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ECCO Guideline/Consensus Paper

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Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders

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This is the third European Crohn's and Colitis Organisation [ECCO] consensus guideline that addresses ulcerative colitis [UC]. It has been drafted by 28 ECCO members from 14 European countries. It is derived from and updates the previous ECCO consensus advice on UC.[1–3] All the authors recognise and are grateful to previous ECCO members who contributed to creating the previous consensus guidelines[1–6] on which some of the text is based. Attention is also drawn to other ECCO consensus guidelines which have contributed to this endeavour, on extra-intestinal manifestations [EIMs],[7] malignancy,[8] imaging,[9] small bowel endoscopy,[10] opportunistic infections [OIs],[11] surgery,[12] endoscopy,[13] pathology,[14] anaemia,[15] reproduction and pregnancy,[16] and paediatric UC.[17]

The guideline has been condensed into two papers, the first detailing definitions, classification, diagnosis, imaging, pathology, and management of special situations [EIMs, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders of UC]; and the second describing current therapeutic management [treatment of active disease and maintenance of medically induced remission].

The strategy to define consensus was similar to that previously described in other ECCO consensus guidelines [available at www.ecco-ibd.eu]. Briefly, an open call for participants was made, with participants selected by the Guidelines' Committee of ECCO [known as GuiCom] on the basis of their publication record and a personal statement. Working parties were established to review the consensus statements published in 2012,[1–3] after which a recommendation was issued on whether they required revision based upon advances in the published literature. There was agreement that extensive review of histopathology, endoscopy, OI, anaemia, EIMs, surgery, and pregnancy was not required, as these subjects are reviewed in other recent ECCO guidelines[7,11–16]; rather, abbreviated text and selected statements from these guidelines specific to UC are provided. Paediatric UC is dealt with in a separate ECCO initiative[17] which is currently being updated.

Provisional ECCO statements and supporting text were written following a comprehensive literature review, then refined following two voting rounds which included national representative participation by ECCO's 35 member countries. The level of evidence was graded according to the Oxford Centre for Evidence-Based Medicine [www.cebm.net]. The ECCO statements were finalised by the authors at a meeting in Barcelona in October 2015 and represent consensus with agreement of at least 80% of participants. Consensus statements are intended to be read in context with their qualifying comments and not in isolation. The supporting text was then finalised under the direction of each working group leader [FM, FC, AD, PG, FR], including an updated literature search to October 2016 of the most relevant [eight] journals, before being integrated by a consensus leader [MH]. This consensus guideline is pictorially represented within the freely available ECCO e-Guide [http://www.e-guide.ecco-ibd.eu/].

Section 1. Definitions

1.1. Introduction

UC is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in developed countries. Its precise aetiology is unknown, and therefore curative medical therapy is not yet available. Within Europe there is an east-west and north-south gradient, but the incidence appears to have increased in southern and eastern countries during recent years.[18–20] Patients may live with a considerable symptom burden and high risk of disability[21] despite medical treatment.[22] Clinicians must advise and treat patients on the basis of currently available information. Despite robust evidence from rigorously conducted randomised trials, the strict and somewhat necessarily restrictive inclusion and exclusion criteria in trial design may limit translation of such evidence to 'real-world' patients.

1.2. Definitions

Ulcerative colitis [UC] is a chronic inflammatory condition that causes continuous mucosal inflammation of the colon, usually without granulomas on biopsy. It affects the rectum and to a variable extent the colon in a continuous fashion, and is characterised by a relapsing and remitting course.[23] Inflammatory bowel disease unclassified [IBDU] is the term best suited for a minority of cases in which a definitive distinction between UC, Crohn's disease, or other causes of colitis cannot be made after taking into account the history, endoscopic appearance, histopathology of multiple mucosal biopsies, and appropriate radiology.[23,24] Indeterminate colitis is a term reserved for pathologists to describe a colectomy specimen with overlapping features of UC and Crohn's disease.[24,25] Detailed information on definitions can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[1,23,24,26–39]

Table 1.1. Distribution of UC [adapted from Silverberg *et al.*[23]].

Term	Distribution	Description
E1	Proctitis	Involvement limited to the rectum [i.e. proximal extent of inflammation is distal to the recto-sigmoid junction]
E2	Left-sided	Involvement limited to the proportion of the colon distal to the splenic flexure [analogous to 'distal' colitis]
E3	Extensive	Involvement extends proximal to the splenic flexure, including pan-colitis

Table 1.2. Disease activity in UC [adapted from Truelove & Witts[32]].

	Mild	Moderate 'in between mild and severe'	Severe
Bloody stools/day	< 4	4 or more *if*	≥ 6 *and*
Pulse	< 90 bpm	≤ 90 bpm	> 90 bpm *or*
Temperature	< 37.5°C	≤ 37.8°C	> 37.8°C *or*
Haemoglobin	> 11.5 g/dl	≥ 10.5 g/dl	< 10.5 g/dl *or*
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h *or*
CRP	Normal	≤ 30 mg/l	> 30 mg/l

Table 1.3. Montréal classification of disease activity in UC [adapted from Silverberg et al.[23] and Satsangi et al.[24].]

	S0 Remission	S1 Mild	S2 Moderate	S3 Severe
Stools/day	Asymptomatic	≤ 4	> 4	≥ 6 *and*
Blood		May be present	Present	Present
Pulse		All normal	Minimal, or no signs of systemic toxicity	> 90 bpm *or*
Temperature				> 37.5°C *or*
Haemoglobin				< 10.5 g/dl *or*
ESR				> 30 mm/h

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; bpm, beats per minute.

Section 2. Classification

2.1. Classification according to disease extent

ECCO statement 2A

Disease extent influences treatment modality, whether oral and/or topical therapy [EL1], and determines onset and frequency of surveillance [EL2]. It is defined by the maximal macroscopic extent at colonoscopy, classified as proctitis, left-sided colitis, and extensive colitis

Extent of inflammation influences the patient's management and the choice of delivery system for a given therapy. For example, topical therapy in the form of suppositories or enemas is usually the first-line choice for proctitis and left-sided colitis, respectively, whereas oral therapy [often combined with topical therapy] is appropriate for extensive colitis. Extent of colitis influences the risk of development of dysplasia or colorectal cancer [CRC], and thus the start and the frequency of colonoscopic surveillance.[40–42]

Patients with extensive colitis have the highest risk of developing CRC, whereas those with proctitis alone have a risk similar to the general population. Patients with left-sided colitis [including procto-sigmoiditis] carry an intermediate risk; however, their risk approaches that of patients with extensive colitis as disease duration increases.[43–46] Therefore, patients with left-sided and extensive colitis are generally advised to have surveillance colonoscopy, whereas patients with proctitis do not need such surveillance[46] [see Section 8].

It should be noted that the macroscopic extent at colonoscopy may underestimate the extent of disease as compared with histology, and biopsies are necessary to determine the full extent of colonic inflammation, providing prognostic information and risk stratification for dysplasia surveillance.[13,47–51] Proximal extension of proctitis or left-sided colitis may occur in 20–50% of adult patients with UC.[52–54]

2.2. Classification according to disease severity

ECCO statement 2B

Disease severity influences treatment modality and route of administration [EL1]. Clinical indices of disease severity have not been adequately validated, although clinical, laboratory, imaging, and endoscopic parameters, including histopathology, impact on patients' management [EL 2]. Remission is defined as stool frequency ≤ 3/day, no rectal bleeding, and normal mucosa at endoscopy [EL5]. Absence of a histological acute inflammatory infiltrate predicts quiescent course of disease [EL3]

2.2.1. Activity and pattern of disease

It should be standard practice to confirm the presence of active colitis by flexible sigmoidoscopy and biopsy before starting treatment, which may identify unexpected causes of symptoms that mimic active disease such as cytomegalovirus [CMV] colitis, rectal mucosal prolapse, Crohn's disease, malignancy, or even irritable bowel syndrome and haemorrhoidal bleeding. In addition, all patients with presumed active disease require stool cultures including *Clostridium difficile* toxin assay to exclude enteric infection. Patients with an appropriate travel history should also have stool microscopy to exclude parasitic infections.

In a population-based study from Copenhagen County, approximately 50% of patients are in clinical remission at any time during a given year.[55] However, 90% had a cumulative probability of a relapsing course after 25 years of follow-up. Disease activity in the first 2 years after diagnosis indicated [probability 70% to 80%] an increased likelihood of five consecutive years of active disease. In a Norwegian study involving 781 patients, an inverse relationship was noted between the time to first relapse and the total number of relapses over a 10-year period.[56] In the IBSEN cohort, the 10-year cumulative relapse rate was 83%, whereas patients older than 50 years had a significantly reduced relapse rate.[28] 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.[33,57,58] A population-based study carried out in the county of Copenhagen[59] described the outcome in 1575 patients in the first 5 years following diagnosis of UC between 1962 and 2005. In the most recent period, the percentage of patients experiencing an 'indolent' course [no relapse during the first 5 years after diagnosis] was 13%, 74% had a 'moderate' course [two or more relapses within the first 5 years, but less than every year], and 13% had an 'aggressive' course [disease activity at least every year during the first 5 years].

Microscopic involvement is also important. In quiescent UC, a chronic inflammatory cell infiltrate was present in all biopsy specimens and crypt architectural irregularities were seen in two-thirds; 52% of patients with an acute inflammatory cell infiltrate relapsed after 12 months of follow-up, compared with 25% who relapsed without such an infiltrate [$p = 0.02$]. Similarly, relapse rates were higher in those with crypt abscesses, mucin depletion, and mucosal breaks.[60] The degree of microscopic bowel inflammation is also a risk factor for CRC in patients with long-standing, extensive UC.[49]

2.2.2. Choice of index

Detailed information on the choice of index can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[32,33]

2.2.3. Clinical and laboratory markers of severity

Among objective clinical features, bloody stool and frequency, body temperature, and heart rate are good predictors of outcome. Laboratory markers have been studied extensively with varying degrees of success. The widely used acute phase C-reactive protein [CRP] is not as useful in UC as it is in Crohn's disease for the assessment of disease activity, except in acute severe colitis where standard values have been established both for adults and children.[61–63] In patients receiving parenteral steroids, a raised CRP > 45 mg/l 48 to 72 h following hospital admission for severe colitis together with three to eight stools a day is highly predictive for colectomy.[64] Elevated erythrocyte sedimentation rate [ESR], elevated serum procalcitonin,[65] and [low] albumin levels have been studied, but none has been demonstrated to be superior to CRP.[66] The most studied stool markers are faecal calprotectin and lactoferrin, though other markers such as elastase and S100A12 have also shown accuracy at detecting colonic inflammation.[67–71] Calprotectin has value for diagnosis and assessment of disease severity [having a good correlation with endoscopic indices, relapse, and response to treatment].[72–76] Calprotectin can be used as a marker for relapse in patients with inactive inflammatory bowel disease [IBD]. Doubling of calprotectin levels was associated with an increased risk of relapse (hazard ratio [HR]: 2.01; 95% confidence interval [CI]: 1.52–2.65). It must be stressed, however, that none of these markers is specific for UC, since they mostly represent active colonic inflammation.

2.2.4. Remission

As with disease activity, there is no fully validated definition of remission. The consensus group agreed that the best way to define remission is a combination of clinical parameters [stool frequency ≤ 3/day with no bleeding] and no mucosal lesions at endoscopy.[77]

2.3. Classification according to age at onset or concomitant primary sclerosing cholangitis

ECCO statement 2C

A classification of ulcerative colitis according to age at onset is of value [EL2], as early-onset disease has a less favourable course. Classification according to the concomitant presence of primary sclerosing cholangitis is important as it increases the need for and frequency of surveillance colonoscopy [EL2]

Young patients (below 40 years [y]) with UC tend to have more aggressive disease and require more immunomodulators [IMs] and surgical intervention compared with later-onset disease.[29] All current available therapies for UC have shown an equivalent efficacy in children when compared with adults. The apparently higher risk of CRC in patients with childhood-onset UC almost certainly reflects the duration of disease. However, concomitant primary sclerosing cholangitis [PSC] is an important feature in patients with UC, as it increases the associated risk for CRC.[7,43]

2.4. Use of molecular markers

ECCO statement 2D

The routine clinical use of genetic or serological molecular markers is not recommended for the classification of ulcerative colitis [EL2]

Detailed information on molecular markers can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[78–101]

Section 3. Diagnosis and Imaging

3.1. Clinical features and risk factors

3.1.1. Clinical features of ulcerative colitis

ECCO statement 3A

Symptoms of ulcerative colitis are dependent upon extent and severity of disease and include bloody diarrhoea, rectal bleeding, tenesmus, urgency, and faecal incontinence. Nocturnal defaecation and fatigue are often reported. Increasing bowel frequency, abdominal pain, anorexia, and fever suggest severe colitis [EL5]

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.[102] UC 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 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 [more common in PSC] and peri-appendiceal patchy inflammation.[103]

More than 90% of patients with active UC report having rectal bleeding. Associated symptoms generally reflect the severity of mucosal disease, and may differ according to disease extent.[104–114] Loose stools [a decrease in stool consistency] for more than 6 weeks differentiates extensive UC from most cases of infectious diarrhoea.[115] Patients with active disease also complain of rectal urgency, tenesmus, mucopurulent exudate, nocturnal defaecation, and crampy abdominal pain. In contrast, patients with proctitis usually present with rectal bleeding, urgency, tenesmus, and occasionally severe constipation.[107,109] Although simple fistulae may occasionally occur in UC, recurrent or complex perianal fistulae should always raise the suspicion of Crohn's colitis.[116]

The onset of UC is usually insidious; symptoms are often present for weeks or even months before medical advice is sought. Presentation with a severe attack occurs in about 15%, with systemic symptoms including weight loss, fever, tachycardia, nausea, and vomiting.[27,117,118] EIMs, in particular axial or peripheral arthropathy, episcleritis, and erythema nodosum may accompany the presentation in about 10–20% of cases and can precede intestinal symptoms in 10% of patients.[7,119–132]

3.1.2. Risk factors for ulcerative colitis

ECCO statement 3B

A family history of ulcerative colitis or Crohn's disease increases the risk for developing ulcerative colitis [EL2]. Appendicectomy for proven appendicitis before adulthood, and smoking, reduce the risk and severity of UC [EL3]. Smoking cessation may predispose to ulcerative colitis [EL3]

Relatives of patients with UC have an increased risk of developing the disease.[133] The risk of UC is greatest in first-degree relatives (incidence rate ratio [IRR]: 4.08; 95% CI: 3.81–4.38), but is also raised in second-degree [IRR: 1.85; 95% CI: 1.60–2.13], and third-degree relatives [IRR: 1.51; 95% CI: 1.07–2.12] of UC patients, as well as in relatives of patients with Crohn's disease although in a less pronounced fashion.[134]

Tobacco intake protects against and reduces the severity of UC,[56,135–137] but may not improve the natural history of the disease.[138] In contrast, ex-smokers have approximately a 70% higher risk of developing the disease, which is often more extensive and refractory to treatment compared with individuals who have never smoked.[139–141] Smoking might protect against PSC or pouchitis, but the data are inconsistent.[142–144]

Appendicitis and mesenteric lymphadenitis during childhood or adolescence are linked to a reduced risk of UC in adulthood.[102,145–150] The protective effect of appendectomy is additional to that of smoking, but does not appear to protect against the development of PSC.[151] When appendectomy is performed after the onset of UC, the effect [if any] on the course of disease is less clear and is subject to ongoing research.[152]

Non-selective non-steroidal anti-inflammatory drugs [NSAIDs] may exacerbate the disease.[56,139–141,153–157] In contrast, preliminary evidence from open-label studies and a double-blind controlled trial suggests that short-term treatment with selective COX-2 inhibitors is safe.[156,158]

3.2. History, examination, and diagnosis

3.2.1. Medical history

ECCO statement 3C

A full medical history should include detailed questioning about the onset of symptoms, rectal bleeding, stool consistency and frequency, urgency, tenesmus, abdominal pain, incontinence, nocturnal diarrhoea, and extra-intestinal manifestations. Recent travel, possible contact with enteric infectious illnesses, medication [including antibiotics and non-steroidal anti-inflammatory drugs], smoking habit, sexual behaviour, family history of inflammatory bowel disease or colorectal cancer, and previous appendectomy should be recorded [EL5]

The diagnosis of UC is suspected in the context of compatible clinical symptoms. Infectious or drug-induced forms of colitis should be excluded. Family history and EIMs should be discussed.[7,159–164]

3.2.2. Examination

ECCO statement 3D

Physical examination should include pulse, blood pressure, temperature, weight and height, and abdominal examination for distension and tenderness. Perianal inspection and digital rectal examination may be performed if appropriate. Physical examination may be unremarkable in patients with mild or moderate disease [EL5]

Findings on physical examination depend on the extent and severity of disease. Examination of patients with mild or moderate activity is usually unremarkable, apart from blood on rectal examination. Patients with a severe attack may exhibit fever, tachycardia, weight loss, abdominal tenderness, abdominal distension, and reduced bowel sounds.[165]

3.2.3. Diagnosis

ECCO statement 3E

A 'gold standard' for diagnosis of ulcerative colitis does not exist. It is established by clinical, laboratory, imaging, and endoscopic parameters, including histopathology. An infective cause should be excluded. Repeat endoscopy with histopathological review after an interval may be necessary if diagnostic doubt remains [EL5]

The natural history of UC is characterised by episodes of relapse and periods of remission. An unremitting, continuous course occurs in approximately 5% of the cases, as does a single acute episode followed by prolonged remission.[55] The IBSEN study noted that approximately 60% of patients experienced a decrease in symptoms over time.[56] The frequency of relapse [pattern of disease] is usually defined during the first 3 years, and may be characterised as continuous [persistent UC symptoms without remission], frequent [≧ 2 relapses/year] or infrequent [≦ 1 relapse/year].[39] In the recent Epicom study, the proportion of patients with UC in remission rose from 11% at the time of diagnosis to 71% after 1 year of follow-up.[27] It is important to rapidly establish the diagnosis, extent, and severity of disease, as these influence treatment options and possibly disease progression.[114] It is unreasonable to expect the histopathological analysis alone to lead to a diagnosis, but normal mucosal biopsies effectively exclude active UC as the cause of symptoms. In 10% of patients, the diagnosis may change to Crohn's disease or be refuted during the first 5 years.[166]

3.3. Investigation and procedures to establish a diagnosis

3.3.1. Initial investigations

ECCO statement 3F

Initial investigations should include full blood count, electrolytes, liver and renal function, iron studies, vitamin D level, C-reactive protein, and faecal calprotectin [EL5]. The immunisation status should be assessed [EL5]. Infectious diarrhoea including *C. difficile* should be excluded [EL2]. Endoscopy and histology should be performed

At diagnosis, every patient should have a full blood count, inflammatory markers [CRP], electrolytes and liver function tests, and a stool sample for microbiological analysis.[165]. Faecal calprotectin is an accurate marker of colonic inflammation. Laboratory markers of chronic inflammation may be normal in mild or moderate UC. The full blood count may reveal thrombocytosis as a result of the chronic inflammatory response, anaemia indicating severe or chronic active disease, and leucocytosis which raises the possibility of an infectious complication. For UC, and with the exception of proctitis, CRP broadly correlates with clinical severity.[62,66,167–169] 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.[63,64,170] CRP above 10 mg/l after a year of extensive colitis predicted an increased risk of surgery.[122,171] Neither CRP nor ESR is specific enough to differentiate UC from infectious or other causes of colitis. Stool specimens should be obtained to exclude common pathogens and specifically assayed for *C. difficile* toxin. Additional tests may be tailored according to the medical history, for instance the examination of fresh, warm stool samples for amoebae or other parasites. Endoscopy [flexible sigmoidoscopy or colonoscopy] together with histological analysis are required at diagnosis and may be required to confirm disease relapse [see 3.2.3.].

3.3.2. Microbial investigations

ECCO statement 3G

Microbial testing is recommended in patients with colitis relapse. This includes testing for *C. difficile* and Cytomegalovirus infection [EL3]

Nosocomial *C. difficile* infection is a growing health problem and has been associated with higher mortality and health resources' utilisation.[172–177] ECCO guidelines now recommend screening with every disease flare.[11] Moreover, microbial stool tests should be performed in the case of treatment-refractory or severe relapse.[178–182]

Reactivation of CMV can occur in UC, particularly [but not invariably] in immunosuppressed patients with severe colitis.[183–185] Although CMV reactivation may not cause disease relapse, CMV infection can cause refractory or severe relapses. It should be excluded in patients who relapse while receiving immunosuppressant therapy. The optimal method for detecting clinically relevant CMV infection in patients with colitis has not been established, but most experts agree it requires histology/immunohistochemistry rather than polymerase chain reaction [PCR] detection of CMV in the blood. Occasional intranuclear inclusion bodies consistent with CMV on histopathology do not necessarily indicate clinically significant infection, but multiple intranuclear inclusions are usually significant.[169,186–188] Further detail, including information on therapy, can be reviewed in the ECCO Consensus on OIs[11] and in a recent review.[189]

3.3.3. Biomarkers

The most widely studied serological markers are perinuclear antineutrophil cytoplasmic antibodies [pANCAs] and anti-*Saccharomyces cerevisiae* antibodies [ASCAs]. Usually, pANCAs are detected in up to 65% of patients with UC and in less than 10% of patients with Crohn's disease.[190,191] Given the current limited sensitivity of these markers, their routine use for the diagnosis of UC and for therapeutic decisions is not clinically justified.

Several neutrophil-derived proteins such as calprotectin, elastase, lysozyme, and lactoferrin have been evaluated as markers of intestinal inflammation in IBD.[192–195] Of these, faecal calprotectin appears to be the most sensitive.[196] Multiple studies emphasise the value of calprotectin in selecting patients for diagnostic investigation, in the assessment of disease severity [it correlates well with endoscopic indices], and in the diagnosis of relapse and response to treatment.[72–75,197] As with all faecal tests, calprotectin lacks the specificity to discriminate between different types of inflammation; nevertheless, it represents a useful non-invasive marker in the follow-up of UC patients.[198,199] Home-based calprotectin assessment provides a rapid method to measure gut inflammation and seems to be a reliable alternative to enzyme-linked immunosorbent assay [ELISA]; it presents a new way of monitoring patients by eHealth.[200]

3.4. Assessment of extent, severity, and activity

3.4.1. Discontinuous inflammation in UC

3.4.1.1. Rectal sparing and caecal patch

Macroscopic and microscopic rectal sparing has been described in untreated children with UC.[201–203] In adults, a normal or patchy inflammation in the rectum is more likely to occur due to topical therapy.[204,205] Patchy inflammation in the caecum is referred to as a 'caecal patch' and may be observed in patients with left-sided colitis. In the presence of macroscopic and histological rectal sparing or a caecal patch in newly diagnosed colitis, evaluation of the small bowel in addition to an ileo-colonoscopy is recommended. The natural history of patients with patchy right colonic inflammation seems to be similar to those with isolated left-sided UC.[187,190]

3.4.1.2. Appendiceal skip lesions

Involvement of the appendix as a skip lesion is reported in up to 75% of patients with UC.[206] Appendiceal inflammation has been associated with a more responsive course and a higher risk of pouchitis after ileal pouch anastomosis.[207–210] Although both findings require confirmation, a recent retrospective study reported a similar clinical course in patients with an atypical distribution of inflammation when compared with those with a typical distribution in terms of remission, relapse, disease extension, colectomy, and mortality.[211]

3.4.1.3. Backwash ileitis

Continuous extension of macroscopic or histological inflammation from the caecum into terminal ileum is termed 'backwash ileitis', and is observed in up to 20% of patients with extensive colitis. Rarely, ileal erosions may occur in patients without caecal involvement, which challenges the pathogenic theory that maintains that backwash ileitis stems from a reflux of caecal contents into the ileum.[212–214] Patients with backwash ileitis seem to be prone to a more refractory course of disease[213] which may include an increased risk of colon neoplasia in proctocolectomy specimens.[215] However, it does not appear to be correlated with poor pouch outcomes.[216] Additional imaging of the small bowel should be considered in cases of macroscopic backwash ileitis, to differentiate UC from Crohn's disease.

3.4.1.4. Small bowel

Small bowel radiology, by follow-through, computer tomographic [CT] or magnetic resonance [MR] enterography, or capsule endoscopy, as reviewed in the ECCO consensus on diagnosis in Crohn's disease[217] and small bowel endoscopy in IBD,[10] is not routinely recommended. When differential diagnosis is difficult [in the presence of rectal sparing, atypical symptoms, and/or macroscopic backwash ileitis], an extended diagnostic workup to exclude Crohn's disease in addition to an ileo-colonoscopy is warranted.

3.4.2. Activity indices

ECCO statement 3H

Instruments for measuring clinical and/or endoscopic disease activity in ulcerative colitis are available. The incorporation of a simple clinical and/or endoscopic scoring system is desirable, to improve care of ulcerative colitis patients and to enhance a standardised IT system for inflammatory bowel disease [EL5]. Immediate admission to hospital is warranted for all patients fulfilling criteria for severe colitis, to prevent delayed decision making which may lead to increased perioperative morbidity and mortality [EL4]

The original classification of severe UC was proposed by Truelove and Witts in 1955.[32] This classification is still considered to be the gold standard for rapid identification of outpatients in need of immediate admission to hospital and intensive treatment.[218,219]

3.4.3. Investigations for acute severe colitis at admission

At the time of admission, patients with acute severe colitis should have full blood count, inflammatory markers [CRP or ESR], electrolytes, and liver function tests, along with a stool sample for culture and assay of *C. difficile* toxin.[219]

A plain abdominal radiograph should be performed to exclude colonic dilatation [≧ 5.5 cm] and 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 a study reporting 51 episodes of severe colitis, the extent of disease was overestimated in 18% and underestimated in 8%.[64] 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 is associated with a poor response to treatment.[220,221]

Flexible sigmoidoscopy should confirm the diagnosis of severe colitis and help exclude infection, particularly CMV.[183,184,222] Empirical treatment may be required if CMV is strongly suspected [such as a patient on IMs with high fever], in which case urgent histopathology should be requested, potentially with a diagnosis within 4 h. Phosphate enema preparation before flexible sigmoidoscopy is considered safe.[223] Full colonoscopy in patients with acute severe colitis is not recommended, in particular in patients on corticosteroids.[224] Endoscopic criteria for severe colitis include haemorrhagic mucosa with deep ulceration, mucosal detachment on the edge of these ulcerations, and well-like ulceration,[225,226] all of which can be assessed by flexible sigmoidoscopy.

3.4.4. Reassessment of extent and severity

ECCO statement 3I

Endoscopic remission is predictive of good outcome [EL2]. Endoscopic reassessment is appropriate at relapse, for steroid-dependent or -refractory ulcerative colitis or when considering colectomy [EL5]

Despite the importance of disease location in determining prognosis, risk of cancer, and choice of therapy, the appropriateness of periodic restaging after index colonoscopy has never been studied. In a Norwegian population-based cohort study, mucosal healing after 1 year of treatment was associated with a low risk of future colectomy, necessary in 1.6% of the patients with mucosal healing compared with 7% of those without healing.[227] Another study showed 40% of patients who achieved endoscopic remission—defined as a lack of significant inflammation at endoscopy and on rectal biopsy—remained asymptomatic during 1 year of follow-up, in contrast to only 18% of patients that failed to achieve endoscopic remission.[228] A hospital-based inception cohort analysis in patients with newly diagnosed UC, who were prescribed corticosteroid therapy, evaluated the disease course using clinical [Powel–Tuck] and endoscopic [Baron] indices after 3 and 6 months and then every 6 months. Outcomes at the third month [early response] were used to identify patients with complete, partial, or no response. After 5 years, significant differences between complete and partial responders in the rates of hospitalisation, immunosuppressive therapy, and colectomy were noted. Absence of mucosal healing was the only factor associated with negative outcomes and a more aggressive disease course.[229] A prospective multicentre study analysed patients with active, mild-to-moderate UC treated with oral and rectal mesalamine. Those in clinical remission that presented with less severe endoscopic scores—defined as normal-looking mucosa with only mild redness and/or friability—were less likely to relapse after 1 year than patients solely in clinical remission.[230]

3.5. Endoscopy, ultrasound, and colonography

3.5.1. Endoscopic features

ECCO statement 3J

The most common endoscopic feature of ulcerative colitis is continuous, confluent colonic involvement with clear demarcation of inflammation and rectal involvement [EL2]. Endoscopically severe ulcerative colitis is defined by mucosal friability, spontaneous bleeding and ulcerations [EL2]

Endoscopic changes characteristically commence at 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.

A wide variation in the endoscopic interpretation of disease activity is acknowledged.[231] Granularity, vascular pattern, ulceration, and bleeding and/or friability have been reported to predict the global assessment of endoscopic severity[232]; bleeding and friability are determinants within the Mayo score for UC, which is widely used for clinical trial recruitment [see Table 2.1.]. The Ulcerative Colitis Endoscopic Index of Severity [UCEIS] evaluates the vascular pattern and the presence of bleeding and ulceration, each with 3 or 4 levels of severity.[231] This is the first validated endoscopic index of severity in UC. The final UCEIS score is the sum of all three descriptors in the worst affected area of the colon visible at sigmoidoscopy. Although the original version of the UCEIS[231] attributed a score of 1 to the normal appearance of a descriptor, a decision was made to change the numbering of the levels: a normal appearance now corresponds to a score of 0, so that the simple sum of the UCEIS ranges from 0 to 8.[233]

The endoscopic features of mild inflammation are erythema, vascular congestion, and at least partial loss of the visible vascular pattern. Moderately active colitis is characterised by a complete loss of vascular pattern, blood adherent to the surface of the mucosa, and erosions, often with a coarse granular appearance and mucosal friability [bleeding to light touch]. Severe colitis is characterised by spontaneous bleeding and ulceration[103,231,233–235] [see Table 3.1., in Dignass et al.[1]]. In contrast to Crohn's disease, ulcers in severe UC are always embedded in inflamed mucosa. The presence of deep ulceration is a poor prognostic sign.[234] In long-standing disease, mucosal atrophy can result in loss of haustral folds, luminal narrowing, and post-inflammatory ['pseudo'] polyps.[236] The meaning of 'mucosal healing' in UC has therefore been the subject of detailed review.[237]

3.5.2. Colon capsule endoscopy

Detailed[238] information on colon capsule endoscopy can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.

3.5.3. Abdominal ultrasound

Detailed information on abdominal ultrasound can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[239–244]

3.6. Colonic stenosis in ulcerative colitis

ECCO statement 3K

If colonic stenosis occurs in ulcerative colitis, multiple endoscopic biopsies should be taken to exclude carcinoma, followed by multidisciplinary team review. Computer tomographic colonography should be performed if biopsies are not obtained or the stricture is not traversed [EL5]

In long-standing UC, a colonic stricture signals an increased risk for CRC and requires careful histological assessment.[245] Initially the

Table 2.1. Mayo score for ulcerative colitis[33,239] [www.gastrojournal.org for full details].

Mayo index	0	1	2	3
Stool frequency	Normal	1–2/day > normal	3–4/day > normal	5/day > normal
Rectal bleeding	None	Streaks	Obvious	Mostly blood
Mucosa	Normal	Mild friability	Moderate friability	Spontaneous bleeding
Physician's global assessment	Normal	Mild	Moderate	Severe

dysplasia should be confirmed by a second pathologist [this is the most important aspect in the diagnosis of dysplasia] and then management discussed in a multidisciplinary team. If colonoscopy is incomplete due to a stricture, CT colonography should assess the mucosal pattern proximal to the stricture and exclude extra-intestinal pathology.[246]

Section 4. Histopathology

4.1. General

Histopathology is used for diagnosis, assessment of disease activity, and identification of intraepithelial neoplasia [dysplasia] and cancer. The following section represents extracts and updates of the ECCO guideline on histopathology.[14]

4.2. Microscopic features

UC is a chronic inflammatory process, limited to the mucosa. A large number of microscopic features have been evaluated, and they can be broadly classified into four main categories[14,169,247]: mucosal architecture, lamina propria cellularity, neutrophil granulocyte infiltration, and epithelial abnormality.

Additional detailed information on microscopic features, specifically on the four main categories, can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[14,169,247–254]

ECCO statement 4A

For a reliable diagnosis of ulcerative colitis, a minimum of two biopsies from at least five sites around the colon [including the rectum] and the ileum should be obtained [EL 2]

ECCO statement 4B

Biopsies should be accompanied by clinical information, including endoscopic findings, duration of disease and current treatment. Samples should be fixed immediately by immersion in buffered formalin or an equivalent solution before transport [EL 5]

4.3. Microscopic features—appraisal of the diagnosis

4.3.1. Early stage disease

Not all the microscopic features found in UC are observed in early stage disease; only about 20% of patients show crypt distortion within 2 weeks of the first symptoms of colitis. The distinction from infectious colitis [acute self-limiting colitis], which is characterised by preserved crypt architecture and acute inflammation, is therefore a major concern.[14,169]

ECCO statement 4C

Basal plasmacytosis is the earliest diagnostic feature with the highest predictive value for the diagnosis of ulcerative colitis [EL 3]. Preserved crypt architecture and the absence of a transmucosal inflammatory cell infiltrate do not rule out ulcerative colitis at an early stage. Repeat biopsies after an interval may help to solve differential diagnostic problems and establish a definitive diagnosis by showing additional features [EL 5]

Focal or diffuse basal plasmacytosis has been recognised as the earliest feature with the highest predictive value for UC diagnosis. It can be identified in 38% of patients within 2 weeks after symptoms presentation. During this period, the distribution pattern of basal plasmacytosis is focal, but may eventually change into a diffuse pattern throughout the disease course.[250] Widespread mucosal or crypt architectural distortion, mucosal atrophy, and an irregular or villous mucosal surface appear later during the evolution of disease [at least 4 weeks after presentation].

4.3.2. Established disease

ECCO statement 4D

The microscopic diagnosis of ulcerative colitis is based upon the combination of widespread crypt architectural distortion and mucosal atrophy, and a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis, with active inflammation causing cryptitis and crypt abscesses [EL 2]

The exact number of features needed for UC diagnosis has not been established. A correct diagnosis of UC is reached in approximately 75% of cases where two or three out of the four following features occur: severe crypt architectural distortion; severe decreased crypt density; an irregular surface; and heavy diffuse transmucosal inflammation, in the absence of genuine granulomas.[251,255]

ECCO statement 4E

A decreasing gradient of inflammation from distal to proximal favours a diagnosis of ulcerative colitis [EL5]. Treatment may change the classical distribution pattern of inflammation. Awareness of these treatment-related effects is important in the evaluation of biopsies from treated patients to avoid misdiagnosis [EL3]

In an untreated patient, UC presents a typical pattern of continuous inflammation that begins in the rectum and extends proximally with a gradual decrease in severity. The transition between the involved and the normal mucosa is abrupt.[14,169] However, unusual distribution patterns can occur.

In long-standing disease, the extent of gut involvement decreases during the natural evolution of the disease or after efficient therapy. Histology may show atypical features, such as change from continuous to discontinuous inflammation ['patchiness'] and/or restoration of the rectal mucosa [rectal sparing].[204,248,256] Awareness of these morphological features is important to avoid misdiagnosis, in particular the erroneous change of diagnosis to Crohn's disease.[14,168]

ECCO statement 4F

In quiescent disease, the mucosa may still show features related to architectural damage and recovery, as well as disappearance of basal plasmacytosis and increased transmucosal cellularity. Active inflammation is usually not observed [EL 3]

Quiescent [or clinically inactive] disease is characterised by the lack of active inflammation, i.e. mucosal neutrophils, whereas features related to chronic mucosal injury, such as crypt distortion and atrophy as well as Paneth cell metaplasia, may persist.[14,169,257] Histological mucosal healing is characterised by the resolution of

crypt architectural distortion and inflammatory infiltrate.[14] However, the mucosa can still show some features of sustained damage, such as decreased crypt density with branching and atrophy [shortening] of crypts. Reduced epithelial regeneration will usually reduce mucin depletion, i.e. restore the mucin content of epithelial cells.[14,168]

4.4. Microscopic features—disease activity

ECCO statement 4G

Histological healing is distinct from endoscopic mucosal healing. Histological inflammation may persist in cases with endoscopically quiescent disease and has been associated with adverse outcomes [EL2]

Disappearance of mucosal inflammation following treatment has been observed[205]; thus biopsies can be used to distinguish between quiescent and active disease, as well as to assess the different grades of disease activity.[14] Different scoring systems have been introduced for this purpose, particularly in therapeutic trials.[60,257–261] No standard definition of histological remission or 'histological mucosal healing' exists.[257] As a consequence, definitions of pathological remission range from residual inflammation with persistent architectural distortion, to normalisation of the colonic mucosa.[257]

Several histological features—such as epithelial damage in association with neutrophils, persistence of an increased transmucosal lamina propria cellularity with basal plasmacytosis and/or presence of basal lymphoid aggregates or a high number of eosinophils—have been associated with a substantial risk of relapse.[14,262–267] The potential value of histopathology to predict relapses and to adequately evaluate the level of inflammation may have implications in therapeutic management.[51,268]

Histological mucosal healing is distinct from endoscopic mucosal healing. Several studies have reported a higher sensitivity for histological diagnosis, with the microscopic analysis yielding more severe diagnoses than those suspected at endoscopy.[266,269–271] Histological and endoscopic activity scores closely correlate in severe and inactive disease, but important misclassifications exist for mild disease.[270] The value of histopathology as the [primary or secondary] endpoint to assess disease activity is frequently overlooked in clinical trials.[257,272,273]

4.5. Microscopic features—upper gastrointestinal tract

Minimal to mild non-specific and focally enhanced gastritis may be present in children and adolescents diagnosed with UC.[255,274–279]

Section 5. Extra-intestinal Manifestations

There follows extracts and updates of the ECCO guideline on EIMs[7] and anaemia.[15]

5.1. Anaemia

Anaemia is common in UC, found in 21% of all patients.[280]

Table 5.1. Simple scheme for estimation of total iron requirement [from Dignass et al.[15]].

Haemoglobin g/dl	Body weight < 70 kg	Body weight ≥70 kg
10–12 [women] 10–13 [men]	1000 mg	1500 mg
7–10	1500 mg	2000 mg

5.1.1. Diagnosis of anaemia

ECCO statement 5A [statement 1D in Dignass et al.[15]]

Diagnostic criteria for iron deficiency depend on the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin < 30 μg/l is an appropriate criterion [EL 2]. In the presence of inflammation, a serum ferritin up to 100 μg/l may still be consistent with iron deficiency [EL 4]

ECCO statement 5B [statement 1E in Dignass et al.[15]]

In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anaemia of chronic disease are serum ferritin > 100 μg/l and transferrin saturation < 20%. If the serum ferritin level is between 30 and 100 μg/l, a combination of true iron deficiency and anaemia of chronic disease is likely [EL2]

The most common forms of anaemia in UC are iron deficiency anaemia [IDA], anaemia of chronic disease, and a combination of both.[281,282] Vitamin B_{12} or folate deficiency, haemolytic anaemia, and drug-induced anaemia are less prevalent forms, but should also be considered.[283] Anaemia is defined by the World Health Organization as a decline in blood haemoglobin to a concentration of < 12 g/dl [120 g/l] in women and < 13 g/dl [130 g/l] in men.[15,284] All UC patients should be screened for anaemia, and this screening should include a full blood count, serum ferritin, and CRP levels.[15]

Anaemia should be investigated with red cell distribution width [RDW], mean corpuscular volume [MCV], reticulocyte count, full blood count [FBC], ferritin, transferrin saturation and CRP levels. Transferrin saturation is low with both IDA and inflammation. The plasma level of transferrin receptor increases with iron deficiency and is unaffected by inflammation.[285] If the cause of anaemia remains unclear, further laboratory tests should include B_{12}, red cell folic acid, haptoglobin, and lactate dehydrogenase [see statement 1C in Dignass et al.[15]].[286,287]

5.1.2. Treatment of ulcerative colitis-associated

ECCO statement 5C [statement 2A in Dignass et al.[15]]

Iron supplementation is recommended in all ulcerative colitis patients when iron deficiency anaemia is present [EL1]

anaemia

Detailed information on iron supplementation, B_{12}, folate, and blood transfusions can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[15,280,281,288–296]

5.2. Arthropathy

Joint involvement is the second most common EIM in UC, occurring in approximately 20% of all patients.[297] Arthritis can be classified as axial and peripheral.[298]

ECCO statement 5D [statement 2D in Harbord et al.[7]]

Diagnosis of peripheral arthropathy and/or enthesitis associated with ulcerative colitis is based on signs of inflammation and exclusion of other specific forms of arthritis [EL3]

5.2.1. Peripheral arthropathy

A classification for peripheral arthropathy has been proposed, but not validated.[298] Type I peripheral arthropathy is pauci-articular and typically affects less than five large joints in an asymmetrical pattern. This arthritis is acute and self-limiting, and is associated with intestinal disease activity. Type II peripheral arthropathy is a symmetrical and polyarticular arthritis, which typically affects more than five small joints, is independent of UC activity, and can persist for months to years.

ECCO statement 5E [statement 2B in Harbord et al.[7]]

Diagnosis of axial spondyloarthritis is on the basis of clinical features of inflammatory low back pain associated with magnetic resonance imaging or radiographic features of sacroiliitis [EL2]

5.2.2. Axial arthropathy

Axial arthropathy includes sacroiliitis and spondylitis.[299–301] The diagnosis of ankylosing spondylitis [AS] is made according to the modified Rome criteria.[302] MR imaging [MRI] is the current gold standard, as it can show inflammation before bone lesions occur and become visible using plain radiology.[303,304]

5.2.3. Treatment of arthropathy related to ulcerative colitis

The target of UC-associated arthritis management is the reduction of inflammation, alleviation of pain, and prevention of disability. So far, no single prospective controlled trial in IBD patients is available.[305–308] In type I arthritis, successful treatment of the underlying UC flare usually resolves symptoms within weeks. Patients may further benefit from sulphasalazine, rest, and physiotherapy. Patients with type II arthritis usually require NSAIDs or systemic corticosteroids for symptom control. Treatment decisions for axial arthropathy should be shared with a rheumatologist. Sulphasalazine, methotrexate, and azathioprine are considered to be ineffective in AS with axial symptoms.[309] In patients with active AS refractory to or intolerant of NSAIDs, anti-tumour necrosis factor [TNF] agents are recommended. The efficacy and safety of infliximab [IFX], adalimumab, and golimumab in AS are now well established.[156,303,310–318] The American College of Rheumatology/Spondylitis Association do not recommend any particular NSAID as the preferred choice to decrease the risk of worsening the underlying IBD. They do recommend treatment with anti-TNF monoclonal antibodies, although not etanercept.[319]

5.3. Metabolic bone disease

Diagnosing osteoporosis is based on bone densitometry [T-score < -2.5], which should be assayed in all patients with persistently active UC, especially if repeatedly exposed to corticosteroids or with long disease duration. Calcium [500–1000 mg/day] and vitamin D [800–1000 IU/day] are recommended should the T score drop below -1.5 [see statements 3A to 3C in Harbord et al.[7]]. Patients on systemic corticosteroid therapy should receive prophylactic calcium and vitamin D. Post-menopausal women or those with a history of spontaneous fractures should be prescribed regular bisphosphonates or other therapies, as these can prevent further bone loss [see statements 3B & 3D in Harbord et al.[7]].

5.4. Cutaneous manifestations

5.4.1. Erythema nodosum

ECCO statement 5F [statement 6A in Harbord et al.[7]]

Diagnosis of erythema nodosum is made on clinical grounds. In atypical cases, a skin biopsy might be helpful [EL3]. Treatment is usually based on that of the underlying ulcerative colitis. Systemic steroids are required in severe cases [EL4]. Relapsing and resistant forms can be treated with immunomodulators or anti-TNF [EL4]

Erythema nodosum usually affects the extensor surfaces of the lower extremities, particularly the anterior tibial areas, and has a symmetrical distribution.[320] It is closely related to disease activity, and its treatment is based on that of the underlying UC. Systemic corticosteroids are usually required. In resistant or recurrent cases, immunomodulation or anti-TNF may be used.[321,322]

5.4.2. Pyoderma gangrenosum

ECCO statement 5G [statement 6B in Harbord et al.[7]]

Pyoderma gangrenosum can be treated with systemic corticosteroids [EL4], infliximab [EL1] or adalimumab [EL3], and topical or oral calcineurin inhibitors [EL4]

Pyoderma gangrenosum lesions are often preceded by trauma, a phenomenon known as pathergy.[323] They most frequently occur on the shins and adjacent to postsurgical stomas. The correlation of pyoderma gangrenosum with disease activity is controversial.[324] Corticosteroids [topical and/or systemic] are considered to be the first line of treatment. IFX has been effective[325–327] and adalimumab has led to successful outcomes in reported cases, therefore anti-TNF treatment should be considered if a rapid response to corticosteroids is not achieved. Topical or oral calcineurin inhibitors are an alternative, but dermatological advice is recommended prior to its prescription.[328,329]

Information on Sweet's syndrome and anti-TNF-induced skin inflammation can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[7,320,330–341]

5.5. Ocular manifestations

Episcleritis generally parallels UC activity. It can be self-limiting and usually responds to topical corticosteroids and NSAIDs prescribed alongside treatment of the underlying UC.[342] Simple episcleritis does not require referral to an ophthalmologist and may self-resolve. Uveitis has potentially more severe consequences. When related to UC, uveitis is frequently bilateral, has an insidious onset, and is long lasting.[342] The possibility of progression to loss of vision should prompt urgent referral to an ophthalmologist. Treatment usually consists of topical or systemic corticosteroid or NSAIDs.[342] Immunosuppressive and anti-TNF treatment have each been reported to be of value in resistant cases [see statements 4A & B in Harbord et al.[7]].

5.6. Hepatobiliary disease

PSC constitutes the most important hepatobiliary condition among UC patients.[343] However, peri-cholangitis, steatosis, chronic hepatitis, cirrhosis, and gallstone formation are also over-represented in these patients. Many of the drugs used to treat UC have the potential to cause hepatotoxicity. PSC is a major risk factor for both cholangiocarcinoma and colon cancer.[344] High-quality MR cholangiography [MRC] is recommended as a diagnostic test in patients with suspicion for PSC. If MRC is normal and small duct PSC is suspected, a liver biopsy should be considered [see statements 7A to 7C in Harbord et al.[7]].

Ursodeoxycholic acid was shown to improve the levels of liver enzymes and to reduce the risk of CRC in PSC, but no therapy has been shown to reduce time to liver transplantation, cholangiocarcinoma, or death.[345–347] On the contrary, high-dose ursodiol treatment [> 20 mg/kg/day] was associated with a worse disease outcome and should therefore be avoided.[348] Endoscopic retrograde cholangiopancreatogram [ERCP] remains the procedure of choice to manage significant biliary strictures.[344] In advanced disease with liver failure, liver transplantation is the only known alternative [see statements 7D to 7F in Harbord et al.[7]].[349] Annual or biennial [2-yearly] surveillance colonoscopy after diagnosis of PSC in UC patients is recommended [see statement 7G in Harbord et al.[7] and 13E in Annese et al.[13]].

Information on pancreatitis, venous thromboembolism, and cardiopulmonary disease can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[7,126,350–361]

Section 6. Opportunistic Infections

6.1. Definitions and risk factors

ECCO statement 6A [statement 2B in Rahier et al.[11]]

Ulcerative colitis patients at risk of opportunistic infections are those treated with immunomodulators [EL1], especially in combination [EL3], and those with malnutrition [EL5]. In addition, comorbidities and a history of serious infections should be considered. Age is an independent risk factor for opportunistic infections [EL3]

Conditions predisposing to OIs are classified according to the Center for Disease Control[362] as: [1] severe immune-depression; [2] human immunodeficiency virus [HIV]-infection related; and [3] limited immune deficits. An OI is defined as a progressive infection by a microorganism that has limited pathogenic capacity under normal conditions.[363] Predisposing factors for OI can be either external [medical treatment, exposure] or inherent [age, comorbidity, malnutrition].[11] UC patients per se are not immunocompromised, but may have altered immune responsiveness as a consequence of their medical treatment [see statement 2A in Rahier et al.[11]]. Older age is an independent risk factor for OI and OI-related adverse events in UC.[364,365] Corticosteroids increase the risk of OI when administered in a dosage greater than 20 mg of prednisolone daily for more than 2 weeks.[366,367] All IMs used for IBD increase the hazard of OI, and the use of more than one IM at a time may carry an increased risk of more than 14-fold.[368] This risk is independent of the dose and type of IMs[369] but may be influenced by patient age.[366,370–372] Anti-TNF drugs alone double the likelihood of OI, especially tuberculosis [TB].[373] However, anti-integrin antibodies have not been shown to increase the risk of OI.[374]

6.2. Viral agents

6.2.1. Hepatitis C virus [HCV], hepatitis B virus [HBV], and HIV

Given the increased risk of OI while receiving IMs, UC patients should be encouraged to receive HIV testing.[11] Seropositivity is not a definite contraindication for IMs [see statement 3F in Rahier et al.[11]].[375–377] UC patients should also be tested for HCV-Ab and, if positive, the result should be confirmed by HCV-RNA detection. IMs per se do not worsen HCV infection, unless a concomitant infection associated with HBV or HIV is present,[378] but they can worsen the liver toxicity of medications in HCV-Ab positive subjects.

Information on CMV, HSV, VZV, EBV, HPV, or influenza virus can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.

ECCO statement 6B [statement 3B in Rahier et al.[11]]

All ulcerative colitis patients should be tested for HBV [HBsAg, anti-HBAbs, anti-HBcAb] at diagnosis. In patients with positive HBsAg, viraemia [HBV-DNA] should also be quantified [EL2]

ECCO statement 6C [statement 3C in Rahier et al.[11]]

HBV vaccination is recommended in all HBV anti-HBcAb seronegative patients with ulcerative colitis [EL5]. Efficacy of hepatitis B vaccination is impaired in inflammatory bowel disease, probably by the disease itself and by the anti-TNF drugs. Anti-HBs response should be measured after vaccination. Higher doses of the immunising antigen may be required to provide protection [EL 4]. Maintenance of HBs antibody should be monitored in patients at risk [EL 5]

ECCO statement 6D [statement 3D in Rahier et al.[11]]

Before, during, and for at least 12 months after immunomodulator treatment has ceased, patients who are HBsAg positive should receive potent anti-viral agents [nucleoside/nucleotide analogues with high barrier to resistance] regardless of the degree of viraemia, in order to avoid hepatitis B flare [EL2]

ECCO statement 6E [adapted from statement 3E in Rahier et al.[11]]

Reactivation of occult HBV rarely occurs with immunosuppressive therapy used in ulcerative colitis [EL2]. Viraemia [HBV DNA] should be assessed every 2–3 months but antiviral therapy is not recommended unless HBV-DNA is detected [EL5]

6.3. Parasites and fungal agents

Additional information on parasites and fungal agents can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[11,185,357,379–400]

6.3.1. *Mycobacterium tuberculosis*

ECCO statement 6F [statement 6A in Rahier et al.[11]]

Reactivation of latent tuberculosis in patients treated with anti-TNF is increased and is more severe than in the background population [EL2]. Latent tuberculosis should be diagnosed by a combination of patient history, chest X-ray, tuberculin skin test, and interferon-gamma release assays according to local prevalence and national recommendations. Screening should be considered at diagnosis and always performed before anti-TNF therapy [EL5]. Interferon-gamma release assays are likely to complement the tuberculin skin test and are preferred in BCG-immunised individuals [EL1]

Reactivation of latent TB is more likely to occur and be more severe in patients being treated with anti-TNF when compared with the background population.[401–403] Patients with latent TB should receive anti-tuberculous therapy before starting anti-TNF. In patients with active UC and latent TB, anti-TNF should be administered only after 3 weeks of anti-TB chemotherapy [see statement 6B in Rahier et al.[11]].[404,405] In case of active TB, anti-tuberculous therapy must be started and anti-TNF withdrawn for at least 2 months [see statement 6C in Rahier et al.[11]].[404,405]

6.3.2. Bacterial agents

Pneumococcal vaccination should be offered to UC patients before starting IM, and should ideally be administered 2 weeks before treatment initiation. IM can impair immunity to *Streptococcus pneumoniae* after polysaccharide vaccination [see statement 7A & 7B in Rahier et al.[11]].[403,406] UC patients taking IM who develop pneumonia should be tested for pneumococcal infections and *Legionella pneumophila*.[407,408] UC patients receiving IM therapy experience more severe infections with *Salmonella spp*. [see statement 7E in Rahier et al.[11]]. Withholding IM until active infections are resolved is recommended [see statements 7C to 7E in Rahier et al.[11]]. IMs, especially anti-TNF, increase the risk of systemic and central nervous infections with *Listeria monocytogenes* [see statement 7F in Rahier et al.[11]].[403] The same applies to *Nocardia spp*.-related systemic or skin infections [see statement 7G in Rahier et al.[11]].[373,409–411] Anti-TNF therapy should be withdrawn during infection, and infectious disease experts should be consulted before reintroducing IM.

ECCO statement 6G [adapted from statement 7H in Rahier et al.[11]]

Ulcerative colitis is an independent risk factor for infection with C. *difficile* [EL3]

ECCO statement 6H [statement 7K in Rahier et al.[11]]

Metronidazole and oral vancomycin are equally effective in treating mild to moderate *C. difficile*-associated disease [EL1]. It remains to be established if this applies to patients with ulcerative colitis. Other antibiotics should be stopped if possible. For severe disease, vancomycin has been shown to be superior in patients without ulcerative colitis [EL1] and is therefore preferable. In *C. difficile*-associated disease, use of immunomodulators should be guided by careful risk benefit evaluation and clinical judgement [EL4]

IMs are independent predictors of severe C. *difficile*-associated disease.[11,413,413] Faecal microbiota transplantation is safe in UC.[414,415] Fidaxomycin has been shown to be non-inferior in terms of clinical cure to vancomycin and showed a lower recurrence rate of C. *difficile*.[416] In addition to an increased risk for infection with C. *difficile*, patients with inflammatory bowel disease are 33% more likely to experience C. *difficile* recurrence.[417]

Additional considerations can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[11,392,418,419]

Section 7. Fertility

ECCO statement 7A [adapted from statement 2A in van der Woude et al.[16]]

There is no evidence that ulcerative colitis affects fertility [EL3]. High levels of voluntary childlessness in women with ulcerative colitis indicate the need for better education [EL4]

UC patients are believed to have similar fertility as the general population,[420] but female patients might benefit from better knowledge of pregnancy-related issues, as they often choose to remain childless.[421–424] Female fertility does not seem to be affected by UC medications.[424] Sulphasalazine, however, can reversibly decrease sperm count and motility [see statement 2B in van der Woude et al.[16]],[425,426] whereas methotrexate [MTX] causes reversible oligospermia[427] and is contraindicated in male patients aiming to father a child. Data about the effect of anti-TNF treatment are limited and conflicting.[428] Ileo-anal pouch surgery in male patients may lead to erectile and ejaculatory dysfunction. However, by eliminating inflammation, surgery often leads to an overall unchanged or even improved sexual function [see statement 7A in van der Woude et al.[16]].[429,430] The *in vitro* fertilisation success rate after pouch surgery is comparable to that of non-UC female subjects [see statement 2D in van der Woude et al.[16]].[431]

ECCO statement 7B [statement 3A in van der Woude et al.[16]]

If conception occurs at a time of quiescent disease, the risk of relapse is the same as in non-pregnant women [EL3]. Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy [EL3]. Pregnancy may influence the course of ulcerative colitis [EL3]

7.1. Pregnancy and delivery

7.1.1. Outcome of mothers

Patients should be advised to conceive during remission.[16,432,433] In order to choose the most appropriate delivery method, a joint approach with gastroenterologist, surgeon, and obstetrician is recommended [see statement 3B in van der Woude et al.[16]].

7.1.2. Outcome of children

ECCO statement 7C [adapted from statement 4B, 4C and 4D in van der Woude et al.[16]]

Disease activity at conception or during pregnancy is associated with preterm birth and low birthweight [EL3]. The risk of congenital abnormalities in offspring from women with ulcerative colitis does not seem to be increased [EL2]. Fetal exposure to most ulcerative colitis medications is considered of low risk to the child, except for methotrexate and thalidomide [EL2]

Additional information on outcome of children can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[16,434–444]

7.2. Pregnancy and ulcerative colitis management

ECCO statement 7D [statement 5A in van der Woude et al.[16]]

Appropriate treatment of ulcerative colitis should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy [EL5]. Acute flares during pregnancy carry a high risk of adverse maternal and fetal outcome, and are best treated appropriately and without delay to prevent these complications [EL3]

UC patients who conceive should be advised to continue their medication to avoid disease flares and possible related pregnancy complications [see statement 5F in van der Woude et al.[16]].[439,445] Due to their safety profile during pregnancy, 5-aminosalicylic acid [5-ASA] derivatives [preferably avoiding 5-ASA with dibutylphthalate coating[446,447]] and corticosteroids should be considered as the first-line treatment should a relapse occur.[448,449] Anti-TNF is an option in specific situations [see statement 5C in[16]]. Sulphasalazine administration should be implemented in a parallel with high-dose folic acid supplementation. Surgery for UC during pregnancy can lead to miscarriage during the first trimester and to preterm labour in the third trimester,[450] but continued illness is considered to represent a greater risk for the fetus [see statement 5E in van der Woude et al.[16]].[451]

Additional information on lactation, endoscopy, and imaging can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[16,452–462]

Section 8. Surveillance for Colorectal Cancer in Ulcerative Colitis

8.1. Risk of colorectal cancer in ulcerative colitis

Although it is generally accepted that long-standing UC is associated with an increased risk of CRC, the reported risk estimates vary widely between studies. In 2001, Eaden *et al.* described a meta-analysis including 116 studies[463] and concluded that after 30 years of disease duration the cumulative risk was 18%. Another meta-analysis revealed that the pooled SIR [standardised incidence ratio] of CRC in UC patients was 2.4.[464] However, the risk of CRC may have been declining over time.[465,466] An Australian study has reported a CRC cumulative incidence of 1% at 10 years, 3% at 20 years, and 7% at 30 years.[467] This may reflect the increased implementation of surveillance strategies, the introduction of drugs that control inflammation more effectively, or the changing approach to maintenance therapy or colectomy.[13]

ECCO statement 8A

The risk of colorectal cancer in ulcerative colitis is increased compared with the general population. Risk is associated with disease duration [EL 2], extent [EL 2], and more severe or persistent inflammatory activity [EL 2]

Although it has been stated that CRC is rarely encountered when disease duration falls below 8 years, a significant number of tumours may still develop by this time,[468,469] especially in patients who are older at colitis onset or in patients with PSC. Patients with extensive colitis carry the highest risk of CRC, whereas left-sided colitis patients present an intermediate risk. CRC risk is not increased in patients with UC limited to the rectum.[463,470] Of note, histological extent, even without endoscopically visible abnormalities, may be an important determinant for CRC risk.[471,472]

ECCO statement 8B

Concomitant primary sclerosing cholangitis [EL 2] and a family history of colorectal cancer [EL 3] confer an additional risk for colorectal cancer

The most consistent risk factors reported for CRC are PSC [with an increased absolute risk of up to 31%][473–477] and histological disease activity.[50,51] Post-inflammatory polyps may be markers of previous inflammatory severity, and have also been found to be a strong risk factor.[247,480] Family history of CRC is associated with an increased risk, although the risk varies across studies.[474,479] Jess *et al.* found that men had a greater risk of developing CRC [SIR: 2.6; 95% CI: 2.2–3.0] than women [SIR: 1.9; 95% CI:1.5–2.3].[464] In multivariate logistic regression analysis, CRC was associated with male gender, disease duration, extensive colitis, concomitant PSC, median albumin levels, and an increased CRP-albumin score.[480]

8.2. Surveillance issues

8.2.1. Screening and surveillance

Given that an increased risk of CRC is associated with dysplastic change in colonic mucosa, surveillance colonoscopy programmes have been developed in order to reduce CRC-associated morbidity and mortality. These surveillance programmes involve not only a systematic colonoscopic assessment, but also a revision of the patients' symptoms, medications, and laboratory test results, as well as an update of personal and family medical histories. At the onset of these programmes, an initial screening colonoscopy is performed to reassess disease extent and confirm the absence of dysplastic lesions.

ECCO statement 8C

Surveillance colonoscopy may permit earlier detection of colorectal cancer with a corresponding improved prognosis [EL 3]

8.2.2. Effectiveness

The efficiency of surveillance colonoscopy programmes has yet to be assessed by randomised controlled trials. However, a large number of case series suggest a positive impact.[13,472,481] Reduced CRC incidence reported in recent studies may be proof of their efficiency, although other potential factors [including better disease control] may also be relevant.[114] A systematic review was unable to demonstrate a benefit of surveillance programmes in the prevention of CRC-related death in UC when limiting the analysis to studies that included a control group.[114] Two large case series have shown improved survival in surveillance patients due to an early detection of CRC.[466,482] Three retrospective case control studies have shown a correlation between surveillance colonoscopy and reduced odds ratio of CRC.[478,483,484] Unequivocal evidence for the benefit of surveillance colonoscopy is still lacking.

8.2.3. Initial screening colonoscopy and surveillance schedules

ECCO statement 8D [adapted from statement 13D in Annese et al.[13]]

Screening colonoscopy should be offered over 8 years following the onset of symptoms to all patients to reassess disease extent and exclude dysplasia [EL 5]

ECCO statement 8E

When disease activity is limited to the rectum without evidence of previous or current endoscopic and/or microscopic inflammation proximal to the rectum, inclusion in a regular surveillance colonoscopy programme is not necessary [EL2]

ECCO statement 8F

In patients with concurrent primary sclerosing cholangitis, annual surveillance colonoscopy should be performed following the diagnosis of primary sclerosing cholangitis, irrespective of disease activity, extent, and duration [EL3]

ECCO statement 8G [adapted from statement 13E in Annese et al.[13]]

Ongoing surveillance should be performed in all patients apart from those with proctitis [EL3]. Patients with high-risk features [e.g. stricture or dysplasia detected within the past 5 years, primary sclerosing cholangitis, extensive colitis with severe active inflammation] should have their next surveillance colonoscopy scheduled for 1 year [EL4]. Patients with intermediate risk factors should have their next surveillance scheduled for 2 to 3 years. Intermediate risk factors include extensive colitis with mild or moderate active inflammation, post-inflammatory polyps, or a family history of colorectal cancer in a first-degree relative diagnosed at age 50 years and above [EL5]. Patients with neither intermediate nor high-risk features should have their next surveillance colonoscopy scheduled for 5 years [EL5]

Supporting information on risk factors for CRC with and without dysplasia on biopsies can be found in Supplementary materials, available as Supplementary data at *ECCO-JCC* online.[3,13,49,50,473,485–495]

8.3. Colonoscopy

ECCO statement 8H

Colonoscopic surveillance is best performed when ulcerative colitis is in remission, because it is otherwise difficult to discriminate between dysplasia and inflammation on mucosal biopsies [EL5]

As happens with screening colonoscopies in the otherwise healthy population, the quality of the preparation in UC patients significantly affects the lesion detection rate.[496] Good bowel preparation is essential for an efficient surveillance colonoscopy. Repetition of the colonoscopy should be considered when excess faecal residue is present.

ECCO statement 8I

Surveillance colonoscopy should take into account local expertise. Chromoendoscopy with targeted biopsies has been shown to increase dysplasia detection rate [EL2]. Alternatively, random biopsies [quadrantic biopsies every 10 cm] and targeted biopsies of any visible lesion should be performed if white light endoscopy is used [EL3]. High-definition endoscopy should be used if available

Endoscopic equipment, patient preparation, and diagnostic techniques have advanced considerably during recent years. High-resolution equipment improves imaging quality, and may therefore improve the dysplasia detection rate. In fact, a recent colitis surveillance study has shown that high-definition colonoscopy improves dysplasia detection in comparison with standard definition.[497] Targeted biopsies have been shown to be non-inferior to random biopsies for neoplasia detection rate per colonoscopy in a randomised controlled trial [RCT].[498]

Dysplasia detection in surveillance colonoscopy can be improved by spraying dyes that highlight subtle changes in the colonic mucosa architecture.[499] Using this technique, random biopsies of apparently normal mucosa are of negligible additional value although they do enable an assessment of microscopic disease extent and activity. The chromo-endoscopic diagnostic yields are similar using methylene blue or indigo carmine.[500–502]

A meta-analysis including six studies [1277 patients] has shown that the difference in dysplasia detection between chromo-endoscopy and white light endoscopy [WLE] was 7% [95% CI: 3.2–11.3], on a per patient analysis (number needed to treat [NNT] 14.3). The absolute difference in lesions detected by targeted biopsies was 44% [95% CI: 28.6–59.1] and flat lesions was 27% [95% CI 11.2–41.9], both in favour of chromo-endoscopy.[503] Another meta-analysis has focused on the diagnostic accuracy of chromo-endoscopy compared with that of histology, and has reported a sensitivity of 83.3% and a specificity of 91.3% for chromo-endoscopy in detection of intraepithelial neoplasia.[504] Superiority of chromoendoscopy compared with white light endoscopy for dysplasia detection has also been shown in real-life studies outside clinical trials.[505] This finding does not vary with operator familiarity or with the availability of high-resolution endoscopy. Currently narrow band imaging as well as endomicroscopy cannot currently be recommended for dysplasia screening in IBD. Additional information can be found in Supplementary materials, available as Supplementary data at *ECCO-JCC* online.[506–510]

8.4. Chemoprevention

8.4.1. Mesalamine and colorectal cancer

Additional information can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[6,245,474,478,484,486,511–521]

8.4.2. Patient selection for chemoprevention with 5-ASA

ECCO statement 8J

Chemoprevention with mesalamine compounds may reduce the incidence of colorectal cancer in ulcerative colitis [EL2]. There is insufficient evidence to recommend for or against chemoprevention with thiopurines

In a nested case-control study of the CESAME cohort, adjusted for the propensity of receiving 5-ASA, a sub-analysis was performed in IBD patients with or without long-standing [> 10 years] and extensive [> 50% of colonic mucosa at any time] colitis.[522] The protective odds ratio was significant for patients with long-standing extensive colitis [OR: 0.5; 95% CI: 0.2–0.9] although it was not in the remaining patients [OR: 0.8; 95% CI: 0.3–1.7]. This suggests a chemopreventive effect of 5-ASA in patients with known risk factors for dysplasia or cancer. However, statements on the chemopreventive effect of 5-ASA in UC are not restricted to high-risk individuals,[6,40,485] which justifies lifelong chemoprevention from diagnosis in all patients, except for those with isolated proctitis.[6,40,49–51,245,471,472,485,512,523–526] Additional information can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[6,40,49–51,238,456,458,465,469,494,505–507]

8.4.3. Immunosuppressants

IMs [e.g. thiopurines and MTX] and biologics [anti-TNF] could theoretically either increase the risk of CRC via immunosuppression, or be chemopreventive via a reduction of chronic mucosal inflammation. There are no data for MTX or anti-TNF, and the data for thiopurines are conflicting.[49–51,478,511,519,527–529] These included the published studies specifically designed to address the chemopreventive effect of thiopurines on the risk of CRC in IBD.[528,529] Overall, a recent meta-analysis failed to show a significant chemopreventive effect of thiopurines [OR: 0.87; 95% CI: 0.71–1.06.][530] This did not change significantly in subgroup analysis of the two population studies [OR:

0.87; 95% CI: 0.71–1.06], the 13 clinic-based studies [OR: 0.87; 95% CI: 0.59–1.09], the seven cohort studies [OR: 0.93; 95% CI: 0.67–1.28], or the eight case-control studies [OR: 0.83; 95% CI: 0.65–1.08]. A recent observational cohort study from the CESAME group, however, indicated that patients with long-standing extensive colitis on thiopurine therapy may have a lower overall risk for CRC compared with patients not on thiopurines [HR: 0.28; 95% CI: 0.1–0.9].[470] There is currently insufficient evidence to recommend for or against chemoprevention with thiopurines; however, thiopurines may increase the risk for urinary tract cancers,[531] acute myeloid leukaemia [AML], myelodysplastic syndrome,[532] lymphoproliferative disorders,[390] and non-melanoma skin cancer.[533]

8.4.4. Other drugs

Additional information on other drugs for chemoprevention can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[6,40,346,485,534]

8.5. Management of dysplasia

Therapeutic recommendations for management of dysplasia in UC are based on macroscopic pattern [polypoid, non-polypoid, or macroscopically invisible] and microscopic characteristics of the lesion [indefinite, low grade or high grade].[535–537]

8.5.1. Microscopic patterns of dysplasia

The current, widely used definition of dysplasia was proposed by Riddell *et al.* in 1983.[537] Dysplasia was defined as an unequivocal neoplasia of the epithelium confined to the basement membrane, without invasion into the lamina propria. Dysplasia is the best and most reliable marker of an increased risk of malignancy in patients with IBD.[538] Dysplasia [intraepithelial neoplasia] is now generally classified according to the grade of neoplastic change into three morphological categories: 'indefinite', 'low-grade' [LGD], or 'high-grade' [HGD].[537] However, dysplasia almost certainly evolves along a progressive [continuous] scale rather than in discrete categories. This contributes to the significant degree of variability in interpretation of the grade of dysplasia even among experienced gastrointestinal pathologists.[539,540] Levels of agreement are highest for the category of HGD and for specimens considered negative for dysplasia, and lower for specimens in the indefinite and LGD categories. These limitations in the assessment of dysplasia have led to the recommendation that histological slides should be reviewed by a second expert gastrointestinal pathologist.

ECCO statement 8K

Presence of low-grade or high-grade dysplasia should be confirmed by an independent gastrointestinal specialist pathologist [EL 5]

8.5.2. Macroscopic patterns of dysplasia

There is inconsistency in the literature about the definitions used to designate the macroscopic characteristics of dysplastic lesions in UC.[493,536] Terms such as dysplasia-associated lesion or mass [known as 'DALM'], adenoma-like, non-adenoma like, and flat, often cause confusion among endoscopists as they are often used to describe a variety of differently shaped lesions. Thus, in agreement with the SCENIC international consensus, these terms should be abandoned.[541] Dysplasia detected during surveillance procedures should be classified into three categories: polypoid, non-polypoid, and endoscopically invisible. A polypoid lesion refers to pedunculated [Paris type Ip—attached to the mucosa by a stalk] or sessile [Paris type Is—not attached to the mucosa by a stalk and the entire base is contiguous with the mucosa] lesions that protrude from the mucosa into the lumen ≥ 2.5 mm.[541] These lesions are usually endoscopically removable by routine endoscopic methods.[40,485] 'Non-polypoid' lesion refers to Paris type IIa [superficially elevated < 2.5mm], IIb [flat—no protrusion], IIc [depressed], velvety patches, plaques, irregular bumps and nodules, wart-like thickenings, stricturing lesions, and broad-based masses,[493,542–544] and may not be amenable to removal by colonoscopic polypectomy. Polypoid and non-polypoid dysplasia are differentiated on the basis of their gross [endoscopic] appearance. Histological features may be helpful,[545] although both types of lesions may appear identical.[546,547] Endoscopically invisible dysplasia refers to dysplasia found during histological examination in the absence of a visible lesion at colonoscopy.

8.5.3. Management of endoscopically visible dysplasia

ECCO statement 8L

Polypoid dysplasia can be adequately treated by polypectomy provided the lesion can be completely excised, and there is no evidence of non-polypoid or invisible dysplasia elsewhere in the colon [EL 2]

ECCO statement 8M

Non-polypoid dysplastic lesions can be treated endoscopically in selected cases. If complete resection can be achieved, with no evidence of non-polypoid or invisible dysplasia elsewhere in the colon, continued surveillance colonoscopy is reasonable [EL 5]. Every other patient with non-polypoid dysplasia should undergo colectomy, regardless of the grade of dysplasia detected on biopsy analysis [EL 2]

ECCO statement 8N

Polyps with dysplasia that arise proximal to segments with macroscopic or histological involvement are considered as sporadic adenomas and should be treated accordingly [EL 2]

Polypoid dysplasia arising in a colonic segment currently, or previously, affected by colitis can be adequately treated with polypectomy and continued surveillance. Four studies have shown no significant difference in the incidence of polyp detection on follow-up between patients with UC and polypoid dysplasia, and patients with UC and a sporadic adenoma, or between either of these two groups of UC patients and a non-UC sporadic adenoma control group.[3,245,545,548,549] Recent literature continues to support this strategy. Data from a St Mark's Hospital, UK, cohort of 172 patients with LGD showed that the cumulative incidence of developing HGD or CRC at 5 years after the initial detection of polypoid dysplasia was 6%.[472] A meta-analysis of 10 studies comprising 376 patients demonstrated that the pooled incidence of CRC after endoscopic resection of polypoid dysplasia was 5.3 cases per 1000 patient-years of follow-up [95% CI: 2.6–10.1 cases].[550] Thus, provided that the polypoid lesion can be completely excised, shows absence of dysplasia at the margins of the specimen, and there is no evidence of

non-polypoid or invisible dysplasia elsewhere in the colon, colectomy is not necessary. It is important to obtain biopsies from the immediate surrounding flat mucosa to ensure that there is no adjacent dysplasia. Patients undergoing endoscopic resection for polypoid lesions have an approximately 10-fold risk of developing further dysplasia.[550] Therefore, close monitoring preferably with chromo-endoscopy is recommended at 3–6 months before reverting to annual surveillance. Partial colonic resection, if dysplasia is visible and not endoscopically resectable, or future surveillance in the context of LGD might also be a potential option.

Non-polypoid dysplasia is a more ominous finding. The natural history of these lesions was recently studied in depth, where authors investigated 172 UC patients diagnosed with LGD in the St Mark's Hospital surveillance cohort.[472] The cumulative incidence of HGD or CRC development after 5 years was 6.0% for polypoid dysplasia and 65.2% for non-polypoid dysplasia. Furthermore, non-polypoid dysplasia was more likely to be multifocal compared with polypoid lesions and often progressed to synchronous CRC. These data support findings from earlier studies, where there was a strong association of metachronous or synchronous carcinoma with non-polypoid dysplasia, ranging from 38% to 83%.[536] For this reason, it is generally recommended that patients with UC and endoscopically unresectable non-polypoid dysplasia should undergo immediate colectomy, regardless of the grade of dysplasia detected by biopsy analysis. Currently, there are no dedicated studies investigating long-term outcome of patients who undergo endoscopic resection for non-polypoid dysplasia. A subgroup analysis of the aforementioned St Mark's study revealed that one of eight patients [12.5%] who underwent endoscopic resection for small non-polypoid LGD [all < 1 cm] developed Dukes' A CRC with a median follow-up time of 44 months.[472] Although this should be interpreted with caution given the small number of cases, it implies that colectomy may not always be necessary for a subgroup of patients diagnosed with non-polypoid dysplasia. Furthermore, one study showed that patients are likely to refuse colectomy if they were told that they have dysplasia and have 20% chance of having CRC 'right now'.[551] Based on this, despite the lack of evidence, continued surveillance can be considered reasonable if the non-polypoid lesion can be resected in full and if there is no evidence of invisible or non-polypoid dysplasia elsewhere in the colon. In all cases, a full discussion should occur with the patient so that they are made aware of the potential risk and benefits of taking either approach [i.e. endoscopic resection versus colectomy]. Again, close monitoring, preferably with chromo-endoscopy, is recommended at 3 to 6 months before reverting to annual surveillance. Finally, if a dysplastic polyp occurs in an area proximal to the microscopic level of inflammation, with no dysplasia in flat mucosa, it can be regarded as a sporadic adenoma and treated accordingly.[549,552]

8.5.4. Management of endoscopically invisible dysplasia

Macroscopically invisible dysplasia describes dysplasia within random biopsies in the absence of visible lesions during colonoscopy. It is difficult to estimate its true risk as many 'invisible' dysplastic lesions reported in previous studies were recorded in the pre-video endoscopic era. This makes it difficult to know whether these represent truly invisible dysplasia or merely subtle non-polypoid lesions that were previously undetected, but that could now be visualised with newer techniques. However, there is indirect evidence suggesting that invisible dysplasia is becoming rare. In the Bernstein *et al.* review of 10 prospective studies performed in the pre-video endoscopic era [published in 1994], the majority of dysplasia was invisible [272/312 = 87%].[515] This is in contrast with the recent data from the St Mark's cohort study of UC patients diagnosed with LGD, where only 16 out of 172 [9%] had invisible dysplasia.

These observations indicate that the majority of invisible dysplasia reported in older studies may have been subtle lesions undetected by older endoscopes. Based on this observation, when dysplasia is identified from random biopsies, the patient should be referred to an endoscopist with expertise in IBD surveillance to have a repeat examination preferably with chromo-endoscopy using a high-definition endoscope, to determine whether a well-circumscribed lesion exists and can be resected and to assess for synchronous dysplasia. Of note, the recent study from St Mark's reported that the detection rate for non-polypoid lesions was significantly higher with chromo-endoscopy compared with standard white-light colonoscopy. Although this should be interpreted with caution given that this was not a dedicated study, it nevertheless supports reassessing these patients with the more advanced techniques.

If a visible lesion is found in the same region of the colon as the invisible dysplasia, patients should be managed appropriately as described in section 8.5.3. If no visible lesion is identified, its management depends on the grade of initial dysplasia. It is generally accepted that the immediate and subsequent risk of CRC in patients with invisible HDG is high enough to warrant recommendation for colectomy [reviewed in 2012 ECCO guidelines[3]].

Recommendations on the optimal management of UC patients with endoscopically invisible LGD are more controversial, as the risk of progression to more advanced neoplasia varies greatly in the literature [reviewed in 2012 ECCO guidelines[3]]. This can be as low as 3% after 10 years[489] to as high as 53% at 5 years[553] since the date of initial detection. In the recent St Mark's series, the 5-year progression rate was 21.9%, which was higher than that of polypoid lesions [6.0%] but lower than that of non-polypoid lesions [65.2%].[472]

Thus, given that the relevance of the existing evidence is questionable and that reports are contradictory, the current evidence is insufficient to assess the balance of risk and benefit of colectomy for endoscopically invisible LGD. The decision to undergo colectomy versus continued surveillance in patients with flat LGD should be individualised and discussed at length between the patient, the gastroenterologist, and the colorectal surgeon. Colectomy will eradicate the risk of CRC, but if a patient is unwilling to undergo colectomy, annual surveillance is recommended.[485] The 2013 ECCO endoscopy guideline recommended that a patient with confirmed LGD detected in mucosa without an associated endoscopically visible lesion should undergo repeat chromo-endoscopic colonoscopy with additional random biopsies within 3 months.[13]

Section 9. Surgery

9.1. General

This section summarises the ECCO consensus guidelines on surgery in UC patients.[12] It should be noticed that the level of evidence of these surgical guidelines is rather modest because robust evidence stemming from randomised studies is still lacking in the literature.

Surgery for UC has been refined to offer a better quality of life to patients who need to undergo a colectomy. Until the early 1980s, and apart from the sporadic use of ileo-rectal anastomosis, the gold standard for surgery was a procto-colectomy with an ileostomy. The Kock continent ileostomy was introduced in the late 1960s but has never achieved universal acceptance, in spite of the fact that the quality of life when compared with procto-colectomy with a conventional stoma seemed to be clearly higher.[554] In the past 20 years,

the new gold standard is the restorative procto-colectomy with an ileal pouch-anal anastomosis [IPAA], offering patients an unchanged body image with no stoma and a preserved anal route of defaecation.[555].Nevertheless, bowel function is not restored, and therefore both functional outcomes and quality of life after an IPAA should be compared with those after an ileostomy.[556]

9.2. Technical considerations

9.2.1. Surgery for acute severe colitis

ECCO statement 9A

Delay in surgery is associated with an increased risk of surgical complications [EL 4]. A staged procedure, initially with sub-total colectomy, is recommended in acute colitis [EL 4] in patients taking ≥ 20 mg prednisolone daily for more than 6 weeks, or in those treated with anti-TNF [EL 3]. If the appropriate skills are available, a laparoscopic approach is preferred [EL 3]

Joint care including senior surgeons and senior gastroenterologists remains essential for the safe management of acute severe colitis. Whereas medical therapy is effective in many cases, there is clear evidence that a delay in appropriate surgery is detrimental to patient outcomes.[557] A staged procto-colectomy [with subtotal colectomy first] is considered to be a wise first step in the surgical treatment of acute severe colitis or if patients have received prolonged steroid therapy [over 20 mg of prednisolone/day for more than 6 weeks]. A subtotal colectomy with an ileostomy will spare patients from the burden of colitis. As a consequence, they will regain general health, normalise nutrition, and have the time to consider carefully the options of an IPAA or of a permanent ileostomy. A preliminary subtotal colectomy also allows the clarification of the pathology, definitively excluding Crohn's. Subtotal colectomy is a relatively safe procedure even in critically ill patients.[558–560] In a recent systematic review of laparoscopic versus open colectomy for non-toxic colitis, laparoscopic surgery resulted in less wound infections and intra-abdominal abscesses and a shorter hospital stay.[561] Emerging evidence supports that the same holds true for emergency colectomy.[562,563]

9.2.2. Managing the rectal remnant

Critical aspects need to be considered when performing a subtotal colectomy leaving a rectal remnant. Leaving as little rectum as possible [i.e. dividing the middle rectum within the pelvis] is not recommended, because such an approach will impose difficulties at subsequent proctectomy, 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 recto-sigmoid junction], or to leave the distal part of the sigmoid colon in situ. This allows the bowel to be anchored to the anterior abdominal wall, which facilitates its subsequent identification and dissection or its relocation through the abdominal fascia, either closed in the subcutaneous fat or brought forward as a mucous fistula. The latter option is considered to be safe, as no closed bowel is left within the abdomen. However, a mucous fistula results in an extra stoma for the patient, which may not be easily managed.[564] Closing the stump and leaving it within the subcutaneous fat is also a safe approach, although the skin should be allowed to heal through secondary intention in order to avoid wound infection.[565] There are no studies yet on the risk of subsequent inflammation or bleeding after leaving different lengths of rectum or recto-sigmoid colon in situ. When the rectum is transected within the abdominal cavity at the promontory level, it is advisable to perform transanal rectal drainage for a few days to prevent a 'blowout' of the rectal stump following mucous retention.

9.2.3. Site of anastomosis for restorative procto-colectomy

ECCO statement 9B

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

A common complication when using a stapling technique to perform an ileo-anal anastomosis is leaving a remnant of anorectal mucosa above the dentate line. This can be a cause of persistent inflammation ['cuffitis'], with pouch dysfunction and a risk of dysplasia or, very rarely, cancer.[393,566] When well performed, the low-stapled anastomosis seems to have better outcomes, particularly with regard to soiling, faecal leakage, and social restriction.[567,568]

Further information on anastomotic technique and site in case of neoplasia complicating colitis can be found in Supplemental material, available as Supplementary data at *ECCO-JCC* online.[569–572]

9.2.4. Role of covering ileostomy for restorative procto-colectomy

ECCO statement 9C

A covering loop ileostomy is generally recommended when performing a restorative procto-colectomy for ulcerative colitis [EL 3]

One of the main complications of IPAA surgery is the occurrence of a leak at the suture line of the anastomosis or pouch. This is also a complication that is most likely to compromise the clinical and functional outcomes of the operation. Whether the consequences of a leak can be ameliorated by a covering ileostomy or not is still under debate.[573,574] However, there is evidence that defunctioning the distal anastomosis may reduce the incidence of a leak.[575] Nevertheless, it might be clear during pouch surgery that the morbidity associated with a stoma does not justify its use [e.g. when there is a thick abdominal wall and a short small bowel mesentery], as long as no problems have occurred when constructing the anastomosis.[576–579]

9.2.5. Number of procedures to maintain competency

ECCO statement 9D

Pouches should be performed in specialist referral centres. High-volume centres have lower complication rates and higher rates of pouch salvage following complications [EL 4]

It has been shown that institutions where a larger number of complex surgical procedures that demand sophisticated perioperative care are performed, have better outcomes,[580] which is also true for pouch surgery.[581] Moreover, it is clear that high-volume institutions manage adverse events better, which leads to better pouch salvage in the face of complications.[582] Therefore, and if available, ileo-anal pouch surgery should be conducted in high-volume specialist institutions. The definition of 'high-volume' remains open for debate.

9.2.6. Salvage surgery for pouches

Lifetime failure rates of IPAA are approximately 15%. Failure implies an ileostomy for an indefinite period, with or without pouch excision. Failures are usually due to septic complications or persistent pouch dysfunction, although they can also be the result of misdiagnosed Crohn's disease with fistulation or of refractory pouchitis. Before deciding that a pouch has failed, the option of salvage surgery [either as a corrective procedure or as pouch reconstruction] has to be considered. Such surgery must be undertaken by colorectal surgeons with special expertise in this area, and patients' opinions and preferences should be heard. Reported series of pouch-rescue surgery report a salvage rate above 50% and a still acceptable functional outcome.[583–586] As in pouch surgery, pouch salvage surgery should be performed in units with expertise and a substantial case volume load, although the definition of 'substantial case volume' remains debatable.

9.3. Follow-up

9.3.1. General pouch follow-up

ECCO statement 9E

Early pouchoscopy is recommended in symptomatic patients with pouch dysfunction, in order to distinguish between pouchitis and other conditions [EL 4]

IPAA may be followed by signs and symptoms related to pouchitis [occurring in up to 50% of patients at 10 years of follow-up] or to other conditions [irritable pouch syndrome, Crohn's disease of the pouch, ischaemic pouch, CMV or *C. difficile* infection].[587–589] Timing of clinical follow-up is adjusted to the development of these conditions, and no standardised schedule is currently available. In patients with signs and symptoms compatible with pouchitis [liquid stools, urgency, tenesmus, pelvic discomfort, or electrolyte imbalance], pouchoscopy should be performed in order to discriminate between pouchitis and the other conditions listed above.[590] The timing of the endoscopic follow-up should be adjusted to each patient's specific condition.[591]

9.3.2. Pouch surveillance

ECCO statement 9F

Annual pouchoscopy is recommended in patients with risk factors such as neoplasia and primary sclerosing cholangitis. No specific pouch follow-up protocol is required in asymptomatic patients [EL 3]

A systematic review of dysplasia after restorative procto-colectomy has reported prevalence rates of 0.15 [range: 0–4.49], 0.98 [range: 0–15.62], and 1.23 [range: 0–25.28 per cent] for HGD, LGD, and indefinite dysplasia, respectively.[588,592] Dysplasia was equally frequent in the pouch and rectal cuff or anal transitional zone. Dysplasia and cancer identified before or at operation seemed to be significant predictors for the development of pouch dysplasia. Data from this systematic review have been confirmed by others, indicating that even if the indication for colectomy was dysplasia or cancer, the risk of having dysplasia in the rectal cuff or pouch remains very low.[593,594] No specific follow-up is therefore recommended after restorative procto-colectomy in the absence of risk factors.

9.4. Fertility and delivery in patients with a restorative procto-colectomy

9.4.1. Impact of pelvic surgery on fecundity

ECCO statement 9G

In a fertile female patient, alternative surgical options such as subtotal colectomy and end ileostomy or ileo-rectal anastomosis should be discussed with the patient, because fecundity is at risk after ileal-pouch anal anastomosis [EL3]. A laparoscopic approach is associated with better preservation of female fertility and is preferred [EL3]

Active UC is associated with poor sexual function. Two prospective studies demonstrated an improvement in sexual function in both genders 12 months after IPAA when compared with preoperative levels.[429,595] On the other hand, it has been convincingly demonstrated in three cohort studies that female fecundity is reduced after an IPAA.[596–599] This reduction is most likely associated with adhesions affecting the fallopian tubes.[600] The magnitude of this problem is under debate, with one study showing more than 70% of fecundity reduction, whereas others point towards approximately 30%. Growing evidence suggests that laparoscopic IPAA is technically feasible and may limit the negative consequences as to female fecundity.[601–604]

Interestingly, data from a study on patients with familial adenomatous polyposis have compared the fecundity reduction in women after an ileo-rectal anastomosis [IRA] or after an IPAA, and have shown that IRA carries no associated reduction in fecundity.[605,606] Again, this appears to be because an IRA does not induce pelvic adhesions to the same extent as an IPAA. Furthermore, there is evidence that IRA provides a safe and functionally acceptable outcome.[607,608]

In male patients, retrograde ejaculation and erectile dysfunction are the main, but still rare, sexuality- and fertility-related complications that may occur after an IPAA. Both complications are avoided when an IRA is chosen.[609] When making the decision on the type of surgical approach, concern about IRA should be considered [see section 9.5.3].

Information on mode of delivery for patients with restorative procto-colectomy can be found in Supplementary materials, available as Supplementary data at *ECCO-JCC* online.[16,610–617]

9.5. Surgical choices in addition to restorative procto-colectomy

9.5.1. Age

ECCO statement 9H

There is no age limit for performing an ileal-pouch anal anastomosis as long the patient retains good anal sphincter function [EL 5]

IPAA may carry a higher risk for comorbidity in patients aged > 65 years. Still, the procedure is apparently safe and effective in this age group, and remains the surgical technique of choice.[618] However, an increased frequency of long-term complications [e.g. pouchitis, anastomotic stricture] has been reported to occur in elderly patients who undergo IPAA.[619] Deterioration in pouch function with faecal incontinence occurs with advancing age, and this may be more

pronounced in the elderly.[620,621] Nevertheless, patients aged over 65 years, who have undergone an IPAA, seem to retain a good quality of life.[622]

9.5.2. Continent ileostomy

Kock's pouch[623] is an alternative to conventional end-ileostomy after a failed IPAA, for patients who are not candidates for IPAA [due to sphincter injury, for instance], and for those in whom an ileostomy represents considerable problems [e.g. leakage, skin problems, etc.]. Many surgeons have discredited the Kock's pouch procedure given its elevated rate of reoperation, as approximately half of the patients will need reoperation, with nipple valve sliding being the most common indication. Currently however, most series present a 10-year continent pouch survival of around 90%.[624,625] Quality of life with a Kock's pouch seems superior to that following an end-ileostomy. According to a study from the Cleveland Clinic, patients with an end-ileostomy were more than twice as likely to report social, work, and sexual restrictions as those who underwent a Kock's continent ileostomy.[624]

9.5.3. Ileo-rectal anastomosis

ECCO statement 9I

Under optimal circumstances, ileo-rectal anastomosis is a reasonable alternative to ileal-pouch anal anastomosis [EL5]. Advantages such as lower morbidity and preserved female fecundity need to be weighed against the need for rectal surveillance and subsequent protectomy in 50% of cases [EL3]

The reluctance of many surgeons to perform an IRA in UC patients[626] is justified by the good long-term functional outcome that follows an IPAA compared with the unpredictable functional outcome after an IRA in a noncompliant and inflamed rectum, as well as by the fear of a subsequent rectal cancer. IRA is a less complex procedure with lower morbidity rates and with reasonable clinical results in highly selected patients. Patients considered for IRA are those that present a relatively spared rectum [or a healed rectum under medical therapy], good rectal compliance, and normal sphincter tone. In these patients, defaecation habits are almost the same as after an IPAA procedure, although urgency seems to be more common in the IRA published series [22–33%].[607] Urgency is the most common cause of IRA failure. The reported probability of having a functioning IRA ranges from 74% to 84% at 10 years and from 46% to 69% at 20 years.[626,627] Surveillance of the retained rectum is necessary.[13]

9.5.4. Non-inflammatory pouch dysfunction and pouch failure

ECCO statement 9J

Non-inflammatory causes of pouch dysfunction include pouch-anal stricture, pouch fistula, problems with pouch capacity, efferent limb dysfunction [S-pouch], retained rectal stump, and chronic pre-sacral sepsis. Deciding on appropriate management requires discussion in a multidisciplinary team setting [EL5]

Detailed information on non-inflammatory pouch dysfunction can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[583,586,588,628–637]

9.6. Surgery and medication

9.6.1. Perioperative prednisolone

Uncontrolled and retrospective studies indicate that patients taking more than 20 mg of prednisolone for > 6 weeks have an increased risk of short-term surgical complications.[638–642] These studies have shown a five-fold risk of infectious complications and an increased risk of short-term postoperative, pouch-specific complications. Therefore, steroids should be weaned before surgery. If weaning is not possible, then pouch construction should be postponed. All recommendations regarding the rate of steroid reduction after colectomy for acute severe colitis are arbitrary but should avoid acute steroid withdrawal [Addisonian crisis], which in its most severe form is characterised by hypotension, hyponatraemia, and hypoglycaemia. Milder symptoms may be interpreted as a slower than normal recovery from surgery. The rate of tapering depends on the dose and duration of steroids preceding to surgery. For patients who have been taking steroids > 6 months, a dose reduction of 1 mg/week over a period of several months might be necessary.

9.6.2. Perioperative thiopurines / calcineurin inhibitors

ECCO statement 9K

Preoperative thiopurines or ciclosporine do not increase the risk of postoperative complications [EL3]

Thiopurines[643–645] and ciclosporine[557,643–646] do not increase the risk of postoperative complications after colectomy. The data for tacrolimus are still very scarce.[646,647]

9.6.3. Perioperative infliximab

TNF is a critical component of the immune response, and its inhibition by IFX or other agents can theoretically lead to serious postoperative complications. An enlarging number of studies that investigated the risk of IFX-associated postoperative complications yield conflicting results. One of these studies, a meta-analysis[648] of five studies including a total of 706 patients, specifically looking at UC patients,[638,649–652] reported that preoperative IFX increased the total number of short-term [30 days] postoperative complications [OR: 1.80; 95% CI: 1.12–2.87]. Although this analysis lacked the power needed to assess the nature of these complications, it did show a trend towards increased postoperative infections [OR: 2.24; 95% CI:0.63–7.95] but not non-infectious complications [OR: 0.85; 95% CI: 0.50–1.45] in those treated with IFX before surgery. Studies published thereafter failed to report an increased rate of IFX-associated complications following procto-colectomy.[653–655] As nearly all data on this subject come from observational studies rather than from randomised controlled trials, there might be significant bias influencing the results. A study from the Mayo Clinic has shown that postoperative anastomotic leaks and pouch-specific and infectious complications were more common in IFX-treated patients then among those who were not prescribed IFX.[649,650] After adjustment for concomitant therapy and severity of colitis, IFX was the only factor independently associated with infectious complications. Likewise, a more recently published study suggested that patients with previous anti-TNF use had a higher rate of pelvic sepsis after one-stage IPAA.[656] Conversely, a large Danish registry including more than 1200 UC patients who underwent a procto-colectomy did not report a significant increase in complications after surgery for previously IFX-exposed patients.[657]

The severity of disease and the sequential use of ciclosporine may also influence the postoperative IFX-associated risk. Patients with less severe forms of the disease and low CRP levels seem to benefit most from IFX therapy,[649,658–660] and there is particular concern that emergency colectomy within a few weeks of IFX may be associated with more septic complications.

Several studies report the efficacy and safety of ciclosporine and IFX as sequential rescue therapy in patients with steroid-refractory UC.[651,661–663] Overall, up to one-third of patients achieve short-term remission, and up to two-thirds avoid short-term colectomy.[662,663] These rates appear to be similar between patients receiving IFX after ciclosporine failure, and patients receiving ciclosporine after IFX failure. However, 16% of all patients experienced serious adverse events including sepsis, with fatal outcomes and herpetic oesophagitis.[661,662] There is no clear evidence on whether the risk of infectious complications is dependent on the drug sequence although theoretically IFX after ciclosporine should be safer, as ciclosporine has a much shorter half-life. Although some studies suggest a similar complication rate to that reported with IFX or ciclosporine alone,[662,663] the risk/benefit ratio of sequential rescue therapy has to be considered carefully in selected patients only, and cannot be recommended routinely. This seems to be especially true if ciclosporine is given as the second rescue therapy after IFX failure. As long as the data on perioperative use of anti-TNF agents remain conflicting, the standing recommendation is to not perform a single stage procto-colectomy with ileo-anal pouch construction in anti-TNF treated patients.

Section 10. Pouchitis

10.1. General

Procto-colectomy with an IPAA is the procedure of choice for most UC patients who require colectomy.[587] Pouchitis is a non-specific inflammation of the ileal reservoir and is the most common complication after an IPAA for UC.[588–594] Its frequency is related to the follow-up duration, occurring in up to 50% of patients 10 years after IPAA.[587,588,590–594,664,665] The cumulative incidence of pouchitis in patients with an IPAA following familial adenomatous polyposis is much lower, ranging from 0% to 10%,[666–668] but reasons for the higher frequency of pouchitis in UC patients remain unknown. Moreover, whether pouchitis develops more commonly within the initial years after IPAA or whether the risk increases continuously with follow-up remains undefined.

ECCO statement 10A

The diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities [EL3]. Extensive ulcerative colitis, primary sclerosing cholangitis, being a non-smoker, pANCA-positive serology, and non-steroidal anti-inflammatory drug use are possible risk factors for pouchitis [EL3]

10.1.1. Symptoms

After procto-colectomy with IPAA, daily median stool frequency is four to eight bowel movements,[587,588,590,591,623,669] with about 700 ml of semi-formed/liquid stool passed per day,[588,623,669] compared with a volume of 200 ml/day in healthy subjects. Symptoms related to pouchitis include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus, and pelvic discomfort.[588,624] Rectal bleeding, fever, and EIM may also occur. Rectal bleeding, however, is more often related to inflammation of the rectal cuff [see section 10.4][625] than to pouchitis. 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,[670–672] cuffitis,[625] and an irritable pouch,[673] among other conditions. This is why the diagnosis depends on endoscopic and histological findings in conjunction with symptoms.

10.1.2. Endoscopy ['pouchoscopy']

Pouchoscopy and pouch mucosal biopsy should be performed in patients with symptoms compatible with pouchitis, in order to confirm the diagnosis.[624,674] Patients with an ileo-anal pouch occasionally have a stricture at the pouch-anal anastomosis, so a gastroscope rather than a colonoscope is preferred. Progression into the afferent ileal limb should always be attempted. Endoscopic findings compatible with pouchitis include diffuse erythema, which may be patchy, unlike that observed in UC. Characteristic endoscopic findings also include oedema, granularity, friability, spontaneous or contact bleeding, loss of vascular pattern, mucous exudates, haemorrhage, erosions, and ulceration.[670] Erosions and/or ulcers along the staple line do not necessarily indicate pouchitis.[671,675,676] Biopsies should be taken from the pouch mucosa and from the afferent limb above the pouch, but not along the staple line.

10.1.3. Histopathology of pouchitis

Additional information on the histopathology of pouchitis can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[675–680]

10.1.4. Differential diagnosis

The clinical history and biopsies help discriminate between pouchitis, ischaemia, Crohn's disease, and other rare forms of pouch dysfunction such as collagenous pouchitis and *C. difficile* or CMV pouchitis.[683–685] 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.[684] The possibility of non-specific ileitis caused by NSAIDs should also be considered.[685]

10.1.5. Risk factors for pouchitis and pouch dysfunction

The aetiology of pouchitis remains unclear. Risk factors, genetic associations, and serological markers of pouchitis suggest that a close interaction between the host immune response and the pouch microbiota plays a relevant role in the aetiology of this idiopathic inflammatory condition.[686] Reported risk factors for pouchitis include extensive UC,[587,687] backwash ileitis,[687] EIM [especially PSC],[592,672,688] being a non-smoker,[143] and regular use of NSAIDs.[685,689] Interleukin-1 receptor antagonist gene polymorphisms[690] and the presence of pANCAs[691] are also associated with pouchitis. Not surprisingly, studies are discordant with regard to the role of each risk factor.[682] In all, 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 when the indication for IPAA was dysplasia, when the patient had never smoked, used NSAIDs, or [perhaps surprisingly] had never used anxiolytics.[682] The risk of a diagnosis of Crohn's disease in the pouch was greatly increased by being a current smoker, and modestly increased with having a pouch of long duration. Cuffitis was associated with symptoms of arthralgia and a younger age. 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 anxiolytics, which suggests that

these patients may have had irritable bowel syndrome contributing to gastrointestinal symptoms before pouch surgery.[682] Similar to irritable bowel syndrome, visceral hypersensitivity has been described in these patients.[692] The same group has recently shown that various perioperative factors may predict pouchitis. On multivariate analysis, pulmonary comorbidity, disease proximal to the splenic flexure, EIM, and S-pouch reconstruction were associated with pouchitis.[693] These risk factors should not preclude procto-colectomy if surgery is appropriate, but should be included in preoperative discussions with the patient and family. Similarly if a patient has PSC, then it is appropriate to discuss the higher risk of pouchitis. These discussions are part of an appropriate management of expectations, and known predictive factors for pouchitis or irritable pouch should not be considered as formal contraindications for pouch surgery.

10.2. Pattern of pouchitis

10.2.1. Acute and chronic pouchitis

On the basis of symptoms and endoscopy, pouchitis can be divided into remission [normal pouch frequency] or active pouchitis [increased bowel frequency with endoscopic appearances and histology consistent with pouchitis].[624,694] 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 have pouchitis refractory to medical treatment.[590] Pouchitis may be classified—according to different perspectives—into: 1] idiopathic versus secondary; 2] in remission versus active; and 3] infrequent [< three episodes/year] versus relapsing [> three episodes/year]. Pouchitis may also be classified based on the response to antibiotic therapy: 1] antibiotic-responsive; 2] antibiotic-dependent [need for continuous antibiotic treatment to maintain remission]; and 3] antibiotic-refractory.[695]

Detailed information on scoring of pouchitis can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[675,694,696–699]

10.2.2. Recurrent pouchitis and complications

Pouchitis recurs in more than 50% of patients.[590,624,692] Patients with recurrent pouchitis can be broadly grouped into three categories: infrequent episodes [< one/year], a relapsing course [one to three episodes/year], or a continuous course. Pouchitis may further be termed treatment responsive or refractory, based on response to antibiotic monotherapy.[665,700] Although these distinctions are largely arbitrary, they help both patients and 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.[594,681,694] The latter complication is exceptional and almost only occurs when there is pre-existing dysplasia or carcinoma in the original colectomy specimen.

10.3. Medical treatment

10.3.1. Acute pouchitis: antibiotics

ECCO statement 10B

The majority of patients respond to metronidazole or ciprofloxacin, although the optimum modality of treatment is not clearly defined [EL2]. Side effects are less frequent using ciprofloxacin [EL2]. Antidiarrhoeal drugs may reduce the number of daily liquid stools, independently of pouchitis [EL5]

Treatment of pouchitis is largely empirical and only small placebo-controlled trials have been conducted. Antibiotics are the mainstay of treatment, with metronidazole and ciprofloxacin the most common initial approaches, often resulting in a rapid response.[701] However, randomised trials of both metronidazole and ciprofloxacin are small.[590,702] Metronidazole and ciprofloxacin have been compared in a small randomised trial.[696] Seven patients received ciprofloxacin 1 g/day, and nine received metronidazole 20 mg/kg/day, for a period of 2 weeks. Both antibiotics significantly decreased the Perianal Disease Activity Index [PDAI] score, but there was a significantly greater benefit with ciprofloxacin compared with 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 of those who were receiving ciprofloxacin]. For the treatment of acute pouchitis [four randomised controlled trials, five agents], ciprofloxacin was more effective at inducing remission than metronidazole. Neither rifaximin nor *Lactobacillus plantarum GG* were more effective than placebo, whereas budesonide enemas and metronidazole were equally effective for inducing remission. In a non-randomised, non-controlled, open-label trial, a highly concentrated probiotic preparation [VSL#3] was shown to be effective in the treatment of mildly active pouchitis.[703,704]

10.3.2. Chronic pouchitis

ECCO statement 10C

In chronic pouchitis a combination of two antibiotics is effective [EL3]. Oral budesonide, oral beclomethasone dipropionate [EL3], and topical tacrolimus [EL3] are alternatives. Infliximab is effective for the treatment of chronic refractory pouchitis [EL4]. Adalimumab may represent an alternative treatment in patients refractory to infliximab [EL4]

For patients who have persistent symptoms, alternative diagnoses should be considered. Approximately 10–15% of patients with acute pouchitis develop chronic pouchitis, which may be 'treatment responsive' or 'treatment refractory' to single antibiotic therapy.[588] Patients with chronic, refractory pouchitis do not respond to conventional therapy and often have ongoing symptoms. This is a common cause of pouch failure. Combination antibiotic therapy or oral budesonide may be effective.[704–709] More recently, oral beclomethasone dipropionate has been shown to be effective in chronic refractory pouchitis. Ten consecutive patients with active pouchitis, not responding to 1-month antibiotic treatment, were treated with beclomethasone dipropionate 10 mg/day for 8 weeks. Eight of 10 patients [80%] achieved remission.[710]

10.3.3. Acute and chronic refractory pouchitis: other agents

Detailed information on other agents for the treatment of acute and chronic refractory pouchitis can be found in Supplementary material, available as Supplementary data at *ECCO-JCC* online.[711–721]

10.3.4. Maintenance of remission: probiotics

Once remission has been achieved in chronic pouchitis, treatment with the concentrated probiotic mixture VSL#3 helps to maintain remission. Two double-blind, placebo-controlled studies have shown the high efficacy of VSL#3 [450 billion bacteria of eight different strains/g] to maintain remission in patients with chronic pouchitis.[722,723] In the Cochrane systematic review, VSL#3 was more effective than placebo in maintaining remission of chronic pouchitis in patients who achieved remission with antibiotics.[703,724]

10.3.5. 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. 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 in their quality of life.[725] A Cochrane systematic review reports that VSL#3 was more effective than placebo for the prevention of pouchitis.[703,724]

10.4. Cuffitis

Cuffitis can cause pouch dysfunction with symptoms that mimic pouchitis or irritable pouch syndrome especially after double-stapled IPAA [see section 9]. Unlike the irritable pouch syndrome [which may coexist], bleeding is a characteristic feature of cuffitis. Diagnosis can be made by endoscopy, but care has to be taken to examine the cuff of columnar epithelium between the dentate line and pouch-anal anastomosis [section 9.2.3].[700] In an open-label trial, 14 consecutive patients with cuffitis treated with 5-ASA suppositories, 500 mg twice daily, experienced a reduction in the total Cuffitis Activity Index [derived from the PDAI] from 11.9 ± 3.17 to 6.21 ± 3.19 [$p < 0.001$].[625] In addition, the symptom sub-score reduced from 3.24 ± 1.28 to 1.79 ± 1.31, endoscopy sub-score from 3.14 ± 1.29 to 1.00 ± 1.52, and histology sub-score from 4.93 ± 1.77 to 3.57 ± 1.39; 92% of patients with bloody bowel movements and 70% with arthralgia [a characteristic clinical feature of cuffitis] improved on therapy. No systemic or topical adverse effects were reported.

Disclaimer

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Supplementary Data

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

References

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