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ECCO Guideline/Consensus Paper

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ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

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1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory bowel disease [IBD] characterised by colonic inflammation extending to a variable extent from the rectum. Care of the patient with UC requires appropriate input from across the multiprofessional team. These guidelines summarise the recommended medical treatment for adults with UC. Other ECCO guidelines consider the approach to UC diagnosis and monitoring,[1–3] nursing care,[4] management of disease complications,[5–7] risk of infection,[8] and technical aspects of surgery.[9] This document was prepared as part of a process that also led to the publication of a related guideline with recommendations on the surgical care of the patients with UC and on the medical aspects of the management of the patient hospitalised with severe UC. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment.

Patients living with UC can have a variable disease course.[10] In this document, we discuss therapeutic approaches stratified by disease severity [mildly-to-moderately active and moderately-to-severely active disease]. Attempts to define disease severity are widely used in setting clinical trial inclusion criteria and can be measured according to several different definitions.[11] Trial populations will inevitably vary, and we reflect the continuum of disease severity by having the moderate disease category span both broad categories. It is also important to remember that these definitions capture severity at a given point in time and may not reflect the cumulative long-term burden of disease experienced by a patient.[12]

It is also important to consider disease extent when planning treatment in UC, as this may affect the optimal route of drug administration. This is typically defined according to disease involving the rectum only [proctitis], disease distal to the splenic flexure [left-sided UC], or disease extending proximal to the splenic flexure [extensive UC].[13] These definitions of disease extent are recognised as somewhat arbitrary; in clinical practice, topically administered therapies are often used for UC whose extent is limited to the rectum and a portion of the sigmoid colon [proctosigmoiditis], with the term 'distal colitis' used to describe this disease distribution. It should be remembered that disease distribution can change[10,14] and that proximal disease extension can be a negative prognostic marker.[15]

2. Methods

This document was compiled following the 'Grading of Recommendations Assessment, Development, and Evaluation' [GRADE] methodology.[16] A panel of 33 experts was selected by the Guidelines Committee of ECCO from a competitive pool of applicants and worked with a team of methodologists and librarians. All panellists received training in the GRADE methodology. Additionally, six patients with UC, representing the European Federation of Crohn's and Colitis Associations [EFCCA], were invited to participate in all face-to-face meetings as full voting members.

Two domains for the medical treatment of UC were identified and used as the basis for the following two working groups based upon disease severity: mildly-to-moderately active disease and moderately-to-severely active disease. We recognise that these divisions are somewhat arbitrary, partially overlapping, and inconsistently defined; therefore, we ensured close collaboration between the working groups to ensure that key topics were covered appropriately with the aim of providing guidance applicable across the continuum of UC severity encountered in clinical practice.

Working group participants first formulated a series of specific questions using the Population, Intervention, Comparator, Outcomes [PICO] system, which were deemed to be clinically important for the medical treatment of UC. These questions were debated in a series of telephone conferences before final agreement at a meeting of the full guideline group in Vienna in November 2019. Voting on the inclusion of PICO questions was conducted, and only those achieving agreement of >80% by the panel were included in the next phase of the process. At this meeting, the panellists also ranked each outcome's importance on a scale of 1 to 9 based on the GRADE definitions.[16] Scores of 7–9 indicated an outcome that is critical to patients for decision making; scores of 4–6 indicated an important outcome, but not critical; and scores of 1–3 indicated an outcome of limited importance. The panellists' agreement on outcomes' importance was assessed using the Disagreement Index, as described in the RAND/UCLA appropriateness method.[17]

The team of librarians performed a comprehensive literature search on PubMed/Medline, Embase, and the Cochrane Central databases, using specific search strings for each PICO question [available as Supplementary data at *ECCO-JCC* online]. Two working group members [one assigned to the PICO question and another from the same group as second reviewer] independently screened titles and abstracts to exclude any irrelevant reports. Subsequently, the working group members assigned to each PICO question assessed the full text of the selected publications for relevance to the specific PICO. Note that studies were only selected if they addressed the PICO as formulated, including data on at least one of the outcomes of interest for the relevant dose of the intervention. In some instances, this meant that randomised controlled trials [RCTs] of a drug of interest were not included because, for example, they did not report at least one outcome defined as being of critical importance.

Most of the evidence informing the guidelines in this document came from randomised controlled trials conducted in adult patients

with UC. The methodologists directly performed the comparisons. The risk ratio [RR] was used to measure treatment effects. Study-level RRs with 95% confidence intervals [CIs] were calculated in accordance with the intention-to-treat principle. When zero events occurred in one group of a trial, we used a continuity correction that was inversely proportional to the relative size of the other group. To synthesise the evidence, we prepared forest plots and calculated the pooled effect estimates using random-effects models [DerSimonian and Laird approach].[18] We used R software for statistical analysis. All *p*-values are two-tailed. For all tests [except for heterogeneity], a *p*-value <0.05 indicates statistical significance.

To calculate absolute benefits and harms, we relied on the pooled event rates in the control groups. The absolute effect was based on the pooled RR and the baseline risk in the control groups.

The quality of evidence was expressed using the following four categories: high, moderate, low, and very low. For each PICO question, we rated the quality of evidence separately for each patient-important outcome, and then determined the overall quality of evidence across outcomes. For a guideline panel, the quality of evidence reflects the extent to which the confidence in the effect estimate is adequate to support a particular recommendation.[16]

To determine the quality of the evidence for each outcome across all studies, we started with rating the evidence from RCTs as 'high' quality, and then assessed the following five factors that could lead to down-rating the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[16] Risk of bias was assessed using the Cochrane tool. Inconsistency was assessed with the Cochrane Q test [using a 0.10 significance level] and the I^2 metric [with values >50% suggesting significant heterogeneity]. Indirectness was determined according to whether the studies addressed a different but related population, intervention, or outcome from the one of interest. Imprecision was based on the number of events [the quality of evidence was downgraded by one level when the total number of events was <100, and by two levels when it was <50]. Publication bias was assessed using funnel plots, and the Begg's and Egger's tests only if there were at least 10 studies included in the meta-analysis.

The overall quality of evidence was a combined rating of the quality of evidence across all outcomes considered critical for decision making; the lowest quality of evidence for any of the critical outcomes determined the overall quality of evidence. Summary-of-Findings [SoF] tables showing all studies used in preparing each recommendation, key data and study findings for each outcome of interest, and our judgements about each of the quality of evidence factors examined are available as Supplementary material, along with documentation of the assessment of evidence quality. We present our rating of quality of evidence for: each one of the outcomes; the risk with control group; the risk with intervention group; the meta-analytic effect estimate; the anticipated absolute effects; and any other relevant information regarding the data reported in the SoF table; along with our rating of the overall quality of evidence across outcomes.

The strength of each recommendation was graded either as 'strong' [meaning that the desirable effects of an intervention clearly outweigh the undesirable effects, or vice versa] or as 'weak' [meaning that the balance is less certain], while also considering the quality of evidence, values and preferences of patients, balance between desirable and undesirable effects, and cost-effectiveness. All recommendations were subject to online voting by the panel members, the ECCO National Representatives [two for each country affiliated with ECCO], six reviewers from the European Society of Coloproctology, and nine additional reviewers from a list of ECCO members involved in ECCO guideline development [see Acknowledgements section]. The final version of all statements/recommendations was discussed among panel members during a final virtual consensus meeting in April 2021 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, supporting text and material, and manuscript draft were critically reviewed by the ECCO Governing Board members, who also approved the final version of these guidelines.

These guidelines are designed to inform and support clinicians in making evidence-based decisions on the medical treatment of UC; they should not be used to signify a minimal acceptable standard of care, should not be used for medicolegal purposes, and should not be interpreted as endorsing the use of any particular proprietary or commercial product. All costs associated with the development and publication of this guideline were met by ECCO. The Governing Board of ECCO played no role in the selection of panel members or the development or selection of PICO questions. A summary of some of the key changes from previous ECCO UC guidelines is presented in the Supplementary material.

3. General Approach to the Management of Ulcerative Colitis

These guidelines set out the evidence for the use of different medical therapies in the treatment of UC. They were developed and written in a manner driven by the available data, which were typically from large-scale clinical trials and usually based upon testing of an intervention against placebo. Nevertheless, the medical care of a patient with UC goes well beyond the selection between a given drug and no treatment. Furthermore, patients encountered in the clinic frequently do not fit the profile of a given clinical trial population. It is therefore important that these guidelines are used first to inform the physician of the quality of evidence behind any given treatment, which the physician must then consider, together with the patient, in formulating a treatment plan.

A key area of debate is when to escalate treatment. There is less evidence in UC than in Crohn's disease on the importance of early treatment escalation. At the same time, the experience of recurrent symptom flares can lead to physical and psychological harm,[19,20] as can repeated exposure to corticosteroids.[21] Although the cost of an intervention is a factor reflected in the GRADE process when forming the strength of recommendation, as international guidelines there will be local health economic considerations that this document can not address. Nevertheless, it is clear that appropriate and timely selection of patients for higher-cost interventions is critical to achieve optimal health economic outcomes.[22,23]

The ultimate goal of treatment in UC is to maintain health-related quality of life [QoL] and avoid disability.[24] To achieve this, it is important to not only provide rapid relief of clinical symptoms, but also achieve endoscopic healing where possible, as this is associated with improved long-term outcomes.[25–27] The importance of these outcomes was reflected in the decision by the expert panel to select endoscopic and clinical outcomes as being of critical importance.

The term 'conventional therapy' has been widely used in the past to differentiate well-established traditional treatments (such as 5-aminosalicylates [5-ASA], corticosteroids, and thiopurine immunomodulators) from biologic therapies and other novel targeted small molecules. This concept is becoming somewhat outdated,

as the costs of and access to biologics therapies evolve [notably with the introduction of biosimilars] and biologics are increasingly viewed as a conventional part of UC treatment. For the purposes of this guideline, we agreed to use the term 'conventional therapy' as it has traditionally been understood, in the absence of any widely accepted alternative nomenclature, while also accepting the limitations of this language. Where specific definitions of conventional therapy have been used in individual studies, these are outlined in the supporting SOF tables.

Dose escalation has been reported for many of the interventions we considered, typically in a non-randomised manner, both for patients showing disease flares during RCTs or in cohort studies. Although appropriate dose escalation or dose optimisation can play a role in clinical practice, there are minimal high-quality trial data in this area, and uncontrolled studies are subject to several potential forms of bias. For this reason, we have restricted our recommendations to the doses studied in a randomised manner in clinical trials. In addition to the initiation and escalation of medical treatments for UC, how and when to consider reducing or stopping treatment to minimise the risks, costs, and burden to patients of prolonged drug therapy is an important consideration. The limited evidence on treatment withdrawal has been reviewed recently and is beyond the scope of this current guideline.[28]

4. Medical Management of Mildly-to-moderately Active Ulcerative Colitis

4.1. Induction of remission in mildly-to-moderately active ulcerative colitis

5-aminosalicylates

Recommendation 1

We recommend 5-aminosalicylates at a dose of ≥2 g/day [d] to induce remission in patients with mildly-to-moderately active UC [strong recommendation; quality of evidence low]

We performed a meta-analysis of 11 eligible RCTs with a total of 2156 patients evaluated for 4–12 weeks; 5-aminosalicylates [5-ASA] had a significantly higher efficacy in achieving **clinical remission** [RR: 1.56] versus placebo [95% CI: 1.24–1.97]. Similarly, the **clinical response** in 14 studies [total 2025 patients] evaluated at 2–10 weeks was significantly better for 5-ASA [RR: 1.58; 95% CI: 1.35–1.86] with response in 59% of patients receiving 5-ASA compared with 35% of those receiving placebo. The efficacy of 5-ASA on **endoscopic response** as evaluated in four RCTs with 416 patients investigated after 4–12 weeks was better with 5-ASA [RR: 1.73; 95% CI: 1.0–3.0]; 5-ASA was generally very well tolerated. The serious adverse event [SAE] rate evaluated in 13 studies with 2141 patients for a maximal follow-up of 12 weeks was 6.1% versus 9% in the placebo arms [RR: 0.81; 95% CI: 0.47–1.38].

The quality of evidence was globally evaluated as low due to significant heterogeneity and possible publication and reporting bias for certain outcomes [SoF Table 1, available as Supplementary data at *ECCO-JCC* online].

A Cochrane meta-analysis confirmed the similar efficacy of once-daily or more frequent dosing regimens across multiple studies.[29] This meta-analysis did not show any apparent differences in outcomes between different formulations of 5-ASA considered. Notably, despite discussion regarding differences of colonic distribution of different mesalazine preparations, no significant differences in outcomes were observed in any mesalazine comparator studies. For this reason, patients with mildly active UC who fail to reach remission with appropriately dosed oral 5-ASA are unlikely to achieve remission upon switching to an alternative oral 5-ASA formulation.

The same Cochrane meta-analysis did not find overall evidence for superior efficacy of higher total daily doses across multiple dose-ranging trials when compared with standard licensed doses of the same formulation.[29] Subgroup evaluation of the ASCEND trials suggested a benefit of 4.8 g/day of a polymer-coated formulation of mesalazine [with pH-dependent release] compared with 2.4 g/day in patients with more active disease or in those with previous treatment with corticosteroids, oral 5-ASA, rectal therapies, or multiple UC medications.[30–32] Likewise, a post-hoc analysis of ASCEND data also showed greater rates of mucosal healing in the 4.8 g/day group than in the 2.4 g/day group.[33] In contrast, subgroup analysis restricted according to disease severity did not reveal any differences in outcomes between 4.8 g/day and 2.4 g/day in trials of a pH-dependent multimatrix (MMX) 5-ASA preparation.[29,34]

Recommendation 2

We recommend topical [rectal] 5-ASA at a dose of ≥1 g/d for the induction of remission in active distal colitis [strong recommendation, low-quality evidence]

We identified eight suitable studies that assessed a dose of ≥1 g topical 5-ASA per day for 2–8 weeks which we used for meta-analysis [SoF Table 2, available as Supplementary data at *ECCO-JCC* online].[35–42] All studies required endoscopic confirmation of rectal inflammation but varied in the maximum proximal limit of disease extent permitted [from a maximum of 20 cm from the anal verge to no upper limit]. There was a significant increase in **clinical response** and **clinical remission** when compared with placebo-treated patients [RR: 2.46; 95% CI: 2.01–3.01 and RR: 3.56; 95% CI: 2.08–6.09, respectively]. In addition, **endoscopic response** in five studies that assessed 1 g 5-ASA daily for 2–8 weeks, as induction therapy in distal colitis, was significantly more frequently achieved in patients treated with 5-ASA than those treated with placebo [RR: 2.75; 95% CI: 2.04–3.7]. No significant differences in **SAEs** between topical 5-ASA treatment and placebo were observed [RR: 0.26; 95% CI: 0.03–2.29].

Overall, the quality of available evidence was classified as low. Despite this, our recommendation is strong considering the extensive clinical experience corroborating efficacy and very few SAEs related to topical 5-ASA administration.

Recommendation 3

We suggest the use of oral 5-ASA [≥2 g/d] combined with topical [rectal] 5-ASA over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent [weak recommendation; very low-quality evidence]

Only a few trials were retrieved that compared the use of oral 5-ASA combined with topical 5-ASA versus oral 5-ASA as monotherapy for induction of remission in adult patients with active UC [SoF Table 3, available as Supplementary data at *ECCO-JCC* online].[43–46] In all of these studies, the desirable effects of 5-ASA combined therapy [compared with oral monotherapy] probably outweigh the undesirable effects of this intervention, although the level of uncertainty is high.

Two trials compared these two therapeutic strategies for **clinical response** in patients with disease of at least rectosigmoid extent.[43,44] The trials were heterogeneous in terms of study design, 5-ASA doses, definition of clinical activity, and definition of clinical improvement. In the pooled analysis, no significant advantage of combined therapy over 5-ASA monotherapy in clinical response was observed [RR: 1.1; 95% CI: 0.95–1.27].

Four trials addressed whether combined 5-ASA therapy is superior to oral monotherapy in inducing **clinical remission** in active UC.[43–46] These studies included 322 patients and treatment duration was 3–8 weeks. All trials were heterogeneous in terms of patient characteristics, criteria used to define disease activity and remission, doses, and 5-ASA regimens. There was a serious inconsistency of evidence [$I^2 = 71\%$] and a serious risk of bias, as the methods of sequence generation and allocation concealment were unclear in three of four studies. The RR of obtaining clinical remission between combined [oral and topical] 5-ASA treatment versus oral monotherapy was 1.45 [95% CI: 0.98–2.13].

There was only one trial on the influence of combined versus oral 5-ASA therapy on endoscopic activity of UC.[44] Patients receiving 2 g of 5-ASA orally plus 2 g of 5-ASA enemas more frequently achieved endoscopic remission than those treated with 4 g of 5-ASA orally plus placebo enemas. However, the difference was not statistically significant [RR: 1.21; 95% CI: 0.91–1.61]. The quality of evidence for this outcome was downgraded because of serious indirectness [the study assessed endoscopic remission, instead of the outcome of interest, which was an **endoscopic response**] and imprecision [only 77 events in the study].

It is difficult to compare the safety of combined versus oral 5-ASA induction treatment since only one trial addressed this question, with very sparse data.[43] Only four **SAEs** were detected; 3/71 patients in the combined treatment group and 1/56 patients in the oral 5-ASA plus placebo enema group experienced SAEs [RR: 2.37; 95% CI: 0.25–22.14]. In parallel to this very serious imprecision, there was also a serious risk of bias. Therefore, the quality of the data for this outcome was assessed to be very low.

Overall, we felt that the trend towards better outcomes for combined therapy, clinical experience, and the low cost and risk of the intervention all justified a weak recommendation in favour of combined therapy in patients for whom combined therapy was acceptable.

Topical corticosteroids

Recommendation 4

We recommend using topical [rectal] steroids for the induction of remission in patients with active distal colitis [strong recommendation, very low-quality evidence]

The use of topically administered steroids has been long established for the induction of remission in patients with proctitis and distal colitis. Topically applied steroids offer the advantage over systemic steroids of a more targeted treatment with fewer systemic side effects; however, topical treatments may be poorly accepted by some patients due to the route of administration.

Several systematic reviews have been conducted on this topic,[47–53] but none included all of the available RCT evidence that was identified here. Therefore, we performed a meta-analysis of five RCTs that compared topical steroids with placebo [SoF Table 4, available as Supplementary data at *ECCO-JCC* online].[54–58] Topical steroids were superior to placebo in induction of **clinical remission** [pooled RR: 2.12; 95% CI: 1.48–3.06], **clinical response** [RR: 2.18; 95% CI: 1.58–3.01], and **endoscopic response** [RR: 1.44; 95% CI: 1.21–1.70]. **SAEs** did not occur more frequently compared with placebo [RR: 0.68; 95% CI: 0.10–4.40]. The number of patients included in each study was quite low and the quality of evidence was very low. This was due to indirectness and imprecision identified for the SAE outcome [a critical outcome, although other critical outcomes were judged to have high-quality evidence]. Overall, we believe that the experience with topical steroids in clinical practice, the favourable balance between their potential benefits and harms (there was no statistically significant difference in adverse events [AE] between topical steroids versus placebo), and their low cost support the recommendation of topical steroids as an option for induction of remission in patients with active UC.

Recommendation 5

We suggest treatment with topical [rectal] 5-ASAs over topical [rectal] steroids for induction of remission in patients with active distal UC [weak recommendation, very low quality of evidence]

The effect of treatment with topical 5-ASA at a dose ≥1 g/day or topical steroids [suppositories or enemas] for induction of remission in adult patients with active distal UC has been investigated in 13 studies.[38,59–70] We performed a meta-analysis of these studies, which included a total of 1395 patients treated with topical 5-ASA at >1 g/day or topical steroids [suppositories or enemas], with outcomes captured at 2–8 weeks [SoF Table 5, available as Supplementary data at *ECCO-JCC* online].

Topical 5-ASAs were superior for the induction of **clinical remission** [RR: 1.36; 95% CI: 1.19–1.56] but were not significantly more effective than topical steroids in inducing **clinical response** [RR: 1.09; 95% CI: 0.97–1.22]. In five studies[68–72] including 376 patients followed for 2–4 weeks, **endoscopic response** was equally likely to be achieved with either topical 5-ASA or topical steroids [RR: 1.08; 95% CI: 0.82–1.44]. In nine studies[61,63,65–69,71,72] including 1306 patients, the rates of **SAEs** did not differ between topical 5-ASA or topical steroids [RR: 1.21; 95% CI: 0.47–3.08]. Overall, the quality of evidence was rated as very low.

Although patients should generally be treated with a single topical agent, there is some [very limited] evidence to suggest that combination rectal 5-ASA and rectal corticosteroid may be of benefit. This may be appropriate for some patients who fail to respond to initial rectal therapy.[69] It is also important to be aware of differences between preparations in terms of delivery systems and formulations, all of which may have differences in patient acceptability. It is appropriate to offer a patient a trial of an alternative preparation if they are unable to tolerate an initial choice.

Colonic-release corticosteroids

Recommendation 6

We suggest the use of colonic-release corticosteroids for induction of remission in patients with active mild-to-moderate UC [weak recommendation, low quality of evidence]

The effect of treatment with colonic-release corticosteroids using once-daily budesonide MMX 9 mg for induction of remission in adult patients with active mild-to-moderate UC has been investigated in three studies[73–75] [SoF Table 6, available as Supplementary data at *ECCO-JCC* online]. A total of 542 patients treated with colonic-release corticosteroids were included and followed for 8 weeks. Colonic-release corticosteroids were superior to placebo in inducing **clinical remission** and **clinical response** [RR: 2.86; 95% CI 1.62–5.04 and RR: 1.46; 95% CI: 1.11–1.93, respectively]. In two studies[73,74] including 510 patients followed for 8 weeks, **endoscopic response** was more likely to be achieved with colonic-release corticosteroids in comparison with placebo [RR: 1.43; 95% CI: 1.10–1.84]. In all three studies, the rates of **SAEs** and of any AEs did not differ between colonic-release corticosteroids and placebo [RR: 0.88; 95% CI: 0.33–2.41 and RR: 1.04; 95% CI: 0.79–1.37, respectively]. The low number of SAEs resulted in a low quality of evidence for this critical endpoint, due to imprecision.

A pooled analysis of data from both phase 3 trials showed a combined clinical and endoscopic remission rate of 17.7% for budesonide MMX 9 mg/day versus 6.2% for placebo (odds ratio [OR]: 3.3; 95% CI: 1.7–6.4).[76] Whereas subgroup analysis of these pooled data revealed that this benefit was seen in patients with left-sided colitis, the difference between drug and placebo was not statistically significant in those with more extensive disease.

Unlike other therapies, including 5-ASA, no data exist for the role of budesonide MMX as a maintenance therapy. This suggests that the most appropriate use of budesonide MMX may be in patients with mildly-to-moderately active disease who are not responding to or are intolerant to optimised 5-ASA therapy. An RCT comparing budesonide MMX 9 mg/day with placebo, in patients with mildly-to-moderately active UC despite oral 5-ASA therapy, revealed a significant improvement in the primary endpoint of combined clinical and endoscopic remission [13% vs 7.5%; $p = 0.049$) and histological healing in the treatment arm [27% vs 17.5%; $p = 0.016$].[77]

Immunomodulators

Recommendation 7

We suggest against the use of thiopurines as monotherapy for the induction of remission in patients with active UC [weak recommendation, very low quality of evidence]

Two studies have reported on the use of azathioprine as monotherapy compared with placebo for induction of remission in patients with UC.[78,79] Overall, only 130 patients in two RCTs were analysed and assessed for **clinical remission** after 1–4 months, with azathioprine given alongside a concomitant course of corticosteroids. We performed a meta-analysis of these studies and did not observe a difference between azathioprine and placebo for induction of clinical remission [RR: 1.22; 95% CI: 0.79–1.88] [SoF Table 7, available as Supplementary data at *ECCO-JCC* online]. No placebo-controlled data on clinical response, endoscopic response, or SAEs were available.

It should be noted that due to the relatively slow onset of action of azathioprine, it may be appropriate to initiate azathioprine in patients with active disease where maintenance therapy with azathioprine is planned, but only when given alongside an effective induction agent.

We did not identify any studies using other thiopurines [mercaptopurine or thioguanine] for the induction of remission. Due to their related mechanism of action, we extend our recommendation against the use of azathioprine in induction of remission across the entire thiopurine class.

4.2. Maintenance of remission in mildly-to-moderately active ulcerative colitis

5-ASAs

Recommendation 8

We recommend the use of oral 5-ASA at a dose ≥2 g/day for maintenance of remission in UC patients [strong recommendation; very low quality of evidence]

We identified two RCTs involving 306 participants with 48–52 weeks of follow-up, which provided evidence relevant to our PICO question. We synthesised these in a meta-analysis [SoF Table 8, available as Supplementary data at *ECCO-JCC* online].

For **clinical remission**, there was moderate-quality evidence that oral 5-ASA [≥2 g/d] was statistically significantly superior to placebo for maintaining remission in adult patients with UC [RR: 1.54; 95% CI: 1.11–2.14]. For **endoscopic remission** there was moderate-quality evidence favouring the use of 5-ASA, but this did not reach significance [RR: 1.20; 95% CI: 1.00–1.44]. Only one RCT contributed evidence [of very low quality] for **SAEs**.[80] Treatment with oral 5-ASA [≥2 g/d] was associated with statistically significantly fewer SAEs [RR: 0.41; 95% CI: 0.23–0.71].

Although the quality of evidence was judged to be overall very low [due to problems with data for SAEs], we nonetheless felt it appropriate to make a strong recommendation, given the safety and relatively low cost of this intervention. An additional consideration may be the reported potential chemopreventive benefits of maintenance 5-ASA treatment, although this finding has been inconsistently reported in the literature and may reflect selection bias seen in referral centre-based cohorts.[81]

Recommendation 9

We suggest the use of topical [rectal] 5-ASA for the maintenance of remission in patients with distal UC [weak recommendation, very low-quality evidence]

We identified four placebo-controlled trials that assessed topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis [SoF Table 9, available as Supplementary data at

ECCO-JCC online].[82–85] Doses used ranged between 1 g three times weekly and 1 g daily, administered as suppositories or enemas over a period of 12 months [three studies] to 24 months [one study]. The quality of evidence was rated as low due a to serious risk of bias and inconsistency. The same studies were identified in a previous Cochrane review.[86] The use of topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis was significantly superior in maintenance of **clinical remission** compared with placebo [RR: 2.22; 95% CI: 1.26–3.90]. For the **maintenance of endoscopic remission**, data on the use of 1-g 5-ASA enemas in distal UC or proctitis are available for just 25 patients treated over the course of 12 months; 5-ASA was superior to placebo [RR: 4.88; 95% CI: 1.31–18.18].[87]

These studies did not report data on SAEs. A previous Cochrane Review found no significant difference in the proportion of patients experiencing AEs or in the rate of withdrawals due to AEs with topical 5-ASA compared with placebo.[86] Although the level of evidence is very low, our recommendation is strong, based on the long clinical experience of efficacy and minimal side effects of rectal formulations of 5-ASA along with the low cost of this intervention. It is important to consider patient acceptability; for some patients, the use of the rectal route for maintenance therapy provides significant advantages both in reducing systemic exposure to drugs and avoiding a greater level of immunosuppression. However, the rectal route of administration may present challenges for medication adherence,[88] with patients facing practical difficulties in administration and enema retention. Patient support and education may increase adherence; otherwise, alternative formulations or drugs should be considered.

Immunomodulators

Recommendation 10

We recommend monotherapy with thiopurines for the maintenance of remission in patients with steroid-dependent UC or who are intolerant to 5-ASA [strong recommendation, moderate quality of evidence]

We identified four placebo-controlled RCTs on maintenance treatment with azathioprine in patients with UC who were steroid-dependent or intolerant to 5-ASA [SoF Table 10, available as Supplementary data at *ECCO-JCC* online].[78,79,89,90] In 232 patients followed for 1 year, azathioprine was superior [56%] to placebo [35%] for the maintenance of clinical remission [RR: 1.59; 95% CI: 1.19–2.11]. No placebo-controlled data on endoscopic or histological remission, sustained clinical remission, or SAEs were available. In contrast to current clinical trials, different disease activity indices and endpoint definitions were used. Hence, indirect comparisons with novel and potentially more potent agents are difficult. Nevertheless, large-scale cohort studies highlighted the apparent clinical benefit of thiopurine monotherapy.[91] Since we do not recommend the use of thiopurines for induction of remission, it is important that any maintenance strategy with thiopurines is planned alongside an effective induction agent. We did not identify any RCTs of thiopurines other than azathioprine, but due to their closely related pharmacology, we extend our recommendation across the drug class.

Significant safety concerns do exist with the use of thiopurines. This is particularly true in patients aged >65 years; use of thiopurines should be discouraged in this age group.[8,92–94]

No evidence supports the use of methotrexate for the maintenance of remission in UC.[95] An RCT of methotrexate against placebo failed to demonstrate any advantage in terms of steroid-free clinical remission.[96]

5. Medical Management of Moderately-to-severely Active Ulcerative Colitis

5.1. Induction of remission in moderately-to-severely active ulcerative colitis

Systemic corticosteroids

Recommendation 11

We recommend oral prednisolone for induction of remission in non-hospitalised patients with moderately-to-severely active UC [strong recommendation; very low quality of evidence]

Despite a limited evidence base, the use of systemic corticosteroids for the induction of remission in moderately-to-severely active UC is well established in clinical practice. The limited evidence is due in part to the large effect size and limited alternative options at the time of the original RCTs.[97,98] A previous meta-analysis[99] included five placebo-controlled RCTs, although only two of them[97,98] used standard systemic corticosteroids. Therefore, we performed a meta-analysis of just these two studies and calculated an RR of 2.83 [95% CI: 1.79–4.46] for the induction of **clinical remission**. The quality of evidence was rated as very low, due to a serious risk of bias, indirectness, and imprecision [in part since the number of patients included in each study was low] [SoF Table 11, available as Supplementary data at *ECCO-JCC* online].

No information regarding AEs with steroid treatment was available in these two studies. Other studies established the side-effect profile of corticosteroids in both short courses and also longer-term exposure in both UC and Crohn's disease.[21,100] Due to the potential for side effects, some of which are irreversible, corticosteroid-free remission represents a desired outcome for patients.[101,102]

Overall, we believe that the ample experience with systemic steroids in clinical practice and the favourable balance between their potential benefits and harms [when used over limited periods] support the recommendation of oral prednisolone [or another equivalent systemic steroid agent, such as methylprednisolone or prednisone] as an option for induction of remission in patients with moderately-to-severely active UC. For these reasons, our recommendation is graded as strong, despite the quality of evidence being very low.

A previous meta-analysis identified six RCTs that compared systemic prednisolone with budesonide, and found a significantly higher chance of induction of remission but increased steroid-related AEs with prednisolone.[99] However, none of these RCTs used a colonic-release budesonide formulation. We restrict our recommendations for budesonide MMX in mild-to-moderately active disease, and prednisolone in moderately-to-severely active UC, to reflect the study populations of the RCTs identified and the likely risk-benefit profile in these different populations.

It is important to note that there are no efficacy data supporting the use of corticosteroids as maintenance therapies, and very limited data on the ability of these drugs to achieve **endoscopic response**. Additionally, longer-term corticosteroid exposure is associated with significant safety concerns. Due to this, along with the availability of drugs with proven ability to maintain corticosteroid-free remission,

we advise monitoring of corticosteroid exposure in patients with UC. Corticosteroid-sparing agents should be initiated for any patient showing corticosteroid-refractory disease or intolerance of or contraindication to corticosteroids. Additionally, courses of corticosteroids should be restricted to a maximum of 3 months, and therapy with a corticosteroid-sparing agent should be considered for any patient who requires more than a single course of systemic corticosteroids in a year or experiences a disease flare upon steroid tapering.

Anti-tumour necrosis factor agents

Recommendation 12

We recommend treatment with anti-tumour necrosis factor [TNF] agents [infliximab, adalimumab, and golimumab] to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate-quality evidence]

We identified nine suitable RCTs that compared anti-TNF agents [infliximab, adalimumab, golimumab] with placebo in patients with moderately-to-severely active UC [SoF Table 12, available as Supplementary data at ECCO-JCC online].[103–111] Patient eligibility required an inadequate response to or intolerance of conventional therapies, which were defined as corticosteroids, immunomodulators, or both in most studies, although three RCTs also permitted inadequate response to or intolerance of oral 5-ASA alone.[103–105] Our meta-analysis revealed evidence of efficacy for induction of **clinical remission** [RR: 2.23; 95% CI: 1.81–2.76] and **clinical response** [RR: 1.56; 95% CI: 1.38–1.76]. We found data supporting efficacy for mucosal healing [RR: 1.49; 95% CI: 1.32–1.68], which is closely related to but defined differently from the outcome of interest used in this guideline [endoscopic response]; evidence was therefore downgraded due to indirectness. There was no difference in terms of AEs when analysed regardless of treatment duration [RR: 0.84; 95% CI: 0.64–1.09]. Safety data for anti-TNF agents from large cohort studies were generally reassuring.[93,94,112]

Studies that directly compared anti-TNF agents are not available. Two network meta-analyses[113,114] that performed indirect comparisons concluded that infliximab is superior to adalimumab for the induction of **clinical remission** [OR: 2.10; 95% CI: 1.21–3.64[113] and OR: 2.10; 95% CI: 1.16–3.79, respectively[114]]. The first network meta-analysis also concluded that infliximab is superior to adalimumab and golimumab for induction of **clinical response** [OR: 2.01; 95% CI: 1.36–2.98 and OR: 1.67; 95% CI: 1.08–2.59, vs adalimumab and golimumab, respectively] and for induction of mucosal healing [OR: 1.87; 95% CI: 1.26–2.79 and OR: 1.75; 95% CI: 1.13–2.73, vs adalimumab and golimumab, respectively].[113]

For patients with a history of previous failure of biologic therapy, there are limited data to guide treatment selection. Subgroup analysis of a phase 3 trial suggests that the clinical effects of induction therapy with adalimumab were markedly lower in patients with previous anti-TNF agent exposure [and non-significantly different from placebo].[110] A previous systematic review of cohort studies identified eight studies that reported the efficacy of adalimumab when used after infliximab in UC. However, meta-analysis was not possible, due to study heterogeneity.[115] In patients with a history of previous infliximab therapy randomised to either adalimumab or vedolizumab, rates of clinical remission and endoscopic response were not significantly different.[116] There are extremely limited data on the use of anti-TNF agents in other biologic sequences.

A key question is whether to combine an anti-TNF agent with an immunomodulator. The combination of infliximab with azathioprine is more effective than infliximab alone.[117] Similar RCT-level data do not exist for adalimumab in combination with thiopurine therapy in UC, although cohort studies suggest a possible benefit for this combination[118] and pharmacokinetic benefits have been reported in patients with Crohn's disease.[119] For patients experiencing loss of response to a first anti-TNF agent used as monotherapy and with evidence of anti-drug antibodies, there is clear RCT evidence in favour of addition of a thiopurine to prevent formation of anti-drug antibodies to the second anti-TNF agent.[120]

The optimal time point for the introduction of anti-TNF therapy has yet to be defined. Unlike in Crohn's disease, no post-hoc analysis has demonstrated increased efficacy of anti-TNF agents used early in the UC disease course. Factors predicting severe or complicated disease, such as young age at first diagnosis, extensive disease, and high inflammatory burden, have been proposed to identify patients who may benefit from early treatment escalation,[121] although the benefits of this approach have not been demonstrated in any strategy trial.

Vedolizumab

Recommendation 13

We recommend treatment with vedolizumab for the induction of remission in patients with moderately-to-severely active UC who have inadequate response or intolerance to conventional therapy [strong recommendation, low quality of evidence]

Two placebo-controlled RCTs were identified that addressed our PICO question. These included 620 patients with moderately-to-severely active UC treated with vedolizumab or placebo; induction of clinical remission, induction of clinical response, and SAEs were reported.[122,123] Patients were followed up to 6–10 weeks [SoF Table 13, available as Supplementary data at ECCO-JCC online].

We included these two studies in a meta-analysis. **Clinical remission** was achieved more often in patients receiving vedolizumab compared with placebo [RR: 2.14; 95% CI:1.03–4.43]. Although the direction of effect for **clinical response** was the same as for clinical remission, the difference between patients treated with vedolizumab and those receiving placebo was not significant [RR: 1.51; 95% CI: 0.99–2.29]. Rates of **SAEs** in patients treated with vedolizumab were not significantly different from those receiving placebo [RR: 0.71; 95% CI: 0.39–1.30]. Safety data from large cohort studies also confirmed this favourable safety assessment.[112]

Evidence was also sought for endoscopic response and biochemical remission; however, data were insufficient. Of note, rates of endoscopic remission at Week 6 in the GEMINI I phase 3 induction study were 40.9% for vedolizumab-treated patients compared with 24.8% for placebo-treated patients [$p = 0.001$].[122] In contrast, endoscopic remission rates at Week 10 in a Japanese phase 3 induction study did not differ significantly between vedolizumab- and placebo-treated patients [36.6% vs 30.5%, $p = 0.32$].[123]

The overall quality of evidence was low. The quality of evidence was low for clinical remission due to serious inconsistency and imprecision. The quality of evidence was moderate for clinical response due to serious inconsistency. The inconsistency for both outcomes

was due to heterogeneity in outcomes between the two RCTs. The quality of evidence for SAEs was moderate due to serious imprecision. However, the overall recommendation was graded as strong, considering the overall evidence available combined with the favourable safety profile of vedolizumab in both RCT and cohort studies.

Tofacitinib

Recommendation 14

We recommend treatment with tofacitinib to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate quality of evidence]

We performed a meta-analysis of data from two RCTs relevant to our PICO question. These included 1220 patients with moderate-to-severe UC who previously had an inadequate response, loss of response, or were intolerant to either conventional therapy [mesalamine plus steroids or thiopurines] or a biologic agent who were treated with tofacitinib or placebo [SoF Table 14, available as Supplementary data at ECCO-JCC online].[124,125] There was evidence for efficacy in induction of **clinical response** [RR: 1.79; 95% CI: 1.49–2.14], **clinical remission** [RR: 3.26; 95% CI: 1.95–5.43], and **endoscopic response** [RR: 5.18; 95% CI: 2.12–12.69]. However, the evidence regarding endoscopic response was downgraded due to indirectness and imprecision [low number of events]. Data on biochemical remission were insufficient. SAEs were comparable [RR: 0.70; 95% CI: 0.45–1.08], although the evidence was also downgraded due to imprecision.

Further safety data are available from post-marketing studies of tofacitinib [discussed under maintenance therapy below], which should be considered when deciding upon choice of induction therapy. The potential benefits of an oral route of administration and the lack of immunogenicity should also be considered. A previous meta-analysis of RCTs on tofacitinib showed similar positive data for clinical and endoscopic endpoints in both the subgroup of patients naïve to anti-TNF agents and the subgroup with previous anti-TNF agent exposure.[126] There were no significant differences in estimates of effect sizes between these subgroups. This was reflected in the findings of indirect network meta-analyses that did not find evidence of a statistical difference between tofacitinib and anti-TNF agents or ustekinumab for clinical and endoscopic outcomes in patients naïve to biologic therapy,[113,114] but suggest a possible benefit over adalimumab or vedolizumab for patients with previous anti-TNF agent exposure.[114]

Ustekinumab

Recommendation 15

We recommend treatment with ustekinumab for the induction of remission in patients with moderately-to-severely active UC with inadequate response or intolerance to conventional therapy. [strong recommendation, moderate quality of evidence]

A single RCT compared ustekinumab with placebo for induction therapy in patients with moderately-to-severely active UC [SoF Table 15, available as Supplementary data at ECCO-JCC online].[127] Patients were required to have not responded to or been intolerant to previous biologic or conventional therapy [defined as corticosteroid or thiopurines], or both, or have corticosteroid-dependent disease. Of these, 51.1% of randomised patients had previously failed treatment with an alternative biologic, including 16.6% who failed treatment with both an anti-TNF agent and vedolizumab. The study demonstrated the benefit of ustekinumab [6 mg/kg] over placebo in induction of **clinical remission** [15.5% vs 5.3%; RR: 2.91; 95% CI: 1.72–4.94], **clinical response** [61.8% vs 31.3%; RR: 1.97; 95% CI: 1.64–2.37], and **endoscopic improvement** [27.0% vs 13.8%; RR: 1.96; 95% CI: 1.41–2.72].

At completion of induction, the change in mean Inflammatory Bowel Disease Questionnaire [IBDQ] score from baseline was greater in those receiving ustekinumab [6 mg/kg] than in those receiving placebo [35.0 vs 16.16; p <0.001]. Median change in faecal calprotectin from baseline also showed a more significant reduction in the treatment arm [-1368.26 vs 17.92; p <0.001]. **SAEs** did not differ between ustekinumab [6 mg/kg] and placebo [5.2% vs 7.9%; RR: 0.67; 95% CI: 0.39–1.17].

Clinical and endoscopic benefit compared with placebo was observed for patients with and without previous biologic failure. An indirect network meta-analysis did not reveal a statistical difference between ustekinumab and anti-TNF agents or tofacitinib for clinical and endoscopic outcomes in patients naïve to biologic therapy, but suggested a possible benefit of ustekinumab over adalimumab or vedolizumab for patients with previous anti-TNF exposure.[114]

5.2. Maintenance of remission of moderately-to-severely active ulcerative colitis

Anti-TNF agents

Recommendation 16

We recommend anti-TNF agents [infliximab, adalimumab, or golimumab] for the maintenance of remission in patients with UC who responded to induction therapy with the same drug [strong recommendation, high-quality evidence]

We performed a meta-analysis of data extracted from 10 placebo-controlled RCTs of anti-TNF agents [infliximab, golimumab, adalimumab] for the maintenance of remission in adult patients with moderately-to-severely active UC [SoF Table 16, available as Supplementary data at ECCO-JCC online].[103–111,128] Anti-TNF agents were effective for the maintenance of **clinical remission** [RR: 1.98; 95% CI: 1.60–2.45], **steroid-free clinical remission** [RR: 2.86; 95% CI: 1.67–4.90], **improvement in quality of life [QoL]** [RR: 1.71; 95% CI: 1.27–2.32], and **sustained clinical remission** [RR: 2.76; 95% CI: 1.78–4.28]. The risk of **SAEs** was not different between anti-TNF agents and placebo [RR: 0.84; 95% CI: 0.64–1.09]. Evidence was also sought for endoscopic remission and biochemical remission; however, data were insufficient. Large-scale cohort studies support the safety of these drugs.[93,94,112]

Recommendation 17

In UC patients who have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of therapeutic drug monitoring to improve clinical outcomes

Multiple studies have shown an association between trough levels of biologic agents, including anti- TNF agents,[129–134] vedolizumab,[135–137] and ustekinumab,[138] and clinical outcomes in UC. Nonetheless, these studies were all retrospective analyses and cannot confirm any causal effect or suggest a benefit of trough-level based dose adjustment for improvement of response to biologics in patients with persistent disease activity. Retrospective analyses of mixed cohorts of patients with IBD, experiencing loss of response to anti-TNF agents, have shown that measurement of adequate infliximab or adalimumab drug levels appears to correlate well with patients who do not respond to subsequent dose escalation and to patients who do respond to switching to non anti-TNF therapies.[139–141] These retrospective data suggest that decisions informed by drug monitoring may be more likely to be successful than clinically guided decision making alone,[140] but this requires validation in a prospective study.

The same challenges and arguments around the need to demonstrate benefit and not just association apply to discussions around the use of prospective monitoring of drug levels to guide dosing in patients who are not experiencing loss of response. One study, published in abstract only, randomised 371 participants with UC, who had responded to induction therapy with adalimumab, to receive adalimumab at standard dose [40 mg every other week], high dose [40 mg every week], or dosing guided by therapeutic drug monitoring.[142] The therapeutic drug monitoring arm was not powered to demonstrate superiority and was considered exploratory. There was a non-significant trend towards higher rates of clinical remission amongst responders to induction therapy who were randomised to receive drug monitoring-guided dosing compared with standard dose [36.5% vs 29%].

Overall, given the lack of appropriate prospective studies, we were unable to make a recommendation [SoF Table 17, available as Supplementary data at ECCO-JCC online] and we suggest further research in this area.

Vedolizumab

Recommendation 18

We recommend vedolizumab for maintenance of remission in patients with UC who responded to induction therapy with vedolizumab [strong recommendation, moderate-quality evidence]

We identified three RCTs that included 441 patients treated with intravenous vedolizumab or placebo, which reported on maintenance of clinical remission and sustained clinical remission in adult patients with moderately-to-severely active UC who responded to induction therapy [SoF Table 18, available as Supplementary data at ECCO-JCC online].[122,123,143,144] Patients in these trials were followed up for 52–60 weeks. We performed a meta-analysis of results from these trials. **Clinical remission** was more common in induction-responders who subsequently received vedolizumab compared with placebo [RR: 2.37; 95% CI: 1.74–3.23]. Likewise, **sustained clinical remission** was also more common in patients receiving vedolizumab maintenance therapy compared with placebo [20.7% vs 9.4%; RR: 2.16; 95% CI: 1.34–3.50]. The quality of evidence for these outcomes was moderate to high. The rate of **SAEs** across five studies involving 1288 patients was not significantly different between vedolizumab and placebo [RR: 0.71; 95% CI: 0.39–1.30]. The quality of evidence for this outcome was moderate due to serious imprecision arising from sparse data. Nevertheless, the safety profile of vedolizumab has been established in a large cohort study.[112] In particular, the rate of serious infections in patients with UC appeared lower in those treated with vedolizumab than with anti-TNF agents, after adjusting for baseline differences [including comorbidities].

More recently, a double-dummy placebo-controlled RCT evaluated both intravenous and subcutaneous preparations of vedolizumab in patients with moderately-to-severely active UC, who had responded to open-label intravenous vedolizumab induction therapy.[143] **Clinical remission**, **endoscopic improvement**, and **sustained clinical remission** were significantly more frequently observed with subcutaneous vedolizumab than with placebo. The study was not powered to compare intravenous and subcutaneous preparations, although all outcomes were numerically similar between these two groups. SAEs occurred at similar frequencies in all three groups, and no distinct safety signals were observed with the subcutaneous preparation.

Recommendation 19

We suggest the use of vedolizumab rather than adalimumab for the induction and maintenance of remission in patients with moderately-to-severely active ulcerative colitis [weak recommendation, low level of evidence]

One RCT compared the efficacy and safety of vedolizumab with those of adalimumab over a 1-year period in patients with moderately-to-severely active UC [SoF Table 19, available as Supplementary data at ECCO-JCC online].[116] A significantly higher percentage of patients in the vedolizumab group than in the adalimumab group achieved **clinical response** [RR: 1.46; 95% CI: 1.29–1.67], **clinical remission** [RR: 1.39; 95% CI: 1.10–1.76), and **endoscopic remission** [RR: 1.43; 95% CI: 1.17–1.75]. There was a numerical trend in favour of vedolizumab for **biochemical remission** [RR: 1.22; 95% CI: 0.96–1.54]. Corticosteroid-free clinical remission occurred in a numerically lower percentage of patients in the vedolizumab group than in the adalimumab group [RR: 0.58; 95% CI: 0.32–1.05]. Of note, the quality of evidence for steroid-free clinical remission was low, as evidence relied on sparse data and the confidence intervals were very wide. Incidence rates of infections and serious infections occurred at similar frequencies with vedolizumab and with adalimumab [RR: 0.80; 95% CI: 0.55–1.17]. It is important to note that dose escalation was not permitted with either drug, despite evidence of improved maintenance outcomes with dose escalation for both drugs.[122,142,145]

Tofacitinib

Recommendation 20

We recommend tofacitinib for maintaining remission in patients with UC who responded to induction therapy with tofacitinib [strong recommendation, moderate quality of evidence]

We identified one RCT that reported outcomes in 593 patients treated with tofacitinib or placebo as maintenance therapy.[125] For patients who responded to induction therapy, tofacitinib at a dose of 5 or 10 mg twice daily was superior to placebo in maintaining **clinical remission** [RR: 3.37; 95% CI: 2.23–5.10] and **endoscopic remission** [RR: 3.88; 95% CI: 1.90–7.95] in patients with moderate-to-severe

UC who had an adequate response to the induction scheme. However, the evidence regarding endoscopic remission was downgraded due to imprecision [low number of events]. **Sustained clinical remission** [RR: 4.71; 95% CI: 2.51–8.84], **corticosteroid-free remission** [RR: 2.54; 95% CI: 1.39–4.65], and improvement in **QoL** [RR: 2.55; 95% CI: 1.93–3.37] were also superior. The evidence regarding corticosteroid-free clinical remission was also downgraded due to imprecision. Data on biochemical remission were insufficient.

SAEs for tofacitinib therapy in RCTs were comparable to placebo [RR: 0.70; 95% CI: 0.45–1.08]. The evidence was again downgraded due to imprecision. However, an increased risk for infections was observed [OR: 1.56; 95% CI: 1.18–2.06]. Most of the serious infections were of bacterial origin, including community-acquired pneumonia and urinary tract and skin infections. A separate meta-analysis of the safety profile of Janus kinase inhibitors across multiple inflammatory diseases showed a particularly high risk of viral infections, especially herpes zoster [RR: 6.53; 95% CI: 0.86–49.58].[146] This signal was also observed in a pooled analysis of safety data from the tofacitinib development programme in UC [incidence rate 4.1 events per 100 person-years; 95% CI: 3.1–5.2],[147] although most cases were uncomplicated and associated with a single dermatome. This risk appears to be dose dependent and is more common with 10 mg twice daily dosing than 5 mg twice daily.[147] A large cohort study in rheumatoid arthritis suggested that the rates of herpes zoster appear higher with tofacitinib than with anti-TNF agents; this risk appeared to be especially significant in older patients or in those receiving concomitant corticosteroid therapy.[148]

A safety study of tofacitinib in patients with rheumatoid arthritis, aged ≥50 years and with at least one known cardiovascular risk factor, revealed a significantly increased risk of venous thromboembolism [VTE] in patients treated with 10 mg twice daily tofacitinib compared with patients treated with anti-TNF agents. This risk was not observed in patients treated with 5 mg twice daily tofacitinib.[149] Although data are sparse, VTE has been reported in patients with VTE risk factors who participated in the UC development programme.[150] Considering these findings, the European Medicines Agency recommended using tofacitinib at the lowest efficacious dose and avoiding tofacitinib 10 mg twice daily as maintenance treatment for patients with known VTE risk factors. In this regard, 140 UC patients treated with tofacitinib 10 mg twice daily for at least 2 consecutive years, and in sustained remission for ≥6 months, were randomised to continue with the same dose or de-escalate to 5 mg twice daily. After 6 months, clinical remission rates were 77% and 90% for the 5 mg twice daily and 10 mg twice daily groups, respectively. No differences in AEs or SAEs were detected between the two groups, although herpes zoster cases were numerically higher in the 10 mg twice daily group.[151] Further post-marketing surveillance data suggest that tofacitinib use is also associated with an increased risk of cardiac events and malignancies.[152] Overall, we reiterate the comments made previously that the efficacy data, including in patients with previous anti-TNF exposure, along with the benefits associated with oral dosing and lack of immunogenicity, support our recommendations for tofacitinib as a treatment option in patients with UC, with the risks and benefits to be considered for each patient.

Ustekinumab

Recommendation 21

We recommend ustekinumab for the maintenance of remission in patients with UC who responded to induction therapy with ustekinumab [strong recommendation, moderate quality of evidence]

A single RCT compared ustekinumab with placebo for maintenance therapy in UC in patients who responded to ustekinumab induction therapy.[127] The study revealed that maintenance treatment with ustekinumab, at approved dosing of 90 mg subcutaneously every 8 weeks, offers benefit when compared with placebo in maintenance of **clinical remission** [RR: 1.82; 95% CI: 1.33–2.49] and maintenance of **steroid-free clinical remission** [RR: 1.79; 95% CI: 1.30–2.47], at Week 44. Although data were not available for endoscopic improvement, we used data for the closely related endpoint of **endoscopic remission** and found benefit compared with placebo [RR: 1.79; 95% CI: 1.36–2.36]. There was a reduction in mean faecal calprotectin for those who remained on ustekinumab during the maintenance period [-434.9 vs 813.3]. The benefits of ustekinumab were also reflected by the IBDQ scores in patients who completed the maintenance study [3.9 vs -15.7]. SAEs did not occur more frequently in the treatment arm [5.2% vs 7.9%; RR: 0.67; 95% CI: 0.39–1.17].

In addition to 8-weekly dosing, the study also evaluated 12-weekly maintenance therapy. Twelve-weekly dosing also showed statistically significant superiority over placebo for **clinical remission** [RR: 1.60; 95% CI: 1.16–2.21], **steroid-free clinical remission** [RR: 1.61; 95% CI: 1.16–2.24], and **endoscopic remission** [RR: 1.53; 95% CI: 1.14–2.04]. Compared with 8-weekly dosing, rates were numerically lower, but this did not reach statistical significance. The differences between outcomes with 8-weekly and 12-weekly dosing were greater in patients with a history of previous biologic failure.[127]

6. Conclusion

These recommendations summarise the current evidence on the medical management of adult patients with UC. Gaps were identified during the analysis of the 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[28,95,153–158] or Position Papers.[159–161] It is important that clinicians use these guidelines within the framework of local regulations, and seek to understand and address the individual needs and expectations of every patient. We recognise that constraints on health care resources are an important factor in determining whether recommendations can be implemented for patients in many countries. The recommendations outlined here should be used to inform treatment decisions and form part of an overall multidisciplinary treatment plan for patients with UC, which may also encompass psychological, nutritional, and other non-pharmacological interventions. ECCO will disseminate these guidelines by educational activities [i.e., educational platforms, ECCO Workshops, e-learning, and e-Guide] and will 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.[162] The e-Guide addresses important practical issues not addressed here, such as how to monitor for both positive and negative effects of medications. These treatment guidelines will be regularly updated according to the Guideline Committee schedule for the update of guidelines on the ECCO website. Updates will use the GRADE approach and consider the most recent evidence emerging from clinical research in the field.

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Conflict of Interest

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Supplementary Data

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

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ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment

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Abstract

This is the second of a series of two articles reporting the European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on the management of adult patients with ulcerative colitis [UC]. The first article is focused on medical management, and the present article addresses medical treatment of acute severe ulcerative colitis [ASUC] and surgical management of medically refractory UC patients, including preoperative optimisation, surgical strategies, and technical issues. The article provides advice for a variety of common clinical and surgical conditions. Together, the articles represent an update of the evidence-based recommendations of the ECCO for UC.

Key Words: Ulcerative colitis [UC]; inflammatory bowel disease [IBD]; surgery

Introduction

Ulcerative colitis [UC] usually presents as a mild condition, but often leads to life-threatening and systemic complications that require urgent interventions.[1–4] Acute severe ulcerative colitis [ASUC] and medically refractory UC represent the main indications for surgery in UC patients.[5,6] The first-line treatment of ASUC consists of intravenous corticosteroid treatment.[7,8] However, up to 30% of patients fail to respond to conservative treatments and require a colectomy.[9] Refractory UC includes steroid dependency and immunomodulator- or biologic-refractory disease. Refractory UC is often accompanied by deteriorated patient condition and is a recognised risk factor of poor postoperative outcomes[10–12]; thus a staged procedure is often preferred, to improve patient status and minimise postoperative complications.[13]

Despite the increasing availability of new pharmacological treatments, multiple attempts at conservative management and consequent therapeutic failures may affect the condition of patients with ASUC and refractory UC and considerably influence postoperative outcomes.[11,12] Accordingly, multidisciplinary [including gastroenterologists and surgeons] management of UC patients is of crucial importance to identify the best therapeutic pathway.

The European Crohn's and Colitis Organisation [ECCO] aims to develop a practical guide for the medical and surgical management of adult patients with UC, based on an interdisciplinary, evidence-based approach. The present article is focused on the first-line treatment of adult ASUC patients and on the surgical management of refractory adult UC patients, including preoperative assessment and technical aspects. The following statements are complementary to the guidelines on medical treatment of adult UC patients, which are presented in a separate article.

Materials and Methods

The present article is part of the ECCO evidence-based consensus on the management of UC and covers the medical treatment of ASUC and the surgical management of medically refractory moderate and severe UC. The current guidelines, together with those on UC medical management, are intended to update the previous ECCO recommendations published in 2017.[14,15] A summary of some of the key changes from previous ECCO UC guidelines is presented in the Supplementary material, available as Supplementary data at *ECCO-JCC* online.

The current guidelines followed the Oxford methodology. A detailed description of the methodology used to develop the guidelines is reported in the Supplementary materials.

General approach to ASUC and surgical management of refractory UC

ASUC usually presents as acute episodes of a chronic disease with a relapsing-remitting pattern. However, ASUC may be the onset feature in up of one-third of UC patients.[16] ASUC is associated with a 30–40% risk of colectomy after one or more severe exacerbations, and 10–20% of patients with ASUC need a surgical intervention at their first admission.[16–19] The definition and classification of ASUC follow the criteria of Truelove and Witts[20] and ECCO, which also include C-reactive protein [CRP] measurement.[15] Patients with ASUC require immediate hospitalisation. The standard initial therapy consists of intravenous corticosteroids.[15] However, approximately 30% of patients fail to respond to conservative treatments.[9] Failure may be predicted using the Travis criterion,[13] which combines the number of stools after 3 days of corticosteroid therapy and the level of serum CRP. In case of failure, different therapeutic strategies may

be considered. However, after 7 days without significant improvements, a surgical intervention is highly recommended to avoid the perioperative complications usually associated with emergent procedures.[21–23] In case of semi-elective surgery, a staged procedure is preferred, including subtotal colectomy with ileostomy during the first operation, followed by ileal pouch-anal anastomosis [IPAA] construction, and then a final operation with ileostomy closure.[24] This standard 'three-step' approach can be replaced by a modified two-step approach, starting also with subtotal colectomy but followed by pouch construction, without temporary stoma, thus avoiding the third operation. A detailed flowchart of the staged procedures is shown in Figure 1. Since early colectomy in ASUC patients is associated with significant improvements in perioperative outcomes and is now widely accepted,[25,26] we will restrict the focus of the ASUC guidelines to the medical therapeutic options for treating ASUC and address surgical management exclusively for medically refractory UC.

The surgical management of moderate-to-severe refractory UC is more varied compared with that of ASUC and there is currently less consensus. Since refractory UC is usually managed in an elective setting, the focus has progressively shifted from sole resolution of symptoms to parallel improvement in functions. Up to 25% of UC patients require a surgical intervention in their lifetime.[27,28] Although total proctocolectomy may provide a definitive resolution of UC symptoms, complete removal of the colon and the associated loss of function may be socially and psychologically unacceptable for the patient.[29] Successful surgical management may provide the resolution of ongoing symptoms and eliminate the need for continuous medical care [including hospitalisations and recurrent transfusions] and immunosuppressive therapies, while protecting the patient from malignancy risk. At the same time, the ideal surgical strategy should ensure acceptable long-term functional outcomes and minimise perioperative complications.[30] In recent decades, the surgical options for the treatment of refractory UC have evolved, combining technical advancements with a more comprehensive management of perioperative pathways. In addition to the medical management of ASUC, the following guidelines also focus on several aspects of the surgical management of medically refractory UC, including indication for surgery, perioperative optimisation, surgical approaches, and related technical strategies.

1. Medical Management of ASUC

1.1.Statement 1.1.

Intravenous corticosteroids as the initial standard treatment for adult patients with ASUC are recommended, as this treatment induces clinical remission and reduces mortality [EL3]

The only randomised controlled trial [RCT] including placebo in the setting of ASUC is the paramount work by Truelove and Witts, who observed that steroids induced clinical remission and decreased mortality without increasing serious adverse events.[20,31] Risk of bias led to downgrading of the evidence level from 2 to 3. No conclusions could be drawn about the need for surgery, as the authors included derivative ostomies and colectomies without distinguishing the type of surgery in the report. Since the results of this pivotal study, placebo-controlled trials to clarify these and other aspects would be unethical.

1.2.Statement 1.2.

Either infliximab or cyclosporine should be used in adult patients with steroid-refractory ASUC. When choosing between these strategies, centre experience and a plan for maintenance therapy after cyclosporine should be considered [EL3]

RCTs and meta-analyses indicate that infliximab is as effective as cyclosporine in inducing clinical response in adult patients with steroid-refractory ASUC (OR [odds ratio]: 1.08; 95% CI [confidence interval]: 0.73–1.60], with no significant differences regarding

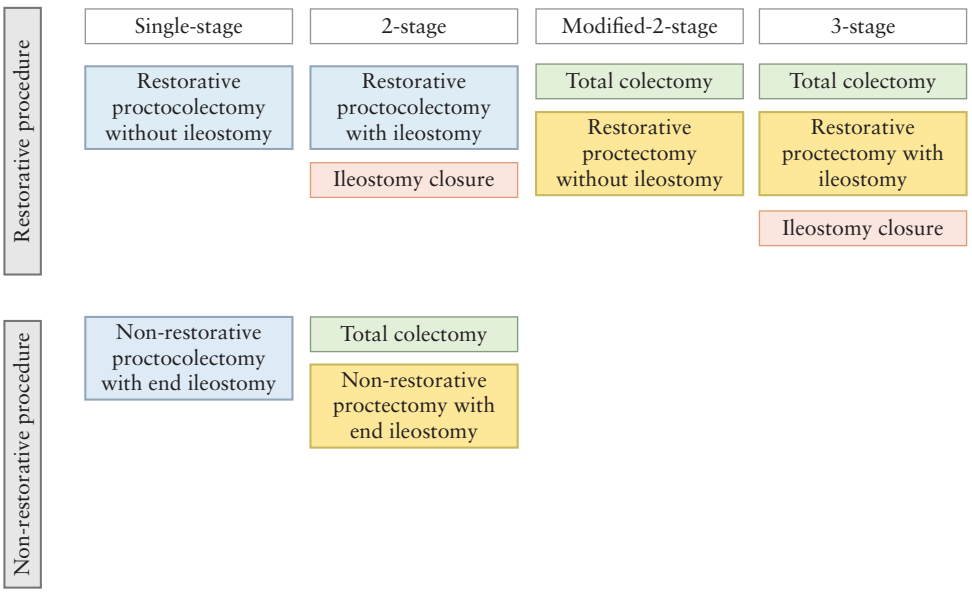

Figure 1. A detailed flowchart of the staged procedures for proctocolectomy. Published with permission from Prof. Antonino Spinelli.!

serious adverse events [OR: 1.78; 95% CI: 0.97–3.27], rate of colectomy at 12 months [OR: 0.76; 95% CI: 0.51–1.14], or in improvement of quality of life [QoL] or mortality [OR: 1.37; 95% CI 0.31–6.10].[32–34] Colectomy-free survival appeared to be similar and also at long-term follow-up [5 years].[35] Length of hospital stay appeared to be shorter with infliximab, although this was only observed in one post-hoc analysis.[36] Quality of evidence was downgraded due to imprecision and publication bias.

1.3.Statement 1.3.

There is currently insufficient evidence to determine the optimal regimen of infliximab rescue therapy in patients with ASUC refractory to corticosteroid therapy [EL4]

A meta-analysis including five RCTs and 30 retrospective and six prospective observational cohort studies reported the colectomy-free survival of ASUC patients after different infliximab induction strategies. Overall, colectomy-free survival following infliximab rescue therapy was 79% [95% CI: 75–84%] at 3 months and 70% [95% CI: 66–74%] at 12 months.[37] We did not find RCTs that compared different induction dosing strategy regimens. A single pilot RCT [that was prematurely terminated] explored the outcomes of different infliximab doses.[38] Colectomy-free survival at 3 months was higher with 5 mg/kg multiple-dose induction compared with 5 mg/kg single dose [OR: 4.24; 95% CI: 2.44–7.36; p <0.001], suggesting that initial treatment with multiple 5 mg/kg infliximab doses may be superior to single-dose salvage.[38,39]

A retrospective cohort study did not reveal differences in short-term [30 days] or long-term [12 months] colectomy rates between ASUC patients treated with accelerated- or standard-dose infliximab.[40]

Patients with ASUC have a high inflammatory burden, with accelerated clearance and faecal loss of infliximab that may lead to low concentrations and immunogenicity. Infliximab concentration is also affected by low albumin levels, which are common among ASUC patients due to malnutrition and protein loss. These considerations may make it reasonable to initiate treatment with intensive dosing regimens of infliximab. However, it is still unclear whether dose intensification will improve clinical outcomes in these circumstances.[41]

Eight observational studies including 736 patients] [9–14] reported that 3-month colectomy rates were comparable between the dose-intensification group [either high-dose or accelerated induction] and the standard induction group [OR: 0.70; 95% CI: 0.39–1.27; p = 0.24], although patients in the dose-intensification group had higher mean CRP and lower albumin levels. However, a recent retrospective propensity score matched cohort study revealed reduced short-term, but not long-term, colectomy rates in patients receiving accelerated infliximab dosing.[42] Recently, the British Society of Gastroenterology guidelines recommended accelerated dosing in patients who have not responded to the standard dose [5 mg/kg] after 3–5 days.[43] Therefore, there is no consensus whether intensive or standard infliximab dosing regimens are recommended. Furthermore, most of the studies were low-quality, uncontrolled, observational cohorts confounded by patient selection bias, heterogeneity, and imprecision. Thus, the optimal regimen for infliximab salvage therapy for ASUC remains unclear. Future RCTs are needed to fill these knowledge gaps and to investigate the role of early therapeutic drug monitoring in IBD patients treated with infliximab and dose optimisation.

1.4.Statement 1.4.

Third-line sequential rescue therapies with calcineurin inhibitors [cyclosporine or tacrolimus] in ASUC refractory to corticosteroid therapy may delay the need for colectomy but are associated with high rates of adverse events and should only be administered in specialised centres [EL2a]

A meta-analysis performed in 2015 found that after sequential treatment with infliximab followed by calcineurin inhibitors [cyclosporine or tacrolimus], 62% [95% CI: 57–68%] and 39% [95% CI: 33–44%] of patients achieved short-term treatment response and remission, respectively. Colectomy rates were 28% [95% CI: 22–34%] at 3 months and 42% [95% CI: 36–49%] at 12 months. Adverse events were experienced by 23% [95% CI: 18–28%] of patients, including serious infections in 7% [95% CI: 4–10%]. Mortality was observed in 1% [95% CI: 0–2%]. However, this meta-analysis was based on low-quality evidence and thus any definite conclusion on appropriate sequence of therapies was not possible.[44] Moreover, sequential third-line therapy is associated with significant adverse events and death.[45] Recent preliminary studies have focused on tofacitinib in ASUC patients refractory to corticosteroid treatment and have shown promising results and a good safety profile, but further investigations are needed to confirm its efficacy.[46,47] In conclusion, third-line therapies with infliximab and calcineurin inhibitors may delay, but not prevent, colectomies and should be carefully balanced with the higher risks of adverse outcomes. Sequential rescue therapy should only be administered at specialised referral centres familiar with the use of calcineurin inhibition.

Venous thromboembolism [VTE]– particularly deep vein thrombosis [DVT] and pulmonary embolism [PE] –is common in UC patients due to multifactorial and disease-related causes,[48–53]and may lead to significant morbidity and mortality.[54–56] The incidence of VTE correlates with disease activity[49,53,57] and increases in hospitalised subjects,[49] making ASUC patients at a high risk of developing VTE among the IBD population. Although several consensus guidelines support the use of anticoagulation prophylaxis in hospitalised UC patients with active disease,[8,58–61] there is still a substantial inconsistency in VTE prophylaxis administration.[62] Prophylaxis with low molecular weight heparin and fondaparinux significantly reduces the risk of VTE in hospitalised IBD patients, with minimal side effects.[61,63,64] However, robust evidence and well-designed clinical trials are lacking on the actual effectiveness of VTE prophylaxis and on the optimal dose regimen for ASUC patients.

2. Medical Versus Surgical Management of Refractory Moderate-to-severe UC

2.1.Statement 2.1.

Reconstructive surgery may be offered to refractory and corticosteroid-dependent patients and improves quality of life despite the risk of early and late complications [EL2b]. Proctocolectomy with end-ileostomy is an alternative for some patients and has lower morbidity and comparable quality of life [EL3a]

Five systematic reviews were performed to define the risk of early and late complications after restorative proctocolectomy with IPAA. Early complications [within 30 days after surgery] occurred in 9–65% of patients, and late complications occurred in 3–55% of patients.[65,66] Systematic reviews indicate that the most frequent complications were pouchitis [2–50%],[30,65–67] wound infection [7–45%],[30,65,66] bowel obstruction [2–33%],[65,66] ileus [14–30%],[66] sepsis [0–20%],[30,65–67] anastomotic leak [0.5–10%],[30,66] and fistula [0–6%].[66] The most common late complications were ileus [3–25%],[66] faecal incontinence [21–22%],[66] pouch loss [0–17%],[30,66] chronic pouchitis [10–16%],[30,67] Crohn's-like disease of the pouch [13%],[67] and fistula [0–8%].[66] The overall mortality rate after surgery was 0.1%.[66]

Despite the rates of early and late complications, most patients were satisfied with the surgical outcomes and more than 50% of patients would have preferred an earlier operation.[68] Delayed surgery may increase morbidity, length of stay, and hospital costs.[69] A recent meta-analysis focused on third-line therapies in severe chronic UC showed that, despite short-term improvements, third-line therapies only delay the need for colectomy and result in higher rates of complications.[68] Moreover, the overall rate of surgery for patients with UC is approximately 30%[30,65,67,68,70] but increases to 53% in steroid-refractory UC patients. The most common reasons to perform surgery are persistent malaise,[68] poor drug compliance,[68] dysplasia or cancer,[30,68] consuming symptoms,[30] and willingness to discontinue constant medical care [e.g., hospitalisations, recurrent transfusions] or immunosuppressive therapy.[30] Three systematic reviews reported that over 90% of patients who had colectomy had a good QoL,[68] with a happiness score of 10/10[30] and a Cleveland global QoL of 9/10.[30] Patients had five to six bowel motions per day[68] and one at night,[30] with a continence over 90%[30,68] and full continence of stool and gas up to 80% at 10 years.[30] Up to 93.3% of patients had a functioning pouch at 30 years, with stable QoL scores.[71]

The studies that compared ileostomy with IPAA were all retrospective and revealed similar results, using a different QoL score. Occasionally the scores obtained in specific domains of health-related QoL differed significantly between the surgical techniques [including body image, travelling, and sexual activity]. Removing the diseased colon offers a good QoL when compared with medical treatment in UC patients, with a morbidity ranging between 20% and 25%.[72]

3. Preoperative Optimisation of Refractory Moderate-to-severe UC

3.1.Statement 3.1.

Correction of altered body composition and nutrition imbalances is advised preoperatively, despite limited evidence [EL5].There is no evidence to support routine enteral or parenteral nutrition to improve the surgical outcomes of patients with UC [EL5]. Iron supplementation is recommended when iron-deficiency anaemia is present [EL1]

Nutritional alterations predict poor postoperative outcomes and mortality and affect QoL.[73,74] Routine perioperative assessment by a nutritionist should be considered in IBD patients in remission, as part of multidisciplinary management.[74] Even if current evidence is limited, it is advisable to correct undernutrition or overnutrition.[73,74] No data support routine perioperative administration of enteral or parenteral nutrition.[73] Delaying surgery by 7–14 days should be considered in patients with malnutrition.[74] High-quality evidence suggests that iron supplementation is recommended when iron deficiency is present, with the goal of normalising haemoglobin [Hb] levels and iron stores.[15,74]

3.2.Statement 3.2.

Patients taking >20 mg prednisolone for >6 weeks are at increased risk of early complications and pouch-specific complications. Steroids should be weaned before restorative proctectomy or proctocolectomy, and if this is not possible, surgery should be postponed [EL4]. Preoperative thiopurines or cyclosporine do not increase the risk of postoperative complications [EL3]. Patients on biologics might be at increased risk of developing early and late pouch-specific complications; three-stage or two-stage modified approaches with deferred pouch construction could be considered under these circumstances [EL4]. Single-stage restorative proctocolectomy should be avoided in patients receiving biologics [EL5]

Low-quality studies reported that patients who have received >20 mg prednisolone for >6 weeks are at 5-fold increased risk of infectious and short-term pouch-specific complications.[15] Steroids should be weaned before surgery; if this is not possible, pouch construction should be postponed.[15] Thiopurines or cyclosporine do not increase the risk of postoperative complications.[15]

Patients on biologics are at increased risk of early and post-ileostomy closure pouch-related complications [OR: 4.12; 95% CI: 2.37–7.15], but study quality is low.[75] Given the conflicting evidence, it would be prudent to avoid single-stage proctocolectomy with ileal pouch construction in patients on anti-tumour necrosis factor [TNF] therapies.[15]

3.3.Statement 3.3.

Prophylactic anticoagulation therapy in adult patients with active UC during hospitalisation is recommended, considering the high risk of venous thromboembolism [VTE] during UC flares [EL4]

One of the extraintestinal manifestations of UC is venous thromboembolism [VTE], which is higher among UC patients who underwent an emergency or elective colectomy [OR: 5.28; 95% CI: 1.93–4.45 and OR: 3.69; 95% CI: 1.30–10.44, respectively] compared with medically responsive UC patients.[76]

Patients with IBD have a 2- to 3-fold increased risk for VTE compared with healthy controls and an up to 8-fold increased risk during a disease flare or hospitalisation.[77,78] An observational study with 439 UC patients revealed a thrombosis prevalence of 5%, and half of the patients developed thrombosis during a UC flare [11% vs. 1%; OR: 8.0].[79]

Among 7078 IBD patients, only 0.6% received post-discharge anticoagulation prophylaxis and 235 patients [3%] developed thromboembolic complications. The strongest predictors of VTE were stoma creation [OR: 1.95; 95% CI: 1.34–2.84] and J-pouch

reconstruction [OR: 2.66; 95% CI: 1.65–4.29].[80] Among 837 IBD patients, 14 VTE events were reported, of which 79% received prophylaxis, but only 36% within 24 h of admission.[81]

A study with 2788 IBD patients reported that pharmacological thromboprophylaxis during IBD-related hospitalisation is associated with reduced risk of post-hospitalisation VTE [hazard ratio: 0.46; 95%CI: 0.22–0.97].[82] Patients who received VTE pharmacological prophylaxis were more likely to be on the surgical service [75% vs. 13%; p <0.001].[63,83]

Several studies suggested that pharmacological prophylaxis does not lead to increased incidence of gastrointestinal bleeding events in UC patients.[63,84–86] A meta-analysis suggested that heparin administration in patients with UC is safe, with no major bleeding events (the average reported dose was Enoxaparin/100 Anti-Xa IU/kg/day subcutaneously [s.c.] for 12 weeks).[87] The Toronto consensus for the management of IBD in pregnancy recommended anticoagulant thromboprophylaxis during hospitalisation over no prophylaxis.[88]

In conclusion, it is essential to emphasise that there are no established RCTs that have evaluated the efficacy of thromboprophylaxis in patients with IBD, due to the incidence of VTE. However, our ECCO consensus group determined that given the higher risk of thrombosis in UC patients with disease flare, VTE prophylaxis should be considered over no prophylaxis.

4. Surgical Strategy of Refractory Moderate-to-severe UC

4.1.Statement 4.1.

After total proctocolectomy for medically refractory UC, IPAA is the procedure of choice, but permanent end-ileostomy is also a reasonable option for some patients. A shared decision-making approach should be used to tailor procedure selection to the patient's preference [EL3]

Although IPAA is the procedure of choice for medically refractory UC patients requiring surgery, both IPAA and total proctocolectomy with end-ileostomy are reasonable options. Total proctocolectomy with end-ileostomy may be offered to patients with contraindications to IPAA. These operations result in similar overall short- and long-term complication rates, QoL, and costs. IPAA is associated with a high risk of pouch-related complications and costs. Total proctocolectomy with end-ileostomy is associated with a high risk for ileostomy-related complications and costs.

Overall, the short-term risks of these procedures appear equivalent and occur in approximately 30% in each group; IPAA is associated with risk of short-term anastomotic leak, fistula, or stricture, and total proctocolectomy is associated with risk of a non-healing perineal wound. The long-term complication profiles for these two procedures are different due to differences in anatomy. IPAA patients are at risk for faecal incontinence, pouchitis, fistula formation, and pouch failure, and total proctocolectomy patients are at risk for parastomal hernia and ileostomy prolapse.[66,89–92] QoL also appears equivalent; in a systematic review of 13 observational studies with 783 IPAA and 820 total proctocolectomy patients, the two procedures were comparable in overall health-related QoL.[72,92] Patients who undergo total proctocolectomy with end-ileostomy have ileostomy supply-related costs, and patients who undergo IPAA have costs related to endoscopic surveillance of the pouch.[91,92]

Although advanced age is a major consideration in procedure selection for patients who are candidates for either procedure, a shared decision-making approach should be used to tailor procedure selection according to the patient's preference.[93]

4.2.Statement 4.2.

IPAA may be performed as a two or three stage procedure. Modified two-stage IPAA may be associated with fewer complications and shorter length of stay than three-stage or two-stage IPAA in patients with medically refractory UC operated in expert centres, but more evidence is needed [EL3]

A modified two-stage IPAA comprises first a total colectomy with end-ileostomy, leaving the rectum in situ, followed by a proctectomy and ileal pouch-anal reconstruction with ileostomy take-down. Patients often undergo total colectomy at a late stage of their disease and present in an exhausted, catabolic state while being heavily medically treated, including with steroids. Hence, the second step is typically performed a few weeks to months after colectomy, allowing time for the patient to recover and for medications to be tapered. Proctectomy and IPAA construction can then be performed together as a modified two-stage approach, thus avoiding a diverting ileostomy which requires a third operative step for reversal and is associated with additional morbidity.[94,95] The modified two-stage IPAA is may become a standard of care, replacing one-stage, two-stage, and three-stage IPAA.[96–99] Clinical results in adults favour a modified two-stage approach, with better anastomotic leak rates,[99,100] fewer postoperative septic complications, and less small-bowel obstruction[101] when compared with two-stage and three-stage IPAA. A modified two-stage IPAA is also associated with less resource consumption and decreased length of hospital stay.[98,99] The IPAA leak rate is approximately 10% with a modified two-stage approach in expert centres. Functional results of IPAA are affected by the occurrence of an anastomotic leak, in particular without a diverting stoma.[102] It is therefore crucial to ensure a diligent postoperative follow-up, including serial CRP measurements and early investigation of any suspicion of leak. Indeed, when detected and addressed early, most leaking IPAAs can be salvaged and long-term pouch function can be preserved.[103]

Pouch-related complications include pouchitis, Crohn's disease of the pouch, cuffitis, and irritable pouch. Among these, pouchitis is the most common complication, occurring in up to 80% of patients after 30 years from the pouch construction.[71,104–106] Pouchitis is commonly diagnosed by endoscopy and histological characterisation. According to the duration and type of symptoms, pouchitis can be classified into acute [symptoms resolving within 4 weeks], chronic [symptoms last >4 weeks], or relapsing [three or more episodes of pouchitis occur in a year]. Treatment for acute pouchitis includes antibiotic administration, mainly consisting of ciprofloxacin and metronidazole.[107–109] However, the evidence of efficacy is low, including only one small RCT demonstrating the superiority of ciprofloxacin over metronidazole in terms of symptoms reduction and endoscopic response.[64] An RCT of rifaximin failed to demonstrate a superiority compared with placebo,[110] and budesonide enemas and metronidazole were equally effective for inducing remission.[111] Patients with chronic pouchitis can develop antibiotic-refractory symptoms. Due to persistent and debilitating symptoms they may ultimately develop pouch failure requiring pouch defunctioning and definitive stoma

construction. Several medications have been investigated to induce remission in chronic antibiotic-refractory pouchitis, including biologic therapy, probiotics, and immunodulators, although the overall quality of evidence is low.[112]

5. Technical Aspects of Surgical Approaches for Refractory Moderate-to-severe UC

5.1.Statement 5.1.

IPAA may be constructed using either a stapled or a handsewn technique, with comparable functional outcomes. Thus, the type of anastomosis should be left to the surgeon's discretion [EL2]

Overall, stapled and handsewn IPAAs seem to result in comparable complication rates, functional outcomes, and QoL. In a meta-analysis of four randomised controlled trials including 184 patients [53% stapled, 43% handsewn], no significant differences were observed in terms of functional outcomes, sphincter resting pressure, or squeeze pressures.[113] Based on low-quality evidence, the stapled technique may be more likely to achieve perfect continence [90% vs. 67%; p <0.0001] compared with the handsewn approach.[114] Despite slightly better functional outcomes after stapled anastomosis, overall QoL appears equivalent between the two groups.[114,115]

Although handsewn IPAA is more commonly performed in patients with dysplasia or cancer, the approach does not reduce the probability of recurrence.[115] In a systematic review of observational studies with 43 rectal cancer patients, most of the cases [70%; 30 patients] occurred after mucosectomy with handsewn anastomosis, and 30% [13 patients] occurred after stapled anastomosis. Of 28 reported cases of dysplasia, 27 [96%] cases occurred after mucosectomy with handsewn anastomosis, and one [4%] occurred after stapled anastomosis. The median time to dysplasia or cancer was 10 years.[116] In a systematic review of 23 observational studies with 2040 patients, the pooled prevalence rate of neoplasia after IPAA was 1.1% and was equally distributed in the pouch, rectal cuff, and anal transition zones. Previous colorectal dysplasia or cancer, but not pouchitis or duration of follow-up, were predictive of rectal cancer or dysplasia,[117] indicating that mucosectomy with handsewn anastomosis does not eliminate the risk of subsequent dysplasia or cancer.

Due to a paucity of high-quality data, no recommendations can be made with regards to sexual function, strictures, and septic complications between stapled and handsewn techniques, although stapled IPAA is likely associated with a higher rate of cuffitis.[118,119]

5.2.Statement 5.2.

Laparoscopic surgery is the preferred approach to patients with medically refractory UC, as it is associated with lower intra- and postoperative morbidity, faster recovery, fewer adhesions and incisional hernias, shorter hospital length of stay, improved female fecundity, and better cosmesis [EL2]

Laparoscopy is the preferred approach to bowel resection for experienced surgeons. Evidence in favour of this recommendation is large, with several meta-analyses in UC reporting benefits in terms of short- and long-term morbidity, functional outcomes, cosmesis, and QoL.[120–125] There is a single RCT including long-term results,[126,127] but nationwide data support minimally invasive approaches,[120] which have long been endorsed by expert centres worldwide. Laparoscopy should be offered for elective and emergent segmental and total colectomy and for reconstructive surgery. Although desirable, laparoscopy is not always possible. Patients with previous abdominal surgery and extensive adhesions or cardiopulmonary instability may require an open procedure. Lack of surgical expertise may also limit access to laparoscopy, particularly in the emergent setting or in remote locations. Operative time tends to be greater when a minimally invasive approach is chosen, and resource consumption may be increased.[123] It is important to note that a previous open procedure does not mandate a second open procedure. For example, a patient who had an open colectomy and end-ileostomy for fulminant colitis should attempt laparoscopic proctectomy and IPAA reconstruction. Beyond functional outcomes, minimally invasive approaches are also associated with better fecundity and pregnancy outcomes.[128–130]

5.3.Statement 5.3.

Although associated with an increased risk of rectal dysplasia, cancer, and dysplasia or cancer recurrence, patients with UC and a minimally affected rectum can be offered the option of an ileo-rectal anastomosis [IRA] [EL4]

IRA is associated with better functional outcomes [number of bowel movements and nocturnal frequency] compared with IPAA.[131–134] Failure rates are similar between IRA and IPAA.[135,136] IRA failure rates were estimated at 27.0% [95% CI: 22–32] and 40.0% [95% CI: 33–47] at 10 and 20 years, respectively, and may be decreased with a two-stage procedure approach [OR: 0.10; 95% CI: 0.03–0.41].[137] Two-thirds of secondary proctectomies were performed for refractory proctitis, and 20% for rectal neoplasia. Acute proctitis occurred in 70% of patients; 76% experienced chronic proctitis.[138] IRA may be associated with an increased risk of rectal cancer development,[135,139] but this was based on limited and low-quality data.

Conclusion

The variability in symptoms and clinical manifestations of UC makes it difficult to establish a unique and predefined therapeutic pathway; the lack of specific protocols may restrict the management of these patients to highly specialised centres, thus limiting accessibility to medical care.

In addition to continuous updates on novel therapeutic strategies and technical trainings, the key to successful management of UC patients is to promote a multidisciplinary approach with close communication between different IBD specialists, who should remember the relevant social and economic burden of UC.

These guidelines were developed using the Oxford methodology, which combines a robust methodological strategy with a multidisciplinary approach. Whereas each statement was drafted by an expert on the topic, identification of the critical questions and discussion on the retrieved evidence involved all members of the committee, which allowed for the identification of aspects that may otherwise have been overlooked.

In addition to the clinical questions addressed in these guidelines, we recognise that many other topics would have been worthy of

discussion. These include early postoperative management of UC patients and the possibility of implementing an enhanced recovery pathway [with related challenges and advantages] and management of pouch-related complications, which are addressed in previous guidelines.[14,15] However, the clinical questions were selected with the aim of providing relevant updates on neglected topics.

The peculiarity of the clinical questions in these guidelines, particularly in the surgical field, often made it difficult to provide specific recommendations. However, the drafting process identified critical needs and revealed gaps in knowledge, thus laying the groundwork for future research.

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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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Supplementary Data

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

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