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SPECIAL ARTICLE

Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis

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1. Definitions

1.1. Introduction

Ulcerative colitis is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in the developed countries of the world. The precise aetiology is unknown and therefore medical therapy to cure the disease is not yet available. Within Europe there is a North–South gradient, but the incidence appears to have increased in Southern and Eastern countries in recent years.[1,2] Patients may live with a considerable symptom burden despite medical treatment (66% describe interference with work and 73% with leisure activities[3]) in the hope that the aetiology of ulcerative colitis will shortly be revealed and a cure emerge. Although this is conceivable in the next decade, clinicians have to advise patients on the basis of information available today. Despite randomised trials there will always be many questions that can only be answered by the exercise of judgement and opinion. This leads to differences in practice between clinicians, which may be brought into sharp relief by differences in emphasis between countries.

This Consensus endeavours to address these differences. The Consensus is not meant to supersede the guidelines of different countries (such as those from the UK,[4] or Germany,[5]) which reach broadly the same conclusions since they are, after all, based on the same evidence. Rather, the aim of the Consensus is to promote a European perspective on the management of ulcerative colitis (UC) and its dilemmas. Since the development of guidelines is an expensive and time-consuming process, it may help to avoid duplication of effort in the future. A European Consensus is also considered important because an increasing number of therapeutic trials recruit from Central and Eastern European countries where practice guidelines have yet to be published.

This document updates the previous European Consensus on the diagnosis and management of UC, and was finalised by the European Crohn's and Colitis Organisation (ECCO) at a meeting held in Dublin in February 2011. ECCO is a forum for specialists in inflammatory bowel disease from 31 European countries. Like the initial Consensus on the diagnosis and management of ulcerative colitis,[6–8] this updated Consensus is grouped into three parts: definitions and diagnosis; current management; and management of special situations. This first section concerns aims, methods and definitions of the Consensus, as well as classification, diagnosis, imaging and pathology of UC. The second section on Current Management includes treatment of active disease, maintenance of medically-induced remission and surgery of UC. The third section on Special Situations includes ileoanal pouch disorders, cancer surveillance, psychosomatics and extraintestinal manifestations. Previously included chapters on pregnancy and pediatrics are no longer included in this guideline, as specific ECCO Consensus Guidelines on Reproduction and Pregnancy and Pediatric UC (together with ESPGHAN) cover these topics extensively.[9–11] Alternative therapies are now covered in Section 2 under management of active disease and maintenance therapy of UC. Attention is also drawn to other ECCO Consensus Guidelines on small bowel endoscopy,[12] opportunistic infections,[13] and forthcoming guidelines on Surgery, Imaging, Endoscopy, Pathology and the management of anaemia in inflammatory bowel disease (www.ecco-ibd.eu).

The strategy to reach the Consensus involved five steps:

1. For the development of the first ECCO guideline published in 2008,[6–8] relevant questions on each of 14 separate topics concerning diagnosis and treatment of UC were devised by the Chairs and their working parties. The questions were focused on current practice and areas of controversy. Participants were asked to answer the questions based on their experience as well as evidence from the literature (Delphi procedure).[14] For this update, an open call for participants was made (see acknowledgements and www.ecco-ibd). Participants were selected by the Guidelines' Committee of ECCO (GuiCom) on the basis of their publication record and a personal statement. Working parties were established who reviewed the Consensus statements published in 2008[6–8] and recommended whether they required revision, based upon advances in the published literature. There was an agreement that there was neither a need for extensive revision of the histopathology section, nor of the section on pregnancy and pediatric UC which will not be included in future UC guidelines, in view of the specific ECCO Consensus Guidelines which serves as a reference for these areas.[9,10]
2. In parallel, the working parties performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed and the Cochrane database, as well as their own files. The evidence level (EL) was graded (Table 1.1) according to the Oxford Centre for Evidence Based Medicine.[15]
3. Revised statements on their topic were then written by the Chairs, based on answers from their working party, as well as the literature evidence and were circulated first among their working party and then among all participants.
4. All working parties met in Dublin in February 2011 to agree the statements. Participants gathered under the Chairmanship of A. Dignass and G. Van Assche to agree the final version of each statement. Technically this was done by projecting the statements and revising them on screen until a consensus was reached. Consensus was defined as agreement by >80% of participants, termed a Consensus Statement and numbered for convenience in the document. Each recommendation was graded (RG) according to the Oxford Centre for Evidence Based Medicine,[15] based on the level of evidence (Table 1.1).
5. The final document on each topic was written by the Chairs in conjunction with their working party. Consensus statements in bold are followed by comments on the evidence and opinion. Statements are intended to be

Table 1.1 Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence Based Medicine (for details see http://www.cebm.net/levels_of_evidence.asp#refs). [a]

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

Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	Level 4 studies *or* extrapolations from level 2 or 3 studies
D	Level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

[a] CfEBM definitions have been updated in 2011 after the consensus meeting, but the previous CfEBM version from March 2009 was used for this Consensus.

read in context with qualifying comments and not read in isolation. The final text was edited for consistency of style by A. Dignass, G. Van Assche and J. O. Lindsay before being circulated and approved by the participants. In some areas the level of evidence is generally low, which reflects the paucity of randomised controlled trials. Consequently expert opinion is included where appropriate.

1.2. Definitions

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

Ulcerative colitis (UC) is a chronic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterised by a relapsing and remitting course.[16]
IBD *unclassified* (IBDU) is the term best suited for the minority of cases where a definitive distinction between UC, Crohn's disease, or other cause of colitis cannot be made after the history, endoscopic appearances, histopathology of multiple mucosal biopsies and appropriate radiology have been taken into account.[16,17].
Indeterminate colitis is a term reserved for pathologists to describe a colectomy specimen which has overlapping features of ulcerative colitis and Crohn's disease.[17,18] It has distinct prognostic factors related to further surgery.

1.2.1. Distribution of disease

The Consensus favours use of the Montréal classification (Table 1.2[16]) for defining the distribution of disease. This is used to describe the maximal, macroscopic extent of disease at colonoscopy, since in the past the extent of disease as defined by barium enema has been used as a predictor for the long-term prognosis of UC. The implications of more

Table 1.2 Distribution of ulcerative colitis (from[16]).

Term	Distribution	Description
E1	Proctitis	involvement limited to the rectum (ie proximal extent of inflammation is distal to the rectosigmoid 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 pancolitis

extensive microscopic disease are still not understood. The poor correlation between macroscopic and microscopic extent of disease (kappa = 0.39) is recognised.[17] This is also valid for an extent-based classification, when the extent varies over time, underlining the dynamic nature of inflammatory bowel disease.[19]

1.2.2. Disease onset

There is some evidence to suggest that patients with UC stratified by age (A1: <16; A2:16–40 and A3: >40 years) have different outcomes. Patients diagnosed before the age of 16 had a more aggressive initial course, while older age at diagnosis was found to be associated with a lower risk of colectomy.[20,21] There is also some evidence that UC diagnosed in the very young has a different aetiology and prognosis. This is taken into consideration by the paediatric modification to the Montréal classification.[22]

1.2.3. Active disease

For the purposes of this Consensus, clinical disease activity is grouped into remission, mild, moderate and severe. This refers to biological activity and not to treatment-responsiveness (see Section 1.2.8). Precise definitions of disease activity are appropriate, since confusion arises if the terms are used to refer only to the least, intermediate or most severe third of cases that the physician can recall at the time. Among 2006 Consensus participants, 31/59 considered Truelove and Witts' criteria useful in clinical practice (summarised in Table 1.3[23]), in conjunction with sigmoidoscopy to confirm active colitis.

The term severe colitis (or 'acute severe colitis') is preferred to 'fulminant' colitis, because the term 'fulminant' is ill-defined. It was coined in 1950 when it referred to a single attack going on to death within 1 year,[26] which no longer has relevance today. Severe colitis as defined according to Truelove and Witts' criteria (Table 1.3 and Section 5.1) is easy to apply in outpatients, mandates hospital admission for intensive treatment and defines an outcome (only 70% respond to intensive therapy). These criteria are recommended for identifying acute severe colitis by The American College of Gastroenterology (ACG)[27] and the Association of Coloproctology of Great Britain and Ireland (ACPGBI),[28] as well as ECCO.

Table 1.3 Disease activity in ulcerative colitis, adapted from Truelove and Witts.[23]

	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*
or CRP	Normal	≤30 mg/L	>30 mg/L

The value of the different indices for the purpose of clinical trials is beyond the scope of the Consensus, but has been reviewed elsewhere.[25] ECCO recognises the need to validate clinical and endoscopic scoring systems.

Moderate colitis has become necessary to distinguish from mildly active disease, because the efficacy of some treatments may differ (Section 5). The simplest clinical measure to distinguish moderate from mildly active colitis is the presence of mucosal friability (bleeding on light contact with the rectal mucosa at sigmoidoscopy). The technique of assessing mucosal friability at flexible sigmoidoscopy has yet to be standardised. One approach is to apply sufficient pressure on the mucosa with closed biopsy forceps to create a dimple, maintain the pressure for 3 s and then define friability if bleeding occurs from the pressure point. This has yet to be validated. For review of the various activity indices see D'Haens et al.[25]

Wide variation in endoscopic interpretation of disease activity is recognised (Section 3.6.1).

1.2.4. Remission

Remission is defined as complete resolution of symptoms and endoscopic mucosal healing (Section 2.2.4). Combining clinical and endoscopic indices is appropriate for clinical trials,[25,29] but reported remission rates vary by as much as two-fold depending on the definition of remission used in the trial.[30] In clinical practice, participants agreed that 'remission' meant a stool frequency ≤3/day with no bleeding and no urgency. Remission defined by individual patients has an 86% sensitivity and 76% specificity for a regulatory-defined remission (absence of visible blood and absent mucosal friability), indicating that sigmoidoscopy to confirm mucosal healing is generally unnecessary in practice.[31]

1.2.5. Response

Response is defined as clinical and endoscopic improvement, depending (for the purpose of clinical trials) on the activity index used. In general, this means a decrease in the activity index of >30%, plus a decrease in the rectal bleeding and endoscopy subscores, but there are many permutations.[25]

1.2.6. Relapse

The term relapse is used to define a flare of symptoms in a patient with established UC who is in clinical remission, either spontaneously or after medical treatment. In the Consensus, 47/59 considered rectal bleeding an essential component of relapse, and 29/59 believed that a combination of rectal bleeding with an increase in stool frequency and abnormal mucosa at sigmoidoscopy was necessary to define relapse. In clinical trials, the criteria for relapse should be predefined with the score that is being used for an individual study.[25]

1.2.7. Early relapse

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

1.2.8. Pattern of relapse

Relapse may be infrequent (≤1/year), frequent (≥2 relapses/year), or continuous (persistent symptoms of active UC without a period of remission).[32] Although the terms are arbitrary, they are considered clinically relevant. An alternative approach that defines disease activity over a 5 year period has been proposed (Section 2.1.1), but this seems more relevant to epidemiological studies, since what matters for

everyday practice is what is likely to happen in the next year. The prognostic significance needs to be determined. Nevertheless, care should be taken to distinguish between terms that describe disease activity at a point in time and those that describe the longitudinal pattern (or 'behaviour') of the disease (Sections 1.2.3 and 2.2.1). The term 'chronic active disease' has been used in the past to define a patient who is dependent on, refractory to, or intolerant of steroids, or who has disease activity despite immunomodulators. Since this term is ambiguous it is best avoided. Instead, arbitrary, but more precise definitions are preferred, including steroid-refractory or steroid-dependence.

1.2.9. Steroid-refractory colitis
Patients who have active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks. The definition is consistent with the definition for steroid-refractory Crohn's disease,[33] however, it is likely to evolve, with a reduction in the duration of steroid therapy as the threshold for biologic therapy changes.

1.2.10. Steroid-dependent colitis
Patients who are either

i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or
ii) who have a relapse within 3 months of stopping steroids.

This is consistent with the definition for steroid-dependent Crohn's disease,[33] although an alternative definition of relapse within 30 days of completing a course of steroids, or steroids at a dose of 15–25 mg/day for at least 6 months has been proposed.[23] As with steroid-refractoriness, the definition is likely to evolve as the threshold for biologic therapy changes.

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

1.2.11. Immunomodulator-refractory colitis
Patients who have active disease or relapse in spite of thiopurines at an appropriate dose for at least 3 months (i.e. azathioprine 2–2.5 mg/kg/day or mercaptopurine 1–1.5 mg/kg/day in the absence of leucopenia). The definition is arbitrary, but has increasing clinical relevance when deciding on the place of biological therapy or surgery.

1.2.12. Refractory distal colitis
Defined as persistent symptoms due to colonic inflammation confined to the rectum (proctitis), or left-side of the colon, despite treatment with oral plus topical steroids and 5ASA for 4–8 weeks. This represents a common clinical dilemma, although whether it is a separate entity is unclear.

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

1.2.14. Alternative therapy
Therapy that is used in place of conventional medicine.

1.2.15. Complementary therapies
Treatments used alongside conventional medicine.

1.2.16. Expert opinion
The term 'expert' is used here to refer to the opinion of the specialists in inflammatory bowel disease representing multiple disciplines from 31 European countries who contributed to the ECCO Consensus. In some sections opinions from individual members of other expert bodies were obtained, including individuals of the European Society of Pathology (ESP) working group on Digestive Diseases, the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).

2. Classification

2.1. Classification according to disease extent

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

There are several reasons why patients with UC should be classified according to disease extent. First, the extent of inflammation will influence the patient's management and the choice of delivery system for a given therapy. For instance, topical therapy in the form of suppositories (for proctitis) or enemas (for left-sided colitis) is often the first line choice, but oral therapy - often combined with topical therapy is appropriate for extensive colitis [EL1b, RG B]. Second, the extent of colitis influences the start and the frequency of surveillance [EL2, RG B]. In the population-based study from Sweden,[34] extent of disease was one of the risk factors for development of colorectal cancer in 3117 UC patients followed up from 1 to 60 years after diagnosis. No increased relative risk (RR) was attributed to disease confined to the rectum, whereas, the RR for left-sided colitis and extensive colitis (previously called pancolitis) were 2.8 (95%CI 1.6–4.4) and 14.8 (95%CI 11.4–18.9) respectively. Therefore, patients with left-sided and extensive colitis are generally advised to have surveillance colonoscopy, but patients with proctitis do not need surveillance (Section 2.2). The contribution of disease extent at diagnosis to the risk of malignancy has been confirmed more recently by the EC-IBD study group.[31]

The Consensus group agreed that the preferred classification is based on endoscopy and divides disease into proctitis, left-sided colitis and extensive colitis (beyond the splenic flexure), as defined by the Montréal Working Group on the Molecular classification of IBD[16,17] (Section 1.1, Table 1.2).

2.2. Classification according to disease severity

ECCO statement 2B

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

2.2.1. Activity and pattern of disease

In a population-based study from Copenhagen County, Langholz et al. showed that approximately 50% of patients will be in clinical remission at any time during a given year.[35] However, the cumulative probability of a relapsing course after 25 years of follow up amounted to 90%. Disease activity in the first 2 years after diagnosis indicated (with 70-80% probability) an increased probability of 5 consecutive years of active disease and was therefore judged to be a good parameter to predict the future pattern of disease.

Microscopic involvement seems to be of importance as well. In patients with quiescent UC, a chronic inflammatory cell infiltrate was present in all biopsy specimens, and crypt architectural irregularities in two thirds. Fifty two percent of patients with an acute inflammatory cell infiltrate relapsed after 12 months of follow-up, whereas only 25% relapsed in the absence of such an infiltrate ($p=0.02$). Similarly, relapse rates were higher in the presence of crypt abscesses, mucin depletion, and breaches in the surface epithelium.[36] The degree of bowel inflammation is also a risk factor for colorectal cancer in patients with long-standing extensive UC.[37]

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

2.2.2. Choice of index

A classification of UC based on disease activity and severity is important because it influences patient management. The severity of the inflammation will determine if no therapy, oral therapy, intravenous or surgical therapy is initiated in a given patient. Many disease activity indices or criteria have been proposed (see Section 1.2.3 and reference[25] for a review), but none have been adequately validated. The Consensus recognises the need for validated clinical and endoscopic indices that relate to outcome or treatment decisions. Although modifications of the original Truelove and Witts' criteria (Section 1.2.3, Table 1.3) are used in daily practice, the modified Mayo score (Section 1.2.3, Table 1.4) is used more frequently in current clinical trials.[23] For clinical practice, the Consensus group judged that a combination of clinical features, laboratory findings, imaging modalities and endoscopic parameters, including histopathology will all assist physicians in their patients' management. Endoscopic scoring is illustrated in Section 3.5 and Table 3.1.

2.2.3. Clinical and laboratory markers of severity

Among objective clinical features, bloody stool frequency, body temperature and heart rate are good predictors of outcome. Laboratory markers have been studied intensively with varying degrees of success. The widely used acute phase C-reactive protein is a less good marker for assessing disease activity in UC than Crohn's disease, except for acute severe colitis, where it has established value in both adults and children.[38–40] A raised CRP >45 mg/L on day 3 following hospital admission for severe colitis together with 3–8 stools a day is highly predictive for colectomy (Section 1.2.5). Other positive (erythrocyte sedimentation rate, serum procalcitonin[41]) or negative (albumin) acute phase proteins have been studied, but none have demonstrated clear superiority (for review see[42]). More recently, faecal markers have demonstrated promising results. The most studied markers are faecal calprotectin and lactoferrin, but elastase and the more recent marker S100A12 have also shown accuracy at detecting colonic

Table 1.4 Mayo score[24,25] and 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

The Montréal classification (Table 1.5)[16,17] is largely based on Truelove and Witts' criteria, since this reflects clinical practice.

Table 1.5 Montréal classification of disease activity in ulcerative colitis.[16]

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

inflammation.[43–47] Recent studies emphasise the value of calprotectin as a tool for diagnosis and the assessment of disease severity (correlating with endoscopic indices, relapse and response to treatment).[48–51] It must be stressed however that none of these markers are specific for UC, since they mostly represent colonic inflammation with an influx of neutrophils into the gut mucosa, with subsequent shedding of cytoplasmic granules into the gut lumen.

2.2.4. Remission

As with the definition of disease activity, there has also not been a fully validated definition of remission. The Consensus group agreed that the best way of defining remission is a combination of clinical parameters (stool frequency ≤3/day with no bleeding) and normal or quiescent mucosa at endoscopy.[30]

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

ECCO statement 2C

A classification of UC according to age at onset is of value [EL2; RG B]. Classification of UC according to the concomitant presence of PSC is important because it influences patients' management (surveillance) [EL2; RG C]

A classification according to age at onset is of value. Young patients with UC tend to have more aggressive disease and use more immunomodulators, while patients diagnosed with UC later in life (A3) tend to have a more mild disease with less need for surgery ([20]). All current available therapies for UC have shown equivalent efficacy in children compared to adults. The apparently higher risk of colorectal cancer in patients with the onset of UC in childhood almost certainly reflects the duration of disease. However, concomitant primary sclerosing cholangitis (PSC) is an important feature in patients with UC given its increased associated risk for colorectal cancer.[34,48] This influences decisions on surveillance colonoscopy [Section 2.2).

2.4. Use of molecular markers

ECCO statement 2D

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

2.4.1. Serology

A number of (auto)antibodies have been described in patients with UC, of which the atypical perinuclear anti-neutrophil cytoplasmatic antibodies (pANCAs) are best known. Positive pANCA serology is found in approximately 50–60% of patients, although large variability exists due to differences in methodology.[52,53] Overall, pANCA has shown good accuracy to differentiate CD from UC,[54–57] but their sensitivity is not high enough to justify their use in diagnosis. These antibodies also lack accuracy in patients with colitis-yet to be classified, where diagnostic markers would be of greatest clinical value. A number of other antimicrobial antibodies as ASCA, OmpC, I2, cBir anti-flagellin, ALCA, ACCA, are found mainly in patients with Crohn's disease.[58–61]

2.4.2. Genotyping

The very active field of IBD genetics has led to the identification of more than 160 confirmed genetic variants, which are implicated in a susceptibility to Crohn's disease or UC. The HLA region is without any doubt the region most associated with UC,[62] but the Interleukin-23 Receptor (IL23R) gene on chromosome 1,[63] the DLG5 gene on chromosome 10,[64] the JAK/ STAT pathway, the Multidrug Resistance gene (MDR)-1 and the Toll like Receptor (TLR) genes have shown associations with UC.[65–73] Recently, a genome wide association identified multiple UC susceptibility loci one of which was at 7q22 and 22q13 (IL17REL).[74–76] Since UC is a complex multifactorial disease, the disease-associated mutations in these genes will never be sufficient to cause disease, nor will the absence of mutations be a guarantee of remaining free of disease. Therefore, testing for these genetic variants is not recommended for clinical purposes.

Table 3.1 Endoscopic scores for ulcerative colitis commonly used in clinical trials.

Score	0	1	2	3
Baron[185]	Normal: matt mucosa, ramifying vascular pattern clearly visible, no spontaneous bleeding, no bleeding to light touch	Abnormal, but non-haemorrhagic: appearances between 0 and 2	Moderately haemorrhagic: bleeding to light touch, but no spontaneous bleeding seen ahead of the instrument on initial inspection	Severely haemorrhagic: spontaneous bleeding seen ahead of instrument at initial inspection and bleeds to light touch
Schroeder[24]	Normal or inactive disease	Mild (erythema, decreased vascular pattern, mild friability)	Moderate (marked erythema, absent vascular pattern, friability, erosions)	Severe (spontaneous bleeding, ulceration)
Feagan[188]	Normal, smooth, glistening mucosa, with vascular pattern visible; not friable	Granular mucosa; vascular pattern not visible; not friable; hyperaemia	As 1, with a friable mucosa, but not spontaneously bleeding	As 2, but mucosa spontaneously bleeding

3. Diagnosis and imaging

3.1. Introduction

Ulcerative colitis (UC) primarily presents in late adolescence and early adulthood, although the diagnosis may be made at any age. A small peak in incidence has been demonstrated in some populations after the fifth decade of life.[77] Ulcerative colitis appears to affect both sexes equally. The inflammation characteristically commences in the rectum and extends proximally in a continuous, confluent and concentric manner to affect a variable extent of the colon, or its entire mucosal surface. The definitions and classification of the extent of UC are covered in Sections 1.1 and 2.1 (Table 1.2).[16] The proximal extent of inflammation may progress or regress over time, but after disease regression the distribution of inflammation tends to match the extent of previous episodes in the event of relapse. The view that UC represents continuous colonic inflammation has, however, been challenged by reports of a rectal sparing variant and peri-appendicecal patchy inflammation.[78] Symptoms depend on the extent and severity of disease, extra-intestinal manifestations and concurrent therapy. Enteric pathogens may alter the clinical presentation.

3.2. Clinical features and risk factors

3.2.1. Clinical features of ulcerative colitis

ECCO statement 3A

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

The primary presenting symptom of ulcerative colitis is visible blood in the stools and is reported by more than 90% of patients. Associated symptoms generally reflect the endoscopic severity of the disease as a measure of mucosal damage and may differ according to disease extent.[79–89] Loose stools (or a decrease in stool consistency) for more than six weeks differentiates UC from most infectious diarrhoea.[90] Patients with extensive active UC present with chronic diarrhoea almost invariably associated with rectal bleeding, or at least visible blood in the stools. Such patients also describe rectal urgency, tenesmus, passage of mucopurulent exudates, nocturnal defaecation and crampy abdominal pain, or ache over the left iliac fossa prior to and relieved by defaecation. In contrast, patients with proctitis usually present with rectal bleeding, urgency, tenesmus, and occasionally severe constipation.[82,84] Anal and minor perianal lesions may complicate severe diarrhoea, but although simple fistulae may occasionally occur in UC, recurrent or complex perianal fistulae should always raise the suspicion of Crohn's colitis.

The onset of UC is usually insidious and symptoms are often present for weeks or even months before medical advice is sought. The disease may present with intermittent episodes of symptoms or as a severe attack (in about 15%) with systemic symptoms including weight loss, fever and tachycardia, or even nausea and vomiting.[91] Extraintestinal manifestations, especially an axial or peripheral arthropathy, episcleritis and erythema nodosum may accompany the presentation in about 10% and rarely precede intestinal symptoms.[92] Thromboembolism is more frequent in UC than the general population, but is generally associated with active disease and pancolitis.[93]

3.2.2. Risk factors for ulcerative colitis

ECCO statement 3B

Appendicectomy for histology proven appendicitis has been shown to provide some protection against subsequently developing UC and in reducing its severity if performed for 'true' appendicitis at a younger age [EL2b, RGB]

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

Active tobacco smoking has a protective effect on the development and severity of UC.[94,95] In contrast, ex-smokers have about a 70% greater risk of developing the disease, which is often more extensive and refractory than in those who have never smoked. Rates of hospital admission and colectomy are also higher in ex-smokers than in never-smokers.[96,97] Improvements in symptoms and a milder course of disease have been reported in ex-smokers who resume smoking,[97,98] but the effect is inconsistent. Smoking may also prevent the development of primary sclerosing cholangitis (PSC), or pouchitis after colectomy and ileal pouch anal anastomosis, but this too has been challenged.[99–101]

Cohort studies and meta-analysis have suggested that appendicectomy performed for true appendicitis at an early age may be protective against the onset and subsequent severity of UC. A 69% risk reduction has been reported for appendicectomy, although a Danish cohort study failed to confirm this.[77,102–106] The protective effect of appendicectomy is additional to that of smoking, but does not appear to protect against the development of PSC.[107] When appendicectomy is performed after the onset of ulcerative colitis, the effect (if any) on the course of the disease is far less clear.

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) appear to carry a significant risk of exacerbating ulcerative colitis. The magnitude of such risk has never been adequately determined and it is unclear whether all patients are affected to the same degree.[95–98,108–111] In contrast, preliminary evidence from open-label studies and a double-blind controlled trial suggest that short-term treatment with selective COX-2 inhibitors is safe.[111,112] Nonetheless, prolonged usage is best avoided because of potential adverse effects on other organ systems.

First-degree relatives of patients with UC have a 10–15 fold risk of developing the disease.[113] In a population-based Danish cohort study, the relative risk for developing UC was 10 amongst relatives with the disease.[114] In other terms, the life time risk of UC for a first degree relative is around 2%, or a 98% chance of *not* developing the disease, which may help reassure a parent with UC concerned about the risk to their children. In familial cases of UC there is a slight female preponderance and younger age of onset compared to sporadic cases.[113,115]

3.3. History, examination and diagnosis

3.3.1. Medical history

ECCO statement 3C

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

The diagnosis of UC is suspected from the clinical symptoms (Section 3.2.1). Infectious or drug-induced forms of colitis should be excluded. Enquiry should be made into the family history of both IBD and CRC and patients asked about possible ocular, oral, joint or skin manifestations.[116–121]

3.3.2. Examination

ECCO statement 3D

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

Findings on physical examination depend on the extent and severity of UC. Examination of patients with mild or moderate activity is usually unremarkable, apart from blood on rectal examination. Patients with a severe attack exhibit fever, tachycardia, weight loss, colonic tenderness, abdominal distension, or reduced bowel sounds.[122]

3.3.3. Diagnosis

ECCO statement 3E

A gold standard for the diagnosis of ulcerative colitis is not available. The diagnosis should be established by a combination of medical history, clinical evaluation, and typical endoscopic and histological findings. An infective cause should be excluded. Where there is doubt about the diagnosis, endoscopic and histological confirmation is necessary after an interval [EL5, RG D]

The natural history of UC is characterised by episodes of relapse and periods of remission, and occasionally by an unremitting, continuous course (about 5%). A single acute episode followed by prolonged remission may also occur in about 5%.[35] In the IBSEN study about 60% of patients experienced a decrease in their symptoms over time.[123]

The frequency of relapse (pattern of disease) is usually defined in the first three years, and may be characterised as frequent (≥2 relapses/year) or infrequent (≤1 relapse/year,[32] Sections 1.2 and 2.2.1).

It helps patients to establish the diagnosis, extent and severity of the disease rapidly, because this influences treatment options and possibly disease progression.[89] Since there is no single pathogenic marker, the diagnosis relies on a combination of medical history, endoscopic findings, histological features on multiple colonic biopsies and negative stool tests for infectious agents. It is unreasonable to expect the histopathologist alone to make the diagnosis (Section 4), but normal mucosal biopsies effectively exclude active UC as a cause of symptoms. In 10% of patients the diagnosis will be changed to Crohn's disease or the diagnosis of inflammatory bowel disease discounted during the first 5 years after symptom onset. Endoscopic and histological confirmation of the diagnosis is considered essential.[124] In a minority of patients it is not possible to characterise the cause of colitis: see Section 1.1 for correct usage of the terms 'IBD Unclassified' and 'indeterminate colitis'.[16,18]

3.4. Investigation and procedures to establish a diagnosis

3.4.1. Initial investigations

ECCO statement 3F

Initial laboratory investigations should include a full blood count, serum urea, creatinine, electrolytes, liver enzymes, iron studies, and C-reactive protein (CRP) [EL5, RG D]. Faecal calprotectin is an accurate marker of colonic inflammation. CRP and erythrocyte sedimentation rate (ESR) are useful markers to monitor the response to treatment in severe colitis [EL2b, RGB]. Microbiological testing for infectious diarrhoea including *Clostridium difficile* toxin is recommended [EL2b, RG B]. Additional stool tests may be necessary for patients who report a recent travel abroad [EL5, RG D]. Patient's immunization status to various viral diseases and tuberculosis status should be assessed [EL5, RG D]

At diagnosis, every patient should have a full blood count, inflammatory markers (CRP or ESR), electrolytes and liver function tests, along with a stool sample for microbiological testing.[122] Faecal calprotectin is an accurate marker of colonic inflammation. Laboratory markers of chronic inflammation may be normal in mild or moderate distal UC. The full blood count may reveal thrombocytosis as a result of the chronic inflammatory response, anaemia indicating disease severity or chronicity and leucocytosis, raising the possibility of an infectious complication.

For UC, excluding proctitis, CRP broadly correlates with clinical activity.[39,42,125–127] 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[40,128,129] (Section 5.2.5). CRP >10 mg/L after a year of extensive colitis, predicted an increased rate of surgery.[126] Neither CRP nor ESR are specific enough to differentiate UC from infectious or other causes.

The initial diagnosis of UC requires the elimination of infectious causes of symptomatic colitis. Stool specimens should be cultured for common pathogens including specific assays for *C. difficile* toxin A and B, *Campylobacter* spp., and *Escherichia coli* 0157:H7. Additional tests may be tailored to the medical history, such as examination of fresh, warm stool samples for amoebae or other parasites.

3.4.2. Microbial investigations

ECCO statement 3G

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

It is not routinely recommended to screen for pathogens such as *C. difficile* at each flare of the disease, due to infrequent positive results.[130–132] However as *C. difficile* infection is a growing health issue in hospitalised UC patients and is associated both with a higher mortality and resource utilization, it is advisable to screen hospitalised patients[133] as well as those with a previous history of antibiotic use. In contrast, microbial stool tests should be performed during a treatment-refractory or severe relapse.[134,135] Flexible sigmoidoscopy may be superior to stool *C. difficile* cytotoxin assay in patients with pseudomembranous colitis and is appropriate for patients with diarrhoea where the stool test is negative.[136]

Reactivation of *Cytomegalovirus* (CMV) can occur in ulcerative colitis, particularly (but not invariably) in immunosuppressed patients with severe colitis.[137–139] The clinical relevance of this finding remains uncertain, but CMV infection may cause refractory or severe relapse. The optimal method for detecting clinically relevant CMV infection in patients with colitis has not been established. The most commonly used technique for diagnosis of CMV infection and disease is detection of CMV DNA through PCR. Occasional intranuclear inclusion bodies consistent with CMV on histopathology do not necessarily indicate clinically significant infection, but multiple intranuclear inclusions are usually significant.[140,141] CMV should be considered in patients with refractory or severe colitis and if detected, advice taken from virologists about the significance and appropriate therapy. Further details can be reviewed in the ECCO Consesnsus on opportunistic infections in IBD.[13]

3.4.3. Biomarkers

The most widely studied serological markers are perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA). In most series pANCA are found in up to 65% of patients with UC and in less than 10% of patients with Crohn's disease. It should be noted that the incidence of pANCA in UC may depend upon

local laboratory expertise and geographical latitude.[142,143] In view of the current limited sensitivity of these markers, their routine use for the diagnosis of UC and for therapeutic decisions is not clinically justified.

Of the faecal markers of intestinal inflammation, neutrophil-derived proteins such as calprotectin, elastase, lysozyme and lactoferin, have been evaluated in IBD.[144–147] Faecal calprotectin appears to be the most sensitive, non-invasive biomarker that reflects intestinal inflammation in established IBD.[148] Recent studies emphasise the value of calprotectin in selecting patients for diagnostic investigation, assessing, disease severity (correlating with endoscopic indices), diagnosing relapse and response to treatment.[48,49,51,149,150] However, as with all faecal tests, calprotectin lacks the specificity to discriminate between types of inflammation. Therefore, its use as a diagnostic tool in UC is limited, although its value may yet prove to be a marker with high negative predictive value in patients with a low likelihood of other pathology.

3.4.4. Procedures recommended to establish the diagnosis

> ECCO statement 3H
>
> For suspected UC, colonoscopy, preferably with ileoscopy, and segmental biopsies including the rectum are the preferred procedures to establish the diagnosis and extent of disease [EL5, RGD]. Patients with a severe attack should have abdominal radiography and active disease confirmed by sigmoidoscopy as a first line procedure [EL5, RGD]

Colonoscopy with intubation of the terminal ileum and segmental mucosal biopsies are preferred to sigmoidoscopy for patients with suspected UC. The clinical context and availability needs to be considered: colonoscopy and bowel preparation is best avoided in patients with acute severe colitis to avoid procedural delays and a higher risk of perforation. Colonoscopy establishes the diagnosis and disease extent in the majority of cases. It appears to be more cost-effective than index sigmoidoscopy.[64,151] Deep ulceration at colonoscopy predicts a worse outcome and higher need for surgery.[152]

A plain abdominal radiograph is not a diagnostic test for UC, but is valuable in the initial assessment of patients with suspected severe UC (Section 3.5.3). Colonic segmental dilatation exceeding 5 cm with an irregular edge outlined by gas, correlates strongly with ulceration.[153] Persistent distension in severe UC correlated with poor response to therapy, higher rate of toxic megacolon and need for surgery.[154] Oesophagogastroduodenoscopy and mucosal biopsy are recommended in patients with upper gastrointestinal symptoms. Wireless capsule endoscopy (WCE) represents an advance in bowel imaging, but large prospective studies are needed to confirm the diagnostic relevance in ulcerative colitis. WCE is a potentially useful clinical technique for categorising those patients with colitis unclassified. Although a normal WCE does not exclude Crohn's disease, it has a very high negative predictive value.[155] Using WCE, Lopes et al. changed the diagnosis from IBDU to Crohn's disease in 7/14 patients, though this did not lead to change in management.[156]

3.5. Assessment of extent, severity and activity

3.5.1. Signs of discontinuous inflammation in ulcerative colitis-

3.5.1.1. Rectal sparing and caecal patch. Macroscopic and microscopic rectal sparing has been described in children presenting with UC prior to treatment.[157–160] In adults, a normal or patchy inflammation in the rectum is more likely to be due to topical or systemic therapy for UC.[161,162] Patchy inflammation in the caecum is referred to as 'caecal patch' and is observed in patients with left-sided colitis. When there is macroscopic and histological rectal sparing, or the presence of a caecal patch in newly diagnosed colitis evaluation of the small bowel in addition to an ileocolonoscopy is indicated. The natural history of patients with patchy right colonic inflammation seems to be similar to those with isolated left-sided UC.[141,142] Whenever there is a discontinuous pattern of inflammation in colitis, a diagnostic work up of the small bowel is indicated to exclude Crohn's disease in addition to an ileocolonoscopy.

3.5.1.2. Appendiceal skip lesions. Involvement of the appendix as a skip lesion is reported in up to 75% of patients with UC.[111–113] Appendiceal inflammation has been associated both with a more responsive course of disease and a higher risk of pouchitis after ileal pouch anastomosis.[163–166] Both findings require confirmation.

3.5.1.3. Backwash ileitis. Continuous extension of macroscopic or histological inflammation from the caecum into the most distal ileum is defined as 'backwash ileitis' (see also Section 4.2.3). It is observed in up to 20% of patients with pancolitis. Rarely, ileal erosions may occur in patients without caecal involvement and this challenges the pathogenic theory that backwash ileitis is caused simply by reflux of caecal contents into the ileum.[167–169] A more refractory course of ulcerative colitis has been suggested in those with backwash ileitis.[168] Additional imaging of the small bowel should be considered in cases of macroscopic backwash ileitis, to differentiate UC from Crohn's disease.

3.5.1.4. Small bowel. Small bowel radiology (by enteroclysis, follow-through, CT enteroclysis, MR enteroclysis, or capsule endoscopy (reviewed in the ECCO Consensus on diagnosis in Crohn's disease[33] and small bowel endoscopy in inflammatory bowel disease[12] is not routinely recommended. Where there is diagnostic difficulty (rectal sparing, atypical symptoms, macroscopic backwash ileitis) then a diagnostic workup to exclude Crohn's disease in addition to an ileocolonoscopy is warranted.

3.5.2. Activity indices in ulcerative colitis

> ECCO statement 3I
>
> Instruments for measuring clinical and/or endoscopic disease activity in UC are available, but none has been subjected to an adequate validation process. In daily routine such indices are barely used. The incorporation of a simple clinical and/or endoscopic scoring system is desirable, intended to improve care of UC patients and to

realise a standardised IT system for IBD. Immediate admission to hospital is warranted for all patients fulfilling Truelove and Witts' criteria for severe colitis to prevent delayed decision-making which may lead to increased perioperative morbidity and mortality [EL4, RGD]

At present, the use of disease activity scores for UC is limited to clinical studies. However, based on the need to standardise documentation of IBD patients on a European level, the incorporation of a simple, valid clinical and/or endoscopic scoring system in electronic patient files is warranted. The original classification of severe UC was proposed by Truelove and Witts in 1955[20] and has stood the test of time, because it is easy to remember and apply. This classification is still considered to the Gold Standard for rapid identification of outpatients in need of immediate admission to hospital and intensive treatment.[153,170]

3.5.3. Investigations for acute severe colitis on admission

Patients should have their full blood count, inflammatory markers (C-reactive protein, or ESR), electrolytes and liver function tests measured, along with a stool sample for culture and assay for *C. difficile* toxin.[170]

A plain abdominal radiograph should be performed, not only to exclude colonic dilatation ($\geq$5.0 cm) but also to estimate the extent of disease and look for features that predict response to treatment. The proximal extent of disease broadly correlates with the distal distribution of faecal residue; in 51 episodes of severe colitis, this guide overestimated the extent in 18% and underestimated it in 8%.[128] The presence of mucosal islands (small, circular opacities representing residual mucosa isolated by surrounding ulceration), or more than two gas-filled loops of small bowel on the radiograph are associated with a poor response to treatment.[171,172]

A flexible sigmoidoscopy should confirm the diagnosis of severe colitis and help exclude infection, particularly with cytomegalovirus.[137,138,173] If it is strongly suspected that CMV might be responsible for deterioration (such as a patient on immunomodulators in association with a high fever), it is appropriate to request urgent histopathology. An answer can be available within 4 h. Phosphate enema preparation before flexible sigmoidoscopy is considered safe, but is probably best avoided in patients with a dilated colon. Full colonoscopy in patients with acute severe colitis is not recommended, since purgative preparation can provoke dilatation and colonic perforation is a real hazard of colonoscopy during active disease. Endoscopic criteria for severe colitis include a haemorrhagic mucosa with deep ulceration, mucosal detachment on the edge of these ulcerations and well-like ulceration,[152,174] all of which can be assessed at flexible sigmoidoscopy.

3.5.4. Reassessment of extent and severity of ulcerative colitis

ECCO statement 3J

Findings at endoscopy for patients with UC in remission are predictive of outcome [EL2, RGB]. Endoscopic reassessment is appropriate at a relapse, or for steroid-dependent or -refractory UC or when considering colectomy [EL5, RGD]

Despite the importance of disease location in determining the prognosis, the risk of cancer and the choice of therapy, the appropriateness of periodic restaging after index colonoscopy has never been studied. In a Norwegian population-based cohort study, mucosal healing after a year of treatment was associated with a low risk of future colectomy (1.6% of the patients with mucosal healing, compared to 7% without mucosal healing).[175] 40% patients who achieved endoscopic remission (defined as a lack of significant inflammation at endoscopy and on rectal biopsy) remained asymptomatic during a year of follow-up in contrast with 18% of patients who did not achieve it.[176] In a prospective multicenter study 78 patients with active, mild-to-moderate UC received oral and rectal mesalamine those in clinical remission with less severe endoscopic scores (defined as normal-looking mucosa, with only mild redness and/or friability), were less likely to relapse at 1 year than patients solely in clinical remission.[177]

Colonoscopy is more sensitive than barium studies for estimating disease extent, but the risk of malignancy is historically based on contrast studies and colonoscopy defines a different extent to histopathology.[78,178–180] Chromoendoscopy better correlates with the disease extent determined by histopathology, but the procedure is time-consuming and requires a level of expertise not universally available.[181] Drug-induced clinical remission may not be associated with endoscopic or histological remission, but the prognostic implications of endoscopic re-evaluation in quiescent disease have yet to be determined.[78] The area calls for systematic study.

3.6. Endoscopy, ultrasound and colonography

3.6.1. Endoscopic features of ulcerative colitis

ECCO statement 3K

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

Endoscopic changes characteristically commence proximal to the anal verge and extend proximally in a continuous, confluent and concentric fashion. The demarcation between inflamed and normal areas is usually clear and may occur abruptly within millimetres, especially in distal disease.

Wide variation in endoscopic interpretation of disease activity is well recognised.[182] Although granularity, vascular

pattern, ulcerations and bleeding-friability have been reported to predict global assessment of endoscopic severity,[183] the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) uses vascular pattern, bleeding and ulceration, each with 3 or 4 levels of severity, to capture the complete range of endoscopic severity and 88% of the variance between endoscopists (Table 3.2).[184] It is the first validated endoscopic index of severity in UC.

The endoscopic features of mild inflammation are erythema, vascular congestion of the mucosa and loss of visible vascular pattern. Moderately active colitis is characterised by 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 (Table 3.1).[78,180,182,184,185] The choice of endoscopic score is complex and has been reviewed.[23,182,186] 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.[180] In longstanding disease, mucosal atrophy can result in loss of haustral folds, luminal narrowing and post-inflammatory ('pseudo') polyps. The meaning of 'mucosal healing' in UC has been the subject of detailed review.[187]

The total 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[182] gave a score of 1 to the normal appearance of a descriptor, a decision was made to change the numbering of the levels, with normality awarded a score of 0, so that the simple sum of the UCEIS ranges from 0 to 8.[184]

3.6.2. Abdominal ultrasound and scintigraphy in ulcerative colitis

ECCO statement 3L

Trans-abdominal ultrasound is helpful in monitoring disease activity and extent as well as treatment success [EL3, RGC]

Abdominal ultrasound can be used to screen for small bowel or colonic inflammation with a sensitivity of 80–90%. Ultrasound has the advantage of being low cost, easy to perform without prior preparation and non-invasive, but the accuracy is very much dependent on the skill of the operator and there is low specificity for differentiating UC from other causes of colonic inflammation.[24,188–191] However, abdominal ultrasound appears to be helpful in monitoring treatment success and there is initial data that ultrasound might help to predict the course of the disease.[192]

Hydrocolonic ultrasound (abdominal ultrasonography in conjunction with retrograde instillation of water in the colon) has a high sensitivity for identifying active colitis, but the method is too cumbersome for day to day clinical practice.[193] *Doppler ultrasound* of the superior and inferior mesenteric arteries has been used to evaluate disease activity and risk of relapse. It should be considered as a complementary technique for assessing disease activity in expert hands.[194,195] For this method to be viable, further prospective, multi-centre studies are needed.

Leukocyte scintigraphy is safe, non-invasive and potentially allows assessment of the presence, extent and activity of inflammation. However the method lacks specificity[196,197] and can therefore currently not be recommended as a standard diagnostic tool for ulcerative colitis. It is unreliable if patients are taking steroids. Novel markers to detect intestinal inflammation which are not associated with exposure to radiation are being developed.

3.6.3. Virtual colonography in ulcerative colitis

ECCO statement 3M

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

Few studies on a limited number of patients have investigated MR-colonography or CT-colonography in UC. The results are conflicting and subtle changes of the mucosa such as erosions or flat polyps are insufficiently visualised.[198,199] Because of these limitations, virtual colonoscopy is no alternative to standard colonoscopy in patients with UC at present.

3.7. Colonic stenosis in ulcerative colitis

ECCO statement 3N

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

In long standing ulcerative colitis, a colonic stricture signals an increased risk for colorectal carcinoma and requires careful histological assessment.[37] If colonoscopy is incomplete due to stricture a double or even single contrast barium enema can be used to assess the stricture and proximal colon.[200] However CT colonography can assess the mucosal pattern proximal to a stricture, as well as extra-intestinal pathology and is therefore becoming the investigation of choice in this situation.[201]

Table 3.2 Ulcerative colitis Endoscopic Index of Severity (UCEIS)[184]

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intra-luminal blood, or visible oozing from a haemorrhagic mucosa
Erosions & Ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny ($\leq$5 mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared to erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

4. Histopathology

4.1. General

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

4.1.1. Considerations

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

4.1.2. Evaluation of the literature

Articles reporting original research into the reproducibility, sensitivity, specificity and predictive value of individual features useful for the histopathological diagnosis of ulcerative colitis were sought from the literature, using Medline and PubMed. Only those features which achieved moderate reproducibility judged by the kappa statistic, or findings confirmed by several studies were considered. In addition, we have reviewed studies describing and defining diagnostic microscopic features. The literature can be divided into groups depending upon the number (one, or multiple) of biopsies examined or the duration of the disease. In ten studies multiple biopsies were examined (including two comparing the diagnostic value of both single and multiple biopsies).[159,202–210] The literature on the duration of the disease can also be divided. The first group is composed of studies with biopsies obtained in patients with an established diagnosis of ulcerative colitis, based on extended clinical follow-up. Disease duration varies between 6±3 weeks and 12 years. A second group is composed of retrospective studies without clear data on the duration of the disease. These papers can be pooled with the first group, because the diagnosis is again established through a period of follow up. A third group applies to studies on biopsies obtained early after onset of the disease, before treatment.[157,159,208,209,211] For early onset disease, the duration of disease varies between 4 and 14 days (3.69±0.52 days after the appearance of rectal bleeding, or 10 days after initial symptoms).[203,211,212] In these studies, the diagnoses was subsequently confirmed by follow-up of the patients and are prospective studies. Children are mainly included in the third group.

Whilst it may seem self-evident to experienced clinicians, care should be taken to avoid confusing the use of histopathology to confirm a diagnosis of UC and histopathology for confirming the presence of active disease. This is particularly relevant to clinical trials of active UC (Section 4.4).

4.2. Microscopic features—definitions

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

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

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

cellularity, basal plasmacytosis, basal lymphoid aggregates, lamina propria eosinophils.

4.2.1. Crypt architectural abnormalities

Crypt branching: two or more branched (bifurcated) crypts in a well oriented section, whether the branching is in the vertical or horizontal axis.[208,211,213–215] When applied to a single crypt, the feature is less specific.[214] The pathogenesis can be accounted for by regeneration following previous damage or destruction (cryptolysis).

Mucosal (crypt) distortion: irregularities in crypt size (i.e. variable diameter), spacing, orientation (i.e. loss of parallelism), or shape (including branching with a cystic configuration).[159,203–205,208,209,211,215] In some studies this includes separation from the underlying muscularis mucosae.[204,211] Samples from the anal transition zone or columnar cuff (sometimes wrongly termed "low rectal biopsies") are not suitable for the assessment of crypt branching or mucosal distortion.

Mucosal (crypt) atrophy and crypt density: a combination of crypt depletion (thinned-out crypts, generally recognised by a distance of more than one crypt diameter between crypts) and an increase in the distance between the muscularis mucosae and the base of the crypts.[211,215,216] Some authors emphasise either crypt depletion[203] or an increased distance between the muscularis mucosae and the base of the crypts[208] rather than both features. An increase in the intercryptal space and the crypt–muscularis mucosae distance may be normal in the caecum and distal rectum.[215] The distance between the muscularis mucosae and the crypt base should not be evaluated in the vicinity of lymphoid follicles. The pathogenesis can be explained as a consequence of crypt death from disease and has been studied in experimental animal models. If all crypt cells die, crypts cannot regenerate and disappear within 48 h. However, if one or more clonogenic cell survives the insult, rapid proliferation regenerates the crypt within 72–96 h. The mucosa subsequently heals by clonal expansion and the number of crypts that survive to regenerate following a cytotoxic insult correlates with symptom severity. A number of growth factors affect crypt regeneration in these murine models.[217] Nevertheless, it remains unclear what size of (uncrushed) biopsy is adequate for proper evaluation and how many levels of the biopsy need to be examined properly to evaluate atrophy.

Surface irregularity: Surface irregularity (synonyms include villous surface, villiform surface, or villous mucosa)[203,214] means wide crypt mouths, giving the mucosal surface a finger-like appearance.[211] The impression is due to separation of crypts[216] and a semantic distinction between "irregular surface" and "villous surface" has been proposed, according to the villous-crypt ratio.[204]

4.2.2. Epithelial cell abnormalities

Paneth cell metaplasia: Paneth cells are normally extremely uncommon in the colon distal to the splenic flexure, being present in 0–1.9% of non-IBD controls.[218] The presence of Paneth cells in the distal colon can be termed Paneth cell metaplasia. The pathogenesis is related to epithelial regeneration and repair.[218]

Mucin depletion: defined as a reduction in number of goblet cells or depleted mucin within cells.[215]

4.2.3. Inflammatory features

Basal plasmacytosis: defined either as the presence of plasma cells around (deep 1/5th of the lamina propria) or below the crypts, alongside or penetrating the muscularis mucosae. Basal plasmacytosis is also referred to as subcryptal plasma cells,[203] plasmacytosis with extension in the base of the mucosa,[159] or accumulation of plasma cells between the base of the crypts and the muscularis mucosae.[208] The abnormality can be focal or diffuse and subcryptal location of the cells is not always present.[203,211]

Lamina propria cellularity: evaluated according to density, composition and distribution. An increase in the total number of plasma cells, lymphocytes, histiocytes and eosinophils is a feature of all types of colorectal inflammation[215] and is of limited discriminant value. In UC the cellular infiltrate is diffuse and transmucosal.

Increased *density* has been described as "a subjectively abnormal" infiltrate,[214] a "prominent" increase (assessed by widening of the intercryptal space by the inflammatory infiltrate[216] or simple "hypercellularity".[203] The increase is difficult to quantify. Increased lamina propria cellularity may also be absent in quiescent disease, following treatment, or in the natural course of the disease.[181,219] Furthermore, increased lamina propria cellularity may persist in infective colitis[220] and is a normal feature of caecal biopsies.

The *composition* has been examined to resolve these dilemmas. Some authors discriminate between an increase in neutrophils alone and an increase in both round cells and neutrophils. Neutrophils may be present in the lamina propria or between epithelial cells, are readily recognised and a reproducible feature of inflammation.[216] More than three neutrophils in the lamina propria outside capillaries may be abnormal,[204] but the exact number has not been agreed. Neutrophils are a feature of cryptitis with migration of neutrophils through the crypt epithelium, inducing crypt disruption and crypt abscesses, which may be responsible for cell surface damage or disruption. The diagnostic value of neutrophils in UC, however, is limited because they are also present in infective colitis and other forms of colitis.[216,203] In contrast, eosinophils in the lamina propria are highly variable. An increase has been noted in UC and a potential diagnostic value has been proposed, but data were obtained from studies of longstanding disease.[205,213]

The *distribution* of the lamina propria cellular inflammatory infiltrate has been divided into: *focal* (normal background cellularity with areas of increased cellularity); *patchy* (abnormal background cellularity with variable intensity); and *diffuse* (abnormal background cellularity with an overall increase in density). These terms are preferred. Confusion is caused when the term "discontinuous" is used to describe both focal and patchy changes in some studies,[215] or used as a synonym for focal in others.[205] A diffuse increase can be either *superficial* (confined to the superficial and middle thirds of the lamina propria) or *transmucosal* (usually maximal in the lower third). The distribution can be evaluated in a single sample or between multiple samples from the same site. To avoid diagnostic error, the criteria of diffuse transmucosal inflammation for diagnosing ulcerative colitis should be avoided in biopsies from early onset disease in children,[159] or after treatment and when disease is resolving or quiescent. In these circumstances the biopsy may be normal or show focal changes.[161,207,221]

Basal lymphoid aggregates: nodular collections of lymphocytes between the crypt base and muscularis mucosae,[214]

without germinal centres[204,214,215,222] At least two aggregates are needed for this feature to be considered abnormal.[204,215,216]

Stromal changes: diffuse thickening of the muscularis mucosae or a double muscularis mucosae (which is unusual, but characteristic when present) have been observed in longstanding active and quiescent UC.[223]

Backwash ileitis: ileal inflammation in UC is called backwash ileitis, despite the fact that the backwash or reflux pathogenesis has never been established. 'Backwash ileitis' should be in continuity with colonic inflammation (see also 3.5.1) and the lesions in the caecum should show a similar, or greater degree of active inflammation. The ileal lesions in 'backwash ileitis' are characterised by active inflammation in the villi and lamina propria, together with shortening and blunting of the villi. Focal, isolated ileal erosions, mucous gland metaplasia or patchy oedema with mild active inflammation are features suggestive of Crohn's disease.[167,169]

ECCO statement 4A

For a reliable diagnosis of ulcerative colitis multiple biopsies from five sites around the colon (including the rectum) and the ileum should be obtained. Multiple implies a minimum of two samples [EL1b, RGB]

ECCO statement 4B

Biopsies should be accompanied by clinical information including the age of the patient, duration of disease and duration and type of treatment [EL1b, R GB]. Biopsies from different regions should be handled in such a way that the region of origin can be identified [EL1c RGA]. This can be done by using different containers, multiwell cassettes, or an acetate strip [EL5, RG D]. All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport. It is recommended that multiple sections from each sample are examined [EL5, RGD]

4.3. Microscopic features—appraisal of the diagnosis

4.3.1. Early stage disease

It has been proposed that a non-specific increase in the inflammatory infiltrate in the lamina propria in combination with absent crypt architectural distortion, indicates a diagnosis of acute, infective colitis[203,216] rather than UC. This finding, however, is not confirmed in those studies of patients with early onset colitis (within 10 days of symptoms).[212,224]

ECCO statement 4C

Basal plasmacytosis at the initial onset has a high predictive value for the diagnosis of IBD [EL 3, RG C]

Repeat biopsies after an interval may help to solve differential diagnostic problems and establish a definitive diagnosis especially in adults, by showing additional features [EL 5, RG D]

Basal plasmacytosis is observed in biopsies obtained at early onset in 38–100% of adult patients[203,211] and can help differentiate between UC and infectious colitis.[211] It is particularly a feature in young children; in these cases it is notably present in rectal biopsies and decreases proximally. It is an early feature, sometimes the first lesion to appear[159,203,208,209,211] and a good predictive marker.

Glandular abnormalities can be identified with good (83-90%) interobserver agreement.[204,222,225] According to most studies, diffuse crypt architectural irregularity and reduced crypt numbers or atrophy indicate UC.[213,215] Nevertheless, these features may still not be present in biopsies obtained from patients with colitis at an early stage.[211] Crypt architectural changes were observed in biopsies obtained between 16 and 30 days after onset,[211] but not in earlier biopsies. In another study[203] abnormal architecture was found in all biopsies obtained within days of onset, but in this study disease onset was defined by loss of blood and not by other symptoms. Crypt distortion and mucosal atrophy may return to normal or remain unchanged after resolution of symptoms.[161,221]

ECCO statement 4D

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

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

4.3.2. Established disease

ECCO statement 4E

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

The exact number of features needed for diagnosis has not been established. A correct diagnosis of UC is reached in approximately 75% of the cases when two or three of the

four features, severe crypt architectural distortion, severe decreased crypt density, irregular surface and heavy diffuse transmucosal inflammation are present, in the absence of genuine granulomas.[204,209]

ECCO statement 4F

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

In established UC a villous surface is present in 17–63 % of the cases (compared to 0-24% for Crohn's disease and 0-7% for infective colitis).[215] The lesion is observed in approximately one third of the initial biopsies of children with ulcerative colitis.[208] In adults this feature was present in approximately 23% of the patients presenting 16–30 days after the initial symptoms, but not in earlier biopsies.[211]

ECCO statement 4G

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

The diagnostic value of basal plasmacytosis is confirmed by studies of biopsies obtained in established disease, being present in up to 63% of cases.[204] The feature is rare in non-IBD colitis,[214] but it is also common in Crohn's disease. Basal plasmacytosis decreases and can disappear during treatment.

A heavy, diffuse, transmucosal, lamina propria cell infiltrate favours a diagnosis of UC,[215] but patchy inflammation[213] can occasionally be seen in ulcerative colitis or, when multiple biopsies are examined, a single piece may have evidence of chronic colitis and others have normal mucosa.[208,221,226] The heavy, diffuse transmucosal lamina propria cell increase can be absent in young children (<12 years). It can decrease in intensity and become patchy during the natural evolution of the disease or subsequent to treatment. This feature is therefore mainly useful for the diagnosis in established disease. Its absence does not exclude a diagnosis of UC.

ECCO statement 4H

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

General or widespread crypt epithelial neutrophils favour a diagnosis of ulcerative colitis, but crypt abscesses and cryptitis can also occur in infective colitis, although they are less prominent.[26] Neutrophils are absent during inactive or quiescent disease.

Basal lymphoid aggregates favour a diagnosis of established UC, but may occur in Crohn's colitis[214,216] and are not useful in early onset disease.

ECCO statement 4I

Paneth cell metaplasia distal to the splenic flexure is a non specific feature. It is suggestive of a diagnosis of ulcerative colitis in established disease [EL 3, RG C]. Severe, widespread mucin depletion is helpful for the diagnosis of ulcerative colitis in active disease [EL 3, RG C]

Paneth cell metaplasia favours a diagnosis of ulcerative colitis.[205] The predictive value is high but the sensitivity is low.[214] It is not seen in biopsies obtained early in the disease[211,216] and appears to be related to established disease.[218] Mucin depletion also favours a diagnosis of ulcerative colitis. It correlates with disease activity, so is a helpful, but not pivotal diagnostic feature.[159] Mucin preservation in association with active disease, however, may favour a diagnosis of Crohn's disease rather than UC.[206]

4.4. Microscopic features—disease activity

ECCO statement 4J

The pathology report should give an indication of the activity of the disease [EL5 RG D]

Disappearance of mucosal inflammation following treatment has been observed,[161] so biopsies are also used for distinguishing between quiescent and active disease, as well as different grades of activity. Scoring systems have been introduced for the assessment of disease activity, particularly for therapeutic trials. The potential value of histopathology for predicting relapse and evaluating adequate control of inflammation has implications for therapeutic management and reducing the risk of neoplasia. Both epithelial damage in association with neutrophils and basal plasmacytosis have been proposed as markers of disease activity and the prediction of relapse.[36,227–229]

The value of histopathology as independent confirmation of disease activity in clinical trials for the treatment of mild- or moderately active UC is frequently overlooked. A lack of

microscopic inflammation on a mucosal biopsy effectively excludes active UC and this is an important measure for validating active disease when recruiting patients to clinical trials, since it can be assessed independently from endoscopy. The problem is prevalent: in one Phase 3 trial of a new agent for treating mild-moderately active UC, 77/511 (15%) patients had inactive UC at study entry, despite clinical and endoscopic criteria indicating active disease, they were excluded.[230] This clearly raises complex issues. There are logistic constraints on the time to histological analysis, especially by a central reader, that effectively prevent it being used as an inclusion criterion, other than to exclude in retrospect those patients with inactive disease. Nevertheless, the European Medicines' Agency in their guidelines to clinical trials of new agents for UC state that the absence of histological evidence of active inflammation effectively excludes active disease (CHMP/EWG/ 18463/2006, adopted 28 Jan 2008).

ECCO statement 4K

The term indeterminate colitis (IC) should be restricted to resection specimens. When patients have colitis that has yet to be classified after all clinical, radiologic, endoscopic and histological results are taken into account, then the preferable term is IBD *unclassified* (IBDU) [EL5 RG D]

4.5. Conclusions

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

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

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

In every patient, including children, the diagnostic yield can be increased when multiple biopsies from different segments of the colon are examined, including the rectum and the ileum, although these should be carefully labelled for proper assessment.[209,210,231,232]

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