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


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KEYWORDS
Ulcerative colitis; Definitions; Diagnosis; Histopathology; Classification; Activity indices

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1. Definitions

1.1. Introduction

Ulcerative colitis is a life long disease arising from an interaction between genetic and environmental factors, but observed predominantly in the developed countries of the world. The precise aetiology is unknown and therefore medical therapy to cure the disease is not yet available. Within Europe there is a North–South gradient, but the incidence appears to have increased in Southern and developing countries in recent years.1,2 Patients may live with a considerable symptom burden despite medical treatment (66% describe interference with work and 73% with leisure activities3) in the hope that the aetiology of ulcerative colitis will shortly be revealed and a cure emerges. Although this is conceivable in the next decade, clinicians have to advise patients on the basis of information available today. Despite randomized trials there will always be many questions that can only be answered by the exercise of judgement and opinion. This leads to differences in practice between clinicians, which may be brought into sharp relief by differences in emphasis between countries.

The Consensus endeavours to address these differences. The Consensus is not meant to supersede the guidelines of different countries (such as those from the UK,4 or Germany5), which reach broadly the same conclusions since they are, after all, based on the same evidence. Rather, the aim of the Consensus is to promote a European perspective on the management of ulcerative colitis (UC) and its dilemmas. Since the development of guidelines is an expensive and time-consuming process, it may help to avoid duplication of effort in the future. A European Consensus is also considered important because an increasing number of therapeutic trials recruit from Central and Eastern European countries where practice guidelines have yet to be published.

This document sets out the current European Consensus on the diagnosis and management of UC, reached by the European Crohn’s and Colitis Organisation (ECCO) at a meeting held in Berlin on 20th October 2006. ECCO is a forum for specialists in inflammatory bowel disease from 23 European countries. Like the initial Consensus on the management of Crohn’s disease,6 the current Consensus is grouped into three parts: definitions and diagnosis; current management; and management of special situations. This first section concerns aims, methods and definitions of the Consensus, as well as classification, diagnosis, imaging and pathology of UC. The second section on current management includes treatment of active disease, maintenance of medically-induced remission and surgery of UC. The third section on special situations includes pouch disorders, cancer surveillance, pregnancy, paediatrics, psychosomatics, extra-intestinal manifestations and alternative therapy.

The strategy to reach the Consensus involved five steps:

1. Relevant questions on each of 14 separate topics concerning diagnosis and treatment of UC were devised by the chairmen and their working party. The questions were focused on current practice and areas of controversy in the task force topic, sent around to the other chairmen to avoid duplication, and then to all 59 participants in the Consensus conference. Participants were asked to answer the questions based on their experience as well as evidence from the literature (Delphi procedure).7

2. In parallel, the working parties performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed and the Cochrane database, as well as their own files. The evidence level (EL) was graded (Table 1.1) according to the Oxford Centre for Evidence Based Medicine.8

3. Provisional guideline statements on their topic were then written by the chairmen, based on answers to the questionnaire as well as the literature evidence and were circulated

<table>
<thead>
<tr>
<th>Level</th>
<th>Diagnostic study</th>
<th>Therapeutic study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic review (SR) with homogeneity of level 1 diagnostic studies</td>
<td>Systematic review (SR) with homogeneity of randomized controlled trials (RCTs)</td>
</tr>
<tr>
<td>1b</td>
<td>Validating cohort study with good reference standards</td>
<td>Individual RCT (with narrow confidence interval)</td>
</tr>
<tr>
<td>1c</td>
<td>Specificity is so high that a positive result rules in the diagnosis (&quot;SpPin&quot;) or sensitivity is so high that a negative result rules out the diagnosis (&quot;SnNout&quot;)</td>
<td>All or none</td>
</tr>
<tr>
<td>2a</td>
<td>SR with homogeneity of level ≥2 diagnostic studies</td>
<td>SR (with homogeneity) of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Exploratory cohort study with good reference standards</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow up)</td>
</tr>
<tr>
<td>2c</td>
<td>&quot;Outcomes&quot; research; ecological studies</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>SR with homogeneity of 3b and better studies</td>
<td>SR with homogeneity of case-control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Non-consecutive study; or without consistently applied reference standards</td>
<td>Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case-control study, poor or non-independent reference standard</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
</tr>
</tbody>
</table>

Grades of recommendation

A Consistent level 1 studies
B Consistent level 2 or 3 studies or extrapolations from level 1 studies
C Level 4 studies or extrapolations from level 2 or 3 studies
D Level 5 evidence or troublingly inconsistent or inconclusive studies of any level
first among the working party and then among the participants.

4. The working parties then met in Berlin on the 20 October 2006 to agree the statements. Participants gathered under the Chairmanship of EF Stange and SPL Travis to agree the final version of each guideline statement. Technically this was done by projecting the statements and revising them on screen until a Consensus was reached. Consensus was defined as agreement by >80% of participants, termed a Consensus Statement and numbered for convenience in the document. Each recommendation was graded (RG) according to the Oxford Centre for Evidence Based Medicine,8 based on the level of evidence (Table 1.1).

5. The final document on each topic was written by the chairmen in conjunction with their working party. Consensus guideline statements in bold are followed by comments on the evidence and opinion. Statements are intended to be read in context with qualifying comments and not read in isolation. The final text was edited for consistency of style by SPL Travis and EF Stange before being circulated and approved by the participants. In some areas the level of evidence is generally low, which reflects the paucity of randomized controlled trials. Consequently expert opinion is included where appropriate.

1.2. Definitions

Common agreement has been reached by ECCO about frequently used terms. While the significance of some terms (such as ‘early-’ or ‘pattern of relapse’) is undetermined, such terms reflect clinical decision-making (such as when to start immunomodulators) and are considered helpful as a consequence. The arbitrariness of some of the definitions is recognised, but the Consensus considers it useful to agree the terminology.

Ulc erative colitis (UC) is a chronic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterised by a relapsing and remitting course.9

Colitis yet to be classified is the term best suited for the minority of cases where a definitive distinction between UC, Crohn’s disease, or other cause of colitis cannot be made after the history, endoscopic appearances, histopathology of multiple mucosal biopsies and appropriate radiology have been taken into account.9,10

Indeterminate colitis is a term preserved for pathologists to describe a colectomy specimen which has overlapping features of ulcerative colitis and Crohn’s disease.10,11 It has distinct prognostic factors related to further surgery (Section 7.5.7, first following paper in same issue).

1.2.1. Distribution of disease (see Section 2.1)

The Montreal classification (Table 1.29) for defining the distribution of disease was favoured by 52/59 participants. This is taken to mean the maximal, macroscopic extent of disease at colonoscopy, since the long-term prognosis in the past has used the extent of disease as defined by barium enema. The implications of more extensive microscopic disease are not understood. The poor correlation between macroscopic and microscopic extent of disease (kappa=0.39) is recognised.10 So too is the limitation of an extent-based classification when the extent varies over time, underlining the dynamic nature of inflammatory bowel disease.12

1.2.2. Active disease

For the purposes of this Consensus, clinical disease activity is grouped into remission, mild, moderate and severe. Precise definitions of disease activity are appropriate, since confusion arises if the terms are used to refer only to the least, intermediate or most severe third of cases that the physician can recall at the time. Among Consensus participants, 31/59 considered Truelove and Witts’ criteria useful in clinical practice (summarized, Table 1.313), in conjunction with sigmoidoscopy to confirm active colitis.

16/59 favoured the Mayo score (Table 1.4),14 with its modifications.15 The value of the different indices for the purpose of clinical trials is beyond the scope of the Consensus,

<table>
<thead>
<tr>
<th>Term</th>
<th>Distribution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>Proctitis</td>
<td>Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to the rectosigmoid junction)</td>
</tr>
<tr>
<td>E2</td>
<td>Left-sided</td>
<td>Involvement limited to the proportion of the colon distal to the splenic flexure (analogous to ‘distal’ colitis)</td>
</tr>
<tr>
<td>E3</td>
<td>Extensive</td>
<td>Involvement extends proximal to the splenic flexure, including pancolitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Term Distribution</th>
<th>Description</th>
</tr>
</thead>
</table>

Table 1.2 Distribution of ulcerative colitis (from9)

Table 1.3 Disease activity in ulcerative colitis, adapted from Truelove and Witts13

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate ‘in between mild and severe’</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody stools/day</td>
<td>&lt;4</td>
<td>4 or more if</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;90 bpm</td>
<td>≤90 bpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt;37.5 °C</td>
<td>≤37.8 °C</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&gt;11.5 g/dL</td>
<td>≤10.5 g/dL</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt;20 mm/h</td>
<td>≤30 mm/h</td>
</tr>
<tr>
<td>or CRP</td>
<td>Normal</td>
<td>≤30 mg/L</td>
</tr>
</tbody>
</table>

Table 1.4 Mayo score14,15 and www.gastrojournal.org for full details]

<table>
<thead>
<tr>
<th>Mayo index</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency</td>
<td>Normal</td>
<td>1–2/day</td>
<td>≥normal</td>
<td>3–4/day</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>None</td>
<td>Normal</td>
<td>Obvious</td>
<td>Mostly blood</td>
</tr>
<tr>
<td>Stools</td>
<td>Normal</td>
<td>&gt;normal</td>
<td>&gt;normal</td>
<td>&gt;normal</td>
</tr>
<tr>
<td>Mucosa</td>
<td>Normal</td>
<td>Moderate friability</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Friability</td>
<td>Mild</td>
<td>Moderate</td>
<td>Spontaneous bleeding</td>
<td></td>
</tr>
<tr>
<td>Physician’s global assessment</td>
<td>Normal</td>
<td>Moderate</td>
<td>Mostly blood</td>
<td></td>
</tr>
<tr>
<td>assessment</td>
<td>Mild</td>
<td>Severe</td>
<td>Spontaneous bleeding</td>
<td></td>
</tr>
</tbody>
</table>
but has recently been reviewed. ECCO recognises the need to validate clinical and endoscopic scoring systems.

The Montreal classification (Table 1.5) is largely based on Truelove and Witts’ criteria, since this reflects clinical practice.

Severe colitis (or ‘acute severe colitis’) is preferred to ‘fulminant’ colitis, because the term ‘fulminant’ is ill-defined. It was coined in 1950 when it referred to a single attack going on to death within 1 year, which no longer has relevance today. Severe colitis defined according to Truelove and Witts’ criteria (Table 1.3 and Section 5.1, first following paper in same issue) are easy to apply in outpatients, determine a course of action (hospital admission for intensive treatment) and an outcome (only 70% respond to intensive therapy). These criteria are recommended for identifying acute severe colitis by The American College of Gastroenterology (ACG) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI), as well as ECCO.

Moderate colitis has become necessary to distinguish from mildly active disease, because the efficacy of some treatments may differ (Section 5, first following paper in same issue). The simplest clinical measure to distinguish moderate from mildly active colitis is the presence of mucosal friability (bleeding on light contact with the rectal mucosa at sigmoidoscopy). The technique of assessing mucosal friability at flexible sigmoidoscopy has yet to be standardised. One approach is to apply sufficient pressure on the mucosa with closed biopsy forceps to create a dimple, maintain the pressure for 3 s and then define friability if bleeding occurs from the pressure point. This has yet to be validated.

1.2.3. Remission
Remission is defined as complete resolution of symptoms and endoscopic mucosal healing (Section 2.2.4). Combining clinical and endoscopy is appropriate for clinical trials, but remission rates vary by as much as two-fold depending on the definition of remission used in the trial. In clinical practice, 33/59 participants agreed that ‘remission’ meant a stool frequency ≤ 3/day with no bleeding and no urgency. Remission defined by individual patients has an 86% sensitivity and 76% specificity for a regulatory-defined remission (absence of visible blood and absent mucosal friability), indicating that sigmoidoscopy to confirm mucosal healing is generally unnecessary in practice.

<table>
<thead>
<tr>
<th>Table 1.5</th>
<th>Montreal classification of disease activity in ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S0</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Stools/day</strong></td>
<td>Asymptomatic ≤ 4</td>
</tr>
<tr>
<td>Blood</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td>All normal</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>or no</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong></td>
<td>&gt;30 mm/h</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td></td>
</tr>
</tbody>
</table>

1.2.4. Response
Response is defined as clinical and endoscopic improvement, depending (for the purpose of clinical trials) on the activity index used. In general, this means a decrease in the activity index of >30%, plus a decrease in the rectal bleeding and endoscopy subscores, but there are many permutations.

1.2.5. Relapse
The term relapse is used to define a flare of symptoms in a patient with established UC who is in clinical remission, either spontaneously or after medical treatment. In the Consensus, 47/59 considered rectal bleeding an essential component of relapse, and 29/59 believed that a combination of rectal bleeding with an increase in stool frequency and abnormal mucosa at sigmoidoscopy was necessary to define relapse. In clinical trials, the criteria for relapse should be predefined with the score that is being used for an individual study.

1.2.6. Early relapse
An arbitrary, but clinically relevant period of <3 months after achieving remission on previous therapy defines early relapse. The therapeutic significance needs to be defined.

1.2.7. Pattern of relapse
Relapse may be infrequent (≤ 1/year), frequent (>2 relapses/year), or continuous (persistent symptoms of active UC without a period of remission). Although the terms are arbitrary, they are considered clinically relevant. An alternative approach that defines disease activity over a 5 year period has been proposed (Section 6.1.2, first following paper in same issue), but this seems more relevant to epidemiological studies, since what matters for everyday practice is what is likely to happen in the next year. The prognostic significance needs to be determined. Nevertheless, care should be taken to distinguish between terms that describe disease activity at a point in time and those that describe the longitudinal pattern (or ‘behaviour’) of the disease (Sections 1.2.2 and 2.2.1). The term ‘chronic active disease’ has been used in the past to define a patient who is dependent on, refractory to, or intolerant of steroids, or who has disease activity despite immunomodulators. Since this term is ambiguous it is best avoided. Instead, arbitrary, but more precise definitions are preferred, including steroid-refractory or steroid-dependence.

1.2.8. Steroid-refractory colitis
Patients who have active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks. This was agreed by 45/58 participants, is consistent with the definition for steroid-refractory Crohn’s disease and others. The definition is however likely to evolve, with a reduction in the duration of steroid therapy as the threshold for biologic therapy changes.

1.2.9. Steroid-dependent colitis
Patients who are either

i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or

ii) who have a relapse within 3 months of stopping steroids.

This was agreed by 52/58 participants and is consistent with the definition for steroid-dependent Crohn’s disease.
Table 2.1 Endoscopic scores for ulcerative colitis commonly used in clinical trials

<table>
<thead>
<tr>
<th>Score</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Moderately haemorrhagic</th>
<th>Severely haemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Matt mucosa, ramifying vascular pattern clearly visible, no spontaneous bleeding, no bleeding to light touch</td>
<td>Abnormal, but non-haemorrhagic appearances between 0 and 2</td>
<td>Bleeding to light touch, but no spontaneous bleeding seen ahead of the instrument on initial inspection</td>
<td>Spontaneous bleeding seen ahead of instrument at initial inspection and bleeds to light touch</td>
</tr>
<tr>
<td>1</td>
<td>Normal or inactive disease</td>
<td>Mild (erythema, decreased vascular pattern, mild friability)</td>
<td>Moderate (marked erythema, absent vascular pattern, friability, erosions)</td>
<td>Severe (spontaneous bleeding, ulceration)</td>
</tr>
<tr>
<td>2</td>
<td>Normal, smooth, glistening mucosa, with vascular pattern visible; not friable</td>
<td>Granular mucosa; vascular pattern not visible; not friable; hyperaemia</td>
<td>As 1, with a friable mucosa, but not spontaneously bleeding</td>
<td>As 2, but mucosa spontaneously bleeding</td>
</tr>
</tbody>
</table>

although an alternative definition of relapse within 30 days of completing a course of steroids, or steroids at a dose of 15–25 mg/day for at least 6 months has been proposed. As with steroid-refractoriness, the definition is likely to evolve as the threshold for biologic therapy changes.

The ECCO definition of steroid-dependence requires that the total duration of steroids does not exceed 3 months before a threshold equivalent to prednisolone 10 mg/day is reached. Patients are still considered steroid-dependent if they relapse within 3 months of stopping steroids. Although these limits are arbitrary, they serve as guidance for clinical practice and may be used for uniformity in clinical trials. The aim should be to withdraw steroids completely.

1.2.10. Immunomodulator-refractory colitis
Patients who have active disease or relapse in spite of thiopturines at an appropriate dose for at least 3 months (i.e. azathioprine 2–2.5 mg/kg/day or mercaptopurine 0.75–1 mg/kg/day in the absence of leucopenia). The definition is arbitrary, but has increasing clinical relevance when deciding on the place of biological therapy or surgery.

1.2.11. Refractory distal colitis
Defined as persistent symptoms due to colonic inflammation confined to the rectum (proctitis), or left side of the colon (more commonly the rectosigmoid colon), despite treatment with oral and topical steroids for 6–8 weeks. This represents a common clinical dilemma, although whether it is a separate entity is unclear.

1.2.12. New patient
A patient with active UC presenting at, or shortly after diagnosis, with no previous therapy for UC.

1.2.13. Alternative therapy
One that is used in place of conventional medicine.

1.2.14. Complementary therapies
Similar treatments used alongside conventional medicine (see section on Alternative therapies for comment).

1.2.15. Expert opinion
The term 'expert' is used here to refer to the opinion of the specialists in inflammatory bowel disease representing multiple disciplines from 23 European countries who contributed to the ECCO Consensus. In some sections opinions from individual members of other expert bodies were obtained, including individuals of the European Society of Pathology (ESP) working group on Digestive Diseases, the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).

2. Classification

2.1. Classification according to disease extent

ECCO Statement 2A
The extent of ulcerative colitis influences the patient’s management. Disease extent influences the treatment modality and determines if oral and/or topical therapy is initiated [EL1b, RG B]. Disease extent influences start and frequency of surveillance [EL2, RG B]. Therefore, a classification according to extent of disease is recommended [EL5, RG D]. The preferred classification is an endoscopic classification as outlined in the Montreal classification into ulcerative proctitis (limited to the rectum), left-sided colitis (up to the splenic flexure) and extensive colitis, and by maximal extent upon follow up [EL5, RG D].

There are several reasons why patients with ulcerative colitis (UC) should be classified according to disease extent. First, the extent of inflammation will influence the patient’s management and influence the choice of delivery system for a given therapy. Indeed, the location and extent of the colitis will determine if oral and/or topical therapy is initiated. For instance, topical therapy in the form of suppositories (for proctitis) or enemas (for left-sided colitis) is often the first line choice, but oral therapy — often combined with topical therapy is appropriate for extensive colitis (beyond the splenic flexure) [EL1b, RG B]. Second, the extent of colitis influences the start and the frequency of surveillance [EL2, RG B]. In the
population-based study from Sweden, population extent of disease was 
one of the risk factors for development of colorectal cancer in 3117 UC 
patients followed up from 1 to 60 years after diagnosis. Whereas no 
increased relative risk (RR) was attributed to disease confined to the 
rectum, the RR for left-sided colitis and extensive colitis (previously 
called pancolitis) were 2.8 (95%CI 1.6–4.4) and 14.8 (95%CI 11.4–18.9) 
respectively. Therefore, patients with left-sided and extensive colitis 
are generally advised to have surveillance colonoscopy from 8 to 10 
years after symptom onset, but patients with proctitis do not need 
surveillance (Section 9.2, second following paper in same issue). The 
contribution of disease extent at diagnosis to the risk of malignancy 
has been confirmed more recently by the EC-IBD study group.24

Once agreed that classification according to disease extent is 
important, the next question is which classification best to use? The 
Consensus group agreed that the preferred classification is an 
endoscopic classification into proctitis, left-sided colitis and extensive 
colitis (beyond the splenic flexure), as defined by the Montreal 
Working Group on the Molecular classification of IBD9,10 (Section 1.2, 
Table 1.2). A fourth extent-group of proctosigmoiditis was abandoned, 
because it lacks any scientific background and does not have 
direct therapeutic consequences.

2.2. Classification according to disease severity

**ECCO Statement 2B**

Classification of ulcerative colitis based on disease severity is useful for clinical practice and dictates the patient's management [EL1b, RG B]. Disease severity influences the treatment modality and determines if no, oral, intravenous or surgical therapy is initiated. Indices of disease severity have not been adequately validated. Clinical, laboratory, imaging and endoscopic parameters, including histopathology assist physicians in patients' management [EL 2, RG B]. There is no fully validated definition of remission. The best way of defining remission is a combination of clinical parameters (i.e. stool frequency ≤3/day with no bleeding) and a normal mucosa at endoscopy [EL5, RG D] (majority vote).

### 2.2.1. Activity and pattern of disease

In a population-based study from Copenhagen County, Langholz et al. showed that approximately 50% of patients will be in clinical remission every year at any time.25 However, the cumulative probability of a relapsing course after 25 years of follow up amounted to 90%. The disease activity in the first 2 years after diagnosis indicated (with 70–80% probability) an increased probability of 5 consecutive years of active disease and was therefore judged to be a good parameter to predict the future pattern of disease. This is a helpful practical point to be used by clinicians when advising patients and making management decisions.

A distinction should be made between disease activity at a point in time (remission, mild, moderate, severe) and the response of disease to treatment (using terms such as 5-ASA or steroid responsive, steroid-refractory, biologic dependent etc.). The two should not be confused by sloppy terminology that describes mildly active disease that is steroid-dependent as 'severe'. The consequences (biologic therapy, colectomy) may indeed be considered 'severe', but disease activity remains mild. See also Section 3.5.

### 2.2.2. Choice of index

A classification of UC based on disease activity and severity is important because it influences patient's management. The severity of the inflammation will be determined if no therapy, oral therapy, intravenous or surgical therapy is initiated in a given patient. Over the years, many disease activity indices or criteria have been proposed (see Section 1.2.2 and Ref. 15 for a review), but none has been adequately validated. The Consensus recognises the need for validated clinical and endoscopic indices that relate to outcome or treatment decisions. Although modifications of the original Truelove and Witts' criteria (Section 1.2.1, Table 1.3) are used in daily practice, the modified Mayo score (Section 1.2.1, Table 1.4) is used more frequently in current clinical trials.15 For clinical practice, the Consensus group judged that a combination of clinical features, laboratory findings, imaging modalities and endoscopic parameters, including histopathology will all assist physicians in their patients' management. Endoscopic scoring is illustrated in Section 3.5 and Table 2.1. There is a need for systematic study of this area.

### 2.2.3. Clinical and laboratory markers of severity

Among objective clinical features, bloody stool frequency, body temperature and heart rate are good predictors of outcome. Laboratory markers have been studied intensively with varying degrees of success. The widely used acute phase protein C-reactive protein in this respect is a less good marker for assessing disease activity in UC than Crohn's disease, except for acute severe colitis, where it has established value in both adults and children.26–28 A raised CRP >45 mg/L at day 3 following hospital admission for severe colitis together with more than 8 stools a day is highly predictive for need for colectomy (Section 5.2.5, first following paper in same issue). Other positive (erythrocyte sedimentation rate, serum procalcitonin) or negative (albumin) acute phase proteins have been studied, but none has demonstrated clear superiority (for review see Ref. 30). More recently, faecal markers have demonstrated promising results. The most studied markers are faecal calprotectin and lactoferrin, but elastase and the more recent marker S100A12 have also shown accuracy at detecting colonic inflammation.31–33 It must be stressed however that none of these markers is specific for UC, since they merely represent colonic inflammation with an influx of neutrophils into the gut mucosa, with subsequent shedding of their granules into the gut lumen.

### 2.2.4. Remission

As with the definition of disease activity, there has also not been a fully validated definition of remission. The Consensus group agreed that the best way of defining remission is a combination of clinical parameters (stool frequency ≤3/day with no bleeding) and normal or quiescent mucosa at endoscopy (majority vote, Section 1.2.3).20
2.3. Classification according to age at onset or concomitant primary sclerosing cholangitis

ECCO Statement 2C
A classification of UC according to age at onset is not useful [EL2; RG C]. Classification of UC according to the concomitant presence of PSC is important because it influences patients’ management (surveillance) [EL2; RG C].

A classification according to age at onset is not useful because it does not affect patient’s management. All current available therapies for UC have shown equal efficacy in children with young age at onset compared to adults. The risk of colorectal cancer in patients with the onset of UC in childhood almost certainly reflects the duration of disease (Section 9.1.2, second following paper in same issue). However, concomitant primary sclerosing cholangitis (PSC) is an important feature to take into account when giving care to patients with UC given its increased associated risk for colorectal cancer. This influences decisions on surveillance colonoscopy (Sections 9.1.2 and 9.2.4, second following paper in same issue).

2.4. Use of molecular markers

ECCO Statement 2D
No evidence-based recommendation can be made to implement the routine clinical use of molecular markers (genetic, serologic) for the classification of UC patients [EL2, RG C].

2.4.1. Serology

A number of (auto)antibodies have been described in UC patients, of which the atypical perinuclear anti-neutrophil cytoplasmatic antibodies (pANCA) are best known. Positive pANCA serology is found in approximately 50–60% of patients, although large variability exists due to differences in methodology. Overall, pANCA has shown good accuracy to differentiate CD from UC, but their sensitivity is far from high enough to justify their use in diagnosis. These antibodies also lack accuracy in patients with colitis yet to be classified, where these markers would be of greatest clinical value. A number of other antimicrobial antibodies as ASCA, OmpC, I2, cBlr anti-flagellin, ALCA, ACCA, are found mainly in patients with Crohn’s disease.

2.4.2. Genotyping

The very active field of IBD genetics has led to the identification of several genes, most of which are implicated in a susceptibility to Crohn’s disease, but some also linked to UC. The HLA region is without any doubt the region most associated with UC, but the Interleukin-23 Receptor (IL23R) gene on chromosome 1, the DLG5 gene on chromosome 10, the Multidrug Resistance gene (MDR)-1 and the Toll Like Receptor (TLR) genes, have shown associations with UC. Since UC is a complex multifactorial disease, the disease-associated mutations in these genes will never be sufficient to cause disease, nor will the absence of mutations be a guarantee of remaining free of disease. Therefore, testing for these genetic variants is not recommended for clinical purposes.

3. Diagnosis and imaging

3.1. Introduction

Ulcerative colitis (UC) primarily presents in late adolescence and early adulthood, although the diagnosis may be made at any age. A small peak in incidence has been demonstrated in some populations after the fifth decade of life. Ulcerative colitis appears to affect both sexes equally. The inflammation characteristically commences in the rectum and extends proximally in a continuous, confluent and concentric manner to affect a variable extent of the colon, or its entire mucosal surface. The definitions and classification of the extent of UC are covered in Sections 1.1 and 2.1 (Table 1.2). The proximal extent of inflammation may progress or regress over time, but after disease regression the distribution of inflammation tends to match the extent of previous episodes in the event of relapse. The view that UC represents continuous colonic inflammation has, however, been challenged by reports of a rectal sparing variant and peri-appendiceal patchy inflammation. Symptoms depend on the extent and severity of disease, extra-intestinal manifestations and concurrent therapy. Enteric pathogens may alter the clinical presentation.

3.2. Clinical features and risk factors

3.2.1. Clinical features of ulcerative colitis

ECCO statement 3A
Symptoms of ulcerative colitis are dependent upon extent and severity of disease, and most commonly include bloody diarrhea, rectal bleeding, and/or rectal urgency. Nocturnal defaecation is also often reported. Systemic symptoms of malaise, anorexia, or fever are features of a severe attack [EL5, RG D].

The primary presenting symptom of ulcerative colitis is visible blood in the stools and is reported by more than 90% of patients. Associated symptoms generally reflect the endoscopic severity of the disease as a measure of mucosal damage and may differ according to disease extent. Loose stools (or a decrease in stool consistency) for more than six weeks differentiates UC from most infectious diarrhea. Patients with extensive active UC present with chronic diarrhoea almost invariably associated with rectal bleeding, or at least visible blood in the stools. Such patients also describe rectal urgency, tenesmus, passage of mucopurulent exudates, nocturnal defaecation and crampy abdominal pain, or ache over the left iliac fossa prior to and relieved by defaecation. In contrast, patients with proctitis usually present with rectal bleeding, urgency, tenesmus, and occasionally severe constipation. Anal and minor perianal lesions may complicate severe diarrhoea, but although simple fistulae may occasionally occur in UC, recurrent or complex perianal fistulae should always raise the suspicion of Crohn’s colitis.
The onset of UC is usually insidious and symptoms are often present for weeks or even months before medical advice is sought. The disease may present with intermittent episodes of symptoms or as a severe attack (in about 15%) with systemic symptoms including weight loss, fever and tachycardia, or even nausea and vomiting. Extra-intestinal manifestations, especially an axial or peripheral arthropathy, episcleritis and erythema nodosum may accompany the presentation in about 10% and rarely precede intestinal symptoms. Thromboembolism is more frequent in UC than the general population, but is generally associated with active disease and pancolitis.

3.2.2. Risk factors for ulcerative colitis

**ECCO statement 3B**

Smoking exerts a universal protective effect against developing UC and is associated with a milder course of disease [EL2b, RGB]. Appendectomy has been shown to provide some protection against subsequently developing UC and in reducing its severity if performed for 'true' appendicitis at a younger age [EL2b, RGB].

The use of non-selective NSAIDs is probably associated with increased risk for exacerbating UC [EL2b, RGB]. Short-term treatment with COX-2 inhibitors is probably safe [EL1b, RGB]. A family history of CD or UC increases the risk for developing UC in another family member [EL2b, RGB].

Active tobacco smoking has a protective effect on the development and severity of UC. In contrast, ex-smokers have about a 70% greater risk of developing the disease, which is often more extensive and refractory than in those who have never smoked. Rates of hospital admission and colectomy are also higher in ex-smokers than in never-smokers. Improvements in symptoms and a milder course of disease have been reported in ex-smokers who resume smoking but the effect is inconsistent. Smoking may also prevent the development of primary sclerosing cholangitis (PSC), or pouchitis after colectomy and ileal pouch anal anastomosis, but this too has been challenged.

Cohort studies and meta-analysis have suggested that appendectomy performed for true appendicitis at an early age may be protective against the onset and subsequent severity of UC. A 69% risk reduction has been reported for appendectomy, although a Danish cohort study failed to confirm this. The protective effect of appendectomy is additional to that of smoking, but does not appear to protect against the development of PSC. When appendectomy is performed after the onset of ulcerative colitis, the effect (if any) on the course of the disease is far less clear.

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) appear to carry a significant risk of exacerbating ulcerative colitis. The magnitude of such risk has never been adequately determined and it is unclear whether all patients are affected to the same degree. In contrast, preliminary evidence from open-label studies and a double-blind controlled trial suggest that short-term treatment with selective COX-2 inhibitors is safer. Nonetheless, prolonged usage is best avoided because of potential adverse effects on other organ systems.

First-degree relatives of patients with UC have a 10–15-fold risk of developing the disease. In a population-based Danish cohort study, the relative risk for developing UC was 10 amongst relatives with the disease. In other terms, the lifetime risk of UC for a first degree relative is around 5%, or a 95% chance of not developing the disease, which may help reassure a parent with UC concerned about the risk to their children. In familial cases of UC there is a slight female preponderance and younger age of onset compared to sporadic cases.

3.3. History, examination and diagnosis

3.3.1. Medical history

ECCO statement 3C

A full medical history should include detailed questioning about the onset of symptoms, particularly recurrent episodes of rectal bleeding or bloody diarrhoea, urgency, tenesmus, abdominal pain, incontinence, nocturnal diarrhoea, and features of extra-intestinal manifestations. Recent travel, food intolerances, contact with enteric infectious illnesses, medication (including antibiotics and non-steroidal anti-inflammatory drugs), smoking habit, sexual practice, family history of IBD and previous appendicectomy should be explored [EL5, RG D].

The diagnosis of UC is suspected from the clinical symptoms (Section 3.2.1). Infectious or drug-induced forms of colitis should be excluded. The absence of rectal bleeding or symptoms in a current smoker should raise questions about a diagnosis of UC, since Crohn’s colitis would be more likely. Enquiry should be made into the family history and patients asked about possible ocular, oral, joint or skin manifestations.

3.3.2. Examination

ECCO statement 3D

In patients with UC physical examination should include general well-being, pulse rate, body temperature, blood pressure, body weight and height, abdominal examination for distension and tenderness, perineal inspection, digital rectal examination, oral inspection, and check for eye, skin and/or joint involvement. Physical examination may be unremarkable in patients with mild or even moderate disease [EL5, RG D].

Findings on physical examination depend on the extent and severity of UC. Examination of patients with mild or moderate activity is usually unremarkable, apart from blood on rectal
3.3.3. Diagnosis

Every patient with active disease at presentation should have a full blood count, inflammatory markers (CRP or ESR), electrolytes and liver function tests, along with a stool sample for microbiological testing. Laboratory signs of chronic inflammation may be normal in mild or moderate distal UC. The full blood count may reveal thrombocytosis as a result of the chronic inflammatory response, anaemia indicating disease severity or chronicity and leucocytosis, raising the possibility of an infectious complication.

For UC excluding proctitis, CRP broadly correlates with clinical activity. In patients with severe clinical activity, an elevated CRP is generally associated with an elevated ESR, anaemia and hypoalbuminaemia. These have been used as predictive biomarkers to assess the need for colectomy in acute severe colitis or refractory disease [EL5].

The natural history of UC is characterised by episodes of relapse and periods of remission, and occasionally by an unremitting, continuous course (about 5%). A single acute episode followed by prolonged remission may also occur in about 5%. The frequency of relapse (pattern of disease) is usually defined in the first 3 years, and may be characterised as frequent (≥ 2 relapses/year) or infrequent (≤ 1 relapse/year) [EL2, Section 1.2.7 and 2.2.1].

It helps patients to establish the diagnosis, extent and severity of the disease rapidly, because this influences treatment options and possibly disease progression. Since there is no single pathogenic marker, the diagnosis relies on a combination of medical history, endoscopic findings, histological features on multiple colonic biopsies and negative stool tests for infectious causes. It is unreasonable to expect the histopathologist alone to make the diagnosis (Section 4), but normal mucosal biopsies effectively exclude active UC as a cause of symptoms. In 10% of patients during the 5 years after initial onset of symptoms, the diagnosis will be changed to Crohn's disease or the diagnosis of inflammatory bowel disease discounted. Endoscopic and histological confirmation of the diagnosis is considered essential. In a minority of patients it is not possible to characterise the cause of colitis: see Section 1.1 for correct usage of the terms 'colitis-yet-to-be-classified' and 'indeterminate colitis'.

3.4. Investigation and procedures to establish a diagnosis

3.4.1. Initial investigations

ECCO statement 3F

Initial laboratory investigations should include a full blood count, serum urea, creatinine, electrolytes, liver enzymes, iron studies, and C-reactive protein (CRP) [EL5, RG D]. CRP and erythrocyte sedimentation rate (ESR) are useful markers to monitor the response to treatment in severe colitis [EL2b, RGB]. Microbiological testing for infectious diarrhoea including Clostridium difficile toxin is recommended [EL2b, RG B]. Additional stool tests may be necessary for patients who report a recent travel abroad [EL5, RG D].

ECCO statement 3G

In patients with an established diagnosis of UC microbial testing is recommended in cases of severe or refractory relapse. This includes testing for Clostridium difficile and Cytomegalovirus infection [EL4, RG C].

It is not routinely recommended to screen for pathogens such as C. difficile at each flare of the disease, due to infrequent positive results. In contrast, microbial stool tests should be performed during refractory or severe relapse, and in those with a history of antibiotic therapy within an arbitrary 3 months, since C. difficile infection is more common in these circumstances and associated with a poor clinical outcome. Flexible sigmoidoscopy may be superior to stool C. difficile cytotoxin assay in patients with pseudomembranous colitis and is appropriate for patients with diarrhoea where the stool test is negative. Reactivation of Cytomegalovirus (CMV) is common in ulcerative colitis, particularly (but not invariably) in immunosuppressed patients with severe colitis. The clinical relevance of this finding remains uncertain, but CMV infection may cause refractory or severe relapse. The optimal method for detecting clinically relevant CMV infection in patients with colitis has not yet been established. Occasional intranuclear inclusion bodies consistent with CMV on histopathology do not necessarily indicate clinically significant infection, but multiple intranuclear inclusions are usually significant.

CMV should be considered in patients with refractory or severe colitis (Section 3.5.3) and if detected, advice taken from virologists about the significance and appropriate therapy.
3.4.3. Biomarkers

**ECCO statement 3H**

Although faecal inflammatory markers are generally not considered sufficient to be included routinely in the diagnostic work up of UC, calprotectin, a neutrophil-derived protein, merits further consideration [EL2b, RGB]

The most widely studied serological markers are perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA). In most series pANCA are found in up to 65% of patients with UC and in less than 10% of patients with Crohn’s disease. It should be noted that the incidence of pANCA in UC may depend upon local laboratory expertise and geographical latitude.121,122 In view of the current limited sensitivity of these markers, their routine use for the diagnosis of ulcerative colitis and for therapeutic decisions is not clinically justified.123

Of the faecal markers of intestinal inflammation, neutrophil-derived proteins such as calprotectin, elastase, lysozyme and lactoferrin, have been evaluated in IBD.124-126 Faecal calprotectin appears to be the most sensitive, non-invasive biomarker that reflects intestinal inflammation in established IBD.127 However, as with all faecal tests, calprotectin lacks the specificity to discriminate between types of inflammation. Therefore, its use as a diagnostic tool in UC is limited.

3.4.4. Procedures recommended to establish the diagnosis

**ECCO statement 3I**

For suspected UC, colonoscopy, preferably with ileoscopy, and segmental biopsies including the rectum are the preferred procedures to establish the diagnosis and extent of disease [EL5, RGD]. Patients with a severe attack should have abdominal radiography and active disease confirmed by sigmoidoscopy as a first line procedure [EL5, RGD]

Colonoscopy with intubation of the terminal ileum and segmental mucosal biopsies are preferred to sigmoidoscopy for patients with suspected UC. The clinical context and availability needs to be considered: colonoscopy and bowel preparation is best avoided in patients with acute severe colitis to avoid procedural delays and a higher risk of perforation. Colonoscopy establishes the diagnosis and disease extent in the large majority of cases. It appears to be more cost-effective than index sigmoidoscopy.60,128

A plain abdominal radiograph is not a diagnostic test for UC, but is valuable in the initial assessment of patients with suspected severe UC (Section 3.5.3). Oesophagogastroduodenoscopy and mucosal biopsy are recommended in patients with upper gastrointestinal symptoms. Wireless capsule endoscopy (WCE) represents an advance in bowel imaging, but large prospective studies are needed to confirm the diagnostic relevance in ulcerative colitis.

WCE is a potentially useful clinical technique for categorising those patients with colitis yet to be classified, although a normal WCE does not exclude Crohn’s disease.129

3.5. Assessment of extent, severity and activity

**3.5.1. Signs of discontinuous inflammation in ulcerative colitis**

**ECCO statement 3J**

When there is macroscopic and histological rectal sparing, or the presence of a caecal patch in newly diagnosed colitis evaluation of the small bowel is indicated [EL 5, RGD]. Involvement of the appendix only in left sided or extensive colitis is a common feature of UC and requires no further diagnostic work up to exclude CD [EL 3a, RGC]

3.5.1.1. Rectal sparing and caecal patch. Macroscopic and microscopic rectal sparing have been described in children presenting with UC prior to treatment.130-133 In adults, a normal or patchy inflammation in the rectum is more likely to be due to topical or systemic therapy for UC.134,135 Patchy inflammation in the caecum is referred to as ‘caecal patch’ and is observed in patients with left-sided colitis. The natural history of patients with patchy right colonic inflammation seems to be similar to those with isolated left-sided UC.136,137 Whenever there is a discontinuous pattern of inflammation in colitis, a diagnostic work up of the small bowel is indicated to exclude Crohn’s disease.

3.5.1.2. Appendiceal skip lesions. Involvement of the appendix as a skip lesion is reported in up to 75% of patients with UC.93-95 Appendiceal inflammation has been associated both with a more responsive course of disease and a higher risk of pouchitis after ileal pouch anastomosis.138-141 Both findings require confirmation.

3.5.1.3. Backwash ileitis. Continuous extension of macroscopic or histological inflammation from the caecum into the most distal ileum is defined as ‘backwash ileitis’. It is observed in up to 20% of patients with pancolitis. Rarely, ileal erosions may occur in patients without caecal involvement and this challenges the pathogenic theory that backwash ileitis is caused simply by reflux of caecal contents into the ileum.142-144 A more refractory course of ulcerative colitis has been suggested in those with backwash ileitis.143 Additional imaging of the small bowel should be considered in cases of macroscopic backwash ileitis, to differentiate UC from Crohn’s disease.

3.5.1.4. Small bowel. Small bowel radiology (by enteroclysis, follow-through, CT enteroclysis, MR enteroclysis, or WCE (reviewed in the ECCO Consensus on diagnosis and imaging in Crohn’s disease145) is not routinely recommended. Where there is diagnostic difficulty (rectal sparing, atypical symptoms, macroscopic backwash ileitis) then clinicians should discuss imaging with an appropriate radiologist and results viewed in the context of the clinical history.145
3.5.2. Activity indices in ulcerative colitis

**ECCO statement 3K**
Instruments for measuring clinical and/or endoscopic disease activity in UC are available, but none has been subjected to an adequate validation process. In daily routine such indices are barely used. The incorporation of a simple clinical and/or endoscopic scoring system is desirable, intended to improve care of UC patients and to realise a standardised IT system for IBD. Immediate admission to hospital is warranted for all patients fulfilling Truelove & Witts’ criteria for severe colitis to prevent delayed decision-making which may lead to increased perioperative morbidity and mortality [EL4, RGD].

Clinical, endoscopic and combined activity indices for ulcerative colitis have been reviewed13 (Sections 1.1.2 and 2.2.2). At present, disease activity scoring for UC is the preserve of clinical studies. However, based on the need to standardise documentation of IBD patients on a European level, the incorporation of a simple, valid clinical and/or endoscopic scoring system in electronic patient files is warranted. The original classification of severe UC was proposed by Truelove and Witts in 195513 and has stood the test of time, ranted. The original classification of severe UC was proposed by Truelove & Witts in 195513 and has stood the test of time, however, based on the need to realise a standardised IT system for IBD. Immediate admission to hospital is warranted for all patients fulfilling Truelove & Witts’ criteria for severe colitis to prevent delayed decision-making which may lead to increased perioperative morbidity and mortality [EL4, RGD].

**3.5.3. Investigations for acute severe colitis on admission**

Patients should have their full blood count, inflammatory markers (C-reactive protein, or ESR), electrolytes and liver function tests measured, along with a stool sample for culture and assay for *C. difficile* toxin.146

A plain abdominal radiograph should be performed, not only to exclude colonic dilatation (≥ 6.0 cm), but also to estimate the extent of disease and look for features that predict response to treatment. The proximal extent of disease broadly correlates with the distal distribution of faecal residue; in 51 episodes of severe colitis, this guide overestimated the extent in 18% and underestimated it in 8%.108 The presence of mucosal islands (small, circular opacities representing residual mucosa isolated by surrounding ulceration), or more than two gas-filled loops of small bowel on the radiograph are associated with a poor response to treatment.146

A flexible sigmoidoscopy should confirm the diagnosis of severe colitis and help exclude infection, particularly with *Cytomegalovirus*.116,117,149 If it is strongly suspected that CMV might be responsible for deterioration (such as a patient on immunomodulators in association with a high fever), it is appropriate to request urgent histopathology. An answer can be available within 4 h. Phosphate preparation before flexible sigmoidoscopy is considered safe, but is probably best avoided in patients with a dilated colon. Full colonoscopy in patients with acute severe colitis is not recommended. Purgative preparation can provoke dilatation and colonic perforation is a real hazard of colonoscopy during active disease. Endoscopic criteria for severe colitis include extensive mucosal abrasions, deep ulcerations, mucosal detachment on the edge of these ulcerations and well-like ulceration,150,151 but all of these can be assessed at flexible sigmoidoscopy.

3.5.4. Reassessment of extent and severity of ulcerative colitis

**ECCO statement 3L**
Routine colonoscopy for patients with UC in remission is unnecessary until the start of a surveillance programme [EL5, RGD]. Endoscopic reassessment is appropriate at a relapse, or for steroid-dependent or -refractory UC or when considering colectomy [EL5, RGD].

Despite the importance of disease location in determining the prognosis, the risk of cancer and the choice of therapy, the appropriateness of periodic restaging after index colonoscopy has never been studied. The value of endoscopic reassessment of disease extent prior to a surveillance programme is much debated. Consequently ECCO statement 3L only represents expert opinion. Colonoscopy is more sensitive than barium studies for estimating disease extent, but the risk of malignancy is historically based on contrast studies and colonoscopy defines a different extent to histopathology.60,152–154 Chromoendoscopy better correlates with the disease extent determined by histopathology, but the procedure is time consuming and requires a level of expertise not universally available.155 Drug-induced clinical remission may not be associated with endoscopic or histological remission, but the prognostic implications of endoscopic re-evaluation in quiescent disease have yet to be determined.60 The area calls for systematic study.

3.6. Endoscopy, ultrasound and colonography

3.6.1. Endoscopic features of ulcerative colitis

**ECCO statement 3M**
No endoscopic feature is specific for UC. The most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation and rectal involvement. [EL2b, RGB] Endoscopic severity of UC may be best reflected by the presence of mucosal friability, spontaneous bleeding and deep ulcerations [EL2b, RGB].

Endoscopic changes characteristically commence proximal to the anal verge and extend proximally in a continuous, confluent and concentric fashion. The demarcation between inflamed and normal areas is usually clear and may occur abruptly within millimetres, especially in distal disease. The endoscopic features of mild inflammation are erythema, vascular congestion of the mucosa and loss of visible vascular pattern. Moderately active colitis is characterised by a coarse granular
3.6.2. Abdominal ultrasound and scintigraphy in ulcerative colitis

**ECCO statement 3N**
Transabdominal and hydrocolonic ultrasound are of secondary value for defining the extent of UC [EL3, RGC]. Doppler ultrasound is a complementary technique for assessing disease activity in expert hands [EL2b, RGD]

Abdominal ultrasound screens for small bowel or colonic inflammation with a sensitivity of 80–90%. Ultrasound has the advantage of being low cost and non-invasive, but the accuracy is very much dependent on the skill of the operator and there is low specificity for differentiating UC from other causes of colonic inflammation.160–162 Hydrocolonic ultrasound (abdominal ultrasonography in conjunction with retrograde instillation of water in the colon) has a high sensitivity for identifying active colitis, but the method is too cumbersome for day to day clinical practice.163 Doppler ultrasound of the superior and inferior mesenteric arteries has been used to evaluate disease activity and risk of relapse. It should not, however, be considered a standard procedure.164,165 For this method to be viable, further prospective, multi-centre studies are needed.

Leukocyte scintigraphy is safe, non-invasive and potentially allows assessment of the presence, extent and activity of inflammation, but the method lacks specificity.166,167 It is unreliable if patients are taking steroids. Novel markers to detect intestinal inflammation which are not associated with exposure to radiation are being developed.

3.6.3. Virtual colonography in ulcerative colitis

**ECCO statement 3O**
Virtual colonography is an evolving technology. The limited data currently available do not demonstrate a diagnostic value for assessing the disease extent in patients with suspected or proven UC [EL4, RGC]

Few studies on a limited number of patients have investigated MR-colonography or CT-colonography in UC. The results are conflicting and subtle changes of the mucosa such as erosions or flat polyps are insufficiently visualized.168–170 Because of these limitations, virtual colonoscopy is no alternative to standard colonoscopy in patients with UC at present.

3.7. Colonic stenosis in ulcerative colitis

**ECCO statement 3P**
Each colonic stenosis in UC should raise the suspicion of colorectal carcinoma. Multiple biopsies should be taken and a surgical opinion should be sought. When endoscopic intubation of the colon is not possible, imaging procedures, such as double contrast barium enema, CT and/or MRI colonography may be employed [EL5, RGD]

In longstanding ulcerative colitis, a colonic stricture signifies an increased risk for colorectal carcinoma and requires histological and surgical expertise.171 If colonoscopy is incomplete due to stricture, then double or even single contrast barium enema is the first choice procedure.172 CT colonography can reveal the mucosal pattern and colitis proximal to a stricture but may not identify all lesions seen on colonoscopy.173

4. Histopathology

4.1. General

In ulcerative colitis, histopathology is used for diagnosis, the assessment of disease activity and the identification of intraepithelial neoplasia (dysplasia). The latter will be addressed separately.

4.1.1. Considerations

Several factors have influenced the accuracy of the histopathological diagnosis of ulcerative colitis, as it has in Crohn’s disease. The advent of colonoscopy as the diagnostic procedure of choice has had consequences. It has allowed the analysis of multiple biopsies from different segments of the colon. More biopsies are obtained, often early in the evolution of the disease. Furthermore, biopsies can be obtained in young children presenting with bloody diarrhoea. In addition, the introduction of new therapies inducing mucosal healing has made the pathologists aware of the impact of treatment upon the microscopic features. This has changed the approach to histopathological diagnosis in the past decade.

4.1.2. Evaluation of the literature

Articles reporting original research into the reproducibility, sensitivity, specificity and predictive value of individual features useful for the histopathological diagnosis of ulcerative colitis were sought from the literature, using Medline and Pubmed. As selection criteria, only those features which achieved moderate reproducibility judged by the kappa statistic, or findings confirmed by several studies were considered. In addition, we have reviewed studies describing and defining diagnostic microscopic features.174–193 The literature can be divided into groups, depending upon the number (one, or multiple) of biopsies examined, or the duration of the disease. In ten studies multiple biopsies were examined (including two comparing the diagnostic value of both single and multiple biopsies).184–193
The literature on the duration of the disease can also be divided. The first group is composed of studies with biopsies obtained in patients with an established diagnosis of ulcerative colitis, based on extended clinical follow up. Disease duration varies between 6 ± 3 weeks and 12 years. In these studies patients with doubtful criteria were generally excluded. A second group is composed of retrospective studies without clear data on the duration of the disease. These papers are retrospective studies and can be pooled with the first group, because the diagnosis is again established through a period of follow up. A third group applies to studies on biopsies obtained early after onset of the disease, before treatment. For early onset disease, the duration of disease varies between 4 and 14 days (3.69±0.52 days after the appearance of rectal bleeding, or 10 days after initial symptoms). In these studies, the diagnosis was subsequently confirmed by follow up of the patients and are prospective studies. Children are mainly included in the third group.

4.2. Microscopic features — definitions

A large number of microscopic features have been evaluated. They can be broadly classified into

- architectural features
- epithelial abnormalities, and
- inflammatory features.

Architectural features include crypt branching, crypt distortion, crypt atrophy and surface irregularity. Epithelial cell abnormalities are mucin depletion and Paneth cell metaplasia. Inflammatory features include increased lamina propria cellularity, basal plasmacytosis, basal lymphoid aggregates, lamina propria eosinophils.

4.2.1. Crypt architectural abnormalities

Crypt branching: two or more branched (bifurcated) crypts in a well oriented section, whether the branching is in the vertical or horizontal axis. When applied to a single crypt, the feature is less specific. The pathogenesis can be accounted for by regeneration following previous damage or destruction (cryptolysis).

Mucosal (crypt) distortion: irregularities in crypt size (i.e. variable diameter), spacing, orientation (i.e. loss of parallelism), or shape (including branching with a cystic configuration). In some studies this includes separation from the underlying muscularis mucosae. Samples from the anal transition zone or columnar cuff (sometimes wrongly termed "low rectal biopsies") are not suitable for the assessment of crypt branching or mucosal distortion.

Mucosal (crypt) atrophy and crypt density: a combination of crypt depletion (thinned-out crypts, generally recognised by a distance of more than one crypt diameter between crypts) and an increase in the distance between the muscularis mucosae and the base of the crypts. Some authors emphasise either crypt depletion or an increased distance between the muscularis mucosae and the base of the crypts rather than both features. An increase in the intercryptal space and the crypt–muscularis mucosae mucosal distance may be normal in the caecum and distal rectum. The distance between the muscularis mucosae and the crypt base should not be evaluated in the vicinity of lymphoid follicles. The pathogenesis can be explained as a consequence of crypt death from disease. If all crypt cells die, crypts cannot regenerate and disappear within 48 h in experimental animals. However, if one or more clonogenic cells survive the insult, rapid proliferation regenerates the crypt within 72–96 h in experimental animals. The mucosa subsequently heals by clonal expansion and the number of crypts that survive to regenerate following a cytotoxic insult correlates with symptom severity in animal models. A number of growth factors affect crypt regeneration in murine models. Nevertheless, it remains unclear what size of (uncrushed) biopsy is adequate for proper evaluation and how many levels of the biopsy need to be examined properly to evaluate atrophy.

Surface irregularity: Surface irregularity (synonyms include villous surface, villiform surface, or villous mucosa) means wide crypt mouths, giving the mucosal surface a finger-like appearance. The impression is due to separation of crypts and a semantic distinction between "irregular surface" and "villous surface" has been proposed, according to the villous–crypt ratio.

4.2.2. Epithelial cell abnormalities

Paneth cell metaplasia: Paneth cells are normally extremely uncommon in the colon distal to the splenic flexure, being present in 0–1.9% of non-IBD controls. The presence of Paneth cells in the distal colon can be termed Paneth cell metaplasia. The pathogenesis is related to epithelial regeneration and repair.

Mucin depletion: defined as a reduction in number of goblet cells or depleted mucin within cells.

4.2.3. Inflammatory features

Basal plasmacytosis: defined either as the presence of plasma cells around (deep 1/5th of the lamina propria) or below the crypts, alongside or penetrating the muscularis mucosae. Basal plasmacytosis is also referred to as subcryptal plasma cells, plasmacytosis with extension in the base of the mucosa, or accumulation of plasma cells between the base of the crypts and the muscularis mucosae. The abnormality can be focal or diffuse and subcryptal location of the cells is not always present.

Lamina propria cellularity: evaluated according to density, composition and distribution. An increase in the total number of plasma cells, lymphocytes, histiocytes and eosinophils is a feature of all types of colorectal inflammation and is of limited discriminant value. In ulcerative colitis the cellular infiltrate is diffuse and transmucosal.

Increased density has been described as "a subjectively abnormal" infiltrate, a "prominent" increase (assessed by widening of the intercryptal space by the inflammatory infiltrate or simple "hypercellularity"). The increase is difficult to quantify. Increased lamina propria cellularity may also be absent in quiescent disease, following treatment, or in the natural course of the disease. Furthermore, increased lamina propria cellularity may persist in infective colitis and is a normal feature of caecal biopsies.
The composition has been examined to resolve these dilemmas. Some authors discriminate between an increase in neutrophils alone and an increase in both round cells and neutrophils. Neutrophils may be present in the lamina propria or between epithelial cells, are readily recognised and a reproducible feature of inflammation. More than three neutrophils in the lamina propria outside capillaries may be abnormal, but the exact number has not been agreed. Neutrophils are a feature of cryptitis with migration of neutrophils through the crypt epithelium, inducing crypt disruption and crypt abscesses, which may be responsible for cell surface damage or disruption. The diagnostic value of neutrophils in ulcerative colitis, however, is limited because they are also present in infective colitis and other forms of colitis. In contrast, eosinophils in the lamina propria are highly variable. An increase has been noted in ulcerative colitis and a potential diagnostic value has been proposed, but data were obtained from studies of longstanding disease.

The distribution of the lamina propria cellular inflammatory infiltrate has been divided into: focal (normal background cellularity with areas of increased cellularity); patchy (abnormal background cellularity with variable intensity); and diffuse (abnormal background cellularity with an overall increase in density). These terms are preferred. Confusion is caused when the term "discontinuous" is used to describe both focal and patchy changes in some studies, or used as a synonym for focal in others. A diffuse increase can be either superficial (confined to the superficial and middle thirds of the lamina propria) or transmucosal (usually maximal in the lower third). The distribution can be evaluated in a single sample or between multiple samples from the same site. To avoid diagnostic error, the criteria of diffuse transmucosal inflammation for diagnosing ulcerative colitis should be avoided in biopsies from early onset disease in children, or after treatment and when disease is resolving or quiescent. In these circumstances the biopsy may be normal or show focal changes.

Basal lymphoid aggregates: nodular collections of lymphocytes between the crypt base and muscularis mucosae, without germinal centres. At least two aggregates are needed for this feature to be considered abnormal. Stromal changes: diffuse thickening of the muscularis mucosae or a double muscularis mucosae (which is unusual, but characteristic when present) have been observed in longstanding active and quiescent ulcerative colitis.

Backwash ileitis: ileal inflammation in ulcerative colitis is called backwash ileitis, despite the fact that the backwash or reflux pathogenesis has never been established. "Backwash ileitis" should be in continuity with colonic inflammation (see also Section 3.5.1) and the lesions in the caecum should show a similar, or greater degree of active inflammation. The ileal lesions in 'backwash ileitis' are characterised by active inflammation in the villi and lamina propria, together with shortening and blunting of the villi. Focal, isolated ileal erosions, mucous gland metaplasia or patchy oedema with mild active inflammation are features suggestive of Crohn's disease.

### 4.3. Microscopic features — appraisal of the diagnosis

#### 4.3.1. Early stage disease

It has been proposed that a non-specific increase in the inflammatory infiltrate in the lamina propria in combination with absent crypt architectural distortion, indicates a diagnosis of acute, infective colitis rather than ulcerative colitis. This finding, however, is not confirmed in those studies of patients with early onset colitis (within 10 days of symptoms, Section 4.1.2). Basal plasmacytosis at the initial onset has a high predictive value for the diagnosis of IBD.

#### ECCO Statement 4A

For a reliable diagnosis of ulcerative colitis multiple biopsies from five sites around the colon (including the rectum) and the ileum should be obtained. Multiple implies a minimum of two samples.

#### ECCO Statement 4B

Biopsies should be accompanied by clinical information including the age of the patient, duration of disease and duration and type of treatment. Biopsies from different regions should be handled in such a way that the region of origin can be identified. This can be done by using different containers, multiwell cassettes, or an acetate strip. All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport. It is recommended that multiple sections from each sample are examined.

#### ECCO Statement 4C

Basal plasmacytosis at the initial onset has a high predictive value for the diagnosis of IBD. Repeat biopsies after an interval may help to solve differential diagnostic problems and establish a definitive diagnosis especially in adults, by showing additional features.
biopsies obtained from patients with colitis at an early stage.\textsuperscript{181} Crypt architectural changes were observed in biopsies obtained between 16 and 30 days after onset,\textsuperscript{181} but not in earlier biopsies. In another study\textsuperscript{185} abnormal architecture was found in all biopsies obtained within days of onset, but in this study disease onset was defined by loss of blood and not by other symptoms. Crypt distortion and mucosal atrophy may return to normal or remain unchanged after resolution of symptoms.\textsuperscript{198,199}

**ECCO Statement 4D**

In young children or patients with an aberrant presentation of colitis, UC should always be considered in the differential diagnosis even if the pathology is not typical [EL1b RG B]

Reliable diagnostic features may be absent from biopsies obtained in early onset disease, in acute severe colitis, or in patients with an atypical immunological response (such as young children, or patients with primary sclerosing cholangitis). The routine use of additional techniques such as immunohistochemistry is not recommended at present.

### 4.3.2. Established disease

**ECCO Statement 4E**

A diagnosis of established ulcerative colitis is based upon the combination of: basal plasmacytosis (defined as presence of plasma cells around (deep part of the lamina propria) or below the crypts (subcryptal)), heavy, diffuse transmucosal lamina propria cell increase and widespread mucosal or crypt architectural distortion [EL 1a, RG A]

The exact number of features needed for diagnosis has not been established. A correct diagnosis of ulcerative colitis is reached in approximately 75% of the cases when two or three of the four features, severe crypt architectural distortion, severe decreased crypt density, irregular surface and heavy diffuse transmucosal inflammation are present, in the absence of genuine granulomas.\textsuperscript{186,191}

**ECCO Statement 4F**

Widespread mucosal or crypt architectural distortion, mucosal atrophy and a villous or irregular mucosal surface appear later during the evolution of the disease (4 weeks or more). They suggest a diagnosis of ulcerative colitis in established disease [EL 2, RG B]

In established ulcerative colitis a villous surface is present in 17–63% of the cases (compared to 0–24% for Crohn's disease and 0–7% for infective colitis).\textsuperscript{194} The lesion is observed in approximately one third of the initial biopsies of children with ulcerative colitis.\textsuperscript{190} In adults this feature was present in approximately 23% of the patients presenting 16–30 days after the initial symptoms, but not in earlier biopsies.\textsuperscript{181}

**ECCO Statement 4G**

Basal plasmacytosis is a good diagnostic feature in established ulcerative colitis [EL 2, RG B]. A heavy, diffuse transmucosal lamina propria cell increase is a good diagnostic feature in established active disease [EL 2, RG B]. Distribution of inflammation along the colon, with a decreasing gradient of inflammation from distal to proximal is in favour of a diagnosis of ulcerative colitis in an untreated patient [EL5 RG D]

The diagnostic value of basal plasmacytosis is confirmed by studies of biopsies obtained in established disease, being present in up to 63% of cases.\textsuperscript{186} The feature is rare in non-IBD colitis,\textsuperscript{182} but it is also common in Crohn's disease. Basal plasmacytosis decreases and can disappear during treatment.

A heavy, diffuse, transmucosal, lamina propria cell infiltrate favours a diagnosis of ulcerative colitis,\textsuperscript{194} but patchy inflammation\textsuperscript{178} can occasionally be seen in ulcerative colitis or, when multiple biopsies are examined, a single piece may have evidence of chronic colitis and others have normal mucosa.\textsuperscript{190,198,205} The heavy, diffuse transmucosal lamina propria cell increase can be absent in young children (<12 years). It can decrease in intensity and become patchy during the natural evolution of the disease or subsequent to treatment. This feature is therefore mainly useful for the diagnosis in established disease. Its absence does not exclude a diagnosis of ulcerative colitis.

**ECCO Statement 4H**

General or widespread crypt epithelial neutrophils (cryptitis and crypt abscesses) favour ulcerative colitis. However these lesions may occur in infections and other types of colitis [EL 2b, RG B]. Lamina propria and intraepithelial neutrophils are absent in inactive or quiescent disease [EL 2b, RG B]

General or widespread crypt epithelial neutrophils favour a diagnosis of ulcerative colitis, but crypt abscesses and cryptitis can also occur in infective colitis, although they are less prominent.\textsuperscript{18} Neutrophils are absent during inactive or quiescent disease.

Basal lymphoid aggregates favour a diagnosis of established ulcerative colitis, but may occur in Crohn's colitis\textsuperscript{177,182} and are not useful in early onset disease.
Paneth cell metaplasia favours a diagnosis of ulcerative colitis.\(^{187}\) The predictive value is high but the sensitivity is low.\(^{182}\) It is not seen in biopsies obtained early in the disease\(^ {177,181}\) and appears to be related to established disease.\(^{196}\) Mucin depletion also favours a diagnosis of ulcerative colitis. It correlates with disease activity, so is a helpful, but not pivotal diagnostic feature.\(^{193}\) Mucin preservation in association with active disease, however, may favour a diagnosis of Crohn’s disease rather than ulcerative colitis.\(^{188}\)

### 4.4. Microscopic features — disease activity

Disappearance of mucosal inflammation following treatment has been observed,\(^{199}\) so biopsies are also used for distinguishing between quiescent and active disease, as well as different grades of activity. Scoring systems have been introduced for the assessment of disease activity, particularly for therapeutic trials. The potential value of histopathology for predicting relapse and evaluating adequate control of inflammation has implications for therapeutic management and reducing the risk of neoplasia. Both epithelial damage in association with neutrophils and basal plasmacytosis have been proposed as markers of disease activity and the prediction of relapse.\(^{206-209}\) The scope of this text does not permit detailed analysis of these scoring systems.

### 4.5. Conclusions

The evolution of the microscopic features that are useful for a diagnosis of ulcerative colitis is a time and disease-activity dependent process. This notion is confirmed by experimental studies. In early onset disease, few or no characteristic features may be present. In established disease the diagnosis can be based upon a combination of basal plasmacytosis, crypt architectural abnormalities, diffuse transmucosal inflammatory infiltrate and epithelial surface irregularity. The natural evolution from active to quiescent disease and treatment also have an impact on microscopic features. In quiescent disease, few features may persist, neutrophils are notably absent and biopsies may be normal.

It appears important to distinguish between different situations for the diagnosis of ulcerative colitis:

- Biopsies obtained during the initial phase of the disease (within two weeks of onset of symptoms, including young children and without treatment)
- Biopsies obtained from patients with established disease before treatment (symptoms for more than 4–6 weeks)
- Biopsies obtained from patients with established disease after treatment (examination of previous biopsies is desirable).

In every patient, including children, the diagnostic yield can be increased when multiple biopsies from different segments of the colon are examined, including the rectum and the ileum, although these should be carefully labelled for proper assessment.\(^{191,192,210,211}\)

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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 Trueove & Wiltts 3: any patient who has a bloody stool frequency ≥6/day and a tachycardia (>90 bpm), or temperature >37.8 °C, or anaemia (haemoglobin <10.5 g/dL), or an elevated ESR (>30 mm/h) has severe ulcerative colitis (Table 1.3). 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 ≥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: beclometasone 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 SASA 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 sulfasalazine (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 \((p<0.01)\) (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\(^{26}\). 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 bioavailability such as beclomethasone dipropionate or budesonide are becoming available. In the largest and most recent study of 177 patients with active left-sided or extensive colitis, beclomethasone dipropionate 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 B]. 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 \((p=0.03)\).\(^{28}\) 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 sulphalazaline and steroid enemas. Similar findings were reported by Lennard-Jones, 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. Oral steroids with low systemic bioavailability (budesonide or prednisolone metabolites, with colonic release mechanisms) are available or being developed.

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

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, 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. Bolus injection is as effective as continuous infusion. Treatment is usually given for about 5 days, since extending therapy beyond 7 to 10 days carries no benefit.

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). 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.

### 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].
Potassium supplementation of at least 60 mmol/day is almost invariably necessary. Hypokalaemia or hypomagnesaemia can promote toxic dilatation.39

- Sigmoidoscopy or proctoscopy 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%). Bowel rest through intravenous nutrition does not alter the outcome, 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, NSAIDs 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 CsA50 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 acquiesce 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 diagnosis51,52 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 Index55,56 (Section 11.3.3).

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 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.66 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 4.5.7). 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 patients64 and 88% of 142 patients65 came to colectomy over 7 years. A Cochrane review66 concluded that numbers in controlled trials were so few (only 5066) 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 4.5.7). 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 Index64 on day 3 identified sicker patients at an earlier stage than the Seo Index65 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 studies78 (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 in 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>
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<th>Case series of tacrolimus for steroid-refractory ulcerative colitis, compared to a case series of ciclosporin therapy in similar patients</th>
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<td>Ciclosporin (iv 4 mg/kg, then oral)</td>
<td>76</td>
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<tr>
<td>Tacrolimus iv 0.01/oral 0.2 mg/kg</td>
<td>38</td>
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<td>Tacrolimus iv 0.01 mg/kg</td>
<td>23</td>
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<td>Tacrolimus oral 0.15 mg/kg</td>
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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. The incidence has never been studied systematically. About 5% of patients with acute, severe colitis admitted to hospital will have toxic dilatation, so these should be corrected or avoided.

Clinical practice guidelines recommend a low threshold for early colectomy will be necessary. Early 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.

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. Nasogastric suction cannot be expected to decompress the colon and is unnecessary. The classic knee-elbow position may relieve distension, 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%. Other complications appear exceptional, including massive haemorrhage (1/66 patients operated on for acute severe colitis in one series), cerebral sinus thrombosis and a poorly recognised panenteritis. 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.

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). 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-oriented 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. 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). 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 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%. 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). 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. There was a significant decrease after surgery in mean (SD) diurnal stool frequency (8.2(4) vs 4.7(2) 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. 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. 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 1.2.2, 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.
### Table 5.2 Summary of therapies for distal colitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Proposed mechanism</th>
<th>Dose and duration</th>
<th>Design</th>
<th>n</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthetic gel</td>
<td>Neuroimmune modulation</td>
<td>Lignocaine (800 mg) daily. 6–34 weeks</td>
<td>Open</td>
<td>100</td>
<td>Remission 10% proctitis, 83% distal colitis. Most had refractory disease; response in 6 patients with pancolitis</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lignocaine (600 mg) daily. 6 weeks</td>
<td></td>
<td></td>
<td>12/22 'excellent', 4/22 'very good' response (refractory UC)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ropivacaine (400 mg) daily. 2 weeks</td>
<td></td>
<td></td>
<td>Clinical and endoscopic improvement ($p&lt;0.05$)</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ropivacaine (200 mg) single dose</td>
<td>Random</td>
<td>33</td>
<td>Rectal eicosanoid &amp; neuropeptide concentrations similar after ropivacaine in 19 distal UC compared to 14 controls</td>
<td>102</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Altered Th1/Th2 balance</td>
<td>Surgery</td>
<td>Cases</td>
<td>16</td>
<td>Remission, with no recurrence for up to 3 years</td>
<td>103</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Uncertain</td>
<td>Acetarsol (500 mg) vs prednisolone (5 mg) suppositories. 2 weeks</td>
<td>Random</td>
<td>20</td>
<td>9/10 clinical/endoscopic improvement (refractory distal colitis). Potential toxicity in 6/10 (1 week) 2/10 (4 weeks)</td>
<td>104</td>
</tr>
<tr>
<td>Bismuth compounds</td>
<td>Enhanced mucosal barrier? Reduced bacterial adhesion</td>
<td>Bismuth carbomer (450 mg) enema vs 5-ASA (2 g) enema. 4 weeks</td>
<td>Random</td>
<td>63</td>
<td>Bismuth 39% remission, 56% 5-ASA ($p=0.16$)</td>
<td>105</td>
</tr>
<tr>
<td>Bovine colostrum</td>
<td>Source of growth factors for epithelial restitution</td>
<td>Colostrum 10% (100 mL enema) vs placebo (albumin) 4 weeks</td>
<td>Random</td>
<td>14</td>
<td>Activity index $-2.9 (-0.3$ to $-5.4$) in colostrum group, $vs +0.5 (-2.4$ to $+3.4$) in placebo</td>
<td>106</td>
</tr>
<tr>
<td>Ciclosporin enemas</td>
<td>T-cell immunosuppression</td>
<td>Cyclosporin 350 mg vs placebo. 4 weeks</td>
<td>Random</td>
<td>40</td>
<td>Cyclosporin 40% improvement vs placebo 45%. Open trials in refractory distal UC more favourable</td>
<td>107</td>
</tr>
<tr>
<td>Epidermal growth factor enemas</td>
<td>Epithelial restitution/repair</td>
<td>EGF 5mcg (100 mL enema) vs placebo. 12 weeks</td>
<td>Random</td>
<td>24</td>
<td>83% remission at 4 weeks vs 8% on placebo. Rapid and promising; needs repeating. Concern about malignancy</td>
<td>108</td>
</tr>
<tr>
<td>Ecabet sodium enema</td>
<td>Mucosal protection</td>
<td>Ecabet sodium 1 g in 20–50 mL. 2 weeks</td>
<td>Open</td>
<td>8</td>
<td>Clinical activity index decreased ($5.3+1.4$ to $0.5+0.8$, $p&lt;0.05$)</td>
<td>109</td>
</tr>
<tr>
<td>Immunoglobulin G enemas</td>
<td>Immune response promoter</td>
<td>IgG enema</td>
<td>Open</td>
<td>7</td>
<td>Ineffective. 1/7 improved</td>
<td>110</td>
</tr>
<tr>
<td>Interleukin-10 enemas</td>
<td>? IL-10 deficiency in UC</td>
<td>IL-10 100mcg enema for 10 days</td>
<td>Open</td>
<td>3</td>
<td>Endoscopic response in refractory left-sided colitis</td>
<td>111</td>
</tr>
<tr>
<td>Leukocytapheresis</td>
<td>? monocyte adsorption Smoking protective.</td>
<td>Weekly for 5 weeks</td>
<td>Open</td>
<td>30</td>
<td>Clinical remission 21/30</td>
<td>112</td>
</tr>
<tr>
<td>Nicotine</td>
<td></td>
<td>Transdermal nicotine (15–25 mg) vs placebo 6 weeks</td>
<td>Random</td>
<td>72</td>
<td>Nicotine 48% remission, placebo 24% ($p=0.03$)</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transdermal nicotine vs placebo. 6 m</td>
<td>Random</td>
<td>80</td>
<td>No difference between groups for maintenance therapy</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transdermal nicotine (15–25 mg) vs prednisolone (5–15 mg). 6 weeks</td>
<td>Random</td>
<td>61</td>
<td>Nicotine 21% remission vs 47% prednisolone ($p=0.035$), intention to treat. 11/31 nicotine withdrawals (side-effects)</td>
<td>115</td>
</tr>
<tr>
<td>Agent</td>
<td>Proposed mechanism</td>
<td>Dose and duration</td>
<td>Design n</td>
<td>Outcome</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>---------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>Smoking protective.</td>
<td>Transdermal nicotine vs placebo. 4 weeks</td>
<td>Random 64</td>
<td>Nicotine 39% clinical response, placebo 9% ($p=0.007$)</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transdermal nicotine (15 mg) with 5ASA enema vs enema + mesalazine 2.4 g. 4 weeks</td>
<td>Random 30</td>
<td>Remission 12/15 on nicotine +5ASA enema, 5/15 on oral 5ASA + enema ($p=0.027$)</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicotine tartrate enemas (3–6 mg). 4 weeks</td>
<td>Open 10</td>
<td>5/7 improved (previously unresponsive UC). 3 withdrawals</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicotine carbomer enemas (6 mg). 4 weeks</td>
<td>Open 22</td>
<td>16/17 improved (previously unresponsive). 6 withdrawals</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Propionyl-L-carnitine (PLC) enemas</td>
<td>Epithelial (SCFA) nutrition</td>
<td>PLC 6 g (200 mL) twice daily.</td>
<td>Open 10</td>
<td>8/10 ‘improved significantly’</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Rebamipide</td>
<td>Cytoprotective proprionic acid</td>
<td>Enema twice daily, oral steroids continued</td>
<td>Open 20</td>
<td>55% remission 9 still on steroids) at 3 weeks</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Short chain fatty acids (variable composition)</td>
<td>Epithelial nutrition</td>
<td>SCFA mixture vs 5-ASA or steroid enema. 6 weeks</td>
<td>Random 45</td>
<td>Most improved in all three groups</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCFA mixture vs placebo. 6 weeks</td>
<td>Random 40</td>
<td>70% SCFA clinical response, 20% placebo No change in endoscopic or histology scores</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCFA mixture. 6 weeks</td>
<td>Open 10</td>
<td>5/10 responded well (refractory distal colitis)</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCFA mixture vs placebo. 6 weeks</td>
<td>Random 103</td>
<td>No difference in clinical or histological response</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCFA vs butyrate or placebo. 6 weeks</td>
<td>Random 47</td>
<td>No difference between three groups</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Butyrate vs placebo. 6 weeks</td>
<td>Random 38</td>
<td>No difference</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sucralfat 4 g vs prednisolone metasulphobenzoate 20 mg enemas. 4 weeks</td>
<td>Random 44</td>
<td>Predenema 71% cessation of bleeding, sucralfat 28%</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sucralfat 10 g vs 5-ASA 2 g vs placebo 4 weeks</td>
<td>Random 50</td>
<td>5-ASA superior. Sucralfat no different from placebo</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sucralfat 10 g vs hydrocortisone 100 mg enemas. 4 weeks</td>
<td>Random 40</td>
<td>Hydrocortisone 42% remission, sucralfat 15%, ($p&lt;0.05$)</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sucralfat 20 g vs methylprednisolone 20 mg (100 mL) twice daily. 4 weeks.</td>
<td>Random 60</td>
<td>No difference between groups</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Enhanced mucosal barrier</td>
<td>Sucralfate 4 g vs prednisolone metasulphobenzoate 20 mg enemas. 4 weeks</td>
<td>Random 44</td>
<td>Predenema 71% cessation of bleeding, sucralfat 28%</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sucralfate 10 g vs prednisolone 20 mg enemas. 4 weeks</td>
<td>Random 40</td>
<td>Hydrocortisone 42% remission, sucralfat 15%, ($p&lt;0.05$)</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sucralfate 20 g vs methylprednisolone 20 mg (100 mL) twice daily. 4 weeks.</td>
<td>Random 60</td>
<td>No difference between groups</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Butyrat 4 g vs prednisolone 20 mg enemas. 6 weeks</td>
<td>Random 38</td>
<td>No difference</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisiolone 30 mg enemas. 4 weeks</td>
<td>Random 40</td>
<td>No difference between three groups</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Butyrat 4 g vs prednisolone 20 mg enemas. 6 weeks</td>
<td>Random 38</td>
<td>No difference</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisiolone 30 mg enemas. 4 weeks</td>
<td>Random 40</td>
<td>No difference between three groups</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Butyrat 4 g vs prednisolone 20 mg enemas. 6 weeks</td>
<td>Random 38</td>
<td>No difference</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Thromboxane A2 inhibitor</td>
<td>Inhibition of inflammatory mediator</td>
<td>Ridogrel 300 mg vs prednisolone 30 mg enemas. 4 weeks</td>
<td>Random 40</td>
<td>Ridogrel 65% endoscopic remission vs prednisolone 75% (no difference)</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ridogrel 300 mg (40 mL)</td>
<td>Open 11</td>
<td>Decrease in mucosal TxB2, but not other PGs</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>Wheat grass juice</td>
<td>Prebiotic and antioxidant Triticum aestivum</td>
<td>WGJ (100 mL) vs placebo</td>
<td>Random 21</td>
<td>Decrease in activity index ($p=0.031$) and rectal bleeding ($p=0.025$) compared to controls</td>
<td>134</td>
<td></td>
</tr>
</tbody>
</table>
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).

Systematic reviews and meta-analyses concur that aminosalicylates are effective for treating active UC. 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). 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 MAX mesalazine) show statistical significance vs placebo. Those with olsalazine 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) 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. 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. Proprietary prescribing of mesalazine is recommended, 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>
<thead>
<tr>
<th>Delivery system</th>
<th>Mean peak plasma [5ASA] (μmol/L)</th>
<th>Mean systemic exposure (AUC, μmol/L.h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azo-bond</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0.7–3.5</td>
<td>9.6–27.5</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>1.2–4.5</td>
<td>–</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>2.3–3.5</td>
<td>13.9–22.8</td>
</tr>
<tr>
<td>Controlled release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentasa®</td>
<td>Ethylcellulose coated microgranules</td>
<td>6.5</td>
</tr>
<tr>
<td>pH7-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asacol®</td>
<td>Eudragit-S coating, dissolves at pH7</td>
<td>2.1–10.5</td>
</tr>
<tr>
<td>Mesren®</td>
<td>Same</td>
<td>–</td>
</tr>
<tr>
<td>Ipocol®</td>
<td>Same</td>
<td>–</td>
</tr>
<tr>
<td>pH6-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salofalk®</td>
<td>Eudragit-L coating, dissolves at pH6</td>
<td>10.9</td>
</tr>
<tr>
<td>Mesasal®</td>
<td>Same</td>
<td>5.2 (median)</td>
</tr>
<tr>
<td>Claversal®</td>
<td>Same</td>
<td>–</td>
</tr>
<tr>
<td>Composite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(‘multimatrix’)Mezavant® (EU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lialda® (US)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit-S coating of hydrophilic polymer with some 5ASA and lipophilic excipients encapsulating 5ASA</td>
<td>–</td>
<td>no published data</td>
</tr>
</tbody>
</table>
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,29,157 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 1.54–6.76). 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 corticosteroids 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

### Table 5.4

Placebo-controlled trials of newer aminosalicylates for active UC

<table>
<thead>
<tr>
<th>Drug</th>
<th>$$n$$</th>
<th>Dose, g (n)</th>
<th>Weeks</th>
<th>Remission (unless otherwise stated)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asacol®</td>
<td>87</td>
<td>4.8 (38), 1.6 (11), 0 (36)</td>
<td>6</td>
<td>24% vs 5% (4.8 vs 0, p=0.047)</td>
<td>140</td>
</tr>
<tr>
<td>Schroeder 1987</td>
<td>158</td>
<td>2.4 (53), 1.6 (53), 0 (52)</td>
<td>6</td>
<td>Response 49% vs 23% (2.4 vs 0, p=0.004)</td>
<td>141</td>
</tr>
<tr>
<td>SNinsky 1991</td>
<td>215</td>
<td>6.75 (72), 4.5 (73), 0 (35)</td>
<td>4</td>
<td>Response 45% vs 45% (6.75 vs 0, ns)</td>
<td>27</td>
</tr>
<tr>
<td>Balsalazine</td>
<td>280</td>
<td>4.8 g × 1 (94), 1.2 g × 2 (93), 0 (93)</td>
<td>8</td>
<td>29% vs 13% (4.8 g × 1 vs 0, p=0.009)</td>
<td>23</td>
</tr>
<tr>
<td>Lichtenstein 2007</td>
<td>343</td>
<td>4.8 g × 1 (85), 2.4 g × 1 (84), 0 (86)</td>
<td>8</td>
<td>41.2% vs 40.5% vs 22.1% vs 32.6% (4.8 g × 1 vs 0, p=0.007)</td>
<td>24</td>
</tr>
<tr>
<td>Pentasa®</td>
<td>374</td>
<td>4 (95), 2 (97), 1 (92), 0 (90)</td>
<td>8</td>
<td>29% vs 12% (4 g vs 0, p=0.0012)</td>
<td>142</td>
</tr>
<tr>
<td>Salix (unpublished)</td>
<td>212</td>
<td>4.8 (38), 1.6 (11), 0 (36)</td>
<td>6</td>
<td>24% vs 5% (4.8 vs 0, p=0.047)</td>
<td>140</td>
</tr>
<tr>
<td>Salix (unpublished)</td>
<td>212</td>
<td>2.4 (53), 1.6 (53), 0 (52)</td>
<td>6</td>
<td>Response 49% vs 23% (2.4 vs 0, p=0.004)</td>
<td>141</td>
</tr>
<tr>
<td>Salix (unpublished)</td>
<td>212</td>
<td>6.75 (72), 4.5 (73), 0 (35)</td>
<td>4</td>
<td>Response 45% vs 45% (6.75 vs 0, ns)</td>
<td>27</td>
</tr>
<tr>
<td>MMx mesalazine</td>
<td>280</td>
<td>4.8 g × 1 (94), 1.2 g × 2 (93), 0 (93)</td>
<td>8</td>
<td>29% vs 13% (4.8 g × 1 vs 0, p=0.009)</td>
<td>23</td>
</tr>
<tr>
<td>Lichtenstein 2007</td>
<td>343</td>
<td>4.8 g × 1 (85), 2.4 g × 1 (84), 0 (86)</td>
<td>8</td>
<td>41.2% vs 40.5% vs 22.1% vs 32.6% (4.8 g × 1 vs 0, p=0.007)</td>
<td>24</td>
</tr>
<tr>
<td>Pentasa®</td>
<td>374</td>
<td>4 (95), 2 (97), 1 (92), 0 (90)</td>
<td>8</td>
<td>29% vs 12% (4 g vs 0, p=0.0012)</td>
<td>142</td>
</tr>
<tr>
<td>Salix (unpublished)</td>
<td>212</td>
<td>4.8 (38), 1.6 (11), 0 (36)</td>
<td>6</td>
<td>24% vs 5% (4.8 vs 0, p=0.047)</td>
<td>140</td>
</tr>
<tr>
<td>Salix (unpublished)</td>
<td>212</td>
<td>2.4 (53), 1.6 (53), 0 (52)</td>
<td>6</td>
<td>Response 49% vs 23% (2.4 vs 0, p=0.004)</td>
<td>141</td>
</tr>
<tr>
<td>Salix (unpublished)</td>
<td>212</td>
<td>6.75 (72), 4.5 (73), 0 (35)</td>
<td>4</td>
<td>Response 45% vs 45% (6.75 vs 0, ns)</td>
<td>27</td>
</tr>
</tbody>
</table>

(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
placebo, or a median 146 days compared to 54 days after then maintained for 6 months in 80% compared to 44% on placebo. Remission was only 14% at 6 weeks, but response was 240 mg enema every night for 6 weeks was more effective than A complex dose-ranging protocol in 112 patients showed that a suspended in Q307 when interim analysis showed no benefit. Phase III study in intravenous steroid-resistant UC, however, was 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 were no different to those expected from large experience of treating Crohn’s disease. 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 neoplasias (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 5 microg/kg given on two consecutive days. A Phase III study in intravenous steroid-resistant UC, however, was suspended in Q307 when interim analysis showed no benefit. Alicateforsen 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, or a median 146 days compared to 54 days after then maintained for moderately active UC with moderately active UC. 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, another CD25 inhibitor, daclizumab, was ineffective in a controlled trial of 159 patients with moderately active UC. Cetolizumab has not yet been evaluated for UC. An American–European review on biological therapy for UC has been published.

5.4.5. Thiopurines

5.4.5.1. Efficacy of azathioprine/mercaptopurine. Data on thiopurines for active UC are few. 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. Data from a recent, well conducted study on steroid-dependent active UC are discussed in Section 5.3.3. The main role for thiopurines are as steroid sparing agents (NNT 3). Immumomodulators 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. 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.

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. 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. 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. The only randomised placebo-controlled trial using a dose of 12.5 mg per week of oral MTX in UC showed no benefit. 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 5-ASA 25% for 5-ASA (p<0.05 vs MP, ns vs MTX). 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 (cyclosporin (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 curve189 and an appropriate target appears to be 700 ng/mL, but this has not been correlated with efficacy for UC.

Tacrolimus is more effective when given at a dose that achieves a trough concentration of 10–15 ng/mL.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 treatment63-65 (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 5.2.4,153–156), 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.188 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 (Cellscorb®, 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 prednisolone193 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 (failure to maintain clinical remission) after 6 or 12 months. 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 and endoscopically defined [EL2, RG B].

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. 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. 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 and endoscopically defined [EL2, RG B].

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. In one study of 92 patients, a shorter duration of current remission and a higher relapse frequency were predictive of further relapse. 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. 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. 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. 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.

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. Among the 63/183 patients treated with corticosteroids, 49% had a prolonged response, 22%
were steroid dependent and 29% came to colectomy, but only 3/183 were treated with AZA/MP (see also Section 5.4.2).

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 suppositories215 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>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Study drug</th>
<th>Dosage (g/day)</th>
<th>Duration (months)</th>
<th>Failure to maintain clinical or endoscopic remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misiewicz207</td>
<td>1965</td>
<td>67</td>
<td>SZP</td>
<td>2</td>
<td>12</td>
<td>29%</td>
</tr>
<tr>
<td>Dissanayake208</td>
<td>1973</td>
<td>64</td>
<td>SZP</td>
<td>2</td>
<td>6</td>
<td>22%</td>
</tr>
<tr>
<td>Riis209</td>
<td>1973</td>
<td>59</td>
<td>SZP</td>
<td>2</td>
<td>6</td>
<td>29%</td>
</tr>
<tr>
<td>Sandberg-Gertzen210</td>
<td>1986</td>
<td>101</td>
<td>OLZ</td>
<td>1</td>
<td>6</td>
<td>23%</td>
</tr>
<tr>
<td>Wright211</td>
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<td>12</td>
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<tr>
<td>Miner212</td>
<td>1995</td>
<td>205</td>
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<td>4</td>
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</tr>
<tr>
<td>Hanauer213</td>
<td>1996</td>
<td>264</td>
<td>MSZ3</td>
<td>0.81.6</td>
<td>6</td>
<td>56%</td>
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<tr>
<td>Hawkey214</td>
<td>1997</td>
<td>323</td>
<td>MSZ3</td>
<td>1.6</td>
<td>6</td>
<td>40%</td>
</tr>
</tbody>
</table>

1p<0.05; 2Pentasa; 3Asacol/Claversal; 4p<0.05 for comparison of 5-ASA (both groups) vs placebo; 5comparison of 5-ASA, zileuton (not shown) and placebo; (sulfasalazine: SZP; olsalazine: OLZ, and mesalazine: MSZ).
and considered comfortable for treatment of at least one year.\textsuperscript{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).\textsuperscript{218} 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.\textsuperscript{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 (\(\geq 3\) 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 \textit{post hoc} analysis must, however, be treated with caution.\textsuperscript{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 (\(p=0.051\)).\textsuperscript{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.

### 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 [ELS, 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].

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

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Number of patients</th>
<th>Study drugs</th>
<th>Dosage (g/day)</th>
<th>Duration (months)</th>
<th>Failure to maintain clinical or endoscopic remission</th>
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<tbody>
<tr>
<td>Sutherland\textsuperscript{227}</td>
<td>1987</td>
<td>29</td>
<td>MSZ enema</td>
<td>2</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ enema</td>
<td>4</td>
<td></td>
<td>46%</td>
</tr>
<tr>
<td>Biddle\textsuperscript{228}</td>
<td>1988</td>
<td>25</td>
<td>MSZ enema</td>
<td>1</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>85% (p&lt;0.05)</td>
</tr>
<tr>
<td>D’Arienzo\textsuperscript{229}</td>
<td>1990</td>
<td>101</td>
<td>MSZ suppository</td>
<td>0.8</td>
<td>12</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>80% (p&lt;0.05)</td>
</tr>
<tr>
<td>D’Albasio\textsuperscript{230}</td>
<td>1990</td>
<td>79</td>
<td>MSZ enema</td>
<td>4 g x 7/month 4 g/3days</td>
<td>24</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ enema</td>
<td></td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral SZP</td>
<td>2g/day</td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ enema</td>
<td>4 g/day</td>
<td>6</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ enema</td>
<td>4 g/2 days</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ enema</td>
<td>4 g/3 days</td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>52% (p&lt;0.05)</td>
</tr>
<tr>
<td>Andreoli\textsuperscript{231}</td>
<td>1994</td>
<td>92</td>
<td>MSZ enema</td>
<td>4 g /2/week</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral SZP</td>
<td>2g/day</td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ enema</td>
<td>4 g /3 day</td>
<td>24</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral MLZ</td>
<td>1.5g/day</td>
<td></td>
<td>48% (p&lt;0.05)</td>
</tr>
<tr>
<td>D’Albasio\textsuperscript{234}</td>
<td>1997</td>
<td>69</td>
<td>MSZ enema + oral MSZ alone</td>
<td>2 x 4 g/week + 1.6 g/day</td>
<td>12</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral MSZ alone</td>
<td>1.6g/day</td>
<td></td>
<td>64% (p&lt;0.05)</td>
</tr>
<tr>
<td>D’Albasio\textsuperscript{235}</td>
<td>1998</td>
<td>111</td>
<td>MSZ suppository</td>
<td>0.5 x 2/day</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSZ suppository</td>
<td>0.5/day</td>
<td></td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>47% (p&lt;0.05)</td>
</tr>
<tr>
<td>Marteau\textsuperscript{215}</td>
<td>1998</td>
<td>95</td>
<td>MSZ suppository</td>
<td>3 x 1 g/week</td>
<td>12</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>47% (p&lt;0.05)</td>
</tr>
<tr>
<td>Hanauer\textsuperscript{236}</td>
<td>2000</td>
<td>65</td>
<td>MSZ suppository</td>
<td>0.5</td>
<td>24</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>-</td>
<td></td>
<td>89% (p&lt;0.05)</td>
</tr>
<tr>
<td>Yokoyama\textsuperscript{237}</td>
<td>2007</td>
<td>24</td>
<td>MSZ enema + oral MSZ alone</td>
<td>1 g x 2/week + 3 g/day</td>
<td>–</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral MSZ alone</td>
<td>3g/day</td>
<td></td>
<td>77%</td>
</tr>
</tbody>
</table>

\(1^{p<0.05}; 2^{p<0.05}\) 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. 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\textsuperscript{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).\textsuperscript{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\textsuperscript{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>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Number of patients</th>
<th>Study drugs</th>
<th>Dosage (g/day)</th>
<th>Duration (months)</th>
<th>Failure to maintain clinical or endoscopic remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azad Khan\textsuperscript{238}</td>
<td>1980</td>
<td>170</td>
<td>SZP</td>
<td>1</td>
<td>6</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SZP</td>
<td>2</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SZP</td>
<td>4</td>
<td></td>
<td>9%\textsuperscript{6}</td>
</tr>
<tr>
<td>Andreoli\textsuperscript{239}</td>
<td>1987</td>
<td>13</td>
<td>MSZ</td>
<td>0.75</td>
<td>12</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SZP</td>
<td>1.5</td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>Ireland\textsuperscript{240}</td>
<td>1988</td>
<td>164</td>
<td>OLZ SZP</td>
<td>1</td>
<td>6</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>26%\textsuperscript{26}</td>
</tr>
<tr>
<td>Riley\textsuperscript{241}</td>
<td>1988</td>
<td>92</td>
<td>MSZSZP</td>
<td>0.82</td>
<td>12</td>
<td>40%</td>
</tr>
<tr>
<td>Mulder\textsuperscript{242}</td>
<td>1988</td>
<td>72</td>
<td>MSZSZP</td>
<td>1.5</td>
<td>12</td>
<td>45%</td>
</tr>
<tr>
<td>McIntyre\textsuperscript{243}</td>
<td>1988</td>
<td>79</td>
<td>BLZ</td>
<td>3</td>
<td></td>
<td>56%</td>
</tr>
<tr>
<td>Rutgeerts\textsuperscript{244}</td>
<td>1989</td>
<td>273</td>
<td>SZP</td>
<td>2</td>
<td>6</td>
<td>49%</td>
</tr>
<tr>
<td>Kiiilerich\textsuperscript{245}</td>
<td>1992</td>
<td>226</td>
<td>OLZ SZP</td>
<td>1</td>
<td>12</td>
<td>54%</td>
</tr>
<tr>
<td>Rijk\textsuperscript{246}</td>
<td>1992</td>
<td>46</td>
<td>OLZ SZP</td>
<td>1.5–2</td>
<td>12</td>
<td>46%</td>
</tr>
<tr>
<td>Courtney\textsuperscript{222}</td>
<td>1992</td>
<td>99</td>
<td>OLZ MSZ\textsuperscript{6}</td>
<td>1.2</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td>Travis\textsuperscript{247}</td>
<td>1994</td>
<td>198</td>
<td>OLZ</td>
<td>0.51</td>
<td>12</td>
<td>52%</td>
</tr>
<tr>
<td>Ardizzone\textsuperscript{248}</td>
<td>1995</td>
<td>88</td>
<td>MSZ\textsuperscript{6}</td>
<td>1</td>
<td>12</td>
<td>38%</td>
</tr>
<tr>
<td>Kruis\textsuperscript{249}</td>
<td>1995</td>
<td>160</td>
<td>OLZ</td>
<td>0.51.25</td>
<td>6</td>
<td>36%</td>
</tr>
<tr>
<td>Nilsson\textsuperscript{250}</td>
<td>1995</td>
<td>156</td>
<td>MSZ</td>
<td>1.5</td>
<td>12</td>
<td>46%</td>
</tr>
<tr>
<td>Fockens\textsuperscript{220}</td>
<td>1995</td>
<td>169</td>
<td>MSZ\textsuperscript{3}</td>
<td>3</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Pauluzi\textsuperscript{218}</td>
<td>2005</td>
<td>156</td>
<td>MSZ\textsuperscript{5}</td>
<td>2.4</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1}Asacol/Claversal; \textsuperscript{2}p<0.05; \textsuperscript{3}failure including relapses plus study withdrawals; \textsuperscript{4}Pentasa; \textsuperscript{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. 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). 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. 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. 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®, 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. The Cochrane meta-analysis published after the Consensus meeting six of these studies on 286 patients were considered. The study quality was judged generally poor and the evidence for using thiopurines in UC is weaker than that for Crohn’s disease. AZA was shown to be superior to placebo on the basis of four trials (OR for failure to maintain remission 0.41, 95% CI 0.24–0.70). The results were similar when analyses were limited to patients who had successful induction of remission (data available for two studies). There was no clear evidence of a dose-response effect for AZA, or for use of co-medication with mesalazine in these studies. 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. 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. The best among these is the 30 year cohort from the Oxford IBD clinic between 1968 and 1999. 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). Retrospective series have suggested that thiopurines reduce the risk of colectomy after the induction period with CsA. 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. 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). 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.

After intravenous CsA, a switch to oral therapy occurs as soon as a clinical response has been achieved, with a view to acting as a 'bridge' until the therapeutic effect of AZA is achieved. Nevertheless, the usefulness of the oral
CsA bridge has been challenged. In a retrospective series from Barcelona, all responders to iv CsA were treated with AZA, without oral ciclosporin. 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. 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. 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. 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. 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, 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. 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. 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. 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 naive 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’), remains debated. This strategy has not yet been tested in UC, but is an acceptable option for thiopurine-naïve patients with steroid-dependent Crohn’s disease. 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) 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). 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

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 25×10⁹ viable E. coli bacteria) for 4 days, and then 200 mg/day. 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. 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. 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

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Number of patients</th>
<th>Study drugs</th>
<th>Dosage</th>
<th>Duration (months)</th>
<th>Failure to maintain clinical or endoscopic remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruis⁷⁷⁴</td>
<td>1997</td>
<td>120</td>
<td>E. coli Nissle Mesalazine</td>
<td>200 mg/day 1.2g/day</td>
<td>4</td>
<td>16%</td>
</tr>
<tr>
<td>Rembacken⁷⁷⁵</td>
<td>1999</td>
<td>116</td>
<td>E. coli Nissle Mesalazine</td>
<td>200 mg/day 1.2g/day</td>
<td>12</td>
<td>73%</td>
</tr>
<tr>
<td>Kruis⁷⁷⁶</td>
<td>2004</td>
<td>327</td>
<td>E. coli Nissle Mesalazine</td>
<td>200 mg/day 1.5g/day</td>
<td>12</td>
<td>45%</td>
</tr>
<tr>
<td>Ishikawa⁷⁷⁷</td>
<td>2000</td>
<td>21</td>
<td>Probiotic mixture¹ number Treatment² Treatment³</td>
<td>100 mL 18 x 10⁹ Lactobacillus GG</td>
<td>12</td>
<td>27%</td>
</tr>
<tr>
<td>Zocco⁷⁷⁸</td>
<td>2006</td>
<td>187</td>
<td>Lactobacillus GG Mesalazine</td>
<td>2.4 g/day Combination</td>
<td>12</td>
<td>15%</td>
</tr>
</tbody>
</table>

¹Bifidobacterium bifidum + Bifidobacterium breve + Lactobacillus acidophilus.
²Open 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. 327 327 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 × 10⁹ 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). 283 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 185 (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 eicosapentenoic acid in particular, may have anti-inflammatory properties by reducing the production of leucotriene B₄. 286,287 Several studies have been conducted in UC with different formulations and dosing of n-3 fatty acids. 288,290 Only three randomized controlled trials were selected for a Cochrane meta-analysis published after the Consensus, 287 which included 138 UC patients who were in remission at the time of recruitment. 291,292,293 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). 296 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.
6.2.5.5. Biological and other therapy. Adalimumab, certolizumab, etanercept, natalizumab, visilizumab, interleukin 10, fontolizumab (an anti-interferon \( \gamma \) antibody), basiliximab, daclizumab, alicaforsen (an anti-ICAM1 anti-sense 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 sulfasalazine 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. 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. 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 histologic remission who had been on sulfasalazine or 5-ASA for at least 1 year. 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 1980s, the gold standard for surgery was proctocolectomy with an ileostomy, apart from the sporadic use of ileorectal anastomosis. The Kock continent ileostomy was introduced in the late 1960s, but never achieved universal acceptance, although the gain in quality of life compared to proctocolectomy with a conventional stoma seemed clear enough. 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. 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.

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. 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. 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. 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 proctocolectomy

ECCO statement 7C
When performing pouch surgery, the maximum length of anorectal mucosa between the dentate line and the anastomosis should not exceed 2 cm [EL 4, RG C]

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. 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.

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 [EL 5, 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.

7.2.4. Anastomotic technique for restorative proctocolectomy

ECCO statement 7E
When the indication for surgery is cancer or dysplasia and restorative proctocolectomy is performed, anastomosis at the dentate line is recommended [EL 4, 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. 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 worldwide) and is not at present a matter for alarm.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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). 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.228

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 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.\textsuperscript{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, hypoproteinaemia 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

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<th>ECCO statement 7U</th>
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<tr>
<td>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.</td>
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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 such 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 1990s 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. 365 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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8. Pouchitis

8.1. General

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients with ulcerative colitis (UC) requiring colectomy.\(^1\) Pouchitis is a non-specific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC.\(^2,7\) Its frequency is related to the duration of the follow-up, occurring in up to 50% of patients 10 years after IPAA in large series from major referral centres.\(^1\) The cumulative incidence of pouchitis in patients with an IPAA for familial adenomatous polyposis is much lower, ranging from 0 to 10%.\(^12\) Reasons for the higher frequency of pouchitis in UC remain unknown. Whether the pouchitis more commonly develops within the first years after IPAA or whether the risk continues to increase with longer follow-up remains undefined.

**ECCO Statement 8A**
The diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities \(\text{[EL3a, RGB]}\). Extensive colitis, extraintestinal manifestations (eg primary sclerosing cholangitis), being a non-smoker, p-ANCA positive serology, and non-steroidal anti-inflammatory drug use are possible risk factors for pouchitis \(\text{[EL3b, RG D]}\).

8.1.1. Symptoms

After total proctocolectomy with IPAA, median stool frequency is 4 to 8 bowel movements\(^1\) with 700 mL of semifomed/liquid stool per day\(^2,13,14\). Symptoms related to pouchitis include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus and pelvic discomfort \(2, 15\). Rectal bleeding, fever, or extraintestinal manifestations may occur. Rectal bleeding is more often related to inflammation of the rectal cuff ("cuffitis"),\(^16\) than to pouchitis. Poor faecal incontinence may occur in the absence of pouchitis after IPAA, but is more common in patients with pouchitis. Symptoms of pouch dysfunction in patients with IPAA may be caused by conditions other than pouchitis, including Crohn's disease of the pouch,\(^17\) \(18\) cuffitis,\(^16\) and an irritable pouch.\(^20\) This is why the diagnosis depends on endoscopy and biopsy in conjunction with symptoms.

8.1.2. Endoscopy ("pouchoscopy")

Pouchoscopy and pouch mucosal biopsy should be performed in patients with symptoms compatible with pouchitis, in order to confirm the diagnosis.\(^15\) Patients with an ileoanal pouch occasionally have a stricture at the pouch-anal anastomosis, so a gastroscope rather than a colonoscope may better be necessary for pouchoscopy. Endoscopic findings compatible with pouchitis include diffuse erythema caused by inflammation of the ileal pouch, which may be patchy, unlike that observed in UC. Characteristic endoscopic findings include oedema, granularity, friability, spontaneous or contact bleeding, loss of vascular pattern, mucous exudates, haemorrhage, erosions and ulceration.\(^17\) Erosions and/or ulcers along the staple line do not necessarily indicate pouchitis. Characteristically, these findings are non-specific and lesions may be discontinuous, unlike the colorectal lesions in UC.\(^16,21,22\) Biopsies should be taken from the pouch mucosa and from the afferent limb above the pouch, but not along the staple line.
8.1.3. Histopathology of pouchitis

Histological findings of pouchitis are also non-specific, including acute inflammation with polymorphonuclear leukocyte infiltration, crypt abscesses and ulceration, in association with a chronic inflammatory infiltrate. There may be discrepancy between endoscopic and histologic findings in pouchitis, possibly related to sampling error. Morphological changes of the epithelium lining the ileal pouch normally develop in the 12–18 months after ileostomy closure, characterised by flattening and a reduced number, or disappearance of the villi, leading to villous atrophy (“colonic metaplasia”). Although the aetiolog of pouchitis remains unknown, it can be inferred from the predilection for patients with UC and the response to antibiotic therapy that the bacterial flora and whatever predisposes to UC itself are involved in the pathogenesis of tissue damage in the ileoanal pouch.

Pouchitis tends to occur only after colonic metaplasia has developed in the pouch, although a causal association is unproven.

ECCO Statement 8B
The most frequent symptoms of pouchitis are increased number of liquid stools, urgency, abdominal cramping and pelvic discomfort. Fever and bleeding are rare. Routine pouchoscopy after clinical remission is not required.

8.1.4. Differential diagnosis

The clinical history and biopsies help discriminate between pouchitis, ischaemia, Crohn’s disease (CD) and other rare forms of pouch dysfunction such as collagenous pouchitis, *Clostridium difficile* or cytomegalovirus pouchitis. Secondary pouchitis, caused by pelvic sepsis, usually causes focal inflammation and should be considered. Biopsies taken from the ileum above the pouch may reveal pre-pouch ileitis as a cause of pouch dysfunction, although this usually causes visible ulceration that may be confused with Crohn’s disease. The possibility of non-specific ileitis caused by NSAIDs should be considered.

8.1.5. Risk factors for pouchitis and pouch dysfunction

Reported risk factors for pouchitis include extensive UC, backwash ileitis, extraintestinal manifestations (especially primary sclerosing cholangitis), being a non-smoker and regular use of NSAIDs, interleukin-1 receptor antagonist gene polymorphisms and the presence of perinuclear neutrophil cytoplasmic antibodies are also associated with pouchitis. Not surprisingly, studies are discordant with regard to the role of each risk factor. Some of the best data on risk factors come from the Cleveland Clinic. 240 consecutive patients were classified as having healthy pouches (n=49), pouchitis (n=61), Crohn’s disease (n=39), cuffitis (n=41), or irritable pouch syndrome (n=50). The risk of developing pouchitis was increased 3–5 fold when the indication for IPAA was dysplasia (OR 3.89; 95% CI 1.69–8.98), or when the patient had never smoked (OR 5.09; 95% CI 1.01–25.69), or used NSAIDs (OR 3.24; 95% CI 1.71–6.13), or (perhaps surprisingly) had never used anxiolytics (OR 5.19; 95% CI 1.45–18.59). The risk of turning out to have Crohn’s disease of the pouch was greatly increased by being a current smoker (OR 4.77; 95% CI, 1.39–16–25), and modestly associated by having a pouch of long duration (OR 1.20; 95% CI 1.12–1.30). Cuffitis was associated with symptoms of arthralgia (OR 4.13; 95% CI 1.91–8.94) and a younger age (OR 1.16; 95% CI 1.01–1.33). Irritable pouch syndrome is probably under-recognised, although it is a common cause of pouch dysfunction when other causes (including a small volume pouch, incomplete evacuation and pouch volvulus) have been excluded and investigations are normal. The principal risk factor is the use of antidepressants (OR 4.17; 95% CI 1.95–8.92) or anxiolytics (OR 3.21; 95% CI 1.34–7.47), which suggests that these people may have had irritable bowel syndrome contributing to symptoms of colitis before pouch surgery.

These risk factors should not preclude proctocolectomy if surgery is appropriate, but should inform pre-operative discussions with the patient and family. In particular the possibility that IBS may be contributing to symptoms of refractory UC should be considered and objective evidence of treatment refractory colitis obtained before surgery. If there is a disparity between preoperative and endoscopic appearance, or if the patient is on antidepressants, then the risk of pouch dysfunction after IPAA needs particularly careful consideration. Similarly, if a patient has primary sclerosing cholangitis, then it is appropriate to discuss the higher risk of pouchitis. This is appropriate management of expectations rather than a contraindication to appropriate surgery.

8.2. Pattern of pouchitis

8.2.1. Acute and chronic pouchitis

On the basis of symptoms and endoscopy, pouchitis can be divided into remission (normal pouch frequency) or active pouchitis (increased frequency with endoscopic appearances and histology consistent with pouchitis). Active pouchitis may then be divided into acute or chronic, depending on the symptom duration. The threshold for chronicity is a symptom duration of >4 weeks. Up to 10% of patients develop chronic pouchitis requiring long-term treatment, and a small subgroup has pouchitis refractory to medical treatment.

8.2.2. Scoring of pouchitis

The Pouchitis Disease Activity Index (PDAI) has been developed to standardize diagnostic criteria and assess the severity of pouchitis. The PDAI is a composite score that evaluates symptoms, endoscopy and histology. Each component score has a maximum of 6 points. Patients with a total PDAI score ≥7 are classified as having pouchitis, so a patient has to have both symptoms and endoscopic or histological evidence of pouchitis and, ideally, all three. The problem is that about a quarter of patients with a high symptom score suggestive of pouchitis may not fulfill criteria for the diagnosis of pouchitis, as assessed by the PDAI, since endoscopic or histological criteria may be absent. Consequently a relatively large number of patients may be unnecessarily treated for pouchitis when symptoms are due to other conditions. Other scoring systems have been devised, including that by Moskowitz and an index from Heidelberg. Comparisons with the PDAI show that they are not interchangeable, but this affects clinical trials rather than clinical practice.
8.2.3. Recurrent pouchitis and complications

Pouchitis recurs in more than 50% of patients. Patients with recurrent pouchitis can broadly be grouped into three categories: infrequent episodes (<1/yr), a relapsing course (1–3 episodes/yr) or a continuous course. Pouchitis may further be termed treatment responsive or refractory, based on response to single-antibiotic therapy (see 8.3.2). Although these distinctions are largely arbitrary, they help both patients and their physicians when considering management options to alter the pattern of pouchitis. Complications of pouchitis include abscesses, fistulae, stenosis of the pouch-anal anastomosis and adenocarcinoma of the pouch. This latter complication is exceptional and almost only occurs when there is pre-existing dysplasia or carcinoma in the original colectomy specimen.

8.3. Medical treatment

8.3.1. Acute pouchitis: antibiotics

ECCO Statement 8C
The majority of patients respond to metronidazole or ciprofloxacin, although the optimum modality of treatment is not clearly defined [EL1b, RG B]. Side-effects are less frequent using ciprofloxacin [EL1c, RG B]. Antidiarrhoeal drugs may reduce the number of daily liquid stools in patients, independent of pouchitis [EL5, RGD].

Treatment of pouchitis is largely empirical and only small placebo-controlled trials have been conducted. Antibiotics are the mainstay of treatment, and metronidazole and ciprofloxacin are the most common initial approaches, often with a rapid response. The odds ratio of inducing a response using oral metronidazole compared with placebo in active chronic pouchitis was 2.67 (95% CI 2.31–3.08, NNT=2). The randomised trials of both metronidazole and ciprofloxacin are, however, small. The two have been compared in another small randomised trial. Seven patients received ciprofloxacin 1 g/day and nine patients metronidazole 20 mg/kg/day for a period of 2 weeks. Ciprofloxacin lowered the PDAI score from 10.1±2.3 to 3.3±1.7 (p=0.0001), whereas metronidazole reduced the PDAI score from 9.7±2.3 to 5.8±1.7 (p=0.0002). There was a significantly greater reduction in the ciprofloxacin compared to metronidazole in terms of the total PDAI (p=0.002), symptom score (p=0.03) and endoscopic score (p=0.03), as well as fewer adverse events (33% of metronidazole-treated patients reported side-effects, but none on ciprofloxacin). Combination antibiotic therapy is an option for persistent symptoms (below).

8.3.2. Chronic pouchitis: combination antibiotic therapy or budesonide

ECCO Statement 8D
In chronic pouchitis, combined antibiotic treatment is effective [EL1b, RG B].

For patients who have persistent symptoms, alternative diagnoses should be considered, including undiagnosed Crohn’s disease, pouch-anal or ileal-pouch stricture, infection with CMV or Cl difficile, collagenous pouchitis, cuffitis, anatomical disorders, or irritable pouch syndrome. Approximately 10–15% of patients with acute pouchitis develop chronic pouchitis, which may be “treatment responsive” or “treatment refractory” to single-antibiotic therapy. Patients with chronic, refractory pouchitis do not respond to conventional therapy and often continue to suffer symptoms, which is a common cause of pouch failure. Combination antibiotic therapy or oral budesonide may work. 16 consecutive patients with chronic, refractory pouchitis (disease >4 weeks and failure to respond to >4 weeks of single-antibiotic therapy) were treated with ciprofloxacin 1 g/day and tinidazole 15 mg/kg/day for 4 weeks. A historic cohort of ten consecutive patients with chronic refractory pouchitis treated with 5–8 g oral and topical mesalazine daily was used as a comparator. These refractory patients had a significant reduction in the total PDAI score and a significant improvement in quality-of-life score (p<0.002) when taking ciprofloxacin and tinidazole, compared to baseline. The rate of clinical remission in the antibiotic group was 87.5% and for the mesalazine group was 50%.

In another study, 18 patients non-responders to metronidazole, ciprofloxacin or amoxyclillin/clavulanic acid for 4 weeks were treated orally with rifaximin 2 g/day (a nonabsorbable, broad spectrum antibiotic) and ciprofloxacin 1 g/day for 15 days. Sixteen out of 18 patients (88.8%) either improved (n=10) or went into remission (n=6). Median PDAI scores before and after therapy were 11 (range 9–17) and 4 (range 0–16), respectively (p<0.002). A British group observed similar benefit in just 8 patients. In another combination study, 44 patients with refractory pouchitis received metronidazole 800 mg–1 g/day and ciprofloxacin 1 g/day for 28 days. 36 patients (82%) went into remission and median PDAI scores before and after therapy were 12 and 3 respectively (p<0.0001). The alternative is oral budesonide CIR 9 mg daily for 8 weeks, which achieved remission in 15/20 (75%) patients not responding after 1 month of ciprofloxacin or metronidazole. The message is simple enough, even if the trials are underpowered: if ciprofloxacin does not work, then try it in combination with an imidazole antibiotic or rifaximin, or try oral budesonide.

8.3.3. Acute and chronic refractory pouchitis: other agents

The variety of approaches illustrates the challenges of trying to find treatment that works for a new disorder. These are largely of historic interest. Budesonide enemas were as effective as metronidazole for acute pouchitis in a randomised controlled trial. Ciclosporin enemas were successful for chronic pouchitis in a pilot study and oral azathioprine may help if patients relapse become budesonide-dependent. Uncontrolled studies of short-chain fatty acid enemas showed little value. Glutamine and butyrate suppositories have been compared for chronic pouchitis. More of recent interest, infliximab has been tried in patients with chronic (very) refractory pouchitis not responding either to metronidazole or ciprofloxacin 1 g/day for 4 weeks or oral budesonide CIR 9 mg/day for 8 weeks. 10/12 (83.3%) such patients treated with infliximab 5 mg/kg at 0, 2 and 6 weeks went into remission. The median PDAI score before therapy was 13 (range 8–18) and 2 (range 0–9) after infliximab (p<0.001) and the IBDQ also significantly improved from 96.
(range 74–184) to 196 (92–230) (p < 0.001). Infliximab has been used when the cause of pouch dysfunction is Crohn’s disease, or fistulation. Benefit been also been reported from allicaforsen enemas (an inhibitor of intercellular adhesion molecule (ICAM)-1) in an open-label trial.

8.3.4. Maintenance of remission: probiotics

In chronic pouchitis, once remission has been obtained, treatment with the highly concentrated probiotic mixture VSL#3 is able to maintain remission. Two double-blind, placebo-controlled studies have shown the efficacy of VSL#3 (450 billion bacteria of 8 different strains/g) to maintain remission in patients with chronic pouchitis. In the first study, 40 patients who achieved clinical and endoscopic remission after one month of combined antibiotic treatment (rifaximin 2 g/day + ciprofloxacin 1 g/day), were randomised to receive either VSL#3, 6 g/day (18 × 10^{11} bacteria/day), or placebo for 9 months. All 20 patients who received placebo relapsed, while 17 of the 20 patients (85%) treated with VSL#3 remained in clinical and endoscopic remission at the end of the study. Interestingly, all 17 patients relapsed within four months after stopping VSL#3. In the second study, 36 patients with chronic, refractory pouchitis who achieved remission (PDx = 0) after 1 month of combined antibiotic treatment (metronidazole + ciprofloxacin) received 6 g/once a day of VSL#3 or placebo for 1 year. Remission rates at one year were 85% in the VSL#3 group and 6% in the placebo group (p < 0.001).

8.3.5. Prevention of pouchitis: probiotics

The same probiotic preparation (VSL#3) has been shown to prevent pouchitis within the first year after surgery, in a randomised, double-blind, placebo-controlled study. Forty consecutive patients undergoing IPAA for UC were randomised within a week after ileostomy closure, to VSL#3 3 g (9 × 10^{11}) per day or placebo for 12 months. Patients were assessed clinically, endoscopically and histologically at 1, 3, 6, 9 and 12 months. Patients treated with VSL#3 had a significantly lower incidence of acute pouchitis (10%) compared with those treated with placebo (40%) (p < 0.05), and experienced a significant improvement of quality of life. The mechanism by which therapy with probiotics works remains elusive, but has been investigated. Mucosa-associated pouch microbiota before and after therapy with VSL#3 shows that patients who develop pouchitis while treated with placebo have low bacterial and high fungal diversity. Bacterial diversity was increased and fungal diversity was reduced in patients in remission maintained with VSL#3 (p = 0.001). Real time PCR experiments demonstrated that VSL#3 increased the total number of bacterial cells (p = 0.002) and modified the spectrum of bacteria towards anaerobic species. Taxa-specific clone libraries showed that the spectrum of Lactobacillus sp. and Bifidobacter sp. was altered on probiotic therapy. The diversity of the fungal flora was repressed. Restoration of the integrity of a “protective” intestinal mucosa related microbiota could therefore be a potential mechanism of probiotic bacteria in inflammatory barrier diseases of the lower gastrointestinal tract.

8.4. Cuffitis

Cuffitis, especially after double-stapled IPAA (see Section 7, preceding paper same issue) can cause pouch dysfunction with symptoms that mimic pouchitis or irritable pouch syndrome (IPS). Unlike IPS (which may coexist) bleeding is a characteristic feature of cuffitis. Endoscopy by an informed endoscopist is diagnostic, but care has to be taken to examine the cuff of columnar epithelium between the dentate line and pouch-anal anastomosis (Section 7.2.3, preceding paper same issue). In an open-label trial, 14 consecutive patients with cuffitis were treated with mesalamine suppositories 500 mg twice daily. Mesoazine suppositories significantly reduced the total Cuffitis Activity Index (derived from the PDx) from 11.9 ± 3.17 to 6.21 ± 3.19 (p < 0.001). Symptom subscore (from 3.24 ± 1.28 to 1.79 ± 1.31), endoscopy subscore (from 3.14 ± 1.29 to 1.00 ± 1.52) and histology subscore (4.93 ± 1.77 to 3.57 ± 1.39) were all significantly reduced. 92% of patients with bloody bowel movements and 70% with arthralgia (a characteristic clinical feature of cuffitis, Section 8.1.5) improved on therapy. No systemic or topical adverse effects were reported.

9. Surveillance for colorectal cancer

9.1. Risk of cancer

9.1.1. Estimation of risk

Patients with longstanding ulcerative colitis appear to have an increased risk of colorectal cancer (CRC) as compared to the general population.

ECCO Statement 9A

Patients with longstanding ulcerative colitis appear to have an increased risk of colorectal cancer (CRC) as compared to the general population [EL2].

ECCO Statement 8E

Rectal cuff inflammation (cuffitis) may induce symptoms similar to pouchitis or irritable pouch syndrome, although bleeding is more frequent [EL2a, RG B]. Topical 5-ASA has shown efficacy [EL4, RG D].

Patients with long standing UC have a higher risk of developing colorectal carcinoma (CRC) than the average population. The magnitude of this risk, however, is still the subject of a debate. Indeed, while older reports included in two meta-analyses confirmed a rapid increase of the risk after ten years of disease, the magnitude of the risk in recent population-based studies appears much smaller. In fact, although Eaden and colleagues computed a cumulative CRC risk of 18% in UC patients after 30 years of disease, risks of only 7.5% and 2.1% respectively were observed in two studies published since 2004. Furthermore, in the largest report of surveillance colonoscopy in at-risk population of patients with extensive UC to date (600 patients over a 30 year period), the cumulative incidence of CRC by colitis duration...
was 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years. In this study from St Mark's, only 30/600 patients (5%) developed CRC. The reasons for such an improvement in the risk of CRC are still unclear but may include improved control of mucosal inflammation, more extensive use of 5-ASA compounds, the implementation of surveillance programmes and timely colectomy. Taken together these studies suggest that the CRC risk in UC patients should be kept under scrutiny. Nevertheless, the best evidence, as provided by concordant meta-analyses, indicates that the risk of CRC development is increased in UC [EL2]. The ECCO Consensus working party, through their answers to questionnaires, supported this evaluation of the data.

9.1.2. Risk factors for cancer development

ECCO Statement 9B
Risk is highest in patients with extensive colitis, intermediate in patients with left-sided colitis, and not increased in proctitis [EL2].

Several independent factors affect the magnitude of the risk of malignant transformation. The duration of disease and extent of mucosal inflammation are the most prominent. There is no uniform definition of the duration of disease, although onset of symptoms has generally been used in the studies that have identified this parameter as a risk factor. In a review of 19 practice and population-based studies, Eaden confirmed that the CRC risk appears to increase 8–10 years after the onset of UC related symptoms and subsequently increases in later decades of the disease [EL2].

ECCO Statement 9C
Patients with early onset of disease (age < 20 years at onset of disease) and patients with UC-associated primary sclerosing cholangitis (PSC) may have a particularly increased risk [EL2]. Persistent inflammation and family history of CRC may contribute to the risk of CRC in patients with UC [EL3].

The extent of mucosal inflammation (including backwash ileitis) has been correlated with the risk of CRC in several studies, as well as in a systematic review [EL2]. Other factors have also been associated with a high CRC risk in all or part of these studies. These include young age at onset of the disease (less than 20 years of age at the time of diagnosis) and an association with primary sclerosing cholangitis (PSC) [EL2]. However, there was no difference in median age at onset of colitis for those with or without CRC in the 600-patient study from St Mark's (p = 0.8, Mann–Whitney) years. The persistence of mucosal inflammation or a family history of CRC may also contribute to an increased risk, but the association has been less consistent across the studies [EL3]. In a nested case-control study from two well-defined, population-based IBD cohorts (Copenhagen County, Denmark and Olmsted County, Minnesota) 43 cases of IBD-associated CRC were matched on six criteria to 1–3 controls (n = 102). Significant associations were found between PSC (OR 6.9, 95% CI 1.2–40.0), the percentage of time with clinically active disease (OR per 5% increase 1.2, 95% CI 1.0–1.4), and ≥ 12 months of continuous symptoms (OR 3.2 95% CI 1.2–8.6). The presence of pseudopolyps, which can be considered a marker of severity of inflammation, have been associated with double the risk of CRC (OR 2.5; 95% CI: 1.4–4.6), which is a useful practice point for clinicians.

9.2. Surveillance colonoscopy programmes

9.2.1. Screening and surveillance

Since dysplastic changes in colonic mucosa are associated with an increased risk of CRC in UC, surveillance colonoscopy programmes have been developed with the aim of reducing morbidity and mortality due to CRC, while avoiding unnecessary prophylactic colectomy. Surveillance for CRC in patients with UC amounts to more than just performing repeated colonoscopies, but includes reviewing patient symptoms, medication use and laboratory values as well as updating personal and familial medical history. At the onset of these programmes, an initial screening colonoscopy is performed, with the goal of reassessing disease extent and confirming the absence of dysplastic lesions. Thereafter surveillance colonoscopies are regularly performed at defined intervals (below).

ECCO Statement 9D
Surveillance colonoscopy may permit earlier detection of CRC, with a corresponding improved prognosis [EL3, RG B]. Unequivocal evidence that surveillance colonoscopy prolongs survival in patients with UC is lacking [EL3, RG B].

The effectiveness of these programmes has been evaluated in some prospective studies, systematically reviewed by the Cochrane collaboration. An American consensus conference, held under the auspices of the Crohn's and Colitis Foundation of America, also reviewed the usefulness of screening and surveillance colonoscopies in 2005. The Cochrane collaboration used death related to CRC as the primary endpoint for the evaluation of surveillance programmes in UC, limiting their analysis to prospective randomised studies that included a control group. The authors were unable to demonstrate a benefit of surveillance programmes for preventing CRC-related death in UC by these strict parameters, but included only two studies in their final analysis. An earlier meta-analysis included a third study yet to be published in full, but concluded that there was an improved 5-year survival in patients undergoing surveillance, compared to UC patients outside surveillance programmes. Furthermore, in the largest and most meticulous screening programme reported to date, involving 600 patients, 2627 colonoscopies, 5932 patient-years of follow-up and a caecal intubation rate of 98.7%, with no significant complications, 16/30 cancers were interval cancers. Unequivocal evidence for the benefit of these programmes is therefore lacking and the apparent benefit could still be linked to lead-time bias. Patients in surveillance programmes may have an earlier diagnosis of CRC even if CRC is detected independently of surveillance colonoscopy. Diagnosis of CRC in patients outside such programmes may arise from later,
symptom-driven investigation [EL3]. These issues are best discussed with patients before entry into a surveillance programme.

The Consensus had divided opinions regarding the ability of surveillance colonoscopy programmes to improve survival in UC patients, in keeping with the contrasting results of the meta-analyses. Only one third of the voting experts considered that the procedure could achieve this goal, while two-thirds remained unconvinced or attributed any benefit to potential lead-time bias. Nevertheless, it should be noted that any benefit estimated in years of life saved may be much greater in UC patients than for general population screening. This is because UC-related CRC tends to occur earlier in life and with a higher frequency than in the general population. Mathematical models have evaluated that the duration of life saved per case screened ranges from 1.2 to 5 years in UC patients, compared to 1.2 to 4 months in general population screening,

ECCO Statement 9E
Screening colonoscopy should be offered 8–10 years after the onset of UC symptoms to all patients to reassess disease extent [EL5, RG D]

As duration of disease is a major risk factor for the development of CRC in UC patients, it is rational to propose a screening colonoscopy when the risk starts to increase, i.e. after 8–10 years from the onset of disease [EL2]. This initial colonoscopy also aims to reassess the extent of disease, since this parameter also impacts on the risk of CRC. Nevertheless, the appropriateness of screening colonoscopy as a way of reassessing disease extent and potential risk has not been formally established. It has been proposed in reviews and a prior consensus report, as well as being agreed during the present Consensus conference by the participating experts [ELS].

9.2.3. Initial screening colonoscopy

ECCO Statement 9F
In extensive colitis, surveillance should start after screening colonoscopy and be performed every other year up to year 20 of disease, then annually [EL2, RG B]. Surveillance should start 15 years after onset of disease in left-sided or distal UC. Proctitis does not require further surveillance [EL2, RG B]

The surveillance schedule is also arbitrary, but because CRC has been observed within 2 years of surveillance colonoscopy, intervals between repeat investigations should not exceed this and should be shorter in patients with particularly high risks such as those with longstanding disease or PSC.

Furthermore, although disease extent is central to CRC risk assessment, this parameter may be difficult to define, implying that surveillance may be offered to large groups of patients. Considerable differences between extent assessed by colonoscopy and histology have been reported, as well as variations in extent over time. Neoplasia has been reported in areas of microscopic involvement without endoscopically visible inflammation. Thus, disease extent should be defined not only by the outcome of screening colonoscopy, but also by the results of previous procedures. In contrast, there is good evidence that the CRC risk is lower in patients with limited disease as defined by colonoscopy or barium enema, so a reasonable compromise is to defer surveillance until later time points in patients with limited macroscopic disease [EL2]. This all assumes that a decision has been made with the patient that surveillance is appropriate. If the risk of CRC complicating colitis is thought to be no higher than the general population, surveillance may be considered unnecessary.

ECCO Statement 9G
If primary sclerosing cholangitis (PSC) is associated to UC, surveillance should be performed annually from the time of PSC diagnosis [EL3, RG B]

In other situations, such as patients with UC-associated PSC, the risk of developing a CRC is not only particularly high, but has been reported to occur early (median 2.9 years) in the course of the disease. These patients should enter in a more intensive surveillance programme once the diagnosis of PSC has been established.

The recommendations by ECCO (Statements 9E–9G) are contingent on a perceived increased risk of CRC in UC (Statements 9A–9C) and widespread acceptance in several European countries that screening for CRC in the general population is appropriate. If the latter applies, it is difficult to justify failure to screen a group of patients with higher risk of CRC more closely. The recommendation grades are appropriate to the strength of the evidence.

9.3. Colonoscopic procedures

9.3.1. Number and site of biopsies
Evidence for procedural techniques during surveillance colonoscopy is better documented than the benefit of the programme itself. At least 33 biopsies should be obtained from the various segments of the colon to achieve 90–95% sensitivity for the detection of dysplasia. A reasonable approach would therefore to perform 4 random biopsies every 10 cm around the colon. Extra biopsies should be obtained from strictured or raised areas and from other abnormal areas in the colon. Full colonoscopy is better documented than the benefit of the programme itself. At least 33 biopsies should be obtained from the various segments of the colon to achieve 90–95% sensitivity for the detection of dysplasia. A reasonable approach would therefore to perform 4 random biopsies every 10 cm around the colon. Extra biopsies should be obtained from strictured or raised areas

The surveillance programme itself. At least 33 biopsies should be obtained from the various segments of the colon to achieve 90–95% sensitivity for the detection of dysplasia. A reasonable approach would therefore to perform 4 random biopsies every 10 cm around the colon. Extra biopsies should be obtained from strictured or raised areas and from other abnormal areas in the colon. Full colonoscopy is necessary because about a third of UC-associated CRC develop in the proximal colon. This strategy is further supported by the observation that most dysplastic lesions are visible during careful colonoscopy. In a study performed on 525 patients who underwent 2204 surveillance colonoscopies, Rutter detected 110 neoplastic areas in 56 patients. Eighty-five (77.3%) were macroscopically visible at colonoscopy and 25 (22.7%) were macroscopically invisible. Fifty patients (89.3%) had macroscopically detectable neoplasia, while only 6 (10.7%) had macroscopically invisible lesions. The value of random biopsies, however, is limited compared to optical techniques that enhance detection of dysplastic epithelium.
9.3.2. Chromoendoscopy

**ECCO Statement 9H**
Random biopsies (4 every 10 cm) and targeted biopsies of any visible lesion should be performed during surveillance colonoscopy [EL2b, RG B]. Methylene blue or indigo carmine chromoendoscopy is an alternative to random biopsies for appropriately trained endoscopists and is superior to random biopsies in the detection rate of neoplastic lesions [EL1b, RG B].

The yield of surveillance colonoscopy can be improved by spraying dyes (such as methylene blue or indigo carmine) that highlight subtle changes in the architecture of the colonic mucosa. All studies have confirmed an improved diagnostic yield for dysplasia detection using chromoendoscopy. With this method, random biopsies of apparently normal mucosa is of no additional value compared to targeted biopsies obtained after dye staining of the mucosa. Comparable diagnostic yields from chromoendoscopy have been obtained with both methylene blue and indigo carmine. Despite these good results, a single from experienced investigators found that no dysplasia was missed even without dye spraying. However, trained endoscopists in chromoendoscopy may even further distinguish neoplastic from non-neoplastic changes, based on surface crypt architecture based on pit pattern recognition with a sensitivity of 93% and 97%, respectively. Colonoscopy with dye staining did not take significantly longer than conventional colonoscopy. This endoscopic approach may not only improve the yield of screening and surveillance colonoscopies, but also decrease the workload of pathologists because fewer biopsies are needed per procedure.

9.4. Dysplasia

The ultimate goal of surveillance colonoscopy is to identify whether the colonic mucosa has already undergone the early steps of malignant transformation (i.e. to detect dysplasia), which identifies UC patients at the highest risk of CRC development. Dysplasia in UC is stratified as low grade, high grade or indefinite for dysplasia, according to the presence or absence of specific histological changes in the epithelium. If biopsies are indefinite for dysplasia and this is confirmed by an experienced pathologist, then follow-up surveillance colonoscopy within 3 to 6 months is recommended, with intensification of UC therapy in the meantime.

**ECCO Statement 9I**
A finding of dysplasia should be confirmed by an independent pathologist [EL2b, RG B].

The grade of dysplasia is important because it impacts on the sensitivity and specificity of the presence or future development of CRC. Dysplasia of any grade has been reported to have a 74% sensitivity and 74% sensitivity for CRC development, while in the same series from the Mayo Clinic, high grade dysplasia had lower sensitivity (34%) but 98% specificity for CRC detection. In the most recent meta-analysis, low-grade dysplasia was found to be associated with a 9-fold increased risk of developing CRC and a 12-fold risk of developing advanced neoplasia. Therefore, the finding of low-grade dysplasia carries a substantial risk: such a finding has important prognostic implications. For this reason, dysplasia should be confirmed by an experienced pathologist, because interobserver variation for the detection of dysplasia is high. Furthermore, individual studies that do not show an increased risk of malignant transformation in low-grade dysplasia need to be placed in the context of the meta-analysis.

9.4.2. Dysplasia and colectomy

**ECCO Statement 9J**
High grade dysplasia in flat mucosa and adenocarcinoma are indications for proctocolectomy [EL2, RG B]. A patient with low-grade dysplasia in flat mucosa should be offered proctocolectomy or repeat surveillance biopsies within 3–6 months [EL2b, RG B].

Once dysplasia is found, the rationale of such a surveillance programme demands that colectomy is performed, because the risk of CRC is appreciably increased. If high grade dysplasia is present, the decision is easier, because the risk of concomitant CRC may be as high as 32%, assuming that the biopsies were indeed obtained from flat mucosa and not from an adenoma. If low-grade dysplasia is detected, the 9-fold increased risk of developing CRC reported in the most recent meta-analysis could reasonably be viewed as justification for colectomy as well, and this option should be discussed with the patient. However, because some follow-up studies of patients with low-grade dysplasia have shown a low rate of CRC development, it seems a reasonable compromise to continue surveillance with extensive biopsy sampling at shorter (perhaps 3–6 month) intervals in those who will adhere strictly to the surveillance program. This remains controversial in the literature and was discussed during the conference as well.

9.4.3. Dysplasia and raised lesions

**ECCO Statement 9K**
A raised lesion with dysplasia should be completely resected. In the absence of dysplasia in the flat surrounding mucosa, meticulous endoscopic surveillance should be proposed [EL2b, RG B]. If endoscopic resection is not possible or if dysplasia is found in the surrounding flat mucosa, proctocolectomy should be recommended [EL2b, RG B].

Raised lesions on a background of UC have been traditionally referred to as “Dysplasia Associated Lesion or Mass” or DALM. Until recently this finding has been considered an absolute indication for colectomy. It is increasingly recognised, however, that some of these raised lesions may resemble sporadic adenomas and that they may be amenable to complete endoscopic resection. If the polypectomy is confirmed complete by histology and if biopsies obtained
from the flat mucosa immediately adjacent to the polypectomy site show no dysplasia and if, in addition, no dysplasia is found elsewhere in the colon, then colectomy may be safely deferred. Careful follow-up, preferably with surveillance colonoscopy at 3 months and then 6 monthly, is needed if this strategy is followed, because at least half of such patients in the four studies quoted developed further raised lesions. If the lesion does not resemble typical adenoma, is not respectable, or is associated with dysplasia in the adjacent mucosa, then colectomy is indicated due to the high risk of concomitant CRC.79,80

9.5. Chemoprevention

The risk of developing CRC has been shown to be higher in patients with persistent mucosal inflammation,73 and thus appropriate therapy may reduce the risk of CRC associated with chronic UC. Several studies suggest that sulfasalazine or mesalazine may lead to a risk reduction, referred to as a chemoprotection. Velayos et al. performed a meta-analysis that included 334 cases of CRC, 140 cases of dysplasia and a total of 1932 subjects extracted from 3 cohort studies and 6 case-control studies.79 This suggested that in a population matched for extent and duration of UC, aminosalicylates may reduce the risk of colorectal cancer. The risk reduction was significant for CRC development (OR 0.51, 95% CI 0.37–0.69), but not for dysplasia (OR 1.18, 95% CI 0.41–3.43). In view of the low toxicity of mesalazine and considering that the number of patients needed to treat (NNT) to prevent one CRC may be as low as 7 in patients with 30 years of disease,116 the Consensus felt that such a therapy should be considered and potentially offered to all UC patients in the absence of contraindications. The limitations of the data are, however, recognised and some large studies have shown no benefit.78 When 76 cases of CRC and UC in a cohort of 18,969 patients in the UK General Practice Research Database were compared to six matched control cases, regular users of 5ASA (defined as six or more prescriptions in the preceding 12 months) had a trend towards a lower risk of CRC compared with irregular uses (unadjusted OR 0.7, 95% CI 0.44–1.03). For mesalazine, but not sulfasalazine, the effect was significant depending on the total number of prescriptions: OR 1.13 (0.49–2.59) for 6–12 prescriptions, OR 0.30 (0.11–0.83) for 13–30 prescriptions and OR 0.31 (0.11–0.84) for >30 prescriptions.117 Patients with UC-associated PSC appear to be at particularly high risk of developing CRC.75 In follow-up to a randomised trial evaluating the benefit of ursodeoxycholic acid in these patients, patients assigned to active medication for their biliary disease had a lower incidence of dysplasia and CRC development compared to patients assigned to placebo.118 This study confirmed prior data from a cross-sectional study in the setting of a prospective randomised trial. The Consensus considered these data sufficient evidence to recommend this therapy in all patients with UC and PSC, considering the potential benefit of the drug on both conditions and low toxicity. Nevertheless, the limitations of the data are again recognised, since not all studies have identified an association between PSC and CRC in patients with UC.79 Interestingly, when the same group examined population-based as opposed to hospital-based cohorts, a significant association between PSC and CRC was identified (OR 6.9, 95% CI 1.2–40), although a protective effect of aminosalicylates could not be discerned (cumulative dose of sulfasalazine (OR per kg 1.1, 95% CI 1.0–1.3) and mesalazine (OR per kg 1.3, 95% CI 0.9–1.9).78

ECCO Statement L
Chemoprevention with 5-ASA compounds may reduce the incidence of colorectal cancer in UC patients and should be considered for all UC patients [EL2, RG B]. Colorectal cancer chemoprevention with ursodeoxycholic acid should be given to patients with PSC [EL1b, RG B].

9.6. Prognosis

The prognosis of CRC complicating UC has generally been considered worse than for sporadic CRC. This may not be valid. In a report from the Mayo Clinic, 290 patients with IBD-associated CRC (241 with chronic ulcerative colitis and 49 with Crohn’s disease) were matched with an equal number of age- and sex-matched sporadic CRC patients between 1976 and 1996. 55% of IBD-related tumours were distal to the splenic flexure compared to 78% of sporadic CRC, but during a median follow-up period of 5 years, 163 IBD-associated CRC patients died (56%), compared with 164 sporadic CRC patients (57%). The 5-year survival rates were 54% in the IBD-CRC subgroup vs. 53% in the sporadic CRC subgroup (p=0.94).120 This is not that dissimilar to experience from St Mark’s Hospital. In the largest experience of surveillance colonoscopy in 600 patients during 5932 patient-years of follow-up, 30 patients (5%) developed CRC, with a 5-year survival rate of 73.3%.69

The prognosis of colorectal dysplasia in IBD is also debated (Section 9.4.1). In a population-based study from Minnesota, 29/725 (4%) IBD patients developed flat dysplasia (n=8), a Dysplasia Associated Lesion or Mass (DALM, n=1), or an adenoma-associated lesion or mass (ALM n=18) in an area of IBD, or an ALM outside the area of IBD (n=2). Among 6 patients with flat low-grade dysplasia (FLGD) who did not undergo colectomy, none progressed during a median of 17.8 (range 6–21) years of observation with a median of 3 (range 0–12) surveillance colonoscopies. Four (22%) patients with ALMs in areas of IBD who did not undergo surgery developed low-grade dysplasia or DALMs. Dysplasia located proximal to the splenic flexure was significantly associated with a risk of recurrence or progression of dysplasia. This population-based cohort did not confirm an increased risk of cancer related to flat low-grade dysplasia,78 which is at odds with the meta-analysis.105

10. Children and adolescents

10.1. Introduction

About 10–15% of patients with inflammatory bowel disease are diagnosed before the age of 18 years.121 During puberty the incidence is 7 per 100,000 per year and increases further during adolescence to about 12 per 100,000 at age 20–29, consistent with a peak around the age of 30 years.122 In children most cohort studies show a lower incidence of ulcerative colitis (UC) compared to Crohn’s disease (CD),123 but the incidence of CD has clearly increased over the past
decade. In contrast, the incidence of UC is stable in some studies, but increasing in other cohorts. The median age of onset of symptoms in UC is 12 years in most paediatric studies, but the diagnostic delay is considerably shorter than for CD. In contrast to adults, the clinical presentation of UC is often more severe in children, which may be explained by the predominance of pancolitis (70–80% of children) at the time of diagnosis.

10.2. Diagnosis

10.2.1. Diagnostic threshold

ECCO Statement 10A
Ulcerative colitis should be suspected in a child with chronic (≥4 weeks) or recurrent (≥2 episodes in 6 months) bloody diarrhoea, after exclusion of infective or other causes. This applies particularly when there is growth failure and/or pubertal delay, a family history of IBD, increased markers of inflammation, or if anaemia is present [EL2b, RG B]

In contrast to paediatric CD and its diverse symptomatology, the clinical manifestation of UC is almost uniformly bloody diarrhoea (84–94% of children), accompanied by tenesmus. Although an infective aetiology should be excluded, its presence does not exclude a diagnosis of UC if other causes are ruled out. The combination of rectal bleeding, anaemia and increased ESR identified 86% of patients with IBD prior to an endoscopic procedure. Other retrospective case series have confirmed the diagnostic value of increased inflammatory markers and anaemia for IBD.

A shorter interval from symptoms to diagnosis of UC probably explains why growth failure is half as common compared to CD. As with adults, the greatest risk factor for developing UC in childhood is to have a family member with ulcerative colitis (relative risk 7–17). The risk for CD in a family member with Crohn’s disease is a relative risk of 15–35. The stronger the family history, the earlier the onset of symptoms. For patients with early-onset UC (<5 years’ age), 26%–44% have a family history of UC, compared to older patients or children with CD. Genetic factors are likely to have a stronger influence in paediatric IBD, especially in early-onset acute severe UC, compared to older children or adults. Nevertheless, most children with IBD have no family history and are considered sporadic.

10.2.2. Documentation

ECCO Statement 10B
In all children with UC, the height, weight (and pre-diagnosis growth curve) and pubertal stage, should be recorded at diagnosis, and regularly during follow-up [EL3b, RG B]

Growth failure is a unique complication of paediatric IBD, caused by a combination of inadequate calorie intake, increased losses and active inflammation. Efficacy of medical treatment and concomitant mucosal remission is characterised by normal linear growth and pubertal development. In contrast, when catch-up growth does not occur after growth failure at diagnosis, or when height velocity decreases during maintenance treatment, it is highly likely that there is persistent disease activity, so therapy should be more aggressive and an adequate calorie intake ensured.

10.2.3. Diagnostic procedures

ECCO Statement 10C
Ileocolonoscopy and biopsies should be performed in all children or adolescents with a suspicion of inflammatory bowel disease (IBD). Upper gastrointestinal endoscopy is recommended when ileocolonoscopy does not confirm a diagnosis of ulcerative colitis [EL2a, RG B]

ECCO Statement 10D
In children and adolescents (up to 16–18 years of age), endoscopy should be performed by a specialist with experience in paediatric gastroenterology, preferably by a paediatric gastroenterologist [EL 5, RG D], in a setting that is suitable for diagnosing and treating children with IBD (paediatric hospital, with access to general anaesthesia)

The IBD working group of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has reached a consensus on the diagnosis of IBD in children, which has been summarised in the ‘Porto Criteria’. This group feels it essential to establish a diagnosis of the type of disease, as well as to determine severity, localisation, and extent of the disease, before treatment is started. Paediatric patients with UC have more extensive disease and rectal sparing in up to 30%, so a complete diagnostic work-up is warranted in children with bloody diarrhoea. Evidence supporting colonoscopy with ileal intubation and multiple biopsies, rather than sigmoidoscopy alone, is provided by retrospective cohort studies. In cases with extensive colitis that cannot be classified, gastroduodenoscopy may allow definitive diagnosis.

The ECCO Consensus agrees that a paediatric gastroenterologist, rather than a specialist in adult endoscopy, should best perform endoscopy in children suspected of IBD. The most important argument is quality of care, particularly because endoscopy in children is preferably done under general anaesthesia: this is preferred for reasons of comfort and care and has been shown to be safe. Moreover, the treatment and follow-up of children and adolescents with IBD should be in the hands of a paediatric gastroenterologist who is aware of age-related differences in disease presentation and treatment. Such specialists are experienced in handling problems such as linear growth retardation and pubertal delay.

10.3. Induction therapy in children

10.3.1. Distal colitis

ECCO Statement 10E
Oral [EL2b, RGB] aminosalicylates and/or topical aminosalicylates (suppositories in proctitis, enemas in left-sided colitis) [EL5, RGD] are appropriate initial induction therapy for mild to moderate distal colitis in children or adolescents
No studies have been performed in children with distal colitis. A questionnaire sent to members of the IBD working group of ESPGHAN, however, revealed great variation of care in the treatment of distal colitis. The first choice was either oral treatment alone (mesalazine 21%, sulfasalazine 36%), or in combination with topical treatment (mesalazine 36%, corticosteroids 7%). Considering the rarity of proctitis in children, no standard treatment protocols exist.

10.3.2. Extensive colitis

**ECCO Statement 10F**

For mild to moderate pancolitis in children, oral mesalazine/sulfasalazine is recommended as first line therapy [EL2b, RG B]. Oral steroids are appropriate if the response is insufficient [EL4, RG D].

Only one prospective study has confirmed the efficacy of oral aminosalicylates in children with active ulcerative colitis. In this trial, a clinical response at 8 weeks was seen in 79% of patients receiving sulfasalazine (60 mg/kg/day) and 50% of patients on olsalazine (30 mg/kg/day). Retrospective studies have also shown that oral aminosalicylates effectively induce clinical remission.

Although sulfasalazine may cause more gastrointestinal side-effects, it is the preferred aminosalicylate treatment in young children who cannot swallow tablets, because it is available as a suspension. Alternatively, mesalazine can be given as an enteric-coated granule formulation. Based on expert opinion and extrapolation from pharmacokinetic studies, the advised dose (oral and rectal mesalazine combined) in children aged 12 years or older of mesalazine, is 50–75 mg/kg/day with a maximum of 4 g/day. For sulfasalazine it is 100 mg/kg/day with a maximum of 6 g/day.

Concerning oral corticosteroids, no studies have been performed in children with UC. Nevertheless, prospectively collected data from the US Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry database provides a useful insight. In 97 children (age <16 yr) with newly diagnosed UC between 2002 and 2005, with a minimum of 1 year of follow-up, 79% received corticosteroids, most (62/77) within 30 days of diagnosis. For those treated within 30 days, disease activity at 3 months was inactive in 60%, mild in 27%, and moderate or severe in 11%. At 12 months, 31 of 62 (50%) of the early corticosteroid-treated patients were considered corticosteroid responsive and 28 (45%) were corticosteroid-dependent. A total of 4 patients receiving corticosteroids required colectomy in the first year. Immunomodulators were used in 61% of all corticosteroid-treated patients. This is similar to adults: early response is excellent, but dependence is common, even with immunomodulators. Evaluation among the IBD working group of ESPGHAN demonstrated that 46% favoured addition of corticosteroids if response to aminosalicylates was found to be insufficient. Oral prednisolone is given as a once daily dose of 1–2 mg/kg/day, with a maximum dose of 40 mg, for 2–4 weeks (until clinical remission), then tapered to zero in 6–8 weeks. Although not supported by clinical evidence from randomised clinical trials, calcium and vitamin D are usually supplemented during a course of steroid treatment.

10.3.3. Severe colitis

**ECCO Statement 10G**

For severe pancolitis in children, corticosteroids are first line therapy [EL4, RG D]. If the response is insufficient, intravenous ciclosporin [EL4, RG C] or infliximab [EL4, RG C], or colectomy are appropriate options.

Although no randomised clinical studies have been performed in children with acute severe UC, all respondents to the ESPGHAN questionnaire agreed that corticosteroids are the first line therapy in severe pancolitis. In a meta-regression of response to steroids in 32 studies involving 1991 patients (1974–2006), only 43 children were included. To evaluate the outcome in children, a retrospective study of 74 admissions in 63 children (57% males, age at diagnosis 10.9±4 yr, 79% extensive colitis) treated at Toronto SickKids Hospital 1995–99 was performed. 41% failed intravenous steroids by discharge and 23 (37%) came to colectomy on that admission. By one year, 54% and by 5 yr 59% had come to colectomy. There was no clear consensus from ESPGHAN as to whether corticosteroids should be given as the only treatment (25% of respondents), or in combination with oral mesalazine (25%), or intravenously with adjunctive parenteral nutrition (50%). Given the similarity in the response of children to steroids compared to adults (Section 5.2.4, preceding paper same issue), it seems unlikely that mesalazine is necessary. Although nutritional support is particularly appropriate in children, TPN in adults has not been shown to offer any advantage when managing acute severe colitis (Section 5.2.4, preceding paper same issue).

When 3–5 days of intravenous corticosteroids are ineffective, rescue therapy with ciclosporin, tacrolimus, or infliximab are the only two options to avoid or postpone colectomy. An objective assessment of the response to steroids facilitates management as it does in adults (see Section 5.2.5, preceding paper same issue). A paediatric index of severity as been developed and when calculated on day 3, strongly predicts failure of intravenous steroids. As with adults, stool frequency (p=0.001) and CRP (p=0.045) on day 3 (but not day 1) predict failure, along with temperature (p=0.001). Case studies with intravenous ciclosporin in children with severe, steroid-refractory colitis who are candidates for surgery, have shown remission of the disease in up to 80% of cases. In many children, however, tapering of oral ciclosporin resulted in a relapse and was followed by colectomy within a year of cessation of treatment. In occasional patients, short term ciclosporin treatment can effectively induce remission while waiting for azathioprine maintenance treatment to take effect.

Infliximab has not been studied prospectively, but small retrospective studies in new-onset steroid-refractory patients show complete remission in 75–88% of patients. With the small numbers of patients studied and limited follow-up, it is currently unknown whether infliximab therapy is effective in avoiding colectomy, or whether it simply defers it. The Consensus view is that rescue therapy with either ciclosporin, tacrolimus, or infliximab should only be initiated in a specialist centre where a paediatric and/or colorectal surgeon are available and involved in the treatment of these severely sick children.
10.4. Maintenance therapy in children

**ECCO Statement 10H**
Oral mesalazine or sulfasalazine are recommended maintenance treatment in the same dose as for induction therapy [EL5, RG D]. For difficult patients with extended and/or relapsing disease, who are steroid-refractory or steroid-dependent, azathioprine/mercaptopurine is recommended [EL4, RG C]. Long-term steroids are contraindicated and ciclosporin is inappropriate.

10.4.1. Aminosalicylates
The efficacy of mesalazine or sulfasalazine maintenance treatment has not been studied in children with UC. From the IBD working group of ESPGHAN questionnaire respondents, 57% advised continuing the same mesalazine dose as used for induction, while 43% advised a lower dose. The Consensus view is based on results from adult studies that indicate that high dose 5-ASA is effective maintenance therapy. Long-term corticosteroids are absolutely contraindicated, because they do not maintain remission and have a negative effect on linear growth and bone mineralisation. Ciclosporin maintenance treatment is ineffective and inappropriate, because serious, sometimes irreversible, side-effects may occur.

10.4.2. Thiopurines
Retrospective cohort studies have demonstrated that maintenance with azathioprine/mercaptopurine is effective, while achieving a steroid-sparing effect. This steroid-sparing effect is more evident when azathioprine treatment is started early in the course of disease, within 2 years after diagnosis. The advised dose for azathioprine in children is 2–3 mg/kg/day and that for mercaptopurine is 1–1.5 mg/kg/day.

10.5. Surgery in children

**ECCO Statement 10I**
Colectomy is indicated for severe colitis with acute complications not responding to medical therapy; persistently active disease with failure or toxicity of medical treatment; failure to taper corticosteroid treatment despite immunosuppressant use; growth retardation or pubertal delay despite medical treatment [EL 4, RG C].

10.5.1. Indications
In acute severe colitis, the decision to perform colectomy should be evaluated on a day-to-day basis by both the medical and surgical team. If the disease is not responding to 7–10 days of either calcineurin inhibitors (ciclosporin, tacrolimus) or infliximab, colectomy is indicated.

Colectomy is also indicated for persistently active disease, when corticosteroid dependency exists despite concomitant therapy with azathioprine/mercaptopurine, or when immunosuppressive treatment has side-effects. Growth failure despite apparently adequate maintenance therapy is also an indication for colectomy, even when clinical symptoms appear mild. Preliminary (and anecdotal) experience with infliximab in children suggests that it may be more effective in acutely ill patients, compared to patients with chronic refractory disease. It rarely achieves steroid-free remission. Therefore, infliximab cannot be recommended for chronic steroid-dependent disease in children.

10.5.2. Procedures

**ECCO Statement 10J**
Colectomy should be performed by an experienced paediatric surgeon, ideally with the assistance of a colorectal surgeon with paediatric experience; ileo-pouch-anal anastomosis (IPAA) should only be performed in a highly specialised centre [EL 4, RG C].

Depending on the local circumstances, a child needing colectomy should be referred for expert care at a specialist centre. Case series of IPAA in children show good results in terms of quality of life, continence and incidence of pouchitis. However, in very young children (<10 years), pouchitis is reported in 75% of the patients. Because IPAA decreases female fecundity, colectomy with ileorectal anastomosis until later IPAA may be a better option in girls. Expert advice should be sought.

10.6. Nutritional support

**ECCO Statement 10K**
Enteral or parenteral nutritional therapy is inappropriate primary treatment. However, a nutritional evaluation is essential and nutritional support should be provided when required [EL5, RG D].

**ECCO Statement 10L**
There is no indication for a "special diet" for ulcerative colitis, because none are effective and there is a risk of nutritional deficiencies [EL5, RG D].

It has not been shown that enteral nutrition has a primary therapeutic role in ulcerative colitis. There are many theories that suggest that diet may be implicated in the aetiology of inflammatory bowel disease. However, there is, as yet, no dietary approach proven to reduce the risk of developing IBD. Children with IBD have increased calorie and protein requirements, so intake should be at least 120% of recommended daily allowances (RDA). If oral intake is poor due to anorexia during a period of disease activity, high-calorie supplements may be indicated and special dietetic advice is appropriate.

10.7. Psychosocial support

**ECCO Statement 10M**
Psychosocial support is important adjunctive treatment, because depressive symptoms are frequent and psychosocial support may be associated with a better outcome and a better quality of life [EL3b, RG B].
Children and adolescents with IBD are at greater risk of developing behavioural difficulties or emotional dysfunction and depression in particular (in almost 25% of patients), as well as anxiety, social dysfunction and low self-esteem compared to healthy children. The quality of life in adolescents with IBD is generally lower than healthy controls. Two large randomised studies have demonstrated that psychosocial support by a patient-orientated self-management approach can have a beneficial influence on the course of disease. Therefore, appropriate medical information and mental health support are recommended, because this may influence disease activity.

10.8. Transition of care to adult services

ECCO Statement 10N
Transitional clinics represent optimal care and are highly recommended [EL5, RG D]

A careful transition of patients from the paediatric service to adult gastroenterologists is vital, because it may reinforce treatment adherence and improve quality of life. There are many differences between paediatric and adult care. In the paediatric service, children and adolescents with IBD are usually seen together with their parents and often receive more attention, because the disease is uncommon in children compared to adults. A paediatric specialist nurse may be on hand to advise and be a point of contact for the child or parents. Endoscopy is performed under general anaesthesia, whereas this is exceptional in adults. On the other hand, the paediatric gastroenterologist rarely discusses long-term issues, such as cancer risk or surveillance. Close collaboration between the paediatric and adult services will overcome these differences. The ideal setting for this is a transitional clinic where adolescent patients are seen by both specialists. The alternative is to establish a parallel clinic, where paediatric and adult IBD clinics run independently but at the same time, so that when a suitable patient is seen, it is then a simple matter for the paediatric or adult gastroenterologist to go down the corridor to contact their opposite number so that the young person can be introduced or seen together. A trained IBD nurse specialist can play an important role coordinating care between the service, the patient and the family during the transitional period.

11. Pregnancy


12. Psychosomatics

12.1. Introduction

While psychosocial factors are generally considered important in ulcerative colitis, controversy still exists about their role. This leads to potential inconsistencies in clinical practice. A biopsychosocial model represents an advantage over a biomedical model, because it embodies the complex biological and psychosocial interactions that explain human illness or its effects. Attention to psychosocial factors associated with ulcerative colitis may have consequences not only on psychosocial well-being and quality of life, but also on the activity of the disease itself. The key words used in the systematic literature review of Medline and Embase for this review were ulcerative colitis as well as inflammatory bowel disease and irritable bowel syndrome – psychology; psychosocial; psychotherapy; quality of life; doctor patient relationship; and psychopharmaceuticals.

12.2. Influence of psychological factors on disease

12.2.1. Aetiology

ECCO Statement 12A
A speculated association between psychological factors and the aetiology of ulcerative colitis cannot be proven. There is, however, an influence of psychological distress and mood disorders on the course of the disease [EL1b, RG B]

Studies about the influence of psychological factors on the development of ulcerative colitis are very limited. There are a few studies with hypothetical interpretations about the influence of psychosocial factors on the aetiology of the disease. Many studies on psychosocial factors relate to inflammatory bowel disease (IBD) rather than ulcerative colitis or Crohn's disease in particular.

12.2.2. Pattern of disease

ECCO Statement 12B
There is evidence of an interaction between psychological factors and IBD activity. Depression and perceived chronic distress represent risk factors for relapse of the disease. It remains controversial whether acute life events trigger relapses [EL 1b, RG B]. Most patients consider stress to have an influence on their illness [EL 4, RG C]

Psychological factors are considered to have an influence on the course of the disease, which is consistent with evidence in the recent literature about the influence of subjective perceived psychological distress on disease activity of ulcerative colitis. Studies about the influence of major life events on the biological disease activity have yielded contradictory results. Patients themselves and the majority of European experts at the Consensus conference consider psychosocial distress as influencing the risk of relapse. One study shows a heightened response to stressors and the greater epithelial damage in IBD patients, which suggests that stress-induced activation of the brain-gut axis and of mucosal mast cells may be important in the initiation and/or flare up of IBD.

12.3. Psychological disturbances in ulcerative colitis

ECCO Statement 12C
Psychological disturbances seem to be a consequence of the illness rather than the cause of, or specific to ulcerative colitis. The degree of psychological distress and disturbances correlates with the disease severity, predicts health-related quality of life and influences the course of disease [EL 1b, RG B]
Patients with ulcerative colitis seem to have no more, or only slightly more, psychological disturbances compared to patients with other chronic diseases. A consistent association between psychological factors and the prevalence of IBS-like symptoms in patients in remission has been reported. There is also evidence that children and adolescents with IBD comprise a population at high risk of developing a psychiatric disorder. A recent study with a large IBD population has shown that IBD patients experience a rate of depression that is triple that of the general population (16.3% vs. 5.6%). In this study 17% of depressed patients had considered suicide in the past 12 months and an additional 30% had considered suicide at an earlier time. In individuals who were currently depressed, female patients were more likely than males ever to have considered suicide (50% vs. 31%). Depressive coping strategies are positively associated and predict health-related quality of life. Furthermore, the psychosocial consequences of the illness become more significant with increasing severity of the disease and quality of life is related to disease activity, symptoms, and female gender.

### 12.4.1. Communication with patients

#### ECCO Statement 12E

The psychosocial consequences and health-related quality of life of patients should be taken into account in clinical practice at regular visits. Individual information and explanation about the disease should be provided through a personal interview. The course of the disease can be improved by combining self-management and patient-centred consultations.

Health perceptions impact on the experience of the illness. Increasing physician awareness of the fact that psychologically distressed patients have difficulty in processing clinically relevant information may lead to improved doctor–patient communication. It is important that patients are informed about their condition through an individual interview, in conjunction with emotional support.

### 12.4.2. Psychological support

#### ECCO Statement 12F

Physicians should assess the patient’s psychosocial status, quality of life and demand for additional psychological care and recommend psychotherapy if indicated. Integrated psychosomatic and gastroenterology care should be available. Patients should be informed of the existence of patient associations.

For assessment of quality of life, two validated IBD-specific questionnaires have been shown to be sensitive, reproducible and responsive for use in clinical trials: the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC). Detection and treatment of psychological distress has the potential to improve health-related quality of life. The presence of psychological disorders contributes to poor quality of life and the number of doctor visits, regardless of the severity of the condition. This is the common experience of doctors caring for patients with IBD, even if the potential or need to treat this aspect of the illness is perceived.

To assess the demand for psychological care in chronic diseases, a validated questionnaire is available, developed and based on inflammatory bowel disease. Most experts (80%) feel themselves able to recommend psychotherapy during a discussion with patients. There is no study on their competence at doing this, but this is consistent with the experience of participants in the European Consensus on the management of Crohn’s disease, the German Consensus on Crohn’s disease, and that on ulcerative colitis. Since strategies aimed at improving social support can have a favourable impact on psychological distress, training of gastroenterologists to integrate psychosocial factors in clinical practice should be taken into consideration.

### 12.4.3. Therapeutic intervention

#### ECCO Statement 12G

Psychotherapeutic interventions are indicated for psychological disorders associated with ulcerative colitis.

Psychotherapy and relaxation methods have a positive influence on IBD, mainly affecting the psychological dimensions of the illness such as psychological well-being, coping strategies and psychological distress, as well as perception of pain. This underpins the recommendation (Statement 12G). The diagnosis of ulcerative colitis is insufficient alone to recommend psychotherapy, since studies of psychotherapy on patients without psychological
disturbance show little or no benefit. One study that combined patients with Crohn's disease and ulcerative colitis reported an influence of psychotherapy on disease activity, but there was inhomogeneity in randomisation of the treatment and control groups, so the results are not included in the evidence-based recommendation.

12.4.4. Therapeutic choice

**ECCO Statement 12G**
The choice of psychotherapeutic method depends on the psychological disturbance and should best be made by specialists (Psychotherapist, Specialist for Psychosomatic Medicine, Psychiatrist). Psychopharmaceuticals should be prescribed for defined indications [EL 5, RG D]

There is no evidence that one psychotherapeutic method should be preferred over another. Relaxation exercises are useful, since they are easy to learn and perform. Expert opinion believes that there is an advantage if the psychotherapist has experience in the treatment of patients with chronic inflammatory bowel diseases and works closely with the patient's gastroenterologist. There are no specific studies on the use of individual psychopharmaceuticals in ulcerative colitis. In spite of this, almost all experts believe that there are clinical situations in which antidepressants should be recommended for treatment of psychological distress associated with ulcerative colitis.

13. Extraintestinal manifestations

13.1. Introduction

Extra-intestinal manifestations (EIMs) occur in up to 30% of patients affected by ulcerative colitis or Crohn's disease, although it is probable that studies from referral centres have over-estimated the prevalence and community studies suggest that their prevalence may be much lower. What is interesting is that the occurrence of one EIM appears to predispose to others. This suggests an underlying generic susceptibility in some patients that is largely genetically determined, although may yet be prone to environmental influence. Female patients with colitis (either ulcerative or Crohn's colitis) appear to be particularly susceptible.

Scoring systems such as the Crohn's disease activity index (CDAI) include EIMs in the assessment. This is a weakness, although not widely recognised, since only some EIMs are related to disease activity and a genetic susceptibility in a minority of patients introduces bias. Those EIMs broadly related to the activity of colitis include oligoarticular peripheral arthritis, erythema nodosum, oral aphthous ulcers and episcleritis. Polyaarticular peripheral arthritis, pyoderma gangrenosum [PG], uveitis and spondylarthropathy tend to pursue a course independent of disease activity, while primary sclerosing cholangitis [PSC] is most prevalent in patients with colitis that follows an apparently mild course.

For those EIMs closely related to ulcerative colitis activity, treatment can parallel that of the underlying disease. Treatment otherwise is mainly on a case-by-case basis as randomised controlled trials are mostly lacking. Specific therapy for EIMs is strongly influenced by current IBD treatment, and may include increasing dosage of existing drugs or the addition of new agents.

Consensus review indicates that gastroenterologists will be comfortable diagnosing and treating the more common extraintestinal manifestations, unless they prove resistant, with the exception of eye involvement for which the advice of an ophthalmologist is selected in a great majority of cases (93%). It is noted however that the frequency with which routine dermatological (46%) and rheumatological (31%) advice would be sought has increased since the review panel was interrogated on their approach to EIMs of Crohn's disease in 2004.

This section concentrates on the more frequently encountered EIMs, for which at least some quantifiable data exist. Thrombotic complications of colitis and their prevention are considered in the section on acute management of colitis. Anaemia in colitis (as in Crohn's disease) is too frequently neglected: authoritative guidelines have been published separately.

13.2. Arthropathies

**ECCO Statement 13A**
Diagnosis of non-axial arthritis and arthropathy associated with UC is made on clinical grounds based on characteristic features and exclusion of other specific forms of arthritis [EL3b, RG C]. Type I is pauciarticular and affects large joints acutely at times of UC activity. Type II is polyarticular, affecting a larger number of peripheral joints independently of UC activity [EL 2b, RG B]. Axial arthritis, including sacroiliitis and ankylosing spondylitis, is diagnosed on conventional rheumatological grounds, and is supported by characteristic radiological changes, magnetic resonance imaging being the most sensitive [EL2b, RG B]. Although HLA B-27 is over-represented in axial arthritis related to UC this is not of diagnostic value [EL2b, RG B]

The diagnosis of non-axial arthritis and arthropathy associated with inflammatory bowel disease (IBD) is made on clinical grounds and t types have been defined by the Oxford group. The distinction is supported by differences in genetic susceptibility.

Type I is a large joint pauciarticular arthropathy that occurs at times of IBD activity, while type II is a polyarticular small joint arthropathy, whose activity is largely independent of IBD activity. Axial arthritis includes sacroiliitis and ankylosing spondylitis which are diagnosed clinically, supported by characteristic radiological changes. Magnetic resonance imaging is the diagnostic tool of choice.

13.2.1. Pauciarticular peripheral arthropathy
Type I arthropathy predominantly affects weight-bearing joints, including the ankles, knees, hips, wrists, elbows and shoulders. Pauciarticular means that fewer than five joints are affected. The arthritis is usually acute, self-limiting, resolves within weeks as disease activity decreases, and leaves no permanent joint damage. Clinical examination reveals painful, tender, swollen joints. Aspiration is unnecessary unless an alternative diagnosis is suspected. The differential diagnosis includes osteoarthritis, septic arthritis, pyrophosphate arthropathy, coincidental rheumatoid
arthritis, or occasionally, gout. If just one hip joint is affected then steroid-induced osteonecrosis should be considered.279

13.2.2. Polyarticular peripheral arthropathy
Type II arthritis predominantly affects the small joints of both hands as a symmetrical arthropathy. Pain is commonly disproportionate to the signs of arthritis. It usually persists for months or years and follows a course independent of IBD activity. It may persist after colectomy or start after ileo-pouch-anastomosis. The differential diagnosis includes osteoarthritis, but also includes treatment side-effects such as steroid-induced pseudorheumatism (which is common after withdrawal of long-term steroids) and mesalazine- or azathioprine-induced arthropathy.278

13.2.3. Axial arthropathy
Asymptomatic sacroiliitis is common, with up to 50% of colitis patients having abnormal radiography.279 Symptomatic sacroiliitis is characterised by pain in the buttocks after rest, which then improves with movement. The clinical sign of discomfort in the sacroiliac joints during bilateral pressure on the pelvic brim is indicative. The principal symptom of ankylosing spondylitis is persistent low back pain, usually beginning before the age of 30. Clinical examination reveals loss of the lumbar lordosis and limited spinal flexion. Conventional radiographs of the back are usually normal in the early stages of disease. Spinal CT scans and radionuclide bone scans are more sensitive than plain radiographs, but the gold standard is now magnetic resonance imaging (MRI).280,281 There is however an impression that minor abnormalities of little or no clinical consequence may be seen on MRI; this remains to be determined by longer-term follow-up. In advanced cases there may be squaring of the vertebral bodies, marginal syndesmophytes and bony proliferation, with ankylosis producing the classical “bamboo spine”. HLA B-27 associations is found in a majority (up to 75%) of patients with axial arthritis, but is less common than in patients with ankylosing spondylitis not associated with IBD. It is unrelated to sacroiliitis and HLA typing has no role in the management of individual patient.282,283

13.2.4. Therapy of arthropathies

ECCO Statement 13B
Treatment of arthritis and arthropathy associated with UC is largely empirical. This includes the use of simple analgesics, sulfasalazine, local steroid injections and physiotherapy, but whether or not to use non-steroidal anti-inflammatory agents is a continuing dilemma, even though short term use appears not to exacerbate colitis.284

For Type I peripheral arthritis the emphasis should be on the treatment of active disease, including steroids, immunomodulation, and anti-TNF therapy as appropriate. Resolution of the arthropathy can be expected. The joint-specific drug of first choice for all forms of IBD-related arthritis appears to be sulfasalazine, but convincing evidence to support this is lacking. Nevertheless, it was favoured by the greatest minority of panel members (41%). Symptomatic relief may be obtained from simple analgesics, rest and physiotherapy.279,284,285,286 Although there is concern that non-steroidal anti-inflammatory agents (conventional and COX II inhibitors) may aggravate the underlying colitis,287,288 they have been used by many gastroenterologists to good effect with limited risk of exacerbating colitis. A previous history of flare related to NSAID intake seems to be the best indicator of individual risk. A randomised study of the safety of celecoxib in colitis283 indicated that short-term use (~2 weeks) did not exacerbate colitis. Local steroid injection into the worst-affected joints often provides rapid, but temporary relief. Type II arthritis generally resolves with effective treatment of the colitis.289

Treatment of axial arthritis should include intensive physiotherapy, together with disease modifying drugs such as sulfasalazine, and methotrexate.279,285,289 The safety and efficacy of infliximab in ankylosing spondylitis is established, but is best reserved for intractable or severely debilitating symptoms.290,291 This is because of the 15% prevalence of immunogenicity and the small, but definable risk of notable adverse events such as sepsis, tuberculosis, or demyelination.

13.3. Cutaneous manifestations

ECCO Statement 13C
Diagnosis of the cutaneous manifestations of UC is made on clinical grounds, based on their characteristic features and (to some extent) the exclusion of other specific skin disorders; biopsy is rarely appropriate or necessary [EL3b, RG C]

13.3.1. Erythema nodosum
Erythema nodosum is usually readily recognised. It is characterised by raised, tender, red or violet subcutaneous nodules of 1 to 5 cm in diameter. It commonly affects the extensor surfaces of the extremities, particularly the anterior tibial area, and usually occurs at times of activity of the colitis. A firm clinical diagnosis can normally be made, and biopsy is not normally appropriate. If performed, the histology reveals a non-specific focal panniculitis.292,293

Because erythema nodosum is closely related to disease activity, despite a genetic link,294 treatment is based on that of the underlying colitis. Systemic steroids are usually required (76% Consensus view). In resistant cases or when there are frequent relapses, immunomodulation with azathioprine and/or infliximab may be added, but it is exceptional to need such measures just because of erythema nodosum. Oral potassium iodide has been used successfully in refractory cases.295
13.3.2. Pyoderma gangrenosum (PG)
Lesions are often preceded by trauma at the site (which may have been many years earlier) through a phenomenon known as pathergy. PG can occur anywhere on the body, including the genitalia, but the commonest sites are the shins and adjacent to stomas. Initially they take the form of single or multiple erythematous papules or pustules, but subsequent necrosis of the dermis leads to the development of deep excavating ulcerations that contain purulent material that is sterile on culture unless secondary infection has occurred.

Treatment of pyoderma gangrenosum has relied on topical and systemic steroids. Steroids were considered the most effective treatment for pyoderma gangrenosum (54% Consensus view), with intravenous ciclosporin or tacrolimus reserved for refractory cases. There are, however, no reliable trials to support the use of high dose steroids or calcineurin inhibitors and these drugs have appreciable potential side-effects. Infliximab has changed the management of PG. In the first controlled trial in pyoderma (which also included patients without IBD) infliximab 5 mg/kg or placebo was given at week 0. At week 2 (the primary end point), significantly more patients in the infliximab group had improved (46% (6/13)) compared with the placebo group (6% (1/17), p = 0.025). Overall, 29 patients received infliximab with 69% (20/29) demonstrating a beneficial clinical response. Remission at week 6 was 21% (6/29). There was no response in 31% (9/29) of patients. Infliximab is stillreserved for more troublesome cases, but is highly effective.

13.3.3. Sweet’s syndrome
Sweet’s syndrome is characterised by tender, red inflammatory nodules or papules, usually affecting the upper limbs, face or neck. It has only been recognised as an extraintestinal manifestation of IBD relatively recently. It is part of the group of acute neutrophilic dermatoses that includes pyoderma gangrenosum, but can be distinguished by its appearance, distribution and histological features. There is a strong predilection for women (87%), patients with colonic disease (100%) and those with other extraintestinal features (77%). The rash is associated with active disease in 67–80%, but may precede the onset of intestinal symptoms in 21% and has been reported 3 months after proctocolectomy for ulcerative colitis.

13.4. Ocular manifestations

Uveitis and episcleritis are probably the most common extraintestinal manifestations of IBD.

**ECCO Statement 13D**
A confident diagnosis of simple episcleritis may not require specific treatment, but if necessary will usually respond to topical steroids [EL4, RG D]. When diagnosis is uncertain referral to an ophthalmologist for expert opinion and slit-lamp examination is recommended [EL4, RG D]. Uveitis is treated with steroids, and it may be necessary to use both topical and systemic routes [EL3b, RG C]. Immunomodulatory therapy has been thought helpful in resistant cases [EL4, RG D].

13.4.1. Episcleritis
Episcleritis may be painless, presenting simply with hyperaemic sclera and conjunctiva, but itching and burning sensations may also occur. Diagnosis of simple episcleritis depends on the exclusion of the more sinister features of uveitis. When this is not possible referral to an ophthalmologist for expert opinion and slit-lamp examination is essential. Episcleritis usually does not require specific treatment other than for underlying disease activity. It will respond to topical steroids if symptoms are troublesome – but take care that infection (including herpetic), ulceration, and uveitis are not overlooked.

13.4.2. Uveitis
Uveitis is less common, but has potentially severe consequences. When related to ulcerative colitis it is frequently bilateral, insidious in onset and long-lasting. Patients complain of eye pain, blurred vision, photophobia and headaches. Potential progression to loss of vision should prompt urgent referral to an ophthalmologist. Slit-lamp examination will confirm the diagnosis and differentiates between anterior and posterior uveitis. Uveitis is treated with steroids, and it may be necessary to use both topical and systemic routes. Infliximab is rapidly effective, but treatment should be guided by specialists.

13.4.3. Cataracts
Chronic corticosteroid use for treatment of UC is associated with numerous complications and may result in posterior subcapsular cataracts develop in a significant proportion (25%) of patients receiving 15 mg or more of prednisone for 1 year. Although steroids do not prevent relapse and have no place in the long-term management of UC, any patient on long-term steroids should undergo routine (probably annual) slit lamp examination.

13.5. Hepatobiliary disease

Hepatobiliary disease is relatively common in IBD and magnetic resonance cholangiography (MRC) indicates that it may be more prevalent than currently estimated in ulcerative colitis. Primary sclerosing cholangitis (PSC) constitutes the most important condition relatively specific to the underlying IBD. Other conditions associated with IBD more commonly than in the general population include pericholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation. Hepatotoxicity from some drugs used for colitis should always be considered, although usually presents within 3 weeks of starting medication and not at later stages.

The finding of abnormal liver function tests, rather than symptoms or signs of liver disease, is the most common presentation. Diagnosis of hepatobiliary disorders then follows the standard investigatory pathways for abnormal liver function tests, with ultrasound scanning, serology to identify specific auto-immune or infective causes, and liver biopsy. Predominantly cholestasis or the biliary-type pain will prompt ultrasonographic assessment, which may reveal gall stones, steatosis, be consistent with cirrhosis, or (less often) show an abnormal duct pattern suggestive of PSC.
13.6. Metabolic bone disease

**ECCO Statement 13E**
Diagnosis of osteoporosis in adults is best made from a T score of less than −2.5 on radiographic bone densitometry [EL1a, RG A], all other diagnostic methods having current limitations [EL2b, RG B]. The presence of osteoporosis identifies patients at above average risk for fracture and who should receive treatment [EL2b, RG B].

**ECCO Statement 13F**
Osteopenia may be a prognostic marker for future osteoporosis, but presents little direct risk [EL2b, RG C]. However if the T score is less than −1.5, treatment with calcium, vitamin D and a bisphosphonate should be considered [EL4, RG C]. Pre-existing history of fracture is of substantial adverse prognostic significance and such patients should be treated for osteoporosis even if the T score is normal [EL4, RG C].

13.6.1. Diagnosis and fracture risk
Osteoporosis and osteopenia are common in patients with IBD (20–50%), but the actual number of fractures in IBD is only slightly increased to the general population. In a study using the general practice research database, the relative risk of hip fracture was 1.62 (95% CI 1.24–2.11) for all IBD, 1.49 (1.04–2.15) for ulcerative colitis and 2.08 (1.36–3.18) for Crohn’s disease. Contributing factors include age, steroid treatment, smoking, low physical activity (including that from hospitalisation), inflammatory cytokines, and probably also resection with pouch formation.

Diagnosis is conventionally based on bone densitometry (DEXA scanning), osteoporosis being defined as a T score of less than −2.5. Ultrasound has been suggested as method of screening, but is not yet reliable. The presence of osteoporosis increases the risk of fracture of long bones and of the spine, although probably a great deal less in young patients than was once thought. It is conventional to use a radiological diagnosis of osteoporosis as an indication for specific therapy.

Osteoporosis (T score less than −1.0) is thought by some to be an important risk factor for fracture in its own right, but this is increasingly questioned. It is, however, probable that it is a marker of increased risk of later osteoporosis even if the risk is not absolute. Therapeutic intervention is probably not justified on present knowledge, but continued surveillance for bone loss is important. It is important to put risks into perspective when discussing with patients.

The risks of osteoporosis (and the potential risks from osteopenia) should be explained. The recommended dietary calcium intake should be 1000–1500 mg/day, which often means supplementation even in patients not taking corticosteroids. It should be noted that recommendations for the treatment of osteoporosis apply only to adults over the age of 25 years, and that evidence for treating osteopenia is circumstantial. The diagnosis of osteoporosis in children and long-term consequences of treatment with bisphosphonates are unknown.

13.6.2. Management

**ECCO Statement 13G**
Weight-bearing exercise [EL2b, RG B], stopping smoking [EL3b, RG C], avoiding alcohol excess [EL4, RG D] and maintaining adequate dietary calcium (>1 g/day) [EL2b, RG B] are beneficial. In post-menopausal women with osteoporosis, regular use of bisphosphonates, calcitonin and its derivatives, and raloxifene reduce or prevent further bone loss [EL2b, RG C]. Data in males with osteoporosis are less secure but bisphosphonates are probably of value [EL3b, RG C]. Newer data also support the use of strontium salts [EL2a, RG B].

The risks of osteoporosis (and the potential risks from osteopenia) should be explained. The treatment of osteoporosis is based on studies that are not specific to IBD. Weight-bearing, isometric exercise, stopping smoking, avoiding alcohol excess and maintaining adequate dietary calcium (>1 g/day) are beneficial, but such advice is often overlooked. Hormone replacement treatment is no longer generally advised in post-menopausal women with osteoporosis, because studies have demonstrated a slightly increased risk of breast cancer and of...
cardiovascular events. Regular use of bisphosphonates, calcitomin and its derivatives, and salazosulfapyridine (a selective oestrogen receptor modulator) may reduce or prevent further bone loss. Data in males with osteoporosis are few, but bisphosphonates are probably of value and an important practice point is that testosterone should be measured. Those with low testosterone may benefit from supplementation. Routine administration of vitamin D is not warranted. Patients on corticosteroids for short periods do not merit routine use of bone protection with bisphosphonates, assuming a normal calcium intake and all other risk factors being equal.315

13.7. Other systems

Other systems are found to be abnormal in UC more often than would be expected by chance and these associations may therefore be considered to be extra-intestinal manifestations. Examples include respiratory complaints (especially asthma), cardiac and pericarditic conditions, nephrological disease (both nephritis and amyloidosis), neurological conditions (especially multiple sclerosis) and urinary tract stones.274,302 Their diagnosis and management is not considered in further detail, because the routes to diagnosis are no different from those in general medical practice and because their management is fundamentally independent of that of the colitis. The issue of interstitial nephritis associated with 5-ASA therapy316 is considered in the section on colitis therapy (Section 5.4.1, preceding paper same issue.)289 Anaemia and ulcerative colitis deserves greater proactive management by gastroenterologists than it generally receives, because it is associated with substantial impairment of the quality of life. Reasons for not treating anaemia effectively often dwell on intolerance to oral iron therapy and difficulty in delivering or risks associated with parenteral iron, but this is no longer tenable and expectations of both patients and physicians should be raised.276

13.8. Organisation of services for EIMs associated with ulcerative colitis

ECCO Statement 13 G
Organisation of services to facilitate expert management of extra-intestinal manifestation may include combined or parallel specialist clinics conducted with clinicians from the other relevant disciplines [EL4, RG D]

The more common extra-intestinal manifestations affecting joints and skin may be profitably managed by a close working relationship between the gastroenterologist and rheumatologist or dermatologist respectively. It is easier to ensure that inter-disciplinary knowledge is used to best advantage for the patient by the existence of periodic clinics for rheumatology, dermatology and other specialties held in parallel, and in some cases by joint consultations. Awareness of atypical presentations and of new exploratory therapies is therefore enhanced.

14. Complementary and alternative medicines

14.1. Introduction

The use of complementary and alternative medicine among UC patients is common, and physicians are frequently confronted with questions about their use. Reasons for using such therapies are worries about conventional treatment, including perceived lack of effectiveness and fear about side-effects, in addition to subjective benefit from complementary or alternative therapies. However, evidence for the efficacy and safety of CAMs is often lacking, because there are very few controlled trials that assessed these therapies in UC and even these are underpowered for what they aim to establish. Consequently, because of the lack of power and other methodological problems in the reported studies, it is difficult for physicians to inform their patients adequately. Nevertheless, complementary and alternative treatments warrant further evaluation from public interest alone. Although complementary medicine appears to be generally safe and non-toxic, this cannot be assumed and potential side-effects should be considered for each substance, particularly when microorganisms are used in conjunction with conventional immunomodulators.

14.2. Definitions

Complementary and alternative medicines represent a diverse group of medical and non-medical products and therapeutic approaches that are not presently considered part of conventional therapy. Products that have established efficacy in UC, such as specific probiotics (E. coli Nissle 1917, for example), are not considered complementary or alternative medicines and are described elsewhere (Section 6.2.4, preceding paper same issue). On the other, hand remedies from different, often non-Western, cultures are included in this group of therapies, as well as those that are unproven. An important distinction between alternative and complementary medicine is its relation to conventional therapy. Alternative medicine explicitly excludes concomitant conventional therapy, but complementary medicine allows the complementary approach in conjunction with conventional therapy. It is helpful if patients are aware of this distinction, not least because alternative medicine for a serious, potentially life-threatening condition such as acute severe colitis would be dangerous.

14.3. Use of CAM

ECCO Statement 13B
Alternative medicine for UC as defined above is strongly discouraged [EL5, RG D]

Since alternative medicine by definition does not allow conventional therapy, even when necessary, this type of UC therapy can lead to severe complications from the underlying condition. In contrast, complementary medicine is usually safe and is possible if patients want to use it. From a practical point of view, if patients discuss complementary therapy in the context of conventional medical consultation, it is usually an indicator
that the patient or their family want to know more about their condition, the conventional medicine that is being prescribed, and the therapeutic strategy. It should alert practitioners to unmet need, if only for more detailed explanation.

**ECCO Statement 13C**

UC patients should be asked about the use of alternative and complementary medicines [EL5, RG D]

Complementary and alternative medicines are commonly used by UC patients. Although the use of complementary medicine is considered largely safe, there are published case reports on systemic fungal infection in immunocompromised patients. In addition, herbal medicine such as St John’s Wort, can interact with immunosuppressive agents and need to be checked for potential interactions. It is therefore appropriate to enquire about the use of alternative and complementary medicine.

**ECCO Statement 13D**

There is insufficient evidence for the use of Trichurus suis ova, Saccharomyces boulardii, or Bifidobacteria in the treatment of UC [EL5, RG D]

Although some probiotics and one helminth have been investigated in clinical studies, these publications are considered of insufficient power to take a view on whether to recommend their use. Their design was single centre and sample size too small.

**ECCO Statement 13E**

There is insufficient evidence for the use of acupuncture, Boswellia serrata gum, germinated barley, aloe vera gel and other herbal medicines in the treatment of UC [EL5, RG D]

Other complementary medicines have been studied in small studies or in countries where randomised, double-blind, placebo-controlled trials are not the practice norm for judging the merits of therapy. Because of sample size, study design, concomitant therapies and questionable transferability, the following agents cannot currently be recommended for treating UC, either active disease or as maintenance: acupuncture, Boswellia serrata gum, prebiotic germinated barley foodstuff, aloe vera gel and other herbal medicines. A report on curcumin maintenance therapy (2 g daily, added to aminosaliclyates for 6 months) showed a signal for benefit in a double-blind, placebo-controlled trial of 89 patients. This both needs confirmation and illustrates the need to explore complementary medicines subject to the same rigorous proof of benefit as conventional therapy.

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**Greece**

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**Hungary**

Lakatos
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CORRIGENDUM

Corrigendum to “European-evidence-based consensus on the management of ulcerative colitis: Current management”  

for the European Crohn’s and Colitis Organisation (ECCO)

The Publisher and Authors regret and apologise that Table 6.5 on page 45 was incorrectly printed. The corrected table is:

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Number of patients</th>
<th>Study drugs</th>
<th>Dosage</th>
<th>Duration (months)</th>
<th>Failure to maintain clinical or endoscopic remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruis274</td>
<td>1997</td>
<td>120</td>
<td>E. coli Nissle Mesalazine</td>
<td>200 mg/day 1.5 g/day</td>
<td>3 16%</td>
<td>11%</td>
</tr>
<tr>
<td>Rembacken275</td>
<td>1999</td>
<td>116</td>
<td>E. coli Nissle Mesalazine</td>
<td>200 mg/day 1.2 g/day</td>
<td>12 67%</td>
<td>73%</td>
</tr>
<tr>
<td>Kruis276</td>
<td>2004</td>
<td>327</td>
<td>E. coli Nissle Mesalazine</td>
<td>200 mg/day 1.5 g/day</td>
<td>12 45%</td>
<td>37%</td>
</tr>
<tr>
<td>Ishikawa277</td>
<td>2000</td>
<td>21</td>
<td>Probiotic mixture a number</td>
<td>100 mL</td>
<td>12 27%</td>
<td>90%</td>
</tr>
<tr>
<td>Zocco278</td>
<td>2006</td>
<td>187</td>
<td>Lactobacillus GG Mesalazine Combination</td>
<td>18 × 10⁹ 2.4 g/day</td>
<td>12 15%</td>
<td>20%</td>
</tr>
</tbody>
</table>

a Bifidobacterium bifidum • Bifidobacterium breve • Lactobacillus acidophilus.

b Open label study.

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CORRIGENDUM


The Publisher and Authors regret the omission of the author (Janneke van der Woude) from the above list. The corrected full list of authors is:

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