



ECCO Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

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1. Introduction

Crohn's disease [CD] is a chronic inflammatory bowel disease [IBD] that can result in progressive bowel damage and disability.¹ CD can affect individuals of any age, from children to the elderly,^{2,3} and may cause significant morbidity and impact on quality of life. Up to one-third of patients present with complicated behaviour [strictures, fistula, or abscesses] at diagnosis.⁴ Most patients over time will develop a complication, with roughly 50% of patients requiring surgery within 10 years of diagnosis.⁵⁻⁷ As the precise aetiology of CD remains unknown, a curative therapy is not yet available.⁸ Several agents are available for the medical treatment of CD. Medical agents include mesalazine [5-ASA], locally active steroids [such as budesonide], systemic steroids, thiopurines such as azathioprine [AZA] and mercaptopurine [MP], methotrexate [MTX], and biologic therapies (such as anti-tumour necrosis factor [TNF], anti-integrins, and anti-interleukin [IL] 12/23).

The European Crohn's and Colitis Organisation [ECCO] produces and regularly updates several guidelines aimed at providing evidence-based guidance on critical aspects of IBD care to all health care professionals who manage patients with IBD. To provide high-quality evidence-based recommendations on medical treatment in CD, ECCO decided to develop these guidelines by adopting the GRADE [Grading of Recommendations Assessment, Development, and Evaluation] approach.⁹ GRADE is a systematic process for developing guidelines which addresses how to frame the health care questions, summarise the evidence, formulate the recommendations, and grade their strength and the quality of the associated evidence. GRADE increases transparency at all levels of this process and makes explicit the three considerations that lead to a particular recommendation: the quality of the evidence, the balance of benefits and harms, and the patients' values and preferences. Therefore ECCO reviewed the available high-quality evidence on the medical management of CD and developed evidence-based recommendations on the medical treatment of adult patients with CD. These guidelines

do not cover specific situations, such as postoperative management of adult patients with CD, which was already covered in the latest ECCO Guidelines on Crohn's disease.¹⁰

2. Methods

Based on the GRADE workflow, the Guidelines Committee of ECCO [GuiCom] selected a panel of 48 experts supported by a team of methodologists and librarians. Selection was based on IBD expertise, scientific background, and knowledge of the GRADE methodology. All panellists received adequate training in GRADE before starting the process. Additionally, four patients with CD representing the European Federation of Crohn's and Colitis Associations [EFCCA] were invited to participate in all face-to-face meetings and to provide their experiences and state their preferences.

Three domains for medical treatment of CD were identified:

- 1] induction therapy;
- 2] maintenance therapy;
- 3] therapy of fistulising perianal disease.

All panellists were assigned to one of three working groups coordinated by one to two working group leaders under the supervision of two Guideline coordinators. The panellists first formulated a series of specific questions using the PICO format [Population, Intervention, Comparator, Outcomes] which were deemed to be clinically important for the medical treatment of CD. The outcomes of all PICO questions were subsequently graded as 'not important', 'important', or 'critical' during a face-to-face kick-off meeting in Vienna, using a Delphi consensus process.

A team of professional librarians performed a comprehensive literature search on EMBASE, PubMed/Medline, and Cochrane Central databases using specific search strings for each PICO question [Supplementary Files 1, 2, and 3, available as Supplementary data at [ECCO-JCC online](#)]. Two independent working group members [one

assigned to the PICO and another one from the same group as a second reviewer] assessed the relevance of each abstract to PICO and included or excluded all the relevant papers for the final data extraction and analysis. Subsequently, the working group members assigned to each PICO question systematically reviewed and summarised the evidence on every outcome, to compile a Summary of Findings [SoF] table for each question. The GRADE method follows a hierarchical approach to synthesise evidence; recent high-quality systematic reviews and meta-analyses of clinical trials were preferentially used to create the recommendations. When these were not available, individual randomised clinical trials [RCTs] followed by observational studies were reviewed; results of individual studies were pooled using random-effects meta-analysis as appropriate and when needed. To define disease activity and severity [mild-to-moderate and moderate-to-severe], we accepted the definitions used by the investigators of the studies selected as an evidence basis for our work.

The quality of evidence was classified into the following four categories in accordance with the GRADE approach: 'high' [meaning that further research is unlikely to change our confidence in the effect estimates], 'moderate' [further research may change our confidence in the effect estimates], 'low' [further research likely to change our confidence in the effect estimates], and 'very low' [meaning that any estimate of effect is very uncertain].⁹ For each PICO question, the quality of evidence was equal to the lowest quality of evidence among those outcomes graded as 'critical'. The strength of each recommendation was graded as either 'strong' [meaning the desirable effects of an intervention clearly outweigh the undesirable effects, or vice versa] or as 'weak' [meaning the balance is less certain], considering also the quality of evidence, values or preferences, and resource use. Whenever the chosen outcomes were not reported in the clinical trials, this was indicated in the corresponding SoF table. To support the recommendations, we either extracted summary effect estimates from the preselected systematic reviews or our group of methodologists directly performed the comparisons. All recommendations were subject to online voting by the panel members, the ECCO National Representatives [two for each country affiliated with ECCO], and 13 additional reviewers from a list of ECCO members who applied to the open call but were not selected to be part of the Working Groups [see Acknowledgements section]. The final version of all statements/recommendations was discussed among panel members during a final consensus meeting in Vienna and put to a vote; final recommendations were approved if at least 80% of the panellists agreed with the statement and its associated strength grading. The list of statements, the supporting text and material, and the draft of the manuscript were critically reviewed by two external Guideline Committee members and by the ECCO Governing Board members, who also approved the final version of these Guidelines.

The literature search strategies, the relevant definitions of patient populations and outcomes, a detailed description of the process, and the SoF tables summarising the evidence can be found in the [Supplementary Material](#), available as Supplementary data at *ECCO-JCC* online.

3. General approach to the management of Crohn's Disease

As CD is a lifelong disease, therapy aims to induce remission in the short term and maintain remission in the long term. The recognition that chronic and untreated inflammation [even if asymptomatic] ultimately results in poor outcomes^{11–14} has led to a recent paradigm shift in medical treatment and disease monitoring; it is nowadays recognised that early intervention and intensive monitoring may prevent

complications.^{15,16} Stratifying patients according to their prognostic risk factors and individualising therapy are crucial steps to optimise patient management, although high-quality evidence is not currently available to support this approach. Many factors affect the choice of medical therapy. These include disease location, disease activity and severity, previous response to therapy, and presence of complications [i.e., perianal or fistulising disease]. In addition, the individual risk factors for progression and complications, the individual patient's characteristics, and the costs and benefit/risk ratio of each drug should be considered. As there is often a disconnect between clinical symptoms and underlying inflammation, it is of crucial importance to monitor disease and therapy at regular intervals based on objective and measurable markers [endoscopy, C-reactive protein [CRP], calprotectin, imaging].¹⁷ This approach will provide the clinician with the possibility to adjust therapy if needed, thereby maximising the probability of achieving tight control of the disease and inflammation, which is believed to be essential to prevent disease progression.^{16–18} In addition to drug therapy, the management of CD should also involve a series of general health care maintenance measures. Patients should be encouraged to stop smoking, nutritional deficiencies should be corrected, therapy-related side effects [i.e., cancer and infections] should be monitored, and appropriate guidance or surveillance for vaccinations, osteoporosis, and sun protection should be implemented, as detailed in previous ECCO guidelines, topical reviews, or both.^{17,19–23}

4. Medical management of Crohn's disease

Section 1 - Induction of Remission

Mild-to-moderate disease

5-ASA compounds

Recommendation 1.1. ECCO CD Treatment GL [2019]

We suggest against the use of 5-ASA for induction of remission of Crohn's disease [weak recommendation, moderate-quality evidence].

We performed a meta-analysis of seven eligible RCTs that compared the use of oral 5-ASA [five trials]^{24–28} or sulphasalazine [two trials]^{29,30} with placebo in patients with active CD [[Supplementary Material](#), [SoF Table 1](#), available as Supplementary data at *ECCO-JCC* online]. The dosage of 5-ASA administered ranged from 1 g to 3.2 g/day; patients with mild-to-moderate disease with ileal, ileocolonic, or colonic disease were included. Overall, there was no significant effect for induction of **clinical remission** (relative risk [RR]: 1.28; 95% confidence interval [CI]: 0.97–1.69) [[Supplementary Figure 1](#), available as Supplementary data at *ECCO-JCC* online]. A recent Cochrane review also found no significant overall effect.³¹ Both 5-ASA and sulphasalazine appeared to be well tolerated in our meta-analysis, as there was no significant increase in withdrawals due to **adverse effects** [AEs] when compared with placebo [RR: 1.13; 95% CI: 0.73–1.84] [[Supplementary Figure 2](#), available as Supplementary data at *ECCO-JCC* online].

Among the five trials of 5-ASA alone there was also no benefit over placebo for inducing **clinical remission** [RR: 1.27; 95% CI: 0.79–2.03] [[Supplementary Figure 3](#), available as Supplementary data at *ECCO-JCC* online]. No significant increase in withdrawal due to AEs was observed in trials that compared 5-ASA alone versus placebo [RR: 1.0; 95% CI: 0.58–1.71] [[Supplementary Figure 4](#), available as Supplementary data at *ECCO-JCC* online]. One published network meta-analysis noted a small statistically significant

effect on **clinical remission** among the study arms that evaluated 5-ASA at daily doses of >2.4 g/day.³² However, another network meta-analysis was unable to confirm any such dose effect.³³ A pooled analysis of three double-blind placebo-controlled trials of a slow-release preparation of 5-ASA reported a significantly greater **reduction in the Crohn's Disease Activity Index [CDAI]** with 5-ASA versus placebo.³⁴ However, the effect size [an 18-point greater reduction in CDAI score comparing 5-ASA and placebo] was not clinically significant.

Two older trials compared sulphasalazine with placebo for **induction of clinical remission**. A pooled analysis showed a small effect of borderline statistical significance [RR: 1.38; 95% CI: 1.00–1.89] [Supplementary Figure 5, available as Supplementary data at ECCO-JCC online]. This was not accompanied by any significant increase in withdrawals for AEs [RR: 1.88; 95% CI: 0.65–5.47] [Supplementary Figure 6, available as Supplementary data at ECCO-JCC online]. Subgroup analyses in both trials suggested that the efficacy of sulphasalazine was limited to patients with colonic CD.^{29,30}

The use of topical 5-ASA [enema or suppository] for the treatment of CD has not been studied in RCTs.

Budesonide

Recommendation 1.2. ECCO CD Treatment GL [2019]

We recommend using budesonide for the induction of clinical remission in patients with active mild-to-moderate Crohn's disease limited to the ileum and/or ascending colon [strong recommendation, moderate-quality evidence].

A Cochrane systematic review and meta-analysis³⁵ included three RCTs^{36–38} that compared budesonide at a dose of 9 mg/day with placebo [Supplementary Material, SoF Table 2, available as Supplementary data at ECCO-JCC online]. Two of these trials^{37,38} evaluated **clinical response** [defined as decrease in CDAI score ≥ 100 or total CDAI score ≤ 150] at 8 weeks. **Clinical remission** [CDAI score ≤ 150] at 8 weeks was reported in all three RCTs. Budesonide was superior to placebo for inducing **clinical response** [RR: 1.46; 95% CI: 1.03–2.07] and **clinical remission** [RR: 1.93; 95% CI: 1.37–2.73] in patients with mildly active CD in the small and/or large intestine limited to the ascending colon. As compared with conventional steroids [e.g., prednisolone], which are usually associated with many systemic side effects, budesonide presented high topical anti-inflammatory activity and low systemic absorption and bioavailability, and therefore had a better safety profile. Budesonide was shown to be safe [AEs; RR: 0.98; 95% CI: 0.77–1.25] in the reviewed meta-analysis.³⁵

A Cochrane systematic review and meta-analysis from 2015 reviewed two RCTs^{39,40} that compared budesonide at a dose of 9 mg/day with mesalazine up to 4.5 g/day. More recently, a Japanese trial⁴¹ also evaluated budesonide versus mesalazine in patients with active CD [Supplementary Material, SoF Table 3, available as Supplementary data at ECCO-JCC online]. All trials evaluated **clinical response** [decrease in CDAI ≥ 100 or total CDAI ≤ 150] and **clinical remission** [CDAI ≤ 150] at 8 weeks. Budesonide was not superior to mesalazine for inducing **clinical remission** [RR: 1.30; 95% CI: 0.98–1.72] in patients with mildly active CD in the small and/or large intestine [Supplementary Figure 7, available as Supplementary data at ECCO-JCC online]. Nevertheless, **clinical response** was more

frequently seen in patients receiving budesonide [RR: 1.22; 95% CI: 1.03–1.45] than in patients receiving mesalazine [Supplementary Figure 8, available as Supplementary data at ECCO-JCC online]. The safety profile of both compounds was comparable, with similar AE [RR: 0.91; 95% CI: 0.79–1.05] and serious AE [RR: 0.94; 95% CI: 0.24–3.75] rates in both intervention groups [Supplementary Figures 9 and 10, available as Supplementary data at ECCO-JCC online].

Antibiotics

Numerous studies have studied the efficacy of antibiotic treatment on luminal CD. Metronidazole, ciprofloxacin, and anti-mycobacterial regimens have been extensively studied. Overall, none has demonstrated efficacy to consistently induce **clinical remission** or mucosal healing compared with placebo.^{42–44} In addition, side effects limit the use of these therapies; recently, the European Medicines Agency has imposed restrictions on the use of ciprofloxacin due to disabling or potentially permanent events [EMA/668915/2018]. Therefore a recommendation was not made specifically on antibiotics to treat luminal CD, although they remain indicated for the treatment of septic complications.

Moderate-to-severe disease

Systemic corticosteroids

Recommendation 1.3. ECCO CD Treatment GL [2019]

In patients with active, moderate-to-severe Crohn's disease, we suggest the use of systemic corticosteroids for the induction of clinical response and remission [weak recommendation, moderate-quality evidence].

Two RCTs reported on the efficacy of systemic corticosteroids [oral prednisolone or oral methylprednisolone] compared with placebo for the treatment of moderately-to-severely active CD.^{29,30} [Supplementary Material, SoF Table 4, available as Supplementary data at ECCO-JCC online]. Oral methylprednisolone was administered at a dose of 48 mg/day and reduced on a weekly basis to 32 mg, 24 mg, 20 mg, 16 mg, and 12 mg.²⁹ Doses of oral prednisolone ranged from 0.50 to 0.75 mg/kg with a maximum daily dose of 60 mg.³⁰ Prednisolone is usually tapered at 5 mg/week over an 8-to 12-week period. Data from these studies have been synthesised in a Cochrane systematic review.⁴⁵

One trial involving 105 patients reported on induction of **clinical response**.²⁹ **Clinical response** was more common in patients receiving methylprednisolone as compared with placebo [93.6% vs 53.4%; RR: 1.75; 95% CI: 1.36–2.25]. Corticosteroids were reported to be twice as effective in inducing **clinical remission** than placebo in the two studies involving 267 patients [RR: 1.99; 95% CI: 1.51–2.64].⁴⁵ Data on the proportion of patients experiencing AEs from the use of systemic corticosteroids was available from one trial involving 162 patients treated with oral prednisolone.^{30,46} The frequency of AEs was 5-fold higher in patients receiving corticosteroids compared with placebo [31.8% vs 6.5%; RR: 4.89; 95% CI: 1.98–12.07]. Steroid-related AEs included Cushing syndrome, acne, infection [increased risk of abdominal and pelvic abscesses in patients with CD], ecchymoses, hypertension, diabetes mellitus, osteoporosis, cataracts, glaucoma, and growth failure in children. Imprecision was serious for the outcomes considered, due to sparse data, which yielded a moderate quality of evidence overall.

Immunosuppressants

Thiopurines

Recommendation 1.4. ECCO CD Treatment GL [2019]

We suggest against the use of thiopurines as monotherapy for the induction of remission of moderate-to-severe luminal Crohn's disease [weak recommendation, very low-quality evidence].

Several studies have reported on the use of thiopurines compared with placebo for induction of remission and response in CD^{30,47-53} [Supplementary Material, SoF Table 5, available as Supplementary data at ECCO-JCC online]. Five trials evaluated the use of thiopurines for induction of clinical remission [12–17 weeks] in comparison with placebo^{30,47,48,51} [using CDAI or Harvey-Bradshaw index]. Overall, 380 patients were analysed. The active comparator was AZA in four of these trials,^{30,47,51} and the active drug was MP in the remaining trial.⁵⁴ The trials were heterogeneous in terms of study design, follow-up time, definition of active disease, and definition of remission. Except for Summers *et al.*,³⁰ most of the trials allowed for the use of concomitant steroids. The pooled analysis was performed on an intention-to-treat basis and revealed no differences for induction of remission between thiopurines and placebo; 48% [95/197] in the active intervention compared with 37% [68/183] in the placebo group achieved remission [RR: 1.23; 95% CI: 0.97–1.55].

Three trials reported on clinical response, albeit not with standardised measures of disease activity.^{49,52,53} In these trials, different types of physician global assessment of disease improvement [clinical response] were used.^{49,52,53} Overall, 42.8% of the patients receiving thiopurines, as compared with 26.9% of those receiving placebo, showed clinical improvement. The RR of obtaining clinical response was 1.87 [95% CI: 0.44–7.96]. Heterogeneity was serious [$I^2 = 69%$] and imprecision very serious due to sparse data and wide confidence intervals; thus the quality of evidence was very low for this outcome [Supplementary Figure 11, available as Supplementary data at ECCO-JCC online].

Only one trial reported on AEs during induction.⁵¹ The pooled RR of any AEs was not significantly different between placebo and thiopurines [86% vs 69%; RR: 0.81; 95% CI: 0.64–1.02]. Serious AEs were reported in two trials^{30,51} including 125 patients; 13.5% of those receiving AZA versus 3.8% of those receiving placebo developed serious AEs [pooled RR: 2.57; 95% CI: 0.92–7.13]. The quality of evidence was deemed low due to a very low number of events [$n = 19$] and wide confidence intervals.

One study reported on a validated quality of life measure [Inflammatory Bowel Disease Questionnaire: IBDQ].⁵¹ The greatest difference between groups was observed at Week 4 [43% for AZA and 30% for placebo]. Regarding biochemical improvement, only some of the trials reported on changes at the end of the induction period; no dichotomous data were available that allowed for a pooled analysis calculation. Overall, most trials reported no differences in biomarkers of inflammation such as erythrocyte sedimentation rate [ESR], CRP, or orosomucoid in those receiving thiopurines as compared with placebo.^{48,52-54} Reinisch *et al.*⁵¹ reported a similar proportion of elevated faecal calprotectin at baseline and at Weeks 4 and 12 for the thiopurines and placebo groups. Candy *et al.*⁴⁷ reported a slight increase of ESR in the group receiving placebo and prednisolone versus a statistically significant decrease in ESR in those receiving AZA and prednisone.

Methodrexate

Only one relevant placebo-controlled RCT was retrieved. In this study,⁵⁵ 141 steroid-dependent patients with active CD were randomised to either 25 mg/week of intramuscular MTX or placebo for 16 weeks, with a concomitant daily dose of prednisolone [20 mg at initiation] that was reduced over a 3-month period [Supplementary Material, SoF Table 6, available as Supplementary data at ECCO-JCC online]. After 16 weeks, a significantly larger proportion of patients treated with MTX were in clinical remission than placebo [RR: 2.06; 95% CI: 1.09–3.89]. The rate of treatment discontinuation for AEs [mainly liver enzyme elevations and nausea] was significantly higher in comparison with placebo [RR: 8.00; 95% CI: 1.09–58.51]. However, this study is strongly limited by imprecision and some confounding factors, such as the concomitant use of steroids. No studies were found that compared MTX monotherapy versus placebo for the induction of remission of moderate-to-severe CD. No agreement was achieved in the Consensus regarding the use of MTX for inducing CD remission, and therefore the Consensus decided to make no recommendation.

Three small and heterogeneous studies compared the efficacy of MTX and thiopurines for induction of remission in CD⁵⁶⁻⁶⁰ [Supplementary Material, SoF Table 7, available as Supplementary data at ECCO-JCC online]. These studies used different dosages and routes of administration. Two studies used oral MTX at doses of 16 mg/week⁵⁹ and 12.5 mg/week,⁵⁶ and one used intravenous [IV] MTX at 25 mg/week.⁶⁰ All patients were steroid-dependent and received systemic steroids at inclusion. None of the individual studies or the pooled analysis demonstrated a significant difference in the likelihood to achieve remission [RR: 0.87; 95% CI: 0.70–1.09] [Supplementary Figure 12, available as Supplementary data at ECCO-JCC online]. Although the risk of AEs is higher with MTX, the data are very sparse and the quality of evidence is very low for both outcomes. Accordingly, no recommendation can be made.

Based on the current evidence, agreement on a recommendation for the use of MTX for inducing clinical remission in patients with CD could not be reached. However, MTX may be considered as an option for steroid-dependent patients with moderate-to-severe disease when alternative options [including surgery] cannot be used. The need to stop therapy in patients planning a pregnancy must be considered.⁶¹

Monoclonal antibodies

Recommendation 1.5. ECCO CD Treatment GL [2019]

We recommend the use of TNF inhibitors [infliximab, adalimumab, and certolizumab pegol] to induce remission in patients with moderate-to-severe Crohn's disease who have not responded to conventional therapy [strong recommendation, moderate-quality evidence].

Monoclonal antibodies directed against TNF- α are fast-acting and potent anti-inflammatory agents. Anti-TNF therapies approved for the treatment of CD include infliximab, adalimumab, and certolizumab pegol [the latter is not approved in the European Union for CD, but is commercially available in Switzerland and Russia]. Infliximab is a chimeric mouse-human immunoglobulin [Ig] G1 monoclonal antibody administered intravenously at a dose of 5 mg/kg at 0, 2, and 6 weeks during induction and every 8 weeks thereafter. Adalimumab is a fully humanised IgG1 monoclonal antibody given subcutaneously [SC] at a dose of 160 mg, and then

80 mg 2 weeks after induction, followed by 40 mg SC every 2 weeks. Certolizumab pegol is a PEGylated Fab fragment against TNF- α , self-administered SC at a dose of 400 mg at Weeks 0, 2, and 4, followed by 400 mg every 4 weeks thereafter.

Data on anti-TNF agents versus placebo [infliximab, adalimumab, and certolizumab pegol] from several meta-analyses of RCTs^{62–64} support their efficacy for induction of **clinical remission** [RR: 1.6; 95% CI: 1.17–2.36] and **clinical response** [RR: 1.43; 95% CI: 1.17–1.73] [Supplementary Material, SoF Table 8, available as Supplementary data at ECCO-JCC online] in patients who did not achieve adequate response or were intolerant to corticosteroids and/or immunosuppressants. Limited endoscopic data were available for the induction period; two studies showed a non-significant trend towards enhanced mucosal healing [RR: 3.25; 95% CI: 0.53–19.8].^{65,66} However, the evidence was downgraded due to imprecision. Data on **clinical remission** were highly heterogeneous [$I^2 = 63\%$], and data on **endoscopic improvement** were affected by high imprecision due to the low number of patients included in the meta-analysis [$n = 35$]. Data on patient-reported outcomes [PRO] **response and remission, biochemical and radiological improvement, and quality of life** are insufficient. There was no difference in terms of AEs [RR: 0.99; 95% CI: 0.90–1.08].

The choice of anti-TNF agent depends on patient preference, availability, cost, and accessibility. However, in a 2015 network meta-analysis, pairwise comparison revealed that infliximab with AZA [OR: 3.1; 95% CI: 1.4–7.7] and adalimumab monotherapy [OR: 2.1; 95% CI: 1–4.6] were superior to certolizumab pegol for **induction of remission**.⁶⁷

The timing of introduction of biologic agents is a matter of debate. It has been suggested that patients presenting with poor prognostic factors [e.g. fistulising perianal disease, extensive disease, deep ulcerations, complicated phenotype] would benefit from the early introduction of anti-TNF to achieve a reduced risk of surgery, hospitalisation, or development of disease-related complications.¹⁵ Furthermore, anti-TNF agents might be more effective if introduced earlier [in the first 2 years] in disease course,^{68–72} although these results are based on post-hoc analyses from clinical trials.

Recommendation 1.6. ECCO CD Treatment GL [2019]

We suggest against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response [weak recommendation, moderate-quality evidence].

Only one RCT [the DIAMOND trial]⁷³ studied the use of combination therapy of adalimumab with thiopurine as compared with adalimumab monotherapy for the induction of **clinical remission** in patients naïve to both therapies [Supplementary Material, SoF Table 9, available as Supplementary data at ECCO-JCC online]. In this trial, combination therapy was not superior to adalimumab monotherapy for inducing **clinical remission** [RR: 0.95; 95% CI: 0.78–1.15]. However, combination therapy was associated with endoscopic improvement at Week 26 [RR: 1.32; 95% CI: 1.06–1.65], although this benefit was lost at the end of 1 year. There was no increase in AEs leading to discontinuation associated with combination therapy [RR: 1.03; 95% CI: 0.60–1.78]. Of note, the dose of AZA used in this trial was lower than the usual dose used in CD patients [25–100 mg/day instead of 2–2.5 mg/kg/day].

Recommendation 1.7. ECCO CD Treatment GL [2019]

We recommend combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe Crohn's disease, who have had an inadequate response to conventional therapy [strong recommendation, moderate-quality evidence].

The SONIC [Study Of Biologic and Immunomodulator Naive Patients In Crohn's Disease] RCT⁷⁰ compared the efficacy of infliximab combined with AZA over infliximab monotherapy in patients naïve to both therapies, who failed to respond to steroids or 5-ASA [Supplementary Material, SoF Table 10, available as Supplementary data at ECCO-JCC online]. Combination therapy resulted in higher rates of **clinical remission at Week 26** as compared with infliximab monotherapy [RR: 1.64; 95% CI: 1.07–2.53]. Combination therapy was also more likely to result in **mucosal healing** at this timepoint [RR: 1.82; 95% CI: 1.01–3.26]. There was no difference in AEs for those receiving combination therapy. Rather, there were significantly lower rates of **serious AEs** in those receiving combination therapy [RR: 0.56; 95% CI: 0.32–0.97].

A commonly encountered scenario in clinical practice is patients who have failed or have had an inadequate response to thiopurines and in whom anti-TNF therapy is planned. No RCT has directly compared whether in such cases thiopurine maintenance in combination with the anti-TNF would carry additional benefits in terms of efficacy. A post-hoc analysis of RCTs has shown no added benefit of the continued use of immunomodulator therapy after starting anti-TNF therapy in this setting.⁷⁴ However, immunogenicity should be considered and, in the absence of direct evidence, an individualised approach should be considered.⁷⁴

Recommendation 1.8. ECCO CD Treatment GL [2019]

We recommend ustekinumab for induction of remission in patients with moderate-to-severe Crohn's disease with inadequate response to conventional therapy and/or to anti-TNF therapy [strong recommendation, high-quality evidence].

Ustekinumab is an IgG1 monoclonal antibody that binds to the p40 subunit shared by the pro-inflammatory interleukins 12 and 23.⁷⁵ In CD, induction should be given IV using a weight-based regimen of approximately 6 mg/kg.^{75,76} One systematic review and meta-analysis pooled the results from RCTs in which ustekinumab was compared with placebo for **induction of remission** in patients with moderate-to-severe active luminal CD⁷⁷ [Supplementary Material, SoF Table 11, available as Supplementary data at ECCO-JCC online]. Four trials^{76,78–80} involving 1947 patients treated with different ustekinumab intravenous doses or equivalent placebo reported **induction of clinical response** and **induction of clinical remission** at Week 6. Data were extracted and a meta-analysis was performed, yielding an RR of obtaining **clinical response** of 1.56 [95% CI: 1.38–1.77] versus placebo [Supplementary Figure 13, available as Supplementary data at ECCO-JCC online]. The quality of evidence was high. The RR of obtaining **clinical remission** was 1.76 [95% CI: 1.40–2.22] [Supplementary Figure 14, available as Supplementary data at ECCO-JCC online]. The quality of evidence was high. An endoscopic substudy involving 252 CD patients revealed that 47.7% of patients receiving ustekinumab achieved **endoscopic improvement** at 8 weeks as compared with 29.9% of those receiving placebo [RR:

1.60; 95% CI: 1.13–2.26]. The quality of evidence was moderate. Four trials^{76,78–80} reported on AEs [2024 patients] or serious AEs [1947 patients] after induction. The pooled RR of any AEs was not significantly different between ustekinumab and placebo [62.0% vs 63.9%; RR: 0.96; 95% CI: 0.90–1.03] [Supplementary Figure 15, available as Supplementary data at ECCO-JCC online]. Similarly, the pooled RR of any serious AEs was not significantly different between ustekinumab and placebo [5.2% vs 6.4%; RR: 0.79; 95% CI: 0.54–1.15] [Supplementary Figure 16, available as Supplementary data at ECCO-JCC online]; the quality of evidence was high. The rate of antibody drug formation seems to be low [under 5%].⁸¹

Recommendation 1.9. ECCO CD Treatment GL [2019]

We recommend vedolizumab for induction of response and remission in patients with moderate-to-severe Crohn's disease with inadequate response to conventional therapy and/or to anti-TNF therapy [strong recommendation, moderate-quality evidence].

Vedolizumab is a monoclonal IgG1 antibody that acts by blocking the $\alpha 4\beta 7$ integrin resulting in gut-selective anti-inflammatory activity.⁸² It is administered intravenously at a fixed dose of 300 mg at 0, 2, and 6 weeks for induction, and every 8 weeks thereafter. Patients who do not achieve response at Week 6 can benefit from an additional administration at Week 10.⁸³ Three randomised trials involving 969 patients treated with vedolizumab or placebo reported on induction of clinical response, induction of clinical remission, and serious AEs in adult patients with moderate-to-severe active CD.^{82,84,85} [Supplementary Material, SoF Table 12, available as Supplementary data at ECCO-JCC online]. Patients in these studies were followed up for 6 to 10 weeks. Clinical remission was more common in patients receiving vedolizumab compared with placebo [RR: 2.01; 95% CI: 1.50–2.71] [Supplementary Figure 17, available as Supplementary data at ECCO-JCC online]. Likewise, clinical response was also more common in patients receiving vedolizumab compared with placebo [40.8% vs 25.7%; RR: 1.55; 95% CI: 1.14–2.11] [Supplementary Figure 18, available as Supplementary data at ECCO-JCC online]. The quality of evidence for these outcomes was high. Rates of serious AEs with vedolizumab were not significantly different with placebo [RR: 0.94; 95% CI: 0.61–1.45] [Supplementary Figure 19, available as Supplementary data at ECCO-JCC online]. The quality of evidence for this outcome was moderate due to serious imprecision arising from sparse data.

Recommendation 1.10. ECCO CD Treatment GL [2019]

We equally suggest the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal Crohn's disease in patients who have previously failed anti-TNF therapy [weak recommendation, very low-quality evidence].

One systematic review and meta-analysis performed an indirect comparison of ustekinumab and vedolizumab for induction of remission in patients with moderate-to-severe active luminal CD who were non-responsive or intolerant to previous anti-TNF agents.⁸⁶

Four trials^{76,79,82,85} involving a total of 1249 patients treated with ustekinumab or vedolizumab reported on induction of clinical response

and clinical remission [Supplementary Material, SoF Table 13, available as Supplementary data at ECCO-JCC online]. The pooled RR of clinical response [35.8% vs 33.1%; RR: 1.14; 95% CI: 0.65–1.99] and clinical remission [16.3% vs. 13.3%; RR: 1.16; 95% CI: 0.54–2.48] were not significantly different between ustekinumab and vedolizumab, but the quality of evidence was very low for both outcomes.

Four trials^{76,79,82,85} involving a total of 1541 patients treated with ustekinumab or vedolizumab reported on AEs or serious AEs after induction. The pooled RR of any AEs was not significantly different between ustekinumab and vedolizumab [64.2% vs 56.2%; RR: 1.00; 95% CI: 0.82–1.23]. Finally, the pooled RR of any serious AEs was not significantly different between ustekinumab and vedolizumab [7.1% vs 7.7%; RR: 0.95; 95% CI: 0.43–2.12]; the quality of evidence was very low. However, surgery should always be considered as an option in refractory patients.

Key Points for Clinical Practice

Budesonide is effective for the induction of remission in patients with mild-to-moderate CD, defined as a CDAI between 150 and 220, and/or presence of mild lesions at endoscopy, or a Simple Endoscopic Score-CD [SES-CD] ≤ 6 , or a Crohn's Disease Endoscopic Index of Severity [CDEIS] ≤ 8 with ileal and/or right colon involvement; 5-ASA compounds and sulphasalazine have no therapeutic effect. There is a knowledge gap on how to treat mild-to-moderate CD localised in different parts of the gastrointestinal tract other than the ileum and right colon, or in patients with extensive disease. Therefore the decision is left to the clinician, who should consider the patient's individual characteristics, prognostic factors, and cost/benefit ratios of therapies.

Although systemic steroids are effective in inducing remission in moderate-to-severe CD, they are limited by important side effects. Additionally, long-term use of corticosteroids does not prevent disease relapse.^{30,87} Therefore we suggest that the presence of corticosteroid dependency or excess [the inability to wean steroids below the equivalent of prednisolone 10 mg/day or budesonide 3 mg/day within 3 months of starting steroids, a relapse within 3 months of stopping steroids, or the need for more than a single course of corticosteroids in 1 year] should all warrant a steroid-sparing strategy. Thiopurines alone are not effective in inducing remission. However, since thiopurines have a slow onset of action [8–12 weeks]⁴³ and are effective for maintaining remission in steroid-dependent CD patients [see Maintenance, 6.2.1., Recommendation 2.2.], they are frequently combined with steroids at the commencement of therapy. In patients with steroid dependency, a combination of steroids and MTX has limited efficacy in inducing remission at Week 16 and is associated with a high risk of AEs. Therefore, this option may be considered only where other medical treatments and surgery are not indicated or are associated with some increased individual risks.⁸⁸

For patients with moderate-to-severe CD [usually defined as a CDAI >220 and/or CDEIS >8 or SES-CD >6] with inadequate response or intolerance to conventional therapy [steroids and/or thiopurines], we recommend the use of monoclonal antibodies. These include anti-TNF agents [such as infliximab, adalimumab, and certolizumab pegol], ustekinumab, or vedolizumab. All these agents are effective both in biologic-naïve and -experienced CD populations. The choice depends on patient characteristics and preferences, costs, and local availability.⁸ For the induction of remission, in treatment-naïve patients, the combination of infliximab with thiopurines is more effective than infliximab alone for achieving steroid-free remission.⁷⁰ For adalimumab, no benefit of combination therapy over

adalimumab alone was observed in the only RCT performed to date.⁷³ The SONIC trial⁷⁰ demonstrated the superiority of either infliximab alone or the combination of infliximab and AZA over AZA monotherapy or even in combination with steroids; this option should be considered and even preferred in steroid-dependent patients. The REACT [Early Combined Immunosuppression for the Management of Crohn's Disease] trial showed that the early use of monoclonal antibodies [adalimumab] combined with immunosuppressants in patients at high risk of complications, as compared with a more conventional stepwise management, was associated with significantly lower rates of complications and need for hospitalisation and/or surgery in patients with early CD.¹⁵ A prospective cohort study demonstrated that concomitant immunomodulator use is associated with lower immunogenicity to anti-TNF.⁸⁹ In clinical practice, the potential added efficacy benefit and lower immunogenicity of combination therapy needs to be balanced against a potential increase in AEs in the long term.^{90,91} Combination therapy does not seem to be associated with safety concerns, at least in the short term. However, a large nationwide cohort study showed that combination therapy is associated with higher risk for lymphoma and serious infection, as compared with anti-TNF monotherapy.^{90,91} Therefore the decision is left to the clinician, who should consider patient characteristics, costs, risks, and local regulations. Importantly, risk needs to be individualised as specific patient groups, such as the elderly, maybe at higher risk for infections or lymphoma and young males maybe at higher risk for specific complications, such as hepatosplenic T cell lymphoma.^{92,93}

In patients who fail anti-TNF therapy, ustekinumab or vedolizumab are indicated. There is currently no direct evidence on the comparison between vedolizumab versus anti-TNF and ustekinumab versus anti-TNF in patients treated either with vedolizumab or ustekinumab as a first biologic. No RCTs have specifically assessed the efficacy and safety of these agents when used in combination therapy as compared with monotherapy; however, overall immunogenicity rates seem to be low. Besides, in the originator trials, no difference in efficacy was observed in those patients treated concomitantly with immunomodulator. However, in patients with moderate-to-severe CD with limited disease extent or refractory to at least one monoclonal antibody, surgery should always be considered as an alternative option.

While RCTs evaluate the efficacy of a drug for induction of remission and thereafter for maintaining remission using validated indices of clinical activity, the clinician usually bases his or her choice of first-line therapy not only on symptoms but also on the perceived disease severity [the impact of disease in the individual patient, the cumulative complications and surgical resections, risk factors for complications, the inflammatory burden of disease, and disease course].¹ Therefore, appropriate studies that address the early use of biologics over a stepwise approach, focusing on the prevention of complications and disease-modification outcomes, and that validate risk factors for disease progression [age, extensive disease, upper tract involvement] should be performed. Such studies were identified by this Consensus as very important research gaps.

Section 2 - Maintenance of Remission

5-ASA compounds

Recommendation 2.1. ECCO CD Treatment GL [2019]

We recommend against the use of oral 5-aminosalicylic acid for maintenance of medically induced remission in patients with Crohn's disease [strong recommendation, low-quality evidence].

Oral 5-ASA compounds have been extensively studied for the maintenance of medically induced remission of CD [Supplementary Material, SoF Table 14, available as Supplementary data at ECCO-JCC online]. No statistically significant benefit has been demonstrated [RR: 1.03; 95% CI: 0.92–1.16] [Supplementary Figure 20, available as Supplementary data at ECCO-JCC online]. Overall, 11 placebo-controlled trials that assessed doses between 1 and 4 g/day were identified. Treatment durations ranged from 4 months to 36 months, with most trials evaluating a 12-month duration of therapy.⁹⁴ There were no significant differences in the proportion of patients experiencing an AE, or withdrawing due to AEs or serious AEs [RR: 1.93; 95% CI: 0.18–21.1]. The safety data were very sparse [three events] and considerably limited this conclusion [Supplementary Figure 21, available as Supplementary data at ECCO-JCC online].

Immunosuppressants

Thiopurines

Recommendation 2.2. ECCO CD Treatment GL [2019]

Thiopurines are recommended for the maintenance of remission in patients with steroid-dependent Crohn's disease [strong recommendation, moderate-quality evidence].

The effect of maintenance treatment with AZA or MP administered to patients with CD who are steroid-dependent has been investigated in one meta-analysis⁹⁵ [Supplementary Material, SoF Table 15, available as Supplementary data at ECCO-JCC online]. This meta-analysis included data from six trials published between 1971 and 2013.^{30,47,53,96–99} A total of 489 patients treated with AZA [1.0 to 2.5 mg/kg/day] were included and followed for 6 to 18 months. Clinical remission was defined according to different criteria [CDAI in three, disease activity score [DAS] two, in others one]. AZA was superior to placebo for the maintenance of remission in steroid-dependent patients [RR: 1.19; 95% CI: 1.05–1.34].

Safety outcomes were reported in four trials published between 1978 and 2013,^{30,96–98} including a total of 556 patients followed for 6 to 18 months. The overall risk of inducing serious AEs during maintenance treatment with thiopurines was significantly higher than with placebo [RR: 2.45; 95% CI: 1.22–4.90]. The rate of serious AEs reported in patients treated with thiopurines versus placebo was 9.0% [22/245] versus 2.9% [9/311]. Pancreatitis, leukopenia, nausea, allergic reaction, and infections were the most frequent serious AEs.

Recommendation 2.3. ECCO CD Treatment GL [2019]

We recommend against the early introduction of thiopurine therapy in patients with newly diagnosed Crohn's disease for maintaining remission [weak recommendation, low-quality evidence]

It has been hypothesised that the early introduction of thiopurines could modify disease course. Two studies have evaluated the efficacy of early use of thiopurines: the AZTEC [AZathioprine for Treatment of Early Crohn's disease in adults]⁹⁸ and the RAPID [Résultat de l'Adjonction Précoce d'ImmunoDépresseurs]¹⁰⁰ trials [Supplementary Material, SoF Table 16, available as Supplementary data at ECCO-JCC online]. The latter has been excluded from our

SoF table because it was not conducted against placebo or no treatment. In the AZTEC study, adult patients with a recent [<8 weeks] diagnosis of uncomplicated CD were randomised to receive either AZA or placebo up to Week 76. Only corticosteroids were allowed to treat active disease in this study population. The results were not statistically significant for any of the critical outcomes evaluated. After 76 weeks of treatment, **clinical remission** did not differ between the two groups [RR: 1.27; 95% CI: 0.94–1.72]; 30 patients treated with AZA [44.1%] and 23 given placebo [36.5%] were in sustained **corticosteroid-free remission** [RR: 1.21; 95% CI: 0.79–1.84]. The rates of relapse [defined as CDAI score >175] and corticosteroid requirements were similar between groups. **Serious AEs** occurred in 14 patients [20.6%] in the AZA group and 7 [11.1%] in the placebo group [RR: 1.85; 95% CI: 0.8–4.29].

Methotrexate

Recommendation 2.4. ECCO CD Treatment GL [2019]

We recommend methotrexate administered parenterally for the maintenance of remission in patients with steroid-dependent Crohn's disease [weak recommendation, moderate-quality evidence].

Data on the use of parenterally administered MTX are derived from one double-blind, placebo-controlled RCT⁵⁵ where patients were administered weekly intramuscular injections of 15 mg MTX, or placebo of identical appearance, for 40 weeks [Supplementary Material, SoF Table 17, available as Supplementary data at ECCO-JCC online]. Patients with previously active CD, who had entered **remission** after 16 to 24 weeks of treatment with 25 mg MTX given intramuscularly once weekly, were randomly assigned to receive either MTX at a dose of 15 mg intramuscularly once weekly or placebo, for 40 weeks. No other treatments for CD were permitted. After 40 weeks, the proportion of patients who remained in **remission** was higher in the MTX group than in the placebo group [65% vs 39%; RR: 1.67; 95% CI: 1.05–2.67]. Fewer than 50% of the patients in the MTX group had relapsed by the end of the study.

There were no differences in severe **AEs** in the MTX group [$n = 40$] as compared with the placebo group [$n = 36$] over the 40-week observational period [one patient had cervical dysplasia and the other had a viral respiratory tract infection]. Nausea and vomiting occurred more frequently among patients in the MTX group [40% vs 25% in the placebo group]. Although none of the symptoms was severe, one patient discontinued treatment because of these symptoms. No patient had leukopenia of sufficient severity to require withholding treatment or withdrawal from the study. The overall incidence of **AEs** was similar in both groups.

Monoclonal antibodies

Recommendation 2.5. ECCO CD Treatment GL [2019]

In patients with Crohn's disease who achieved remission with anti-TNF agents, maintenance treatment using the same treatment is recommended [strong recommendation, moderate-quality evidence].

Two systematic reviews analysed the effect of maintenance treatment with anti-TNFs [infliximab, adalimumab, and certolizumab pegol]

administered to patients with CD who had achieved disease **remission** with the same anti-TNF drug^{62,63} [Supplementary Material, SoF Table 18, available as Supplementary data at ECCO-JCC online]. Five landmark trials published between 2002 and 2007^{71,101–104} were pooled in the meta-analysis from Stidham *et al.*⁶²; one study was on infliximab, two on adalimumab, and two on certolizumab pegol. A total of 1771 patients were included and followed for 24 to 30 weeks. Four of the five studies included primary responders only, and one study included all subjects. **Clinical remission** was defined as a CDAI score <150 . The overall likelihood of maintaining **remission** with anti-TNFs versus placebo was 1.78 [95% CI: 1.51–2.09]. The following values were achieved with infliximab: 1.86 [95% CI: 1.21–2.86]; with adalimumab: 2.06 [95% CI: 1.59–2.82]; and with certolizumab pegol: 1.62 [95% CI: 1.30–2.02]. A network meta-analysis⁶² found no statistically significant differences between the three agents.

There are no pooled data available on **serious AEs** of all anti-TNFs as against placebo. In a network analysis performed in the framework of a Cochrane collaboration,¹⁰⁵ the dose-adjusted odds ratios [Ors] [95% CI] for **SAEs** for adalimumab, infliximab, and certolizumab pegol were 1.01 [0.64–1.59], 1.13 [0.79–1.62], and 1.57 [0.96–2.57], respectively. Thus monotherapy with anti-TNFs is considered safe as compared with placebo for the **maintenance of remission** in CD patients, although the relatively small sample size and short follow-up of RCTs do not allow the detection of **AEs** that may appear in larger and longer observational studies.

Recommendation 2.6. ECCO CD Treatment GL [2019]

We recommend vedolizumab for maintaining clinical remission in patients with moderate-to-severe Crohn's disease who achieved remission with vedolizumab [strong recommendation, moderate-quality evidence].

Vedolizumab monotherapy, given IV at 300 mg every 8 weeks, was superior to placebo in maintaining **clinical remission** in patients with moderate-to-severe CD who achieved **remission** with vedolizumab [RR: 1.81; 95% CI: 1.26–2.59] [Supplementary Material, SoF Table 19, available as Supplementary data at ECCO-JCC online]. At Week 52, 60/154 patients [39.0%] receiving vedolizumab every 8 weeks and 56/154 patients [36.4%] receiving vedolizumab every 4 weeks were in **clinical remission** as compared with 33/153 patients [21.6%] receiving placebo [$p < 0.001$ and $p = 0.004$, respectively]. Moreover, vedolizumab was effective at maintaining **steroid-free clinical remission** [RR: 2.00; 95% CI: 1.11–3.61] and showed a similar incidence of **AEs** compared with placebo through week 54 [RR: 1.21; 95% CI: 0.73–2.00].⁸² Longer-term data beyond 52 weeks are required to correctly evaluate the **safety profile**.

Recommendation 2.7. ECCO CD Treatment GL [2019]

We recommend the use of ustekinumab to maintain clinical remission in patients with Crohn's disease who achieved remission with ustekinumab [strong recommendation, moderate-quality evidence].

One RCT reported outcomes for the **maintenance of remission** with ustekinumab in CD patients [Supplementary Material, SoF Table 20, available as Supplementary data at ECCO-JCC online].⁷⁹ Patients responding to ustekinumab in the induction period were re-randomised to receive ustekinumab every 8 or 12 weeks or placebo. Over a 44-week period, 51% of the patients receiving SC ustekinumab were in **clinical remission** as compared with 35.9%

of those receiving placebo [RR: 1.42; 95% CI: 1.10–1.84]. A subgroup analysis demonstrated that at Week 44, **clinical remission** was achieved by 53.1% of patients receiving ustekinumab every 8 weeks and by 48.8% of patients receiving ustekinumab every 12 weeks, as compared with 35.9% in the placebo group. The difference between treatment every 8 weeks and placebo was 17.2% [95% CI: 5.3–29.2] and was 13% between treatment every 12 weeks and placebo [95% CI: 1.1–24.9]. Therefore there was no difference between ustekinumab administered every 8 or 12 weeks. At 44 weeks, **corticosteroid-free remission** was achieved in 29.8% of patients receiving placebo versus 44.7% of patients receiving ustekinumab [RR: 1.50; 95% CI: 1.12–2.02]. The pooled RR of any AEs was not significantly different between patients who were given placebo and those administered ustekinumab [15.0% vs 11.0%; RR: 0.73; 95% CI: 0.43–1.25].

There are limited data on **endoscopic remission**, as this was assessed in a subgroup analysis of 70 patients [46 receiving ustekinumab vs 24 receiving placebo] at 44 weeks. There was no statistically significant difference in **endoscopic remission** between patients in the placebo group as compared with patients in the treatment arm [RR: 2.61; 95% CI: 0.32–21.08].

There were no deaths during the 44 weeks of maintenance. Common AEs were headache, nausea, and arthralgia, with no significant difference in occurrence between the ustekinumab and placebo groups. There was an identical occurrence of non-melanoma skin cancers in the maintenance groups [$n = 4$ patients in placebo and ustekinumab groups]. Longer-term data beyond 52 weeks are required to correctly evaluate the safety profile.

There are no randomised head-to-head trials comparing vedolizumab or ustekinumab with anti-TNF agents for the maintenance of **clinical remission** in patients with moderate-to-severe CD who have achieved response or remission with the same agent. A network meta-analysis¹⁰⁶ included nine RCTs [all trials used the CDAI to define **clinical remission**] with varying follow-up times. The certolizumab pegol trial had a follow-up time of only 26 weeks. All comparisons were indirect [through the placebo, the ‘common comparator’]. Therefore, the quality of evidence was very low. No specific agent was safer than the others in the maintenance phase. Based on efficacy data, there is no evidence to support switching to vedolizumab or ustekinumab in patients who responded to induction treatment with any anti-TNF, or vice versa. There is a clear need to identify biomarkers that could guide therapeutic choices, and to conduct appropriately sized head-to-head trials that could allow for the identification of patient subgroups who would benefit from a given biologic over the other.

Maintenance strategies

Recommendation 2.8. ECCO CD Treatment GL [2019]

In Crohn's disease patients in clinical remission under anti-TNF treatment, there is currently insufficient evidence to recommend for or against the use of proactive therapeutic drug monitoring to improve clinical outcomes as compared to routine care [weak recommendation, moderate-quality evidence].

Data from two RCTs with a total of 395 patients with CD were used to support this recommendation [Supplementary Material, SoF

Table 21, available as Supplementary data at ECCO-JCC online]. These two RCTs showed no advantage of therapeutic drug monitoring [TDM] over clinically based anti-TNF dosing for any of our critical outcomes, namely **clinical remission** [one study; 62.6% vs 54.9%; RR: 1.14; 95% CI: 0.89–1.47], **steroid-free clinical remission** [one study; 30.5% vs 40.0%; RR: 0.76; 95% CI: 0.46–1.26], **endoscopic remission** [one study; 51.2% vs 52.5%; RR: 0.98; 95% CI: 0.68–1.40], **biochemical remission** [one study; 62.6% vs 54.9%; RR: 1.14; 95% CI: 0.89–1.47], or **serious AEs** [one study; 34.1% vs 27.5%; RR: 1.24; 95% CI: 0.68–2.23].^{107,108}

In the TAXIT trial, a total of 273 IBD patients with stable response to maintenance infliximab therapy were randomised either to concentration- or clinically-based infliximab dosing. Both groups were dose-optimised or dose-reduced to achieve a baseline trough level between 3 and 7 µg/mL. This dose-optimisation phase of the study showed that in patients in clinical remission, a trough level <3 µg/mL or >7 µg/mL was observed in 29% and 27% of patients, respectively. No differences in **clinical** or **biochemical remission** at 1 year were observed between clinically- [66%] and proactive TDM- [69%] based groups.¹⁰⁷ Nevertheless, the group who received proactive monitoring had fewer relapses during follow-up [7% vs 17%; $p = 0.018$].

In the TAILORIX trial, 122 biologically naïve patients with CD, treated with an induction combination therapy with infliximab and immunosuppressant, were randomised after 14 weeks to the following three groups: dose intensification based on clinical features, biomarkers, and trough levels of infliximab, with optimisation steps of 2.5 mg/kg [TDM1]; or of 5 mg/kg [TDM2]; or dose intensification based on clinical features alone [control group].¹⁰⁸ The infliximab dose was adapted to maintain a trough level >3 µg/mL. There was no difference in sustained **steroid-free clinical remission** with **mucosal healing** [CDAI <150 from Weeks 22 to 54] in the three randomisation arms [33% in TDM1; 27% in TDM2; 40% in control; $p = 0.50$].

Both studies have important limitations in their study designs,^{107,108} which collectively have lowered the strength of our recommendation. The outcomes in both studies were **clinical remission** but other important issues, such as costs and immunogenicity, also need to be considered. The prospective cohort study PANTS [Personalised Anti-TNF Therapy in Crohn's Disease Study] showed that anti-TNF failure is highly dependent on low drug concentrations and immunogenicity, and that dose intensification, especially during the induction period, may improve outcomes and treatment success.⁸⁹ Therefore, the Consensus believes that large, well-powered prospective RCTs with adequate stratification of patients are still required.

Recommendation 2.9. ECCO CD Treatment GL [2019]

In Crohn's disease patients who have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of reactive therapeutic drug monitoring to improve clinical outcomes [weak recommendation, low-quality evidence].

Reactive TDM refers to the practice of measuring anti-TNF trough level drug concentration and/or antidrug antibodies [ADA] in patients on anti-TNF therapy with active disease, to elucidate the mechanism of loss of response [LOR] and to guide clinical decision making. Reactive TDM was compared with empirical IFX

optimisation [based on clinical judgment alone] in only one randomised, controlled, single-blind, multicentre study in a cohort of 69 patients with CD with secondary IFX failure.¹⁰⁹ Patients were randomised to IFX dose intensification [5 mg/kg every 4 weeks; $n = 36$] or interventions based on serum IFX and IFX ADA levels using the proposed algorithm [$n = 33$]. There was no difference in regaining **clinical response** between the TDM-based group [19/33, 57.6%] and the symptom-based group [19/36, 52.8%] [RR: 1.09; 95% CI: 0.71–1.67; $p = 0.81$] [Supplementary Material, SoF Table 22, available as Supplementary data at ECCO-JCC online].

However, numerous studies have shown a positive association between adequate drug concentration and various clinical outcomes from **clinical response** to **mucosal healing**. Based on these observational data, recent clinical practice guidelines and a group of 25 international experts supported the use of reactive TDM, despite recognising the very low quality of evidence.^{110,111} Supporting evidence comes from case-control observational studies.^{112,113} In a retrospective study of 312 patients with endoscopically active IBD treated with IFX who underwent dose escalation, TDM-based [$n = 149$] and clinical decision-based [$n = 163$] cohorts were compared for **endoscopic remission** and CRP at a median of 6 months after adjustment. Post-adjustment, **endoscopic remission** was observed in 63% of patients in the TDM cohort as compared with 48% in the non-TDM cohort [$p = 0.05$]; **clinical response** was observed in 69% versus 57% [$p = 0.01$], and there were fewer hospitalisations in the TDM group [22% TDM vs 35% non-TDM; $p = 0.025$].¹¹² In another study, a modified version of the Steenholdt optimisation algorithm,¹¹³ using a cut-off of 3 µg/ml, was applied to a prospective cohort. **Clinical response** at 12 weeks was compared between this group and a retrospective control group in which dosing decisions were made independently of TDM results. There was no significant difference in clinical outcomes,¹¹³ but the TDM approach was significantly more cost-effective [$>10\%$ decrease in costs]. Therefore, the existing limited evidence does not support an association between a reactive TDM strategy and superior clinical outcomes but does suggest a cost savings benefit even after considering biosimilar use.¹¹⁴

Recommendation 2.10. ECCO CD Treatment GL [2019]

We suggest continuation of thiopurines in Crohn's disease patients in long-term remission on thiopurine maintenance therapy, as the risk of relapse is higher when the treatment is discontinued [weak recommendation, low-quality evidence].

We conducted our own meta-analysis to compare the two strategies [i.e., cessation vs continuation of treatment] in 215 CD patients in long-term **remission** on thiopurine maintenance therapy [Supplementary Material, SoF Table 23, available as Supplementary data at ECCO-JCC online]. Data from four trials were included.^{96,97,115–117} Patients included received AZA from 6 to 42 months before being randomised to continue or stop AZA¹¹⁵ or to continue AZA or placebo.^{96,97,116} All studies had a follow-up time of 12 to 18 months. Our results revealed that the RR of **clinical relapse** is 2.39 [95% CI: 1.38–4.13] [Supplementary Figure 22, available as Supplementary data at ECCO-JCC online]. Our meta-analysis effect estimate for **serious AEs** was RR 0.32 [95% CI: 0.04–2.92]. Although the data showed a trend towards fewer **serious AEs** occurring with discontinuation of treatment, the results were not statistically significant [Supplementary Figure 23, available as Supplementary data at

ECCO-JCC online]. However, regular assessment for the long-term risks/benefits should be performed considering the long-term safety data from the population base. To summarise, the evidence for the **prevention of clinical relapse** is in favour of continuation of treatment, as significantly more relapses occurred when the treatment was discontinued; the risk of SAEs was not different between AZA and placebo/no treatment. Data from studies that compared patients receiving AZA versus placebo/no treatment for more than 18 months are lacking, and this represents an important research gap. Data from observational population studies suggest caution and regular monitoring, especially for the risk of non-melanoma skin cancer and lymphoma in patients exposed to long-term treatment with thiopurines.²⁰ The limited follow-up time and the number of patients included in the studies of the meta-analysis are unable to capture AEs and **serious AEs** that may occur in the long term.

We also reviewed the literature to compare the approach of using long-term, low-dose thiopurines versus drug discontinuation. After an exhaustive literature search, we did not find evidence comparing the two treatment strategies. Only one trial was identified where dose reduction of thiopurines was compared with discontinuing thiopurines in the setting of combination therapy in patients with IBD. The information was incomplete as it was not possible to separate data from ulcerative colitis and CD patients.¹¹⁸ Therefore, no specific recommendation was made.

Recommendation 2.11. ECCO CD Treatment GL [2019]

In patients with Crohn's disease who have achieved long-term remission with the combination of infliximab and immunosuppressants, we suggest monotherapy with infliximab [weak recommendation, very low-quality evidence].

A Cochrane review¹¹⁷ based on two RCTs^{118,119} revealed the same relapse rate among patients who continued combination therapy with AZA [27/56; 48%] or infliximab monotherapy [27/55; 49%] [RR: 1.02; 95% CI: 0.68–1.52] [Supplementary Material, SoF Table 24, available as Supplementary data at ECCO-JCC online]. The same meta-analysis¹¹⁷ analysed the rates of AEs for infliximab versus combination therapy [RR:1.11; 95% CI: 0.44–2.81; very low-quality evidence] or **serious AEs** [RR: 1.00; 95% CI: 0.21–4.66; very low-quality evidence]. These results are rather uncertain due to an unclear risk of bias. Common AEs in the combination therapy studies included infections, elevated liver values, arthralgia, and infusion reactions. For some infrequent AEs, longer follow-up studies [>12 months] are necessary to correctly evaluate the safety profile. A higher risk of lymphoma exists when anti-TNF agents are combined with conventional immunosuppression. However, the absolute rates remain very low [3.23; 95% CI 1.5–6.9] and were estimated as 1.9 per 10 000 patient-years in one meta-analysis consisting of almost 9000 patients included in the SEER database.¹²⁰

Recommendation 2.12. ECCO CD Treatment GL [2019]

In patients with Crohn's disease who have achieved long-term remission with the combination of adalimumab and immunosuppressants, we suggest monotherapy with adalimumab [weak recommendation, low-quality evidence].

On the basis of a meta-analysis of nine studies on adalimumab by Chalhoub *et al.*,¹²¹ the data included were re-analysed because the intervention and control groups had to be reversed to match the relevant PICO question. The result of this recalculation did not reveal any differences in maintenance of **clinical remission** [RR: 1.01; 95% CI: 0.91–1.13] between combination therapy and monotherapy [Supplementary Material, SoF Table 25 and Supplementary Figure 24, available as Supplementary data at ECCO-JCC online]. Whereas this meta-analysis was limited to 1 year of follow-up [Week 56] in the sensitivity analysis, studies with a longer follow-up [>52 weeks] showed similar results. There are no quality data available for **steroid-free clinical remission**. However in the ADHERE cohort, which is an open-label extension study that prospectively follows up the cohort of patients originally enrolled in the CHARM study on adalimumab,⁷¹ the rates of **steroid-free remission** were similar in patients with or without concomitant immunosuppression at baseline after 3 years of follow-up.¹²² The meta-analysis by Chalhoub *et al.*¹²¹ which was re-calculated did not show any differences in **serious AEs** between monotherapy with adalimumab and combination therapy [RR: 0.88; 95% CI: 0.62–1.26] [Supplementary Figure 25, available as Supplementary data at ECCO-JCC online].

Recommendation 2.13. ECCO CD Treatment GL [2019]

There is insufficient evidence to recommend either continuation or withdrawal of anti-TNF therapy in Crohn's disease patients after achieving long-term remission. Therefore, the decision to continue anti-TNF therapy should be individualised and potential consequences [risks and benefits] should always be discussed with the patient.

Currently, no randomised controlled study data regarding the withdrawal of anti-TNF therapy in CD patients with inactive disease are available.¹²³ This is true for anti-TNF therapy as monotherapy or when used in a combination therapy regimen. Several observational studies investigated disease course in CD patients following withdrawal of anti-TNF therapy. A prospective study followed 115 patients with CD on combination therapy for at least 1 year, who discontinued anti-TNF after being in steroid-free clinical remission for at least 6 months. The relapse rates at 12 and 24 months were $43.9\% \pm 5.0\%$ and $52.2\% \pm 5.2\%$, respectively.⁷⁰ A systematic review and meta-analysis included 23 observational cohort studies of 920 CD patients and found an overall relapse rate of 44% [95% CI: 36–51%; follow-up range: 6–125 months].¹²⁴ Furthermore, the relapse rate was 38% [95% CI: 13–63%; 126 patients] at 6 months after discontinuation, 40% [95% CI: 33–48%; 813 patients] at 12 months, and 49% [95% CI: 31–68%; 228 patients; range of follow-up 28–125 months] at >25 months. The meta-analysis included studies in children and patients with perianal disease.

Following the aforementioned meta-analysis, 10 observational cohort studies reported relapse rates in accordance with the findings of the meta-analysis.^{125–134} Two of these studies represent extensions of studies included in the meta-analysis.^{131,132} One study investigated the risk of relapse in patients treated with a combination of anti-TNF and an immunomodulator, who discontinued either of the two drugs.¹³⁴ The study found no difference in relapse rates with regards to the withdrawn drug; that is, 17/55 patients [30.9%] on biologic therapy withdrawal relapsed compared with 4/20 patients [20%] in which the immunomodulator was withdrawn [$p = 0.401$].

In conclusion, observational studies report that up to half of patients will experience a relapse within the following 12 months after withdrawal. However, in the absence of controlled studies, the evidence surrounding withdrawal of anti-TNF therapy in patients with long-term remission remains scarce and inconclusive. Hence, no recommendation regarding anti-TNF therapy can be made. The management decision therefore lies with the clinician, who should carefully consider the patient's profile, values, and preferences, and any resource implications.¹³⁵

Key Points for Clinical Practice

Immunosuppressants and biologic agents are the most effective therapies to maintain medically-induced **remission** in moderate-to-severe CD patients. Aminosalicylates and steroids are not recommended in this setting due to lack of efficacy and long-term risk of **serious AEs** [steroids]. For patients with mild disease, no data are available which suggest any specific treatment strategy; no therapy and tight monitoring may be considered in this patient population in the maintenance phase.

Our literature search and data analysis showed that immunosuppressants, such as thiopurines and MTX, are recommended to maintain **remission** in steroid-dependent patients. As discussed in the previous section, the role of adding MTX or thiopurines to steroids for the **induction of remission** is limited. However, after steroids are stopped, maintenance with thiopurines or MTX [administered parenterally] can be an appropriate strategy. The choice between the two drug classes depends on careful consideration of patient's individual characteristics and preferences, safety profile, and drug availability. There is low-quality evidence supporting the continuation of thiopurines for long-term **remission**, as studies that directly compared long-term treatment with AZA, versus no treatment or placebo, did not have follow-up times >18 months. Clinicians should balance the increased risk of relapse of thiopurine discontinuation with the increased risk of **AEs**. Many observational studies have now reported an increased risk of lymphoma and skin cancer for patients treated with thiopurines.^{136,137} Therefore, regular monitoring should be provided to patients continuing thiopurines in the long term. Given the increased risk of **AEs** due to thiopurines, monoclonal antibodies can also be considered in this particular group of patients.

For CD patients where medically-induced **remission** has been achieved by a biologic agent-based strategy, the use of the same agent is recommended to maintain **remission**. There is high-quality evidence in favour of this approach for anti-TNF agents, vedolizumab, and ustekinumab. There is no evidence to support switching to a different monoclonal antibody after treatment induction with a monoclonal antibody that was successful. Longer-term data beyond 52 weeks are required to correctly evaluate the **safety** profile of monoclonal antibodies, as the relatively small sample size and short follow-up of RCTs does not allow for detection of some **AEs**, particularly very rare **AEs**, which may appear in larger and longer observational studies.

The combination of an anti-TNF agent and thiopurines is effective and safe both for induction and for maintenance. The risk of lymphoma with infliximab and thiopurines remains very low, but should be considered¹⁹ and adequately addressed with the same screening and prevention and regular monitoring recommended for thiopurine therapy.¹⁹ Therefore, when remission is achieved with combination therapy with anti-TNF agents, maintenance with the same biologic agent in monotherapy can be suggested.

Routine strategies to monitor and optimise biologic therapy in CD by a TDM approach are not supported by the available controlled evidence, although we recognise the limitations. There is no clear clinical benefit in favour of a proactive or reactive TDM approach, from the current data. However, some recent data suggest that a reactive TDM approach can result in cost savings also in the era of biosimilars,¹¹⁴ potentially justifying the use of such an approach where TDM is available. TDM can at least be used to guide dose optimisation.

There is currently no evidence to give any recommendation regarding dose reduction of thiopurines during maintenance and there is no evidence on the benefits of withdrawing or continuing biologic agents in patients with stable long-term remission, due to the lack of controlled studies. As stated in our Consensus, the decision is left to the clinicians and should be individualised and discussed with the patient, carefully considering the risk of relapse, disease progression and development of complications, and the risks of potential side effects. The long-term management of patients in remission is therefore an important research gap.

Section 3 - Perianal Fistulising Disease

Therapeutic management of complex perianal fistulising disease

Recommendation 3.1. ECCO CD Treatment GL [2019]

We recommend infliximab for the induction and maintenance of remission in complex perianal fistulae in Crohn's disease [strong recommendation; low quality of evidence].

Infliximab was the first agent shown to be effective in an RCT for inducing closure of perianal fistulae and for maintaining this response over 1 year. Complete response [defined as the absence of any draining fistulae at two consecutive visits at least 4 weeks apart] was observed in 4/31 placebo patients [12.9%] versus 29/63 infliximab patients [46%] [RR: 3.57; 95% CI: 1.38–9.25¹³⁸] [Supplementary Material, SoF Table 26, available as Supplementary data at ECCO-JCC online]. Subsequently, the ACCENT II trial evaluated the efficacy of infliximab [5 mg/kg every 8 weeks] in a maintenance trial in 195 patients who had a response [defined as a reduction of 50% of draining fistulae in two visits at least 4 weeks apart] at Week 14 after open-label induction treatment with infliximab. A complete response was maintained until Week 54 in 19 of 99 placebo patients [19.2%] versus 33 of 96 infliximab patients [34.4%] [RR: 1.79; 95% CI: 1.10–2.92].¹³⁹ A meta-analysis of the existing data revealed that infliximab was found to be effective in inducing fistula healing [RR: 3.57; 95% CI: 1.38–9.25] and in maintaining clinical fistula healing [RR: 1.79; 95% CI: 1.10–2.92] with no significant risk of serious AEs as compared with placebo [RR: 1.31; 95% CI: 0.11–15.25] [Supplementary Figure 26, available as Supplementary data at ECCO-JCC online]. A combined evaluation of both RCTs for safety revealed a risk of serious AEs of 18.9% [33/175 patients] in placebo groups versus 11.9% [24/201] in infliximab patients. These data from RCTs have been confirmed in several uncontrolled studies.¹⁴⁰

In clinical practice, infliximab is often used in combination with immunosuppressants, antibiotics, and surgical treatment.^{141–144} Some retrospective data suggest that fistula healing is more likely in patients with higher infliximab trough levels, which suggests the need for personalised dosing in this setting.^{145,146}

Recommendation 3.2. ECCO CD Treatment GL [2019]

We suggest adalimumab may be used for induction and maintenance of remission in complex perianal fistulae in Crohn's disease [weak recommendation, very low-quality evidence].

Fistula healing in the subgroup of patients with enterocutaneous and/or perianal fistulae at baseline [$n = 117$] was a secondary endpoint of the CHARM double-blind, placebo-controlled, randomised trial.¹⁴⁷ A subsequent post-hoc analysis that focused specifically on the efficacy of adalimumab over time in this subgroup confirmed the superiority of adalimumab over placebo [RR: 2.57; 95% CI: 1.13–5.84] for fistula healing after 56 weeks¹⁴⁷ [Supplementary Material, SoF Table 27, available as Supplementary data at ECCO-JCC online]. Data from CHARM combined with data from the open-label extension study ADHERE showed that there was no significant increase in serious AEs for patients treated with adalimumab [RR: 1.21; 95% CI: 0.43–3.38].^{71,148} Evidence was also sought for maintenance of fistula healing beyond 56 weeks, resolution of perianal sepsis, stoma-free survival, and quality of life; however, data were insufficient. Although we strongly recommend infliximab as first-line biologic therapy in complex perianal CD [Recommendation 3.1], adalimumab may have a role in patients with previous infliximab failure due to immunogenicity [either primary non-responders or secondary loss-of-responders]. The open-label CHOICE trial indeed demonstrated that complete fistula healing [mainly perianal fistula] could be achieved in 39% of patients [34/88] who initiated adalimumab after infliximab failure.¹⁴⁹ This finding has also been reported in a limited case series.¹⁵⁰

Recommendation 3.3. ECCO CD Treatment GL [2019]

In patients with Crohn's disease and complex perianal fistula there is insufficient evidence regarding the effect of adding immunomodulators to anti-TNF on fistula healing [weak recommendation, very low-quality evidence].

We identified a single study⁷⁴ [a pooled analysis of individual data from the intervention arms only of studies] that compared anti-TNF versus placebo. Only a pooled effect estimate was provided [i.e., OR of complete fistula closure in those on immunomodulators vs those not on immunomodulators was 1.10; 95% CI: 0.68–1.78] without further information on numbers of patients by compared group. Therefore, event rates and absolute risk differences could not be calculated. Furthermore, a retrospective study revealed a hazard ratio of 2.58 [95% CI: 1.16–5.6] for fistula healing in favour of the intervention arm [combination infliximab and immunomodulator] in patients with CD naïve to immunosuppressive therapy.¹⁵¹ There is thus insufficient evidence to support a decision for or against the use of immunomodulators in this context. Further research is necessary to reduce uncertainty and may be warranted, considering the anticipated costs and side effects of combination therapy. In particular, we note the evidence in luminal CD, where addition of immunomodulators reduces immunogenicity of long-term anti-TNF therapy. We therefore recommend further research that should focus on the additional treatment effect of combination therapy and the impact on immunogenicity to anti-TNF agents.

Recommendation 3.4. ECCO CD Treatment GL [2019]

In patients with Crohn's disease and complex perianal fistula there is insufficient evidence to recommend the use of ustekinumab for fistula healing [weak recommendation, moderate-quality evidence].

No randomised trial has directly assessed the role of ustekinumab in fistula healing. A post-hoc analysis of 238 patients who entered the phase 2 CERTIFI and phase 3 UNITI 1/2 studies with fistulae at baseline has been reported¹⁵² [Supplementary Material, SoF Table 28, available as Supplementary data at ECCO-JCC online]. This study included only patients with perianal fistulae and did not differentiate between simple and complex fistulae. The analysis showed a measurable but statistically insignificant effect of ustekinumab for **induction of remission** [RR: 1.77; 95% CI:0.93–3.37] but no difference in comparison with placebo was found for **maintenance of remission**.¹⁵³ We also sought evidence for the effect of ustekinumab on longer-term maintenance of fistula remission, serious AEs, resolution of perianal sepsis, stoma-free survival, and quality of life; however, data were insufficient. Further research is therefore warranted to determine if ustekinumab is beneficial to patients with perianal fistulae.

Recommendation 3.5. ECCO CD Treatment GL [2019]

In patients with Crohn's disease and complex perianal fistula there is insufficient evidence to recommend the use of vedolizumab for fistula healing [weak recommendation, low-quality evidence].

A post-hoc analysis of 45 patients, who entered the GEMINI 2 study with complex perianal fistulae at baseline, demonstrated a trend in favour of vedolizumab compared with placebo for fistula healing [RR: 2.23; 95% CI: 0.57–8.72] although this result was not statistically significant^{153,154} [Supplementary Material, SoF Table 29, available as Supplementary data at ECCO-JCC online]. The interpretation of this study was limited by sparse data [only 13 patients met the endpoint across treatment arms] and specification of fistulae type [perianal in only 74% of patients]. Evidence was sought also for long-term maintenance of clinical **fistula healing**, **serious AEs**, **quality of life**, **resolution of perianal sepsis**, and **stoma-free survival**; however, data were insufficient. The only RCT [NCT02630966]¹⁵⁵ that compared two different induction schedules of vedolizumab [300 mg at Weeks 0, 2, 6, 10, and 14 vs 300 mg at Weeks 0, 2, 6, and 14] was prematurely stopped due to slow recruitment and therefore is inconclusive. However, significant differences were observed between the two study groups. The efficacy of vedolizumab for fistula healing remains an important research gap.

Recommendation 3.6. ECCO CD Treatment GL [2019]

We suggest against using antibiotics alone for fistula closure in patients with Crohn's disease and complex perianal fistulae [weak recommendation, low-quality evidence].

Antibiotics are widely used in the treatment of perianal CD, but most published studies are uncontrolled.¹⁴¹ To our knowledge, there is only one RCT that compared placebo with antibiotics in

perianal fistulae [Supplementary Material, SoF Table 30, available as Supplementary data at ECCO-JCC online]. **Remission** at Week 10 was observed in 1/8 [12.5%] placebo patients versus 3/17 [17.6%] patients treated with antibiotics [RR: 1.41; 95% CI: 0.17–11.54].¹⁵⁶ **Complete healing** was observed in 3/10 [30%] patients treated with ciprofloxacin and 0/8 patients treated with metronidazole. Uncontrolled data or data from studies on combination therapy with anti-TNF suggest that ciprofloxacin can improve the efficacy of anti-TNF in the short term with good **safety**. However, this combination does not impact on longer-term healing rates.^{42,157} Despite the lack of evidence to support their role as monotherapy in closing perianal fistulae, antibiotics remain indicated and recommended to treat and control perianal sepsis.

Recommendation 3.7. ECCO CD Treatment GL [2019]

We suggest against using thiopurine monotherapy [azathioprine, mercaptopurine] for fistula closure in patients with Crohn's disease and complex perianal fistulae [weak recommendation, very low-quality evidence].

The effect of AZA on **fistula healing** in complex perianal CD has been numerically reported in RCTs in 18 patients only.^{49,52,53,158} A meta-analysis on this limited group of patients demonstrated that AZA is not superior to placebo for **fistula healing** [RR: 2.00; 95% CI: 0.67–5.93].⁹⁵ A fourth study⁵⁰ reported complete **fistula closure** in 9/29 [31%] fistulae during MP therapy, in contrast to 1/17 [6%] in placebo-treated fistulae [Supplementary Material, SoF Table 31, available as Supplementary data at ECCO-JCC online]. Nevertheless, these data could not be incorporated in the pooled analysis, as data were reported as number of **fistulae closing** rather than number of patients who had complete **fistulae closing**. With the availability of effective anti-TNF agents, the group felt that it would be inappropriate to recommend any further randomised, placebo-controlled, double-blind trial studying the efficacy of AZA in complex perianal fistulae.

Key Points for Clinical Practice

This section contains recommendations on the medical treatment of perianal disease. However, the management of complex perianal disease should be considered together with the concomitant treatment of luminal disease.

For the medical treatment of perianal fistulae, no evidence supports the use of monotherapy with antibiotics or thiopurines. The highest-quality evidence supports the use of infliximab as first choice. In patients refractory or intolerant to infliximab, there is low-quality evidence to support the use of adalimumab. The current evidence is too limited to support the use of ustekinumab and vedolizumab in clinical practice. However, ustekinumab or vedolizumab may be considered in patients where anti-TNFs are ineffective or contraindicated and there are no treatment options, especially when concomitant luminal disease is present. There is insufficient evidence on the use of combination therapy [specifically infliximab] combined with thiopurines. However, this can be considered when chosen as a therapy for concomitant luminal disease or for anti-immunogenicity purposes.

Although there is no randomised study that compared the combination of surgical treatment and infliximab with infliximab alone, joint management and approach by IBD clinicians and surgeons is

considered the standard of care for treatment of complex perianal disease. This is important, since control of sepsis and prevention of perianal infections is necessary before starting any treatment that affects the immune system response. Any immunosuppressive treatment must be stopped in case of onset of septic complications in patients with IBD.

5. Conclusion

These recommendations summarise the current evidence on the medical management of patients with CD. Several research gaps have been identified during the revision and analysis of data, which should be addressed by further research. Where evidence is lacking or is very weak and evidence-based recommendations cannot be given, ECCO provides alternative tools, such as Topical Reviews^{21,92,135,159–161} or Position Papers.¹⁶² We state that Guidelines aim to guide the clinicians' decisions with the best evidence available, but it is up to every clinician to adapt these Guidelines to local regulations and to the patient's individual characteristics and needs. ECCO will also aim to disseminate these guidelines by educational activities [i.e., educational platforms, ECCO Workshop, e-learning, and e-Guide] and to support any initiative to integrate ECCO Guidelines into clinical practice; the ECCO e-Guide will primarily serve as a resource to examine how the Guideline recommendations can be implemented into daily clinical practice and patient care pathways.¹⁶³ These guidelines will be regularly updated according to the Guideline Committee outline for the update of Guidelines in the future, using the GRADE approach and considering the most recent evidence emerging from clinical research in the field.

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Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of *JCC*, but are also open to public scrutiny on the ECCO website [<https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html>], providing a comprehensive overview of potential conflicts of interest of the authors.

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Author Contributions

JT, GF, MA, OZ coordinated the project; SB, TL, and MG-L advised on GRADE methodology, trained the working group members, and performed the analysis of data; GD, TK, JG, TR, AS, and JW coordinated the working groups; all the authors listed contributed to the identification of relevant data and data interpretation, and drafted and discussed the final recommendations; all the authors participated in the final Consensus; GF, JT, SB, GD, TK, JG, and TR drafted this manuscript; all authors, the ECCO Guideline Committee [GuiCom], and the ECCO Governing Board approved the final version of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

- Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;**389**:1741–55.
- Keyashian K, Dehghan M, Sceats L, et al. Comparative incidence of inflammatory bowel disease in different age groups in the United States. *Inflamm Bowel Dis* 2019;**25**:1983–1989.
- Jones GR, Lyons M, Plevris N, et al. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. *Gut* 2019;**68**:1953–60.
- Cosnes J, Cattán S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244–50.
- Kruis W, Katalinic A, Klugmann T, et al. Predictive factors for an uncomplicated long-term course of Crohn's disease: a retrospective analysis. *J Crohns Colitis* 2013;**7**:e263–70.
- Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut* 2017;**66**:2179–87.
- Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**:289–97.
- Gomollón F, Dignass A, Annese V, et al.; ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016. Part 1: diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3–25.
- Atkins D, Best D, Briss PA, et al.; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490.
- Gionchetti P, Dignass A, Danese S, et al.; ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016. Part 2: surgical management and special situations. *J Crohns Colitis* 2017;**11**:135–49.
- Nahon S, Lahmek P, Lesgourgues B, et al. Diagnostic delay in a French cohort of Crohn's disease patients. *J Crohns Colitis* 2014;**8**:964–9.
- Schoepfer AM, Dehlavi MA, Fournier N, et al.; IBD Cohort Study Group. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. *Am J Gastroenterol* 2013;**108**:1744–53; quiz 1754.
- Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010;**139**:1147–55.
- Vavricka SR, Spigaglia SM, Rogler G, et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:409–505.
- Khanna R, Bressler B, Levesque BG, et al.; REACT Study Investigators. Early combined immunosuppression for the management of Crohn's

- disease [REACT]: a cluster randomised controlled trial. *Lancet* 2015;386:1825–34.
16. Colombel JF, Panaccione R, Bossuyt P, *et al.* Effect of tight control management on Crohn's disease [CALM]: a multicentre, randomised, controlled phase 3 trial. *Lancet* 2018;390:2779–89.
 17. Maaser C, Sturm A, Vavricka SR, *et al.* ECCO-ESGAR Guideline for Diagnostic Assessment in IBD. Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;13:144–64.
 18. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al.* Selecting therapeutic targets in inflammatory bowel disease [STRIDE]: determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;110:1324–38.
 19. Annesse V, Beaugerie L, Egan L, *et al.*; ECCO. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;9:945–65.
 20. Rahier JF, Magro F, Abreu C, *et al.*; European Crohn's and Colitis Organisation [ECCO]. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014;8:443–68.
 21. Sigall-Boneh R, Levine A, Lomer M, *et al.* Research gaps in diet and nutrition in inflammatory bowel disease. a topical review by D-ECCO working group [Dietitians of ECCO]. *J Crohns Colitis* 2017;11:1407–19.
 22. Harbord M, Annesse V, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;10:239–54.
 23. Adamina M, Gerasimidis K, Sigall-Boneh R, *et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2019.
 24. Ford AC, Kane SV, Khan KJ, *et al.* Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:617–29.
 25. Rasmussen SN, Lauritsen K, Tage-Jensen U, *et al.* 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. *Scand J Gastroenterol* 1987;22:877–83.
 26. Singleton JW, Hanauer SB, Gitnick GL, *et al.* Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993;104:1293–301.
 27. Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine [5-ASA] preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994;19:278–82.
 28. Ferring Pharmaceuticals. PEACE study: a study with Pentasa in patients with active Crohn's disease. 2012. <https://clinicaltrials.gov/ct2/show/NCT00862121> Accessed Sep 16, 2019
 29. Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease Study [ECCDS]: results of drug treatment. *Gastroenterology* 1984;86:249–66.
 30. Summers RW, Switz DM, Sessions JT Jr, *et al.* National cooperative Crohn's disease study: results of drug treatment. *Gastroenterology* 1979;77:847–69.
 31. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosaliclates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2016;7:CD008870.
 32. Coward S, Kuenzig ME, Hazlewood G, *et al.* Comparative effectiveness of mesalamine, sulfasalazine, corticosteroids, and budesonide for the induction of remission in Crohn's disease: a Bayesian network meta-analysis: republished. *Inflamm Bowel Dis* 2017;23:E26–37.
 33. Moja L, Danese S, Fiorino G, Del Giovane C, Bonovas S. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine [mesalamine] for Crohn's disease. *Aliment Pharmacol Ther* 2015;41:1055–65.
 34. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004;2:379–88.
 35. Rezaie A, Kuenzig ME, Benchimol EI, *et al.* Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015;6:CD000296.
 36. Greenberg GR, Feagan BG, Martin F, *et al.* Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994;331:836–41.
 37. Tremaine WJ, Hanauer SB, Katz S, *et al.*; Budesonide CIR United States Study Group. Budesonide CIR capsules [once or twice daily divided-dose] in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002;97:1748–54.
 38. Suzuki Y, Motoya S, Takazoe M, *et al.* Efficacy and tolerability of oral budesonide in Japanese patients with active Crohn's disease: a multicentre, double-blind, randomized, parallel-group Phase II study. *J Crohns Colitis* 2013;7:239–47.
 39. Thomsen OO, Cortot A, Jewell D, *et al.* A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998;339:370–4.
 40. Tromm A, Bunganič I, Tomsová E, *et al.*; International Budenofalk Study Group. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011;140:425–34.e1; quiz e13–4.
 41. Yokoyama T, Ohta A, Motoya S, *et al.* Efficacy and safety of oral budesonide in patients with active Crohn's disease in Japan: a multicenter, double-blind, randomized, parallel-group phase 3 study. *Inflamm Intest Dis* 2018;2:154–62.
 42. Khan KJ, Ullman TA, Ford AC, *et al.* Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:661–73.
 43. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018;113:481–517.
 44. Selby W, Pavli P, Crotty B, *et al.*; Antibiotics in Crohn's Disease Study Group. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology* 2007;132:2313–9.
 45. Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008;2:CD006792.
 46. Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. *Gastroenterology* 1979;77:870–82.
 47. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;37:674–8.
 48. Ewe K, Press AG, Singe CC, *et al.* Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. *Gastroenterology* 1993;105:367–72.
 49. Klein M, Binder HJ, Mitchell M, Aaronson R, Spiro H. Treatment of Crohn's disease with azathioprine: a controlled evaluation. *Gastroenterology* 1974;66:916–22.
 50. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;302:981–7.
 51. Reinisch W, Panés J, Lémann M, *et al.* A multicenter, randomized, double-blind trial of everolimus versus azathioprine and placebo to maintain steroid-induced remission in patients with moderate-to-severe active Crohn's disease. *Am J Gastroenterol* 2008;103:2284–92.
 52. Rhodes J, Bainton D, Beck P, Campbell H. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;2:1273–6.
 53. Willoughby JM, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971;2:944–7.
 54. Oren R, Moshkowitz M, Odes S, *et al.* Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997;92:2203–9.
 55. Feagan BG, Rochon J, Fedorak RN, *et al.* Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;332:292–7.
 56. Oren R, Arber N, Odes S, *et al.* Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996;110:1416–21.

57. Oren R, Moshkowitz M, Odes S, et al. Erratum: methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial [*Am J Gastroenterol* 1997;92:2203–9]. *Am J Gastroenterol* 2015;110:608.
58. Oren R, Moshkowitz M, Odes S, et al. Corrigendum: methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 2015;110:608.
59. Maté-Jiménez J, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2000;12:1227–33.
60. Ardizzone S, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003;35:619–27.
61. van der Woude CJ, Ardizzone S, Bengtson MB, et al.; European Crohn's and Colitis Organization. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2015;9:107–24.
62. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2014;39:1349–62.
63. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthkrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther* 2017;45:1291–302.
64. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:644–59, quiz 60.
65. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;63:433–42; quiz 464.
66. Rutgeerts P, Van Assche G, Sandborn WJ, et al.; EXTEND Investigators. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;142:1102–11.e2.
67. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015;148:344–54.e5; quiz e14–5.
68. Colombel JF, Reinisch W, Mantzaris GJ, et al. Randomised clinical trial: deep remission in biologic and immunomodulator naive patients with Crohn's disease a SONIC post hoc analysis. *Aliment Pharmacol Ther* 2015;41:734–46.
69. Colombel JF, Sandborn WJ, Allez M, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014;12:423–31.e1.
70. Colombel JF, Sandborn WJ, Reinisch W, et al.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
71. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52–65.
72. Schreiber S, Reinisch W, Colombel JF, et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis* 2013;7:213–21.
73. Matsumoto T, Motoya S, Watanabe K, et al.; DIAMOND study group. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. *J Crohns Colitis* 2016;10:1259–66.
74. Jones JL, Kaplan GG, Peyrin-Biroulet L, et al. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2015;13:2233–40.e1–2; quiz e177–8.
75. European Medicine Agency. Stelara Ustekinumab. 2009. https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf Accessed Sep 16, 2019.
76. Sandborn WJ, Gasink C, Gao LL, et al.; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;367:1519–28.
77. MacDonald JK, Nguyen TM, Khanna R, Timmer A. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;11:CD007572.
78. Sandborn WJ, Feagan BG, Fedorak RN, et al.; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;135:1130–41.
79. Feagan BG, Sandborn WJ, Gasink C, et al.; UNIFI-IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;375:1946–60.
80. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology* 2018;155:1045–58.
81. Hanauer SB, Sandborn WJ, Feagan BG, et al. IM-UNITI: 3 year efficacy, safety, and immunogenicity of ustekinumab treatment of Crohn's disease. *J Crohns Colitis* 2020;14:23–32.
82. Sandborn WJ, Feagan BG, Rutgeerts P, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711–21.
83. European Medicine Agency. Entyvio Summary of Product Characteristics. 2014. https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf Accessed Sep 16, 2019.
84. Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol* 2008;6:1370–7.
85. Sands B, Feagan B, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;3:618–27.e3.
86. Kawalec P, Moćko P. An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients. *J Comp Eff Res* 2018;7:101–11.
87. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2003;4:CD000301.
88. Kalman RS, Hartshorn K, Farraye FA. Does a personal or family history of malignancy preclude the use of immunomodulators and biologics in IBD? *Inflamm Bowel Dis* 2015;21:428–35.
89. Kennedy NA, Heap GA, Green HD, et al.; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019;4:341–53.
90. Kirchgerner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;155:337–46.e10.
91. Lemaitre M, Kirchgerner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA* 2017;318:1679–86.
92. Sturm A, Maaser C, Mendall M, et al. European Crohn's and Colitis Organisation topical review on IBD in the elderly. *J Crohns Colitis* 2017;11:263–73.
93. Beaugerie L. Lymphoma: the bête noire of the long-term use of thiopurines in adult and elderly patients with inflammatory bowel disease. *Gastroenterology* 2013;145:927–30.
94. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;9:CD003715.

95. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015;10:CD000067.
96. Lémann M, Mary JY, Colombel JF, et al.; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;128:1812–8.
97. O'Donoghue DP, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978;2:955–7.
98. Panés J, López-Sanromán A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. *Gastroenterology* 2013;145:766–74.e1.
99. Rosenberg JL, Levin B, Wall AJ, Kirsner JB. A controlled trial of azathioprine in Crohn's disease. *Am J Dig Dis* 1975;20:721–6.
100. Cosnes J, Bourrier A, Laharie D, et al.; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif [GETAID]. Early administration of azathioprine vs conventional management of Crohn's Disease: a randomized controlled trial. *Gastroenterology* 2013;145:758–65.e2; quiz e14–5.
101. Hanauer SB, Feagan BG, Lichtenstein GR, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002;359:1541–9.
102. Sandborn WJ, Feagan BG, Stoinov S, et al.; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;357:228–38.
103. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;56:1232–9.
104. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al.; PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;357:239–50.
105. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011;2:CD008794.
106. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018;48:394–409.
107. Vande Castele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015;148:1320–9.e3.
108. D'Haens G, Vermeire S, Lambrecht G, et al.; GETAID. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology* 2018;154:1343–51.e1.
109. Steenholdt C, Brynskov J, Thomsen OØ, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;63:919–27.
110. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology* 2017;153:827–34.
111. Mitrev N, Leong RW. Therapeutic drug monitoring of anti-tumour necrosis factor- α agents in inflammatory bowel disease. *Expert Opin Drug Saf* 2017;16:303–17.
112. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic Drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. *Inflamm Bowel Dis* 2017;23:1202–9.
113. Guidi L, Pugliese D, Panici Tonucci T, et al. Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multi-centre study. *J Crohns Colitis* 2018.
114. Ricciuto A, Dhaliwal J, Walters TD, Griffiths AM, Church PC. Clinical outcomes with therapeutic drug monitoring in inflammatory bowel disease: a systematic review with meta-analysis. *J Crohns Colitis* 2018;12:1302–15.
115. Vilién M, Dahlerup JF, Munck LK, Nørregaard P, Grønbaek K, Fallingborg J. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. *Aliment Pharmacol Ther* 2004;19:1147–52.
116. Wenzl HH, Primas C, Novacek G, et al. Withdrawal of long-term maintenance treatment with azathioprine tends to increase relapse risk in patients with Crohn's disease. *Dig Dis Sci* 2015;60:1414–23.
117. Boyapati RK, Torres J, Palmela C, et al. Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease. *Cochrane Database Syst Rev* 2018;5:CD012540.
118. Roblin X, Boschetti G, Williet N, et al. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther* 2017;46:142–9.
119. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008;134:1861–8.
120. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;7:874–81.
121. Chalhoub JM, Rimmani HH, Gumaste VV, Sharara AI. Systematic review and meta-analysis: adalimumab monotherapy versus combination therapy with immunomodulators for induction and maintenance of remission and response in patients with Crohn's disease. *Inflamm Bowel Dis* 2017;23:1316–27.
122. Kamm MA, Hanauer SB, Rutgeerts P, et al. Results from an open-label extension of CHARM: Steroid-free remission in patients with Crohn's disease who received Adalimumab therapy for at least 3 years. *Gastroenterology* 2009;136:A653.
123. Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. *Gastroenterology* 2015;149:1716–30.
124. Gisbert JP, Marín AC, Chaparro M. The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2016;111:632–47.
125. Kennedy NA, Warner B, Johnston EL, et al.; UK Anti-TNF withdrawal study group. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. *Aliment Pharmacol Ther* 2016;43:910–23.
126. Casanova MJ, Chaparro M, García-Sánchez V, et al. Evolution after anti-TNF discontinuation in patients with inflammatory bowel disease: a multicenter long-term follow-up study. *Am J Gastroenterol* 2017;112:120–31.
127. Helwig U, Lutter F, Koppka N, Schreiber S. Proposal for an anti-tumour necrosis factor-exit strategy based on trough serum level. *J Crohns Colitis* 2016;10:S252–3.
128. Papamichael K, Rivals O, Billiet T, et al. Long-term outcome of IBD patients with primary non-response to anti-TNF therapy. *J Crohns Colitis* 2015;9:S864.
129. Hlavaty T, Krajcovicova A, Letkovsky J, et al. Relapse rates of inflammatory bowel disease patients in deep and clinical remission after discontinuing anti-tumor necrosis factor alpha therapy. *Bratislav Lek Listy* 2016;117:205–11.
130. Bortlik M, Duricova D, Machkova N, et al. Discontinuation of anti-tumor necrosis factor therapy in inflammatory bowel disease patients: a prospective observation. *Scand J Gastroenterol* 2016;51:196–202.
131. Molander P, Färkkilä M, Kempainen H, et al. Long-term outcome of inflammatory bowel disease patients with deep remission after discontinuation of TNF α -blocking agents. *Scand J Gastroenterol* 2017;52:284–90.
132. Reenaers C, Mary JY, Nachury M, et al.; Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif. Outcomes 7 years after

- infliximab withdrawal for patients with Crohn's disease in sustained remission. *Clin Gastroenterol Hepatol* 2018;16:234–43.e2.
133. Hu H, Xiang C, Qiu C, et al. Discontinuation of scheduled infliximab in Crohn's patients with clinical remission: a retrospective single-center study. *Gastroenterol Res* 2017;10:92–9.
 134. Ampuero J, Rojas-Feria M, Castro-Fernández M, Millán-Lorenzo M, Guerrero-Jiménez P, Romero-Gómez M. Remission maintained by monotherapy after biological + immunosuppressive combination for Crohn's disease in clinical practice. *J Gastroenterol Hepatol* 2016;31:112–8.
 135. Doherty G, Katsanos KH, Burisch J, et al. European Crohn's and Colitis Organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J Crohns Colitis* 2018;12:17–31.
 136. Beaugerie L, Brousse N, Bouvier AM, et al.; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617–25.
 137. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al.; Cesame Study Group. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011;141:1621–8.e1–5.
 138. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398–405.
 139. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;350:876–85.
 140. Bermejo F, Guerra I, Algaba A, López-Sanromán A. Pharmacological approach to the management of Crohn's disease patients with perianal disease. *Drugs* 2018;78:1–18.
 141. Panés J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. *Nat Rev Gastroenterol Hepatol* 2017;14:652–64.
 142. Kotze PG, Shen B, Lightner A, et al. Modern management of perianal fistulas in Crohn's disease: future directions. *Gut* 2018;67:1181–94.
 143. Steinhart AH, Panaccione R, Targownik L, et al. Clinical practice guideline for the medical management of perianal fistulizing Crohn's disease: the Toronto Consensus. *Inflamm Bowel Dis* 2019;25:1–13.
 144. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis* 2003;9:98–103.
 145. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017;45:933–40.
 146. Davidov Y, Ungar B, Bar-Yoseph H, et al. Association of induction infliximab levels with clinical response in perianal Crohn's disease. *J Crohns Colitis* 2017;11:549–55.
 147. Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut* 2009;58:940–8.
 148. Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther* 2013;38:1236–47.
 149. Lichtiger S, Binion DG, Wolf DC, et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Aliment Pharmacol Ther* 2010;32:1228–39.
 150. Echarri A, Castro J, Barreiro M, Carpio D, Pereira S, Lorenzo A. Evaluation of adalimumab therapy in multidisciplinary strategy for perianal Crohn's disease patients with infliximab failure. *J Crohns Colitis* 2010;4:654–60.
 151. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol* 2013;11:975–81.e1–4.
 152. Sands BE, Gasink C, Jacobstein D, et al. Fistula healing in pivotal studies of ustekinumab in Crohn's disease. *Gastroenterology* 2017;152:S185.
 153. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;16:1879–92.
 154. Feagan BG, Schwartz D, Danese S, et al. Efficacy of vedolizumab in fistulizing Crohn's disease: exploratory analyses of data from GEMINI 2. *J Crohns Colitis* 2018;12:621–6.
 155. National Library of Medicine [US]. Vedolizumab IV 300 mg in the Treatment of Fistulizing Crohn's Disease [ENTERPRISE]. 2015. <https://clinicaltrials.gov/ct2/show/study/NCT02630966> Accessed April 1, 2019.
 156. Thia KT, Mahadevan U, Feagan BG, et al. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009;15:17–24.
 157. Dewint P, Hansen BE, Verhey E, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial [ADAFI]. *Gut* 2014;63:292–9.
 158. Willoughby JM, Kumar P, Beckett J, Dawson AM. A double-blind trial of azathioprine in Crohn's disease. *Gut* 1971;12:864.
 159. Maaser C, Langholz E, Gordon H, et al. European Crohn's and Colitis Organisation topical review on environmental factors in IBD. *J Crohns Colitis* 2017;11:905–20.
 160. Rieder F, Latella G, Magro F, et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis* 2016;10:873–85.
 161. van Rheenen PF, Aloï M, Biron IA, et al. European Crohn's and Colitis Organisation topical review on transitional care in inflammatory bowel disease. *J Crohns Colitis* 2017;11:1032–8.
 162. Danese S, Fiorino G, Raine T, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease—an update. *J Crohns Colitis* 2017;11:26–34.
 163. European Crohn's Colitis Organisation ECCO e-Guide. 2013. <https://www.ecco-ibd.eu/publications/ecco-guidelines-science/ecco-e-guide.html> Accessed Oct 2, 2019.



ECCO Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment

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Abstract

This article is the second in a series of two publications relating to the European Crohn’s and Colitis Organisation [ECCO] evidence-based consensus on the management of Crohn’s disease. The first article covers medical management; the present article addresses surgical management, including preoperative aspects and drug management before surgery. It also provides technical advice for a variety of common clinical situations. Both articles together represent the evidence-based recommendations of the ECCO for Crohn’s disease and an update of previous guidelines.

Key Words: Crohn’s disease; surgery; inflammatory bowel disease [IBD]

1. Introduction

The incidence and prevalence of Crohn’s disease [CD] is rising globally, with yearly increases in incidence ranging from 4% to 15% over the past three decades.¹ A cure remains elusive, and efficient management of CD is essentially multidisciplinary and interprofessional. At least half of patients with CD undergo one or more surgical procedures during their lifetime. CD patients frequently suffer from malnutrition and psychological comorbidities, and may have to live with a stoma.^{2–5} Care for CD has become more complex for both medical and surgical disciplines. Several new drugs have entered the market, and surgical subspecialisation for inflammatory bowel disease has evolved. The best possible outcomes are currently achieved within dedicated expert centres providing personalised medicine.^{6–10} Care for CD is exemplary in an interrelated clinical world where the actions of individual health care providers need coordination, common knowledge, and shared expectations to optimise clinical management and research in terms of diagnosis, treatment, and side-effects. The European Crohn’s and Colitis Organisation [ECCO] provides an interdisciplinary framework with the present evidence-based Consensus Guidelines to inform and guide clinicians and allied health care providers caring for patients with CD. The present

Guidelines focus on surgery for CD, including preoperative aspects and drug management before surgery, and provide technical advice for a variety of common clinical presentations. Further guidance on most aspects of interdisciplinary and interprofessional care for CD has been elaborated by ECCO in separate publications.^{3,11–16}

2. Methods

A detailed description of the methodology used is presented in the Supplementary materials, available at *ECCO-JCC* online. This article is the second in a series of two publications relating to the ECCO evidence-based consensus on the management of CD. The first article [Torres J *et al.* ECCO guidelines on therapeutics in Crohn’s disease. *Journal of Crohn’s and Colitis* 2020; in press] covered medical management; the present article addresses surgical management. Both articles together represent the evidence-based recommendations of the ECCO for CD and they update previous Guidelines published in 2016.^{17,18} These Guidelines abide by the GRADE methodology in terms of framing clinically relevant questions to draw evidence-based statements and recommendations. However, due to the peculiarities of the surgical literature, appraisal of the systematically

researched literature was conducted according to the Oxford methodology (Oxford Centre for Evidence-Based Medicine: the Oxford 2011 Levels of Evidence 2—grading from evidence level [EL] 1: systematic review of randomised controlled trials to EL 5: expert opinion).¹⁹ This allowed us to formulate statements and practice recommendations that can be operationalised and can guide clinical management.

3. Surgery for perineal disease

Section 1. Complex perianal fistula

Medical therapy and surgical drainage

Statement 1.1. ECCO CD Treatment GL [2019]

No prospective study directly compares medical or surgical treatment of complex perianal Crohn's disease fistulae, either in isolation or in combination with both modalities. Observational studies support a combined medical/surgical approach to control sepsis and luminal activity [EL5].

No randomised controlled trials [RCT] or prospective studies were found which compared anti-tumour necrosis factor [TNF] treatment alone versus anti-TNF and surgery combined to treat complex perianal CD fistulae. A heterogeneous group of retrospective studies that compared anti-TNF treatment with a variety of surgical approaches was combined in a meta-analysis published in 2014.²⁰ The results of this analysis suggest that combined treatment 'may have additional beneficial effects compared to surgical or medical treatment alone'. However, the heterogeneity of the included studies, the retrospective nature of the included analysis, and low study quality preclude any firm conclusions or recommendations. Recently, results of the PISA study were presented as an abstract.²¹ PISA randomised patients with high perianal CD fistula and a single internal opening initially drained for 6 weeks to: chronic seton drainage; or anti-TNF for 1 year; or advancement plasty under anti-TNF for 4 months. Primary outcome was fistula-related re-intervention [surgery and/or re-initiation of anti-TNF]. This RCT was stopped after inclusion of 44 of 126 planned patients, based on futility analysis. Chronic seton drainage was associated with the highest re-intervention rate within 1.5 year [10/15 patients vs 6/15 anti-TNF patients and 3/14 advancement plasty + anti-TNF patients; $p = 0.02$]. No differences in quality of life and perianal disease activity index were observed. In a further prospective analysis of 50 patients, inferiority of chronic seton treatment could not be observed any more for any outcome. The authors concluded that chronic seton treatment should not be recommended as the sole or superior treatment for perianal CD fistula.

In practice, management decisions remain with the physician and surgeon, considering clinical information and any resource implications. The key role of surgery is in controlling perianal sepsis by examination under anaesthesia and appropriate seton drainage. In this regard, successful medical therapy and minimising the risk of anti-TNF therapy depend upon a close liaison between the physician and surgeon. According to the summary of product characteristics registered and approved by the regulatory agencies, active sepsis or any infection is a clear contraindication to the use of infliximab or adalimumab. Therefore, any procedure likely to treat and prevent

perianal sepsis is recommended as good clinical practice and must be performed swiftly in the presence of signs of infection.

Surgical techniques

Statement 1.2. ECCO CD Treatment GL [2019]

Advancement flaps are a therapeutic option for patients with Crohn's disease and complex perianal fistulae [EL4].

A systematic review identified 11 retrospective studies that reported data from 135 patients with CD perianal fistulae treated with an advancement flap.²² The pooled success rate was 66%. However, definitions of success and length of follow-up were highly variable, the results were heterogeneous, and the overall evidence level was low. In a more recent meta-analysis, Stellingwerf *et al.* observed a 61% success rate in 35 patients with CD perianal fistula, which did not differ significantly from the success rate of a ligation of the intersphincteric fistula tract [LIFT] procedure [53%]. However, incontinence rates were significantly higher after flaps [7.8% versus 1.6%].²³

As an RCT comparing advancement flap to no surgery would be unethical, collaborative efforts to collect larger numbers of cases undergoing advancement flap for perianal CD, with defined outcomes and follow-up, are required to better define the role of this technique in CD.

Statement 1.3. ECCO CD Treatment GL [2019]

Fibrin glue may be a potential treatment, with limited efficacy, for patients with complex perianal Crohn's disease [EL4].

The use of fibrin glue for the treatment of CD perianal fistulae was assessed in an open-label RCT with 71 patients randomised to instillation of fibrin glue into the fistula tract or no further treatment after removal of seton.²⁴ Overall clinical remission rates at Week 8 were 38% for fibrin glue and 16% in the observation group [$p = 0.04$]. There was no significant difference in adverse events, which were non-significantly higher in the observation group. Follow-up length in this RCT was insufficient for a definitive judgement on the true success rate. Several cohort studies with small numbers of CD patients reported a wide range of success rates with fibrin glue treatment. A uniform characteristic of all these studies is the relatively good safety profile of this technique, with no reported injury to the sphincter muscles, which may potentially justify attempting this technique in cognisant patients.²⁵

Statement 1.4. ECCO CD Treatment GL [2019]

Ligation of the intersphincteric fistula tract is an option for treatment of patients with Crohn's disease and complex perianal fistulae [EL4].

LIFT is a recent option in the armamentarium of surgical treatments for perianal fistulae. Sirany *et al.* performed a systematic literature

review and identified 26 studies that included a total of 713 patients, of whom 13 had CD.²⁶ Among these studies was a single RCT [which however excluded CD patients] and 25 cohort or case series. Studies were heterogeneous, with a wide range of outcome measures and follow-up times. The techniques used were only partially described and included seven technical variations. Primary healing rates ranged from 47% to 95%; thus even the lower end of this range appears promising when compared with other therapeutic options. Very few and minor complications were associated with classic LIFT or any of its variations [three complications were reported in six studies]. Göttgens *et al.* recently reported a retrospective cohort series of 46 patients mainly operated on for high trans-sphincteric fistulae [87%], excluding CD patients.²⁷ The primary healing rate was disappointingly low [37%] and the median time to failure was 4.2 months. Moreover, 20% had new, mildly impaired faecal continence postoperatively. Conversely, a prospective study by Gingold *et al.* on 15 CD patients with complex perianal fistulae treated with LIFT revealed a 67% healing rate at 12 months and a significant improvement of faecal continence.²⁸ Overall, due to the paucity of data, the role of LIFT for the treatment of perianal CD fistulae remains unclear, although the complication rate seems to be reasonably low. RCTs are needed to clarify the role of LIFT in CD fistulae, perhaps by comparing LIFT with advancement flap as a control arm.

Statement 1.5. ECCO CD Treatment GL [2019]

Anal fistula plugs [AFP] should not be routinely considered for ano-perineal fistula closure in Crohn's disease, as seton removal alone is equally effective [EL3].

The use of collagen anal fistula plugs [AFP] in patients with CD perianal fistulae was assessed in a single RCT, which compared seton removal and insertion of AFP into the fistula tract with seton removal and observation only, in 106 CD patients.²⁹ After 12 weeks, the fistula closure rate in the AFP group was 33.3% in patients with complex fistulae and 30.7% in patients with simple fistulae, as compared with 15.4% and 25.6% with seton removal alone, respectively. These differences were not statistically significant, perhaps because of an underpowered trial design. Importantly, there was a trend towards more adverse events at 12 weeks in the AFP group [17% vs 8%; $p = 0.07$]. However, cumulative adverse event rates at 12 months follow-up were similar.

A systematic review of 12 observational studies included 84 patients with a median follow-up time of 9 [3–24] months.³⁰ The overall fistula closure rate was 58.3%, with 40% success in the very small subgroup with a recurrent anal fistula after previous treatments. However, there was no uniform definition for fistula closure or follow-up regimen. The quality of evidence for this systematic review was rated low due to the risk of bias and imprecision.

In the three largest studies that included both CD fistulae and non-CD fistulae,^{31–33} the overall healing rate for CD fistulae was 47.0% versus 72.2% for non-CD fistulae. Repeating the plug procedure produced a lower success rate. Finally, an RCT that excluded CD compared 48 patients treated with a plug versus 46 patients treated with an advancement flap. Quality of life and anal pain improved in both groups, but the fistula closure rate at 1 year was significantly lower in the plug group than in the advancement flap group [34% vs 62%; $p = 0.006$].

The use of AFP in patients with CD appears to be relatively safe and may be considered for selected patients aware of the low success rate.

Statement 1.6. ECCO CD Treatment GL [2019]

Ano- and rectogenital fistulae related to Crohn's disease are very complex and rare; accordingly, they should be treated by an experienced multidisciplinary team [EL5].

There is limited scientific evidence on the treatment of CD-associated rectovaginal fistulae. A systematic review by Kaimakliotis identified 23 studies [including one RCT, six prospective studies, and 16 retrospective studies], with 137 CD-associated rectovaginal fistulae.³⁴ Of 23 reported studies, three studies included 43 rectovaginal fistulae, focused on combined medical and surgical treatment, and revealed a healing rate of 44.2%.

Hotouras *et al.* reviewed 17 studies, including 106 patients, on the use of gracilis muscle interposition for rectovaginal fistulae.³⁵ Most studies were retrospective and non-randomised, and only 34 patients with CD fistulae were included. At a median follow-up of 21 months, 50% of the CD fistulae undergoing gracilis muscle interposition had healed, as compared with 60–90% for non-CD rectovaginal fistulae.

The repair of rectovaginal fistulae of CD is challenging, and the selection of medical and/or surgical treatment should be considered on a case-by-case basis within an expert multidisciplinary team.

Stem cell therapy

Statement 1.7. ECCO CD Treatment GL [2019]

Allogeneic adipose-derived stem cell therapy could be an effective and safe treatment for complex perianal fistulae in patients with Crohn's disease [EL2].

The use of allogeneic adipose-derived stem cells in patients with perianal fistulae of CD was assessed in a pivotal phase 3 RCT [ADMIRE CD trial] including 212 patients.^{36,37} All patients underwent curettage of the fistula tract and closure of the internal opening and were randomised to injection of stem cells or placebo around the internal opening and alongside the fistula tracts. Patients with more than two internal and three external openings, patients with rectovaginal fistula, and those with anal and rectal stenosis or proctitis were excluded from the study. At 1 year, there was significantly higher combined remission (defined as closure of the external opening on physical examination and absence of abscess in magnetic resonance imaging [MRI]) in the stem-cell treated patients compared with placebo [56.3% vs 38.6%; $p = 0.010$].

A meta-analysis of 11 studies, including three RCTs of which the ADMIRE CD was the largest,³⁸ showed improved healing rates when compared with the control arms.

Allogeneic stem cell therapy seems to be safe. In the ADMIRE CD trial, serious adverse events did not significantly differ between the two groups, although the adverse event rate, mainly abscesses and fistulae, was slightly and not significantly higher in the treatment group compared with placebo [24.3% vs 20.6%]. There

are currently no long-term follow-up data available on safety and effectiveness.

The mode and technique of delivery of stem cells was not compared in any of the studies. Dozois *et al.* reported higher healing rates when stem cells were combined with fibrin glue or impregnated on a Gore Bio-A fistula plug versus direct injection [71% and 83%, respectively, vs 50%].³⁹ Allogeneic stem cell therapy may be an effective and safe approach to treat complex perianal fistula and patient selection, optimal mode of delivery, and dose and frequency of injections should be determined in further studies.

Statement 1.8. ECCO CD Treatment GL [2019]

Autologous adipose-derived stem cells may have positive effect for patients with Crohn's disease and complex perianal fistulae with good tolerability and safety [EL4].

Autologous adipose-derived stem cells [ASC] have the advantage of originating from the patient considered for treatment, as opposed to donor-based therapy. Yet, both autologous and allogenic stem cells require cost- and resource-intensive culture, expansion, and cryopreservation of the harvested ASC.⁴⁰

The best evidence on the use of ASC for perianal fistula of CD comes from an open-label, phase 2 study including 43 patients.⁴¹ Treatment included curettage, irrigation, and suturing of the internal opening. The fistula tract was filled with a mixture of ASCs and fibrin glue. ASCs were injected into the lesion site[s]. A second injection of ASCs was performed for patients who did not show complete closure of the fistula at 8 weeks. After 12 months, 88.5% of the patients showed sustained fistula healing. A second trial was performed in six hospitals and included 24 patients, also allowing repeat ASC treatment when fistula closure was incomplete at Week 12. At 6 months of follow-up, 56.3% achieved complete clinical and MRI-confirmed healing of the treated fistula.⁴² A further phase 1 study included 12 patients and applied ASC in a bioabsorbable matrix [fistula plug] placed into the fistula, obtaining clinical and MRI-confirmed healing at 6 months in 10 of 12 patients [83%].⁴³ In contrast to allogeneic stem cells, the use of autologous stem cells requires cell harvesting that entails an additional procedure [liposuction]. Overall, the procedures appeared safe, and the most common AEs were postoperative pain and anal bleeding. There are no studies comparing autologous and allogeneic stem cells for CD perianal fistula.

Last, a recent prospective study investigated the effects of injecting freshly collected autologous adipose tissue into perianal CD fistulas. A total of 21 patients were treated with repeat injections offered when no healing was observed at 6 weeks, or later relapse occurred. Six months following the last adipose tissue injection, 12/21 patients [57%] had complete fistula healing confirmed by MRI, and AE were minimal.⁴⁴ Harvesting, preparation, and administration of adipose tissue were performed as a single and inexpensive procedure. Further studies are required to define the true potential of this approach.

Key points for clinical practice

Complex perineal disease remains a challenging CD presentation. Innovative approaches, such as LIFT and stem cell-based treatment, have enriched the therapeutic armamentarium. However, such novel approaches have yet to demonstrate effectiveness and consistent results in a properly designed RCT with an adequate follow-up time [more than 1 year] and consistent imaging [MRI].

Section 2. Refractory pelvic sepsis

Statement 2.1. ECCO CD Treatment GL [2019]

Pelvic sepsis and symptoms from complex perineal Crohn's disease refractory to medical or surgical interventions can be controlled by a diverting stoma. However, the fistula healing rate and stoma closure rate are limited [EL4].

The quality of evidence for the use of defunctioning stoma in perianal CD is low, and no RCTs have compared defunctioning stoma with other surgical or medical interventions. There are several small and heterogeneous case series⁴⁵⁻⁴⁷ with variable stoma types and definitions of success. A meta-analysis of 16 cohort series including 556 patients reported a clinical response in 63.8% of patients.⁴⁸ Clinical response was similar in the pre-biologic era and in the biologic era, respectively, and in patients failing biologics as in those not receiving biologics.^{48,49} Restoration of bowel continuity was attempted in 34.5% of patients but was successful in only 16.6%. Absence of rectal involvement was consistently associated with restoration of continuity. Moreover, a quarter of the reversed patients required re-diversion [without proctectomy] because of severe recurrence. Ultimately, 41.6% of patients failed temporary diversion and required proctectomy. Similar results were reported in a later single-centre report of 77 patients, of whom 57 were concomitantly treated with biologics. Here, successful restoration of continuity was somewhat higher [27%] and reached 48% in the absence of ongoing perineal disease.

Quality of life was not discussed in any of the studies. Despite the low evidence and the low rate of fistula healing, diverting stoma may offer an alternative to extensive resection or proctocolectomy and may allow time for acceptance of a permanent stoma.⁴⁶

Key points for clinical practice

The control of pelvic sepsis is multidisciplinary and draws from interventional radiology, infectious disease, gastroenterology, and surgery. Nutritional support is often key for optimal outcomes in this context, particularly if a stoma is created. Imaging [pelvic MRI or endosonography], swift seton drainage, antibiotics, intensified medical therapy, and specialist nursing care are the mainstay of treatment [Torres J. *et al.* ECCO guidelines on therapeutics in CD. *Journal of Crohn's and Colitis* 2020; in press]. In cases of poor sepsis control, a diverting stoma can provide relief and allow for clinical optimisation before undertaking pelvic surgery.

4. Surgical management of abdominal Crohn's disease

Section 3. Approach to intra-abdominal abscess

Statement 3.1. ECCO CD Treatment GL [2019]

Percutaneous image-guided drainage of well-defined accessible intra-abdominal abscesses is recommended as the primary approach [EL4].

The treatment of active CD complicated by intra-abdominal abscesses is challenging. Immunosuppression can be hazardous and antibiotic therapy may be insufficient for large abscesses. Furthermore, surgical drainage has an additional risk in the emergency setting/unfit patient, including the potential need for a stoma. Percutaneous drainage [PD] is advised as the primary treatment for well-defined unilocular abscesses when accessible by interventional radiology, and has reported successful drainage rates of 74–100%.⁵⁰ PD under ultrasonographic or computed tomographic guidance is a safe procedure with a low complication rate. When successful, PD may avoid subsequent emergency surgery in 14–85% of patients with CD-related intra-abdominal abscesses.^{50,51}

Statement 3.2. ECCO CD Treatment GL [2019]

Following successful image-guided drainage of an intra-abdominal abscess, medical management without surgery may be considered. A low threshold for surgery is recommended in the event that medical management is not successful [EL4].

There is a limited evidence on the optimal management of CD patients with intra-abdominal abscess who have undergone PD. In particular, the optimal timing of surgical intervention after abscess drainage is unknown. Up to 30% of patients may avoid surgery following successful PD.⁵² Identifying those who may be treated without further surgery is challenging and presently relies on clinical judgment rather than on evidence. Nevertheless, elective surgery should be considered after sepsis control/resolution by PD and antibiotic therapy, as abscess recurrence is up to 6.5 times greater following PD as stand-alone therapy than PD followed with surgical resection. Medically refractory disease, the presence of stenosis, or an enterocutaneous fistula—be it primary established or as a consequence of PD—increase the likelihood of surgery. Conversely, emergency surgery without preceding PD and sepsis control is associated with a higher rate of complications and stoma than with initial PD followed by surgery.⁵³ Successful PD can be considered as a bridge to elective surgery, allowing nutritional and medical optimisation and hence improved postoperative outcomes.^{3,54}

Key points for clinical practice

The control of intra-abdominal abscesses resembles the approach to pelvic sepsis with interventional radiology, infectious disease, gastroenterology, and surgery involved, together with nutritional support. Frequent monitoring and surgical consultation are critical. Fortunately, surgery can be deferred in most cases. Definitive non-surgical management may be successful but must be carefully balanced and discussed with the individual patient.

Section 4. Preoperative optimisation

Statement 4.1. ECCO CD Treatment GL [2019]

Preoperative nutritional assessment should be performed for all patients with Crohn's disease who need surgery. Nutritional optimisation prior to surgery, with enteral or parenteral nutrition, is recommended for those patients with nutritional deficiencies [EL3].

Nutritional deficiencies are common in CD patients who require surgery. Persistent or recurrent mucosal inflammation, enteric fistulae or strictures, chronic diarrhoea, and medication side effects impede nutritional status, which in turn is a major driver of medical and surgical outcomes.^{55,56} Although RCTs are lacking, IBD referral centres have long integrated nutritional support into multidisciplinary teams. Several observational studies have shown that preoperative optimisation in malnourished patients improves outcomes, including a meta-analysis of 1111 CD patients who received preoperative enteral or parenteral supplementation versus standard care.⁵⁷ Preoperative nutritional supplementation reduced postoperative complications (20% vs 61.3%, odds ratio [OR] 0.26, 95% confidence interval [CI] 0.07–0.99; $p < 0.001$). Enteral nutrition in particular led to markedly reduced postoperative morbidity [21.9% vs 73.2%, OR 0.09, 95% CI 0.06–0.13, $p < 0.01$] with a number needed to treat of two. Goal-driven parenteral nutrition should be considered whenever enteral nutrition is hampered. Perioperative dietary therapy, including systematic nutritional screening, correction of deficits, and optimal preparation for surgery have been covered by Adamina *et al.* in a recent ECCO topical review addressing the needs of IBD patients before and after surgery.³

ECCO Statement 4.2.

Preoperative corticosteroid use is associated with increased risk of postoperative complications [EL3]. Preoperative reduction of corticosteroid doses may reduce postoperative complications but should be monitored carefully to avoid increasing disease burden [EL4].

Treatment with 20 mg prednisolone daily, or equivalent, for >6 weeks is an acknowledged risk factor for surgical complications and hyperglycaemia, as reported in previous ECCO Guidelines.^{11,18} This has been extensively reported, although no large RCTs were dedicated to this issue. Two meta-analyses of prospective and retrospective cohort studies, including 1714 IBD patients⁵⁸ and 3807 CD patients,⁵⁹ reported up to a doubling of surgical site infections for patients on steroids. Cut-offs for increased surgical complications were observed between 10 mg and 40 mg prednisolone daily for more than 3–6 weeks, together with a uniform recommendation of tapering down steroids whenever possible before surgery. Conversely, thiopurines can be safely continued perioperatively.^{7,11,18,58–62} A staged procedure with a temporary stoma may be considered when high-dose steroids cannot be weaned [emergency surgery] and/or when other risk factors are present [e.g., sepsis, malnutrition, smoking]. Last, little evidence supports the common practice of steroid stress dose administration perioperatively for patients on long-term corticosteroids over plain continuation of the preoperative dose, converted to intravenous equivalents where necessary.⁶³ Two small RCTs [37 patients] and five cohort studies [462 patients] did not demonstrate any benefit of steroid stress dose administration.⁶⁴ Testing of the hypothalamic-pituitary-adrenal axis can be considered on an individual basis to assess adrenal suppression.⁶⁵

Statement 4.3. ECCO CD Treatment GL [2019]

Current evidence suggests that preoperative treatment with anti-TNF therapy [EL3], vedolizumab [EL4], or ustekinumab [EL4] does not increase the risk of postoperative complications in patients with CD having abdominal surgery. Cessation of these medications prior to surgery is not mandatory.

Anti-TNF therapy

The use of biologics in CD patients scheduled for surgery has been controversial. Concern was raised that by modulating the immune response, biologics may increase surgical site infections and morbidity. Some recent guidelines still caution against the use of anti-TNF therapy in this context; however, the safest period of omission remains unknown.¹¹ The most recent meta-analysis on this subject included 18 non-randomised controlled studies with 1407 patients who were receiving infliximab and 4589 who were not.⁶⁶ There were no differences in the occurrence of any complications between patients on infliximab or not: OR for major complications 1.41, 95% CI 0.85–2.34; OR for minor complications 1.14, 95% CI 0.81–1.61; OR for infectious complications 1.23, 95% CI 0.87–1.74; OR for non-infectious complications 1.06, 95% CI 0.88–1.28; OR for readmission 1.46, 95% CI 0.8–2.66. This was also true for reoperation and mortality considered alone or included into major complications. Finally results from the large prospective PUCCINI cohort study presented as an abstract at the 2019 Digestive Disease Week, which included 955 IBD patients, showed that exposure to anti-TNF therapy, including the measurement of drug levels, had no effect on the occurrence of any surgical site infection or anastomotic leak.

Vedolizumab

Early data, including a retrospective multicentre analysis comparing the postoperative outcomes of 146 patients receiving vedolizumab versus 289 patients on anti-TNF therapy, revealed a significantly increased rate of surgical site infections after abdominal surgery in patients on vedolizumab.⁶⁷ However the most recent meta-analysis, comparing 307 IBD patients treated with vedolizumab versus 490 patients on anti-TNF and 535 patients not exposed to preoperative biologic therapy, revealed no differences in postoperative infectious and overall complications between vedolizumab patients and patients without biologic therapy [OR 0.99, respectively 1.00]. A similar outcome was observed, when comparing patients on vedolizumab with those on anti-TNF therapy, for the occurrence of postoperative infectious and overall complications [OR 0.99, resp. 0.92].⁶⁸ Although larger, randomised studies including perioperative drug monitoring remain necessary, treatment with vedolizumab appears to be safe in the surgical context.

Ustekinumab

Two retrospective multicentre cohort studies compared CD patients exposed preoperatively to either ustekinumab [for 3–6 months] or to anti-TNF therapy [follow-up to 6 months postoperatively]. In univariate analysis, patients on ustekinumab were more likely to receive a stoma [70% vs 12.5%; $p < 0.001$], to be on combination therapy [25% vs 2.5%; $p = 0.01$],⁶⁹ and to be reoperated [16% vs 5%; $p = 0.01$].⁷⁰ Nevertheless, no increases in early or late postoperative complications were noted in multivariate analysis when comparing the surgical outcomes of those 60 patients on ustekinumab versus 209 patients receiving anti-TNF therapy.^{69,70} Again, studies of better design and larger patient numbers are required to confirm these results.

Statement 4.4. ECCO CD Treatment GL [2019]

Preoperative control of sepsis is recommended prior to abdominal surgery for Crohn's disease [EL4].

Surgery in the context of sepsis carries a high risk for postoperative complications, including anastomotic leaks and continued abdominal sepsis.⁵⁹ Preoperative control of sepsis with antibiotic therapy and PD of intra-abdominal abscess followed by elective surgery leads to lower rates of stoma creation, fewer complications, and shorter hospital length of stay when compared with emergency surgery and surgical drainage.^{53,59,71} Prolonged [>6 weeks] and high-dose [≥ 20 mg prednisolone equivalent] steroids use are associated with poorer control of preoperative sepsis.⁶²

Key points for clinical practice

Preoperative optimisation is a key element in successful management of complex situations and chronic disease. Many aspects of optimal perioperative care are generic and common to all abdominal procedures,⁷² although some aspects are particularly important in the context of CD [venous thromboembolism prophylaxis, nutrition, iron management, drug management, minimally invasive approaches, and bowel- and sphincter-sparing techniques].^{54,73} A good relationship across disciplines and professions is critical.

Section 5. Small-bowel obstruction

Statement 5.1. ECCO CD Treatment GL [2019]

Deferred surgery is the preferred option in adult patients with Crohn's disease presenting with acute small-bowel obstruction without bowel ischaemia or peritonitis [EL4].

Intestinal stenosis frequently occurs in the course of CD. Acute small-bowel obstruction typically presents with intractable nausea/vomiting, abdominal distension, and absence of gas or stool passage per anum. Conservative management is the preferred option in the absence of peritonitis, including bowel rest, gastric decompression, and intravenous fluid therapy. In the presence of active inflammatory disease, intravenous steroids should be considered^{11,17} [and Torres J. *et al.* ECCO guidelines on therapeutics in CD *Journal of Crohn's and Colitis* 2020; in press]. Primary conservative management allows optimisation of the nutritional and immunosuppression status before a potential elective surgery.³ Conversely, whenever clinical or radiological signs indicate an intestinal perforation, emergency surgery and resection of the diseased bowel loop are required. Early surgical consultation is strongly recommended to assess surgical indication and to jointly monitor the progress of a conservative approach. Episodes of [sub]acute small-bowel obstruction also tend to recur over time; hence surgical advice is important in the context of interdisciplinary care and discussion of treatment options.

Statement 5.2. ECCO CD Treatment GL [2019]

Endoscopic balloon dilatation or surgery are both suitable treatment options for patients with short [<5 cm] strictures of the terminal ileum in Crohn's disease. The choice of treatment depends on local expertise and patient preference [EL5].

Although symptomatic short strictures are frequent in CD patients, no RCT comparing surgery versus balloon dilatation has

been performed. The largest study investigating the benefits and risks of balloon dilatation is a pooled analysis published in 2017 by Bettenworth *et al.*, with 1493 patients who underwent a total of 3213 endoscopic balloon dilatations.⁷⁴ A total of 98.6% the strictures were ileal and 62% were anastomotic. The primary technical success rate [passage of the endoscope through the stricture] was 89.1% and was 80.8% for clinical efficacy [symptom-free at completion of follow-up]. Complications [perforation and/or bleeding] occurred in 2.8% of the procedures. Despite the high initial success rate, 73.5% of the patients underwent re-dilatation within 24 months and 42.9% required surgical resection.

Similar results were reported in a systematic review by Morar *et al.* who analysed 1089 patients and 2664 dilatations and reported a technical success rate of 90.6% and a clinical success rate of 70.2%. Complications occurred in 6.4% of the balloon dilatations. At 5 years of follow-up, 75% of the patients had undergone surgery.⁷⁵ There were no differences in outcomes when primary or anastomotic strictures were dilated. Recent observational studies revealed comparable results^{76-79, 76-79} Hence, balloon dilatation of both primary and anastomotic short CD strictures appears safe and effective in the short term. However, recurrence is the rule and the need for surgery is frequent in the following 5 years.

Statement 5.3. ECCO CD Treatment GL [2019]

Strictureplasty is a safe option to treat small-bowel strictures related to Crohn's disease. Strictureplasty may be preferable to resection of long segments of bowel, with potential reduction in surgical recurrence rates [EL3].

Strictureplasty is an established and safe surgical option for treating strictures related to CD and is an alternative to bowel resection.^{80,81} Strictureplasty is recommended whenever reasonable and technically feasible, particularly with multiple fibrotic strictures that would otherwise require more than a minimal bowel resection.^{11,82} A meta-analysis of 1112 patients who underwent 3259 strictureplasties [81% HeinekeMikulicz, 10% Finney, 5% side-to-side isoperistaltic] before the biologic era revealed a 5-year recurrence rate of 28%.⁸³ HeinekeMikulicz is the preferred technique for stenotic segments up to 6–8 cm, whereas Finney and side-to-side isoperistaltic techniques address longer or multiple strictures and require more expertise.⁸⁴ Surgical morbidity is in the range of 8–15% and is unrelated to stricture length.^{84,85} Favourable long-term results have been reported^{81,84,85} and suggest better results for strictureplasty compared with resection. A large Japanese series reviewed 526 patients, of whom 435 underwent only bowel resections and 91 had a total of 199 strictureplasties. At 10 years, the site-specific cumulative rate of reoperation was 18% at the anastomosis site versus 7% at the strictureplasty site [$p < 0.01$].⁸⁶

Key points for clinical practice

Whenever possible, elective surgery is preferable to an emergency procedure in acute small-bowel obstruction due to a CD stenosis. This can be achieved in most scenarios with primary conservative management, such as rehydration and nasogastric decompression. An interdisciplinary discussion of the treatment options, which

should also include the patient's views, should follow. When surgery becomes necessary, it is important to thoroughly assess the bowel, ideally preoperatively with MRI enterography. MRI enterography may reveal a distinction between inflammatory strictures [amenable to intensified medical therapy] and fibrotic strictures. Assessing the bowel during surgery can also be very useful in identifying strictures. To maximise bowel preservation, the IBD surgeon should be familiar with the different kinds of strictureplasties, including non-conventional strictureplasties. Nonetheless, strictureplasty of the colon is not recommended.¹¹

Section 6. Surgical techniques for abdominal CD

Statement 6.1. ECCO CD Treatment GL [2019]

Laparoscopic surgery should be offered as the first-line approach in surgery for Crohn's disease, dependent on appropriate expertise [EL2].

A meta-analysis and a Cochrane review of two RCTs^{87,88} showed no statistical difference in any outcomes between laparoscopic and open surgery for small-bowel CD. A more recent meta-analysis, which included RCTs and observational studies, revealed fewer complications and fewer incisional hernias in favour of the laparoscopic approach.⁸⁹ A further meta-analysis assessed laparoscopic resection for recurrent CD, confirming feasibility and safety in the presence of appropriate expertise.⁹⁰ Conversion to open surgery was 2.5 times more frequent in this context, although complications did not increase. Hence, patients benefit from a laparoscopic approach in surgery for primary and recurrent small-bowel CD, with fewer postoperative complications and fewer incisional hernias. In the absence of expertise to perform laparoscopic surgery, emergency operations should not be delayed.

Statement 6.2. ECCO CD Treatment GL [2019]

A temporary stoma should be considered if steroids cannot be withdrawn or significantly reduced prior to surgery [EL5].

The decision to create a stoma [primary anastomosis and protective stoma or no anastomosis and split stoma] in the context of steroid intake relies mostly on clinical grounds and experience. There are no data comparing strategies between primary anastomosis or secondary anastomosis, in CD patients treated with steroids. However, prolonged [>6 weeks] and high-dose [≥ 20 mg prednisolone equivalent] steroid use are associated with postoperative infectious complications, including anastomotic leakage.^{58,59,61,62}

Statement 6.3. ECCO CD Treatment GL [2019]

Primary anastomosis may safely be performed in the presence of anti-TNF therapy [EL3], vedolizumab [EL4], and ustekinumab [EL4], provided other risk factors have been accounted for.

As discussed earlier in these Guidelines, the effect of anti-TNF therapy on anastomosis healing has been largely studied, although large RCTs that definitively address this important issue are lacking. Overall, the administration of anti-TNF therapy does not seem to increase anastomotic risk. However, anti-TNF therapy cannot be isolated from its clinical context, either when facing an individual patient or in appraising the literature in which several biases confound the evaluation of the true effect of anti-TNF therapy [e.g., heterogeneity of inclusion criteria and clinical presentation/risk factors, duration and dose of anti-TNF therapy administered, combination therapy, absence of drug monitoring]. The same considerations apply to vedolizumab and ustekinumab, in which the challenges of data evaluation are further compounded by less clinical experience and lower patient numbers^{59,67,68,70,91-118, 59,67,68,70,91-118}

Statement 6.4. ECCO CD Treatment GL [2019]

Laparoscopic resection in patients with limited, non-stricturing, ileocaecal Crohn's disease [diseased terminal ileum <40 cm] is a reasonable alternative to infliximab therapy [EL2].

Previous ECCO Guidelines have declared [laparoscopic] resection as the preferred option in patients with localised ileocaecal CD with obstructive symptoms but no active inflammation.¹¹

For active non-stenotic disease, a recent randomised multicentre European trial compared 143 patients with active, non-stricturing disease involving <40 cm of the terminal ileum, in whom conventional therapy had failed, randomized to either infliximab or laparoscopic ileocaecal resection.¹¹⁹ There was no difference in the primary outcome of quality of life on the Inflammatory Bowel Disease Questionnaire at 12 months nor in general quality of life as measured by the Short Form-36 Health Survey. However, operated patients scored 3.1 points better [95% CI 4.2–6.0] in the physical subscale of this survey. Serious complications were not different between medical and surgical groups. Over a median follow-up of 4 years, 37% of the infliximab-treated patients required resection, whereas 26% of the primarily resected patients were put on infliximab. Hence, laparoscopic resection of both stricturing, fibrotic disease of the terminal ileum and of an actively diseased terminal ileum [<40 cm] can be offered as a sound therapeutic option in an interdisciplinary context, with a benefit and risk profile comparable to medical therapy.

Statement 6.5. ECCO CD Treatment GL [2019]

Stapled small-bowel or ileocolic side-to-side anastomoses are associated with lower rates of postoperative complications than end-to-end anastomoses, in Crohn's disease [EL3].

Technical aspects are important to surgeons and can be influenced by many factors, including previous training, personal experience, available resources, and clinical situation. The optimal choice of anastomosis technique in small-bowel and ileocolic resection has been controversial. In the past 10 years, evidence in favour of a side-to-side anastomosis has emerged and was confirmed over

time. The first large meta-analysis by Simillis *et al.* included 661 patients and revealed that the anastomotic leak rate was higher for an end-to-end anastomosis versus side-to-side anastomosis [OR 4.37; $p = 0.02$], including the subgroup of ileocolic anastomosis [OR 3.8; $p = 0.05$].¹²⁰ Overall postoperative complications [OR 2.64; $p < 0.001$] and length of hospital stay were accordingly higher [by 2.81 days; $p = 0.007$] when an end-to-end anastomosis was performed. A later meta-analysis by Guo *et al.* confirmed the superiority of a side-to-side anastomosis over other configurations in terms of overall postoperative complications [OR 0.6; $p = 0.01$]. However, there were no statistically significant differences for leak rate, endoscopic and symptomatic recurrence, and reoperation for recurrence.¹²¹ A further meta-analysis by He *et al.* compared 396 stapled side-to-side with 425 hand-sewn end-to-end anastomoses. Stapled side-to-side anastomoses were superior in all endpoints: overall postoperative complications [OR 0.54, 95% CI 0.32–0.93], anastomotic leak [OR 0.45, 95% CI 0.20–1.00], recurrence [OR 0.20, 95% CI 0.07–0.55], and reoperation for recurrence [OR 0.18, 95% CI 0.07–0.45].¹²² Finally, a network meta-analysis of 11 trials and 1113 patients confirmed the superiority of stapled side-to-side anastomosis in terms of overall complications, clinical recurrence, and reoperation for recurrence. Leak rate, surgical site infections, mortality, and length of stay were not affected by the choice of the anastomosis technique.¹²³ The quality of the studies included in all meta-analyses was low, with a minority of patients included in RCTs. The general conclusion favours stapled side-to-side anastomosis. The diameter of the anastomosis likely plays a role, with an assumption that a wider anastomosis will have a lower rate of clinical and surgical recurrences.

Statement 6.6. ECCO CD Treatment GL [2019]

Segmental colectomy is appropriate for patients with a single involved colonic segment in Crohn's disease [EL3].

When a single colonic segment is involved, a segmental colectomy is indicated. Multiple involved colon segments generally indicate a [sub]total colectomy as the preferred approach. A meta-analysis by Tekkis *et al.* compared between 223 subtotal/total colectomies with ileorectal anastomosis and 265 segmental colectomies for colonic CD.¹²⁴ Although the recurrence rates, complications, and need for a permanent stoma were not different, recurrence occurred 4.4 years later in the subtotal/total colectomy [$p < .001$]. A recent meta-analysis by Angriman *et al.* evaluated 1436 patients who received segmental colectomy [$n = 500$], subtotal colectomy [$n = 510$], or total proctocolectomy [$n = 426$].¹²⁵ Complications were more frequent after segmental colectomy than after subtotal colectomy [OR 2.84, 95% CI 1.16–6.96] and after proctocolectomy than after subtotal colectomy [OR 0.19, 95% CI 0.09–0.38]. Hence, subtotal colectomy appeared to be the safer procedure, although segmental colectomy resulted in fewer permanent stomas than subtotal colectomy [OR 0.52, 95% CI 0.35–0.77]. Regarding CD recurrence, subtotal colectomy showed higher CD recurrence [OR 3.53, 95% CI 2.45–5.10] and need for repeat surgery [OR 3.52, 95% CI 2.27–5.44] than total proctocolectomy, whereas no difference in recurrence was observed between segmental colectomy and subtotal colectomy. In the rare situation where two distinct colon segments are involved, two segmental resections can be considered instead of a subtotal colectomy,¹¹ particularly for the patient who has suffered

an extensive loss of small bowel. In summary, the extent of colonic resection is indicated by the clinical situation [elective vs emergency surgery] and the number of colonic segments involved. Segmental colectomy is preferred whenever possible.

Statement 6.7. ECCO CD Treatment GL [2019]

A defunctioning stoma for non-acute refractory Crohn's colitis may delay or avoid the need for colectomy [EL5].

The following two options may be discussed in the presence of refractory CD colitis: a [sub]total colectomy, particularly as a potentially life-saving procedure in fulminant colitis, and a defunctioning ileostomy to divert the faecal stream and allow for remission, together with intensified medical therapy.¹²⁶ A diverting ileostomy may delay further procedures, facilitate perioperative optimisation, and allow for a limited resection if required at a later stage [i.e., segmental colectomy]. The clinical scenario in which a diverting stoma is performed to aid the management of extensive perineal disease is covered elsewhere and is not the focus of the present statement.

The literature preceding the biologic era reports initial remission rates of up to 90%^{45,127–129} following creation of a defunctioning stoma, which is less than the 50–80% reported in more recent series.^{130,131} Lasting restoration of bowel continuity/stoma reversal was effective in up to two-thirds of the patients but was much less when perineal disease was also present [i.e. 29–42%].^{130,131} Surgical complications of defunctioning stoma creation were in the expected range of 3–10% for stoma prolapse/hernia and <5% renal failure due to high-output stoma.¹³⁰ Further bowel resection was reported in up to half of the patients in recent series.^{130,131} Risk factors for [procto]colectomy were severe refractory perineal disease, requirement for combined medical therapy, and a history of more than one biologic drug. For these patients, early colectomy and end ileostomy [as opposed to a defunctioning ileostomy] may be discussed.

Statement 6.8. ECCO CD Treatment GL [2019]

Restorative proctocolectomy with ileal pouch-anal anastomosis can be considered in selected patients with refractory pancolonic Crohn's disease without history of perianal disease, taking into account the high risk of pouch failure [EL4].

Several expert centres have reported their experience with restorative proctocolectomy and ileal pouch-anal anastomosis [IPAA] for refractory pancolonic CD. Previous ECCO Guidelines stressed the higher complication and failure rates of CD-IPAA, which should be restricted to highly motivated patients and to multidisciplinary teams, and only in the absence of small-bowel and perineal diseases.¹¹

Panis *et al.* compared 31 CD-IPAA patients, without small-bowel or perianal involvement, with 71 ulcerative colitis IPAA [UC-IPAA] patients. No differences in postoperative outcomes were reported, whereas the 5-year definitive end ileostomy rate was 10% in CD-IPAA versus 2% in UC-IPAA patients.¹³² At 10 years of follow-up, rates of CD-related complications were 35%, with 10% of the pouches excised.¹³³

Manilich *et al.*¹³⁴ and Fazio *et al.*¹³⁵ reported two large comparative series from the same institution for a total of 3754 consecutive patients, of whom 150 were CD-IPAA patients. Again, no differences in early complications [pelvic sepsis, anastomotic leaks] were observed. However, CD-IPAA patients had a higher pouch failure rate [13.3%] compared with ulcerative colitis and indeterminate colitis patients [5.1% and 4.8%, respectively]. At 10 years, 80% of CD-IPAA patients retained a functional pouch versus 95% in UC-IPAA and indeterminate colitis IPAA.

Reese *et al.*¹³⁶ performed a meta-analysis of 3103 patients, of whom 225 were CD-IPAA and suffered in comparison from twice as many anastomotic strictures and six times more pouch failures [32% vs 4.8%, $p < 0.01$]. However, in patients with isolated colonic CD, no significant difference in postoperative complications or pouch failure [8% in CD-IPAA patients vs 7.1% in UC-IPAA patients] was observed. Importantly, patients with isolated colonic CD did not have more complications or pouch failures than UC patients. Nevertheless, IPAA function was poorer in CD patients [two times more incontinence and urgency], although stool frequency did not differ. Similarly, no difference in quality-of-life scores were reported in the large Cleveland series, irrespective of the indication of IPAA.¹³⁵

5. Conclusion

There are many options and crossroads in decision making for surgery in CD. Some approaches have been tested over time and were described in these surgical guidelines.

Although sufficient training, technical expertise, and an adequate caseload to achieve and maintain subspecialisation in IBD surgery are important, the key to success in managing CD is a multidisciplinary team, as no specialist alone can solve the CD equation.

The present Guidelines have been written with this interdisciplinary spirit in mind and summarise the current knowledge at hand. The degree of certainty in some aspects of surgery for CD is closer to eminence than evidence, thus paving the way for further research and better answers. Revealing gaps in evidence is the first step to resolution, as research focused on clinical needs and gaps in the current evidence will inform guideline updates. Meanwhile, dynamic integration of gains in knowledge into the ECCO e-Guide will allow for rapid dissemination. Guidelines provide guidance to clinicians, who adapt expert knowledge and generic evidence to individualise care. It is hoped that the present work will contribute to optimising care for patients with CD.

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Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of JCC, but is also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of authors.

Author Contributions

MA, GF, JT, and OZ coordinated the project; SB, TL, and MG-L provided expert methodology advice, trained the working group members, and performed the analysis of data; GD, TK, JPG, TR, AS, and JW coordinated the working groups; all the authors listed contributed to the identification of relevant data, data interpretation, and drafted and discussed the final recommendations; all the authors participated in the final Consensus; MA and OZ drafted this manuscript; all authors, the ECCO Guideline Committee [GuiCom], and the ECCO Governing Board approved the final version of the manuscript.

Disclaimer

The ECCO Consensus Guidelines are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Consensus Guidelines. The ECCO and/or any of their staff members and/or any Consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines. This manuscript is a joint expert consensus activity. Hence all authors participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the concept, design, data interpretation, and writing of the manuscript.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

- Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769–78.
- Frolkis AD, Dykeman J, Negrón ME, *et al.* Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013;145:996–1006.
- Adamina M, Gerasimidis K, Sigall-Boneh R, *et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2019, Sep 24. doi: 10.1093/ecco-jcc/jjz160. [Epub ahead of print.]
- Bouguen G, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? *Gut* 2011;60:1178–81.
- Burke JP, Velupillai Y, O'Connell PR, Coffey JC. National trends in intestinal resection for Crohn's disease in the post-biologic era. *Int J Colorectal Dis* 2013;28:1401–6.
- Bemelman WA; S-ECCO Collaborators. Evolving role of IBD surgery. *J Crohns Colitis* 2018;12:1005–7.
- Lightner AL, Shen B. Perioperative use of immunosuppressive medications in patients with Crohn's disease in the new 'biological era'. *Gastroenterol Rep [Oxf]* 2017;5:165–77.
- Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos PL. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. *World J Gastroenterol* 2018;24:3567–82.
- Reinglas J, Restellini S, Gonczi L, *et al.* Harmonization of quality of care in an IBD center impacts disease outcomes: Importance of structure, process indicators and rapid access clinic. *Dig Liver Dis* 2019;51:340–5.
- Koltun WA. Better together: improved care of the IBD patient using the multi-disciplinary IBD center. *Expert Rev Gastroenterol Hepatol* 2017;11:491–3.
- Bemelman WA, Warusavitarne J, Sampietro GM, *et al.* ECCO-ESCP consensus on surgery for Crohn's disease. *J Crohns Colitis* 2018;12:1–16.
- Harbord M, Annese V, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation. The First European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;10:239–54.
- Kemp K, Dibley L, Chauhan U, *et al.* Second N-ECCO Consensus Statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis. *J Crohns Colitis* 2018;12:760–76.
- Maaser C, Sturm A, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;13:144–64.
- Sturm A, Maaser C, Calabrese E, *et al.*; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. *J Crohns Colitis* 2019;13:273–84.
- Sturm A, Maaser C, Mendall M, *et al.* European Crohn's and Colitis Organisation topical review on IBD in the elderly. *J Crohns Colitis* 2017;11:263–73.
- Gomollón F, Dignass A, Annese V, *et al.*; ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis* 2017;11:3–25.
- Gionchetti P, Dignass A, Danese S, *et al.*; ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. *J Crohns Colitis* 2017;11:135–49.
- Howick J, Chalmers I, Glasziou P *et al.* Explanation of the 2011 Oxford Centre For Evidence-Based Medicine [OCEBM] levels of evidence [background document]. 2011. <https://www.cebm.net/index.aspx?o=5653> Accessed November 09, 2019
- Yassin NA, Askari A, Warusavitarne J, *et al.* Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. *Aliment Pharmacol Ther* 2014;40:741–9.
- Wasmann K, de Groof EJ, Stellingwerf M, *et al.* Dop73 treatment of perianal fistulas in Crohn's disease, seton vs. anti-TNF vs. surgical closure following anti-TNF [PISA]: a randomised controlled trial. *J Crohns Colitis* 2019;13:S074.
- Rozalén V, Parés D, Sanchez E, *et al.* Advancement flap technique for anal fistula in patients with Crohn's disease: a systematic review of the literature. *Cir Esp* 2017;95:558–65.
- Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ. Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and Crohn's high perianal fistulas. *BJS Open* 2019;3:231–41.
- Grimaud JC, Munoz-Bongrand N, Siproudhis L, *et al.*; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif. Fibrin

- glue is effective healing perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2010;138:2275–81.
25. Fichera A, Zoccali M; Crohn's & Colitis Foundation of America, Inc. Guidelines for the surgical treatment of Crohn's perianal fistulas. *Inflamm Bowel Dis* 2015;21:753–8.
 26. Sirany AM, Nygaard RM, Morken JJ. The ligation of the intersphincteric fistula tract procedure for anal fistula: a mixed bag of results. *Dis Colon Rectum* 2015;58:604–12.
 27. Göttgens KWA, Wasowicz DK, Stijns J, Zimmerman D. Ligation of the intersphincteric fistula tract for high transsphincteric fistula yields moderate results at best: is the tide turning? *Dis Colon Rectum* 2019;62:1231–7.
 28. Gingold DS, Murrell ZA, Fleshner PR. A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with Crohn's disease. *Ann Surg* 2014;260:1057–61.
 29. Senéjoux A, Siproudhis L, Abramowitz L, et al.; Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif [GETAID]. Fistula plug in fistulising ano-perineal Crohn's disease: a randomised controlled trial. *J Crohns Colitis* 2016;10:141–8.
 30. Nasseri Y, Cassella L, Berns M, Zaghiyan K, Cohen J. The anal fistula plug in Crohn's disease patients with fistula-in-ano: a systematic review. *Colorectal Dis* 2016;18:351–6.
 31. Cintron JR, Abcarian H, Chaudhry V, et al. Treatment of fistula-in-ano using a porcine small intestinal submucosa anal fistula plug. *Tech Coloproctol* 2013;17:187–91.
 32. Ellis CN, Rostas JW, Greiner FG. Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas. *Dis Colon Rectum* 2010;53:798–802.
 33. Ky AJ, Sylla P, Steinhagen R, Steinhagen E, Khaïtov S, Ly EK. Collagen fistula plug for the treatment of anal fistulas. *Dis Colon Rectum* 2008;51:838–43.
 34. Kaimakliotis P, Simillis C, Harbord M, Kontovounisios C, Rasheed S, Tekkis PP. A systematic review assessing medical treatment for rectovaginal and enterovesical fistulae in Crohn's disease. *J Clin Gastroenterol* 2016;50:714–21.
 35. Hotouras A, Ribas Y, Zakeri S, Murphy J, Bhan C, Chan CL. Gracilis muscle interposition for rectovaginal and anovaginal fistula repair: a systematic literature review. *Colorectal Dis* 2015;17:104–10.
 36. Panés J, García-Olmo D, Van Assche G, et al.; ADMIRE CD Study Group Collaborators. Long-term efficacy and safety of stem cell therapy [Cx601] for complex perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2018;154:1334–42.e4.
 37. Panés J, García-Olmo D, Van Assche G, et al.; ADMIRE CD Study Group Collaborators. Expanded allogeneic adipose-derived mesenchymal stem cells [Cx601] for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet* 2016;388:1281–90.
 38. Lightner AL, Wang Z, Zubair AC, Dozois EJ. A systematic review and meta-analysis of mesenchymal stem cell injections for the treatment of perianal Crohn's disease: progress made and future directions. *Dis Colon Rectum* 2018;61:629–40.
 39. Dozois EJ, Lightner AL, Mathis KL, et al. Early results of a phase I trial using an adipose-derived mesenchymal stem cell-coated fistula plug for the treatment of transsphincteric cryptoglandular fistulas. *Dis Colon Rectum* 2019;62:615–22.
 40. Tavares MMR, Barbosa LER. Adipose tissue-derived stem cells: a new approach to the treatment of Crohn's disease-associated perianal fistulae. *J Coloproctol* 2018;38:240–5.
 41. Lee WY, Park KJ, Cho YB, et al. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula. *Stem Cells* 2013;31:2575–81.
 42. de la Portilla F, Alba F, Garcia-Olmo D, et al. Expanded allogeneic adipose-derived stem cells [EASCS] for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIA clinical trial. *Int J Colorectal Dis* 2013;28:313–23.
 43. Dietz AB, Dozois EJ, Fletcher JG, et al. Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2017;153:59–62.e2.
 44. Dige A, Hougaard HT, Agnholt J, et al. Efficacy of injection of freshly collected autologous adipose tissue into perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2019;156:2208–16.e1.
 45. Edwards CM, George BD, Jewell DP, Warren BF, Mortensen NJ, Kettlewell MG. Role of a defunctioning stoma in the management of large bowel Crohn's disease. *Br J Surg* 2000;87:1063–6.
 46. Hong MK, Craig Lynch A, Bell S, et al. Faecal diversion in the management of perianal Crohn's disease. *Colorectal Dis* 2011;13:171–6.
 47. Régimbeau JM, Panis Y, Cazaban L, et al. Long-term results of faecal diversion for refractory perianal Crohn's disease. *Colorectal Dis* 2001;3:232–7.
 48. Singh S, Ding NS, Mathis KL, et al. Systematic review with meta-analysis: faecal diversion for management of perianal Crohn's disease. *Aliment Pharmacol Ther* 2015;42:783–92.
 49. Martí-Gallostra M, Myreliid P, Mortensen N, Keshav S, Travis SP, George B. The role of a defunctioning stoma for colonic and perianal Crohn's disease in the biological era. *Scand J Gastroenterol* 2017;52:251–6.
 50. de Groof EJ, Carbonnel F, Buskens CJ, Bemelman WA. Abdominal abscess in Crohn's disease: multidisciplinary management. *Dig Dis* 2014;32[Suppl 1]:103–9.
 51. Pugmire BS, Gee MS, Kaplan JL, et al. Role of percutaneous abscess drainage in the management of young patients with Crohn disease. *Pediatr Radiol* 2016;46:653–9.
 52. Clancy C, Boland T, Deasy J, McNamara D, Burke JP. A meta-analysis of percutaneous drainage versus surgery as the initial treatment of Crohn's disease-related intra-abdominal abscess. *J Crohns Colitis* 2016;10:202–8.
 53. He X, Lin X, Lian L, et al. Preoperative percutaneous drainage of spontaneous intra-abdominal abscess in patients with Crohn's disease: a meta-analysis. *J Clin Gastroenterol* 2015;49:e82–90.
 54. Zangenberg MS, Horesh N, Kopylov U, El-Hussuna A. Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: a systematic review. *Int J Colorectal Dis* 2017;32:1663–76.
 55. Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. *Aliment Pharmacol Ther* 2016;44:807–16.
 56. Patel KV, Darakhshan AA, Griffin N, Williams AB, Sanderson JD, Irving PM. Patient optimization for surgery relating to Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2016;13:707–19.
 57. Brennan GT, Ha I, Hogan C, et al. Does preoperative enteral or parenteral nutrition reduce postoperative complications in Crohn's disease patients: a meta-analysis. *Eur J Gastroenterol Hepatol* 2018;30:997–1002.
 58. Subramanian V, Saxena S, Kang JY, Pollak RC. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol* 2008;103:2373–81.
 59. Huang W, Tang Y, Nong L, Sun Y. Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: a meta-analysis of observational studies. *J Crohns Colitis* 2015;9:293–301.
 60. Serradori T, Germain A, Scherrer ML, et al. The effect of immune therapy on surgical site infection following Crohn's Disease resection. *Br J Surg* 2013;100:1089–93.
 61. Aberna FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003;125:320–7.
 62. Rizzo G, Armuzzi A, Pugliese D, et al. Anti-TNF-alpha therapies do not increase early postoperative complications in patients with inflammatory bowel disease. An Italian single-center experience. *Int J Colorectal Dis* 2011;26:1435–44.
 63. Khazen BF, El-Hussuna A. The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence a systematic review. *Dan Med J* 2018;65. pii: A5488.
 64. Groleau C, Morin SN, Vautour L, Amar-Zifkin A, Bessisow A. Perioperative corticosteroid administration: a systematic review and descriptive analysis. *Perioper Med [Lond]* 2018;7:10.

65. Hicks CW, Wick EC, Salvatori R, Ha CY. Perioperative corticosteroid management for patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:221–8.
66. Xu Y, Yang L, An P, Zhou B, Liu G. Meta-analysis: the influence of preoperative infliximab use on postoperative complications of Crohn's disease. *Inflamm Bowel Dis* 2019;25:261–9.
67. Lightner AL, Mathis KL, Tse CS, et al. Postoperative outcomes in vedolizumab-treated patients undergoing major abdominal operations for inflammatory bowel disease: retrospective multicenter cohort study. *Inflamm Bowel Dis* 2018;24:871–6.
68. Law CCY, Narula A, Lightner AL, McKenna NP, Colombel JF, Narula N. Systematic review and meta-analysis: preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *J Crohns Colitis* 2018;12:538–45.
69. Shim HH, Ma C, Kotze PG, et al. Preoperative ustekinumab treatment is not associated with increased postoperative complications in Crohn's disease: a Canadian multi-centre observational cohort study. *J Can Assoc Gastroenterol* 2018;1:115–23.
70. Lightner AL, McKenna NP, Tse CS, et al. Postoperative outcomes in ustekinumab-treated patients undergoing abdominal operations for Crohn's disease. *J Crohns Colitis* 2018;12:402–7.
71. da Luz Moreira A, Stocchi L, Tan E, Tekkis PP, Fazio VW. Outcomes of Crohn's disease presenting with abdominopelvic abscess. *Dis Colon Rectum* 2009;52:906–12.
72. Adamina M, Gié O, Demartines N, Ris F. Contemporary perioperative care strategies. *Br J Surg* 2013;100:38–54.
73. Barnes EL, Lightner AL, Regueiro M. Peri-operative and post-operative management of patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol* 2019, Oct 4. doi: 10.1016/j.cgh.2019.09.040. [Epub ahead of print.]
74. Bettenworth D, Gustavsson A, Atreja A, et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017;23:133–42.
75. Morar PS, Faiz O, Warusavitarne J, et al.; Crohn's Stricture Study [CroSS] Group. Systematic review with meta-analysis: endoscopic balloon dilatation for Crohn's disease strictures. *Aliment Pharmacol Ther* 2015;42:1137–48.
76. Hirai F, Andoh A, Ueno F, et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: a nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018;12:394–401.
77. Lan N, Stocchi L, Ashburn JH, et al. Outcomes of endoscopic balloon dilation vs surgical resection for primary ileocolic strictures in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2018;16:1260–7.
78. Shivashankar R, Edakkanambeth Varayil J, Scott Harmsen W, et al. Outcomes of endoscopic therapy for luminal strictures in Crohn's disease. *Inflamm Bowel Dis* 2018;24:1575–81.
79. Lian L, Stocchi L, Remzi FH, Shen B. Comparison of endoscopic dilation vs surgery for anastomotic stricture in patients with Crohn's disease following ileocolonic resection. *Clin Gastroenterol Hepatol* 2017;15:1226–31.
80. Ozuner G, Fazio VW, Lavery IC, Milsom JW, Strong SA. Reoperative rates for Crohn's disease following strictureplasty. Long-term analysis. *Dis Colon Rectum* 1996;39:1199–203.
81. Bellolio F, Cohen Z, MacRae HM, et al. Strictureplasty in selected Crohn's disease patients results in acceptable long-term outcome. *Dis Colon Rectum* 2012;55:864–9.
82. Schlussek AT, Steele SR, Alavi K. Current challenges in the surgical management of Crohn's disease: a systematic review. *Am J Surg* 2016;212:345–51.
83. Yamamoto T, Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2007;50:1968–86.
84. Ambe R, Campbell L, Cagir B. A comprehensive review of strictureplasty techniques in Crohn's disease: types, indications, comparisons, and safety. *J Gastrointest Surg* 2012;16:209–17.
85. Campbell L, Ambe R, Weaver J, Marcus SM, Cagir B. Comparison of conventional and nonconventional stricturoplasties in Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2012;55:714–26.
86. Uchino M, Ikeuchi H, Matsuoka H, Matsumoto T, Takesue Y, Tomita N. Long-term efficacy of stricturoplasty for Crohn's disease. *Surg Today* 2010;40:949–53.
87. Dasari BV, McKay D, Gardiner K. Laparoscopic versus open surgery for small bowel Crohn's disease. *Cochrane Database Syst Rev* 2011:CD006956.
88. Tan JJ, Tjandra JJ. Laparoscopic surgery for Crohn's disease: a meta-analysis. *Dis Colon Rectum* 2007;50:576–85.
89. Patel SV, Patel SV, Ramagopalan SV, Ott MC. Laparoscopic surgery for Crohn's disease: a meta-analysis of perioperative complications and long term outcomes compared with open surgery. *BMC Surg* 2013;13:14.
90. Shigeta K, Okabayashi K, Hasegawa H, Tsuruta M, Seishima R, Kitagawa Y. Meta-analysis of laparoscopic surgery for recurrent Crohn's disease. *Surg Today* 2016;46:970–8.
91. Appau KA, Fazio VW, Shen B, et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *J Gastrointest Surg* 2008;12:1738–44.
92. Billioud V, Ford AC, Tedesco ED, Colombel JF, Roblin X, Peyrin-Biroulet L. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta-analysis. *J Crohns Colitis* 2013;7:853–67.
93. Brouquet A, Maggiori L, Zerbib P, et al.; GETAID chirurgie group. Anti-TNF therapy is associated with an increased risk of postoperative morbidity after surgery for ileocolonic Crohn disease: results of a prospective nationwide cohort. *Ann Surg* 2018;267:221–8.
94. El-Hussuna A, Andersen J, Bisgaard T, et al. Biologic treatment or immunomodulation is not associated with postoperative anastomotic complications in abdominal surgery for Crohn's disease. *Scand J Gastroenterol* 2012;47:662–8.
95. El-Hussuna A, Krag A, Olaison G, Bendtsen F, Gluud LL. The effect of anti-tumor necrosis factor alpha agents on postoperative anastomotic complications in Crohn's disease: a systematic review. *Dis Colon Rectum* 2013;56:1423–33.
96. Fumery M, Seksik P, Auzolle C, et al.; REMIND study group investigators. Postoperative complications after ileocecal resection in Crohn's disease: a prospective study from the REMIND Group. *Am J Gastroenterol* 2017;112:337–45.
97. Holubar SD, Holder-Murray J, Flasar M, Lazarev M. Anti-tumor necrosis factor- α antibody therapy management before and after intestinal surgery for inflammatory bowel disease: a CCFA position paper. *Inflamm Bowel Dis* 2015;21:2658–72.
98. Jouvin I, Lefevre JH, Creavin B, et al.; Saint-Antoine IBD Network. Postoperative morbidity risks following ileocolic resection for Crohn's disease treated with anti-TNF alpha therapy: a retrospective study of 360 patients. *Inflamm Bowel Dis* 2018;24:422–32.
99. Kanazawa A, Yamana T, Okamoto K, Sahara R. Risk factors for postoperative intra-abdominal septic complications after bowel resection in patients with Crohn's disease. *Dis Colon Rectum* 2012;55:957–62.
100. Kasperek MS, Bruckmeier A, Beigel F, et al. Infliximab does not affect postoperative complication rates in Crohn's patients undergoing abdominal surgery. *Inflamm Bowel Dis* 2012;18:1207–13.
101. Kotze PG, Magro DO, Martinez CAR, et al. Adalimumab and postoperative complications of elective intestinal resections in Crohn's disease: a propensity score case-matched study. *Colorectal Dis* 2017, Oct 20. doi: 10.1111/codi.13929. [Epub ahead of print.]
102. Kotze PG, Saab MP, Saab B, et al. Tumor necrosis factor alpha inhibitors did not influence postoperative morbidity after elective surgical resections in Crohn's disease. *Dig Dis Sci* 2017;62:456–64.
103. Myrelid P, Marti-Gallostra M, Ashraf S, et al. Complications in surgery for Crohn's disease after preoperative antitumour necrosis factor therapy. *Br J Surg* 2014;101:539–45.
104. Nørgård BM, Nielsen J, Qvist N, Gradel KO, de Muckadell OB, Kjeldsen J. Pre-operative use of anti-TNF- α agents and the risk of post-operative complications in patients with Crohn's disease – a nationwide cohort study. *Aliment Pharmacol Ther* 2013;37:214–24.

105. Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: a systematic review and meta-analysis. *J Crohns Colitis* 2013;7:868–77.
106. Scarpa M, Martinato M, Bertin E, et al. Intestinal surgery for Crohn's disease: role of preoperative therapy in postoperative outcome. *Dig Surg* 2015;32:243–50.
107. Yamamoto T, Spinelli A, Suzuki Y, et al. Risk factors for complications after ileocolonic resection for Crohn's disease with a major focus on the impact of preoperative immunosuppressive and biologic therapy: A retrospective international multicentre study. *United European Gastroenterol J* 2016;4:784–93.
108. Ferrante M, de Buck van Overstraeten A, Schils N, et al. Perioperative use of vedolizumab is not associated with postoperative infectious complications in patients with ulcerative colitis undergoing colectomy. *J Crohns Colitis* 2017;11:1353–61.
109. Kotze PG, Ma C, McKenna N, et al. Vedolizumab and early postoperative complications in nonintestinal surgery: a case-matched analysis. *Therap Adv Gastroenterol* 2018;11:1756284818783614.
110. Lightner AL, McKenna NP, Moncrief S, Pemberton JH, Raffals LE, Mathis KL. Surgical outcomes in vedolizumab-treated patients with ulcerative colitis. *Inflamm Bowel Dis* 2017;23:2197–201.
111. Lightner AL, McKenna NP, Tse CS, Raffals LE, Loftus EV Jr, Mathis KL. Postoperative outcomes in vedolizumab-treated Crohn's disease patients undergoing major abdominal operations. *Aliment Pharmacol Ther* 2018;47:573–80.
112. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. *J Crohns Colitis* 2017;11:185–90.
113. Lightner AL, Tse CS, Potter DD Jr, Moir C. Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease. *J Pediatr Surg* 2018;53:1706–9.
114. Mitsuya JB, Gonzalez R, Thomas R, El-Baba M. The effect of biologics on postoperative complications in children with inflammatory bowel disease and bowel resection. *J Pediatr Gastroenterol Nutr* 2019;68:334–8.
115. Park KT, Sceats L, Dehghan M, et al. Risk of post-operative surgical site infections after vedolizumab vs anti-tumour necrosis factor therapy: a propensity score matching analysis in inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;48:340–6.
116. Yamada A, Komaki Y, Patel N, et al. Risk of postoperative complications among inflammatory bowel disease patients treated preoperatively with vedolizumab. *Am J Gastroenterol* 2017;112:1423–9.
117. Yung DE, Horesh N, Lightner AL, et al. Systematic review and meta-analysis: vedolizumab and postoperative complications in inflammatory bowel disease. *Inflamm Bowel Dis* 2018;24:2327–38.
118. Zimmerman LA, Zalieckas JM, Shamberger RC, Bousvaros A. Postoperative complications of pediatric patients with inflammatory bowel disease treated with vedolizumab. *J Pediatr Surg* 2018;53:1330–3.
119. Ponsioen CY, de Groof EJ, Eshuis EJ, et al.; LIRIC study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017;2:785–92.
120. Simillis C, Purkayastha S, Yamamoto T, Strong SA, Darzi AW, Tekkis PP. A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease. *Dis Colon Rectum* 2007;50:1674–87.
121. Guo Z, Li Y, Zhu W, Gong J, Li N, Li J. Comparing outcomes between side-to-side anastomosis and other anastomotic configurations after intestinal resection for patients with Crohn's disease: a meta-analysis. *World J Surg* 2013;37:893–901.
122. He X, Chen Z, Huang J, et al. Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for Crohn's disease: a meta-analysis. *Dig Dis Sci* 2014;59:1544–51.
123. Feng JS, Li JY, Yang Z, Chen XY, Mo JJ, Li SH. Stapled side-to-side anastomosis might be benefit in intestinal resection for Crohn's disease: a systematic review and network meta-analysis. *Medicine [Baltimore]* 2018;97:e0315.
124. Tekkis PP, Purkayastha S, Lanitis S, et al. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. *Colorectal Dis* 2006;8:82–90.
125. Angriman I, Pirozzolo G, Bardini R, Cavallin F, Castoro C, Scarpa M. A systematic review of segmental vs subtotal colectomy and subtotal colectomy vs total proctocolectomy for colonic Crohn's disease. *Colorectal Dis* 2017;19:e279–87.
126. Uzzan M, Stefanescu C, Maggiori L, Panis Y, Bouhnik Y, Treton X. Case series: does a combination of anti-TNF antibodies and transient ileal fecal stream diversion in severe Crohn's colitis with perianal fistula prevent definitive stoma? *Am J Gastroenterol* 2013;108:1666–8.
127. Harper PH, Truelove SC, Lee EC, Kettlewell MG, Jewell DP. Split ileostomy and ileocolostomy for Crohn's disease of the colon and ulcerative colitis: a 20 year survey. *Gut* 1983;24:106–13.
128. Spivak J, Landers CJ, Vasiliauskas EA, et al. Antibodies to I2 predict clinical response to fecal diversion in Crohn's disease. *Inflamm Bowel Dis* 2006;12:1122–30.
129. Burman JH, Thompson H, Cooke WT, Williams JA. The effects of diversion of intestinal contents on the progress of Crohn's disease of the large bowel. *Gut* 1971;12:11–5.
130. Mennigen R, Heptner B, Senninger N, Rijcken E. Temporary fecal diversion in the management of colorectal and perianal Crohn's disease. *Gastroenterol Res Pract* 2015;2015:286315.
131. Bafford AC, Latushko A, Hansraj N, Jambaulikar G, Ghazi LJ. The use of temporary fecal diversion in colonic and perianal Crohn's disease does not improve outcomes. *Dig Dis Sci* 2017;62:2079–86.
132. Panis Y, Poupard B, Nemeth J, Lavergne A, Hautefeuille P, Valleur P. Ileal pouch/anal anastomosis for Crohn's disease. *Lancet* 1996;347:854–7.
133. Regimbeau JM, Panis Y, Pocard M, et al. Long-term results of ileal pouch-anal anastomosis for colorectal Crohn's disease. *Dis Colon Rectum* 2001;44:769–78.
134. Manilich E, Remzi FH, Fazio VW, Church JM, Kiran RP. Prognostic modeling of preoperative risk factors of pouch failure. *Dis Colon Rectum* 2012;55:393–9.
135. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013;257:679–85.
136. Reese GE, Lovegrove RE, Tilney HS, et al. The effect of Crohn's disease on outcomes after restorative proctocolectomy. *Dis Colon Rectum* 2007;50:239–50.