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

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5. Medical management of active ulcerative colitis

5.1. General

The general principles for treating active ulcerative colitis are to consider the activity, distribution (proctitis, left-sided, extensive,[1] and pattern of disease (relapse frequency, course of disease, response to previous medications, side-effect profile of medication, extra-intestinal manifestation), before treatment decisions are made in conjunction with the patient.

5.1.1. Disease activity

The principal scoring systems used for clinical trials are covered in Section 5.1.2 and have been comprehensively reviewed.[2] Some additional points are clinically relevant. In clinical practice it matters most to distinguish severe ulcerative colitis necessitating hospital admission from those with mild or moderate disease who can generally be treated as outpatients. The simplest, best validated and most widely used index for identifying acute severe UC remains that of Truelove & Wi_tts [3]: any patient who has a bloody stool frequency $\geq$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). This index has been used in 20/32 studies of intensive intravenous treatment for severe UC.[4] Only one additional criterion in addition to the bloody stool frequency $\geq$6/day is needed to define a severe attack.[5] While these criteria have the major limitation of being unresponsive and cannot track the course of disease, they do distinguish the severe from the moderate or mild and have value in everyday practice because they are easy to use, which no other index achieves. It should be standard practice to confirm active colitis by sigmoidoscopy or proctoscopy before starting treatment. Rectal mucosal biopsy helps exclude unexpected causes of symptoms similar to active disease (such as cytomegalovirus, amoebic, or other infection, rectal mucosal prolapse, Crohn's disease, or even irritable bowel syndrome and haemorrhoidal bleeding).

5.1.2. Approach

Patients should be encouraged to participate actively in therapeutic decisions. In a systematic review of clinical trials, a mean 15% (95%CI 10–21%) of patients entered remission when receiving placebo.[9] Prescribing no treatment, however, is rarely an option, because rectal bleeding and urgency are sufficiently concerning to the patient to justify topical therapy even if no systemic therapy is recommended.

The appropriate choice of medication depends on many factors that are best tailored to the individual. 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.[7] Different galenic preparations are released at different sites and may have local activity (such as mesalazine preparations, budesonide, or types of enema). The choice is influenced by the balance between drug potency and side-effects; previous response to treatment (especially when considering treatment of a relapse, treatment of steroid-dependent or -refractory disease, or immunomodulator-refractory disease, Section 5.3); and the presence of extraintestinal manifestations (indicating the need for systemic therapy).

5.2. Treatment according to site of disease and disease activity

5.2.1. Proctitis

> ECCO statement 5A
> Mesalazine 1 g suppository daily is the preferred initial treatment for mild or moderately active proctitis [EL1b, RG B]. Mesalazine foam enemas are an effective alternative [EL1b]. 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, may be more effective than either alone and should be considered for escalation of treatment [EL1b, RG B]. Oral mesalazine alone is less effective [EL1b]

Active colitis limited to the rectum should first be treated topically. Suppositories are more appropriate than enemas, because suppositories target the site of inflammation; only 40% of foam enemas and 10% of liquid enemas can be detected in the rectum after 4 hr.[10] Topical mesalazine (5-ASA) induced remission in active proctitis and distal colitis in 31–80% (median 67%) compared to 7–11% given placebo in a meta-analysis of 11 trials in 778 patients.[11] Topical mesalazine is at least twice as effective as topical steroids whether for symptoms (OR 2.42, 95%CI 1.72–3.41), endoscopy (OR 1.89, 95%CI 1.29–2.76), or histology (OR 2.03, 95%CI 1.28–3.20).[12] Mesalazine suppositories 1 g daily are highly effective.[13] There is no dose response to topical therapy above a dose of 1 g mesalazine daily. Clinical (and endoscopic) remission can occur in up to 64% (52%) within 2 weeks.[13] Topical steroids should be reserved as second line therapy for patients who are intolerant of topical mesalazine.[14] Topical mesalazine is more effective than oral mesalazine for proctitis,[15] but the combination of oral and topical mesalazine may be better than either alone for colitis <50 cm from the anal verge.[16] There have been no trials on combination therapy for proctitis alone. Combining topical mesalazine and steroids also helps: beclomethasone dipropionate (3 mg) and mesalazine (2 g) enemas produced significantly better clinical, endoscopic and histological improvement than either agent alone.[17] Patients who fail to improve on topical mesalazine and topical corticosteroids should be treated with additional oral mesalazine or, alternatively, oral prednisolone, as if the colitis was more extensive or severe (below). Treatment of refractory proctitis is discussed in Section 5.2.7.

5.2.2. Left sided colitis

ECCO statement 5B
Left-sided active ulcerative colitis of mild-moderate severity should initially be treated with topical aminosalicylates [EL1b, RG B] combined with oral mesalazine >2 g/day [EL1a, RG A]. Topical steroids or mesalazine alone are also effective, but less effective than combination therapy [EL1b, RG B]. Topical mesalazine is more effective than topical steroid [EL1a, RG A]. Oral aminosalicylates alone are less effective [EL1a, RG A]. Systemic corticosteroids are appropriate if symptoms of active colitis do not respond rapidly 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]

Combined oral and topical mesalazine therapy is recommended.[14] There has been just one trial on 60 patients of combined therapy for distal colitis compared to oral or topical therapy alone, showing it to work more rapidly and effectively.[16] However, extrapolation from a trial of combination therapy for extensive colitis,[18] evidence that topical therapy achieves higher rectal mucosal 5ASA concentrations than oral therapy[19] and is associated with improved clinical outcome,[19,20] are consistent with the recommendation.

Most therapeutic trials of mild or moderate active colitis include patients with any disease distribution other than proctitis, but both oral and topical aminosalicylates (mesalazine) are effective for left-sided colitis. In a meta-analysis of oral 5-ASA compounds for active colitis,[21] mesalazine was more than twice as effective as placebo (OR 0.40, 95%CI 0.30–0.53), but not significantly better than sulphasalazine (OR 0.83, 95%CI 0.60–1.13) for the failure to induce global clinical improvement or remission. There was a trend for mesalazine to be better than sulfasalazine for endoscopic improvement (OR 0.66, 95%CI 0.42–1.04) and mesalazine is better tolerated than sulfasalazine.[21] This is a modest benefit — (NNT to induce remission = 10 (95% CI 7–21), and NNT = 4 to induce response or remission (95% CI 3–6)[22]). A systematic review of 9 placebo controlled trials of oral aminosalicylates for active ulcerative colitis showed the overall remission rate to be only 20%.[22] Two further placebo controlled trials of a multimatrix mesalazine formulation for mild-moderate UC have been published more recently,[23,24] as well as a combined analysis.[25] The first study randomized 280 patients to either MMx 4.8 g once daily, MMx 1.2 g twice daily, or placebo for 8 weeks. The primary endpoint was remission at 8 weeks. Once and twice daily dosing produced similar results, with remission rates of 29% and 34% respectively, compared to 13% on placebo ($p<0.01$)[23] (see also Section 6.2.1). A further placebo-controlled study compared MMx mesalazine with Asacol® in 346 patients with active, mild-to-moderate UC.[24] Clinical and endoscopic remission was achieved in 40.5% given MMx mesalazine 2.4 g/day once daily and 41.2% given 4.8 g/day once daily compared to 22.1% on placebo ($p=0.01$ and 0.007 respectively) and 32.6% given Asacol® (ns).

Meta-analysis of mesalazine for active UC shows a dose-response for *improvement* from <2.0 g, 2.0–2.9 g and >3.0 g daily ($p=0.002$), but not for remission.[21] This trend is confirmed by a trial of 4.8 g mesalazine (Asacol®) vs 2.4 g mesalazine daily in 268 patients with moderately active UC, half of whom had distal disease. Treatment response was 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).[8] Treatment worked just as well for left-sided disease as for extensive colitis, and there was no increase in side-effects at the higher dose, so higher doses of mesalazine are recommended for moderately active colitis. A peripheral benefit is a reduction in the median time to cessation of rectal bleeding (from 16 days to 9 days ($p<0.05$)) at the higher dose. This gives a useful timescale for determining the speed of response. If rectal bleeding persists beyond 10–14 days, then the response can be said to be slow and therapy augmented, which usually means decisive treatment with steroids.

There is something of a transatlantic divide on the threshold for using steroids. The practice in many European countries is to introduce oral steroids at an early stage, because aminosalicylates cannot match the speed of response for patients suffering miserable symptoms. The US concern about steroid-induced side-effects is shared by their patients, but may also be self-fulfilling. Late introduction of steroids selects a more refractory population. Steroids with a colonic release mechanism and low systemic bioavailabilty such as beclomethasone diproprionate or budesonide are becoming available. In the largest and most recent study of 177 patients with active left-sided or extensive colitis, beclomethasone diproprionate 5 mg/day had an effect similar to that of 2.4 g mesalazine, but without systemic steroid side-effects.[26]

5.2.3. Extensive ulcerative colitis

ECCO statement 5C
Extensive ulcerative colitis of mild-moderate severity should initially be treated with mesalazine >2 g/day [EL1a, RG A], combined with topical mesalazine [EL1b, RG A]. Oral aminosalicylates alone induce remission only in a minority of patients [EL1a, RG A]. Systemic corticosteroids are appropriate if symptoms of active colitis do not respond rapidly to mesalazine [EL1b, RG C], or who are already taking appropriate maintenance therapy. Severe extensive colitis is usually an indication for hospital admission for intensive treatment [EL1b, RG B]

The approach is similar to that described for left-sided colitis, with the important caveat that there should be a lower threshold for decisive treatment with systemic steroids. Oral mesalazine is effective,[27] but combination with topical mesalazine is better. Oral mesalazine (Pentasa®) 4 g/day with a 1 g mesalazine enema in 116 patients induced clinical remission by 8 weeks in 64% compared to 43% on oral mesalazine alone ($p=0.03$).[18] This confirms that added benefit of topical mesalazine for extensive colitis. Failure of mild or moderately active disease to respond within 2 weeks to mesalazine is an indication to consider oral prednisolone. Similarly, if a

patient already on mesalazine >2 g/day or immunomodulators as maintenance therapy has a relapse, decisive treatment with steroids is considered appropriate. The reason for this proactive approach is the risk of complications (including toxic dilatation) in patients with extensive disease who are under-treated.

Treatment with oral and rectal corticosteroids is based on two early studies on active UC of any extent, including extensive colitis. Oral prednisolone (starting at 40 mg daily, with steroid enemas) induced remission in 77% of 118 patients with mild to moderate disease within 2 weeks, compared to 48% treated with 8 g/day sulphasalazine and steroid enemas.[28] Similar findings were reported by Lennard-Jones,[29] 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, 30 mg/day for 1 week, then 20 mg/day for 1 month before decreasing by 5 mg/day/week. 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.[30] Oral steroids with low systemic bioavailability (budesonide or prednisolone metasulphobenzoate, with colonic release mechanisms) are available or being developed.[31,32]

5.2.4. Severe ulcerative colitis of any extent

Acute severe ulcerative colitis is a potentially life-threatening condition. The only prevalence data date from 1963: 47/250 (18.8%) first attacks and 109/619 (17.6%) of all patients have a severe attack as defined by the criteria in Statement 5D.[33] To grasp the implications of current medical and surgical therapy requires knowledge of the historical context.

In 1933, 16/21 (75%) died in the first year after acute presentation with ulcerative colitis in Birmingham[34] and in 1950 a mortality of 22% was reported from Oxford among 129 cases in the first year after diagnosis.[6] In 1955 the introduction of steroid therapy reduced mortality of severe colitis to 7%, compared to 24% in the placebo group[3] and it is now <1% in specialist centres.[35] Nevertheless, the response to steroids of severe colitis has remained unchanged for 50 years.[3,4] In view of this and the 29% colectomy rate (95%CI 28–31%[4]), the Consensus believes that patients meeting these criteria are best admitted to hospital for intensive treatment. Management involves more than pharmacotherapy.

> ECCO statement 5D
> Severe active ulcerative colitis is best defined by Truelove and Witts' criteria [EL3, RG C]. Patients with bloody diarrhoea ≥6/day and signs of systemic toxicity (tachycardia >90 bpm, fever >37.8 °C, Hb <10.5 g/dL, or an ESR >30 mm/h) should be admitted to hospital for intensive treatment [EL5, RG D]

5.2.4.1. Investigations on admission. See Section 7.5.3.

5.2.4.2. Therapeutic approach. Intravenous corticosteroids remain the mainstay of conventional therapy for acute severe colitis,[36] although details (such as the value of antibiotics or parenteral nutrition) are debated by some. As therapeutic options increase (ciclosporin, tacrolimus, or infliximab among others), so too does the opportunity for procrastinating about surgical decisions. The principal clinical dilemmas are how to identify at an early stage those who are likely to need colectomy, and when to start rescue medical therapy in time so that surgery, if it becomes necessary, is not inappropriately delayed. The two are not mutually exclusive and management demands the most taxing clinical judgement. Only one patient in a hundred need die as a result of complications caused by operating too late to negate any benefits of medical therapy. This is why it is recommended that patients should be treated in hospital jointly by a specialist Gastroenterologist and Colorectal surgeon.

5.2.4.3. Conventional therapy.

> ECCO statement 5E
> Severe active ulcerative colitis with signs of systemic toxicity should be treated in hospital [EL5, RG D] with intravenous steroids (such as methylprednisolone 60 mg or hydrocortisone 400 mg daily) [EL1b, RG B]. Monotherapy with intravenous ciclosporin (to achieve a minimum therapeutic concentration) [EL1b, RG C] is an option for patients intolerant of intravenous steroids. Patients are best cared for jointly by a gastroenterologist and colorectal surgeon [EL5, RG D]

Treatment with corticosteroids should not be delayed awaiting microbiological results for possible infective causes. Corticosteroids are generally given intravenously using, for example, methylprednisolone 40 mg or hydrocortisone 100 mg four times daily. Higher doses (including 500 mg–1 g methylprednisolone) are no more effective, but lower doses are less effective.[4,37] Bolus injection is as effective as continuous infusion.[38] Treatment is usually given for about 5 days, since extending therapy beyond 7 to 10 days carries no benefit.[4]

In a systematic review of 32 trials of steroid therapy for acute severe colitis involving 1991 patients from 1974–2006, the overall response to steroids (intravenous hydrocortisone, methylprednisolone, or betamethasone) was 67% (95%CI 65–69%, or 1429/1991).[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 (R^2=0.07, p=0.8). Because of substantial heterogeneity, it was not possible to discriminate between complete and partial responses to steroids. Only a minority (100/1991) received ciclosporin (below).

Other measures are considered appropriate in addition to intravenous steroids:

- 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.[39]
- Sigmoidoscopy or proctosopy and biopsy to confirm the diagnosis and exclude cytomegalovirus infection.
- Stool cultures and assay for *Cl difficile* toxin.
- Subcutaneous heparin to reduce the risk of thromboembolism.[40]
- 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%[41],). Bowel rest through intravenous nutrition does not alter the outcome,[42] but some centres use a food challenge after 5 days in an attempt to discriminate between complete and partial responders to intensive therapy.
- Withdrawal of anticholinergic, antidiarrhoeal agents, NSAID and opioid drugs, which risk precipitating colonic dilatation.[39]
- Topical therapy (corticosteroids or mesalazine) if tolerated and retained, although there have been no systematic studies in acute severe colitis.[36]
- Antibiotics only if infection is considered (such as in an acute, first attack of short duration, or after recent admission to hospital), 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.[43–48]
- Blood transfusion to maintain a haemoglobin >10 g/dl.

Ciclosporin monotherapy (CsA, 4 mg/kg/day intravenously) is as effective as intravenous methylprednisolone (MeP) 40 mg/day for acute severe colitis. In a randomized trial there was a response in 10/15 CsA patients vs 8/15 MeP patients.[49] Furthermore, half of all patients in another study comparing low dose with high dose CsA[50] also received CsA monotherapy, without concomitant intravenous steroids. Consequently monotherapy with CsA is a useful option in those patients with severe colitis when steroids are best avoided, such as those susceptible to steroid-psychosis (schizophrenics or previous psychosis), or for some other reason (concomitant osteoporosis, diabetes, or personal preference).

5.2.5. Intravenous-steroid resistant ulcerative colitis of any extent

The timing of colectomy for severe colitis remains one of the most difficult decisions that a gastroenterologist has to make. No individual patient wants a colectomy, but it is becoming easier for physicians to aquiesce with every patient who does not want a colectomy as therapeutic options increase. The question is how to do this safely. There are two principal options that can be added to intravenous steroids: calcineurin inhibitors (ciclosporin or tacrolimus) or infliximab (IFX).

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. Genetic polymorphisms have the potential to predict the outcome of disease in an individual from the time of diagnosis[51,52] but they cannot be used for decision-making when colectomy is imminent.

Clinical markers depend on the objective measures of stool frequency, or temperature. A stool frequency >12/day on day 2 was associated with 55% colectomy,[53] while a frequency >8/day on day 3 of intensive treatment predicted colectomy in 85% on that admission ('Oxford index').[5] This latter measure has been validated: a frequency >4 and CRP >25 mg/L on day 3 (or when the stool frequency×0.14CRP is >8 on day 3: 'Sweden index') predicted colectomy in 75%.[54] More recently, CRP and stool frequency on day 3, as well as temperature in children with acute severe colitis predicted the need for colectomy, in studies that developed a Pediatric UC Activity Index[55,56] (Section 11.3.3).

> ECCO statement 5F
> The response to intravenous steroids is best assessed objectively (by stool frequency, CRP and abdominal radiography) on or about the third day [EL2b, RGB]. Surgical options should be considered and discussed at this stage or earlier. Second line therapy with *either* ciclosporin [EL1b, RG B], *or* infliximab [EL1b, RG B] *or* tacrolimus [EL1b, RG B] will often be appropriate. If there is clinical deterioration colectomy is recommended. If there is no improvement within a further 4–7 days, colectomy should usually be recommended [EL5, RG D]. Third line therapy may be considered at a specialist centre

Biochemical markers include CRP, albumin and pH. An ESR >75 or a pyrexia >38 °C on admission have been associated with a 5–9-fold increase in the need for colectomy in a prospective study of 67 patients.[57] 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. 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%.[58] This needs prospective validation.

Radiological 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).[53] The presence of an ileus (indicated by 3 or more small bowel loops of gas) was associated with colectomy in 73% in a retrospective study,[59] but only 50% in a prospective study from the same institution.[5] The depth of colonic ulceration after gentle air insufflation identified 42/49 patients with deep ulcers that were associated with the need for colectomy,[60] but this is not widely used in clinical practice.

Indices exist to be applied, as a threshold for triggering appropriate action at an early stage. This means surgical consultation and assessment by a stomatherapist *in addition to* augmenting medical treatment. The CRP and stool frequency criteria[5] are the simplest objective measure, but neither immutable nor always reproduced. Other criteria may do as well, but must be as straightforward so that a decision to start a calcineurin inhibitor, infliximab, or proceed to colectomy is not inappropriately delayed.

5.2.5.1. Ciclosporin (CsA). A placebo-controlled trial in 1994 identified CsA as potential rescue therapy for intravenous steroid-resistant UC (IVSR-UC).[61] Nine of 11 patients failing steroids improved on ciclosporin whilst all 9 on placebo failed to improve (RR 0.18, 95%CI 0.05–0.64). However, 3/11 and 4/9 eventually underwent colectomy in the treatment and placebo groups respectively. The narrow therapeutic index of CsA and its side-effect profile has limited acceptability. In 2001, out of the 116 consecutive patients admitted to 29 UK hospitals with severe UC, only 17 (15%) received CsA and only 7 of 33 (21%) who came to colectomy had received CsA.[62] In nine studies that used CsA as rescue therapy in the systematic review of severe colitis, only 100/622 (16%) patients treated received CsA.[4] The short term response was 51% (95% CI 41–60%) and 29% colectomy (95% CI 25–32), but other case series report 70–80% early response.[63–65] Concerns about early toxicity have been partly addressed by low dose (2 mg/kg) intravenous induction therapy (Section 5.4.7). In the largest randomized study of CsA to date, 73 patients were randomized to either 2 mg/kg or 4 mg/kg of intravenous CsA.[50] 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. The long-term outcome indicates that a minority avoid colectomy. In two series, 58% of 76 patients[64] and 88% of 142 patients[65] came to colectomy over 7 years. A Cochrane review[66] concluded that numbers in controlled trials were so few (only 50[49,61]) that there was limited evidence for CsA being more effective than standard treatment alone for severe UC.

5.2.5.2. Tacrolimus. Tacrolimus is another calcineurin inhibitor, acting through a mechanism similar to CsA (Section 5.4.7). One randomised controlled trial has been performed in ulcerative colitis that included 27/60 patients with acute severe colitis.[67] 9/16 had a partial response to 0.05 mg/kg/day adjusted to trough levels (up to 15 ng/mL), compared to 2/11 on placebo and the remainder had no response. Results did not reach significance. 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 (Table 5.2). It carries many of the risks (including nephrotoxicity) of ciclosporin, although tacrolimus is a more effective immunomodulator than ciclosporin in renal or liver transplantation (see Table 5.1).[68,69]

5.2.5.3. Infliximab. Infliximab as a single dose (5 mg/kg) may also be effective rescue therapy. A Swedish–Danish study treated 45 patients (24 IFX and 21 placebo with continued intravenous betamethasone).[73] 7/24 in the IFX group and 14/21 in the placebo group had a colectomy within 3 months (p=0.017; OR 4.9, 95% CI 1.4–17). No patient died. Two different scores were used to identify patients before randomization to IFX or placebo. The Sweden Index[54] on day 3 identified sicker patients at an earlier stage than the Seo Index[74] calculated on day 5–7. It was the group with less active disease after 5–7 days of intravenous steroids who benefited most from IFX. There have been other small studies of IFX for acute severe colitis refractory to steroids that have not shown a difference in colectomy.[75–77] It should be noted that hospitalized patients with severe colitis represent a very different population to the outpatients in the ACT 1 & 2 studies[78] (see Section 5.4.3). A large controlled trial is needed, because case series report 20%, 33%, 57% or 75% ultimately coming to colectomy after IFX for intravenous-steroid resistant ulcerative colitis.[79–82]

5.2.5.4. Selection. A recommendation on the best choice between calcineurin inhibitors and IFX in addition to intravenous steroids is not possible until there has been a comparative, randomised controlled trial. Controlled trials comparing CsA and IFX are n progress (2007/08). The individual circumstances of each patient have always to be considered. If a patient has acute severe colitis despite existing treatment with an immunomodulator at an appropriate dose and duration, then there is little that medical therapy can hope to offer since it is unlikely that remission can be maintained. The effect of IFX as maintenance therapy in these circumstances is unclear: such patients are a different to those in the ACT trials and 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 IFX compared to CsA or tacrolimus. The short half life of CsA, however, is a potential advantage compared to IFX. Consequently if CsA does not work, it is only a matter of hours before it disappears from the circulation, while IFX will circulate for weeks. This may matter if colectomy is performed, since septic complications are the major cause of post-operative morbidity and mortality.[82] Although IFX is reported not to increase post-operative sepsis,[83] no data are available that relate only to emergency colectomy for sick patients with acute severe UC (Section 7.6.3). In general only a single attempt at rescue therapy with a calcineurin inhibitor or IFX should be considered before colectomy, after careful discussion between the patient, gastroenterologist and colorectal surgeon about the options and potential outcomes. If doubt persists, specialist advice should be sought at an

Table 5.1 Case series of tacrolimus for steroid-refractory ulcerative colitis, compared to a case series of ciclosporin therapy in similar patients

Series	*n*	Response	Colectomy at			Ref
			1–3mo	1 year	2 year	
Ciclosporin (iv 4 mg/kg, then oral)	76	56/76	10/76	16/76	16/76	64
Tacrolimus iv 0.01/oral 0.2 mg/kg	38	18/38	3/38	12/38	19/38	70
Tacrolimus iv 0.01 mg/kg	23	22/23		2/23	3/23	71
Tacrolimus oral 0.15 mg/kg	9	9/9	1/9	–	3/9	72

early stage from a referral centre. Use of IFX with CsA has been associated with a particularly high rate of adverse events (see Section 7.6.3).

5.2.6. Toxic dilatation and complications of severe ulcerative colitis

5.2.6.1. Toxic megacolon. Toxic dilatation (megacolon) represents the end of a spectrum of severe colitis that has been unrecognized, undertreated, or refractory to appropriate treatment. It is defined as total or segmental non-obstructive dilatation of the colon >6.0 cm associated with systemic toxicity.[39,84] The incidence has never been studied systematically. About 5% of patients with acute, severe colitis admitted to hospital will have toxic dilatation.[39] Metabolic disturbance (hypokalaemia or hypomagnesaemia), bowel preparation, or anti-diarrhoeal therapy have been associated with toxic dilatation,[39] so these should be corrected or avoided. Earlier diagnosis of severe colitis, more intensive medical management and earlier surgery has reduced the incidence of toxic megacolon complicating ulcerative colitis, but the incidence for infective colitis is rising, reflecting the increasing prevalence and severity of pseudomembranous colitis.[85]

The key aspects of management are aggressive medical therapy and early surgical decision making. It is no different to conventional therapy for acute severe colitis, except that metronidazole 500 mg three times daily is appropriate on empirical grounds in case of an infective aetiology. The combination of steroids and antibiotics is safe even for infective colitis; steroids reduce inflammation in pseudomembranous colitis.[86] Nasogastric suction cannot be expected to decompress the colon and is unnecessary. The classic knee-elbow position may relieve distension,[87] but is generally impracticable. A senior surgical opinion is best sought on the day of admission. It should be made clear to all that there is a 24 h window of opportunity for medical treatment to work and that if there is no improvement then early colectomy will be necessary.

5.2.6.2. Perforation, haemorrhage and others. Perforation is the most serious complication of acute severe colitis, almost invariably associated with colonoscopy or toxic dilatation where colectomy has been inappropriately delayed. It carries a mortality of up to 50%.[39] Other complications appear exceptional, including massive haemorrhage (1/66 patients operated on for acute severe colitis in one series[88]), cerebral sinus thrombosis[40] and a poorly recognised panenteritis.[89–91] In a review of 158 middle-aged or older American patients with ulcerative colitis, however, 20/158 had toxic dilatation, perforation or massive haemorrhage and 7/20 died.[92]

5.2.6.3. Long term outcome of severe colitis. The long term outcome after admission with acute severe ulcerative colitis is not good. When the outcome of a small, but prospectively-collected cohort of patients who had avoided surgery on the index admission was reexamined after 15 years, 8/22 (36%) complete responders to steroids came to colectomy, compared to 8/10 incomplete responders (stool frequency >3/day, or those with visible blood in the stools at day 7, $p=0.082$).[93] Median time to colectomy was 33.0 months (CI 12.6–67.1) for complete responders vs 6.0 months (95% CI 0.9–17.7) for incomplete responders ($p=0.033$). The longest period of steroid-free remission was a median 45.0 months (CI 28.2–63.2, range 0–120) for complete, but a median 8.5 months (CI 4.3–22.1, range 1–35) for incomplete responders ($p=0.017$). Data on the burden of medical and surgical treatment of severe colitis and attendant complications, related to patient-orientated outcomes (hospitalization, 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.[94,95] There are few trials on this specific population, but a coherent therapeutic strategy is needed if patients (and their doctors) are not to get frustrated by persistent symptoms.

Reasons for refractoriness include poor adherence with therapy, inadequate concentrations of the active drug, the wrong drug, unrecognised complications (such as proximal constipation or infection) or inappropriate diagnosis (such as co-existent irritable bowel syndrome, unrecognised infection, Crohn's, mucosal prolapse, or very rarely, cancer). The first step is therefore an empathetic review of symptoms and treatment to date, followed by reassessment of the diagnosis by colonoscopy and serial biopsy. Commonly, a co-existent irritable bowel accounts for more symptoms than active disease. The next step is to ensure that conventional therapy (Sections 1.2.1 and 1.2.2) has been vigorously applied. Attention in particular should be paid to topical therapy (topical mesalazine together with topical steroids, after considering suppositories and the type of enema for the distribution of disease) in conjunction with oral therapy. The next step is to treat proximal constipation, since abnormal intestinal motility induces proximal colonic stasis in patients with distal colitis and this affects drug delivery. In 12 patients with active left-sided disease, scintigraphy showed that 91% of a labelled, Eudragit-coated resin remained in the proximal colon, so that only 9% (95%CI 4–15) reached the distal colon compared to 31% (95%CI 24–37) in 22 healthy controls ($p<0.001$).[96] Consequently, if sigmoidoscopic inflammation persists after treatment with topical mesalazine and oral steroids, a plain abdominal radiograph is appropriate. If there is visible faecal loading in the descending colon, a vigorous laxative is appropriate, after explaining the paradox of proximal constipation despite distal diarrhoea. If symptoms do not resolve within another 2–4 weeks, distal colitis is best treated as if it was more extensive or severe.

Refractory distal colitis responds more rapidly and better to intensive treatment than oral or topical therapies. In 39 patients with distal disease refractory to outpatient treatment with oral steroids and mesalazine, remission was achieved by intensive treatment within a week in 90%.[97] Should the response be poor, CsA, tacrolimus, or IFX can be tried, but only if there is a prospect for maintaining remission. There is a tendency to opt for these treatments before admission for intensive therapy, with a view to continuing treatment as an outpatient. 56% in the ACT 1&2 studies had left-sided or distal colitis. However, the patient must realise that the steroid-free remission rate after 7 months (30 weeks) on IFX is only 21%78 (see also Section 5.3.3). 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 be precipitate and a range of topical or anecdotal

therapies are available (Table 5.2).[98–134]. The choice depends on local availability and personal preference, since many have to be made up individually by pharmacy. 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. A total colectomy has to be performed, usually with ileoanal pouch formation (Section 7.2), because segmental resection leaves that part of the colon most affected and is almost invariably followed by relapse affecting previously normal bowel. 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.[135] There was a significant decrease after surgery in mean (SD) diurnal stool frequency (8.2(4) vs 4.7 (2) $p<0.05$), nocturnal stool frequency and urgency ($p<0.001$). Previously unknown 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 differ between patients at initial presentation and subsequent relapse, depending on the pattern of relapse and previous response to therapy. Some patients have active disease that persists in spite of appropriate treatment and these are best considered as a separate group with steroid-refractory disease (see definitions). It helps management to recognise other treatment-refractory groups (immunomodulator-refractory, or anti-TNF-refractory), but precise definitions have not been agreed (Section 5.2). They represent an important group of patients who merit study.

5.3.1. Treatment of relapse compared to new cases

> ECCO statement 5G
> Patients who relapse should usually be treated with the therapy that was previously effective [EL5, RG D]

The initial treatment of relapse best uses the treatment that worked first time, but consideration should be given to other factors and maintenance therapy should be optimised. These include the views of the patient (adverse effects, necessary speed of response, convenience, etc), timing of relapse, concurrent therapy (whether a relapse occurred during treatment with immunomodulators) and adherence with maintenance therapy.

5.3.2. Early relapse

Any patient who has an early (<3 months) relapse is best started on azathioprine (AZA) or mercaptopurine (MP), because the treatment strategy should think beyond the current relapse and aim to reduce the risk of a further relapse. Opinion is divided whether to use the same treatment to induce remission and taper more slowly, use more potent induction therapy, or to increase maintenance 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

Azathioprine is significantly more effective than mesalazine at *inducing* clinical and endoscopic remission in the treatment of steroid-dependent UC. 72 patients with steroid-dependent, active UC were randomised to receive AZA 2 mg/kg/day or oral mesalazine 3.2 g/day, in addition to prednisolone 40 mg/day.[136] 53% on AZA achieved steroid-free clinical and endoscopic remission after 6 months compared to 21% on mesalazine (OR 4.78, 95%CI 1.57–14.5). Infliximab also has a steroid-sparing effect when administered every 8 weeks for up to 1 year.[78]. 408/728 (56%) were taking steroids at study entry in the two ACT studies. After 7 months (30 weeks), 10/139 (7%) on placebo and 28/130 (21%) on 5 mg/kg IFX every 8 weeks had achieved steroid-free remission ($p=0.01$). After 12 months (ACT 1), the figures were 9% and 26% respectively ($p=0.006$) (Section 5.3.4). AZA should be the first choice of therapy in apparent steroid dependence. The balance in decision-making between IFX and surgery is addressed above (Sections 1.2.3, 1.2.4) and the efficacy of continued AZA or IFX for maintaining remission in Sections 2.2.2 and 2.2.3.

5.3.4. Oral steroid-refractory ulcerative colitis

> ECCO statement 5H
> Patients with persistently active, steroid-refractory disease should be treated with azathioprine/mercaptopurine [EL1b, RG B], although surgical options should also be considered and discussed. Intravenous steroids, infliximab [EL1b, RG B] or calcineurin inhibitors [EL3, RG C] should also be considered

For active UC that is refractory to steroids, other causes of persistent symptoms including coexistent cytomegalovirus, or cancer should be considered. If active UC is confirmed, immunomodulators should be added and calcineurin inhibitors, biological therapy or surgery considered (Section 5.2.5, 5.4.3). Infliximab is indicated if sepsis has been excluded and surgery thought inappropriate at that stage. The timing of surgery depends on the severity of symptoms, inflammatory burden and other considerations (Sections 1.2.4, 1.2.5, 1.4.3). 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 views of the patient.

5.3.5. Immunomodulator-refractory ulcerative colitis

Immunomodulator-refractory disease is also best reassessed by colonoscopy 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

Table 5.2 Summary of therapies for distal colitis

Agent	Proposed mechanism	Dose and duration	Design	n	Outcome	Ref
Anaesthetic gel	Neuroimmune modulation	Lignocaine (800 mg) daily. 6–34 weeks	Open	100	Remission 10% proctitis, 83% distal colitis. Most had refractory disease; response in 6 patients with pancolitis	99
		Lignocaine (600 mg) daily. 6 weeks	Open	22	12/22 'excellent', 4/22 'very good' response (refractory UC)	100
		Ropivacaine (400 mg) daily. 2 weeks	Open	12	Clinical and endoscopic improvement ($p<0.05$)	101
		Ropivacaine (200 mg) single dose	Random	33	Rectal eicosanoid & neuropeptide concentrations similar after ropivacaine in 19 distal UC compared to 14 controls	102
Appendicectomy	Altered Th1/Th2 balance	Surgery	Cases	16	Remission, with no recurrence for up to 3years	103
Arsenic	Uncertain	Acetarsol (500 mg) vs prednisolone (5 mg) suppositories. 2 weeks	Random	20	9/10 clinical/endoscopic improvement (refractory distal colitis). Potential toxicity in 6/10 (1 week) 2/10 (4 weeks)	104
Bismuth compounds	Enhanced mucosal barrier? Reduced bacterial adhesion	Bismuth carbomer (450 mg) enema vs 5-ASA (2 g) enema. 4 weeks	Random	63	Bismuth 39% remission, 56% 5-ASA ($p=0.16$)	105
Bovine colostrum	Source of growth factors for epithelial restitution	Colostrum 10% (100 mL enema) vs placebo (albumin) 4 weeks	Random	14	Activity index −2.9 (−0.3 to −5.4) in colostrum group, vs +0.5 (−2.4 to +3.4) in placebo	106
Ciclosporin enemas	T-cell immunosuppression	Cyclosporin 350 mg vs placebo. 4 weeks	Random	40	Cyclosporin 40% improvement vs placebo 45%. Open trials in refractory distal UC more favourable	107
Epidermal growth factor enemas	Epithelial restitution/repair	EGF 5mcg (100 mL enema) vs placebo. 12 weeks	Random	24	83% remission at 4 weeks vs 8% on placebo. Rapid and promising; needs repeating. Concern about malignancy	108
Ecabet sodium enema	Mucosal protection	Ecabet sodium 1 g in 20–50 mL. 2 weeks	Open	8	Clinical activity index decreased (5.3+1.4 to 0.5+0.8, $p<0.05$)	109
Immunoglobulin G enemas	Immune response promoter	IgG enema	Open	7	Ineffective. 1/7 improved.	110
Interleukin-10 enemas	? IL-10 deficiency in UC	IL-10 100mcg enema for 10 days	Open	3	Endoscopic response in refractory left-sided colitis	111
Leukocytapheresis	?monocyte adsorption	Weekly for 5 weeks	Open	30	Clinical remission 21/30	112
Nicotine	Smoking protective.	Transdermal nicotine (15–25 mg) vs placebo 6 weeks	Random	72	Nicotine 48% remission, placebo 24% ($p=0.03$)	113
		Transdermal nicotine vs placebo. 6 m	Random	80	No difference between groups for maintenance therapy	114
		Transdermal nicotine (15–25 mg) vs prednisolone (5–15 mg). 6 weeks	Random	61	Nicotine 21% remission vs 47% prednisolone ($p=0.035$), intention to treat. 11/31 nicotine withdrawals (side-effects)	115

(continued on next page)

Table 5.2 (*continued*)

Agent	Proposed mechanism	Dose and duration	Design	n	Outcome	Ref
Nicotine	Smoking protective.	Transdermal nicotine vs placebo. 4weeks	Random	64	Nicotine 39% clinical response, placebo 9% ($p=0.007$)	116
		Transdermal nicotine (15 mg) with 5ASA enema vs enema + mesalazine 2.4 g. 4 weeks	Random	30	Remission 12/15 on nicotine + 5ASA enema, 5/15 on oral 5ASA + enema ($p=0.027$)	117
		Nicotine tartrate enemas (3–6 mg). 4 weeks	Open	10	5/7 improved (previously unresponsive UC). 3 withdrawals	118
		Nicotine carbomer enemas (6 mg). 4 weeks	Open	22	16/17 improved (previously unresponsive). 6 withdrawals	119
Propionyl-L-carnitine (PLC) enemas	Epithelial (SCFA) nutrition	PLC 6 g (200 mL) twice daily.	Open	10	8/10 'improved significantly'	120
Rebamipide	Cytoprotective proprionic acid	Enema twice daily, oral steroids continued	Open	20	55% remission 9still on steroids) at 3 weeks	121
Short chain fatty acids (variable composition)	Epithelial nutrition	SCFA mixture vs 5-ASA or steroid enema. 6 weeks	Random	45	Most improved in all three groups	122
		SCFA mixture vs placebo. 6 weeks	Random	40	70% SCFA clinical response, 20% placebo No change in endoscopic or histology scores	123
		SCFA mixture. 6 weeks	Open	10	5/10 responded well (refractory distal colitis)	124
		SCFA mixture vs placebo. 6 weeks	Random	103	No difference in clinical or histological response	125
		SCFA vs butyrate or placebo. 6 weeks	Random	47	No difference between three groups	126
		Butyrate vs placebo. 6 weeks	Random	38	No difference	127
Sucralfate	Enhanced mucosal barrier	Sucralfate 4 g vs prednisolone meta-sulphobenzoate 20 mg enemas. 4 weeks	Random	44	Predenema 71% cessation of bleeding, sucralfate 28%	128
		Sucralfate 10 g vs 5-ASA 2 g vs placebo 4 weeks	Random	50	5-ASA superior. Sucralfate no different from placebo	129
		Sucralfate 10 g vs hydrocortisone 100 mg enemas. 4 weeks	Random	40	Hydrocortisone 42% remission, sucralfate 15%, ($p<0.05$)	130
		Sucralfate 20 g vs methylprednisolone 20 mg (100 mL) twice daily. 4 weeks.	Random	60	No difference between groups	131
Thromboxane A2 inhibitor	Inhibition of inflammatory mediator	Ridrogel 300 mg vs prednisolone 30 mg enemas. 4 weeks	Random	40	Ridrogel 65% endoscopic remission vs prednisolone 75% (no difference)	132
		Ridogrel 300 mg (40 mL)	Open	11	Decrease in mucosal TxB2, but not other PGs	133
Wheat grass juice	Prebiotic and antioxidant *Triticum aestivum*	WGJ (100 mL) vs placebo	Random	21	Decrease in activity index ($p=0.031$) and rectal bleeding ($p=0.025$) compared to controls	134

ECCO statement 5I
Infliximab [EL1b, RG B] or surgical options should be considered. Continued medical therapy that does not achieve steroid-free remission is not recommended [EL5, RG D]

absence of contraindications infliximab should be considered (Section 5.4.3) as well as colectomy, which may be most appropriate.

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 5.2); the current section considers drug-specific aspects of treatment not addressed in that section.

5.4.1. Aminosalicylates

5.4.1.1. Efficacy of aminosalicylates. Much is made of how different delivery systems may influence response, but evidence that it matters in clinical practice is remarkably thin. Delivery systems can be divided into azo-compounds, controlled release, pH-dependent (either pH6 or pH7) and composite (pH-dependent combined with controlled release) (Table 5.3[137–139]).

Systematic reviews and meta-analyses concur that aminosalicylates are effective for treating active UC.[21,22,27] The NNT to induce remission is 10 (95%CI 7–21), although for the lesser target of response or remission the NNT is 4 (95%CI 3–6)[22]). Available data do not suggest a difference in efficacy between any of the 5-ASA preparations for active UC. Six trials with mesalazine (including two trials on MMX mesalazine) show statistical significance vs placebo.[23, 24,140–142,147] Those with olsalazine[143–146] or balsalazide [unpublished, see ref 27] do not.

Mesalazine is shown to be as effective as sulfasalazine for inducing response or remission (OR 0.83, 95%CI 0.60–1.13[21]) in the most recent meta-analysis, and is better tolerated. There have been few clinical trials comparing the efficacy of newer aminosalicylates for inducing remission. In 2 of 3 trials of balsalazide vs mesalazine, results for defined primary and secondary endpoints failed to demonstrate statistically significant differences.[148–150] Another study compared Ipocol, a pH7-dependent release mesalazine, with Asacol and found no significant difference in remission rates after 2.4 g/d for 8 weeks.[151] Proprietary prescribing of mesalazine is recommended,[152] 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, but absorption might conceivably influence adverse events. Despite variable differences in peak serum concentrations, ratio of 5ASA to its metabolite *N*-acetyl 5ASA, however, the systemic exposure to equimolar doses of all 5-ASA compounds is similar

Table 5.3 Delivery systems for 5-ASA[137,138]

	Delivery system	Mean peak plasma [5ASA] (μmol/L)	Mean systemic exposure (AUC, μmol/L.h)
Azo-bond			
Sulfasalazine	Sulfapyridine carrier	0.7–3.5	9.6–27.5
Olsalazine	5-ASA dimmer	1.2–4.5	–
Balsalazide	4-amino-benzoyl-β-alanine	2.3–3.5	13.9–22.8
Controlled release			
Pentasa®	Ethylcellulose coated microgranules	6.5	28.5
pH7-dependent			
Asacol®	Eudragit-S coating, dissolves at pH7	2.1–10.5	21.5–25.1
Mesren®	Same	–	–
Ipocol®	Same	–	–
pH6-dependent			
Salofalk®	Eudragit-L coating, dissolves at pH6	10.9	38.3
Mesasal®	Same	5.2 (median)	21.5 (median)
Claversal®	Same	–	
Composite			
('multimatrix')Mezavant® (EU) Lialda® (US)	Eudragit-S coating of hydrophilic polymer with some 5ASA and lipophilic excipients encapsulating 5ASA	–	no published data

Table 5.4 Placebo-controlled trials of newer aminosalicylates for active UC

	n	Dose, g (n)	Weeks	Remission (unless otherwise stated)	Ref
Asacol®					
Schroeder 1987	87	4.8 (38), 1.6 (11), 0 (36)	6	24% vs 5% (4.8 vs 0, $p=0.047$)	140
Sninsky 1991	158	2.4 (53), 1.6 (53), 0 (52)	6	Response 49% vs 23% (2.4 vs 0, $p=0.004$)	141
Balsalazide					
Salix (unpublished)	180	6.75 (72), 4.5 (73), 0 (35)	4	Response 45% vs 45% (6.75 vs 0, ns)	27
MMx mesalazine					
Lichtenstein 2007	280	4.8 g×1 (94), 1.2 g×2 (93), 0 (93)	8	29% vs 13% (4.8 g×1 vs 0, $p=0.009$)	23
Kamm 2007	343	4.8 g×1 (85), 2.4 g×1 (84), 0 (86) Asacol 0.8g×3 (86)	8	41.2% vs 40.5% vs 22.1% vs 32.6% (4.8g×1 vs 0, $p=0.007$)	24
Pentasa®					
Hanauer 1993	374	4 (95), 2 (97), 1 (92), 0 (90)	8	29% vs 12% (4g vs 0, $p=0.0012$)	142
Olsalazine					
Meyers 1987	66	3 (15), 1.5 (16), 0.75 (15), 0 (20)	3	Improvement 50% vs 16% (3 vs 0, $p=0.055$)	143
Hetzel 1988	30	2 (15), 0 (15)	8	Improvement 40% vs 11% ($p=0.11$)	144
Feurle 1989	105	2 (52), 0 (53)	4	Improvement (ns, no absolute numbers)	145
Zinberg 1990	15	3 (7), 0 (8)	4	Improvement (4/7 vs 0/8, $p<0.05$)	146
Rowasa®					
Sutherland 1990	136	4 (47), 2 (45), 0 (44)	6	Improvement 45% vs 18% (4 vs 0, $p<0.05$)	147

(Table 5.4). 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 or olsalazine.[153] Acute intolerance in 3% may resemble a flare of colitis since it includes bloody diarrhoea. Recurrence on rechallenge provides the clue. 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 disease severity rather than the dose or type of mesalazine.[154]

5.4.1.3. Monitoring. Patients with pre-existing renal impairment, other potentially nephrotoxic drugs, or co-morbid disease 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

5.4.2.1. Efficacy of steroids. There have been only two placebo controlled trials of conventional oral steroids for outpatients with active UC,[29,155] giving an NNT of 2 (95%CI 1.4–5).[22] More recently, when 86 (out of a total of 136) newly diagnosed patients with UC were treated with steroids, 51%, 31% and 18% had a complete response, partial or no response respectively at 30 days.[156] However, this includes a group of 22/86 who had acute severe colitis needing intravenous treatment. At one year, 55% were in steroid-free remission, 17% were steroid-dependent, 21% had surgery and 7% lost to follow up, but the inclusion of severe colitis makes this difficult to extrapolate to outpatient therapy. Adverse effects and monitoring of steroid therapy are the same as described in the Consensus guidelines on Crohn's disease.[157]

5.4.3. Infliximab (IFX)

5.4.3.1. Efficacy of IFX. A systematic review of the efficacy of IFX 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.[158] The review took the description of 'severe' at face value and failed to discriminate between out-patients and in-patients with acute severe colitis. Nevertheless, in seven RCTs, IFX (three intravenous infusions at 0, 2, and 6 weeks) was more effective than placebo in inducing clinical remission (RR 3.22, 95%CI 2.18–4.76). It was also more effective than placebo at inducing endoscopic remission (RR 1.88, 95%CI 1.54–2.28) and clinical response (RR 1.99, 95% CI 1.65–2.41) at 8 weeks.[78,159–162] 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).[73] The ACT 1&2 studies are pivotal.[78] They are impressively consistent, showing double the remission rate compared to placebo. ACT 1 was a 364 patient study in moderately active UC refractory to oral steroids and/or thiopurines, given IFX 5 mg/kg, 10 mg/kg, or placebo at 0, 2 and 6 weeks, then every 8 weeks for a year. The primary endpoint at week 8 was response (>30% and a 3 point decrease in the Mayo activity index, with virtual cessation of rectal bleeding). This was achieved: 37.2% (placebo), 69.4% (5 mg/kg) and 61.5% (10 mg/kg), $p<0.001$). So too were pre-defined secondary endpoints of remission (14.9%, 38.8% and 32.0% respectively) and mucosal healing

(33.9%, 62.0%, and 59.0%). Duration of effect was maintained through week 30 in all respects (remission in 15.7%, 33.9% and 36.9%, $p<0.001$). The same goes for ACT 2, an almost identical trial of a further 364 patients, but who could have moderately active UC despite 5-ASA alone (26%) and was 6 months' duration. Response (and remission) rates at week 8 were 29.3% (5.7%, placebo), 64.5% (33.9%, 5 mg/kg) and 69.2% (27.5%, 10 mg/kg, $p<0.001$). The flat dose-response is comparable to that of IFX for Crohn's disease.[157] Unfortunately, a large therapeutic gap persists despite being on 5 mg/kg IFX every 8 weeks, because only 21% (at 7 months) and 26% (at 12 months) achieved steroid-free remission (see Section 5.3.3). This is important because the Consensus stresses the importance of achieving steroid-free remission. Further analysis of the ACT 1 & 2 trial data indicates that there was an associated reduction in colectomy (hazard ratio 0.57, 95% CI 0.37–0.89) during the trial,[165] but whether this benefit is maintained remains unclear. The actual role of IFX for UC refractory to conventional therapy for both outpatients and inpatients is discussed in Sections 1.2.5, 1.2.7, 1.3.3, 1.3.4 and 1.3.5.

5.4.3.2. Adverse effects of IFX. Treatment with IFX is relatively safe if used for appropriate indications. Adverse events in the ACT studies[78] were no different to those expected from large experience of treating Crohn's disease.[163,164] Nevertheless, in common with other biological therapy there is a risk of serious infection, demyelinating disease and associated mortality. In the combined analysis of 484 patients with UC who received IFX 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-tumor 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 therapy

Despite the proliferation of biological therapies, only few have been applied to UC. *Adalimumab* is an anti-TNF agent similar to IFX, but given subcutaneously with less immunogenicity. There are current trials in UC. *Visilizumab* is an anti-CD3 monoclonal antibody binding to activated T-cells to induce apoptosis. A dose-ranging study in 69 patients with severe, intravenous steroid-resistant UC showed a 30 day remission rate of 30% (60% response) to 5microg/kg given on two consecutive days.[166] A Phase III study in intravenous steroid-resistant UC, however, was suspended in Q307 when interim analysis showed no benefit. *Alicaforsen* is an anti-sense oligonucleotide to human ICAM1. A complex dose-ranging protocol in 112 patients showed that a 240 mg enema every night for 6 weeks was more effective than placebo. Remission was only 14% at 6 weeks, but response was then maintained for 6 months in 80% compared to 44% on placebo,[167] or a median 146 days compared to 54 days after mesalamine enemas in another study.[168] Another selective anti-adhesion molecule strategy is also effective for UC. Intravenous *MLN-02* (an $\alpha 4\beta 7$ integrin antagonist) was given to 181 patients with moderately active UC.[169] 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 ($p=0.03$). Although one IL-2 receptor (CD25) inhibitor, *basiliximab*, has shown potential in open studies for steroid-refractory UC[170] another CD25 inhibitor, *daclizumab*, was ineffective in a controlled trial of 159 patients with moderately active UC.[171] *Certolizumab* has not yet been evaluated for UC.[172] An American–European review on biological therapy for UC has been published.[173]

5.4.5. Thiopurines

5.4.5.1. Efficacy of azathioprine/mercaptopurine. Data on thiopurines for active UC are few.[167] There have been five placebo-controlled trials of AZA for active UC, of between 20 and 80 patients each, with differing entry criteria, dose and duration.[136,174–178] Data from a recent, well conducted study on steroid-dependent active UC[131] are discussed in Section 5.3.3. The main role for thiopurines are as steroid sparing agents (NNT 3). Immunomodulators should be started in steroid-dependent or steroid-refractory patients. For arbitrary but practical purposes, thiopurines are considered appropriate for the same indications as for Crohn's disease: patients who have a severe relapse; those who require two or more corticosteroid courses within a 12 month period; those whose disease relapses as the dose of steroid is reduced below an arbitrary 15 mg; and relapse within 3 months of stopping steroids.[158] There is some evidence from a retrospective multicentre study of 1176 patients that those on AZA for UC are more likely to relapse if it is discontinued after 4 years than are patients who have Crohn's disease.[179]

5.4.5.2. Dose, monitoring and adverse effects of thiopurines. All aspects are considered similar to the use of thiopurines for Crohn's disease.[158] More recent work on measuring thiopurine methyl transferase (TPMT) and ITPA genotypes, TPMT activity, TPMT gene expression and thiopurine metabolites, is consistent with previous reports that the development of different types of toxicity is unpredictable.[180] This prospective study on 60 patients (27 with UC) study did, however, find that measurement of meTIMP early in the steady state phase might identify patients at risk of developing myelotoxicity. No recommendation can be made about routine measurement of TPMT activity or genotype prior to initiating thiopurine therapy, although all agree that monitoring of the full blood count before and after starting therapy is appropriate.

5.4.6. Methotrexate (MTX)

5.4.6.1. Efficacy of MTX. Studies on MTX for UC are small, use varying doses or routes of administration and have inconsistent outcomes.[181–183] The only randomised placebo-controlled trial using a dose of 12.5 mg per week of oral MTX in UC showed no benefit.[181] The low dose may account for disappointing efficacy as well as the lack of side effects. A randomized comparison of oral MTX 15 mg/week (still a relatively low dose) with mercaptopurine (MP) 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 MP, 58% for MTX 25% for 5-ASA ($p<0.05$ vs MP, ns vs MTX).[182] This is the only published comparison of MP and MTX. Until more data are available it cannot generally be considered an alternative to thiopurines for steroid-resistant UC (see also Section 6.2.5).

5.4.6.2. Dose and monitoring and adverse effects of MTX. As with thiopurines, all aspects are considered similar to Crohn's disease, for which evidence from controlled trials supports its use.[158,184]

5.4.7. Calcineurin inhibitors (ciclosporin (CsA) and tacrolimus)

5.4.7.1. Efficacy of CsA. Details of the role of CsA and tacrolimus for severe UC are given in Sections 1.2.4 and 1.2.5.

5.4.7.2. Dose and monitoring. Low dose CsA (2 mg/kg iv) induction therapy has largely addressed concerns about early toxicity. In the largest randomized study of CsA to date, 73 patients were randomized to either 2 mg/kg or 4 mg/kg of intravenous CsA.[50] 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 CsA side-effects are dose-dependent. At the 2 mg/kg dose, the mean CsA concentration on day 4 was 246+64 ng/mL, but 345+146 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 100–200 ng/ml using a monoclonal radioimmunoassay 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 curve[185] 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/m.[67] The initial oral dose in this randomized trial of 60 steroid-refractory patients with active UC was 0.05 mg/kg/day, increased according to the trough level after 24 hr. 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. Oral dosing may be an alternative to intravenous administration but only retrospective data are available.[70]

In practice, either calcineurin inhibitor appears able to induce remission, although whether either alter the long-term pattern of disease is unknown. First principles indicate that treatment is best continued until immunomodulator therapy (AZA/MP/MTX) is established. Although this reduces the short-term colectomy rate, the risk of clinical relapse remains high in the first year after treatment[63–65] (see Section 6.2.2).

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 patients.[67] Tacrolimus may induce diabetes mellitus. Opportunistic infection is the main concern; 3/86 patients (3.5%) died of opportunistic infections (1 of *Pneumocystis jiroveci (carinii)* pneumonia and 2 of *Aspergillus fumigatus* pneumonia) in a series from a major specialist centre.[186] Opportunistic infections and the value of chemoprophylaxis is the topic of a separate ECCO Consensus.

5.4.8. Alternative therapies whose role remains to be established

5.4.8.1. Antibiotics. Antibiotics as an adjunct to steroids do not alter the outcome of severe colitis (Section 5.2.4,[43–48]), but treatment of refractory colitis UC associated with *Fusobacterium varium* has been reported.[187] Two weeks' triple therapy with amoxicillin 500 mg, tetracycline 500 mg and metronidazole 250 mg all three times daily improved clinical, endoscopic and histological scores in a randomised trial of 20 patients.[187] More evidence is needed.

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. *T suis*, the pig whipworm, transiently colonises the gut, but is non-pathogenic in man. 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 ($p=0.04$).[188] 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.[189] It cannot currently be recommended, although novel delivery systems are being developed.

5.4.8.4. Interferon-alpha. Interferon alpha induces anti-inflammatory cytokines ((IL-1RA, among 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 mcg/kg, 0.5 mcg/kg, or placebo for 12 weeks showed no consistent differences between the groups.[190]

5.4.8.5. 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 while 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. There have been a multiplicity of observational studies, two unusually designed randomised trials comparing leucocytapheresis with prednisolone[191] or a sham column,[192] and one large trial comparing it with sham apheresis for active UC that has yet to report. It appears that leucocytapheresis does something for active UC, but quite what and how much is difficult to define.[193] 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.

5.5. Preparation for the period after treatment of active disease

A patient's response to initial therapy should be assessed within 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.

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 1.1.5). This approach to the evaluation of maintenance therapy is not cast in stone, because in two recent studies, both induction and subsequent maintenance therapy were assessed in the same trial of infliximab.[78] Using this approach, the clinical response at week 8 was defined as the primary endpoint, and the efficacy of maintenance therapy evaluated by the secondary endpoints of clinical response, clinical remission and mucosal healing at weeks 30 and 54 (Section 6.2.3). The pivotal endpoint that matters to patients is clinical remission with complete corticosteroid discontinuation in those who were receiving steroids at baseline.

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 among patients receiving placebo range from 29% to 43% at 6 months, and from 38% to 76% at 12 months.[2,9,194] A population-based study carried out in the county of Copenhagen,[195] described the outcome in1575 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%, while 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 using the term 'moderate' to refer sometimes to the pattern of disease and also to the activity at a point in time, which can be the source of confusion (Sections 5.1.2, 1.1.6, 5.2.1). Furthermore, grouping activity into quintiles seems too long a period for everyday practice, although highly relevant from an epidemiological perspective. The alternative is to define relapse as infrequent (<1/yr), frequent (>2 relapses/y), or continuous (persistent symptoms of active UC without a period of remission)[33] (Section 1.1.6).

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]

6.1.3. Risk factors for relapse

Few prospective studies have assessed risk factors for relapse in patients with inactive UC.[196–200] In one study of 92 patients, a shorter duration of current remission and a higher relapse frequency were predictive of further relapse.[196] 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.[197] 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.[198] 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.[201,202] The impact of life events in relapse of UC has been examined by a number of studies[199,200,203] with contradictory results (Section 11.3). Adherence to medical therapy 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) among 99 patients who collected <80% of their prescriptions for maintenance mesalazine.[204]

ECCO statement 6C
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.[205] Among the 63/183 patients treated with corticosteroids, 49% had a prolonged response, 22%

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]. Maintenance with topical 5-ASA is a valuable alternative in proctitis and 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]

were steroid dependent and 29% came to colectomy, but only 3/183 were treated with AZA/MP (see also Section 5.4.2).

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.

6.2.1. Aminosalicylates

6.2.1.1. Oral 5-ASA. The most recent version of the Cochrane meta-analysis showed that the Peto odds ratio for the failure to *maintain* clinical or endoscopic remission (withdrawals and relapses) for oral 5-ASA vs placebo was 0.47 (95% CI, 0.36–0.62), with a number-needed-to-treat (NNT) of 6.[206] Randomised controlled trials (RCTs) designed to evaluate the efficacy of oral 5-aminosalicylates (5-ASA) – including sulfasalazine, mesalazine and olsalazine – for maintaining remission are shown in Table 6.1.[207–214]

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 (Table 6.2).[215,227–237] 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 suppositories[215] 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).[11]

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 (Table 6.2). Remission rates were higher in patients receiving the combination. There are also three small RCTs comparing sulfasalazine 2 g/day or oral mesalazine 1.6 g/day to intermittent rectal mesalazine, with a trend in favour of the rectal treatment (Table 6.2).

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.[216] However, in another study in Spain, 5-ASA suppositories were generally well tolerated

Table 6.1 Placebo-controlled trials of oral 5-aminosalicylates for maintaining remission in UC

Author [ref]	Year	Number of patients	Study drug	Dosage (g/day)	Duration (months)	Failure to maintain clinical or endoscopic remission
Misiewicz[207]	1965	67	SZP	2	12	29%
			Placebo			76%[1]
Dissanayake[208]	1973	64	SZP	2	6	22%
			Placebo			55%[1]
Riis[209]	1973	59	SZP	2	6	29%
			Placebo			24%
Sandberg-Gertzen[210]	1986	101	OLZ	1	6	23%
			Placebo			45%[1]
Wright[211]	1993	101	OLZ	2	12	63%
			Placebo			69%
Miner[212]	1995	205	MSZ[2]	4	12	43%
			Placebo			62%[1]
Hanauer[213]	1996	264	MSZ[3]	0.81.6	6	56%
			MSZ			56%
			Placebo			71%[4]
Hawkey[214]	1997	323	MSZ[3]	1.6	6	40%
			Placebo			59%[1]

[1]$p<0.05$; [2]Pentasa; [3]Asacol/Claversal; [4]$p<0.05$ for comparison of 5-ASA (both groups) vs placebo; [5]comparison of 5-ASA, zileuton (not shown) and placebo; (sulfasalazine: SZP; olsalazine: OLZ, and mesalazine: MSZ).

ECCO statement 6E
The minimal effective dose of oral 5-ASA is around 1 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 may be useful [EL5, RG D]. 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]. At the moment, there is no robust evidence to support the choice of any specific 5-ASA preparation for maintenance [EL1a, RG A]

and considered comfortable for treatment of at least one year.[217] 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.

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 (Tables 6.1–6.3). 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.[218] 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 vs 47 days, $p<0.005$). When the results for patients in remission at 12 months were analysed after stratifying for frequently relapsing (>3 relapses per year) vs less frequent relapses, 2.4 g/day was also performed significantly better than 1.2 g/day (75% vs 33%, respectively). This *post hoc* analysis must, however, be treated with caution.[219] 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).[220] As with other studies of high doses of 5-ASA, there was no increase in the frequency of adverse events. It is possible that high 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,

Table 6.2 Randomized controlled trials of rectal mesalazine compared to placebo or oral formulations for maintaining remission in distal UC

Author [ref]	Year	Number of patients	Study drugs	Dosage (g/day)	Duration (months)	Failure to maintain clinical or endoscopic remission
Sutherland[227]	1987	29	MSZ enema	2	6	40%
			MSZ enema	4		46%
Biddle[228]	1988	25	MSZ enema	1	12	25%
			Placebo	-		85%[1]
D'Arienzo[229]	1990	101	MSZ suppository	0.8	12	20%
			Placebo	–		80%[1]
D'Albasio[230]	1990	79	MSZ enema	4 g×7/month 4 g/3days	24	31%
			MSZ enema			28%
			Oral SZP	2g/day		39%
Miner[231]	1994	92	MSZ enema	4 g/day	6	19%
			MSZ enema	4 g/2 days		28%
			MSZ enema	4 g/3 days		35%
			Placebo	–		52%[1]
Andreoli[232]	1994	31	MSZ enema	4 gx2/week	12	25%
			Oral SZP	2g/day		40%
Mantzaris[233]	1994	38	MSZ enema	4 g /3 day	24	26%
			Oral MLZ	1.5g/day		68%[1]
D'Albasio[234]	1997	69	MSZ enema + oral	2×4 g/week + 1.6 g/day	12	39%
			Oral MSZ alone	1.6g/day		64%[1]
D'Albasio[235]	1998	111	MSZ suppository	0.5×2/day	12	10%
			MSZ suppository	0.5/day		32%
			Placebo	–		47%[1]
Marteau[215]	1998	95	MSZ suppository	3×1 g/week	12	48%
			Placebo	–		62%[2]
Hanauer[236]	2000	65	MSZ suppository	0.5	24	46%
			Placebo			89%[1]
Yokoyama[237]	2007	24	MSZ enema + oral	1 g×2/week + 3 g/day	–	18%
			Oral MSZ alone	3g/day		77%

[1]$p<0.05$; [2]$p<0.05$ at months 3,6 and 9, but the difference did not reach the significance level at month 12.
MSZ: mesalazine; SZP: sulfasalazine.

but at present, there is no good evidence to support this.[221] There are also no data supporting a dose-response relationship with rectal 5-ASA for maintaining remission in distal UC (Table 6.2), and no more than 1 g/day is necessary for rectal 5-ASA therapy.

6.2.1.5. Comparison of oral 5-ASA formulations. In the Cochrane meta-analysis[206] the odds ratio for the failure to maintain clinical or endoscopic remission (withdrawals and relapses) was calculated for the trials in which sulfasalazine and 5-ASA were compared (Table 6.3).[238–250] 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. There is only one, single-blind RCT[218,220,222] comparing olsalazine 1 g/day head to head with oral mesalazine 1.2 g/day as maintenance for UC. At 1 year, remission rates were 75% and 54%, respectively ($p=0.02$). The frequency of adverse events was low in this study, especially the rate of diarrhoea in the olsalazine group, perhaps because there was a predominance of patients with distal UC. This study has not been replicated and the dose inequivalence noted, although this is unlikely to have mattered (above). No controlled trial has yet been published on maintenance of remission with mesalazine MMx.

6.2.1.6. Adherence to 5-ASA treatment. Adherence to 5-ASA appears to be important for improving outcome of

Table 6.3 Trials comparing different oral 5-aminosalicylate formulations and dosages for maintaining remission in UC

Author [ref]	Year	Number of patients	Study drugs	Dosage (g/day)	Duration (months)	Failure to maintain clinical or endoscopic remission
Azad Khan[238]	1980	170	SZP	1	6	33%
			SZP	2		14%
			SZP	4		9%[2,6]
Andreoli[239]	1987	13	MSZ	0.75	12	43%
			SZP	1.5		17%
Ireland[240]	1988	164	OLZ SZP	1	6	43%
				2		26%[2]
Riley[241]	1988	92	MSZSZP	0.82	12	40%
						46%
Mulder[242]	1988	72	MSZSZP	1.5	12	45%
				3		56%
McIntyre[243]	1988	79	BLZ	2	6	49%
			SZP	2		37%
Rutgeerts[244]	1989	273	MSZ[1]SZP	0.75–1.5	12	54%
				2		42%
Kiilerich[245]	1992	226	OLZ	1	12	54%
			SZP	2		49%
Rijk[246]	1992	46	OLZ	1.5–2	12	46%
			SZP	3–4		48%
Courtney[222]	1992	99	OLZ	1	12	25%
			MSZ[1]	1.2		46%[2]
Travis[247]	1994	198	OLZ	0.51	12	52%
			OLZ	2		40%
			OLZ			40%[3]
Ardizzone[248]	1995	88	MSZ[1]	1	12	38%
			SZP	2		51%
Kruis[249]	1995	160	OLZ	0.51.25	6	36%
			OLZ	2		49%
			OLZ	2		24%
			SZP			32%
Nilsson[250]	1995		OLZ			
			SLZ			
Fockens[220]	1995	169	MSZ	1.5	12	46%
			MSZ[4]	3		33%[5]
Paoluzi[218]	2005	156	MSZ[1]	1.2	12	74%
			MSZ[1]	2.4		70%

[1]Asacol/Claversal; [2]$p<0.05$; [3]failure including relapses plus study withdrawals; [4]Pentasa; [5]$p=0.057$; unacceptable side-effects were frequent in the 3 g group.

patients with UC. When the adherence rate in 94 outpatients on 5-ASA with clinically quiescent UC for at least 6 months was studied, the overall adherence rate was 40% and the median amount of medication dispensed per patient was 71% (8–130%) of the prescribed regimen.[223] Logistic regression identified a history of four or more prescriptions and 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. The same group conducted a prospective study to determine the effects of non-adherence with 5-ASA among 99 patients with quiescent UC. After 12 months, patients who collected <80% of their prescriptions had a 5-fold higher OR (5.5, 95% CI 2.3–13.0).[204] In a pilot study, patients were randomized to receive either once-daily or conventional (twice or three times daily), mesalazine for maintenance of remission in UC.[224] 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 due to their ability to offer comparable efficacy and improved adherence. This premise appears correct. 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 single daily dose group.[225] Patient questionnaires showed significantly greater compliance ($p<0.05$) and acceptability ($p<0.001$) in the once daily group. The study has yet to be reported in full, but given comparable efficacy between once daily and divided dosing regimes for the treatment of active UC with mesalazine MMx (Mezavant®/Lialda®) and Salofalk®,[23-25,226] the effect is likely to be generic rather than compound-specific.

6.2.2. Thiopurines

> ECCO statement 6F
> Azathioprine/mercaptopurine is recommended for patients who have experienced early or frequent relapse while 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]. Azathioprine/6-MP can also be considered in a patient responding to intensive treatment with intravenous steroids for induction of remission [EL5, RG D]. Addition or continuation of oral 5-ASA can be recommended with special attention to potential myelotoxicity [EL5, RG D]

6.2.2.1. Efficacy of thiopurines for maintenance of remission. Seven RCTs evaluating the efficacy of thiopurines azathioprine (AZA) and mercaptopurine (MP) for maintenance of remission in UC are listed in Table 6.4.[136,175,182,251–254] In the Cochrane meta-analysis published after the Consensus meeting,[255] 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.[158] 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. The two open label studies that compared MP to mesalazine and AZA to sulfasalazine showed significant heterogeneity and could not be pooled. 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.[136] 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 in support of the thiopurines for UC also comes from observational cohorts in retrospective series.[256–262] The best among these is the 30 year cohort from the Oxford IBD clinic between 1968 and 1999.[262] In this series, the overall remission rate in the 346 patients with UC who were treated with AZA was 58%, but increased to 87% among 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 (see Section 5.2.5). Since calcineurin inhibitors are best discontinued within 6 months because of nephrotoxicity, these agents are generally proposed as induction therapy until slower-acting immunomodulators such as AZA or MP become effective. AZA or MP are introduced while 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[63–65]). Restrospective series have suggested that thiopurines reduce the risk of colectomy after the induction period with CsA.[63,263–265] In 1996, a series of 29 patients successfully treated with ciclosporin were followed for a median 92 weeks, and 22% of patients taking MP required a colectomy, compared to 72% of those not taking MP.[263] 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 ($p=0.01$).[265] 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 thiopurines during the 5 year follow up.[63]

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

Table 6.4 Randomized trials of thiopurines compared to placebo or oral 5-aminosalicylates for maintaining remission in UC

Author [ref]	Year	Number of patients	Study drugs	Dosage	Study design	Duration (months)	Failure to maintain clinical or endoscopic remission
Jewell[175]	1974	80	Azathioprine	2.5 mg/kg/day then reduced to 1.5–2 mg/kg/day after 3 months	Double-blind	12[1]	60%
			Placebo	–			77%
Hawthorne[251]	1992	67[2]	Azathioprine	100 mg/day	Double-blind	12	36%
			Placebo	–			59%[3]
Mate-Jimenez[182]	2000	34	6–mercaptopurine	1 .5 mg/kg/day	Open label	18[1]	50%
			Methotrexate	15 mg/week			85%
			MSZ	3g/day			93%[3]
Sood[252]	2000	50	Azathioprine[4]	2.mg/kg/day	Single (patient)-blind	12[1]	44%
			Placebo	–			60%[3]
Sood[253]	2002	35	Azathioprine[4]	2.5 mg/kg/day	Double-blind	12[1]	23%
			Placebo	–			56%
Sood[254]	2003	25	Azathioprine + SZP	2 .5 mg/kg/day + 6 g/day	Open label	18[1]	77%
			SZP	6g/day			44%[3]
Ardizzone[136]	2006	72	Azathioprine	2 m g/kg/day	Single (Investigator)-blind	6	47%
			MSZ	3.2g/day			79%[3]

[1]Inclusion of patients with active disease who initially received steroids for induction of remission.
[2]All patients included in this study were in remission on azathioprine for at least 6 months (withdrawal design); co-medication with 5-ASA was permitted and taken by 82% of patients.
[3]$p<0.05$.
[4]Co-medication with sulfasalazine 6 g/day in all patients.

CsA bridge has been challenged. In a retrospective series from Barcelona, all responders to iv CsA were treated with AZA, without oral ciclosporin.[266] 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. This needs more investigation.

Three retrospective studies have assessed the long term outcome of patients after an attack of UC treated with intravenous CsA.[63–65] All describe a high rate of relapse and colectomy. In 76 patients treated with CsA for intravenous steroid-refractory UC, 65% relapsed within 1 year, and 90% within 3 years 90%.[64] Unusually, a beneficial effect of AZA (given to 35/56 who could tolerate it) could not be demonstrated either to maintain remission or prevent colectomy (ns). After 5 years 47% in the non-AZA and 40% in the AZA-treated patients came to colectomy, and after 7 years the overall colectomy rate was 58%. The Leuven experience described 142 patients, 118 (83%) of whom had an initial response to CsA and avoided colectomy during initial hospitalization.[65] 64/118 (54%) subsequently required colectomy. The rate of colectomy in those already on AZA compared with those starting AZA concurrently with CsA was 59% *vs* 31%, respectively ($p<0.05$). Life-table analysis showed that 33% of patients required colectomy at 1 year, but the probability increased to 88% at 7 years if CsA was used in patients already on AZA. Consequently CsA has little role for patients who have failed AZA of an appropriate dose and duration.

6.2.3. Infliximab (IFX)

> ECCO statement 6G
> In a patient responding to infliximab, infliximab is recommended for maintenance treatment [EL1b, RG A]. In azathioprine naïve patients responding to infliximab induction, azathioprine is an option instead of infliximab for maintenance [EL5, RG D]

6.2.3.1. Efficacy for maintenance. Details of the ACT 1 & 2 studies are given in Section 5.4.3.[78]. The design of these studies was different to standard maintenance trials (Section 6.1.1). Patients included in the maintenance phase were not necessarily in steroid-free clinical or endoscopic remission. Moreover, non-responders to IFX were taken into account in the calculation of week 30 and week 54 response or remission rates. 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".

6.2.3.2. Combining IFX and immunomodulators.

> ECCO statement 6H
> Combination of infliximab with an immunosuppressant for at least 6 months, or premedication with steroids, is currently recommended in order to decrease immunogenicity [EL3, RG C]

As with Crohn's disease,[158] 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.[267,268] Since antibodies to IFX occur early in the treatment, the question of discontinuing the immunomodulator has been addressed by the Leuven group for Crohn's disease. Results from a single centre open-label randomized, withdrawal trial suggest that the immunomodulator can be stopped after 6 months with no loss of response to IFX over 2 years.[269] These results should still be interpreted with caution, because circulating concentrations of IFX declined over time when the immunomodulator was discontinued. On the other hand, the report of eight cases of a rare form of hepatosplenic T cell lymphoma occurring in young patients treated concurrently with IFX and thiopurines must also be taken into account.[270] Short-term combination (6 months) appears to offer a good balance between risks and efficacy for those in whom IFX is continued. If a patient is naïve to AZA when given IFX, a reasonable option is to determine whether remission will be maintained by AZA alone, without committing that patient to maintenance IFX.

Whether IFX acts as a bridge to remission that is maintained by thiopurines, or whether AZA simply slows the rate of descent to inevitable relapse (the 'parachute'[271]), remains debated. This strategy has not yet been tested in UC, but is an acceptable option for thiopurine-naive patients with steroid-dependent Crohn's disease.[272] The 2 year follow up of patients who received a single dose of IFX as rescue therapy for intravenous steroid-refractory UC (Section 5.2.5[73]) presented after the Consensus meeting, 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 (ns).[273] Consequently, whether maintenance IFX (with or without thiopurines) is better than thiopurines alone to prevent relapse and avoid late colectomy cannot be deduced.

6.2.4. Probiotics

> ECCO statement 6I
> *E. coli* Nissle is an effective alternative to 5-ASA for maintenance [EL1b, RG A]

E. coli strain Nissle 1917.

Three RCTs have compared the E. coli strain Nissle 1917 (Mutaflor®) to mesalazine for maintenance of remission in UC (Table 6.5). 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.[274] 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, because relatively few patients relapsed, but an 11–16% relapse rate within 3 months seems rather high. Subsequently 116 patients with active UC were randomized 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.[275] All patients also received an initial 7 day course of oral gentamicin and either rectal or oral steroids in variable doses.

Table 6.5 Randomized trials of probiotics for maintaining remission in UC

Author [ref]	Year	Number of patients	Study drugs	Dosage	Duration (months)	Failure to maintain clinical or endoscopic remission
Kruis[274]	1997	120	*E. coli* Nissle	200 mg/day	4	16%
			Mesalazine	1.2g/day		12%
Rembacken[275]	1999	116	*E. coli* Nissle	200 mg/day	12	73%
			Mesalazine	1.2g/day		73%
Kruis[276]	2004	327	*E. coli* Nissle	200 mg/day	12	45%
			Mesalazine	1.5g/day		36%
Ishikawa[277]	2000	21	Probiotic mixture[1]number	100 mL	12	27%
			Treatment[2]			90%[3]
Zocco[278]	2006	187	*Lactobacillus GG*	18×10^9	12	15%
			Mesalazine	2.4 g/day		20%
			Combination			16%

[1] *Bifidobacterium bifidum* + *Bifidobacterium breve* + *Lactobacillus acidophilus*.
[2] Open label study.

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.[275] 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. The corresponding one-sided upper 95% confidence interval for the difference in treatment was 12.8%, which is within the equivalence range of 20% required for acceptance of the non-inferiority hypothesis. 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.[206]

6.2.4.1. Other probiotics. No other probiotic has been subject to properly powered RCTs. When 100 ml/day of fermented milk containing *Bifidobacterium bifidum* YIT 4007, *B. breve* YIT 4065, and *L. acidophilus* YIT 0168 was given to 21 UC patients over 1 year,[277] neither investigators nor patients were blinded, and other treatments could be administered. There were fewer relapses in the treatment arm (27% in the milk group vs 90% in the controls), but no differences in endoscopic lesions. Another group of 187 patients with UC in remission for less than 12 months were randomised to receive either *Lactobacillus* GG 18×10^9 viable bacteria/day, 5-ASA 2.4 g/day, or the combination.[278] There were no differences in sustained clinical or endoscopic remission rates at 6 and 12 months between the three treatment groups. In a post-hoc analysis, however, treatment with *Lactobacillus* GG appeared to prolong the relapse-free time compared to 5-ASA. Relapse rates at 12 months were 136/10,000 person-months on *Lactobacillus* GG alone and 181/10 000 person-months on 5-ASA ($p=0.01$). Further studies are needed.

6.2.5. Other treatments

6.2.5.1. Antibiotics. The potential benefit of adding ciprofloxacin to conventional therapy has been investigated.[279] In a randomized, 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. Treatment failure was the primary end point, defined as both symptomatic and endoscopic failure to respond. 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 criticized.[280] Consequently ciprofloxacin should not be considered effective for maintaining remission in UC. In another double-blind, randomized 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.[281] 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 are 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 (12.5 mg/week) that is probably sub-therapeutic (see Section 5.4.6).[181] The proportions of patients who relapsed after first remission (MTX 64% vs placebo, 44%) were not significantly different. An open-label study compared MP, MTX and 5-ASA in 72 steroid-dependent IBD patients, including 34 with UC[182] (Table 6.4). Patients on prednisone were randomly assigned in a 2:2:1 ratio to receive oral MP 1 mg/kg, MTX 15 mg/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%). Too many questions were being addressed by this study for conclusions on the relative efficacy of MP and MTX in UC to be drawn.

Several retrospective series have also been published,[183,282–285] to a total of 91 patients. Most had failed or been intolerant of AZA and were treated with MTX at various doses and routes of administration. The response or remission rates ranged from 40% to 75%, suggesting that some patients with UC may respond well to methotrexate. One study distinguished between patients given MTX for AZA-intolerance and AZA-failure.[285] 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 *vs* 5/31 patients who were intolerant of AZA ($p<0.05$). 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.

6.2.5.3. Omega-3 fatty acids (fish oil). Preparations containing omega-3 fatty acids and eicosapentaenoïc acid in particular, may have anti-inflammatory properties by reducing the production of leucotriene B_4[286,287] Several studies have been conducted in UC with different formulations and dosing of n-3 fatty acids.[288–296] Only three randomized controlled trials were selected for a Cochrane meta-analysis published after the Consensus,[297] which included 138 UC patients who were in remission at the time of recruitment.[291,293,294] The pooled analysis showed a similar relapse rate in the n-3 treated patients and controls (RR 1.02, 95%CI 0.51–2.03, $p=0.96$). No significant adverse events were recorded.

6.2.5.4. Appendicectomy. Studies have focused on the role of appendicectomy in the UC pathogenesis. A meta-analysis included 13 case-control studies and suggested that appendicectomy gives a 69% reduction in the risk of developing UC (OR 0.31, 95%CI 0.25–0.38; $p<0.0001$).[298] The influence of potential confounders such as smoking was excluded. The protective effect of appendicectomy for the development of UC appears to be limited to patients who undergo appendicectomy before age 20 years and is mainly observed for primary appendicectomy

(surgery for appendicitis) and not for incidental appendicectomy (removal of the appendix for other reasons).[299] The outcome of 41 UC patients with an appendicectomy before diagnosis and 466 with no previous surgery, who were all prospectively included in an IBD database, has been compared.[300] Previous appendicectomy has a beneficial effect on the course of UC, with a less marked year-by-year disease activity and a decreased risk of colectomy. This protective effect was additive to that of current smoking. Similar results have been reported from the Brisbane group, who have explored the subject in detail and shown an association between previous appendicetomy for appendicitis and a mild course of extensive colitis, but no influence on the pattern of primary sclerosing cholangitis.[301,302] There are only anecdotal data on the course of UC when appendicectomy is performed after UC diagnosis.[103] Consequently, the Consensus considered that there is no enough evidence to recommend appendicectomy for preventing relapse in UC.

6.2.5.5. Biological and other therapy. Adalimumab, certolizumab, etanercept, natalizumab, visulizumab, interleukin 10, fontolizumab (an anti-interferon γ antibody), basiliximab, daclizumab, alicaforsen (an anti-ICAM1 antisense molecule), anti-IL12 and anti-IL6 antibodies have not yet been evaluated for maintenance of remission in UC, and nor have leucocytapheresis, tacrolimus, or cyclophosphamide in any meaningful way.

6.3. Duration of maintenance therapy

ECCO statement 6J
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]

In 1973, two studies from Sweden and the UK were published to assess whether sulfasalzine was still effective at preventing relapse in UC patients with a long duration of remission (Table 6.1). 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.[209] 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.[208] 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.[303] Patients were randomized to oral Asacol® 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 (Asacol® 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. The debate about the merits of 5-ASA for chemoprevention of colorectal cancer is covered in Section 9.5.

ECCO statement 6 K
Due to lack of 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]

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 1980 s, 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 1960 s, but never achieved universal acceptance, although the gain in quality of life compared to proctocolectomy with a conventional stoma seemed clear enough.[304] 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.[305] 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.[306]

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 are 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 9.4.2).

7.2. Technical considerations

7.2.1. Surgery for acute severe colitis

ECCO statement 7A
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 or more of prednisolone for more than 6 weeks [EL 4, RG C]

A staged proctocolectomy (subtotal colectomy first) is considered by many surgeons to be a wise first step in the surgical treatment of ulcerative colitis in acute severe colitis or if patients are saturated with steroids. This is probably even wiser today when medical therapy for acute severe colitis is prolonged for more than 5 days. 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.[307–309] However it is seldom considered the final solution. Thus patients have to go through additional surgery which incurs further risks, additional costs and a prolonged time under surgical care.

7.2.2. Managing the rectal remnant

ECCO statement 7B
When performing a colectomy for ulcerative colitis in emergency circumstances, the whole rectum should be preserved [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 technical implications when the patient comes to a later proctectomy. Leaving as little rectum as possible (i.e., dividing the middle rectum within the pelvis) is not to be recommended, as 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 either 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.[310] Closing the stump and leaving it within the subcutaneous fat is as safe, although the skin is probably best be left to heal through secondary intention in order to avoid wound infections.[311] 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 transsected within the abdominal cavity at the level of the promontory, then this warrants transanal rectal drainage for some days, to prevent blow out of the rectal stump due to retention.

7.2.3. Site of anastomosis for restorative poctocolectomy

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]

The now commonly used stapling technique for performing the ileo-anal anastomosis usually leaves 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.[312] On the other hand, a very short length of mucosa (<1 cm) above the dentate line would exclude many (or even most) male patients from the stapling technique, due to technical problems achieving a low anastomosis in the narrow male pelvis. Both have to be balanced against the advantage of the stapling technique, which gives patients better nocturnal continence.[313]

7.2.4. Anastomostic 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 seldom room for re-stapling and the only way of avoiding a permanent stoma is to hand-sew the anastomosis. Stapling is generally inappropriate when performing IPAA for dysplasia or cancer complicating colitis, since the Consensus is to remove all mucosa (Statement 7E, below). All these eventualities mean being able 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, anastomosis at the dentate line is recommended [EL4, RG C]

Since the stapling technique commonly leaves epithelium which may still have malignant potential, the alternative is to perform a mucosectomy from the dentate line. In theory, but not necessarily in practice, this removes all of the potentially diseased (and pre-malignant) mucosa. Consequently if the indication for proctocolectomy is cancer complicating colitis, this might influence the subsequent risk of cancer.[314] However, the literature reports cancers both in patients with a stapled anastomosis as well as in

those who have had a mucosectomy, but almost exclusively in those who had pre-existing malignancy in the resected colon. The number of reported cancers is limited (<30 out of tens of thousands of IPAA performed world wide) and is not at present a matter for alarm.[315,316] When there is colonic dysplasia alone rather than cancer, the literature gives no advice on whether to staple or perform a mucosectomy. A total mesorectal excision is, however, mandatory when the indication is dysplasia or cancer.

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 might jeopardise the final outcome of the operation, 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.[317,318] There are some small comparative studies, but no definitive answer. However, when performing a coloanal anastomosis after rectal excision for cancer, it is now established that a covering loop ileostomy reduces the risk of clinical leakage. 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.[319–321]

7.2.7. Number of procedures to maintain competency

> ECCO statement 7G
> An institution performing pouch surgery should do more than ten cases per year [EL 5 RG D]

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.[322] There are no details pertaining to IPAA, but it seems reasonable to assume that this holds for pouch surgery and the figure of ten per year for the unit is arbitrary, but considered reasonable by surgical members of ECCO.

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]

From the perspective of a 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.[323–327] 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 (Section 8.1), 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 7C, above), poses an additional problem compared to the hand-sewn IPAA, 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, which does not represent a risk or clinical problem for most patients.[316]

7.3.2. Pouch surveillance

> ECCO statement 7J
> There are not enough data to give a recommendation on surveillance of pouches with respect to malignant changes. However, patients operated on for cancer or dysplasia should be followed long term [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. Fewer than 30 pouch cancers have been reported (2007), almost all in patients operated with

dysplasia or cancer already present in the specimen at primary surgery. Many of the cancers originate from anorectal mucosal remnant, which is the basis of the recommendation for mucosectomy (statement 7E, above).[314,315] 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.[328]

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 the option of an ileorectal anastomosis should always be considered, 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.[329–332] The reason for this is most probably adhesions affecting the fallopian tubes.[333] 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.[334,335] This appears to be because an IRA does not induce pelvic fibrosis to nearly the same extent as an IPAA. This has lead to a modification in practice at some centres, offering fertile female patients an IRA, provided the rectum is not grossly inflamed, with a view to later pouch surgery when the family is complete. 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 7.5.3. 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
> With regard to bowel function a caesarean route of delivery in a female with an IPAA is recommended [EL 5, RG D]

Vaginal delivery has a 0.5–3.5% risk of inflicting serious maternal sphincter tears.[336,337] The risk is highest at the first delivery. On the other hand, multiple deliveries have been shown to prolong pudendal nerve terminal motor latency.[338,339] 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. Nevertheless, in a cohort where caesarian section was recommended only for obstetric reasons, this group experienced very little or no difference in early postoperative continence and bowel function.[340] Although it suggests that vaginal delivery is safe in selected cases, it remains contrary to two other papers that support the recommendation for caesarian delivery both in Europe and the US.[341,342]

7.5. Surgical choices in addition to restorative proctocolectomy

7.5.1. Age

> ECCO statement 7 M
> No defined age limit for performing an IPAA can be recommended [EL 5, RG D]

Faecal continence in both men and women deteriorates with increasing age. Females that have given birth carry a higher risk of poor continence, probably because sub-clinical injuries add to age-related changes in nerve function, collagen elasticity and muscle strength. Consequently it is reasonable to consider whether an upper age limit for IPAA should apply. It has however been demonstrated that IPAA will function reasonably well in people 70 years of age and older in carefully selected cases.[343–345]

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 potential for complications affecting the valve mechanism that provides continence. However, with a functioning continent ileostomy patients report excellent quality of life with a next-to-normal body image.[346–348] Furthermore a failed pelvic pouch can still be converted to a continent ileostomy, providing an alternative in those patients that absolutely cannot accept a conventional stoma.[325,349] A major problem is that this operation is still performed at only a few centres in Europe.

7.5.3. Ileorectal anastomosis

> ECCO statement 7O
> An ileorectal anastomosis should be considered only in special cases (such as for reasons of fertility) [EL4, RG C]

An ileorectal anastomosis is historically burdened. It 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.[350,351] Its role in the management of women facing surgery before they have completed their family is discussed above (Section 7.4.1). It can be assumed that the cancer risk with medical therapy and surveillance is at least less than in those who have not had surgery.

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, although it can be left in situ if the patient so wishes [EL5, RG D]

The literature gives no direct guidance in this matter. Some patients that come to colectomy with an ileostomy as a first operation get accustomed to living with a stoma and have very few problems from their retained rectum. If a patient has no wish for further surgery, the question arises whether there is any reason for rectal excision. The balance is between the risk of a cancer in the disconnected bowel and the inconvenience and risks of a proctectomy. Taking out the rectum is a major operation with a considerable surgical morbidity with wound healing problems and risk of sexual dysfunction both in women and men.[352,353] Options of proctectomy or surveillance of the retained rectal remnant should be discussed with the patient.

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]

The dilemma is similar in the patient with a failed, disconnected pelvic pouch. Some of these patients do not have any further pouch-related problems. There is as yet no evidence that the risk of malignant change is increased in the disconnected pouch. The morbidity of pouch excision is probably no less than for proctectomy.[324] For individuals who have had severe septic complications, it is reasonable to assume that the risk of pelvic nerve injury is increased.

7.5.6. Laparoscopic pouch surgery

> ECCO statement 7R
> Laparoscopic restorative proctocolectomy with an IPAA is a feasible operation; it gives shorter scars but there is no evidence for additional benefit to the patient [EL 2a, RG B]

Minimally invasive surgery is gradually being incorporated into colorectal practice and is a feasible alternative for many patients, provided that surgeons are adequately trained in this technique. No randomised studies have yet shown any major differences from open surgery.[354,355]

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 5. There are reports of less favourable outcomes when performing pouch surgery for patients with indeterminate colitis, although others find no significant differences.[356,357] In most series that report outcome after pouch surgery, those with a secondary diagnosis of Crohn's disease are burdened with 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.[358] 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 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.[359,360] The rate of steroid reduction after colectomy for acute severe colitis depends on the dose

and duration of steroids prior to surgery. Any recommendations of the rate 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. As a general guide, if patients have been on corticosteroids for <1 month, steroids can usually be stopped abruptly after surgery without ill effect. For those on steroids for 1–3 months, a reduction from 20 mg/day after colectomy of 5 mg/day each week is generally appropriate. For patients on steroids for 3–6 months, a reduction of 2.5 mg/d each week is probably more appropriate, while for the occasional patient on steroids for longer than 6 months, then a dose reduction of 1 mg/week (or even more slowly) is advisable.

7.6.2. Perioperative azathioprine

> ECCO statement 7U
> Pre-operative azathioprine does 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 [EL2b, RG D], while there are no sufficient data yet available for infliximab

Azathioprine does not appear to increase the risk of surgical complications although debate continues.[360–363]

7.6.3. Perioperative anti-TNF therapy

TNFα is a key player in the immune response. Inhibition of TNF by infliximab (IFX) or other agents could potentially lead to serious post-operative complications. There is particular concern that emergency colectomy within a few weeks of infliximab may be associated with more septic complications. Even if IFX does not increase the risk of sepsis, it is still likely that should a septic complication occur, then it will be more severe in the presence of circulating anti-TNF antibody. Whilst it is generally accepted that elective surgery for Crohn's disease in the presence of IFX is not associated with higher rates of sepsis,[83,364] the same may not apply to emergency colectomy for acute severe colitis (Section 5.2.5). In a Scottish survey 13/39 patients came to colectomy after IFX treatment for acute severe colitis. One patient who initially responded to infliximab died of septic shock from bronchopneumonia 3 weeks after treatment, and another had severe post-operative sepsis resistant to anti-bacterial therapy and only responding to intensive antifungal treatment.[82] There has also been a worrying report of 20 patients receiving ciclosporin (for a mean 3.8 months, range 0.5–12.2) before IFX, or IFX (mean 2 infusions, range 1–3) before ciclosporin for severe steroid-refractory colitis.[365] One patient died from *E. coli* septicaemia, another became jaundiced and another developed herpetic oesophagitis. Such therapy in combination in an endeavour to avoid colectomy carries high risks and cannot be recommended. Similar concerns have been raised from the Mayo clinic relating to IPAA after IFX.[366] Between 2002 and 2005, 47 patients received IFX before IPAA, and 254 patients received none. IFX patients were younger than non-IFX patients (mean age 28.1 to 39.3 years, $p<0.001$), probably reflecting concern that all medical options were explored before surgery. Overall surgical morbidity was similar (61.7% and 48.8%, IFX and non-IFX respectively, $p=0.10$), with no mortality. Anastomotic leaks ($p=0.02$), pouch-specific ($p=0.01$) and infectious ($p<0.01$) complications were more common in IFX patients. Multivariate analysis revealed IFX as the only factor independently associated with infectious complications (OR 3.5; 95%CI 1.6–7.5). When age, corticosteroid dose, azathioprine, and severity of colitis were factored into the analysis, IFX remained significantly associated with infectious complications (OR 2.7; 95% CI, 1.1–6.7). This illustrates the need for caution when using IFX in the perioperative period of severe colitis.

7.7. Colectomy in practice

The rate of colectomy varies according to the patient cohort, duration of follow up and geographical location. Studies published in the early 1990 s reported an overall colectomy rates of 23%, 28% and 34% after 10 years of follow up, with rates as high as 35% at 5 years and 42% and 54% at 10 years for extensive colitis.[367–369] It is unclear whether the overall rate is changing, even in areas with excellent population-based data such as Copenhagen, where there has traditionally been a high rate of colectomy. When patients diagnosed with UC in Copenhagen during 2003–2005 were followed prospectively only 6% of patients underwent surgery during the year of diagnosis, significantly less than earlier reported.[370] This might reflect an increasing prevalence of proctitis and milder initial course diagnosed in the 1990s, but when 3 consecutive population-based IBD cohorts from Copenhagen (1962–2005), were assessed the cumulative surgery rate in 1575 patients with ulcerative colitis did not decrease significantly.[195] Nevertheless, in a 781 patient European inception cohort (1991-93) from 7 countries, the overall 10 year cumulative risk of colectomy was only 8.7%.[371] Colectomy rates for extensive colitis at diagnosis in Denmark, Norway and the Netherlands were 22.1% compared to 8.5% for Greece, Italy, Spain and Israel. The extent of disease did not differ between northern and southern centres, but the prevalence of proctitis or distal colitis was remarkably high (75%, or 557/745 patients). This is as likely to explain the low overall colectomy rate as are cultural differences or acceptance of symptoms between countries. The 10 year colectomy rate was 2% for proctitis/distal disease, 18% for extensive disease at diagnosis, and 39% for the 11% (62/557) patients with proctitis progressing to extensive colitis during follow up.

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