapse versus risk of taking medication during pregnancy.

⇒ Explore concerns: such as risk of disease inheritance.

⇒ General health: advise folic acid (400 µg/day for everyone and 5 mg/day for those taking sulfasalazine, those with significant small bowel resections or active small bowel disease), nutrition, cervical smear, smoking cessation and vaccinations.

⇒ Disease assessment: Is the patient as well as possible with their IBD? Consider objective assessments: faecal calprotectin, endoscopy and small bowel non-ionising imaging in small bowel Crohn’s disease. If necessary, escalate treatment.

⇒ Remission: Aim for a minimum of 3 months' remission prior to conception.

⇒ Medication: Is the patient receiving the safest possible combination of medicines for pregnancy? Pre-conception advice regarding vitamin D and folic acid supplementation.

⇒ Stop methotrexate, JAK inhibitors or S1P inhibitors >3 months prior to conception.

⇒ Individual plan for disease monitoring and management during pregnancy.

**During pregnancy:**

⇒ Treat both maintenance and relapses as normal with 5-ASA, purine analogues, biologics (most safety data for anti-TNF, less but reassuring data for vedolizumab and ustekinumab), nutrition and steroids. Indications for surgery in pregnant women with IBD are the same as for non-pregnant patients.

⇒ Use therapies with the best evidence base for safety in pregnancy.

⇒ Use imaging as needed, but minimise radiation exposure with emphasis where possible on ultrasound and MR. Essential endoscopic investigations only when needed for clinical decision-making. Avoid the use of gadolinium as part of MR enterography during pregnancy.

⇒ VTE prophylaxis for hospitalised patients, and outpatients with active IBD, for the duration for the third trimester.[779]

⇒ Involve the IBD MDT where required.

⇒ All patients with IBD should be assessed at least once in a consultant-led obstetric clinic. Joint IBD antenatal clinics may offer optimal care.[780]

⇒ Mental health screening and referral to appropriate services before, during and after pregnancy.

**Delivery and post partum:**

⇒ Mode of delivery should be determined by obstetric considerations and patient preference, except for active perianal disease, and ileoanal pouch or ileorectal anastomosis where caesarean section is often preferred.

⇒ VTE prophylaxis is important after caesarean section.

⇒ Medicines low risk in pregnancy are also low risk in breast feeding and should continue.

⇒ Breast feeding is the preferred method of feeding and does not affect the course of IBD.

⇒ Postpone live vaccinations for the infant for the first 12 months in those who had biologic exposure in pregnancy.[592]



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had a twofold increased risk of disease relapse during pregnancy compared with those in clinical remission. In a prospective study of 229 Dutch women with IBD (157 Crohn's disease, 66 ulcerative colitis, and 6 IBD unidentified, active disease at conception had a nearly fourfold risk of ongoing disease activity and/or new relapses during pregnancy (RR=3.8, 95% CI 2.8 to 5.2).[583] Patients with ulcerative colitis relapsed more often during pregnancy than those with Crohn's disease (aOR=3.71, 95% CI 1.86 to 7.40).[583]The increased risk of relapse with ulcerative colitis has been shown in other studies. The 2021 pregnancy IBD and neonatal outcomes (PIANO) registry, a prospective multicentre cohort study of 1490 completed pregnancies in the USA, showed that birth parents with ulcerative colitis had a significantly lower rate of remission per trimester compared with birth parents with Crohn's disease (p=0.002 trimester 1, p<0.0001 trimesters 2, 3).[584] A prospective study of 298 Israeli women with quiescent IBD also showed that those with ulcerative colitis have a higher risk of active disease in pregnancy: 48.1% of those with ulcerative colitis had a relapsing episode versus 31.8% of those with Crohn's disease (p=0.005). The use of biologic therapies was protective against disease relapse (25.0% vs 43.9%, p=0.001).[585]

### Foetal outcomes

A 2021 meta-analysis of 28 studies showed active IBD in pregnancy was significantly associated with low birth weight (LBW), preterm birth, small for gestational age (SGA), spontaneous abortion and stillbirths compared with women with inactive IBD.[586] A Korean population study of 2058 patients with IBD (589 Crohn's disease, 1469 ulcerative colitis) with 20 580 matched controls, not included in the meta-analysis, showed similar pregnancy outcomes between patients with quiescent to mild IBD and the controls.[587] However, pregnant women with moderate to severe IBD had higher rates of spontaneous abortion (14.9% vs 11.9%, OR=1.33, 95% CI 1.04 to 1.68) and intrauterine growth retardation (3.4% vs 1.0%, OR=3.20, 95% CI 1.75 to 5.84). In the PIANO registry, active disease was associated with spontaneous abortion (HR=3.41, 95% CI 1.51 to 7.69) and preterm birth with increased infant infection (OR=1.73, 95% CI 1.19 to 2.51).[588]

### Monitoring and management

Disease activity at conception strongly influences the course of IBD during pregnancy and affects maternal and foetal outcomes. The aim prior to conception should ideally be 3 months of corticosteroid-free remission on stable therapy.[584] Clinical assessment as well as objective measures: full blood count, haematinics, C-reactive protein, faecal calprotectin, endoscopy and imaging, should be considered. Therapeutic drug monitoring for purine analogue metabolites and trough drug and anti-drug antibody TNF levels will allow drug optimisation and aid in guiding treatment options in the case of a disease relapse in pregnancy requiring a drug switch.

### Monitoring of pregnancy in IBD

If possible, a review in each trimester, which may include non-invasive assessments, should guide maternal IBD care. Bloods tests such as haemoglobin, albumin and CRP can be affected by pregnancy[589]; however, their overall trends may be useful in the assessment of the patient. Faecal calprotectin correlates with disease activity throughout pregnancy and is useful as a non-invasive marker.[589 590] Patients with IBD with ileostomies have been shown to be at high risk of developing significant stoma complications in a multicentre audit.[591] A total of 19/82 (23%) pregnancies were affected: nine stoma prolapses (two required surgery), three parastomal hernias (two required surgery) and seven small bowel obstructions (three required surgery). Women with ileostomies should be educated regarding symptoms to watch out for, and monitored closely in pregnancy.

Further investigations should be guided by whether active disease develops. Routine endoscopy is not recommended, but if clinically required, it should be aimed for beyond the first trimester, procedure time minimised, no or lowest dose of sedation used, and the patient positioned in the left lateral position to avoid vena cava or aortic compression.[592] Capsule endoscopy is not currently recommended in pregnancy due to lack of data on safety of the electromagnetic field of the capsule recorder.[593] The benefits of routine imaging are unclear and therefore not recommended. If clinically required, MRI without the use of gadolinium is preferred over CT to avoid radiation exposure. If local expertise is available, gastrointestinal ultrasound provides an alternative objective assessment of disease activity. A multicentre observational study of 90 patients and 127 ultrasound scans showed that adequate colonic and terminal ileal views were obtained up to week 20 of gestation (respectively 91% and 93%).[18] Terminal ileal views deteriorated from week 20, though colonic views were deemed adequate up to week 33 as 78% could be assessed, but this was only in nine patients.[594]

### Conventional therapies in pregnancy

#### *5-ASAs*

5-ASA crosses the placenta, but their use during pregnancy is not associated with adverse foetal outcomes.[595] Sulfasalazine affects folate absorption and thus, folate supplementation of 5 mg/day is recommended.[596] 5-ASAs have negligible excretion in breast milk and are deemed low risk for breast feeding.[597]

#### *Purine analogues*

Purine analogues may be used in pregnancy as a single agent, or with anti-TNF medications. Two meta-analyses and more recent controlled studies have not shown adverse foetal outcomes, including congenital abnormalities, with purine analogues compared with women with IBD not treated with purine analogues.[588 598–600] A multicentre retrospective IBD study reviewed infant outcomes up to 5 years for 1000 children where 24% were exposed to purine analogues monotherapy, and the drug was not associated with long-term health problems in the children. Self-limiting intrahepatic cholestasis of pregnancy was associated with purine analogues use during pregnancy.[600] If the patient is in remission on purine analogues, continuation of the drug is advised. Pregnancy could affect metabolism of purine analogues, so it is reasonable to check drug metabolite levels if active disease or abnormal liver function develops in pregnancy. Co-therapy with allopurinol may increase the risk of malformations, although this is based on only 40 pregnancy reports with two similar malformations. Ideally, alternatives should be used (biologics or purine analogue therapy without allopurinol).[601]

#### *Methotrexate*

Methotrexate is teratogenic and associated with miscarriage, and therefore not to be used during pregnancy.[602] Patients of childbearing age should be counselled about these risks and advised to use contraception while taking the drug. If conception is planned, methotrexate should be stopped ideally for 3 months, but at least 1 month in both male and female patients. If pregnancy accidentally occurs on methotrexate, the drug should be stopped, and close involvement of the obstetric team is advised.



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*Calcineurin inhibitors*

Cyclosporin and tacrolimus are now rarely required for the induction of remission in corticosteroid refractory acute ulcerative colitis due to their significant side-effect profile since the advent of biologics. The safety data of calcineurin inhibitors in pregnancy in patients with IBD are limited but meta-analysis in transplant medicine suggests they are low risk in pregnancy and are not associated with congenital malformations or preterm labour.[603 604]

*Corticosteroids*

Studies assessing the effect of corticosteroids on foetal and maternal outcomes are confounded by the impact of the underlying disease for which they are prescribed. In IBD their use is inextricably linked to the presence of active disease, which is known to cause adverse outcomes in pregnancy. Maternal intravenous corticosteroids are detectable in the fetus at an 8–10-fold lower concentration; however, even small increases in corticosteroids can have a significant impact on foetal physiology.[605] The literature in non-IBD patients suggests an association between corticosteroid use and congenital abnormalities, such as cleft lip/palate, preterm labour, intrauterine growth retardation, small-for-gestational age, within the limitations noted above.[606] Additional factors that are important in corticosteroid use in pregnancy is their timing and duration and it is possible that other medical conditions, in comparison with IBD, may require longer-term dosing. In IBD, the PIANO registry showed that birth parents exposed to corticosteroids had an increase in preterm birth (OR=1.79, 95% CI 1.18 to 2.73), low birth weight (OR=1.76, 95% CI 1.07 to 2.88) and neonatal intensive care unit admission (OR=1.54, 95% CI 1.03 to 2.30).[607] Corticosteroid use in the second and/or third trimester was also associated with serious infections at 9 and 12 months for the infant (4% vs 2% and 5% vs 2%, respectively, p=0.03 and p=0.001).[607] Women requiring corticosteroid use during pregnancy are at an increased risk of gestational diabetes (aOR=4.3, 95% CI 1.2 to 16.3) and should be closely monitored for this.[608] The overall picture strengthens the importance of controlling disease activity pre-conception and during pregnancy with steroid-sparing therapy if feasible. As an alternative, for milder active disease, budesonide has a reduced placental transfer compared with prednisolone, and although data are limited, no associated adverse outcomes have been associated with its use in pregnancy.[609] Active disease should be treated, and corticosteroids may be the most appropriate therapeutic choice. If other therapeutic choices are not appropriate, sufficiently fast acting or when the disease is severely active, corticosteroids remain the preferred treatment.

## Biological therapies and small molecules

### GPS 100

For patients with IBD receiving anti-TNF therapy, we suggest the drug is continued throughout pregnancy to minimise the risk of relapse and the adverse outcomes associated with active disease, with low-certainty evidence of no increased risk of pregnancy-related adverse outcomes (conditional recommendation, low-certainty evidence). We suggest continuing anti-TNF therapy throughout the whole of pregnancy as this confers no increased risk compared with discontinuing therapy in the third trimester.

### GPS 101

Tofacitinib, filgotinib, upadacitinib, ozanimod and etrasimod are contraindicated during conception, pregnancy and lactation due to serious malformations found in animal studies.

### GPS 102

In patients with IBD in remission receiving non-anti-TNF biologics, there are fewer data on risk of relapse in stopping the drug versus the risk to the fetus of drug exposure. Overall data from several studies have suggested that continuation of vedolizumab or ustekinumab is not associated with adverse maternal or foetal outcomes.

Active transfer of IgG from the maternal to foetal circulation occurs at the surface of the syncytiotrophoblast placental layer through the selective binding of the Fc gamma portion of the maternal IgG antibody to the foetal circulation.[610] Active transport of IgG starts at approximately week 13 of gestation, progressing continually until delivery with a preferential transport of IgG1 followed by IgG4, IgG3 and then IgG2.(630, 631). Anti-TNF agents, such as infliximab, adalimumab and golimumab, are IgG1 monoclonal antibodies, whereas certolizumab is a Fab fragment of IgG1, (without the Fc portion of IgG1) and so there is significantly less transfer through the placenta. Vedolizumab, ustekinumab and risankizumab are also IgG1 monoclonal antibodies.[611–613]

Pregnancy affects the pharmacokinetics of biologics: adalimumab and ustekinumab levels remain stable, while infliximab levels increase and vedolizumab levels decrease.[614 615] The prospective PIANO study assessed infant and cord serum biologic concentration in those exposed to infliximab (n=99), adalimumab (n=66), certolizumab pegol (n=33), vedolizumab (n=22), ustekinumab (n=7), natalizumab (n=4) and golimumab (n=4).[588] Infants had detectable concentrations of all drugs at delivery, bar certolizumab, as expected. Drug concentration in the infant's blood was higher than the maternal concentration for most biologics, apart from golimumab (same level) and vedolizumab (8.2 µg/mL for the infant compared with 13 µg/mL). [6] The use of infliximab and adalimumab during pregnancy has been associated with foetal and cord blood levels of drug up to fourfold higher than in maternal blood.[616–618]

Following delivery, infliximab levels were detectable for up to 7 months and adalimumab levels remained detectable for up to 11 weeks from birth in the infant.[616] Mean time for drug clearance has been reported as 7.3 months for infliximab, 4 months for adalimumab and 3.8 months for vedolizumab (not detectable levels at 6 months).[619 620] In a small prospective study, median time to ustekinumab clearance in nine infants was 9 weeks (range 6–19).[615]

Discontinuing biological therapies in the second trimester will limit drug exposure during the time of highest transmission of immunoglobulins from the birth parent to the fetus. Although the timing of the last biologic appears to correlate with maternal serum and cord blood levels, the relationship is not linear with variability due to differences in maternal dose and interval, individual pharmacokinetics and the immaturity of the newborn reticuloendothelial system. Due to the increase in infliximab levels during pregnancy, there may be a role for therapeutic drug monitoring. While low levels of infliximab, adalimumab,



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certolizumab, natalizumab and ustekinumab can be detected in breast milk from birth parents receiving these biologics, breastfed infants of birth parents receiving biologics, immunosuppressants or combination therapy have similar risks of infection and similar milestone achievement at 12 months to those of non-breastfed infants or infants unexposed to these drugs.[621]

### Cessation of anti-TNF therapy in the second trimester in quiescent IBD

A small case–control study and a cohort study of pregnancy in women with clinically quiescent IBD did not show a significant increase in risk of disease relapse if anti-TNF therapy (infliximab and adalimumab) is stopped between weeks 25 and 30.[622] However, a retrospective study of 8726 women with IBD, of which 1457 pregnancies (1313 Crohn's disease, 144 ulcerative colitis), mainly treated with infliximab (n=800) or adalimumab (n=631), found the opposite. In corticosteroid-naïve patients, suggesting previously clinically quiescent and stable disease, women who stopped anti-TNF therapy before 24 weeks (60/131, 45.8%) had significantly more relapses than those who continued anti-TNF therapy (63/206, 30.6%, p=0.005).[623] This difference remained after adjustment for disease severity, age, IBD type and duration and concomitant mercaptopurine use (aOR=1.98; 95% CI 1.25 to 3.15).[623] Anti-TNF therapy was associated with a higher risk of overall maternal complications (aOR=1.49; 95% CI 1.31 to 1.67) and infections (aOR=1.31; 95% CI 1.16 to 1.47), but maintaining anti-TNF after 24 weeks did not increase these risks.[623] There is no benefit in stopping anti-TNF in the third trimester as infant infection rates were similar in those whose birth parents were and were not exposed during the third trimester. Therefore, discontinuation of anti-TNFs during pregnancy in those with quiescent disease is not advised due to the risk of a flare.

#### *Continuation of anti-TNF therapy throughout pregnancy in patients with IBD at high risk of flare*

In a Danish study of 219 women with IBD, 144 (66%) experienced active disease and had anti-TNF therapy continued in the third trimester (92 treated with infliximab, 44 with adalimumab, 1 with certolizumab and 7 treated with more than one drug) with no increased risk of low birth weight or preterm birth associated with the drug.[624] Of the 144 women with disease activity, 55 were categorised with mild disease and 89 with moderate to severe disease. Disease activity was associated with low birth weight (OR=2.05) and preterm birth (OR=2.64, increasing to an OR of 3.6 in moderate to severe disease).[624] Discontinuation of therapy may be associated with a risk of relapse during pregnancy and in the postpartum period.[579 617]

#### *Risk to the fetus of continuing anti-TNF therapy throughout pregnancy*

A 2016 meta-analysis of six studies confirmed no increased risk of adverse pregnancy outcomes, congenital abnormality, preterm birth or low birth weight in those exposed to anti-TNF during pregnancy.[625] A large retrospective cohort study in 1457 pregnancies in women exposed to anti-TNF therapy for IBD showed no increased infection rates in children for up to 1 year of life (aOR=0.89, 95% CI 0.76 to 1.05).[623] In this study, treatment with anti-TNF was associated with a higher risk of overall maternal complications (aOR=1.49, 95% CI 1.31 to 1.67) and infections (aOR=1.31, 95% CI 1.16 to 1.47), but ongoing use of anti-TNF therapy beyond 24 weeks did not increase maternal complications.[623] The primary analysis from the multicentre prospective PIANO study of 869 women with exposure to biologics, of which the majority were anti-TNF (421 infliximab, 279 adalimumab, 135 certolizumab pegol, 11 golimumab, and 52 exposed to more than one), showed that drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight and infections over the first year of life[584] Infection rates did not differ by individual biologic agent or combined use of purine analogues. Higher disease activity was associated with risk of spontaneous abortion (HR=3.41, 95% CI 1.51 to 7.69), and preterm birth increased infant infection (OR=1.73, 95% CI 1.19 to 2.51).[584]

Despite significant foetal exposure to anti-TNF drugs, there is no evidence that continuing anti-TNF therapy through pregnancy has a negative impact on the pregnancy or neonatal outcomes, including neonatal susceptibility to infection.

#### *Long-term infant outcomes of anti-TNF therapy during pregnancy*

A multicentre retrospective study from the Netherlands has reviewed outcomes up to 5 years for 1000 children born to 626 birth parents with IBD (61% Crohn's disease, 36% ulcerative colitis and 3% IBD unclassified).[600] Twenty percent had intrauterine exposure to anti-TNF and 24% were exposed to purine analogue monotherapy. Neither anti-TNF nor purine analogue exposure was associated with adverse birth outcomes or long-term health outcomes of the children, including infections requiring antibiotics, severe infections requiring admission, adverse reactions to vaccinations, growth failure, autoimmune diseases and malignancies.[600]

The TEDDY study, a retrospective multicentre European study, followed up 841 children born to women with IBD, of whom 46% were exposed to anti-TNF either during pregnancy or within 3 months prior to conception and a non-exposed comparator group.[626] Median follow-up after delivery was 47 months in the exposed group and 68 months in the non-exposed group. The incidence of severe infections was similar between groups, and anti-TNF exposure during pregnancy was not associated with a higher risk of severe infections (HR=1.2, 95% CI 0.8 to 1.8).[626] The exposed group had more caesarean sections, low birth weight neonates and neonatal intensive care unit admissions.[626] The PIANO study reported no impact on developmental delay up to 4 years in children exposed to biologics.[600]

#### *Infant vaccinations after exposure to biologics*

**GPS 103**

We suggest that BCG vaccination (if indicated) should be withheld until at least 12 months after birth for infants exposed in utero to biological therapies. Although administering the live rotavirus vaccine infants exposed in utero to biological therapies is probably low risk, this should be discussed against the modest benefits in well-resourced healthcare settings like the UK. Non-live vaccinations should be given according to standard vaccination schedule and all live vaccinations should be given at, or after, 12 months. Breast feeding while on biological therapy does not likely confer an additional risk and vaccination decisions should be based on in utero exposure only.

Offspring exposed to biologics in utero are able to mount appropriate antibody responses to inactivated vaccines and should complete the inactivated vaccine programme as scheduled.[52] However, live vaccinations can be fatal due to the risk



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of immunosuppression from placental transfer of biologic in pregnancy.

A 2022 systematic review assessed the safety of live vaccinations in infants exposed to anti-TNF therapy.[627] Six of the 10 studies included were in patients with IBD. Of the 215 infants who received the Bacillus-Calmette-Guerin (BCG) vaccine there was one fatally disseminated (BCG) infection following vaccination at 3 months and seven adverse reactions. Six out of seven had received BCG vaccination at <1 month of age,[627] and all of these infants had foetal exposure to infliximab. Four fatal cases of disseminated BCG infection were reported from the Medicines and Healthcare products Regulatory Agency from anti-TNF foetal exposure: two from infliximab, one from adalimumab and one unspecified anti-TNF.[627]

Recent European guidelines recommend a delay of 1 year for all live vaccinations for infants exposed to biologics in utero or until the biologic is no longer detected in the infant's serum. Ultimately, the risk of vaccination should be balanced with the risk of the child acquiring the disease. We recommend the BCG vaccination is deferred to 12 months of age. There remains uncertainty about administration of rotavirus vaccine following exposure in utero to biologics. A prospective cohort study of 191 infants published in 2023[628] suggested rotavirus vaccination was low risk, and some guidelines are now recommending consideration of giving this vaccine. Overall, the risk and benefit of administering the vaccine should be considered in the specific clinical and geographic context, and the benefit in in the UK may be very limited given the good availability of care for rotavirus infections.

### Anti-integrin (vedolizumab)

A 2021 meta-analysis assessing pregnancy outcomes in women exposed to vedolizumab included four studies.[629] Vedolizumab exposure was associated with adverse pregnancy-related outcomes (OR=2.18, 95% CI 1.52 to 3.13), increased preterm births (OR=2.16, 95% CI 1.28 to 3.66) and early loss of pregnancies (OR=1.79, 95% CI 1.06 to 3.01) but no difference in number of live births or congenital malformations (OR=1.56, 95% CI, 0.56 to 4.37).[629] However, the authors noted that disease activity in those exposed to vedolizumab confounded the results as the studies included patients with higher disease activity or increased number of relapses during conception and or pregnancy in the vedolizumab exposed cohort.[629–631]

Numerous studies have indicated the safety of vedolizumab in pregnancy, including prospective studies not part of the meta-analysis: the multicentre NOVA study (50 patients), an Israeli study (24 patients), the PIANO registry (22 patients) and an American study (41 patients).[619 632] In addition, the NOVA study showed normal developmental milestones at 12 months and no risk of infections in the infant.[619]

#### *Anti-IL-12 and anti-IL-23 (ustekinumab, risankizumab)*

For ustekinumab, two small retrospective studies of 29 and 57 patients, and a prospective study of 18 patients suggest it is probably low risk in pregnant women.[631] There were comparable rates of prematurity, live births, spontaneous abortions and congenital abnormalities and maternal complications in the ustekinumab-exposed groups to those in the general population and those exposed to anti-TNF therapy.[631]

Human data on risankizumab's safety in pregnancy are limited. It is currently approved for use in Crohn's disease in the UK. Physicians' communication from Abbvie shows that 60 pregnancies have occurred with risankizumab exposure, which included 11 spontaneous abortions, 2elective terminations. 18 live births. To date, risankizumab has not been associated with major congenital abnormalities.

#### *JAK inhibitors (tofacitinib, upadacitinib, filgotinib)*

Owing to their small size, tofacitinib and upadacitinib can cross the placenta from the critical first trimester. Data from animal studies on tofacitinib showed a reduction in live birth and teratogenicity in pregnant rabbits and rats, but at doses of 73 and 6.3

**Table 11** Summary table of the safety of medications used in pregnancy and the postpartum period.

| Medication | Pregnancy | Postpartum period | Advice |
|---|---|---|---|
| 5-ASA | Low risk | Low risk for breastfeeding. | Continue |
| Purine analogues | Low risk | Low risk for breastfeeding. | Consider checking metabolite levels if active disease or altered liver function tests |
| Corticosteroids | Moderate risk, likely lower risk for budesonide, but limited data. | Low risk for breastfeeding | |
| Calcineurin inhibitors | Low risk, although significant side effect profile | Low risk for breastfeeding. | |
| Anti-TNF<br>Adalimumab<br>Infliximab<br>Golimumab | Increased risk of maternal infection not greater than non-pregnant state.<br>Reduces relapses throughout pregnancy even in those in remission. | No increased adverse foetal outcomes.<br>No live vaccination for neonate for 12 months.<br>Safe to breastfeed. | Advise continuation even in remission due to risk of relapse.<br>GRADE recommendation |
| Vedolizumab | Likely low risk, but limited data | No increased adverse foetal outcomes.<br>No live vaccination for neonate for 12 months.<br>Low risk for breastfeeding. | |
| Ustekinumab | Likely low risk, but limited data | No increased adverse foetal outcomes.<br>No live vaccination for neonate for 12 months.<br>Low risk for breastfeeding. | |
| JAK inhibitors<br>Tofacitinib<br>Upadacitinib | Not recommended.<br>Stop 3 months before conception. | Not recommended for breastfeeding. | |
| S1P inhibitors Ozanimod<br>Etrasimod | Not recommended<br>Stop 3 months before conception. | Not recommended for breastfeeding. | |

5-ASA, 5-aminosalicylic acid; S1P, sphingosine-1-phosphate .



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times the recommended human dose. A review of 158 pregnancy outcomes from maternal and paternal exposure to tofacitinib in the intervention studies for rheumatoid arthritis, psoriasis and psoriatic arthritis indicated the rates of congenital abnormalities and live birth to be comparable to those of the general population. Eleven cases of maternal exposure and 14 cases of paternal exposure to tofacitinib occurred pre-conception or during pregnancy in the ulcerative colitis interventional studies. In this small cohort, there were no foetal death or neonatal deaths, no congenital malformations, two spontaneous abortions and two medical terminations.[633] Animal studies showed skeletal and cardiovascular malformations in pregnant rats and rabbits exposed to high doses of the upadacitinib.

Owing to the limited safety data in pregnant women with IBD and the findings from the animal studies, JAK inhibitors are not advised when pregnancy is being planned or during pregnancy. The manufacturer advises at least 4 weeks between the last dose of the medication and attempting conception.sphi

*Sphingosine-1-phosphate inhibitors (ozanimod and etrasomid)*

Studies in animals have shown reproductive toxicity, including foetal loss and anomalies, notably, malformations of blood vessels, generalised oedema (anasarca) and malpositioned testes and vertebrae. Sphingosine-1-phosphate is known to be involved in vascular formation during embryogenesis. The ozanimod clinical development programme has presented an abstract of 83 pregnancies with maternal and paternal exposure to ozanimod in the first trimester in patients with multiple sclerosis and IBD (12 patients).[634] The rate of spontaneous abortion and preterm labour was comparable to those of the general population, and no congenital abnormalities were present.

Ozanimod is not recommended for use during pregnancy and breast feeding. The manufacturer advises 3 months between the last dose and conception. No data relating to etrasimod are currently available. Please see table 11 for a safety summary for IBD medications used in pregnancy.

### Delivery

Women with IBD are more likely to have a caesarean section, with a meta-analysis reporting 1.5 times increased likelihood (95% CI 1.26 to 1.79; p<0.001).[635 636] A caesarean section is strongly recommended in those with active perianal disease or previous vaginal fistulae. Vaginal delivery in these patients is associated with worsening of perianal disease in two-thirds and increased risk of significant perineal tears (OR=10.9; 95% C, 8.3 to 4.1; p<0.001).[636 637] Women without these complications, including those with stomas, should be reassured in proceeding with a vaginal delivery. Specifically, they are not at increased risk of perineal tearing, poor wound healing or recurrence of perianal disease.[636 637] A multicentre UK retrospective audit of 82 pregnancies from 77 patients with stomas (ileostomy in 72 and colostomy in 10 women) found a 73% rate of caesarean sections (58 cases: 44 electively and 14 emergency).[591] In those who had caesarean sections, there were three bladder injuries, two postoperative wound infections, one postoperative collection required radiological drainage and in two patients, significant intra-abdominal adhesions were encountered during surgery that required adhesiolysis. Only 19 cases had an IBD reason listed for the need for caesarean sections. Patients with IBD with stomas should be counselled regarding the risks of caesarean sections as surgery can be more difficult in these patients and is likely to lead to further adhesions.

In those with an ileal pouch anal anastomosis or in those where an ileal pouch anal anastomosis is being planned, the decision is complex as even a minor impairment of sphincter function could increase likelihood of faecal incontinence and impaired quality of life. A 2017 meta-analysis assessed continence outcomes by delivery method in those with ileal pouch anal anastomosis in eight studies (358 patients).[636 637] Uncomplicated vaginal delivery had no significant impact on continence or stool frequency. However, studies suggested that a complicated vaginal delivery (instrumentation, episiotomy, significant vaginal tears, baby weight >4.5 kg, prolonged second-stage labour and an emergency caesarean section after failed vaginal delivery) did affect rates of faecal incontinence.[591] In addition, only one study of 58 patients evaluated objective measures using anorectal manometry and endo anal sonography and found that women who had a vaginal delivery had significantly lower anorectal squeeze pressures and more anal sphincter defects.[638] As it is difficult to predict the course of delivery, in those with ileal pouch anal anastomosis or in those in whom an ileal pouch anal anastomosis is being planned, a shared decision-making approach with patient, obstetrician and colorectal surgeons suggested.

Post partum, the risk of venothromboembolism in patients with active IBD, especially after a caesarean section should be managed. If complications such as infection occur, suspension of biological therapy should occur temporarily.

### Breast feeding

Breast feeding provides the best nutrition and immune protection for the infant. Women with IBD should be supported in their decision for infant feeding and reassured that the majority of medications used in IBD are considered low risk while breast feeding.

Animal studies in both tofacitinib and upadacitinib, showed the drug is excreted in milk and that drug concentration was higher than in the birth parent. Breast feeding is not recommended for women on JAK inhibitors or S1P modulators.

## Managing pain in IBD

**GPS 104**

For patients with IBD and chronic pain, after ruling out stricturing disease, abscess, or uncontrolled inflammation, it is essential to explore other psychological factors and IBS overlap.

**GPS 105**

We suggest that in patients with IBD, psychological therapies may be offered to interested patients, particularly those with psychological symptoms, as an adjunctive therapy to improve symptom control and quality of life.

Pain is a frequent symptom in IBD, affecting patients both during active disease and periods of remission.[639–641] Pain has a negative impact on the quality of life,[642–644] and is more prevalent in women and those who experience stress, anxiety, or depression.[645 646] In addition to these psychological factors, potential causes of pain can encompass factors such as overlap with IBS,[85] visceral hypersensitivity, possibly linked to microscopic inflammation, fibromyalgia and bacterial overgrowth.[647 648]

Due to the overlap of IBS and IBD, often accompanied by visceral hypersensitivity, psychological interventions like



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**GPS 106**

We recommend that for patients with coexisting IBS overlap in IBD, the BSG IBS treatment recommendations are followed to enhance symptom control and improve overall quality of life.

cognitive behavioural therapy (CBT), counselling, relaxation therapies and gut hypnotherapy may offer potential benefits and are considered safe in addressing pain even though strong evidence is limited.[649–652] Additionally, IBS diets have demonstrated benefits, and consulting the BSG-IBS guidelines is advisable.[653]

### Fatigue in IBD

**GPS 107**

Patients with IBD with disabling fatigue who have no demonstrable correctable metabolic or nutritional deficiency, and no active IBD, or patients with IBD whose fatigue persists despite treatment for these factors, may wish to consider non-pharmacological interventions.

An RCT of psychoeducation about IBD and fatigue, plus solution-focused therapy (a brief form of psychotherapy), for 3 months in patients with quiescent IBD, showed a reduction in fatigue for up to 3 months after completion of therapy. However, the effect diminished during follow-up. By 9 months there was no difference between the treatment group and controls.[654] Another RCT compared professionally led stress management with self-directed self-management and with conventional therapy in 45 patients with Crohn's disease. After eight sessions, professionally led stress management achieved a greater reduction in tiredness than other interventions. The reduction remained beneficial at 12 months. However, the difference was not statistically significant. Also, tiredness was not the sole endpoint of the study.[655]

A longitudinal study showed that regular exercise improved physical fatigue in IBD.[656] Additionally, an RCT of physical activity advice and/or omega 3 supplementation in IBD, published in abstract form, showed that fatigue scores (Functional Assessment of Chronic Illness Therapy (FACIT) Scale) were better than those in the placebo group for those receiving both interventions and also for those receiving physical activity advice alone, but the certainty of evidence was low.[657]

A prospective randomised study of electroacupuncture in IBD, based on the FACIT Fatigue Scale, showed a significant reduction in fatigue in both treatment and sham groups in comparison with controls at 8 weeks post-therapy, although no difference was observed between the groups.[658] An RCT showed that high doses of oral thiamine resulted in a reduction in fatigue at 4 weeks, but was not effective when continued for 12 weeks and was also ineffective at 6 months.[659 660] Similar positive findings have been observed with vitamin D supplementation as well.

Fatigue is a key concern for patients and significantly affects their quality of life and well-being regardless of disease activity. Currently, little evidence exists for the causes of fatigue and effective treatment options. Research on the pathogenesis of IBD-related fatigue is needed to develop welldefined treatment algorithms and options.

### Inflammatory bowel disease and primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic condition characterised by bile duct inflammation, fibrosis and stricturing, leading to progressive liver dysfunction. Pathogenesis is incompletely understood, although PSC is thought to occur in those with a genetic predisposition following environmental exposures; dysbiosis and a dysregulated immune response are strongly implicated.[661] The strongest clinical risk factor for developing PSC is its close association with IBD, creating a distinct PSC-IBD subtype with unique clinicopathological features.[662] Management of PSC is challenging as no proven medical therapy exists to modify the natural history of the disease to prevent progression to cirrhosis and end-stage liver disease.[663]

#### Epidemiology

Patients with PSC usually have concurrent IBD. Most population-based studies of patients with PSC report comorbid IBD, mainly ulcerative colitis, in greater than 50% of patients, ranging from 20% in Singapore to 88% in Iceland.[664] Conversely, a much smaller proportion of patients with IBD develop PSC. The overall pooled prevalence of PSC was 2.16% in a systematic review and meta-analysis of 776 700 patients with IBD.[665] The pooled prevalence in patients with ulcerative colitis, Crohn's disease, and IBD unclassified was 2.47%, 0.96% and 5.01%, respectively, and was significantly higher in ulcerative colitis than in Crohn's disease (OR=1.69, 95% CI 1.24 to 2.29).[665] There appears to be a geographical variation with higher rates of PSC-IBD in American and European populations, and a lower association in Asian populations.[666] The age of IBD onset in patients with PSC-IBD is contentious; some studies report a lower median age of IBD onset compared with controls without PSC,[667–669] while others report a higher median age.[662] Typically, IBD is diagnosed before PSC, although the timing of diagnosis may be shifting in recent years with PSC being diagnosed first.[670]

##### *Phenotype of patients with PSC-IBD and disease activity*

Patients with PSC-IBD have distinct clinical features in contrast to patients with IBD without PSC.[671] When coexistent, either can run a subclinical course, particularly in the early stages of disease, and may be underdiagnosed. PSC-ulcerative colitis is characterised by a pan-colonic or right colonic inflammation, but the severity appears to be milder, with reduced corticosteroid use and reduced rates of hospitalisations.[669 671–675] Histologically, colonic inflammation also appears to be mild with focal basal plasmacytosis and occasional mild cryptitis rather than active cryptitis with crypt abscesses, surface erosions or ulceration.[674] Additionally, patients with PSC-IBD have higher rates of rectal sparing and backwash ileitis than non-PSC-IBD.[12 662 673 676] In PSC-Crohn's disease, colonic inflammation is reported most commonly (36.8–82.1%), followed by ileocolonic involvement (21.8–57.9%); isolated small bowel Crohn's disease in PSC-Crohn's disease is rare (2–5%).[671] PSC-Crohn's disease also runs a quiescent disease course, and stricturing or penetrating phenotypes are uncommon. Given the atypical, milder disease of patients with PSC-IBD, it is important for gastroenterologists to have a lower threshold for investigation. All patients with PSC should initially undergo an ileocolonoscopy with biopsies, and patients found to have colitis should then have annual surveillance colonoscopy because of the increased risk of colorectal cancer.[677] Conversely, persistently abnormal liver functions in a patient with IBD requires a prompt liver aetiology evaluation, including a magnetic resonance cholangiopancreatography and



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referral to a liver specialist if no cause is found on a standard screen.[678]

There are data to suggest an inverse relationship between PSC disease severity and IBD activity following liver transplantation. Patients with severe PSC requiring transplantation had more quiescent ulcerative colitis with fewer ulcerative colitis relapses, requiring less immunosuppressive drug treatment than those not requiring transplant.[679] However, studies observing IBD disease course following liver transplantation are conflicting as several report worsening IBD activity despite the use of immunosuppressive drugs,[680 681] and another reported improved clinical and histo-endoscopic IBD scores compared with the non-transplanted cohort.[673]

### *Colorectal cancer risk*

A potential link between PSC and increased dysplasia and colorectal cancer risk in patients with IBD was first described in the early 1990s.[682] Since then, numerous studies have demonstrated that PSC is a critical risk factor for the development of colorectal cancer in patients with IBD.[671] This is alongside heightened risks for hepatobiliary malignancy, particularly cholangiocarcinoma. A meta-analysis including 13 379 patients with IBD, of whom 1022 (7.6%) had concomitant PSC, demonstrated a threefold increased risk of colorectal dysplasia and cancer among patients with PSC-IBD compared with the IBD-only population (OR=3.24; 95% CI 2.14 to 4.90).[683] In a recent 10- year UK-wide study of 284 560 incident IBD cases, development of PSC in 2588 cases was associated with increased risk of death and colorectal cancer (HR=3.20 and 2.43, respectively; p<0.001) and a lower median age at colorectal cancer diagnosis (59 years vs 69 years without PSC; p<0.001). Compared with patients with IBD alone, patients with PSC-IBD had a fourfold higher risk of colorectal cancer if they received a diagnosis of IBD at an age younger than 40 years.[684] The risk of colorectal cancer in PSC-Crohn's disease has been shown to either be comparable to PSC-ulcerative colitis[685] or lower.[686] Data here are limited as PSC-Crohn's disease is less prevalent, and cases are complicated by the difficulties in discerning IBD subtype given the typical PSC-IBD characteristics. Nonetheless, annual surveillance colonoscopy is advocated at the point of IBD diagnosis for patients with concurrent PSC, even after liver transplantation, to enable early detection of dysplasia and neoplasia.

**GPS 108**

Commencement of colonoscopy surveillance:
⇒ 8 Years after IBD symptom onset.
⇒ From diagnosis if primary sclerosing cholangitis.
Ongoing colonoscopy surveillance for PSC-IBD.
⇒ Patients with primary sclerosing cholangitis (including post-orthotopic liver transplant) fall into the high-risk category for colorectal cancer and require annual surveillance.

### *Surgery in PSC*

For patients with IBD-PSC who undergo proctocolectomy and ileal pouch anal anastomosis (IPAA), there is a higher rate of complications and pouch failure. The most common complication is pouchitis, and in a systematic review of 11 406 patients with PSC-IBD, pouchitis affected 14% to 90% of patients compared with 12% to 53% in ulcerative colitis without PSC.[671] Pouch failure was similar in patients with PSC-IBD and seen in 1.5% to 16% compared with 3% to 11% in patients with IBD without PSC after IPAA.[671] For patients with IPSC with ulcerative colitis undergoing liver transplantation, graft outcomes are better for those who have an end ileostomy after colectomy compared with colectomy and IPAA.[687] Graft loss was mainly associated with hepatic artery thrombosis and biliary strictures. The risk associated with IPAA is not dependent on the timing of colectomy in relation to the liver transplantation. A more recent study showed higher rates of pouchitis, but not pouch failure, in patients receiving a liver transplant, compared with non-transplanted patients.[688] Patients with PSC may be offered IPAA as long as they understand the potential implications.

**GPS 109**

Patients undergoing colectomy who have coexistent ulcerative colitis and primary sclerosing cholangitis should be advised that there is an increased risk of pouchitis, to inform decision-making regarding ileoanal pouch formation or permanent ileostomy.

## Patient education

There is evidence that patient educational interventions can have beneficial effects on patients' disease control and quality of life in IBD. Educational interventions can take different forms of delivery including face-to-face, virtual sessions or workshops, printed or online educational material, online educational guides or mobile smartphone applications. It is envisaged that education can enhance patient knowledge of IBD in order to empower them to manage their condition; however, the question on how this might affect disease outcomes is complex and poorly understood. A patient summary is given in Appendix 5.

Educational interventions can be divided into those that ensure patients have the information and support:

1. To recognise a relapse of their condition.
2. To improve medication adherence and recognise adverse side effects.
3. To educate themselves on self-management and quality of life.
4. To educate themselves on environmental factors, diet and exercise.
5. To use psychology tools to improve their quality of life.

Several studies in recent years have looked at a variety of educational interventions and their potential impact on IBD outcomes.

Patients with IBD were randomised to an educational programme versus control in an RCT carried out by the GETAID group.[689] The primary endpoint of an increase in a specific psycho-pedagogic score of >20% was met in 46% vs 24% of the educated and control groups, respectively (p=0.0003). These findings support the set-up of educational programmes in the management of IBD.

**GPS 110**

We recommend that patient education interventions may be offered to patients with IBD as an adjuvant to routine clinical practice, with the aim of improving patient engagement, medication adherence and reducing hospital attendances.



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Berding *et al* randomised patients into an intervention group (two-part IBD education programme) versus control.[690] They concluded that an IBD education programme can have a positive impact on psychological distress and self-management skills, but no effect was observed on disease activity, health-related quality of life (QoL) or symptoms of anxiety and depression. Another recent RCT assessed the impact of patient-centred information on level of knowledge and QoL of patients with newly diagnosed IBD.[691] The authors concluded from their findings that an educational intervention shortly after diagnosis can improve patients' knowledge and QoL regardless of disease activity. Looking at forms of education delivery, a smaller RCT assessed the effect of web-based education versus standard education via books.[692] Symptom severity, disease activity and QoL were found to be improved in both groups, suggesting that patient education can improve outcomes, but that the content of patient education is more important than the form of delivery. The effect of intensified IBD nurse care was assessed by Barkan *et al*.[693] Patients were randomised to standard or intensified nurse care and outcomes of patients' uncertainty scores and PROMs were evaluated at recruitment and after therapy initiation. At week 14, uncertainty scores were found to significantly differ between both groups, with an improvement seen in the IBD nurse care group. They also found that intensified IBD nurse care was associated with improvement in certain PROMs, such as defaecation management, well-being and sexual dysfunction.

With more of a focus on mindfulness, González-Moret *et al* carried out a RCT looking at the effect of mindfulness-based therapy in IBD versus standard care.[694] Significant decreases were observed in objective biomarkers of inflammation (CRP and faecal calprotectin) in the mindfulness group compared with standard care. Similarly, another study explored the benefits of a lifestyle modification programme versus control in patients with ulcerative colitis in clinical remission with impaired QoL.[695] Improvements in QoL were observed in both groups. In contrast to González-Moret *et al*, there was no effect seen on clinical disease activity. A systematic review and meta-analysis of seven RCTs (n=655) looked specifically at the effects of cognitive behavioural therapy (CBT).[696] They concluded that CBT appeared to support higher QoL in patients with IBD than in those receiving standard treatment, but had no effect on disease activity, anxiety or perceived stress in patients with IBD, suggesting that CBT could be an acceptable adjunctive therapy, but its effect was limited.

Several recent studies have focused specifically on medication adherence interventions. Three recent studies looked at the impact of an educational intervention (namely, an education programme,[697] novel patient education tool,[698] and once daily versus divided dosing regimen[699]). All the studies found no significant improvement in adherence rates between groups.[697–699] A systematic review of 17 studies (n=1144) looked at medication adherence interventions.[700] The interventions included were online educational resources or courses, telemedicine, automatic reminders, text messages, electronic needle containers. Although each study demonstrated some level of success in improving medication adherence in patients with IBD, overall, the studies were of poor quality and poor statistical analysis.

In another systematic review from 2022 (n=2637), Nguyen *et al* looked at mixed online or mobile phone educational resources or courses and their impact on disease activity monitoring, treatment adherence, quality of life and healthcare utilisation.[701] Digital interventions were of average usefulness in all the outcome areas measured, with medication adherence being the most successful, but this outcome was looked at in the fewest studies. The review summarised the possibility of digital interventions to improve outcomes but did not demonstrate a majority of studies enabling this.

The most comprehensive overview on this topic available to date is a Cochrane systematic review and meta-analysis performed by Gordon *et al*.[702] A total of 2708 patients, from 14 RCTs, were included. The interventions were educational seminars, educational text messages, e-learning modules, group and solo education programmes, guidebooks, educational sessions via IBD pocket guides, interactive educational videos. Four studies looked at the outcome of disease activity, 5 studies at relapses, 10 studies at quality of life, 4 studies at healthcare utilisation, 5 studies at medication adherence and seven studies at patient knowledge. Overall, the studies were limited, and poor reporting of outcome measures severely limited the scope of the meta-analysis and affected the certainty of evidence. Gordon *et al* concluded that there is evidence that education is probably of no benefit to disease activity or quality of life in comparison with standard care and may be of no benefit to occurrence of relapse in comparison with standard care. However, the authors stressed that the utility of these findings is questionable. Based on the outcomes of these analyses, and the likely mechanism of action of education for patients with IBD as well as the intended goals of the educational interventions and their impact on stakeholders, they suggested that further research to investigate the impact of education on primary outcomes of disease activity, disease state and quality of life is probably not indicated.

Suggested future key research areas are to ensure educational interventions are reported in a manner that supports transparency, dissemination and replication, and to focus on outcomes that educational interventions can be directly targeted to address. Medication adherence and healthcare access are recommended as good targets for future work. Furthermore, specific subsets of patients such as those with newly diagnosed IBD or socially and financially disadvantaged patients who may be in greater need of educational support should also be encouraged. It should be emphasised that educational programmes should be patient centred—ultimately, they need to provide information and provide support that patients need in order to empower them to manage their condition. Education, information and support resources are available to patients from charities including Crohn's and Colitis UK (https://crohnsandcolitis.org.uk/).

### Transition from paediatric to adult services

The BSG IBD GDG consider transition from paediatric to adult care and the support of young people undergoing this process as a fundamental component of high-quality care. A specific guideline was published on this topic by BSG in 2017 and is now undergoing review. It is beyond the scope of this document to revisit this whole area; however, we endorse the parallel BSG guidelines on this topic.[703] In brief, 16 recommendations were made across four headings in the last guideline—namely, patient populations involved in transition; risks of failing transition or poor transition; models of transition; patient and carer/parent perspective. Ultimately, the guideline promoted structured transition with overlap between paediatric and adult gastroenterology and proposed a pathway to support this.[703]. A topical review on transition was also published by European Crohn's and Colitis Organisation (ECCO) in 2017 with 14 practice points highlighted.[704] The ECCO document was perhaps a little less process-orientated and a little more patient-orientated and



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so the two are complementary. Irrespective, there was agreement on the need for a structured approach to transition.

Subsequent to the last BSG transition guidelines, a systematic review has been published on the topic within IBD, encompassing 23 studies, only 10 of which were published as full-text articles. The overall quality of evidence was considered very low by GRADE. Eleven of the studies suggested improved outcomes with structured transition.[705]

## Smoking and IBD

**GPS 111**

All patients with IBD should be advised to stop smoking, and national guidance on smoking cessation should be followed. Patients with IBD should be warned of the risks of continued smoking.

Smoking is a proven and highly significant cause of illness and death in the UK, irrespective of any consideration of IBD. In particular, smoking increases the risk of multiple cancers as well as serious cardiovascular and pulmonary sequalae. All patients with IBD should be asked about their smoking history, including vaping/e-cigarette use, specifically asking about active, passive or social smoking. Those exposed to smoking should be advised of the harm to their health and, if applicable, offered smoking cessation referral. Without support there is a less than 10% likelihood of long-term abstinence, but this can be reversed with interventions.[706 707] Interventions include behavioural therapy alongside pharmacological interventions such as nicotine replacement and other prescription medications such as bupropion and varenicline. The approach to smoking cessation in patients with IBD does not differ from the approach in other patient groups, therefore we recommend that IBD teams should follow existing national guidance as the best approach to this intervention.

The arrival and growth of e-cigarette use since the last BSG IBD Guidelines has generated an area where advice is warranted but evidence is lacking, hence the need for caution and a need to review this topic area as our understanding develops. One prevalent English study in 2019 described at least 3% uptake of e-cigarettes in an outpatient IBD population.[708] A single retrospective case–control study from the USA suggested e-cigarette use was not associated with indices of severe IBD disease, including surgery or escalation to/switching of biologics.[709] At present, the evidence suggests that nicotine-containing e-cigarettes are more effective at promoting abstinence from smoking than other conventional approaches and the risk of serious adverse events appears low, although with limited long-term data.[710] It is not our role as IBD clinicians to review the evidence of risk/benefit of e-cigarettes, outwit the context of our disease expertise, however, colleagues in the British Thoracic Society have recently completed an excellent document on smoking cessation which includes discussion of e-cigarettes. We would like to endorse this document as useful reading for the BSG membership, but would reiterate four particular points here: people who do not smoke should not vape; when people use vapes to stop smoking, they should switch completely to vaping from smoking; vaping is not risk-free; vaping should not be used by an individual under 18 years of age.

**GPS 112**

Preoperative counselling advising smoking cessation is recommended. Before elective Crohn's disease surgery, patients should be informed of the increased risks of surgery including higher rates of stoma formation and the increased risk of disease recurrence in smokers.

## Smoking with Crohn's disease

Smoking is more common in patients with Crohn's disease than in the general population and more likely in those diagnosed at an older age.[711 712] A study in the USA showed that 47% of those diagnosed with Crohn's disease over the age of 40 were active smokers, compared with 27% in the background population.[712] Smoking is associated with a worse IBD disease course than in never smokers,[711 713] more adverse effects in women who smoke than men[714] and a higher risk of surgery and worse outcomes post-surgery. A meta-analysis showed a 2.5 times increased risk of repeat surgery and 2 times risk of clinical recurrence in patients with Crohn's disease.[715] Smoking also worsens all outcomes in colorectal surgery, regardless of the indication for this surgery.[716 717] Passive or occasional light smoking (less than 10 cigarettes per day) does not reduce the damaging effects of smoking in Crohn's disease, therefore it is important that we advocate complete cessation.[718] There are benefits of stopping smoking at any stage of a patient's disease journey.[719] Despite poor awareness in patients with Crohn's disease of the benefits of stopping,[720 721] and the knowledge that smoking cessation services can be underused,[722] setting up a smoking cessation service can be cost-effective when disease management costs are considered.[723] In the TABACROHN study, a smoking cessation programme supported 31% of patients with Crohn's disease to stop smoking completely, with 23% (74% of those stopping) remaining abstinent 18 months later.[724]

### Smoking with ulcerative colitis

The interplay of smoking and ulcerative colitis remains a clinical challenge, which may increase in complexity with the advent of e-cigarettes. Nonetheless, there is solid evidence on which to base specific guidance, which we will summarise here. Ulcerative colitis is more likely to develop in those who have recently stopped smoking and is more common in non-smokers.[713 725] In those who previously smoked, the highest risk period for ulcerative colitis onset is in the first 2–5 years after stopping.[726] Ex-smokers present with ulcerative colitis later in life than never-smokers.[727 728] patients with ulcerative colitis who smoke have better outcomes overall, such as reduced colectomy rates, less primary sclerosing cholangitis and less backwash ileitis, than never smokers.[718] Higher overall smoking is associated with less extensive disease and a reduced need for therapy. Patients with ulcerative colitis who stop smoking have a significantly worse disease course than those who continue, with increased steroid and immunomodulator use and increased hospitalisation rates.[718] Ex-smokers with refractory ulcerative colitis who resumed smoking had high rates of steroid-free remission.[729] However, smoking does not reduce the risk of pouchitis after ileal pouch-anal anastomosis for ulcerative colitis, neither smoking at the time of operation nor later.[730] In spite of the perceived benefits of smoking in ulcerative colitis, the risk versus benefit remains heavily in favour of cessation because of the well-recognised cardiovascular, respiratory and carcinogenesis risks of smoking. Every effort should therefore be made to encourage patients to stop, even if this includes an escalation of IBD pharmacotherapy or consideration of surgery. In no circumstance should smoking be advocated on medical grounds as a therapeutic option in



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ulcerative colitis. a proactive plan should therefore be offered to mitigate the risk of worsening disease, including an increase in medical treatment, at the time of smoking cessation.

### Digital health technology

**GPS 113**

We recommend that the use of digital health technology should be offered to patients with IBD as an adjunct to face-to-face interactions, particularly with regard to improving patient engagement and medication adherence and reducing hospital attendances. Care must be taken not to disadvantage those affected by digital poverty and alternative inclusive parallel strategies must be developed.

Over the past decade, technology has advanced at an increasingly rapid pace, offering powerful opportunities to collect and analyse large datasets. Telemedicine, through digital health technology, includes the use of mobile phones, tablets, web platforms and wearables to improve health outcomes. Its revolutionary impact on healthcare contributes towards personalised health. Despite the major impact of new technology on all medical fields, including IBD, the scientific evidence currently available is still preliminary and relies on moderate- or low-quality studies.

Sparse clinical trials have provided inconsistent evidence regarding the impact of new tools on clinical disease outcomes. Nevertheless, the current evidence supports the use of digital technology in view of its safety and its complementary benefit to traditional management. Five areas of clinical care that can benefit from digital health technology are education (disease knowledge), monitoring, treatment, follow-up and patient satisfaction.[694 731–740]

A recent systematic review and meta-analysis published by Gordon *et al*[741] on remote telehealth care for patients with IBD included 19 RCTs with a total of 3489 participants. The interventions were either web-based or telephone-based. The evidence suggested that, for disease activity, flare-ups, relapses, and quality of life, web-based disease monitoring is probably no different from standard of care in adults. One study showed that medication adherence probably increases with web-based monitoring compared with usual care (MD 0.24 points, 95% CI 0.01 to 0.47, moderate certainty). The review could not draw conclusions on the effects of telephone-based disease monitoring, or web-based disease monitoring compared with usual care on healthcare access, participant engagement, attendance rate, interactions with healthcare professionals, or cost- or time-effectiveness (very low evidence).[741]

Another recent systematic review and meta-analysis by Kuriakose Kuzhiyanjal, *et al*[742] also showed no benefits of digital technology on disease activity, number of relapses or clinical remission, with moderate certainty of evidence in adults and low certainty in children. However, it identified benefits of remote tools for quality of life, number of outpatient visits and emergency admissions.[742]

An umbrella review of eight systematic reviews, including four meta-analyses, reported patient benefits limited to satisfaction, quality of life, quality of care, medication adherence and reduced hospital attendances but found no impact on disease activity.[743]

In summary, systematic reviews of the RCTs on digital health technology in IBD performed so far, highlight mixed results from highly heterogeneous studies. Most found no statistical difference between controls and intervention groups in achieving and maintaining remission or preventing flare-ups. A common weakness of the studies is the insufficient description of the nature, frequency and duration of the digital interventions.[743] Nevertheless, the data available suggest that digital health technology contributes to higher medication adherence and reduced hospital assessments compared with usual care. While the reviews to date support the potential of digital interventions to improve outcomes, they do not demonstrate this in the majority of studies. Telemedicine should be regarded as a promising mode of healthcare delivery and as an important adjuvant to routine clinical practice.

Digital health technology is also likely to offer a virtual monitoring context that will support point-of-care testing such as home faecal calprotectin. Further research is needed to identify which patients with IBD would most benefit from telemedicine, allowing these approaches to be tailored to specific patient populations. In addition, assessing and quantifying the impact of remote care, telemedicine and digital health technology on sustainability and carbon footprint deserves prioritisation in the current era of global warming, pollution and other environmental threats.[744]

Further research is required to assist planning and providing appropriate services that best meet patient needs and preferences. Future RCTs should include a follow-up duration of at least 2 years and detailed intervention descriptions to ensure reproducibility. These trials should evaluate the benefits of digital health technology on both IBD-related and patient-reported outcomes. The research needs for adolescents and young adults with IBD were explored in a research priority setting partnership supported by BSG and BSPGHAN and will guide future funding directions in this population.[745]

### Inflammatory bowel disease and spondyloarthropathies

**GPS 114**

⇒ In people simultaneously diagnosed with IBD and SpA (including axial/peripheral SpA and psoriatic arthritis (PsA)), monoclonal TNFα inhibitors (or their biosimilars) are the recommended choice of treatment, in view of their efficacy in IBD.
⇒ Tofacitinib (JAK inhibitor) is effective in ulcerative colitis and licensed for ulcerative colitis and PsA in the UK. However, tofacitinib is not licensed for Crohn's disease in the UK.
⇒ Upadacitinib is licensed in the UK for Crohn's disease, ulcerative colitis, PsA and axial SpA (including ankylosing spondylitis).
⇒ Ustekinumab is licensed in the UK for Crohn's disease, ulcerative colitis, PsA and psoriasis (PsO), but not for axial SpA (including ankylosing spondylitis).
⇒ Risankizumab is licensed in the UK for Crohn's disease, PsA and PsO, but not for axial SpA (including ankylosing spondylitis).
⇒ Etanercept, abatacept, secukinumab, ixekizumab and brodalumab should be avoided owing to the lack of efficacy and to the risk of causing exacerbation of IBDs.

The effectiveness of IBD treatments on SpA (including axial/peripheral spondyloarthritis and PsA) needs to be broken down according to the different domains that characterise SpA—namely:



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- Peripheral arthritis; enthesitis/dactylitis.
- Axial disease (no current evidence about the efficacy of IL-23 pathway inhibition for treating this domain).

For clinicians taking care of patients with IBD and a related concomitant SpA, we would recommend signposting to the BSR recommendations for PsA or the ASAS-EULAR recommendations for axial SpA.[746 747] No phase II or III clinical trial so far has formally assessed the efficacy of therapies for IBD in people who have concomitant SpA (regardless of specific domain manifestations). No head-to-head comparisons of the drugs listed above suggest that any of these treatments are superior to another when treating SpA (including axial/peripheral SpA and PsA). A multidisciplinary approach to management, with elements of cooperation across different specialties (gastroenterology, rheumatology, dermatology, ophthalmology and others) should be adopted whenever possible. There is no evidence of the efficacy of vedolizumab in SpA. Some studies point to increased risk of arthritis (flare/de novo development) in patients treated with vedolizumab for IBD.[748–750] However, the effect of withdrawal of prior treatment with steroids or TNFα inhibitors should be factored in when appraising this evidence.[751]

### Peripheral arthritis

Data favour the use of a number of different treatments over placebo for peripheral arthritis. These are methotrexate, sulfasalazine, TNFα- nhibitors, IL-12/23 inhibitor ustekinumab, IL-23 inhibitors and JAK inhibitors. No head-to-head data suggest that any of the target treatments are superior to another when treating peripheral arthritis. Although UK regulations allow the use of IL-17A and IL-17A/F inhibitors for treatment of PsO and PsA, we would recommend clinicians to be cautious when considering the use of these drugs in patients who have concomitant IBD, even if inactive.[752–756] Abatacept is licensed for use in PsA, although it is not effective in the treatment of IBD or PsO.[757]

### Enthesitis/dactylitis

As above, data favour the use of a number of different treatments over placebo for this domain. These are methotrexate (conditional recommendation, limited evidence), TNFα inhibitors, the IL-12/23 inhibitor ustekinumab, IL-23 inhibitors and JAK inhibitors. Again, no head-to-head data suggest that any of these treatments are superior to another.

### Axial disease

In axial SpA or patients with PsA and related axial involvement, fewer efficacious medications are available. Evidence-based effective treatments in axial disease include TNFα inhibitors, JAK inhibitors and IL-17 inhibitors—though the last of these requires caution when considered for patients with IBD. In patients with IBD and concomitant psoriatic axial disease, no robust evidence is yet available to suggest that IL-12/23 and IL-23 inhibitors might have efficacy in the axial setting. However, there are no trials directly addressing axial PsA in IBD, and expert recommendations in rheumatology shun the use of IL-23 pathway blockers in this PsA axial setting.

The lack of medical literature on this specific, narrow matter brings to the attention of the gastroenterology community one scientific unmet need. Yet, it is important to highlight the difficulties expected in setting up—and running—clinical trials aimed at ascertaining the simultaneous effect of any intervention on double outcome measures (that is, pertaining to SpA alongside to IBD). So far, no robust evidence suggests response of axial manifestations of SpA (including ankylosing spondylitis (AS)) to the IL-23 pathway blockade—either p40 or p19 blockersused in the treatment of PsA.[752]

Some non-biologic agents are useful for the treatment of SpA and unlikely to induce IBD relapses at the same time. Sulphasalazine—a drug licensed in the UK for the treatment of both ulcerative colitis and Crohn's disease has some efficacy on PsA, though not on PsO or axial manifestations of SpA. Methotrexate is useful in peripheral manifestations of PsA, skin PsO and all IBD (though predominantly in Crohn's disease), but it is not effective on axial manifestations of SpA.

The JAK inhibitors can be beneficial to both SpA and IBD. Tofacitinib's UK licence allows use in PsA and ulcerative colitis, though not in Crohn's disease. Upadacitinib has efficacy, and a licence, for the treatment of AS, PsA, Crohn's disease and ulcerative colitis and is effective in PsO. To the best of our knowledge, literature has not reported so far on paradoxical flares of IBD relapses or uveitis linked to small molecules.

The PDE4 blocker apremilast, licensed for PsA and PsO, is not associated with the induction of IBD relapses. Although not effective in axial SpA and not commonly used in IBD, some evidence points to its beneficial effect on ulcerative colitis.[758] With regard to the biologic agent, all TNFα inhibitors belonging to the monoclonal antibodies class—and certolizumab—have demonstrated effect on IBDs, PsA, PsO and axial manifestations of SpA. A few caveats stand when biologic agents come to consideration, though. Etanercept was associated with IBD relapses when used for SpA.[759] The IL-23 blocker ustekinumab, while effective on IBDs, PsO and peripheral manifestations of SpA and PsA, has not so far shown beneficial effects on axial manifestations of SpA. The same broadly applies to IL-23 inhibitors. The use of IL-17 blockers requires attention, owing to their association with gastrointestinal effects, and gastroenterologists should avoid them in active IBD.[753 760]

TNFα inhibitors have the ability to induce a form of paradoxical psoriasis in 2–5% of treated cases, possibly via a mechanism of selective overexpression of type I interferons driven by dermal accumulation of plasmacytoid dendritic cells. According to recent estimates, incidence of PsO or psoriasiform lesions in patients with IBD treated with TNFα inhibitors is 6% (95% CI 5.0% to 7.0%),[761] pointing to the possibility that this paradoxical reaction may occur slightly more frequently in IBD. The same study found that factors associated with paradoxical PsO development were: smoking (OR=1.97, 1.56 to 2.48); Crohn's disease affecting the ileo-colonic tract (OR=1.48, 1.03 to 2.13); female gender (OR=1.46, 1.23 to 1.73); younger age at initiation of TNFα inhibitors (OR=1.03, 1.00 to1.05).[761] Occasional reports of de novo articular inflammatory manifestations—for example, PsA occurring in patients with IBD receiving TNFα inhibitors, have emerged in the medical literature. However, such events appear to be less frequent than those affecting the skin.[762] Multiple studies linked vedolizumab to the emergence of SpA-related pathology following successful therapy for IBD. However, these events are uncommon.[748 750 751]

Ocular complications in IBD are infrequent and occur in <10% of cases.[27] The use of systemic steroids may cause side effects, including cataract after prolonged use and raised intraocular pressure leading to secondary open-angle glaucoma. Corticosteroid-induced glaucoma, however, is more common with the use of topical ocular formulations, rather than systemic formulations of steroids. Total parenteral nutrition may be associated with retinal maculopathy. The same authors highlighted that the use of anti-cholinergic agents can cause disturbances of accommodation and pupillary dilatation. The use of some immunosuppressive therapy—namely, cyclosporin, is associated with optic neuropathy, opthalmoplegia and nystagmus.[763]



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Methotrexate is an uncommon cause of periorbital oedema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis, decreased reflex tear secretion and non-arteritic ischaemic optic neuropathy.[764] Low-quality evidence points to the possibility of occurrence of some forms of ocular inflammation (inclusive of optic neuritis and uveitis) following treatment with TNFα inhibitors.[765] Gastroenterologists should be aware of such potential treatment-related side effects. Limited evidence is available about ocular side effects with the newer biologics. One case report of ustekinumab-induced sclerouveitis was published in 2022,[766] suggesting uncommon occurrence.

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