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REVIEW ARTICLE

Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Current management

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5. Medical management of active ulcerative colitis

5.1. General

When deciding the appropriate treatment strategy for active ulcerative colitis one should consider the activity, distribution (proctitis, left-sided, extensive¹), and pattern of disease. The disease pattern includes relapse frequency, course of disease, response to previous medications, side-effect profile of medication and extra-intestinal manifestations. The age at onset and disease duration may also be important factors.

5.1.1. Disease activity

The principal disease activity scoring systems used in clinical trials are covered in Section 1.2 and have been comprehensively reviewed.² However there are some practical points that are relevant for routine clinical use. For example, it is most important to distinguish patients with severe ulcerative colitis necessitating hospital admission from those with mild or moderately active disease who can generally be managed as outpatients. The simplest, best validated and most widely used index for identifying severe UC remains that of Truelove and Witts³: any patient who has a bloody stool frequency ≥ 6 /day and a tachycardia (>90 bpm), or temperature >37.8 °C, or anaemia (haemoglobin <10.5 g/dL), or an elevated ESR (>30 mm/h) has severe ulcerative colitis (Table 1.3). Only one additional criterion in addition to the bloody stool frequency ≥ 6 /day is needed to define a severe attack.^{4,5}

It should be standard practice to confirm the presence of active colitis by sigmoidoscopy before starting treatment. Flexible sigmoidoscopy and biopsy may exclude unexpected causes of symptoms that mimic active disease such as cytomegalovirus colitis, rectal mucosal prolapse, Crohn's disease, malignancy, or even irritable bowel syndrome and haemorrhoidal bleeding. There may be a significant overlap between other diseases that mimic ulcerative colitis and the broad spectrum of UC damage.^{6,7} In addition, all patients with active disease require stool cultures with *Clostridium difficile* toxin assay to exclude enteric infection. Patients with an appropriate travel history should also have stool microscopy to exclude parasitic infections such as amoebiasis.

5.1.2. Approach

Patients should be encouraged to participate actively in therapeutic decisions which should be tailored to the individual.⁸ In a systematic review of clinical trials, 15% (95% CI 10–21%) of patients entered remission when receiving

placebo,⁹ although placebo rates are lower if the endpoints assessed are more stringent. However, prescribing no treatment is rarely an option as rectal bleeding and urgency are sufficiently concerning to the patient to justify topical therapy even if no systemic therapy is recommended. Despite general agreement that treatment decisions for active UC should be based on the distribution, activity and pattern of disease, numbers in clinical trials often become too small for statistically valid conclusions to be drawn when patients are stratified according to the distribution and pattern of disease. In addition, it is important to remember that different preparations containing the same active compound may have different release profiles and may have either local or systemic activity. Finally, the choice of therapeutic strategy should be influenced by the balance between drug potency and side-effect profile; previous response to treatment (especially when considering treatment of a relapse, treatment of steroid-dependent or -refractory disease, or immunomodulator-refractory disease); and the presence of extraintestinal manifestations which may require systemic therapy.

5.2. Treatment according to site of disease and disease activity

5.2.1. Proctitis

ECCO statement 5A

A mesalazine 1 g suppository once daily is the preferred initial treatment for mild or moderately active proctitis [EL1b, RGA]. Mesalazine foam enemas are an alternative [EL1b RG B]. Suppositories may deliver drug more effectively to the rectum and are better tolerated than enemas [EL3, RG C]. Combining topical mesalazine with oral mesalazine or topical steroid is more effective than either alone and should be considered for escalation of treatment [EL1b, RG B]. Oral mesalazine alone is less effective [EL1b, RG B]. Refractory proctitis may require treatment with immunosuppressants and/or biologics [EL4, RG C]

The first line therapy for active colitis limited to the rectum is topical mesalazine (5ASA). A Cochrane database systematic review of 38 clinical trials of treatment of proctitis and left sided colitis confirmed the superiority of this therapy over placebo for inducing symptomatic, endoscopic and histological improvement and remission.¹⁰ The

pooled odds' ratio (POR) for symptomatic remission was 8.3 (8 trials, 95% CI 4.28 to 16.12; $p < 0.00001$), for endoscopic remission was 5.3 (7 trials, 95% CI 3.15 to 8.92; $p < 0.00001$), and for histologic remission was 6.3 (5 trials, 95% CI 2.74 to 14.40; $p < 0.0001$). Suppositories are more appropriate than enemas in patients with proctitis as they target the site of inflammation (only 40% of foam enemas and 10% of liquid enemas can be detected in the rectum after 4 h).¹¹ There is no dose response for topical therapy above a dose of 1 g mesalazine daily. Once daily suppository therapy is as effective as divided doses.^{12,13}

Topical mesalazine is more effective than topical steroids, whether assessing symptomatic remission (OR 2.42, 95% CI 1.72–3.41), endoscopic remission (OR 1.89, 95% CI 1.29–2.76), or histological remission (OR 2.03, 95% CI 1.28–3.20).¹⁴ The results of this meta-analysis were confirmed in the Cochrane Database systematic review.⁸ Consequently topical steroids should be reserved as second line therapy for patients who are intolerant of topical mesalazine.¹⁵

Topical mesalazine is more effective than oral mesalazine alone for proctitis.¹⁶ However, if using oral mesalazine therapy alone, 3.6 g of a pH-dependent release profile preparation was more effective than lower doses or placebo.¹⁷ The combination of oral and topical mesalazine appears to be more effective than either alone in patients with disease extending < 50 cm from the anal verge.¹⁸ There have been no trials on combination therapy for proctitis alone. Combining topical mesalazine and topical steroid also helps: beclomethasone dipropionate (3 mg) and mesalazine (2 g) enemas produced significantly better clinical, endoscopic and histological improvement than either agent alone.¹⁹ Patients who fail to improve on oral/topical mesalazine and topical corticosteroids should be treated with the addition of oral prednisolone. The management of refractory proctitis is discussed in Section 1.2.2.

5.2.2. Left sided colitis

ECCO Statement 5B

Left-sided active ulcerative colitis of mild–moderate severity should initially be treated with an aminosalicilate enema 1 g/day [EL1b, RG B] combined with oral mesalazine > 2 g/day [EL1a, RG A]. Topical therapy with steroids or aminosalicylates alone [EL1b, RG B] as well as mono-therapy with oral aminosalicylates [EL1a, RG A] is less effective than oral plus topical 5ASA therapy. Topical mesalazine is more effective than topical steroid [EL1a, RG A]. Once daily dosing with 5ASA is as effective as divided doses [EL1b, RG A]. Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine [EL1b, RG C]. Severe left-sided colitis is usually an indication for hospital admission for intensive treatment with systemic therapy [EL1b, RG B].

Although most therapeutic trials of mild to moderate active colitis include patients with any disease distribution other than proctitis, there is clear evidence that both oral and topical mesalazine are effective for left-sided colitis compared to

placebo.^{10,20} First line therapy for mild to moderately active left sided colitis is combined oral and topical mesalazine therapy.¹⁵ This strategy has been investigated in a single trial of 60 patients with distal colitis which demonstrated that combined therapy was more effective and worked more rapidly than either oral or topical therapy alone.¹⁸ Further support for the use of combined oral and rectal mesalazine therapy in patients with left sided colitis comes from an extrapolation of a trial of combination therapy for extensive colitis.²¹ Furthermore, there is evidence that topical therapy achieves higher rectal mucosal 5ASA concentrations than oral therapy²² and is associated with improved clinical outcome.^{22,23}

Mesalazine foam enemas are not inferior to liquid enemas for inducing remission,²⁴ so either are appropriate treatments for left-sided colitis. Low volume enemas are not inferior to high volume enemas in patients with left sided colitis and may be better tolerated.²⁵ Although several meta-analyses have confirmed the superiority of rectal 5ASA over rectal corticosteroids,^{10,14} a recent meta-analysis of three trials has suggested that rectal beclomethasone dipropionate is equivalent to rectal 5ASA.²⁶

Oral mesalazine has not been shown to be any more effective than oral sulfasalazine (OR 0.83, 95% CI 0.60–1.13 for clinical improvement or remission) but is better tolerated.²⁷ An initial systematic review of 9 placebo controlled trials of oral aminosalicylates for active ulcerative colitis showed the overall remission rate to be only 20%.²⁸ However, additional placebo controlled trials of a multimatrix mesalazine formulation for mild–moderate UC,^{29,30} as well as a combined analysis³¹ have since been published. These included 626 patients and showed remission rates after 8 weeks of therapy of up to 40% with evidence of mucosal healing in 32%. Importantly, these were the first studies to demonstrate that once daily dosing is as effective at inducing remission in mild to moderately active UC as an equivalent total dose delivered twice daily.³⁰ This finding was confirmed in a double blind, double dummy randomised non-inferiority trial of 3 g/day mesalazine granules delivered either once daily or as 1 g three times daily.³² Indeed, in the subgroup of 197 patients with left sided colitis, clinical remission was more common at week 8 in the once daily compared to the divided dose group (86% vs 73%; $p = 0.0298$). Therefore once daily dosing with mesalazine is preferred in patients with left sided disease. The potential additional benefit of combining once daily oral mesalazine with a mesalazine enema has not been assessed in a clinical trial.

A meta-analysis of mesalazine for active UC confirms the suggestion^{27,33} that there is a dose–response for mesalazine with doses of ≥ 2.0 g/day being more effective than < 2.0 g/day for the induction of remission (RR=0.91; 95% CI 0.85–0.98).²⁰ The additional clinical benefit of doses greater than 2 g/day was assessed in the ASCEND II trial in 268 patients with moderately active disease, half of whom had distal disease.³³ Responses to treatment were 71.8% in the 4.8 g group and 59.2% in the 2.4 g group ($p = 0.036$), although remission rates were only 20.2% and 17.7% respectively (ns).³³ Mucosal healing rates at week 6 were higher in the 4.8 g/day group.³⁴ The ASCEND III trial confirmed the non-inferiority and safety of 4.8 g/day mesalazine delivered as 800 mg tablets compared to 2.4 g/day delivered as 400 mg tablets, in terms of achieving clinical response at 6 weeks and also suggested a benefit of the higher dose strategy for induction of remission (43% vs 35%; $p = 0.04$).³⁵ However, the MMX mesalazine trial showed no additional

benefit of 8 weeks on 4.8 g/day compared to 2.4 g/day.³⁰ Therefore doses of at least 2 g mesalazine per day are recommended.

The threshold for the introduction of oral steroids in patients with mild to moderately active left sided colitis depends upon the response to and tolerance of mesalazine, patient preference and the physician's practice. The balance between desired time to response and steroid-induced side effects should be discussed with the patient. A guide to the expected time to response for oral mesalazine can be taken from the pivotal clinical trials (which included patients with extensive colitis as well as left sided disease). In the ASCEND II trial the median time to cessation of rectal bleeding was 9 days in patients receiving 4.8 g mesalazine/day and 16 days in those receiving 2.4 g/day.³³ Likewise, the time to the first day with no rectal bleeding was 7 days for 4.8 g/day MMX mesalazine, although 37–45 days therapy was required before sustained complete remission was achieved.^{29,30} Combination oral and rectal mesalazine reduces the time to cessation of rectal bleeding compared to oral therapy alone.²¹ Therefore, if a patient's symptoms deteriorate, rectal bleeding persists beyond 10–14 days, or sustained relief from all symptoms has not been achieved after 40 days of appropriate mesalazine therapy, additional therapy should be commenced. This would normally involve the addition of oral corticosteroids. There are, however, open label data suggesting that a significant proportion of patients who have not responded to 8 weeks' oral mesalazine may enter clinical remission with a further 8 weeks of 4.8 g MMX mesalazine irrespective of the initial dosing regime.³⁶

5.2.3. Extensive ulcerative colitis

ECCO Statement 5C

Extensive ulcerative colitis of mild–moderate severity should initially be treated with oral 5-ASA >2 g/day [EL1a, RG A], which should be combined with topical mesalazine to increase remission rates if tolerated [EL1b, RG A]. Once daily dosing with 5ASA is as effective as divided doses [EL1b, RG A]. Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine [EL1b, RG C]. Severe extensive colitis is an indication for hospital admission for intensive treatment [EL1b, RG B]

As the majority of clinical trials in mild to moderate ulcerative colitis include patients with both pancolitis and left sided colitis much of the evidence base for this statement is discussed in [Section 1.2.2](#). Oral mesalazine is clearly more effective than placebo for the induction of remission of mild to moderately active extensive ulcerative colitis.^{20,27,37} The benefit of combining oral and rectal mesalazine was shown in a trial of 116 patients randomised to oral mesalazine 4 g/day with a 1 g mesalazine enema vs oral mesalazine with a placebo enema.²¹ Combined oral and rectal mesalazine achieved clinical remission at week 8 in 64% compared to 43% on oral mesalazine alone ($p=0.03$).²¹ Once daily mesalazine is as effective as divided doses in patients with extensive colitis.^{30,32} Failure of mild or moderately active disease to respond to mesalazine is an indication to start oral prednisolone. Similarly, if a patient already on mesalazine >2 g/day

or immunomodulators as maintenance therapy has a relapse, treatment with steroids is considered appropriate.

Evidence for the benefit of oral corticosteroids therapy comes from two early studies of active UC which included patients with extensive colitis. Oral prednisolone (starting at 40 mg daily combined with steroid enemas) induced remission in 76% of 118 patients with mild to moderate disease within 2 weeks, compared to 52% treated with 8 g/day sulfasalazine plus steroid enemas.³⁸ Similar findings were reported by Lennard-Jones,³⁹ who found the combination of oral and rectal steroids to be better than either alone. An appropriate regimen for moderately active disease is prednisolone 40 mg/day for 1 week, reducing by 5 mg/day every week resulting in an 8 week course. Many different regimes are used, but it is sensible to have a standard approach at any single centre, so that steroid-dependence is recognised at an early stage and a decision to start immunomodulators is facilitated. Shorter courses (<3 weeks) are associated with early relapse and doses of prednisolone ≤ 15 mg/day are ineffective for active disease.⁴⁰

The efficacy of budesonide for active UC was the subject of a Cochrane database systematic review of 3 trials which concluded that oral budesonide was significantly less likely to induce clinical remission than oral mesalazine (RR 0.72, 95% CI 0.57 to 0.91) and had no benefit over placebo (RR 1.41, 95% CI 0.59 to 3.39).⁴¹ Therefore budesonide in its current formulation is not recommended in routine clinical practice. Oral steroid preparations with a colonic release mechanism and low systemic bioavailability such as beclomethasone dipropionate or budesonide are becoming available. One large study of 177 patients with active left-sided or extensive colitis reported that beclomethasone dipropionate 5 mg/day had an effect similar to that of 2.4 g mesalazine without systemic steroid side-effects.⁴² A novel budesonide MMX preparation has recently completed phase III trials at present with preliminary data suggesting significant benefit over placebo for the induction of remission in UC.⁴³

5.2.4. Severe ulcerative colitis of any extent

Acute severe ulcerative colitis is a potentially life-threatening condition. Historical prevalence data demonstrate that 47/250 (18.8%) of initial disease flares are severe and that 109/619 (17.6%) of all patients have a severe attack as defined by criteria in [Statement 1D](#) at some stage in their disease course.⁴⁴ Understanding the implications of the current medical and surgical strategies requires knowledge of the historical context. In 1933, 16/21 (75%) patients died within the first year after acute presentation with ulcerative colitis⁴⁵ and in 1950 a mortality of 22% was reported amongst 129 cases in the first year after diagnosis.⁴⁶ The pivotal clinical trial of steroid therapy for severe colitis in the 1950s reported a mortality of 7% in those treated with corticosteroids compared to 24% in the placebo group.³ The 2008 IBD audit in the UK reported a mortality of 2.9% in patients admitted with acute severe colitis, although it may be as low as <1% in specialist centres.⁴⁷ The response rate to appropriately dosed intravenous steroids has not changed over the last 30 years.⁴ Therefore the reduction in mortality reported in the recent series is likely to reflect improvements in the supportive care of patients with severe UC and timely surgical intervention when appropriate. Therefore, the Consensus participants believe that all patients meeting the criteria for severe colitis should be admitted to hospital for intensive treatment

under the care of a multidisciplinary team including a specialist Gastroenterologist and Colorectal surgeon.

ECCO Statement 5D

Patients with bloody diarrhoea ≥ 6 /day and any signs of systemic toxicity (tachycardia > 90 bpm, fever > 37.8 °C, Hb < 10.5 g/dL, or an ESR > 30 mm/h) have severe colitis and should be admitted to hospital for intensive treatment [EL5, RG DJ].

5.2.4.1. Therapeutic approach. All patients admitted with severe colitis require appropriate investigations to confirm the diagnosis and exclude enteric infection.⁴⁸ Intravenous corticosteroids remain the mainstay of conventional therapy.⁴⁹ It is essential to ensure that the therapeutic alternatives for rescue of steroid-refractory disease (ciclosporin, tacrolimus, or infliximab) are considered early (on or around day 3 of steroid therapy) and that the decision making process is not delayed. Patients remaining on ineffective medical therapy including corticosteroids suffer a high morbidity associated with delayed surgery.^{50,51} Therefore, the principal clinical dilemmas remain how to identify at an early stage patients likely to require colectomy, and when to start rescue medical therapy. The two are not mutually exclusive and management demands careful clinical judgement.

5.2.4.2. Conventional therapy.

Corticosteroids are generally given intravenously using methylprednisolone 60 mg/24 h or hydrocortisone 100 mg four times daily. Higher doses are no more effective, but lower doses are less effective.^{4,52} Bolus injection is as effective as continuous infusion.⁵³ Treatment should be given for a defined period as extending therapy beyond 7 to 10 days carries no additional benefit.⁴ A systematic review of 32 trials of steroid therapy for acute severe colitis involving 1991 patients from 1974 to 2006 reported an overall response to steroids (intravenous hydrocortisone, methylprednisolone, or betamethasone) of 67% (95% CI 65–69%).⁴ Out of the 1991 patients, 565 (29%, 95% CI 28–31%) came to colectomy. Mortality was 1% (22/1991, 95% CI 0.7–1.6%) and none of these outcomes changed between 1974 and 2006 (R²=0.07, p=0.8). Because of substantial heterogeneity, it was not possible to discriminate between complete and partial responses to steroids.

One small randomised clinical trial demonstrated that ciclosporin monotherapy (ciclosporin, 4 mg/kg/day intravenously) was as effective as intravenous methylprednisolone 40 mg/day for acute severe colitis. A clinical response was reported in 10/15 ciclosporin patients versus 8/15 steroid patients.⁵⁴ Furthermore, half of all patients in another study comparing low dose with high dose ciclosporin⁵⁵ also received ciclosporin monotherapy, without concomitant intravenous steroids. Consequently monotherapy with ciclosporin (normally at 2 mg/kg/day) is a useful option in those patients with severe colitis when steroids are best avoided, such as those susceptible to steroid-psychosis, patients with concomitant osteoporosis or those with poorly controlled diabetes.

Other measures that are considered appropriate in addition to intravenous steroids include:

- Intravenous fluid and electrolyte replacement to correct and prevent dehydration or electrolyte imbalance. Potassium

supplementation of at least 60 mmol/day is almost invariably necessary. Hypokalaemia or hypomagnesaemia can promote toxic dilatation.⁵⁶

- Unprepared limited flexible sigmoidoscopy and biopsy to confirm the diagnosis and exclude cytomegalovirus infection^{57,58} which is often associated with a steroid refractory disease course⁵⁹ and requires appropriate treatment.⁶⁰
- Stool cultures and assay for co-existing *Clostridium difficile* toxin, which is becoming more prevalent in patients admitted with severe colitis and is associated with increased morbidity, mortality and health care costs.^{61–64} If detected appropriate antibiotic therapy should be administered. Consideration should be given to stopping immunosuppressive therapy where possible,⁶⁵ although this may not always be appropriate.⁶⁰
- Subcutaneous prophylactic low molecular weight heparin to reduce the risk of thromboembolism which has been shown to be increased in patients with IBD compared to controls, especially during a disease flare and is not related to other thromboembolic risk factors.^{66,67}
- Nutritional support if the patient is malnourished. Enteral nutrition is most appropriate and associated with significantly fewer complications than parenteral nutrition in acute colitis (9% vs 35%).⁶⁸ Bowel rest through intravenous nutrition does not alter the outcome.⁶⁹
- Withdrawal of anticholinergic, anti-diarrhoeal, NSAID and opioid drugs, which may risk precipitating colonic dilatation.^{56,70,71}
- Topical therapy (corticosteroids or mesalazine) if tolerated and retained, although there have been no systematic studies in acute severe colitis.⁴⁹
- Antibiotics only if infection is considered (such as in an acute, first attack of short duration, after recent admission to hospital or after travel to an area where amoebiasis is endemic), or immediately prior to surgery. Controlled trials of oral or intravenous metronidazole, tobramycin, ciprofloxacin or vancomycin in acute colitis have shown no consistent benefit in addition to conventional therapy.^{72–74}
- Blood transfusion to maintain a haemoglobin above 8–10 g/dL.
- A multidisciplinary approach between the gastroenterologists and colorectal surgeons looking after the patient is essential.

5.2.5. Intravenous-steroid refractory ulcerative colitis of any extent

ECCO Statement 5F

The response to intravenous steroids is best assessed objectively around the third day [EL2b, RGB]. Treatment options including colectomy should be discussed with patients with severely active UC not responding to intravenous steroids. Second line therapy with *either* ciclosporin [EL1b, RG B], *or* infliximab [EL1b, RG B] *or* tacrolimus [EL4, RG C] may be appropriate. If there is no improvement within 4–7 days of salvage therapy, colectomy is recommended [EL4, RG C]. Third line medical therapy may be considered at a specialist centre [EL4, RG C].

The timing of colectomy for severe colitis remains one of the most difficult decisions that a gastroenterologist has to

make. Over the recent past, clinical trials of different salvage therapies for patients with severe colitis refractory to intravenous steroids have been published. However, it is important that physicians do not acquiesce with the patient's understandable desire to delay surgery with inappropriate or unduly prolonged courses of therapy as this will increase the morbidity and mortality associated with subsequent surgery.^{50,51} Therefore, the important issues that must be considered and discussed with the patient include:

- 1) Can one predict who will fail to respond to iv corticosteroids early, so that appropriate salvage therapy can be started in a timely fashion?
- 2) Are the available salvage therapies (calcineurin inhibitors or infliximab) equally effective? Are there subgroups of patients in whom one strategy is preferred over another?
- 3) When should the response to salvage therapy be assessed, and if a patient fails to respond to one salvage therapy should a second therapy be commenced?

Simple, objective measures are needed to aid decision-making. Factors that predict the need for colectomy in acute severe colitis can broadly be divided into clinical, biochemical and radiological markers. Several scoring systems in clinical practice use a combination of clinical and biochemical markers⁵ (for a review, see⁷⁵). Genetic polymorphisms have the potential to predict the outcome of disease in an individual from the time of diagnosis,^{76,77} but they cannot be used for decision-making when colectomy is imminent. In addition to triggering a decision to commence salvage therapy, meeting the criteria for steroid failure with one of these predictive indices should mandate surgical consultation and assessment by a stomatherapist, if this has not already occurred.

- *Clinical markers* depend on measures such as stool frequency or pyrexia. A stool frequency >12/day on day 2 of iv corticosteroids was associated with rate of colectomy of 55%,⁷⁸ whilst a frequency >8/day or a stool frequency between three and eight together with a CRP >45 mg/L on day 3 predicted colectomy in 85% on that admission: the Oxford Criteria.⁵ Similarly a stool frequency \times 0.14 CRP being \geq 8 on day 3 predicted colectomy in 75%: the Sweden Index.⁷⁹
- *Biochemical markers* include a high CRP, low albumin and pH. An ESR >75 or a pyrexia >38 °C on admission was associated with a 5–9-fold increase in the need for colectomy in a prospective study of 67 patients.⁸⁰ In this study, lack of response to steroids was predicted by <40% reduction in stool frequency within 5 days. Nevertheless, patients (and their doctors) prefer to know an absolute estimate of the likelihood of colectomy, rather than relative measures.
- *Radiological/endoscopic criteria* include the presence of colonic dilatation >5.5 cm (associated with a 75% need for colectomy), or mucosal islands on a plain abdominal radiograph (75% colectomy).⁷⁸ A retrospective study reported that the presence of an ileus (indicated by 3 or more small bowel loops of gas) was associated with colectomy in 73% patients.⁸¹ The depth of colonic ulceration after gentle air insufflation identified 42/49 patients with deep ulcers that were associated with the need for colectomy,⁸² but this is not widely used in clinical practice. Endoscopic appearances at admission may also predict the need for colonoscopy (although patients with severe colitis

should not undergo complete colonoscopy due to the increased risk of perforation). Thus 43/46 (93%) patients with severe ulceration went onto have colectomy compared to 10/39 (26%) of those without such lesions.⁸³ A retrospective study of 167 patients in whom a high proportion (40%) came to colectomy, developed a numerical score combining mean stool frequency over 3 days, presence or absence of colonic dilatation and hypoalbuminaemia (<30 g/L) on admission that was associated with the need for colectomy in up to 85%.⁸⁴

5.2.5.1. Ciclosporin. Two placebo controlled trials have confirmed the efficacy of ciclosporin in the treatment of severe UC.^{54,85} The study by Lichtiger included only patients who had failed iv corticosteroids.⁸⁵ Nine of 11 patients failing steroids improved on 4 mg/kg/day iv ciclosporin, whilst all 9 on placebo failed to improve (RR 0.18, 95% CI 0.05–0.64). In a further trial, 73 patients were randomised to either 2 mg/kg or 4 mg/kg of intravenous ciclosporin.⁵⁵ Response rates at 8 days were similar in both groups (83% and 82% respectively), with 9% coming to colectomy in the 2 mg/kg group and 13% in the 4 mg/kg group. Although not all patients were failing iv corticosteroids at entry, 2 mg/kg/day has become the standard dose used in current clinical practice. Pooling results from controlled and non controlled clinical trials, between 76% and 85% of patients will respond to iv ciclosporin and avoid colectomy in the short term.^{54,55,85–87} These suggest a median time to response of 4 days which allows timely colectomy in non responders.⁵⁵ However, the narrow therapeutic index of ciclosporin and its side-effect profile (including mortality rates of 3–4%) have limited acceptability, such that in the 2008 UK National IBD audit only 24% of patients admitted with steroid-refractory severe UC received ciclosporin. A Cochrane review⁸⁸ concluded that numbers in controlled trials were so few that there was limited evidence for ciclosporin being more effective than standard treatment alone for severe UC.

Reluctance to use ciclosporin in this patient group may also reflect concerns about its ability to prevent colectomy in the longer term. In two series, 58% of 76 patients⁸⁹ and 88% of 142 patients⁸⁷ came to colectomy over 7 years. A single centre review of the long term outcome of 71 patients treated with iv ciclosporin for severe colitis reported that successful transition to an oral thiopurine was a significant factor in preventing future colectomy (OR 0.01, 95% CI 0.001–0.09, $p < 0.0001$).⁹⁰ Successful transition to thiopurine therapy and being thiopurine-naïve at baseline have been confirmed as factors that reduce the risk of long term colectomy in this patient group.^{87,91,92} Patients that have UC refractory to adequate thiopurine therapy may therefore be less suitable candidates for ciclosporin rescue therapy.

5.2.5.2. Tacrolimus. Tacrolimus is a calcineurin inhibitor that acts via a mechanism similar to ciclosporin (Section 5.4.7). One randomised placebo controlled trial of two tacrolimus dosing strategies has shown significant benefit over placebo in patients with UC.⁹³ This included 27/60 patients with severe colitis. No patient entered complete remission in any group. A partial response was seen in 67% (4/6) of patients on tacrolimus adjusted to trough levels of 10–15 ng/mL, 50% (5/10) of patients on tacrolimus adjusted to trough levels of 5–10 ng/mL and 18% (2/11) of patients on placebo ($p = ns$). This study was

clearly underpowered to detect a difference in patients with severe colitis. However, case series have shown broadly similar results to ciclosporin after both intravenous (0.01 to 0.02 mg/kg) and oral (0.1 to 0.2 mg/kg) administration.^{94–96} The long term cumulative colectomy free survival in patients with UC treated with tacrolimus has been reported to be 57% at 44 months, although this included a very heterogeneous population.⁹⁷

5.2.5.3. Infliximab. Infliximab as a single dose (5 mg/kg) has also been shown to be an effective salvage therapy in patients with severe UC refractory to iv steroids. A pivotal, but small randomised controlled study included 45 patients (24 infliximab and 21 placebo) who were all initially treated with iv betamethasone.⁹⁸ Colectomy rates at 3 months were significantly lower in patients receiving infliximab than placebo (7/24 vs 14/21; $p=0.017$; OR 4.9, 95% CI 1.4–17). Two different scores were used to identify patients before randomization to infliximab or placebo. Patients with less active disease who were randomised after 5–7 days of iv steroids seemed to benefit more than patients with more severe disease randomised at day 3. An earlier pilot study and retrospective review of infliximab for acute severe colitis refractory to steroids have shown variable results.^{99,100} Long term follow up of patients in the placebo controlled trial revealed a colectomy rate at 3 years of 12/24 (50%) patients given infliximab and 16/21 (76%) given placebo ($p=0.012$), although use of thiopurine therapy was not controlled and differed between groups.¹⁰¹ Case series report 20%, 33%, 57% or 75% colectomy rates after infliximab for iv steroid-refractory UC.^{100,102–104}

Few studies have assessed predictors of response to infliximab in patients with severe corticosteroid refractory disease. A study which included patients with both moderate and severe disease reported increased short term response in patients with a high disease activity at baseline and patients who were seronegative for ANCA or were homozygous for the IBD risk increasing variants in the IL23R gene.¹⁰⁵ A retrospective study of 83 Italian patients suggests that patients receiving a single infusion are more likely to require colectomy at 2 months than those who receive 2 or more infusions (9/26 compared to 3/57; $p=0.001$, OR=9.53).¹⁰⁶

5.2.5.4. Selection between calcineurin inhibitors and infliximab. A retrospective review of two cohorts of patients receiving salvage therapy for steroid-refractory severe UC (49 treated with infliximab and 43 with ciclosporin) suggests a lower immediate colectomy rate in the ciclosporin group.¹⁰⁷ After adjusting for potential confounding factors, Cox regression analysis yielded adjusted hazard ratios for risk of colectomy in infliximab-treated patients of 11.2 (95% CI 2.4–53.1, $p=0.002$) at 3 months and of 3.0 (95% CI 1.1–8.2, $p=0.030$) at 12 months in comparison with ciclosporin-treated patients. In contrast, the open label CYSIF trial randomised 111 thiopurine-naive patients with severe colitis (Lichtiger score >10) despite 5 days of iv steroids to iv ciclosporin 2 mg/kg/day for 8 days (levels 150–250 ng/mL) followed by 4 mg/kg/day oral therapy, or infliximab 5 mg/kg at weeks 0, 2 and 6.¹⁰⁸ All responders at day 7 received oral azathioprine and tapered steroids from day 8. The trial was initially powered to demonstrate less treatment failure with ciclosporin than infliximab between days 7 and 98 (lack of

response at day 7, relapse between day 7 and 98, lack of steroid free remission at day 98, colectomy or treatment interruption before day 98). Approximately 85% of patients in both groups responded to treatment by day 7. Treatment failure at day 98 (the primary endpoint) was reported in 60% of patients in the ciclosporin arm compared to 54% of patients in the infliximab arm (treatment difference 6.4% 95% CI –12 to 24.8%; $p=0.49$). The colectomy rates by day 98 in the ciclosporin versus the infliximab groups were 18% and 21% respectively ($p=0.66$).¹⁰⁸ Serious adverse events were numerically more common in the infliximab group (17/56, vs 9/55 on ciclosporin), with 9 serious infections in total within the 98 day study, but the differences did not reach significance. One patient who received ciclosporin died of a myocardial infarct. A large UK based pragmatic clinical trial (CONSTRUCT) using quality of life and health economic endpoints is still recruiting (2012). Thus at present there are no randomised trials comparing the two drugs that show clear advantages of one strategy over the other.

Therefore, in the absence of an absolute or relative contra-indication to a particular strategy, the individual circumstances of each patient should be considered when deciding between options for salvage therapy. Intravenous ciclosporin should be avoided in patients with low cholesterol or magnesium in view of the increased incidence of neurological side effects in this patient group. If a patient has acute severe colitis despite existing treatment with an immunomodulator at an appropriate dose and duration, it is important to consider whether there are options for long term maintenance of remission. The long term benefit of infliximab as maintenance therapy in these circumstances has not been tested in a controlled trial, because these patients are a different population to those recruited to the ACT 1 and 2 trials.¹⁰⁹ In this situation, the risks, as well as the potential benefit, of deferring (or even avoiding) colectomy need careful discussion with individual patients. Many gastroenterologists will be more familiar with the adverse-event profile of infliximab compared to ciclosporin or tacrolimus. However, the short half life of ciclosporin gives it a potential advantage over infliximab. In the event that salvage therapy fails and colectomy is required, ciclosporin will clear from the circulation far quicker than infliximab. This may have advantages given that septic complications are the major cause of post-operative morbidity and mortality.¹⁰⁰ However, prolonged use of corticosteroids appears to remain the main risk factor for post-operative complications after colectomy.¹¹⁰ One small series reported that ciclosporin did not increase the risk of complications after colectomy.¹¹¹ In contrast, there is ongoing debate as to whether infliximab increases the risk of surgical complications^{112–115} and no data are available that relate only to emergency colectomy for patients with acute severe UC (see Section 7.6.3, Statement 7V).

5.2.5.5. Third line medical therapy. In general only a single attempt at rescue therapy with a calcineurin inhibitor or infliximab should be considered before referral for colectomy. However, treatment success has been reported for sequential use of calcineurin inhibitors and infliximab after iv corticosteroids. The initial reports of patients receiving ciclosporin after infliximab or vice versa for

refractory severe UC suggested an unacceptable rate of morbidity and mortality.¹¹⁶ However, a more recent cohort from France assessed outcome after third line medical therapy in 86 patients, the majority of whom received ciclosporin followed by infliximab.¹¹⁷ The probability of colectomy-free survival (\pm s.e.) was $61.3 \pm 5.3\%$ at 3 months and $41.3 \pm 5.6\%$ at 12 months, although clinical remission was achieved in only 30% and three year colectomy rates were 63%. Remission has been reported in 25%–50% of patients receiving infliximab for severe UC refractory to tacrolimus although not all these patients were hospitalised.^{118,119} Therefore, in highly selected cases, after careful discussion between the patient, gastroenterologist and colorectal surgeon, third line medical therapy can be considered in a specialist referral centre.

5.2.6. Toxic dilatation and complications of severe ulcerative colitis

5.2.6.1. Toxic megacolon. Toxic dilatation (megacolon) is defined as total or segmental non-obstructive dilatation of the colon ≥ 5.5 cm associated with systemic toxicity.⁵⁶ Although its true incidence has not been reported, approximately 5% of patients with acute, severe colitis admitted to hospital will have toxic dilatation.⁵⁶ Risk factors include hypokalaemia, hypomagnesaemia, bowel preparation, and the use of anti-diarrhoeal therapy.⁵⁶ Earlier diagnosis of severe colitis, more intensive medical management and earlier surgery have reduced the incidence and mortality of toxic megacolon complicating UC. In addition to iv hydrocortisone, empirical treatment with oral vancomycin should be considered until stool is confirmed negative for *Clostridium difficile* toxin. Nasogastric suction cannot be expected to decompress the colon and is unnecessary. The classic knee–elbow position may relieve distension,¹²⁰ but is generally impracticable. An opinion from an experienced colorectal surgeon is required on the day of admission. It should be made clear to all that there is a limited window of opportunity for medical treatment to work and that if there is no improvement early colectomy will be necessary.

5.2.6.2. Perforation, haemorrhage and others. Perforation is the most serious complication of acute severe colitis and is often associated with inappropriate total colonoscopy or toxic dilatation where colectomy has been inappropriately delayed. It carries a mortality of up to 50%.⁵⁶ Other complications include massive haemorrhage, and thromboembolism including cerebral sinus thrombosis.^{66,67}

5.2.6.3. Long term outcome of severe colitis. There is evidence that achieving complete clinical remission on the index hospital admission improves long term outcome and delays the need for colectomy.¹²¹ As mentioned above, patients needing ciclosporin for acute severe colitis who are naïve to immunomodulator therapy and successfully transition to thiopurine maintenance therapy are less likely to require colectomy in long term follow-up.^{87,90,91} Perhaps unsurprisingly, irrespective of whether ciclosporin or infliximab is used as salvage therapy, patients with clinical, biochemical or endoscopic evidence of more severe disease at presentation are more likely to require colectomy.¹²² Data on the burden of

medical and surgical treatment of severe colitis and attendant complications, related to patient-orientated outcomes (hospitalisation, time off work, colectomy and mortality) are still required.

5.2.7. Refractory proctitis and distal colitis

Refractory proctitis and distal colitis present common clinical dilemmas (review in¹²³). There are few appropriately controlled rigorous clinical trials in this specific population, but a coherent therapeutic strategy is needed if patients are not to get frustrated by persistent symptoms. It is clearly important to consider and identify the aetiology of the refractory disease course. One obvious explanation is that the disease is refractory to medication being prescribed. However, alternative explanations include:

- 1) Poor adherence to prescribed therapy
- 2) Delivery of an inadequate concentration of the active drug to the inflamed mucosa
- 3) Unrecognised complications (such as proximal constipation or infection)
- 4) Inappropriate diagnosis (such as co-existent irritable bowel syndrome, Crohn's disease, mucosal prolapse, or cancer).

Therefore, the initial step is to review current symptoms and treatment to date, with a careful discussion about adherence. This should be followed by reassessment of the diagnosis by stool culture, endoscopy and biopsy. The next step is to ensure that conventional therapy (Sections 5.2.1 and 5.2.2) has been used appropriately. Attention in particular should be paid to the formulation of topical therapy and whether it was used in conjunction with an adequate dose of oral therapy. An abdominal X-ray can be useful to diagnose proximal constipation, since abnormal intestinal motility induces proximal colonic stasis in patients with distal colitis which may affect drug delivery.¹²⁴ If there is visible faecal loading, a laxative should be considered.

Patients with endoscopically documented active colitis who fail oral corticosteroids combined with oral and rectal 5ASA therapy have refractory proctitis or distal colitis. Therapeutic options include admission for intravenous steroid therapy which has been reported to induce remission in a high proportion of patients.¹²⁵ Alternatively, there is open label evidence, often from retrospective case reviews, supporting the use of salvage medical therapies such as oral or rectal ciclosporin, oral or rectal tacrolimus, or infliximab.^{126–129}

If disease persists in spite of these approaches, surgery is likely to be the outcome, but if the patient is not acutely ill then the decision should never precipitate and a range of topical or anecdotal therapies are available. Placebo controlled trials have suggested a benefit of short chain fatty acid enemas,^{130,131} although difficulties with production and availability limit their widespread use. Historical small open label trials have suggested benefit from alternative topical therapies such as lidocaine enemas, acetarsol (arsenic) suppositories, Epidermal Growth Factor enemas, and transdermal nicotine patches.^{132–135} The choice depends on local availability and personal preference, since many have to be made up individually by pharmacy (reviewed in¹³⁶). There is evidence from retrospective

cohort studies that appendicectomy may improve outcome in patients with refractory proctitis.¹³⁷ Clinical judgement and an honest appraisal about the impact of symptoms on the quality of life or employment are necessary. Up to 10% of patients who have a colectomy for refractory UC only have distal disease. The outcome of colectomy and pouch formation for distal colitis is usually good. In 263 patients who had a restorative proctocolectomy at one French centre (1986–96), 27 had surgery for distal disease.¹³⁸ There was a significant decrease in daytime and nocturnal stool frequency after surgery and previously undiagnosed severe dysplasia was identified in 2 patients. All but one patient were satisfied with the results and 25/27 wished that they had had surgery sooner.

5.3. Treatment according to the course or behaviour of disease

Treatment decisions may differ between patients at initial presentation and subsequent relapse, depending on the pattern of relapse and previous response to therapy. Some patients have refractory disease that remains active in spite of prescribed treatment, others relapse when therapy such as corticosteroids are tapered (steroid dependent). Treatment decisions should also be influenced by clinical factors that predict adverse treatment outcomes including colectomy. In outpatients with active ulcerative colitis factors associated with an increased risk of colectomy include: steroid-dependent disease course, serum CRP levels ≥ 20 mg/L, high clinical disease activity, and moderate to severe UC with a disease duration ≤ 3 years.¹³⁹ Lack of mucosal healing at one year after treatment is another risk factor for future colectomy.¹⁴⁰

5.3.1. Treatment of relapse compared to new cases

The initial treatment of relapse may include the treatment that worked for the previous disease flare, although maintenance therapy should also be optimised. Other factors to consider include patient opinion (adverse effects, necessary speed of response, convenience, etc.), timing of relapse, concurrent therapy (whether a relapse occurred during treatment with immunomodulators) and adherence to maintenance therapy.

5.3.2. Early relapse

Patients who have an early (<3 months) relapse require further induction therapy, but should also commence azathioprine or mercaptopurine to reduce the risk of a subsequent relapse. Opinion is divided whether to use the same induction treatment as before to achieve remission or to use more potent therapy. It is generally unnecessary to re-evaluate the distribution of disease unless this will influence medical or surgical management. Continued medical therapy that does not achieve steroid-free remission is not recommended.

5.3.3. 'Steroid-dependent', active ulcerative colitis

ECCO Statement 5F

Patients with steroid-dependent disease should be treated with azathioprine/mercaptopurine [EL1b, RG B]

Azathioprine is significantly more effective than mesalazine at achieving clinical and endoscopic remission in the treatment of steroid-dependent UC. 72 patients were randomised to receive azathioprine 2 mg/kg/day or oral mesalazine 3.2 g/day, in addition to prednisolone 40 mg/day.¹⁴¹ This demonstrated that 53% on azathioprine achieved steroid-free clinical and endoscopic remission after 6 months compared to 21% on mesalazine (OR 4.78, 95% CI 1.57–14.5). In addition, an open label observational cohort study in 42 steroid dependent patients reported steroid-free remission with azathioprine at 12, 24, and 36 months of 55%, 52%, and 45%, respectively.¹⁴² Therefore thiopurines should be the first choice of therapy for patients who flare when steroids are withdrawn. Patients with active disease despite steroid therapy require appropriate induction therapy (Section 5.3.4), including consideration of anti-TNF therapy (adalimumab or infliximab).

5.3.4. Oral steroid-refractory ulcerative colitis

Statement 5H

Outpatients with moderately active steroid refractory disease should be treated with *anti TNF therapy* [EL1b, RG B] or tacrolimus [EL2b, RG C], although surgical options or admission for parenteral steroid therapy could also be considered [EL5 RG D]

For active UC that is refractory to steroids, other causes of persistent symptoms including coexistent cytomegalovirus, *Clostridium difficile* or cancer should be considered. If active steroid-refractory UC is confirmed, alternative therapy to induce steroid-free remission is required. Anti-TNF therapy has clear evidence of benefit in this patient group. The ACT 1 and 2 studies included 408/728 (56%) patients taking oral steroids at study entry,¹⁰⁹ although their dose of steroids may have been sub-optimal. At 30 weeks, significantly more of these patients receiving scheduled infliximab than placebo achieved steroid free remission (28/130 (21%) vs 10/139 (7%); $p=0.01$); at one year (ACT 1 alone), the figures were 26% and 9% respectively ($p=0.006$). The recently presented UC-SUCCESS trial suggests that steroid-refractory patients with moderately active UC who are naïve to immunomodulator therapy are significantly more likely to enter steroid-free remission after 16 weeks if they receive a combination of azathioprine and infliximab (induction and maintenance therapy) than either agent alone.¹⁴³ This double-blind placebo-controlled trial reported that steroid free remission at week 16 was achieved in 24% of the 70 patients receiving azathioprine monotherapy, 22% of 77 patients given infliximab monotherapy and 40% of 78 patients receiving infliximab and azathioprine combination therapy ($p=0.032$ for combination vs azathioprine monotherapy and $p=0.017$ for combination vs infliximab monotherapy).

Adalimumab has also shown benefit over placebo for the induction of remission in 390 outpatients with moderately active UC.¹⁴⁴ Patients randomised to receive 160 mg/80 mg/40 mg every other week (eow) were

significantly more likely to achieve remission at week 8 than those receiving placebo (18.5% compared to 9.2%; $p=0.031$). Remission rates at week 8 for patients who were on steroids at baseline in the adalimumab 160 mg/80 mg/40 mg eow compared to placebo groups were 12/71 (16.9%) and 8/89 (9%) respectively. In a separate randomised placebo-controlled trial of adalimumab for induction and maintenance of remission, which included patients with prior infliximab exposure, the sub group of patients on corticosteroids at baseline was significantly more likely to be in steroid free remission at week 52 if treated with 160 mg/80 mg/40 mg eow than placebo (13.3% vs 5.7%, $p=0.035$).¹⁴⁴ Adalimumab is now licenced (2012) for the treatment of moderate or severely active UC in Europe.

A single placebo-controlled trial of tacrolimus at two different dosing strategies compared to placebo in 65 patients included 60 patients with moderate or severely active disease despite concomitant steroid therapy, of whom 15 patients were refractory to at least 30 mg oral prednisolone for 2 weeks.⁹³ Although patients were hospitalised in this study, they did not all meet the criteria for severe steroid-unresponsive UC used in Section 1.2.5. No patient with steroid-refractory disease at baseline entered complete remission at week 2 in any group. However partial response was seen in 13/19 (68%) patients randomised to receive tacrolimus adjusted to trough levels of 10–15 ng/mL, 8/21 (38%) patients randomised to receive tacrolimus adjusted to trough levels 5–10 ng/mL and 2/20 (10%) patients on placebo ($p<0.01$ for high trough compared to placebo). After a further 8 week open-label therapy, there was a significant reduction in the mean daily dose of prednisolone, although the exact numbers of patients in each group able to withdraw from steroids completely is not reported. A subsequent Cochrane database systematic review which included this trial alone, concluded that caution should be used in interpreting the data due to inadequacies in study design and the small number of patients included.¹⁴⁵

It should be noted that none of the treatments discussed above have achieved steroid-free remission at any time point in the majority of patients. Therefore the expectations of the patient (and the physician) have to be managed and thought given to admission for intravenous steroid therapy, as well as semi-elective colectomy. The patient's gender, age, fecundity and extent of disease should be taken into account. The sequence (or hierarchy) of therapy has to depend on the individual circumstances and acceptability to the patient.

5.3.5. Immunomodulator-refractory ulcerative colitis

ECCO Statement 51

Patients with moderately active ulcerative colitis refractory to thiopurines should be treated with *anti TNF therapy* [EL1b, RG B] or tacrolimus [EL4, RG C] although colectomy should also be considered. Continued medical therapy that does not achieve a clear clinical benefit is not recommended [EL5, RG D]

Immunomodulator-refractory disease is also best reassessed by endoscopy and biopsy to confirm the diagnosis and exclude complications. A therapeutic strategy that includes consideration of how steroid-free remission will be achieved and maintained should be discussed with the patient. In the absence of contraindications, anti TNF therapy should be considered (Section 5.4.3). There is case series evidence to support the use of tacrolimus,^{146,147} but no controlled clinical trial has included this patient group. Careful discussion with the patients is required as to the relative risks and benefits of immunosuppressive therapy compared to colectomy, which may be a more appropriate option for some patients.

The ACT 1 and ACT 2 trials included 334/728 (46%) patients with active disease refractory to immunomodulator therapy.¹⁰⁹ Infliximab at either dose used (5 mg/kg or 10 mg/kg) achieved clinical remission in a significantly greater proportion of patients at week 8 than placebo, although the exact response rate for the subgroup of immunomodulator-refractory patients was not reported. A Cochrane database systematic review of the efficacy of 7 trials of infliximab for treating patients with moderate to severe UC refractory to corticosteroids and/or immunomodulators concluded that infliximab (three intravenous infusions at 0, 2, and 6 weeks) was more effective than placebo in inducing clinical remission at week 8 (RR 3.22, 95% CI 2.18–4.76).¹⁴⁸ Again, this review did not report the benefit in the subgroup of patients refractory to immunomodulator therapy.

In the trial demonstrating the superiority of adalimumab over placebo for the induction of remission of UC discussed in Section 1.3.4, 155 of the 390 (39.7%) patients were on concomitant immunosuppression at baseline.^{144,149} Adalimumab 160 mg/80 mg/40 mg eow induced clinical remission at week 8 in 8/53 (15.1%) patients compared to 2/52 patients receiving placebo (3.8%). A prospective single centre cohort study of 53 patients receiving either infliximab or adalimumab for moderately active UC reported short term clinical response in 88.7% patients with no significant difference in the response rates between drugs.¹⁵⁰ All patients recruited had failed or were intolerant to immunomodulator therapy although only 5/25 patients treated with adalimumab and 15/28 patients treated with infliximab were on concomitant immunomodulator therapy at baseline.

5.4. Therapy-specific considerations

The therapeutic goal should be to induce steroid-free clinical remission, but it is essential to keep in mind how remission will be maintained (Section 6). The treatment strategy depends primarily on the activity and distribution of UC (Section 1.2); the current section considers drug-specific aspects of treatment not addressed in that section.

5.4.1. Aminosalicylates for active UC

5.4.1.1. Efficacy of aminosalicylates. There is much discussion of how different delivery systems may influence response, but evidence from appropriately designed comparative trials is scarce. Delivery systems can be divided into azo-compounds, controlled release, pH-dependent (either pH6 or pH7) and composite (pH-dependent combined with

controlled release) Systematic reviews and meta-analyses concur that oral aminosalicylates are effective for treating active UC.^{20,27,28,37} The most recent systematic review quotes a relative risk of no remission with 5-ASA compared to placebo of 0.79 (95% CI 0.73–0.85; NNT=6).²⁰ Available data do not suggest a difference in efficacy between any of the 5-ASA preparations for active UC. As discussed in Section 1.2.2, doses of ≥ 2.0 g/day are more effective than < 2.0 g/day for remission (RR=0.91; 95% CI 0.85–0.98).²⁰ Several trials have reported that once daily dosing is as effective as divided doses for the induction of remission.^{30,32,151,152}

Mesalazine has been shown to be as effective as sulfasalazine for inducing response or remission in 2 separate meta-analyses, and is better tolerated^{27,153}. There have been few clinical trials comparing the efficacy of newer aminosalicylates for inducing remission. In 2 of 3 trials of balsalazide versus mesalazine, results for defined primary and secondary endpoints failed to demonstrate statistically significant differences,^{154–156} although a more recent meta-analysis reports a slight but statistically significant advantage.¹⁵⁷ Another study compared Ipocol, a pH7-dependent release mesalazine, with Asacol and found no significant difference in remission rates after 2.4 g/days for 8 weeks,¹⁵⁸ although insufficiently powered for a non-inferiority design. It is important to remember that many of the placebo-controlled trials demonstrating efficacy for different mesalazine preparation have used different definitions of remission. This is important as it is not possible to compare the remission rates reported between trials to determine relative efficacy. Indeed when the clinical outcome data from the ASCEND I/II trials were re-analysed using the different definitions of remission from other 5ASA trials, the rate of remission reported varies from 22% to 50%.¹⁵⁹ It is clear that the more stringent the definition of remission used, the more likely it is that the patient will maintain that remission during follow up. Proprietary prescribing of mesalazine has been recommended,¹⁶⁰ but for active UC the choice of 5ASA cannot be made on the grounds of efficacy alone. The route of delivery, dose frequency, cost and availability are more relevant factors in the choice.

5.4.1.2. Adverse effects of aminosalicylates. Mesalazine has a topical action on colonic epithelial cells, where it is also metabolised. Systemic exposure is therefore unnecessary. This means that drug efficacy cannot be deduced from pharmacokinetic comparisons, although absorption might conceivably influence adverse events. Mesalazine intolerance occurs in up to 15%. Diarrhoea (3%), headache (2%), nausea (2%), rash (1%) and thrombocytopenia ($< 1\%$) are reported, but a systematic review has confirmed that all new 5-ASA agents are safe, with adverse events that are similar to placebo for mesalazine.¹⁶¹ A subsequent clinical trial has confirmed no difference in adverse events between Eudragit-L and ethycellulose mesalazine compounds.¹⁶² Acute intolerance occurs in 3% and may resemble a flare of colitis. Renal impairment (including interstitial nephritis and nephrotic syndrome) is rare and idiosyncratic. A population-based study found the risk (OR 1.60, CI 1.14–2.26 compared to normal) to be associated with the disease as a rare extra-intestinal manifestation, rather than the dose or type of mesalazine.¹⁶³

5.4.1.3. Monitoring. Patients with pre-existing renal impairment, significant co-morbidity or those taking additional potentially nephrotoxic drugs should have renal function monitored during 5-ASA therapy. Many clinicians believe that creatinine and full blood count should be monitored every 3–6 months during aminosalicylate therapy, although there is no evidence favouring one monitoring regime over another.

5.4.2. Corticosteroids for active UC

5.4.2.1. Efficacy of steroids. There have been only two placebo controlled trials of conventional oral steroids for outpatients with active UC,^{39,164} giving an NNT of 2 (95% CI 1.4–5.0).²⁸ A meta-analysis confirms clinical benefit of standard glucocorticosteroids over placebo for UC remission (RR of no remission=0.65; 95% CI 0.45–0.93).²⁰ The benefit of intravenous steroids for patients admitted with severe colitis is discussed in Section 1.2.4. Adverse effects and monitoring of steroid therapy are the same as described in the Consensus guidelines on Crohn's disease.^{165,166}

5.4.3. Anti-TNF therapy for active UC

5.4.3.1. Efficacy of infliximab. A systematic review of the efficacy of infliximab for treating patients with moderate to severe UC refractory to corticosteroids and/or immunomodulators concluded that it was effective for inducing clinical remission, clinical response, promoting mucosal healing, and reducing the need for colectomy in the short term.¹⁴⁸ It comprised seven RCTs and reported that infliximab (three infusions at 0, 2, and 6 weeks) was more effective than placebo in inducing clinical remission at week 8 (RR 3.22, 95% CI 2.18–4.76). A single infusion of infliximab was also more effective than placebo in reducing the need for colectomy within 90 days after infusion (RR 0.44, 95% CI 0.22–0.87).⁷⁶ The ACT 1 and 2 studies are the pivotal placebo controlled trials demonstrating benefit for infliximab over placebo in outpatients with active UC refractory to one or more conventional therapies.¹⁰⁹ ACT 1 was a 364 patient study comparing infliximab 5 mg/kg, 10 mg/kg, or placebo at 0, 2 and 6 weeks, then every 8 weeks for a year. The primary endpoint was clinical response at week 8 ($\geq 30\%$ and a 3 point decrease in the Mayo activity index, with virtual cessation of rectal bleeding). This was achieved in 37.2% (placebo), 69.4% (5 mg/kg) and 61.5% (10 mg/kg, $p < 0.001$). Pre-defined secondary endpoints included remission (14.9%, 38.8% and 32.0% respectively) and mucosal healing (33.9%, 62.0%, and 59.0%). ACT 2 was an almost identical trial of 364 patients, which also included patients refractory to 5-ASA alone (26% of the trial population). Response (and remission) rates at week 8 were 29.3% (5.7%) for placebo, 64.5% (33.9%) for 5 mg/kg, and 69.2% (27.5%) for 10 mg/kg ($p < 0.001$ for infliximab groups compared to placebo). Further analysis of the ACT 1 and 2 trial data reports a cumulative incidence of colectomy through 54 weeks of 10% for infliximab and 17% for placebo ($p = 0.02$; absolute risk reduction 7%).¹³⁹

5.4.3.2. Efficacy of adalimumab. Two recently presented placebo-controlled trials have assessed the efficacy of adalimumab in patients with moderately active UC despite

conventional therapy (one included patients with prior exposure to anti-TNF therapy).^{144,167} A randomised double-blind placebo-controlled trial compared adalimumab 160 mg/80 mg/40 mg eow, adalimumab 80 mg/40 mg eow and placebo in 390 anti TNF naïve outpatients with active UC.¹⁴⁴ The primary endpoint of clinical remission at week 8 was achieved in 18.5% of patients in the adalimumab 160/80 group ($p=0.031$ vs placebo), 10.0% in the adalimumab 80/40 group ($p=0.833$ vs placebo) compared with 9.2% in the placebo group. The second trial included 494 patients with active treatment refractory UC (40.3% with prior exposure to anti-TNF) randomised to adalimumab 160 mg/80 mg/40 mg eow or placebo.¹⁶⁷ The co-primary endpoints were proportion of patients with (1) clinical remission at week 8; (2) clinical remission at week 52. Clinical remission was achieved in significantly more patients receiving adalimumab than placebo at week 8 (16.5% and 9.3%; $p=0.02$) and week 52 (17.3% and 8.5%; $p=0.01$). Clinical remission rates with adalimumab were higher in patients who were naïve to anti-TNF therapy at baseline than those who had prior exposure at both week 8 and week 52 (21.3% vs 9.2% and 22% vs 10.2% respectively). Finally several small case series have reported benefit of adalimumab in patients with active UC previously exposed to infliximab with up to 27% entering clinical remission in the short term.^{168–171}

Most recently, the anti-TNF antibody golimumab has been shown to induce clinical remission and mucosal healing. Treatment with golimumab in a randomised controlled trial at weeks 0 and 2 (400/200 mg, 200/100 mg, or placebo, $n=771$) significantly induced clinical remission (17.8% and 18.7% vs 6.3% on placebo, respectively $p<0.0001$), as well as mucosal healing at week 6 (400 mg/200 mg: 45%; $p=0.0001$; 200 mg/100 mg: 43%; $p=0.0005$ vs. placebo: 29%) suggesting that several anti-TNF antibodies favour mucosal healing in ulcerative colitis.¹⁷²

5.4.3.3. Summary. Despite positive large well conducted placebo-controlled clinical trials for both infliximab and adalimumab in patients with active UC, a large therapeutic gap persists. Induction and maintenance infliximab achieves steroid free remission in 21% of patients at 7 months and 26% at 12 months (see Section 5.3.3).¹⁰⁹ Adalimumab 160 mg/80 mg/40 mg eow delivers steroid-free remission in 13.3% at week 52.¹⁷³ It is important to consider these results, because the Consensus stresses the importance of achieving steroid-free remission. It is possible that the rigid endpoints and assessments used in clinical trials mask the true clinical impact of the therapy. A real life observational cohort study has reported short term clinical response rates for both adalimumab and infliximab in excess of 80% with no difference between the two drugs.¹⁵⁰ Patient selection and the use of concomitant therapies may also be important. The recently presented UC-SUCCESS trial (Section 5.3.4) suggests that early use of infliximab and azathioprine combination therapy in patients with active colitis naïve to immunomodulator therapy may yield steroid-free remission rates of up to 40% at week 16.¹⁴³ The benefit of concomitant thiopurine therapy with infliximab was confirmed by enhanced clinical outcomes in the small number of patients (23/121) with UC included in a large cohort study.¹⁷⁴

Predictors of a poor response to infliximab that have been reported include older age at first infusion, ANCA+ve/ASCA–ve serotype,¹⁰⁴ an undetectable trough infliximab level¹⁷⁵ and specific gene array profiles.¹⁷⁶ Further studies are needed to define the appropriate patient population, the benefits of concomitant medication and any difference in efficacy for the available anti-TNF therapies.

5.4.3.4. Adverse effects of anti-TNF therapy. Treatment with anti-TNF therapy is relatively safe if used for appropriate indications. Adverse events in the ACT studies¹⁰⁹ were not different to those expected from large experience of treating Crohn's disease.^{177,178} Likewise no new safety signals were detected in the adalimumab trials.^{144,149,173} Nevertheless, in common with other biological therapies there is a risk of serious infection, demyelinating disease and associated mortality. In the combined analysis of 484 patients with UC who received infliximab in the ACT trials there were 8 who developed pneumonia, 1 tuberculosis and 1 histoplasmosis (who later died) as well as 4 neoplasia (all probably pre-existing, but presenting in the trial period) and 3 neuropathies (2 optic neuritis, 1 multifocal motor), equivalent to 3.5% (17/484). By contrast, in the 244 who received placebo there was just 1 basal cell carcinoma. Prolonged medical therapy for a potentially pre-malignant condition with anti-tumour necrosis factor therapy creates its own anxieties. Tighter surveillance to detect dysplasia may be necessary, although no evidence-based recommendations can currently be given.

5.4.4. Other biological therapies

Despite the proliferation of biological therapies, only few have shown benefit in appropriately designed clinical trials in UC.

Vedolizumab (MLN-02– $\alpha 4\beta 7$ integrin antagonist) was given to 181 patients with moderately active UC.¹⁷⁹ Clinical remission rates at week 6 were 33% and 32% for 0.5 mg and 2.0 mg/kg respectively, compared to 14% on placebo ($p=0.03$). The phase 3 study for ulcerative colitis (300 mg iv at days 1 and 15; $n=225$ vs placebo $n=149$) has reported clinical remission in 16.9% vs 5.4% on placebo and mucosal healing (Mayo endoscopy score <2) at week 6 (41% compared to 25% on placebo) suggesting that blockade of T cell homing in the gut may favour mucosal healing in ulcerative colitis.¹⁸⁰ It was well tolerated and its novel mechanism of action as well as its potential to maintain remission make it very appealing. The apparently low remission rates with this and other recently reported studies (e.g. golimumab, above) are a feature of increasingly robust endpoints for defining remission.¹⁵⁹

Visilizumab, an anti-CD3 monoclonal antibody binding to activated T-cells, induces apoptosis. A Phase III study in intravenous steroid-resistant UC showed no benefit in patients with iv steroid refractory severe UC.¹⁸¹

Although one IL-2 receptor (CD25) inhibitor, *basiliximab*, has shown potential in open studies for steroid-refractory UC¹⁸² another CD25 inhibitor, *daclizumab*, was ineffective in a controlled trial of 159 patients with moderately active UC.¹⁸³

Abatacept (CTLA4-Ig: a co-stimulatory receptor inhibitor) has not shown benefit in a phase III trial in ulcerative colitis.¹⁸⁴

Interferon-alpha induces anti-inflammatory cytokines (IL-1RA, amongst others) and down regulates IL-13, giving it a potential role in the treatment of active UC. A trial of 60 patients randomised to weekly injections of pegylated interferon alpha at 1.0 µg/kg, 0.5 µg/kg, or placebo for 12 weeks showed no consistent differences between the groups.¹⁸⁵ An American–European review on biological therapy for UC has been published.¹⁸⁶

Tofacitinib, an oral inhibitor of Janus kinases 1, 2, and 3, which is expected to block signalling involving gamma chain-containing cytokines including interleukins 2, 4, 7, 9, 15, and 21, has been evaluated in a double-blind, placebo-controlled, phase 2 trial in 194 adults with moderately to severely active ulcerative colitis.¹⁸⁷ Patients were randomly assigned to receive tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for 8 weeks. Clinical response at 8 weeks occurred in 32%, 48%, 61%, and 78% of patients receiving tofacitinib at a dose of 0.5 mg ($p=0.39$), 3 mg ($p=0.55$), 10 mg ($p=0.10$), and 15 mg ($p<0.001$), respectively, as compared with 42% of patients receiving placebo. Clinical remission (defined as a Mayo score ≤ 2 , with no subscore >1) at 8 weeks occurred in 13%, 33%, 48%, and 41% of patients receiving tofacitinib at a dose of 0.5 mg ($p=0.76$), 3 mg ($p=0.01$), 10 mg ($p<0.001$), and 15 mg ($p<0.001$), respectively, as compared with 10% of patients receiving placebo. There was a dose-dependent increase in both low-density and high-density lipoprotein cholesterol. Three patients treated with tofacitinib had an absolute neutrophil count of less than 1500. Long-term data on efficacy and on long-term safety are needed, as potential immunosuppression and increase in lipids may affect long-term use.

5.4.5. Thiopurines

5.4.5.1. Efficacy of azathioprine/mercaptopurine. A meta-analysis which reviewed 30 non controlled studies and analysed 7 controlled studies has confirmed that thiopurine drugs are more effective than placebo for the prevention of relapse in UC, with an NNT of 5 and an absolute risk reduction of 23%.¹⁸⁸ However, data on thiopurines for active UC are few.¹⁸⁹ Data from the well conducted study on steroid-dependent active UC¹⁴¹ are discussed in Section 1.3.3. Immunomodulators should be started in steroid-dependent and steroid-refractory patients. Their successful introduction is associated with colectomy-free survival in patients with severe UC treated with ciclosporin to induce remission.⁹⁰ The use of concomitant thiopurine therapy in patients receiving induction and maintenance infliximab has been discussed in Section 5.4.3.^{143,174} The role of thiopurines for maintenance of remission is discussed in Section 6.2.2.

5.4.6. Methotrexate

5.4.6.1. Efficacy of methotrexate. Prospective studies on methotrexate for UC are small, use varying doses or routes of administration and have inconsistent outcomes.^{190–192}

The only randomised placebo-controlled trial using a dose of 12.5 mg per week of oral methotrexate in UC showed no benefit¹⁹⁰ and a Cochrane database systematic review concludes that there is insufficient evidence to support its use at present.¹⁹³ A randomised comparison of oral methotrexate 15 mg/week with mercaptopurine 1.5 mg/kg/day and 3 g/day 5-ASA for 72 steroid-dependent patients (34 UC and 39 Crohn's) showed a remission rate at 30 weeks of 79% for mercaptopurine, 58% for methotrexate 25% for 5-ASA ($p<0.05$ vs MP, ns vs methotrexate).¹⁹¹ A retrospective review also suggests benefit in both thiopurine-intolerant and thiopurine-refractory patients.¹⁹⁴ However until data from well designed randomised placebo-controlled trials such as the GETAID-ECCO Meteor trial are available, it cannot be considered an alternative to thiopurines for steroid-dependent UC (see also Section 6.2.5).

5.4.7. Calcineurin inhibitors (ciclosporin and tacrolimus)

5.4.7.1. Efficacy of ciclosporin. Details of the role of ciclosporin and tacrolimus for UC are given in Sections 5.2.4, 5.2.5, 5.3.4 and 5.3.5.

5.4.7.2. Dose and monitoring. Low dose ciclosporin (2 mg/kg iv) induction therapy has largely addressed concerns about early toxicity. In the largest randomised study of ciclosporin to date, 73 patients were randomised to either 2 mg/kg or 4 mg/kg of intravenous ciclosporin.⁵⁵ Response rates at 8 days were similar in both groups (86% and 84% respectively), with 9% coming to colectomy in the 2 mg/kg group and 13% in the 4 mg/kg group. The study was too small to show a difference in serious side effects, but there was less hypertension in the lower dose group. The majority of ciclosporin side-effects are dose-dependent. At the 2 mg/kg dose, the mean ciclosporin concentration on day 4 was 24664 ng/mL, compared to 345146 ng/mL with the 4 mg/kg dose. Suitable target levels to induce remission are not known, but in responders on oral medication, whole-blood trough levels of 150–250 ng/mL using a monoclonal radio-immunoassay are generally considered satisfactory. It is said that 2 h post-dose peak levels give the best estimate of drug exposure by correlating with the pharmacokinetic area under the curve¹⁹⁵ and an appropriate target appears to be 700 ng/mL, but this has not been correlated with efficacy for UC.

Tacrolimus is more effective when given at a dose that achieves a trough concentration of 10–15 ng/mL.⁹³ The initial oral dose in this randomised trial of 60 steroid-refractory patients with active UC was 0.05 mg/kg/day, increased according to the trough level after 24 h. 13 (68%) achieving this trough level responded within 2 weeks, compared to 8 (38%) achieving a lower trough level and 2 (10%) in the placebo group. None had a complete response. Possession of specific ACB1 single nucleotide polymorphisms may predict response to appropriately dosed tacrolimus.¹⁹⁶

5.4.7.3. Adverse effects of calcineurin inhibitors. Hypertension, paraesthesiae, or tremor and headache are the commonest adverse events. Hypomagnesaemia, renal impairment, or gastrointestinal upset affect around half of the patients.⁹³ Intravenous ciclosporin should be avoided in

patients with low serum magnesium or cholesterol as this patient group experience increased neurological side effects. Tacrolimus may induce diabetes. Opportunistic infection is the main concern; 3/86 patients (3.5%) died of opportunistic infections (1 of *Pneumocystis jirovecii* (carinii) pneumonia and 2 of *Aspergillus fumigatus* pneumonia) in a series of patients treated with ciclosporin from a major specialist centre.¹⁹⁷ Opportunistic infections and the value of chemoprophylaxis is the topic of a separate ECCO Consensus.⁶⁰

5.4.8. Alternative therapies whose role remains to be established

5.4.8.1. Antibiotics. The main role of antibiotics in patients with active UC is the treatment of co-existing enteric infection with *Cl. difficile*.^{61–63} Antibiotics as an adjunct to steroids do not alter the outcome of severe colitis (Section 5.2.4,^{72–74,198–200}). A randomised placebo-controlled trial in 210 patients reported that a combination of amoxicillin 1500 mg/day, tetracycline 1500 mg/day, and metronidazole 750 mg/day for 2 weeks resulted in clinical response at 3 months of 44.8% compared to 22.8% in the placebo group ($p=0.0011$).²⁰¹ A meta-analysis of the benefit of antibiotics in patients with active UC that only included parallel-group randomised controlled trials studied 9 RCTs with 662 patients.²⁰² There was a statistically significant benefit for antibiotics inducing remission (RR of UC not in remission=0.64; 95% CI=0.43–0.96). However, there was moderate heterogeneity ($I^2=69\%$) and the antibiotics assessed were different single or combination strategies. The authors concluded that antibiotic therapy may induce remission in active UC, but the diverse number of antibiotics tested means the data are difficult to interpret.

5.4.8.2. Helminths. Observations that there is an epidemiological mismatch between UC and helminth infections, together with experimental evidence that several helminths moderate immune-mediated models of colitis lead to therapeutic trials of *Trichuris suis ova*. In a randomised trial of 54 patients with mild-moderately active UC, 3/30 of those treated with 2500 *T. suis ova* every 2 weeks for 12 weeks achieved remission compared to 1/24 given placebo (ns), with a response in 43% and 17% respectively ($p=0.04$).²⁰³ The optimal dose, interval and duration of treatment need to be established and the response confirmed in a larger study.

5.4.8.3. Heparin. Heparin promotes epithelial restitution and repair in addition to anticoagulant properties. Out of two small controlled trials of unfractionated heparin and three using low molecular weight heparin in up to 100 patients, only the smallest trial has shown benefit for active UC (review in²⁰⁴). A novel colonic delivery system for low molecular weight heparin using MMx technology appeared safe and effective in a small open label trial,²⁰⁵ although results from larger controlled trials are required to confirm its therapeutic impact.

5.4.8.4. Leucocytapheresis. Leucocytapheresis involves extracorporeal removal of leucocytes through an adsorptive system of cellulose acetate beads (Adacolumn®, Otsuka Pharmaceuticals), or a polyester fibre filter (Cellsorba®,

Asahi Medical Company). The former removes 65% of neutrophils, 55% monocytes, and 2% lymphocytes whilst the latter removes up to 100% of neutrophils and monocytes, and 20–60% lymphocytes. Sessions last an hour, during which time 2–3 L of blood is drawn from one arm, filtered, and infused into the other arm. A course of treatment is typically 5–10 sessions at intervals of 1–2/week. Several observational and randomised studies^{206–213} and two unusually designed randomised trials comparing leucocytapheresis with prednisolone²¹² or a sham column²¹¹ have suggested benefit. A large well designed clinical trial comparing active to sham apheresis has shown no significant benefit for the treatment in 168 patients with active UC.²¹⁰ A subsequent systematic review concludes that although there may be some benefit in selected patients groups, methodological issues with the majority of published trials prevented a rigorous meta-analysis.²¹⁴ It has wide-spread acceptance in Japan. Expense may limit its use, but the outcome of controlled trials will govern its future role in Europe.

5.4.8.5. Probiotic therapy. There is insufficient evidence for the use of *T. suis ova*, *Saccharomyces boulardii*, or Bifidobacteria in the treatment of UC [EL5, RG D]. The majority of trials of probiotics for ulcerative colitis have assessed their benefit in the maintenance of remission.²¹⁵ A Cochrane database systematic review of trials that investigated the therapeutic benefit of probiotics for the induction of remission in patients with active ulcerative colitis did not find any study that reported a benefit over placebo.²¹⁶ Since that time a placebo-controlled trial of VSL#3 in 144 patients with relapsing, mild to moderate UC despite mesalazine and or immunosuppressants reported significantly more patients experiencing a clinical response with VSL#3 than placebo.²¹⁷

5.4.8.6. Other complementary therapies. Other complementary medicines have been studied in small studies or in countries where randomised, double-blind, placebo controlled trials are not the practice norm for judging the merits of therapy. Because of sample size, study design, concomitant therapies and questionable transferability, the following agents can not currently be recommended for treating UC, either for active disease or as maintenance: acupuncture,^{218–220} *Boswellia serrata* gum,^{221,222} prebiotic germinated barley foodstuff,^{223–226} aloe vera gel²²⁷ and other herbal medicines.²²⁸ A report on curcumin maintenance therapy (2 g daily, added to aminosalicylates for 6 months) showed a signal for benefit in a double-blind, placebo controlled trial of 89 patients.²²⁹ This needs confirmation and illustrates the need to explore the benefit of complementary medicines using the same rigorous clinical trials as conventional therapy.²³⁰ In a recent study an extract of the herb *Andrographis paniculata* (HMPL-004)—used in Chinese medicine and shown to prevent colitis in animal models—was compared to 4500 mg/day of slow release mesalazine in patients with mild-to-moderately active ulcerative colitis.²³¹ In this clinical trial 120 patients at five centres in China were randomised. There was no significant difference between the two treatment groups indicating a treatment effect of the herbal product. However, this was a pilot study. It was not powered to demonstrate non-inferiority. HMP-004 is an ethanolic

extract, the main known components are diterpene lactones; however, the exact composition may vary between batches. The effective component is not known; therefore it is difficult to standardise the preparation. The study has only been performed in China and therefore no data in Caucasian patients are available. As outlined above confirmation for those data is required before further conclusions can be drawn.

5.5. Preparation for the period after treatment of active disease

A patient's response to remission induction therapy should be followed for several weeks. If treatment is effective, the patient should continue until symptomatic remission is achieved or further improvement ceases. An outcome other than steroid-free remission after treatment of active disease is considered unacceptable, whether or not immunomodulators or biological therapy is used. Maintenance therapy is recommended after successful medical treatment of active disease. If a patient experiences a disease flare whilst taking maintenance therapy appropriate induction therapy for the acute flare is required.

6. Maintenance of remission

6.1. General

6.1.1. Maintenance therapy trial design

Most trials of maintenance therapy for UC have enrolled patients in clinical and endoscopic remission. In such studies, steroids are typically not permitted as concomitant therapy. The endpoint is the absence of relapse (or failure to maintain clinical remission) after 6 or 12 months.² Clinical relapse is defined by an increase in stool frequency and recurrence of rectal bleeding, confirmed by endoscopy (Section 1.2.6). This is not the only approach to the evaluation of maintenance therapy, as more recent trials have assessed both induction and subsequent maintenance at the same time (e.g. ACT trials of infliximab¹⁰⁹). Using this approach, the clinical response at week 8 was defined as the primary endpoint, and the efficacy of maintenance therapy evaluated as a secondary endpoint (Section 6.2.3). However, the pivotal endpoint that matters to patients is clinical remission with complete, corticosteroid discontinuation in those who were receiving steroids at baseline. Nevertheless, the definition of remission varies between trials, which makes comparisons difficult.¹⁵⁹

ECCO Statement 6A

The goal of maintenance therapy in UC is to maintain steroid-free remission, clinically [EL1, RG A] and endoscopically defined [EL2, RG B]

6.1.2. Pattern of disease

More than half of patients with UC have a relapse in the year following a flare. In clinical trials designed for the maintenance of remission in patients with clinical remission at baseline,

clinical relapse rates amongst patients receiving placebo range from 29% to 43% at 6 months, and from 38% to 76% at 12 months.^{2,9,232} A population-based study carried out in the county of Copenhagen,²³³ described the outcome in 1575 patients in the first 5 years following diagnosis of UC between 1962 and 2005. In the most recent period, the percentage of patients experiencing an 'indolent' course (no relapse during the first 5 years after diagnosis) was 13%, whilst 74% had 'moderate' course (two or more relapses within the first 5 years, but less than every year), and 13% had an 'aggressive' course (disease activity at least every year during the first 5 years). This highlights potentially confusing use of the term 'moderate' to refer to the pattern of disease, rather than the activity at a point in time (Sections 11.2, 3.2.1). Furthermore, grouping activity into 5-year periods seems too long for everyday practice, although relevant from an epidemiological perspective. The preferred alternative is to define relapse as infrequent ($\leq 1/\text{yr}$), frequent (≥ 2 relapses/yr), or continuous (persistent symptoms of active UC without a period of remission).⁴⁴

6.1.3. Impact of the definition of remission on long term outcome

It is possible that the absence of a standardised definition of remission has contributed to a self-perpetuating cycle of suboptimal therapy in UC.¹⁵⁹ Long-term prognostic studies show low rates of remission (<50% of patients), and therefore new and better (or better use of old) therapies are needed. It is only now becoming apparent that a stringent endpoint for remission (clinical plus endoscopic remission) is related to longer duration of remission. For example, an endoscopic score of 0 (defined as complete mucosal healing) applied to a post-hoc analysis of the ACT 1 and 2 trials revealed that patients with healing at week 8 had a four-fold increased likelihood of remission at week 30 of infliximab treatment.²³⁴ This may be expected, but needs to be confirmed if clinical practice is to change. Patients assessed after induction therapy by an index that did not incorporate endoscopy were less likely to be in remission one year later than those whose remission was defined by endoscopic, as well as clinical criteria.^{235,236} Finessing the endoscopic mucosal friability component of the Sutherland Index to develop the more stringent 'Modified UC-DAI' has affected long term remission rates in prospective clinical studies. Using the Modified UC-DAI, patients receiving Multi-Matrix System (MMX) mesalazine achieved and maintained remission rates >60% at four months and one year follow-up.^{237,36}

ECCO Statement 6B

Maintenance treatment is recommended for all patients [EL1a, RG A]. Intermittent therapy is acceptable in a few patients with disease of limited extent [EL5, RG D]

6.1.4. Risk factors for relapse

Few prospective studies have assessed risk factors for relapse in patients with inactive UC.^{238–242} In one study of 92

patients, a shorter duration of current remission and a higher relapse frequency were predictive of further relapse.²³⁸ In a second study of 64 patients, the frequency of previous relapses, extraintestinal manifestations and a low-fibre diet were independent variables associated with a higher risk of relapse.²³⁹ In another study of 74 patients including various biomarkers and clinical measures, a younger age, multiple previous relapses (for women), and basal plasmacytosis on rectal biopsy specimens were independent predictors of relapse.²⁴⁰ This study did not confirm the two-fold increase in relapse rate in those with persisting active inflammation (polymorphonuclear leukocytes in the rectal mucosa) observed in two earlier histopathology studies.^{243,244}

The impact of life events on relapse of UC has been examined by a number of studies^{241,242,245} with contradictory results. Nevertheless, in the best prospective study to date, 704 patients with quiescent IBD (38% with UC) from the University of Manitoba IBD disease registry were followed with questionnaires every 3 months for 12 months.²⁴⁶ Only stress (HR 2.46; 95% CI 1.56–3.89) whether perceived, negative affect, or any major stressful event and being single (OR 1.79, 95% CI 1.03–3.13) were associated with a higher risk of relapse on multivariate analysis and not use of NSAIDs, antibiotics, or infection. Adherence to medical therapy still appears to be the governing factor associated with relapse, since the risk of relapse was more than 5-fold higher (OR 5.5, 95% CI 2.3–13.0) amongst 99 patients who collected <80% of their prescriptions for maintenance mesalazine.²⁴⁷

ECCO Statement 6F

Choice of maintenance treatment in UC is determined by disease extent [EL1b, RG B], disease course (frequency of flares) [EL5, RG D], failure of previous maintenance treatment [EL5, RG D], severity of the most recent flare [EL5, RG D], treatment used for inducing remission during the most recent flare [EL5, RG D], safety of maintenance treatment [EL1b, RG B], and cancer prevention [EL2a, RG B]

Patients with disease requiring steroids probably have a different outcome to the overall population of patients with UC. In a population-based study from Olmsted County, Minnesota, the outcome of 183 patients with UC diagnosed between 1970 and 1993 was analysed one year after a first course of steroids.²⁴⁸ Amongst the 63/183 patients treated with corticosteroids, 49% had a prolonged response, 22% were steroid dependent and 29% came to colectomy, but only 3/183 were treated with AZA/MP (see also Section 5.4.2).

Both mucosal healing and a previous episode of acute severe colitis impact on the key outcome of colectomy. In a population-based study from South East Norway, 423/519 patients with UC completed the 10-year follow-up. 53 died and 43 were lost to follow-up. The cumulative colectomy rate after 10 years was 9.8% (95% CI 7.4–12.4%). Initial presentation with extensive colitis or acute severe colitis tripled the risk of subsequent colectomy (HR 3.57, 95% CI 1.60–7.96), whilst age \geq 50 years at diagnosis reduced the risk by 3-fold (HR 0.28, 95% CI 0.12–0.65). Relapsing disease occurred in 83%, but half (48%) of the patients were relapse

free during the last 5 years. Mucosal healing 12 months after diagnosis was associated with a lower colectomy rate (2% vs 8% without mucosal healing, $p=0.02$).²⁴⁹ Two studies have now shown that admission to hospital is a key factor in predicting colectomy.^{250,251} In the Oxford cohort of 750 patients, 186 had at least one episode of acute severe colitis. The overall colectomy rate was 12.4% (93/750), but it was 39.8% (74/186) of patients with one or more episodes of ASC ($p<0.0001$) and just 3.4% (19/564) in those with no admission.²¹⁵

6.2. Medications for maintenance of remission

Details of the action, dosage, side effects and monitoring of aminosalicylates, steroids, thiopurines, and infliximab are in the Active Disease section.

Options for a stepwise escalation of maintenance therapy include dose escalation of oral/rectal aminosalicylates [EL1, RG A], the addition of azathioprine/mercaptopurine [EL2, RG B] or Infliximab/anti TNF therapy [EL1, RG A]. Short term use of systemic or topical steroids may be required when a rapid response is needed [EL1, RG A].

6.2.1. Aminosalicylates

ECCO Statement 6D

Oral 5-aminosalicylate (5-ASA) containing compounds are the first line maintenance treatment in patients responding to 5-ASA or steroids (oral or rectal) [EL1a, RG A]. Rectal 5-ASA is the first line in maintenance in proctitis and an alternative in left-sided colitis [EL1b, RG A]. A combination of oral and rectal 5-ASA can be used as a second line maintenance treatment [EL1b, RG B]

6.2.1.1. Oral 5-ASA. The most recent version of the Cochrane meta-analysis showed that the Peto odds ratio for failure to *maintain* clinical or endoscopic remission (withdrawals and relapses) for oral 5-ASA versus placebo was 0.47 (95% CI 0.36–0.62), with a number-needed-to-treat (NNT) of 6.²⁵² Numerous randomised controlled trials (RCTs) designed to evaluate the efficacy of oral 5-aminosalicylates (5-ASA)—including sulfasalazine, various mesalazine formulations and olsalazine—for maintaining remission have been conducted in the past.^{34,236,237,253–262}

6.2.1.2. Rectal 5-ASA. Several RCTs have compared rectal mesalazine in various formulations and regimens with placebo for maintenance of remission in distal UC.^{263–268} At 12 months, failure to maintain clinical or endoscopic remission was 20–48% in the active arms compared to 47–89% in the placebo arms. In all but one of the trials, the differences in failure to maintain remission between active and placebo groups were statistically significant. The only RCT that failed to demonstrate efficacy of 5-ASA suppositories²⁶⁴ followed a three times a week regimen; the difference between the two arms was significant at 3, 6 and 9 months but did not reach the significance level at 12 months. Other trials have

demonstrated efficacy with similar intermittent rectal 5-ASA regimens, either alone or in combination with oral 5-ASA. A meta-analysis which included the two placebo-controlled trials, showed a superiority of rectal mesalazine over placebo for remission maintenance at 1 year (OR 16.2, 95% CI 4.7–55.9).²⁶⁹

6.2.1.3. Combining oral and topical 5-ASA therapy. There have been two RCTs comparing combination treatment with oral mesalazine plus intermittent mesalazine enema to oral mesalazine alone for maintaining remission. Remission rates were higher in patients receiving the combination.^{266,270}

It is therefore clear that oral or rectal 5-ASA is superior to placebo in maintaining remission in UC. The data suggest that rectal 5-ASA has equivalent or slightly superior efficacy to oral mesalazine in distal UC. The combination of oral mesalazine and intermittent rectal 5-ASA appears to provide further benefit. Although most authors in the studies claimed that patients found long-term rectal treatment acceptable, a postal survey of the UK patients showed that 80% preferred oral treatment alone.²⁷¹ However, in another study in Spain, 5-ASA suppositories were generally well tolerated and considered comfortable for treatment of at least one year.²⁷² The choice and options should be discussed with patients. Adding rectal therapy is a treatment option for patients who have relapsed on oral 5-ASA alone, although adherence to prescribed therapy should be addressed.

ECCO Statement 6E

The minimum effective dose of oral 5-ASA is 1.2 g per day [EL1a, RG A]. For rectal treatment 3 g/week in divided doses is sufficient to maintain remission. The dose can be tailored individually according to efficacy and in some cases higher doses ± topical 5-ASA is useful [EL5, RG D]. Once daily administration of 5-ASA has been proven to be at least as effective as twice or three-times daily administration, with no increased side effects [EL1a, RG A]. Although sulfasalazine is equally or slightly more effective [EL1a, RG A], other oral 5-ASA preparations are preferred for toxicity reasons. All the different available preparations of oral 5-ASA are effective [EL1a, RG A]. There is no robust evidence to support the choice of any specific 5-ASA preparation for maintenance [EL1a, RG A]

6.2.1.4. Dose–response effect. A dose–response for maintenance of remission with mesalazine at doses greater than 0.8 g/day has not been established. In an Italian study, no difference was found in relapse rates at 1 year on mesalazine 1.2 g compared to 2.4 g/day.²³⁵ Patients taking the higher dose were in remission for longer than those on the lower dose (median time in remission of 175 days vs 129 days, $p < 0.001$), but it may be debated whether this is clinically significant. For those with extensive UC, however, the benefit of the higher dose was more marked (143 days versus 47 days, $p < 0.005$). When the results for patients in remission at 12 months were analysed after stratifying for frequently relapsing disease (>3 relapses

per year) versus less frequent relapses, 2.4 g/day also performed significantly better than 1.2 g/day (75% versus 33%, respectively). This post hoc analysis must, however, be treated with caution.²⁷³ Another trial has also reported a trend for benefit in subjects receiving the higher dose of Pentasa 3 g/day compared with 1.5 g/day ($p = 0.051$).²⁷⁴ As with other studies of high doses of 5-ASA, there was no increase in the frequency of adverse events. It is possible that higher doses of maintenance oral mesalazine are required in some patients, perhaps in those that required high doses of oral 5-ASA to induce remission or those with frequently relapsing disease, but at present, there is no robust evidence to support this.²⁷⁵ There are also no data supporting a dose–response relationship with rectal 5-ASA for maintaining remission in distal UC, and no more than 1 g/day is required.

Several studies^{236,237,261,262} have compared different dosing regimens for various 5-ASA formulations. Without exception, they have all concluded that once daily administration is, at least, as effective as twice or three times administration of 5-ASA. The comparable efficacy between once daily and divided dosing regimes in the maintenance treatment of UC, obtained with different mesalazine formulations, suggests that this effect is generic to 5-ASA rather than compound-specific. Interestingly, once daily administration of mesalazine has not been found associated to an increase rate of side effects in any of these studies. Taken together, in conjunction with the likely improvement in patient convenience and adherence to treatment, this make once daily administration of 5ASA compounds the first choice in maintenance therapy in patients with UC.

6.2.1.5. Comparison of oral 5-ASA formulations. In a Cochrane meta-analysis²⁵² the odds ratio for the failure to maintain clinical or endoscopic remission (withdrawals and relapses) was calculated for several trials in which sulfasalazine and different 5-ASA formulations were compared.^{235–237,260,274,276–284,259,236,237,261} The odds ratio was 1.29 (95% CI 1.05–1.57), with a negative NNT, suggesting greater therapeutic effectiveness for sulfasalazine. Sulfasalazine and 5-ASA had similar adverse event profiles (OR 1.16, 95% CI 0.62–2.16, and OR 1.31, 95% CI 0.86–1.99 respectively). However, the trials that compared 5-ASA and sulfasalazine are likely to have been biased in favour of sulfasalazine, because most trials enrolled sulfasalazine-tolerant patients, which would have minimized sulfasalazine-related adverse events.

Other studies have addressed the issue of whether 5-ASA formulation influence its efficacy as maintenance treatment. In a study by Ito et al.¹⁷ no differences were observed between a pH-dependent and a time-dependent 5-ASA formulation. In a study by Prantera et al. MMX mesalazine, 2.4 g once daily, was as effective as Asacol® in maintaining UC remission.²⁵⁹

6.2.1.6. Adherence to 5-ASA treatment. Adherence to 5-ASA therapy appears to be pivotal for improving outcome in patients with UC. The adherence rate in 94 outpatients on 5-ASA with clinically quiescent UC for at least 6 months was 40% and the median amount of medication dispensed per patient was 71% (8–130%) of that prescribed.²⁸⁵ Logistic

regression found that a history of four or more prescriptions or male gender increased the risk of non-adherence. Being married, having extensive disease or having an endoscopy within the past 24 months reduced non-adherence. In a pilot study, patients were randomised to receive either once-daily or conventional (two or three times daily), mesalazine for maintenance of remission in UC.²⁸⁶ After 6 months, patients in the once-daily arm appeared more satisfied with their regimen and consumed more medication than those in the conventional arm (90% vs 76%; $p=0.07$). The authors concluded that once-daily oral formulations of 5-ASA were likely to be a better therapeutic option with comparable efficacy and improved adherence. An investigator-blinded study of 362 patients randomised to receive Pentasa 2 g once daily or 1 g twice daily, showed a 12% better remission rate at 1 year (73.8% vs 63.6% respectively) in the once daily dose group.²³⁶ Patient questionnaires showed significantly greater compliance ($p<0.05$) and acceptability ($p<0.001$) in the once daily group. Given the comparable efficacy between once daily and divided dosing regimens for the treatment of active UC with other mesalazine formulations, this effect is likely to be generic rather than compound-specific.^{236,237,261,262}

6.2.2. Thiopurines

6.2.2.1. Efficacy of thiopurines for maintenance of remission. Several RCTs evaluating the efficacy of thiopurines azathioprine (AZA) and mercaptopurine (MP) for maintenance of remission in UC have been performed.^{141,191,287–291} In a Cochrane meta-analysis,²⁹² six of these studies on 286 patients were considered. The study quality was judged generally poor and the evidence for using thiopurines in UC is weaker than that for Crohn's disease. AZA was shown to be superior to placebo on the basis of four trials (OR for failure to maintain remission 0.41, 95% CI 0.24–0.70). The results were similar when analyses were limited to patients who had successful induction of remission (data available for two studies). There was no clear evidence of a dose–response effect for AZA, or for use of co-medication with mesalazine in these studies. Adverse effects occurred in 11/127 patients receiving AZA, including acute pancreatitis (3 cases) and bone marrow suppression (5 cases). Since this meta-analysis, a further RCT has been published by Ardizzone et al.¹⁴¹ 72 patients with active steroid-dependent UC were randomised (investigator-blind) to AZA 2 mg/kg/day or mesalazine 3.2 g/day for 6 months. Steroid-free, clinical and endoscopic remission was achieved in 53% on AZA, compared to 21% given 5-ASA (intention to treat analysis: OR 4.78, 95% CI 1.57–14.5). This is the best trial to date.

Evidence to support the use of thiopurines for UC also comes from observational cohorts in retrospective series.^{293–298} The best amongst these is the 30 year cohort from the Oxford IBD clinic between 1968 and 1999.²⁹⁴ In this series, the overall remission rate in 346 patients with UC who were treated with AZA was 58%, but increased to 87% amongst patients on therapy for more than 6 months. The proportion of patients in remission at 5 years was 62% applying a strict definition of relapse, or 81% allowing for a brief relapse with a short corticosteroid course. The median time to relapse after stopping AZA was 18 months.

6.2.2.2. Thiopurines after ciclosporin (or tacrolimus) for induction of remission. Calcineurin inhibitors are rescue therapy options for steroid-refractory UC (Section 5.2.5). Since calcineurin inhibitors are best discontinued within 6 months because of side effects, these agents are generally proposed as induction therapy until slower-acting immunomodulators such as AZA or MP become effective. AZA or MP is introduced whilst the patient is still on ciclosporin (CsA) or tacrolimus and steroids are being tapered. The justification of thiopurines in this setting, even in patients who are 5-ASA naive, is the high colectomy rate (36–69% in the 12 months following introduction of CsA, Section 5.2.5^{86,87,299,300}). Retrospective series have suggested that thiopurines reduce the risk of colectomy after the induction period with CsA.^{86,87,301,264} In another series 5/19 patients receiving AZA (26%) underwent colectomy during the follow-up, compared to 9/11 subjects (81%) who did not receive AZA maintenance ($p=0.01$).²⁹⁹ Similar results have been reported from Chicago: of 36/42 initial responders to CsA, 25 (69%) also received MP or AZA, of whom 20% required colectomy vs 45% who did not receive thiopurines during the 5 year follow-up.⁸⁶

After intravenous CsA, a switch to oral therapy occurs as soon as a clinical response has been achieved, with a view to acting as a 'bridge' until the therapeutic effect of AZA is achieved. Nevertheless, the usefulness of the oral CsA bridge has been challenged. In a retrospective series from Barcelona, all responders to iv CsA were treated with AZA, without oral ciclosporin.³⁰² Cumulative probabilities of relapse were 42%, 72% and 77% at 1, 3 and 5 years, and cumulative probabilities of colectomy were respectively 29%, 35% and 42%. These are similar to or better than those reported in the literature, so the authors concluded that the 'bridging step' with oral CsA may not be necessary.

6.2.3. Anti-TNF therapy

ECCO Statement 6F

Azathioprine/mercaptopurine is recommended for patients with mild to moderate disease activity who have experienced early or frequent relapse whilst taking 5-ASA at optimal dose or who are intolerant to 5-ASA [EL5, RG D], patients that are steroid-dependent [EL1a, RG A] and for patients responding to ciclosporin (or tacrolimus) for induction of remission [EL3, RG C]. In patients responding to anti-TNF agents, both maintaining remission with azathioprine/mercaptopurine [EL4, RGC] and continuing anti-TNF therapy with or without thiopurines [EL1a, RGA] are appropriate. In patients with severe colitis responding to intravenous steroids, intravenous ciclosporin or infliximab, azathioprine/mercaptopurine should be considered to maintain remission [EL2b, RG3]. However, in patients responding to infliximab continuing infliximab is also appropriate [EL4, RGC]. The prior failure of thiopurines favours maintenance with anti-TNF therapy [EL5, RGD]

6.2.3.1. Efficacy for maintenance. Details of the ACT 1 and 2 studies are given in Section 5.4.3.¹⁰⁹ In both studies, a

significantly higher proportion of patients had a clinical response or remission on IFX at weeks 8 and 30 (and at week 54 in the ACT 1 trial), compared to placebo. In ACT 1, remission rates at week 54 were 35% (5 mg/kg), 34% (10 mg/kg) and 17% (placebo). In ACT 2, remission rates at week 30 were 26% (5 mg/kg), 36% (10 mg/kg) and 11% (placebo). The proportion of patients with a sustained clinical remission at *all* time points was 7% (placebo) and 20% (5 mg/kg) after 54 weeks in ACT 1, and 2% (placebo) and 15% (5 mg/kg) after 30 weeks in ACT 2. The steroid-free remission rates in the 74 patients receiving corticosteroids at baseline were very modest, although still statistically significant. In ACT 1, steroid-free remission at week 54 was achieved in 24% (5 mg/kg), 19% (10 mg/kg) and 10% (placebo). In ACT 2, the corresponding values at week 30 (7 months) were 18%, 27% and 3%. The rates of clinical response and remission were similar between the subpopulations of patients who were "corticosteroid-refractory" (i.e., those receiving corticosteroids at baseline) and those who were "not corticosteroid-refractory".

In long-term follow up, 121 outpatients with refractory UC treated with IFX were analysed for colectomy-free survival. Secondary measures were sustained clinical response and serious adverse events. From the 81 patients (67%) with an initial clinical response to IFX, 68% had a sustained clinical response. No independent predictors of sustained clinical response could be identified. Over a median (IQR) follow-up period of 33.0 (17.0–49.8) months, 21 patients (17%) came to colectomy. Independent predictors of colectomy were absence of short-term clinical response (Hazard Ratio 10.8, 95% CI 3.5–32.8, $p < 0.001$), a baseline CRP level ≥ 5 mg/L (HR 14.5, 95% CI 2.0–108.6, $p = 0.006$) and previous intravenous treatment with corticosteroids and/or ciclosporin (HR 2.4, 95% CI 1.1–5.9, $p = 0.033$).³⁰³ Complete mucosal healing has independently been shown to be associated with a lower colectomy rate (95% colectomy-free at week 54, compared to 80% with an endoscopic Mayo Clinic subscore of 3, $p = 0.0004$).²³⁴

Two randomised controlled trials have also demonstrated the efficacy of the anti-TNF adalimumab (ADA) for maintaining remission in patients with moderate to severe UC.^{149, 167} In a trial by Reinisch et al.,¹⁴⁹ patients could enter a 52-week open-label extension to receive ADA 40 mg every other week (eow) as maintenance therapy after an 8-week, randomised, placebo-controlled induction period with adalimumab or placebo. Of 390 patients in the primary analysis population, 360 received open-label ADA eow and 117 had their dosages increased to weekly ADA. Remission rates at Week 52 were 25.6% (non-responder imputation, NRI) and 29.5% (mNRI). No deaths or cases of tuberculosis were reported.¹⁴⁹ In another study¹⁶⁷ on the efficacy and safety of ADA for induction and maintenance of clinical remission in patients with moderate-to-severe ulcerative colitis, adult patients with UC were randomised to placebo or ADA (160 mg/80 mg, then 40 mg eow). Patients were allowed previous anti-TNF therapy. In this trial, significantly more ADA-treated patients achieved clinical remission, clinical response, and mucosal healing at Week 8, Week 52, and both Weeks 8 and 52, compared to placebo. Amongst patients with corticosteroid use at baseline, significantly more ADA-treated patients discontinued corticosteroids before Week 52 and achieved clinical remission at Week 52, compared with placebo (13.3% vs. 5.7%).

6.2.3.2. Combining IFX and immunomodulators. As with Crohn's disease,³⁰⁴ the combination of IFX and a thiopurine analogue or corticosteroids is probably justified to decrease immunogenicity, which is the source of infusion reactions and loss of response.³⁰⁵ The efficacy of IFX, AZA, or IFX plus AZA was investigated in a 16-week, randomised, double-blind, controlled trial (UC-SUCCESS trial) in biologic-naïve patients with moderate–severe UC. A significantly greater proportion of patients achieved steroid-free remission at week 16 in the IFX+AZA arm compared to the AZA arm or IFX monotherapy arm. Clinical response and mucosal healing were higher in both IFX groups compared to the AZA alone.¹⁴³ Since antibodies to IFX occur early in the treatment, the question of discontinuing the immunomodulator has been addressed for Crohn's disease by the Leuven group. Results from a single centre open-label randomised, withdrawal trial suggest that the immunomodulator can be stopped after 6 months with no loss of response to IFX over 2 years.³⁰⁶

A 2 year follow up of patients who received salvage therapy with IFX for intravenous steroid-refractory UC showed that 13/16 patients who received AZA avoided colectomy (with or without oral 5-ASA) compared to 5/8 who received 5-ASA alone.¹³²

6.2.4. Probiotics

ECCO Statement 6G

E. coli Nissle is an effective alternative to 5-ASA for maintenance [EL1b, RG A]

6.2.4.1. Escherichia coli strain Nissle 1917. Three RCTs have compared the *E. coli* strain Nissle 1917 to mesalazine for maintenance of remission in UC. In the first study, 120 outpatients in a multicentre, double-blind, study received 1.5 g/day 5-ASA or 100 mg/day *E. coli* strain Nissle (corresponding to 25×10^9 viable *E. coli* bacteria) for 4 days, and then 200 mg/day.³⁰⁷ No concomitant medications were permitted. After 12 weeks, 11% of patients receiving 5-ASA and 16% of those receiving the probiotic patients relapsed. The statistical power was limited by the short duration of the study as relatively few patients relapsed. In addition, an 11–16% relapse rate within 3 months seems rather high. Subsequently 116 patients with active UC were randomised to receive either 5-ASA 2.4 g/day, reducing to 1.2 g/day after remission, or 200 mg/day of *E. coli* strain Nissle.³⁰⁸ All patients also received an initial 7 day course of oral gentamicin and either rectal or oral steroids in variable doses. The remission rate was 75% in the corticosteroid plus 5-ASA group, and 68% in the corticosteroid plus *E. coli* group (ns). During the one year follow-up, relapse occurred in 73% of the 5-ASA group and 67% of the *E. coli* group (ns) after weaning off steroids. This is a very high relapse rate for reasons that are unclear, but the probiotic was no less effective than 5-ASA. Finally, an equivalence study was conducted.³⁰⁹ 327 patients with UC in remission for no longer than 12 months were treated with either 5-ASA 1.5 g/day or *E. coli* Nissle 1917 for 1 year. The relapse rate

was 45% in the *E. coli* group vs 36% in the mesalamine group. It was concluded that *E. coli* strain Nissle 1917 is not inferior to the established standard 5-ASA for maintenance of remission in UC, although the relapse rate in this last study was still higher than expected.

In addition to these RCT, a more recent open-label pilot study investigated the clinical benefit of *E. coli* Nissle (EcN) 1917 for maintenance therapy in young patients with UC. 34 patients with UC in remission aged between 11 and 18 years were allocated either to EcN (2 capsules daily n=24) or 5-ASA (median 1.5 g/day, n=10), observed over one year. This trial is clearly underpowered to show any difference or equivalence, but the relapse rate was 6/24 in the EcN group and 3/10 in the 5-ASA group. Data on the patients' global health and development were favourable and no serious adverse events were reported.³¹⁰

6.2.4.2. Other probiotics. No evidence has yet been reported that any other probiotic is effective for maintaining remission in patients with UC.^{311,312} With regard to the probiotic mixture VSL#3, a 1-year placebo-controlled, double-blind study assessed its efficacy for induction and maintenance remission in children with active UC.³¹³ A total of 29 consecutive patients with newly diagnosed UC were randomised to receive either VSL#3 or placebo in conjunction with concomitant steroid induction and mesalazine maintenance. All 29 patients responded to the induction therapy. Remission (according to their definition) was achieved in 13/14 patients (93%) treated with VSL#3 and IBD therapy and in 4/11 patients treated with placebo and IBD therapy (per protocol analysis $p < 0.001$). During follow up, 3/14 (21%) patients treated with VSL#3 and IBD therapy, and 11/15 (73%) patients treated with placebo and IBD therapy relapsed within 1 year of follow-up. No conclusions about efficacy can be drawn.

6.2.5. Other treatments

6.2.5.1. Antibiotics. The potential benefit of adding ciprofloxacin to conventional therapy has been investigated.³¹⁴ In a randomised, placebo-controlled, double-blind clinical trial, ciprofloxacin (1–1.5 g/day) or placebo was administered for 6 months to 83 patients referred with active UC refractory to conventional treatment. All the patients were initially treated with a high, but decreasing dose of prednisone and with 5-ASA. The treatment failure rate was 21% in the ciprofloxacin-treated group and 44% in the placebo group ($p = 0.02$). The study design was more appropriate for an induction rather than a maintenance study and inclusion criteria, definition of clinical response and concomitant therapies have been criticised.³¹⁵ Consequently ciprofloxacin should not be considered effective for maintaining remission in UC. In another double-blind, randomised trial, metronidazole (0.6 g/day) and sulfasalazine (2 g/day) were compared for maintenance of remission in 40 patients with UC in remission for less than 12 months.³¹⁶ After 1 year, metronidazole was found to be slightly more effective than sulfasalazine. No significant side effects were noted, and in particular, no paraesthesiae were reported. These data were regarded as insufficient by the Consensus to recommend antibiotics for maintenance of remission in UC.

6.2.5.2. Methotrexate. Data on methotrexate (MTX) for maintenance of remission in UC are few. The single RCT was principally designed for induction of remission in refractory, active UC and used a dose of 12.5 mg orally/week that is probably sub-therapeutic.¹⁹⁰ Proportions of patients who relapsed after first remission (MTX 64% vs placebo 44%) were not significantly different. An open-label study compared mercaptopurine (MP), MTX and 5-ASA in 72 steroid-dependent IBD patients, included 34 with UC.¹⁹¹ Patients on prednisone were randomly assigned in a 2:2:1 ratio to receive MP 1 mg/kg, MTX 15 mg orally/week, or 5-ASA 3 g/day. All patients who achieved remission at week 30 were then included in a maintenance study for 76 weeks. A significantly higher proportion of patients achieved remission in the MP group (79%) than in the 5-ASA group (25%), with no statistical differences compared to the MTX group (58%). For maintenance of remission, the higher rate was found in the MP group (64%) compared to MTX (14%) and 5-ASA (0%).

Several retrospective series have been published.^{194,317} Most of the included patients had failed or were intolerant of azathioprine and were treated with MTX at various doses and routes of administration. The response or remission rates ranged from 30% to 80%, when the drug was given by parenteral route in doses between 20 and 25 mg, suggesting that some patients with UC may respond to MTX. MTX (median oral dose 20 mg/week) was tolerated by 27/31 (87%) patients who had been unable to tolerate AZA. Of those treated with MTX after failure with AZA, 5/11 patients had a colectomy, compared to 5/31 patients intolerant of AZA.³¹⁷ In another study, MTX induced a response in 65% (15/23) of those who were either previously intolerant and in 78% (7/9) of those who previously failed with thiopurines.¹⁹⁴ The results are heterogeneous and it is possible that the dose of MTX is an important determinant of efficacy, but the Consensus considered that there is currently insufficient evidence to recommend MTX for UC. A Cochrane systematic review reached the same conclusion.¹⁹³

6.3. Duration of maintenance therapy

ECCO Statement 6H

The general recommendation is to continue 5-ASA maintenance treatment long-term [EL3b, RG C] since this may reduce the risk of colon cancer [EL4, RG D]

6.3.1. Aminosalicylates

Two studies from Sweden and the UK were published to assess whether sulfasalazine was still effective at preventing relapse in patients with UC with a long duration of remission. In the Swedish study, the authors found no statistical benefit to maintaining sulfasalazine for patients who had been symptom-free on sulfasalazine for more than a year.²⁵⁵ However, the number of patients was small, the duration of follow-up only 6 months and patients were selected on clinical symptoms without endoscopic or histologic criteria. In the UK study, sigmoidoscopy and rectal biopsy were used at entry.²⁵⁴ The authors found that maintenance

treatment with sulfasalazine 2 g/day continued to have a major effect at reducing relapse, even in the subgroup of patients who had been on sulfasalazine for more than 3 years. Twenty-six years later, an Italian double-blind withdrawal RCT included 112 patients with UC in clinical, endoscopic and histological remission who had been on sulfasalazine or 5-ASA for at least 1 year.³¹⁸ Patients were randomised to oral mesalazine 1.2 g/day or placebo for 1 year. Despite the small numbers, patients were stratified according to the length of disease remission prior to randomization. In patients with disease remission for 1–2 years, mesalazine appeared significantly more effective than placebo for preventing relapse at 12 months (mesalazine 23% and placebo 49%, $p=0.035$). For patients who had been in remission for more than 2 years however, no statistically significant difference was observed between relapse rates (5/28 vs 6/23, or 18% vs 26%, respectively), but numbers were very small. The results of this study should be regarded with caution, not only because of the low power, but also because the trend was in favour of continuing mesalazine.

ECCO Statement 6I

Due to limited evidence, no recommendation can be given for the duration of treatment with azathioprine or infliximab, although prolonged use of these medications may be considered if needed [EL4, RG D]

6.3.2. Thiopurines

There are few data on factors predicting response to azathioprine (AZA) and uncertainty regarding the optimal duration of treatment. In a retrospective analysis with 622 patients with either CD or UC, the remission rates at month six were 64% and 87%, respectively. The proportions of patients remaining in remission at one, three, and five years were 0.95, 0.69, and 0.55, respectively. There was no difference in relapse rates between CD and UC. After stopping AZA, the proportions of patients remaining in remission at one, three, and five years were 0.63, 0.44, and 0.35 (222 patients) respectively. The duration of AZA treatment did not affect the relapse rate after stopping treatment ($p=0.68$).²⁹⁴

6.3.3. Anti-TNF therapy

Several studies, most of them neither prospective nor randomised have reported long-term efficacy data of in UC [reviewed in³¹⁹]. A prospective study reported the long-term outcome of IFX in less severe UC.³²⁰ The long-term effect of IFX on disease activity, corticosteroid use and quality of life in patients who had completed the ACT 1/2 trials and had responded to IFX, who had then been enrolled in the ACT-extension ($n=229$) study is reported. Of these 229 patients, 181 have been followed for 1 year and 92 for 2 years. The rates for little or no activity at weeks 56 and 104 from the ACT extension baseline were 92% and 97% respectively. The 2-year rates of corticosteroid-free remission were 75% and 98%, respectively. Data on Adalimumab beyond 1 year for UC have yet to be reported, but maintenance of effect in those who maintain response to anti-TNF therapy after 1 year can be expected with continued

treatment. No withdrawal study of anti-TNF therapy has been reported in UC.

7. Surgery

7.1. General

Surgery for ulcerative colitis has been refined to offer patients needing colectomy a better quality of life. Until the early 1980s, the gold standard for surgery was proctocolectomy with an ileostomy, apart from the sporadic use of ileorectal anastomosis. The Kock continent ileostomy was introduced in the late 1960s, but never achieved universal acceptance, although the gain in quality of life compared to proctocolectomy with a conventional stoma seemed clear enough.³²¹ In the past 20 years, the new gold standard has become the restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA), offering patients an unchanged body image with no stoma and a preserved anal route of defaecation.³²² Nevertheless, bowel function is not restored to normal and both functional outcome and quality of life after IPAA have still to be compared to living with an ileostomy.³²³

This section deals with some aspects on surgery for ulcerative colitis. IPAA is probably one of the most frequently described procedures in colorectal surgery. There have been a vast number of publications (498 papers, 58 reviews), but despite this good quality evidence in terms of randomised studies is scarce (5 on different aspects of pouch surgery), as is so often the case in surgery. The indications and timing of surgery for UC are found in the appropriate sections (acute severe colitis, [Section 5.2.4](#); refractory colitis, [Section 5.2.5](#); dysplasia or cancer, [Section 9.5](#)).

7.2. Technical considerations

7.2.1. Surgery for acute severe colitis

ECCO Statement 7A

Delay in appropriate surgery is associated with an increased risk of surgical complication [EL4, RG C]
A staged procedure (colectomy first) is recommended in the acute case when patients do not respond to medical therapy [EL 4, RG C], or if a patient has been taking 20 mg daily or more of prednisolone for more than 6 weeks [EL 4, RG C]
If the appropriate laparoscopic skills are available, a minimally invasive approach is feasible and may convey some advantages [EL4, RG C]

Joint care between senior surgeons and senior gastroenterologists remains essential for the safe management of acute severe colitis. Whilst medical therapy is effective in many cases there is clear evidence that to delay appropriate surgery is detrimental to patient outcomes.⁵¹ A staged proctocolectomy (subtotal colectomy first) is considered to be a wise first step in the surgical treatment of acute severe colitis or if patients are saturated with steroids. A subtotal

colectomy with an ileostomy will cure the patient from the burden of the colitis, allowing them to regain general health, normalise nutrition and give the patient time to consider carefully the option of an IPAA or, perhaps, permanent ileostomy. A preliminary subtotal colectomy also allows the pathology to be clarified and Crohn's to be excluded. Subtotal colectomy is a relatively safe procedure even in the critical ill patient^{324–326} and if the appropriate expertise is available, there is emerging evidence that it is safe to perform minimally invasive or laparoscopic surgery.^{327,328}

7.2.2. Managing the rectal remnant

ECCO Statement 7B

When performing a colectomy for ulcerative colitis in emergency circumstances, the whole rectum and the inferior mesenteric artery should be preserved. This facilitates subsequent pouch surgery [EL 4, RG C]. Whether to preserve additional recto-sigmoid colon and how to deal with bowel closure is left to the surgeon's decision [EL 4, RG C]

There are some technical aspects on how to deal with the rectum when performing an emergency subtotal colectomy. These might have a bearing on the complication rate and have implications when the patient comes to a later proctectomy and IPAA. Leaving as little rectum as possible (i.e. dividing the middle rectum within the pelvis) is *not* to be recommended, because this will render subsequent proctectomy difficult, with a probable increase in the risk of pelvic nerve injury. The alternatives are to divide the rectum at the level of the promontory (i.e. at the proper rectosigmoid junction), or to leave in addition the distal part of the sigmoid colon. This allows the bowel to be anchored to the anterior abdominal wall, facilitating subsequent identification and dissection, or to bring the bowel up through the abdominal fascia either closed in the subcutaneous fat, or brought forward as a mucous fistula. The latter option is considered very safe, because no closed bowel is left within the abdomen, but the mucous fistula gives the patient another stoma that is not so easily managed.³²⁹ Closing the stump and leaving it within the subcutaneous fat are as safe, although the skin is probably best to be left to heal through secondary intention in order to avoid wound infection.³³⁰ There are no studies that give information on the risk of subsequent inflammation or bleeding after leaving differing lengths of rectum or rectosigmoid colon. When the rectum is transected within the abdominal cavity at the level of the promontory, transanal rectal drainage is advised for some days, to prevent blow-out of the rectal stump due to mucous retention.

7.2.3. Site of anastomosis for restorative proctocolectomy

ECCO Statement 7C

When performing pouch surgery, the maximum length of anorectal mucosa between the dentate line and the anastomosis should not exceed 2 cm [EL 4, RG C]

A common complication of using a stapling technique to perform the ileo-anal anastomosis is leaving a remnant of anorectal mucosa above the dentate line. This can be a cause of persistent inflammation ('cuffitis'), with pouch dysfunction and a risk of dysplasia or (very rarely) cancer.³³¹ Careful surgical technique even in the face of a narrow male pelvis should prevent this from happening. Done well, the stapled anastomosis seems to have better outcomes, particularly with regard to soiling, faecal leakage and social restriction.^{332,333}

7.2.4. Anastomotic technique for restorative proctocolectomy

ECCO Statement 7D

When performing an IPAA it is mandatory that the surgical team can also perform a mucosectomy and a hand-sewn anastomosis should the stapled anastomosis fail [EL5, RG D]

Nevertheless, the stapling technique occasionally fails, is impossible, or inappropriate. There is then no room for re-stapling and the only way of avoiding a permanent stoma is to hand-sew the anastomosis.

7.2.5. Site of anastomosis for neoplasia complicating colitis

ECCO Statement 7E

When the indication for surgery is cancer or dysplasia and restorative proctocolectomy is performed, a stapled anastomosis has equally low rates of subsequent cancer as hand sewn [EL4, RG C]

The suggestion that a stapled anastomosis leaves mucosa behind and is thus less safe than doing a mucosectomy and hand sewn anastomosis in patients who have had cancer or dysplasia in the resected colon or rectum, does not appear to be true. The literature reports cancers both in patients with a stapled anastomosis as well as in those who have had a mucosectomy, and there is evidence that a mucosectomy does not necessarily clear all remnants of mucosa.³³⁴ In addition, there is evidence that the stapled technique is as safe under these circumstances as hand sewn.³³⁵ The number of reported cancers is limited (<30 out of tens of thousands of IPAA performed worldwide) and is not at present a cause for alarm.^{336,337}

7.2.6. Role of covering ileostomy for restorative proctocolectomy

ECCO Statement 7F

When performing a restorative proctocolectomy for ulcerative colitis a covering loop ileostomy is generally recommended, but it can be avoided in selected cases [EL 3b, RG C]

One of the main complications of IPAA surgery, and also the complication that is most likely to compromise the clinical and functional outcome, is a leak in the suture lines of the anastomosis or pouch. Whether the consequences of a leak can be ameliorated by a covering ileostomy or not is still under debate.^{338,339} However there is emerging evidence that defunctioning the distal anastomosis may well reduce the incidence of a leak.³⁴⁰ Nevertheless, in pouch surgery it is sometimes clear at the time of surgery that the morbidity associated with a stoma will not justify its use, such as when there is a thick abdominal wall and a short small bowel mesentery, as long as there have been no problems constructing the anastomosis.^{341–343} Some authors have even attempted to construct nomograms in an attempt to predict who will benefit most from defunctioning.³⁴⁴

7.2.7. Number of procedures to maintain competency

ECCO Statement 7G

Pouches should be performed in specialist referral centres. Evidence exists that patients undergoing pouch surgery in high volume centres do better than low volume non specialist units. This appears to be the result of reduced complications and better pouch salvage in the face of complication [EL 4 RG C]

When performing complex surgical procedures that also demand sophisticated perioperative care, it has been shown that institutions performing larger numbers of operations have better outcomes than those who only operate on such cases occasionally.³⁴⁵ There is now evidence to support this view in institutions undertaking pouch surgery.³⁴⁶ Furthermore, this extends beyond competence to perform the procedure itself and it is clear that high volume institutions manage adverse events better and that this leads to better pouch salvage in the face of complications.³⁴⁷ It therefore seems logical and appropriate that, if available, ileoanal pouch surgery should be conducted in high volume specialist institutions. The numbers required to establish a 'specialist high volume unit' clearly remain for debate.

7.2.8. Salvage surgery for pouches

ECCO Statement 7H

Salvage surgery for complications of IPAA should only be done in special centres with adequately skilled staff and a reasonable number of procedures performed per annum [EL5, RG D]

Lifetime failure rates for IPAA will probably be in the region of 15%. Failure implies that the patient has an

ileostomy for an indefinite period, with or without pouch excision. Failures are usually due to septic complications or persistent pouch dysfunction, but sometimes the reason is a missed diagnosis of Crohn's disease with fistulation, or refractory pouchitis. Before deciding that a pouch has failed, the option of salvage surgery either as a corrective procedure or a complete "redo" has to be considered. The patient will invariably have a view on this and it should only be undertaken by colorectal surgeons with special expertise in this area. Reported series of pouch-rescue surgery describe a salvage rate above 50% and a still acceptable functional outcome.^{348–351} If pouch surgery is sufficiently complex to recommend a minimum case-load each year for a unit, it seems appropriate that salvage surgery, which is even more challenging, should only be performed in units with a substantial case volume load and expertise, although it is impossible to quantify a 'reasonable number'.

7.3. Follow-up

7.3.1. General pouch follow-up

ECCO Statement 7I

Follow up should be individualised and focus on those patients with signs of chronic inflammation in their mucosa [EL 5, RG D]

General follow-up of people with an IPAA is a matter of debate. There are no data to suggest that lack of follow-up incurs any risk for the patient, disregarding the debate on the risk of cancer. A proportion of patients (perhaps 20–30%) will develop pouchitis, which may be recurrent or persisting. These patients will need continuing specialist care, because primary care physicians or generalists will not have the expertise necessary for management. The stapled IPAA where there is a varying length of mucosa below the anastomosis (see [Statement 3C](#), above), poses an additional problem since these patients in principle have not had a curative procedure. However the remaining mucosa represents a very minute fraction compared to the original colon and does not represent a clinical problem for most patients.³³⁶

7.3.2. Pouch surveillance

ECCO Statement 7J

There are not enough data to give a general recommendation on surveillance of pouches with respect to malignant changes. However, patients with high risk features, such as: PSC or previous malignancy or dysplasia should undergo long term surveillance for pouch or pouch-anal dysplasia [EL5, RG D]

The risk of malignant changes arising from the pouch mucosa as a result of colonic metaplasia in the pouch has generated much debate. Approximately 30 pouch cancers have been reported, almost all in patients operated with dysplasia or cancer already present in the specimen at primary surgery. If we are to regularly follow up patients with IPPAs it would therefore seem sensible to concentrate on those at highest risk.^{352–354} The frequency of small bowel cancers in the background population is very low and the risk of developing a pouch cancer *de novo* is likely to be as uncommon, but remains undefined.³⁵⁵

7.4. Fertility and delivery in patients with a restorative proctocolectomy

7.4.1. Impact of pelvic surgery on fecundity

ECCO Statement 7K

In a fertile female patient alternative surgical options such as subtotal colectomy and end ileostomy or ileorectal anastomosis should be discussed with the patient, because fecundity is at risk after IPAA [EL3b, RG B]

It has been convincingly demonstrated in three cohort studies that female fecundity or fertility is reduced after IPAA.^{356–359} The reason for this is most probably adhesions affecting the fallopian tubes.³⁶⁰ The magnitude of this problem is under debate, with one study showing >70% reduction and the others demonstrating around 30% reduced fecundity. There is however good evidence from a study on patients with familial adenomatous polyposis, comparing women with an ileo-rectal anastomosis (IRA) with those with an IPAA, showing that there is no reduction in fecundity associated with an IRA.^{361,362} This appears to be because an IRA does not induce pelvic adhesions to nearly the same extent as an IPAA. Furthermore there is evidence that IRA provides a safe and functionally acceptable outcome.^{363,364} Not every woman is a candidate for this approach. Symptoms are less when there has been a colectomy, since the inflamed colon has been removed, but the rectum can be expected to remain inflamed. The persisting risk of rectal malignancy is discussed in Section 7.5.4. On the other hand, IRA does not disturb sphincter function, unlike IPAA, does not impair fecundity and can be discussed as a temporising option.

7.4.2. Mode of delivery for patients with restorative proctocolectomy

ECCO Statement 7L

There is not enough evidence to recommend a particular mode of delivery in pregnant women who have a pouch. Management should be individualised following an appropriate discussion with the patient, colorectal surgeon and obstetrician [EL 5, RG D]

Vaginal delivery has a 0.5–3.5% risk of inflicting significant maternal sphincter tears.^{365,366} The risk is highest at the first delivery. On the other hand, multiple deliveries have been shown to prolong pudendal nerve terminal motor latency.^{367,368} People with an IPAA have a very limited margin for maintaining faecal continence compared to the general population. This is because many factors considered important for normal continence, such as solid stools, rectal sensation, recto-anal nervous interplay through a recto-anal inhibitory reflex, are absent in people with an IPAA. Consequently they rely heavily on their sphincter for maintaining continence. Principally on these grounds many surgeons recommend that their patient have a caesarian section rather than a vaginal delivery. However the literature remains controversial. In both a cohort study and meta-analysis vaginal delivery appears safe and does not effect early continence.^{369–371} Other authors from both Europe and the US support the recommendation for caesarian delivery.^{286,372} More detailed information can be reviewed in the ECCO Consensus on pregnancy in IBD.³⁷³

7.5. Surgical choices in addition to restorative proctocolectomy

7.5.1. Age

ECCO Statement 7M

Whilst advancing age may lead to poorer outcome, no defined age limit for performing an IPAA can be recommended [EL 5, RG D]

Despite the evidence that there are higher levels of co-morbidity in patients over the age of 65 undergoing IPAA, the procedure appears safe and effective in this age group.³⁷⁴ However, an increased frequency of long term complications such as pouchitis or anastomotic stricture in elderly patients undergoing IPAA has been reported.³⁷⁵ Deterioration in pouch function with advancing age applies to all patients undergoing IPAA and faecal incontinence in particular, with evidence that this may be more pronounced in the elderly.^{376,377} However, it appears that despite this burden of worsening continence patients over the age of 65 with IPAA still retain a good quality of life.³⁷⁸ Decisions about what operation to perform on this elderly group must therefore be tailored to the individual.

7.5.2. Continent ileostomy

ECCO Statement 7N

The continent ileostomy is still a viable option that can be used when there is no possibility of performing an ileal pouch anal anastomosis, or when the IPAA fails for other reasons than pouchitis, or when the patient specifically requests this solution [EL 4, RG C]

The continent ileostomy ('Kock pouch') was the forerunner to the IPAA. It is a complex procedure with a high risk of re-operation. However, well motivated patients with a

functioning continent ileostomy patients report excellent quality of life with a next-to-normal body image.^{350,379–382} Furthermore a failed pelvic pouch can still be converted to a continent ileostomy which may restore a good quality of life.^{380,381,383}

7.5.3. Ileorectal anastomosis

ECCO Statement 7O

An ileorectal anastomosis should be considered only in special cases (such as for reasons of fertility). Long term surveillance of the retained rectum is advised [EL4, RG C]

An ileorectal anastomosis is not only non-curative, but also leaves patients with the likelihood of persistent symptoms from refractory rectal inflammation and a risk of later cancer. Even so, recent series show a better than expected durability, with half of the patients still living with an IRA after 10 years.^{364,384,385} Its role in the management of women facing surgery before they have completed their family is discussed above (Section 7.4.1). Despite the reduced risk of subsequent colitis-related dysplasia and malignancy following colectomy, interval surveillance of the retained rectum is still recommended.³⁸⁶

7.5.4. Cancer surveillance of the rectal remnant after colectomy

ECCO Statement 7P

For patients who have a colectomy and ileostomy, surveillance of the retained rectum is appropriate, which may be left in situ if the patient so wishes [EL5, RG D]

The literature gives no direct guidance in this matter. The balance is between the adverse quality of life and cancer risk of a retained rectal stump and the surgical risks of proctectomy. Taking out the rectum is a major operation with a potential for surgical morbidity including delayed wound healing and risk of sexual dysfunction both in women and men.^{387,388} Alternatively, a retained rectum can lead to a significant reduction in quality of life.³⁸⁹ The issue of cancer risk in the retained mucosa is also unresolved. Whilst the risk would seem to be low, reports do exist of interval rectal cancers and so the recommendation should be that retained rectal stumps undergo periodic surveillance along the lines of patients with UC.^{390,391}

7.5.5. Pouch excision after pouch failure

ECCO Statement 7Q

In a patient where the pouch has failed and there is no hope of re-establishing the anal route of defecation, there are not enough data to make any recommendation on whether or not the pouch should be removed [EL5, RG D]

Patients whose pouches fail, face a similar dilemma, balancing these risks and adverse quality of life associated with a retained pouch with the risk of surgery to remove failed pouch. The little evidence that exists would suggest that the quality of life for both retained pouch and those whose pouches have been removed is similar. However, men who had their pouches removed were more likely to suffer from sexual dysfunction. In addition, there were no dysplastic or malignant changes seen in those patients with retained pouches at 12 years follow-up.^{392,393}

7.5.6. Laparoscopic pouch surgery

ECCO Statement 7R

Laparoscopic restorative proctocolectomy with an IPAA is a technically demanding but feasible operation. Aside from cosmesis there is no evidence for additional benefit to the patient [EL 2a, RG B]

There is now an abundance of data to suggest that a laparoscopic approach to IPAA is both feasible and safe. No randomised trial has yet been published however there are a number of potential benefit to a laparoscopic approach including; faster recovery, better cosmesis, reduced burden of adhesions and thus improved fecundity.^{394–398, 399–403} As yet the only objective analysis of the data has been a Cochrane review and the authors' conclusions suggested that there was to date little advantage in the short and medium term but that large, quality randomised trials were needed.⁴⁰⁴

7.5.7. Pouch surgery for indeterminate colitis, or IBD yet-to-be classified

ECCO Statement 7S

In indeterminate colitis or colonic IBD yet-to-be classified, an IPAA can be offered with the information that there is an increased risk of complications and pouch failure [EL4, RG C]

About 10% of patients with colitis will not have a definitive diagnosis that discriminates between Crohn's and ulcerative colitis. Terminology is discussed in Section 1 of this Consensus. There are reports of less favourable outcomes when performing pouch surgery for patients with indeterminate colitis, although others find no significant differences.^{395,405} In most series that report outcome after pouch surgery, those with a secondary diagnosis of Crohn's disease suffer very high complication and failure rates. Although one group has reported outcomes equivalent to those with UC for patients with a pre-operative Crohn's diagnosis, none had pre-operative small bowel or perianal disease.⁴⁰⁶ Pouch surgery for patients with a definitive diagnosis of Crohn's disease cannot be recommended. For those in whom it is considered an option, very careful discussion with the patient about increased risks of sepsis and pouch failure is appropriate.

7.6. Surgery and medication

7.6.1. Perioperative prednisolone

ECCO Statement 7T

Prednisolone 20 mg daily or equivalent for more than six weeks is a risk factor for surgical complications [EL3b, RG C]. Therefore, corticosteroids should be weaned if possible

Uncontrolled or retrospective series indicate that patients taking >20 mg prednisolone for >6 weeks have an increased risk of surgical complications.^{110,407–411} Any recommendations of the rate of steroid reduction after colectomy for acute severe colitis are arbitrary, but the aim is to avoid acute steroid withdrawal ('Addisonian') crisis, characterised by hypotension, hyponatraemia and hypoglycaemia in its most severe form. Milder symptoms may be disguised as a 'slower than normal' recovery from surgery. There is little science to steroid withdrawal and it seems reasonable to reduce the steroid dose after colectomy immediately to the upper limit of the daily physiological production of cortisol, which is about 25 mg. Thus, a daily dose of 25–30 mg cortisol (hydrocortisone) or of 5–7.5 mg prednisolone seems appropriate (two thirds of the dose in the morning and one third in the evening). The rate of further weekly steroid tapering depends on the dose and duration of steroids prior to surgery. For patients on steroids for longer than 6 months, a dose reduction of 1 mg/week over a period of several months might be advisable.

7.6.2. Perioperative azathioprine

ECCO Statement 7U

Pre-operative thiopurines do not increase the risk of postoperative complications [EL3b, RG C]. Colectomy for ulcerative colitis immediately following or in the medium term after the use of ciclosporin, appears to have no higher rate of postoperative complications [EL3b, RG C]. Pre-operative use of infliximab may increase the risk of post-operative complications [EL2a, RG B]

Azathioprine/mercaptopurine does not appear to increase the risk of post-operative complications after colectomy.^{412–414} Whereas several studies do not describe an enhanced post-operative risk associated with ciclosporin,^{412,413,51,414,415} the data for tacrolimus are very limited.⁴¹⁵

7.6.3. Perioperative infliximab

ECCO Statement 7V

Perioperative use of infliximab does not appear to increase the risk of infective complications. There may however be an increase in short term surgical complications [EL 3a, RG C]

TNF α is a critical component of the immune response and its inhibition by infliximab or other agents could potentially lead to serious post-operative complications. There are a growing number of studies investigating the risk of post-operative complications associated with IFX leading to conflicting results. A recently published meta-analysis¹¹⁴ included 5 studies with 706 patients.^{98,110,416–418} The pre-operative use of IFX increased the total number of short-term (30 days) post-operative complications (OR 1.80, 95% confidence interval (CI) 1.12–2.87). However, the subgroup analysis was underpowered to assess the nature of these complications, but shows a trend towards increased post-operative infection (OR 2.24, 95% CI 0.63–7.95) whereas non-infectious complications were not increased (OR 0.85, 95% CI 0.50–1.45). Studies published after that meta-analysis did not describe an increased rate of complications after proctocolectomy associated with IFX.^{419–421} Since nearly all data come from observational studies and not from randomised controlled trials significant bias may probably influence the results. In a study from the Mayo Clinic assessing outcome from IPAA after IFX, anastomotic leaks, pouch-specific and infectious complications were more common in patients treated with IFX than in those who did not receive IFX.^{98,416} After adjustment for concomitant therapy and severity of colitis IFX was the only factor independently associated with infectious complications. However, IFX patients were significantly younger than non-IFX patients, probably reflecting concern that all medical options were explored before surgery.

The severity of disease and sequential use of ciclosporin can also influence the post-operative risk associated with preoperative IFX treatment. Patients with less active disease and low CRP-level, respectively, seem to benefit most from IFX therapy^{98,175,303,422} and there is particular concern that emergency colectomy within a few weeks of IFX may be associated with more septic complications. However, no data are available that relate only to emergency colectomy for patients with acute severe ulcerative colitis treated with IFX prior to surgery.

Several studies report efficacy and safety of ciclosporin and IFX as sequential rescue therapy in patients with steroid-refractory ulcerative colitis.^{116,417,423,424} Up to one third of patients achieved short-term remission and up to two thirds could avoid short-term colectomy.^{423,424} These rates appear similar for patients receiving IFX after failing ciclosporin as well as for patients receiving ciclosporin after failing IFX. However, serious adverse events occurred in up to 16% of patients including sepsis with fatal outcome and herpetic oesophagitis.^{116,423} There is no clear evidence if the risk of infectious complications is dependent on the sequence of the medications. The short half life of ciclosporin, however, is a potential advantage compared to IFX if ciclosporin is given first. Although some of the studies suggest similar complication rates to those reported with IFX or ciclosporin alone,^{423,425} the risk/benefit ratio of sequential rescue therapy has to be considered carefully in selected patients only and cannot be recommended routinely due to the high complication risk. This seems to be especially true if ciclosporin is given as a second rescue therapy after failing IFX.

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