



CONSENSUS/GUIDELINES

# European evidence based consensus for endoscopy in inflammatory bowel disease ☆

Vito Annese <sup>a,\*,1,2</sup>, Marco Daperno <sup>b,2</sup>, Matthew D. Rutter <sup>c,d,2</sup>, Aurelien Amiot <sup>e</sup>, Peter Bossuyt <sup>f</sup>, James East <sup>g</sup>, Marc Ferrante <sup>h</sup>, Martin Götz <sup>i</sup>, Konstantinos H. Katsanos <sup>j</sup>, Ralf Kießlich <sup>k</sup>, Ingrid Ordás <sup>l</sup>, Alessandro Repici <sup>m</sup>, Bruno Rosa <sup>n</sup>, Shaji Sebastian <sup>o</sup>, Torsten Kucharzik <sup>p</sup>, Rami Eliakim <sup>q,\*\*,1,2</sup> on behalf of ECCO

<sup>a</sup> Dept. Gastroenterology, University Hospital Careggi, Largo Brambilla 3, 50139 Florence, Italy

<sup>b</sup> S.C. Gastroenterologia, A.O. Ordine Mauriziano, Corso Re Umberto 109, 10128 Torino, Italy

<sup>c</sup> Tees Bowel Cancer Screening Centre, University Hospital of North Tees, Hardwick Road, TS19 8PE Stockton-on-Tees, Cleveland, UK

<sup>d</sup> Durham University, County Durham, UK

<sup>e</sup> Gastroenterology, CHU Henri Mondor, 51 Av. du Maréchal de Lattre de Tassigny, 94010 Creteil, France

<sup>f</sup> Gastroenterology, AZ Imeldaziekenhuis, Imeldalaan 9, 2820 Bonheiden, Belgium

<sup>g</sup> Translational Gastroenterology Unit, Experimental Medicine Division, Nuffield Dept. of Clinical Medicine, Oxford University, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK

<sup>h</sup> Department of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium

<sup>i</sup> Innere Medizin 1, Universitätsklinikum Tübingen, Otfried-Müller-Str. 10, 72076 Tübingen, Germany

<sup>j</sup> Department of Gastroenterology, Medical School, University of Ioannina, Stavrou Niarxou Avenue, 45110 Ioannina, Greece

<sup>k</sup> I. Med. Klinik und Poliklinik, Johannes-Gutenberg-Univ. Mainz, Langenbeckstr. 1, 55131 Mainz, Germany

<sup>l</sup> Department of Gastroenterology, Hospital Clinic Barcelona, c/Villarroel 170, 08036 Barcelona, Spain

<sup>m</sup> Digestive Endoscopy, IRCCS Humanitas, Via Manzoni 56, 20089 Rozzano, Italy

<sup>n</sup> Gastroenterology, Centro Hospitalar do Alto Ave, Guimarães, Rua dos Cutileiros, Creixomil, 4835 Guimarães, Portugal

<sup>o</sup> Gastroenterology, Hull & East Yorkshire NHS Trust, Anlaby Road, HU3 2JZ Hull, UK

<sup>p</sup> Innere Medizin und Gastroenterologie, Städtisches Klinikum Lüneburg, Bögelstraße 1, 21339 Lüneburg, Germany

<sup>q</sup> Gastroenterology, Sheba Medical Center, 52621 Tel Hashomer, Israel

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\* Correspondence to: V. Annese, Department of Gastroenterology, University Hospital Careggi, Largo Brambilla 3, 500139 Florence, Italy.

\*\* Correspondence to: R. Eliakim, Department of Gastroenterology, Sheba Medical Center, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

E-mail addresses: [annesev@aou-careggi.toscana.it](mailto:annesev@aou-careggi.toscana.it) (V. Annese), [ramieliakim@yahoo.com](mailto:ramieliakim@yahoo.com) (R. Eliakim).

<sup>1</sup> AV and RE acted as convenors of the Consensus.

<sup>2</sup> VA, MD, MR and RE contributed equally to this work.

**KEYWORDS & ABBREVIATIONS**

Ulcerative colitis (UC);  
Crohn's disease (CD);  
Endoscopy;  
Colorectal cancer (CRC)

**1. Introduction**

Endoscopy plays an essential role in the diagnosis, management, prognosis, and surveillance of inflammatory bowel disease (IBD), but surprisingly there are few available guidelines.<sup>1,2</sup> This prompted the ECCO Guidelines Committee (GuiCom) members to promote a Consensus on the appropriate indication and application of different endoscopic modalities in IBD. Since the development of guidelines is an expensive and time-consuming process, this Consensus may help to avoid duplication of effort in the future. It may also identify issues where the evidence is lacking and controlled studies are awaited.

The strategy to reach the Consensus involved five steps:

1. Two members of the GuiCom (VA and RE) identified four main topics: a) Diagnosis and follow-up; b) Score of endoscopic activity; c) Small bowel endoscopy; and d) Surveillance. During 2012 a call for participants to the Guideline was made to ECCO members. In addition, expert endoscopists recognised for their active research in the field were invited. Participants were selected by the Guicom and four working groups were created. Each working group had a chair (VA, MD, MT, and RE), two ECCO members including young members (Y-ECCO) and one experienced endoscopist. For the development of the guideline, relevant questions on separate topics were devised by the chairmen and their working parties. The questions were focused on current practice and areas of controversy. Participants of the Consensus process were asked to answer the questions based on evidence from the literature as well as their experience (Delphi procedure)<sup>3</sup>;
2. The working parties working in parallel performed a systematic literature search of their topic with the appropriate key words using Medline/Pubmed and the Cochrane database, as well as other relevant sources;
3. Provisional guideline statements on their topic were then written by the chairmen. These were circulated and commented on first by working party members and then among the applicants not included in the working groups and the ECCO National representatives (see Acknowledgement) on a web-based platform ([www.cpg-development.org](http://www.cpg-development.org));
4. The working parties then met in Vienna in January 2013 chaired by VA and RE to revise and agree the statements. Each statement was projected and revised until a consensus was reached. Consensus Statement was reached when there was agreement by >85% of participants. For each statement the level of evidence (EL) was given according to the Oxford Centre for Evidence Based Medicine (Table 1.1)<sup>4</sup>;

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

In addition, ECCO has diligently maintained a disclosure policy of potential conflicts of interests (Col). The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors (ICMJE). The Col statement is not only stored at the ECCO Office and the editorial office of JCC but also open to public scrutiny on the ECCO website (<https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html>) providing a comprehensive overview of potential conflicts of interest of the consensus participants and guideline authors.

**2. Diagnosis****2.1. Ileocolonoscopy****ECCO Statement 2A**

For suspected IBD, ileocolonoscopy with biopsies is the preferred procedure to establish the diagnosis and extent of disease [EL 2] [Voting results: 100% agreement].

Ileocolonoscopy represents the most important and potent tool in the diagnosis of suspected IBD and must be performed soon after patient referral and possibly before the initiation of any medical treatment. In Ulcerative colitis (UC) 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, especially in distal disease.<sup>5</sup> Macroscopic and microscopic rectal sparing has been described in children presenting with UC prior to treatment.<sup>6–9</sup> In adults, a normal or patchy inflammation in the rectum is more likely due to previous topical therapy.<sup>10</sup> Patchy inflammation in the caecum referred to as "caecal patch"<sup>11,12</sup> is observed in patients with left-sided colitis. When there is macroscopic and histological rectal sparing or the presence of a caecal patch in a newly diagnosed colitis, evaluation of the small bowel in addition to an ileocolonoscopy is indicated. Appendiceal skip lesions are reported in up to 75% of patients with UC.<sup>13–17</sup> It has been associated with a better response to medical therapy<sup>17</sup> and a higher risk of pouchitis after ileal pouch anastomosis.<sup>13–17</sup> Continuous extension of macroscopic or

**Table 1.1** Levels of evidence based on the 2011 version of Oxford Centre for Evidence Based Medicine (for details see [http://www.cebm.net/mod\\_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf](http://www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf)).<sup>3</sup>

| Questions   | Level 1   | Level 2  | Level 3  | Level 4   | Level 5                   |
|---|---|--|--|---|---------------------------|
| How common is the problem?                                  | Local and current random sample surveys (or censuses)   | Systematic review of surveys that allow matching to local circumstances <sup>a</sup>         | Local non-random sample <sup>a</sup>   | Case-series <sup>a</sup>  | n/a                       |
| Is this diagnostic or monitoring test accurate? (Diagnosis) | Systematic review of cross sectional studies with consistently applied reference standard and blinding  | Individual cross sectional studies with consistently applied reference standard and blinding | Non-consecutive studies, or studies without consistently applied reference standards <sup>a</sup>  | Case-control studies, or poor or non-independent reference standard <sup>a</sup>          | Mechanism-based reasoning |
| What will happen if we do not add a therapy? (Prognosis)    | Systematic review of inception cohort studies   | Inception cohort studies   | Cohort study or control arm of randomized trial <sup>b</sup>   | Case-series or case control studies, or poor quality prognostic cohort study <sup>a</sup> | n/a                       |
| Does this intervention help? (Treatment Benefits)           | Systematic review of randomized trials or n-of-1 trials   | Randomized trial or observational study with dramatic effect                                 | Non-randomized controlled cohort/follow-up study <sup>a</sup>  | Case-series, case-control studies, or historically controlled studies <sup>a</sup>        | Mechanism-based reasoning |
| What are the COMMON harms? (Treatment harms)                | Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect | Individual randomized trial or (exceptionally) observational study with dramatic effect      | Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.) <sup>a</sup> | Case-series, case-control, or historically controlled studies <sup>a</sup>                | Mechanism-based reasoning |
| What are the RARE harms? (Treatment harms)                  | Systematic review of randomized trials or n-of-1 trial  | Randomized trial or (exceptionally) observational study with dramatic effect                 |  |   |                           |
| Is this (early detection) test worthwhile? (Screening)      | Systematic review of randomized trials  | Randomized trial   | Non-randomized controlled cohort/follow-up study <sup>a</sup>  | Case-series, case-control, or historically controlled studies <sup>a</sup>                | Mechanism-based reasoning |

<sup>a</sup> As always, a systematic review is generally better than an individual study.

<sup>b</sup> Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

histological inflammation from the caecum into the most distal ileum defined as 'backwash ileitis' is observed in up to 20% of patients with pancolitis<sup>18,19</sup> and is associated with a more refractory course of disease.<sup>20</sup>

The endoscopic hallmark of Crohn's disease (CD) is the patchy distribution of inflammation with skip lesions (areas of inflammation interposed between normal appearing mucosa). CD ulcers tend to be longitudinal and may be associated with a cobblestone appearance of the ileum or colon, fistulous orifices and strictures. Rectal sparing is often encountered and circumferential, continuous inflammation is rare. Biopsy specimens taken from the edges of ulcers and aphthous erosions maximise the possibility of discovering granulomas which are pathognomonic in CD.<sup>21,22</sup>

There is no consensus on whether IBD patients undergoing colonoscopy are at increased risk of complications. When there is severe, active disease in both CD and UC, the value of full colonoscopy is counterbalanced by a higher risk of bowel perforation. Older age, severe disease, steroid use, female gender and endoscopic dilations appeared to be associated with an increased risk of perforation (0.3% to 1%).<sup>23,24</sup> In these circumstances, initial flexible sigmoidoscopy is safer and ileocolonoscopy should be postponed until the clinical condition improves. However, a more recent study in a referral centre cohort suggested that the risks are not increased in experienced hands.<sup>25</sup>

## 2.2. Upper GI endoscopy

### ECCO Statement 2B

Upper GI endoscopy is routinely performed in assessment of paediatric and adolescent IBD to accurately classify IBD [EL3]. While upper GI endoscopy and biopsies may be useful in all patients at diagnosis to evaluate the extension and disease location, whether it should be performed routinely in asymptomatic adult patients remains unclear [EL5] [Voting results: 100% agreement].

Upper gastrointestinal (GI) tract inflammation has become increasingly recognised, even in the absence of specific localizing symptoms in IBD patients. The Montreal classification system and its modified version for paediatric use (Paris classification)<sup>26</sup> allowed classification of upper GI involvement in CD, independent of other locations. Upper GI endoscopy is mandatory in the paediatric population with suspected IBD where growth failure matters, for differentiating between UC and CD and to confirm a diagnosis of CD.<sup>27,28</sup>

In adult IBD, there are no specific recommendations. However, CD patients with dyspepsia, abdominal pain and

vomiting would benefit from an upper GI endoscopy.<sup>29</sup> Upper GI endoscopy may also be important in specific cases to establish the diagnosis of Crohn's disease, to assess disease extension and severity and to aid in tailoring therapy.<sup>30</sup> However, a minority of UC patients may also have upper GI tract inflammation, manifesting as diffuse duodenitis or gastritis, characterised by oedema, erythema, erosions and thickened mucosal folds.<sup>31</sup> Finally, upper GI endoscopy is mandatory in patients with suspected concomitant coeliac disease.<sup>32</sup>

## 2.3. Quality of endoscopy in IBD patients

Although currently no special certification to perform endoscopy in IBD patients is required, the consensus recommends that gastroenterologists performing endoscopy in IBD patients should be experienced and adequately trained in recognizing endoscopic patterns in IBD.<sup>33</sup> This is to assure consistency, quality and safety.

A standard terminology to describe IBD lesions during endoscopy is important. So far, common agreement has been reached by previous ECCO consensus about frequently used endoscopic terms. Substantial work has been recently done on endoscopic assessment and descriptors in UC,<sup>34,35</sup> with subsequent validation.<sup>36,37</sup> The arbitrariness of some of the definitions is recognised but the consensus supported the agreed terminology (Table 2.1).

Endoscopy in children and adolescents should be performed with deep sedation or general anesthesia, by expert endoscopists based on national recommendations in a setting that is suitable for diagnosing and treating children and adolescents with IBD.<sup>38</sup>

## 2.4. Endoscopic biopsies in IBD

### ECCO Statement 2C

For a reliable diagnosis of CD and UC multiple biopsies from six segments (terminal ileum, ascending, transverse, descending, sigmoid and rectum) should be obtained. Multiple biopsies imply a minimum of two representative samples from each segment including macroscopically normal segments [EL2] [Voting results: 100% agreement].

Normal mucosal biopsies effectively exclude active IBD. For IBD diagnosis multiple representative biopsies in a standard protocol are needed. At least two biopsies from five sites around the colon including the rectum and terminal ileum, if possible, should be taken. Biopsies should be representative from areas of minor and major inflammation to mirror correctly the intensity and spectrum of inflammation. In addition, biopsies must be taken also from 'normal appearing' mucosa.<sup>22</sup> Targeted biopsies from areas of stenosis, from any unusual polypoid lesions or from any other lesion that may attract the endoscopists' attention should be labeled in separate bottles. Biopsies should always be accompanied by detailed clinical information to aid the histopathologist to

provide an accurate diagnosis. It is important to consider that histological activity may correlate poorly with clinical and endoscopic activity. For more detailed information on this issue refer to the forthcoming ECCO Pathologic Consensus on IBD.<sup>39</sup>

## 2.5. Follow-up: need for repeat scope and biopsies

### 2.5.1. Uncertain diagnosis

#### ECCO Statement 2D

When diagnosis remains in doubt, repeat endoscopic and histologic assessment is appropriate. Investigation may include repeat ileocolonoscopy, upper GI endoscopy, wireless capsule endoscopy or enteroscopy [EL5] [Voting results: 100% agreement].

One of the pitfalls in diagnosing IBD is the failure to consider other diseases. In 10% of adult patients the diagnosis will be changed to CD or vice versa and the diagnosis of IBD discounted during the first 5 years after symptom onset.<sup>40</sup> Diagnostic misclassification has been documented in patients enrolled in IBD genetic studies and frequently involves assigning the diagnosis of IBD to non-affected individuals.<sup>41</sup> In addition undifferentiated colitis accounts for about 5% of initial diagnoses of IBD.<sup>42</sup> In about 80% of patients with undifferentiated colitis at presentation, a diagnosis of either UC or CD is made within 8 years of follow up on reevaluation and some clinical and demographic features can help in identifying the final diagnosis.<sup>42</sup>

### 2.5.2. Repeat endoscopy during remission

#### ECCO Statement 2E

Routine endoscopy for patients in clinical remission is unnecessary, unless it is likely to change management [EL5] [Voting results: 100% agreement].

The appropriateness of periodic endoscopic reassessment after index colonoscopy has never been formally studied and the value of it is much debated.<sup>43</sup> However, endoscopy could be used for disease monitoring and reassessment may help to optimise management strategies in a given patient. Disease extent and activity influence medical management, including choice of medical therapy and the route of administration. In addition, there is evidence that with immunosuppressive treatment, particularly with anti-TNF $\alpha$  agents, long-term mucosal healing can be achieved and this may affect the outcome in IBD.<sup>44–49</sup>

Endoscopy is still considered the standard for evaluating disease activity, it is used to confirm mucosal healing, but it is invasive and costly. Increased faecal levels of calprotectin and lactoferrin have been used more recently as surrogate markers of active inflammation.<sup>50</sup> As is the case for the more traditionally used inflammatory marker serum CRP, faecal markers may not be elevated in some patients with endoscopically active disease. This is more likely in ileal compared to colonic disease.<sup>51–54</sup> However, the sensitivity of raised faecal markers (60–70%) in predicting endoscopically active disease is superior to that of serum CRP and CDAI.<sup>52</sup> Björkesten CG et al.<sup>53</sup> prospectively collected data from 210 endoscopies in 64 CD patients treated with anti-TNF $\alpha$  agents. Neither the clinical indices nor CRP were reliable at identifying endoscopic remission, however raised calprotectin had a sensitivity of 84% and specificity of 74%. In the study by D'Haens et al.<sup>54</sup> a calprotectin level of  $\leq 250$   $\mu\text{g/g}$  predicted endoscopic remission (CDEIS  $\leq 3$ ) with sensitivity 94.1%, specificity 62.2%, PPV 48.5% and NPV 96.6%. Recent studies emphasise the value of calprotectin in assessing disease severity (correlating with endoscopic indices), diagnosing relapse and response to treatment in UC.<sup>55,56</sup> In summary, faecal levels of calprotectin or lactoferrin are emerging as a surrogate marker of mucosal healing and may reduce the need for endoscopic reassessments.

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 and formally investigated. Recently the Italian Group for IBD reported a multicentre study in 81 consecutive patients with mild to moderate UC. All patients received an endoscopic evaluation 6 weeks following treatment with oral plus topical mesalazine. Sixty-one (75%) of patients achieved clinical remission, but five of them (8%) were not in endoscopic remission. Interestingly, the cumulative relapse rate at 1 year was 23% in patients with both clinical and endoscopic remission compared to 80% ( $p < 0.0001$ ) in patients with only clinical remission.<sup>57</sup>

### 2.5.3. Repeat endoscopy to change management

#### ECCO Statement 2F

Endoscopic reassessment should be considered in cases of relapse, refractoriness, new symptoms, or when surgery is considered [EL5] [Voting results: 100% agreement].

The usefulness of endoscopic reassessment should be evaluated on a case by case basis in patients not responding to therapy, those with frequent relapse, or steroid-dependency, and in general terms when a significant change to medical management is contemplated. This is often the case in paediatric IBD, as the overall rate of management change after endoscopic evaluation can be in up to 42% of cases.<sup>58</sup> In both CD and UC a number of population-based and cohort studies have demonstrated the relevance of endoscopic

**Table 2.1** Terminology of endoscopic lesions in IBD.

| Mucosal damage                                      | Description  | Grading  |
|---|--|--|
| Loss of vascular pattern                            | Loss of normal mucosal appearance without well-demarcated, arborizing capillaries  | From patchy or blurred to complete loss  |
| Erythema  | Unnaturally reddened mucosa  | From discrete or punctiform to diffuse erythema  |
| Granularity   | Mucosal pattern produced by a reticular network of radiolucent foci of 0.5–1 mm of diameter with a sharp light reflex                            | From fine to coarse or nodular, due to abnormal light reflection   |
| Friability/bleeding                                 | Bleeding or intramucosal haemorrhage before or after the passage of the endoscope  | From contact bleeding (bleeding with light touch) to spontaneous bleeding  |
| Erosion   | A definite discontinuation of mucosa less than 3 mm in size. Also described as pinpoint ulceration   | Isolated, diffuse  |
| Aphthous ulcer                                      | White depressed center surrounded by a halo of erythema; (some consider this synonymous with 'erosion')  | Isolated, multiple   |
| Ulcer   | Any lesion of the mucosa of unequivocal depth, with or without reddish halo  | Isolated or multiple based on morphology: circular, linear, stellar, serpiginous, irregular shape Superficial or deep      |
| Ulcer size (no underscore)                          | Defined in mm or classified as: ≤ 5 mm; 5–20 mm; >20 mm  | Diffuse, mucosal abrasion with residual mucosa producing a polypoid appearance   |
| Ulcer depth (no underscore)                         | Shallow (localized to submucosa)—no border<br>Deep (beyond muscularis propria)—e.g. edges elevated >1 mm   |  |
| Stenosis  | Narrowing of the lumen   | Single, multiple, passable (by standard adult endoscope), un-passable, passable after dilation<br>Ulcerated, non-ulcerated |
| Post-inflammatory polyps (previously 'pseudopolyp') | Polypoid lesion, usually small, glistening, isolated or multiple, scattered throughout the colon. Sometimes cylindrical or giant (>2 cm) in size | Isolated, diffuse, occluding ('giant')   |
| Cobblestone   | Mucosal pattern with raised nodules, resembling the paving of a "Roman" road   | With or without ulceration   |

findings after treatment in predicting the need for surgery (see further).

### 3. Endoscopy after surgery

#### ECCO Statement 3A

Ileo-colonoscopy is the gold standard in the diagnosis of post-operative recurrence, by defining the severity of lesions and predicting the clinical course [EL2]. It is recommended 6–12 months after surgery where treatment decisions may be affected [EL2] [Voting results: 100% agreement].

In the natural history of CD, intestinal resection is unavoidable in a significant proportion of patients. A majority of patients develop disease recurrence at or above the anastomosis and endoscopic recurrence precedes the development of clinical symptoms. Data from endoscopic follow-up

of patients after resection of ileo-caecal disease have shown that in the absence of treatment, the post-operative recurrence rate is around 65–90% within 12 months and 80–100% within 3 years of the operation.<sup>59,60</sup> In another single centre 15-year retrospective study,<sup>61</sup> 55 patients underwent total proctocolectomy with definitive ileostomy for Crohn's disease. None of them received preventive post-operative treatment. Probabilities of reoperation for Crohn's disease recurrence were 0%, 10% and 18% at 1, 5 and 8 years, respectively. However, symptomatic recurrence after intestinal resection in Crohn's disease is still unpredictable in some patients.<sup>62,63</sup> Identification and treatment of early mucosal recurrence may therefore prevent clinical recurrence. Ileocolonoscopy is the gold standard in the diagnosis of post-operative recurrence by defining the presence and severity of morphologic recurrence. Ileocolonoscopy is recommended within the first year after surgery where treatment decisions may be affected.

### 4. Endoscopy during pregnancy

The safety and utility of endoscopic examinations in the setting of pregnancy in IBD has not been thoroughly

evaluated. Nevertheless, small cohort and case controlled studies indicate that flexible sigmoidoscopy gives a high diagnostic yield of over 80% when used for an appropriate indication, such as non haemorrhoidal rectal bleeding and bloody diarrhoea without significant increase in endoscopic complications for the mother or injury to the foetus (reviewed in<sup>64</sup>). Similarly pregnancy and foetal outcomes in a small study of pregnant patients undergoing colonoscopy was not different in the second trimester when compared to matched controls.<sup>64</sup> There are no data on the safety of bowel preparation and sedatives used in pregnant patients undergoing endoscopic evaluation.<sup>64</sup>

## 5. Endoscopy for differential diagnosis

### 5.1. Differential diagnosis: CD vs. UC

#### ECCO Statement 5A

No endoscopic feature is specific for UC or CD. The most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation, and rectal involvement [EL2]. The most useful endoscopic features in Crohn's disease are discontinuous lesions, presence of strictures and fistula and perianal involvement (EL2) [Voting results: 100% agreement].

While none of the endoscopic features are specific for UC or CD, in the absence of extra colonic disease, certain endoscopic findings may suggest a diagnosis of Crohn's colitis over that of UC. The most prominent of these is the detection of 'skip lesions' of macroscopically and microscopically uninvolved mucosa. The mucosal features of deep, stellate, linear, or serpiginous ulcers, multiple aphthous ulcers and cobblestoning of mucosa are supportive of a diagnosis of colonic Crohn's disease.<sup>50,65–67</sup> In addition, presence of ileitis, perianal disease or visible fistulous opening is indicative of Crohn's disease. The pattern of mucosa involvement in UC, in contrast, is continuous in most cases with a characteristic sharp demarcation of inflamed and uninvolved colonic mucosa and the rectum is almost always involved particularly at index endoscopy.<sup>1,22,50,65–69</sup> Strictures are exceedingly rare in UC and should raise the possibility of CD or underlying malignancy. The acquisition of the detailed information from index colonoscopy is important, because once therapy is started, inflammation often appears segmental, often with relative rectal sparing.<sup>70,71</sup> Patchiness has also been recorded de novo in paediatric literature.<sup>6</sup>

There are other pitfalls in the differentiation of UC and CD. One of these is the concept of backwash ileitis which typically occurs in up to 20% patients with pancolitis and is characterised by mild inflammation of a few cms of terminal ileum without any ulceration.<sup>20</sup> Features that favour CD ileitis include discrete ulcers, strictures of the terminal ileum or ileocecal valve and absence of pancolitis. In this

scenario additional imaging of the small bowel should be considered.<sup>19,22,68</sup>

Upper GI endoscopic lesions suggestive of Crohn's disease are described in another section. Upper GI endoscopic findings of focally active gastritis have been described in Crohn's disease in the absence of *Helicobacter pylori*<sup>72</sup> and in fact this feature has been incorporated as diagnostic of upper GI Crohn's in some guidelines.<sup>5,9</sup> But it has also been described in patients with UC as well and thus is little of help in differentiating the two diagnoses.<sup>73</sup> Diffuse duodenitis in UC has also been reported particularly in younger patients.<sup>74</sup>

Endoscopy together with other diagnostic modalities can differentiate CD from UC in 85% of patients but the diagnosis may change over time.<sup>75</sup> In a prospective study of more than 350 patients with IBD followed up for more than 22 months, index colonoscopy and biopsy were accurate in distinguishing CD from UC in 89% of cases. IBD diagnosis was revised in 4% of cases and the diagnosis of indeterminate colitis remained in 7% of cases.<sup>76</sup> In a more recent Scandinavian cohort, 10% of patients had their diagnosis changed from UC to Crohn's disease or the diagnosis of inflammatory bowel disease discounted during the 5 years after initial onset of symptoms.<sup>40</sup> IBD restricted to the colon cannot be allocated to the CD or UC category in about 5% of cases despite extensive evaluation and the disease is defined as unclassified IBD.<sup>22,41,68</sup>

### 5.2. Differential diagnosis: IBD vs. non-IBD colitides

Patients with other colitides can have similar endoscopic features to those with IBD. The common endoscopic differential for IBD includes infectious colitis, drug induced colitis, ischemic colitis, and radiation colitis. Unfortunately, despite careful history taking and various endoscopic and histologic findings, it might be difficult in some cases to distinguish enteric infections from IBD. In a prospective study investigating patients with acute mucoid bloody diarrhoea, up to one third were found to have an infectious aetiology.<sup>77</sup> Some of infectious diseases such as *Salmonella* spp., *Shigella* spp. or *Campylobacter* spp. have endoscopic features similar to UC while other infections such as *Yersinia* spp. or cytomegalovirus (CMV) enterocolitis resemble CD. Superimposed infections on IBD due to *Clostridium difficile* or CMV can make the situations more complicated in some instances. While there are no reliable specific features, some clues on endoscopic appearance may point towards a non-IBD infective colitis pending appropriate microbiological testing.<sup>78</sup>

Several reports have examined colonoscopic findings related to CMV infection. However, most of these reports looked at immunocompromised patients such as those with HIV and post-transplant patients.<sup>79–81</sup> The spectrum of colonoscopic findings in those patients was variable and ranged from patchy erythema, exudates, and micro-erosions to diffusely oedematous mucosa, multiple mucosal erosions, deep ulcers and pseudotumors.<sup>82–87</sup> In addition, colonoscopic findings of UC complicated by CMV infection with haemorrhagic appearance of the inflamed mucosa have rarely been reported.<sup>88</sup> It is, however, important

to obtain histological confirmation by demonstrating the typical CMV inclusions.

In endemic areas of tuberculosis, it is not an easy task to differentiate between CD and intestinal tuberculosis endoscopically even after histopathological examinations.<sup>89</sup> The majority of TB cases will involve the ileo-caecal area with varying degrees of contiguous colon and small bowel involvement. In patients with suspected or proven CD, ileocolonoscopy provided similar sensitivity (67% vs. 83%) but significantly higher specificity (100% vs. 53%) compared to video capsule endoscopy in identifying patients with TB and CD.<sup>90</sup> The incremental diagnostic yield of ileoscopy is reported to be low at 3.7% but this may be diagnostic in difficult cases.<sup>91</sup> Segmental colonic involvement occurs in 20% of patients in the absence of ileo-caecal involvement<sup>92,93</sup> and skip lesions, may be seen over 40% of patients.<sup>92,94</sup> Approximately 5% may even mimic pancolitis indistinguishable from UC.<sup>95,96</sup> Isolated small intestinal or upper gastrointestinal tract disease is also well described.<sup>97</sup> A recent systematic analysis revealed that colonoscopic findings were very useful in the differential diagnosis of intestinal tuberculosis and CD.<sup>98</sup> In this study, anorectal lesions, longitudinal as well as aphthous ulcers, and cobblestone appearance were parameters favouring CD, while localised involvement, patulous ileocecal valve, transverse ulcers, and scar or pseudopolyp were parameters favouring intestinal tuberculosis. With this method, a positive predictive value for CD of 94.9% and 88.9% for intestinal TB was achieved. In a more recent prospective study, skip lesions in the colon were significantly more frequent in patients with CD compared to patients with intestinal TB (66% vs. 17%),<sup>99</sup> as were aphthous ulceration (54% vs. 13%), linear ulceration (30% vs. 7%) and superficial ulceration (51% vs. 17%). Cobblestoning of the colonic mucosa was seen only in CD (17% vs. 0%). Nodularity of the colonic mucosa was significantly more common in patients with TB than in those with CD (49% vs. 24.5%). However, still the differentiation should be based on epidemiology, clinical presentation, supportive radiology, histology and immunological assays.<sup>100,101</sup>

Another differential diagnosis is a well localised inflammatory process involving only the sigmoid colonic segment associated with diverticulosis. This is called segmental colitis associated with diverticulosis (SCAD), and has become increasingly recognised as a distinct clinical and pathological disorder, usually described in older adults, often presenting with rectal bleeding.<sup>102</sup> Recent studies have confirmed that the incidence of SCAD ranged from 0.3% to 2%.<sup>103–105</sup> SCAD has a self-limited clinical course that resolves without further recurrence or need for treatment. Because of its similarities to other forms of inflammatory bowel disease, particularly Crohn's colitis, it is important to make an accurate diagnosis.<sup>106,107</sup> The endoscopic characteristic of SCAD is that inflammation is mainly detected within the inter-diverticular mucosa without involvement of the diverticular orifices. There is normal mucosa of the rectum and proximal colon.<sup>108</sup> SCAD has been further classified endoscopically with four different patterns.<sup>108,109</sup>

Ischaemic colitis (IC) is another differential to consider and may present with typical clinical features mimicking

acute presentation of IBD (both UC and CD). Endoscopic findings that suggest the diagnosis of ischemia include a normal rectum, sharply defined segments of involvement particularly of the 'watershed territory' from sigmoid colon to splenic flexure, petechial haemorrhages, longitudinal ulcerations and rapid resolution on serial examinations.<sup>110–114</sup> Because colonoscopy is able to establish the diagnosis of IC in more than 90% of cases,<sup>110</sup> it remains the diagnostic procedure of choice but it may be risky in the acute setting and diagnosis can be established by a sigmoidoscopy with supportive radiology such as abdominal CT.

Unfortunately, none of the novel endoscopic modalities (i.e. high resolution, digital filtering) have yet been able to improve the accuracy in differential diagnosis among IBD and other colitides but this may change in the future.

## 6. Endoscopy in acute colitis

### ECCO Statement 6A

Endoscopic evaluation with biopsies from at least one site is essential in acute severe colitis for diagnosis and excluding other causes of acute colitis (EL3). In most cases flexible sigmoidoscopy is sufficient and colonoscopy and bowel purgatives can usually be avoided (EL5) [Voting results: 100% agreement].

If an urgent diagnosis is needed in a patient suspected to have IBD presenting acutely with bloody diarrhoea, flexible sigmoidoscopy with mucosal biopsy is an appropriate initial investigation.<sup>115,116</sup> This will aid in differentiating ulcerative colitis from other causes of acute colitis.<sup>117–119</sup> In one prospective study of patients presenting with acute hemorrhagic colitis-type symptoms, infectious colitis was found to be the cause in 38% of the cases.<sup>77</sup> However, stool cultures are positive in only 40%–60% of cases, so a negative stool culture does not rule out infection<sup>120</sup> and hence endoscopy can be a useful adjunct to microbiological tests in these patients.<sup>121</sup> In addition, endoscopic appearances on treatment naive colon in the acute setting may be helpful in determining the pattern of inflammation pointing towards ulcerative colitis or Crohn's.<sup>122</sup>

In established cases of IBD, endoscopy during an acute flare is an important tool in determining the severity of the disease flare.<sup>123,124</sup> There is poor correlation between clinical and endoscopic indices of severity during acute colitis flare both in ulcerative colitis and in Crohn's disease.<sup>125–128</sup> However, the presence of extensive and deep ulcerations at endoscopy is associated with an increased risk of colectomy for UC in that admission.<sup>128–133</sup> In addition endoscopy can be useful in predication of response to rescue therapy using cyclosporine<sup>134</sup> or infliximab.<sup>135</sup> In an established patient with IBD, co-existent enteric infections account for a significant proportion of flares<sup>136,137</sup> and in these patients sigmoidoscopy can be a useful adjunct to indicate superadded infections such



as CMV by detecting specific inclusions and in *C. difficile* by demonstrating pseudomembranes. However, pseudo membranes may be absent in IBD patients with *C. difficile* infection.<sup>70,138,139</sup> The data on the safety of sigmoidoscopy and colonoscopy during the acute phase of colitis is scarce.<sup>71,115,130</sup> Most patients will only need a flexible sigmoidoscopy and colonoscopy may be potentially harmful.<sup>140</sup> Similarly it is advised that purgatives, especially fleet enemas and oral sodium phosphate preparations should be avoided in this setting.<sup>117</sup>

## 7. Endoscopy of ileoanal pouch

### ECCO Statement 7A

Endoscopy with biopsies should be performed in the assessment of pouch-related symptoms (EL3) [Voting results: 100% agreement].

Although ileal pouch–anal anastomosis (IPPA) in UC patients improve patients health related quality of life, inflammatory, non-inflammatory complications and sequelae are common with frequency of pouch failure up to 7% at 3 years and 9% at 5 years.<sup>141,142</sup> Endoscopy plays a significant role in diagnosing and guiding therapy in such patients.<sup>143–147</sup> Pouchitis occurs in 23–46% of patients following IPPA<sup>142</sup> and is a heterogeneous entity with no specific symptoms and signs. In addition, the severity of symptoms does not always correlate with the endoscopic or histological findings.<sup>148,149</sup> Therefore a cumulative clinical, endoscopic and histological assessment is needed. Several diagnostic criteria are available and the commonest in clinical use is the pouch disease activity index.<sup>150</sup> Furthermore, it is valuable to classify the phenotype of pouchitis before initiating therapy to provide guidance as to treatment modalities and duration of treatment.<sup>151–153</sup> In case of antibiotic refractory pouchitis, endoscopic evaluation can aid in excluding contributory factors such as ischemic pouchitis and infections.<sup>154,155</sup>

Pouch endoscopy is essential in the diagnosis of Crohn's disease of the pouch.<sup>156</sup> However, endoscopic appearances are not specific particularly in *de novo* CD.<sup>157</sup>

Endoscopic balloon dilatation can be used for therapy of stricture of the pouch in experienced hands.<sup>157,158</sup>

Another indication for pouch endoscopy is surveillance of dysplasia. There is a small risk of carcinomas (<5%) arising in the pouch which can present as flat or polypoid lesions.<sup>159–162</sup> In a systematic review, the prevalence of dysplasia in the rectal cuff and pouch was found to be similar indicating that surveillance should be identical in these 2 groups.<sup>163</sup> Annual surveillance pouchoscopy is recommended in patients with high risk features such as associated PSC, atrophic pouch mucosa, ileal pouch-rectal anastomosis and presence of dysplasia in the original colectomy specimen.<sup>92,164–166</sup> In selected patients with pouch problems upper gastrointestinal endoscopy can yield valuable information for differential diagnosis.<sup>93</sup>

## 8. Therapeutic endoscopy

### ECCO Statement 8A

Endoscopic dilatation of strictures in Crohn's disease is a safe and effective alternative to surgery in experienced hands and should be considered before surgery in selected patients [EL2]. The best outcomes are obtained in short strictures (<4 cm) and anastomotic strictures (EL2). The possibility of a malignant stricture must be ruled out [EL3] [Voting results: 100% agreement] [Voting results: 100% agreement].

Intestinal strictures are a major cause for morbidity and need for surgery in Crohn's disease. Traditional treatment involved surgical resection and stricturoplasty but there is a high rate of recurrence needing reoperation.<sup>94,167</sup> Over the last 15 years there is increasing evidence for endoscopic balloon dilatation as a safe and effective alternative to surgery, particularly of ileocecal and anastomotic strictures.<sup>168–192</sup> However these studies are all mainly retrospective with observational study design, and while few studies are prospective with long term follow up<sup>171,173,176,184,185,187,190,192</sup> controlled studies are lacking. The technical success for endoscopic balloon dilatation is reported to vary between 86 and 93% in different series, and the clinical success (defined as resolution of obstructive symptoms) is 64–70%, increasing to 78% when patients with failed procedures due to technical reasons are excluded.<sup>168</sup> On long term follow up studies, the cumulative proportion of patients needing surgery at 1, 3 and 5 years vary from 13–17%, 28–42%, and 36–42% respectively. Strictures recur following dilatations and re-dilatations may be required in up to 20% of patients at 1 year and up to 50% by 5 years.<sup>170,171,173,178,183,186</sup> These are comparable to recurrence rates following stricturoplasty of 45% at 5 years.<sup>191</sup> Balloon dilatation has also been used successfully in gastro-duodenal strictures although the numbers of reported cases are small.<sup>193–195</sup> Best results in terms of surgery free outcome are obtained when stricture length is <4 cm and for anastomotic strictures when compared to *de novo* strictures.<sup>168,181,184,186</sup> Influence of other factors on success such as concurrent medical therapy, smoking status and disease activity status is currently uncertain.<sup>196–198</sup> Most dilatations can be performed without anaesthetic using conscious sedation.

Major complications, including bowel perforation and significant bleeding, occurs in about 2% of patients.<sup>168</sup> This is probably acceptable in comparison to the stricturoplasty having major complication rates of over 5%.<sup>193</sup> There is data to suggest balloon diameters of 25 mm have increased risk of complications.<sup>179,186</sup> So far no mortality past balloon dilatation has been reported. Intra-lesional steroids<sup>199–203</sup> and Infliximab<sup>204</sup> to prolong the results of endoscopic dilatation have been attempted in some studies with variable results. In a small randomised placebo controlled trial of paediatric Crohn's patients,<sup>203</sup> intralesional steroids reduced the need for re-dilatation and recurrence surgery, but this has not been confirmed in the only randomised pilot study in adults.<sup>199</sup>

Enteroscopy and dilatation of small bowel strictures<sup>205–208</sup> and dilation of ileal pouch strictures<sup>158</sup> are reported to be successful in expert hands. Since there are no randomised studies comparing stricturoplasty and dilatation, the decision on individual patients should be based on stricture length, patient preference and the available expertise. The use of metallic and biodegradable stents<sup>209,210</sup> in the setting of Crohn's disease strictures needs further studies.

## 9. Endoscopic activity in IBD

### 9.1. Ulcerative colitis scoring systems

#### ECCO Statement 9A

Instruments for measuring endoscopic disease activity in UC are available, but in daily routine such indices are barely used.

The ulcerative colitis endoscopic index of severity (UCEIS) and the ulcerative colitis colonoscopic index of severity (UCCIS) received formal validation [EL2]. Several other endoscopic scoring systems for disease severity are available and commonly used, albeit lacking formal validation [EL5] [Voting results: 86% agreement]. The Mayo score has been extensively used in randomised controlled trials to assess endoscopic response. Endoscopic remission has been defined as a Mayo subscore  $\leq 1$  [EL1], however complete endoscopic remission should be restricted only to score 0 (normal or completely healed mucosa) [EL2] [Voting results: 100% agreement].

The first attempt to classify endoscopic ulcerative colitis (UC) severity was made by Truelove and Witts back in 1955 during a placebo-controlled trial evaluating cortisone for the treatment of active UC.<sup>211</sup> Mucosal appearance was classified into three categories: (1) normal or near normal (slight hyperaemia or slight granularity), (2) improved, or (3) no change or worse. However, this classification lacks well-defined endoscopic descriptors.

A decade later, in 1964, Baron et al. evaluated the inter-observer agreement in describing the mucosal appearance of 60 patients with UC using rigid sigmoidoscopy.<sup>212</sup> The degree of disease activity was based on a 4-point scale (0–3) according mainly to the severity of bleeding. Mucosal friability, described as bleeding to light touch of the mucosa was pivotal in discriminating between mild and moderately active disease. Of note, the presence of ulceration was not taken into account when defining the severity of mucosal inflammation. A Baron score  $\leq 1$  (0: normal mucosa; 1: abnormal mucosa but non-haemorrhagic) was defined as endoscopic remission. Remarkably, after more than four decades since the Baron score was first described, it has still not been formally validated.

The Powell-Tuck<sup>213</sup> index, known as the St. Mark's index, also graded the severity of inflammation using a 3-point scale (0–2) focusing on mucosal bleeding as the predominant

variable (non-haemorrhagic mucosa, bleeding on light touch, and spontaneous bleeding).

The Sutherland index (UC-Disease Activity Index; UC-DAI)<sup>214</sup> was developed during a placebo-controlled trial evaluating the efficacy of mesalamine enemas for the treatment of distal UC. The mucosal appearance was described on a 4-point scale (0–3) evaluating three endoscopic findings: (1) friability, (2) exudation, and (3) spontaneous haemorrhage.

The endoscopic component of the Mayo score<sup>215</sup> was developed in 1987 by Schroeder et al. during a placebo-controlled trial evaluating the efficacy of an oral delayed release mesalamine for the treatment of active UC. The degree of endoscopic rectal inflammation was based on a 4-point scale (0–3) according to the following findings: (0) normal, (1) erythema, decreased vascular pattern, mild friability, (2) marked erythema, absent vascular pattern, friability, erosions, and (3) ulceration, spontaneous bleeding. The Mayo endoscopic subscore is the most commonly used in clinical trials for the evaluation of treatment efficacy in terms of endoscopic remission. Mucosal healing has been defined as a subscore of 0–1.<sup>216</sup> However, some studies have used a more strict definition of complete mucosal healing as Mayo endoscopic subscore of 0.<sup>217</sup> Nevertheless, these definitions have not been properly validated, and the current recommendation of the Food and Drug Administration (FDA) is to consider any friability as non-healed mucosa.

The Rachmilewitz endoscopic index<sup>218</sup> was developed during a controlled trial comparing a coated mesalamine with sulfasalazine for the treatment of active UC. The index included four variables: (1) vascular pattern, (2) granularity, (3) mucosal damage (mucus, fibrin, exudate, erosions, ulcers), and (4) bleeding. Scores range from 0 to 12 points, the cut-off for defining endoscopic remission being  $\leq 4$  points.

In 2005, in a placebo-controlled trial of a humanised antibody to the  $\alpha 4\beta 7$  integrin (MNL02), Feagan et al. described the modified Baron score.<sup>36</sup> Endoscopic activity was categorised on a 5-point scale (0–4) taking into account the following variables: vascular pattern, granularity, hyperaemia, friability, ulceration, and bleeding. Endoscopic response was defined as an improvement of at least 2 points from baseline. Endoscopic remission was defined as a score of 0 points (normal mucosa, with a visible vascular pattern and no friability).

None of the above listed indices and the definitions of endoscopic response/remission have been properly validated.

In an attempt to construct and validate a reliable instrument to measure endoscopic severity in UC, Travis et al. derived a new tool, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), based on the intra- and inter-individual variability of 10 endoscopic descriptors.<sup>34</sup> This new index grades three endoscopic findings, (1) vascular pattern, (2) bleeding, and (3) erosions/ulcers, each of them with precise definitions, on three to four levels, capturing 90% of the variance in the overall assessment of endoscopic severity. A notable finding is that friability has been excluded from the index. Validation of remission and severity is still in progress as well as the operating properties of the index (responsiveness and reliability)<sup>37</sup>. Once further

validated, the UCEIS will be available for clinical trials bringing consistency to endoscopic assessment of disease severity in UC.

More recently Samuel S et al. prospectively validated a further index named Ulcerative Colitis Colonscopic Index of Severity (UCCIS).<sup>219</sup> The index includes six variables: (1) vascular pattern, (2) granularity, (3) ulceration, (4) bleeding/friability, (5) grading of segmental and global assessment of endoscopic

severity with a predefined 4-point scale, and (6) global assessment of endoscopic severity on a 10-cm VAS scale. Interobserver agreement was good to excellent for the 4 mucosal lesions evaluated. A significant correlation with clinical activity and some biomarkers (i.e. C reactive protein) was also demonstrated, but a definition of a cut off level for endoscopic response and remission is still lacking (Table 9.1).

**Table 9.1** Comparison of Endoscopic Scoring indexes in Ulcerative Colitis (UCEIS: Ulcerative Colitis Endoscopic Index of Severity, UCCIS: Ulcerative Colitis Colonscopic Index of Severity).

| Score   | Endoscopic variables   | Strengths  | Weaknesses  | Proposed remission score |
|---|--|--|---|--------------------------|
| Truelove and Witts Sigmoidoscopic assessment <sup>211</sup> | Lack of endoscopic descriptors definitions   | –  | –   | –                        |
| Baron Score <sup>212</sup>                                  | Vascular pattern, friability, bleeding   | Easy to calculate  | Do not evaluate ulcers<br>Subjective interpretation of friability and bleeding<br>Poor inter-observer agreement | 0–1                      |
| Powell-Tuck index (St. Mark's Index) <sup>213</sup>         | Bleeding (non-haemorrhagic vs. haemorrhagic mucosa)  | –  | Only evaluates bleeding<br>Subjective interpretation  | Not defined              |
| Sutherland Index <sup>214</sup>                             | Friability, exudation, spontaneous haemorrhage   | –  | Do not evaluate ulcers<br>Not accurate to discriminate between mild to moderate friability                      | 0                        |
| Mayo Endoscopic Subscore <sup>215</sup>                     | Erythema, vascular pattern, friability, erosions, ulcers, bleeding                                 | Easy to calculate<br>Widely used in clinical trials  | Not accurate to discriminate between mild to moderate friability  | 0–1                      |
| Rachmilewitz Index <sup>218</sup>                           | Vascular pattern, granularity, mucosal damage (mucus, fibrin, exudate, erosions, ulcers, bleeding) | Easy to calculate  | Subjective interpretation of mucosal damage and bleeding  | 0–4                      |
| Modified Baron Score <sup>36</sup>                          | Vascular pattern, granularity, hyperaemia, friability, ulceration, bleeding                        | Easy to calculate<br>used in clinical trials   | No discrimination between superficial and deep ulceration   | 0                        |
| UCEIS <sup>34</sup>   | Vascular pattern, bleeding, erosions/ulcers,   | Accurate for the assessment of disease severity<br>Developed following rigorous methodology<br>Currently undergoing independent validation (responsiveness, reliability) | Low agreement for normal appearance of the mucosa   | Under evaluation         |
| UCCIS <sup>220</sup>  | Vascular pattern, granularity, ulceration, bleeding/friability                                     | Accurate, easy to be scored as based only on only four different parameters<br>Developed and validated following rigorous methodology<br>Covers the entire colon         | Single center development, high expertise: larger validation needed   | Under evaluation         |

## 9.2. Crohn's disease scoring systems

### ECCO Statements 9B

The severity of post-surgical Crohn's disease recurrence in the neo-terminal ileum should be classified according to Rutgeerts' score [EL3] [Voting results: 93% agreement]. The Crohn's disease endoscopic index of severity (CDEIS) [EL1] and the simple endoscopic score for Crohn's disease (SES-CD) [EL1] are validated and reproducible scoring systems dedicated to luminal Crohn's disease endoscopic activity measurement, but their use in routine clinical setting has still to be determined. [EL5] [Voting results: 100% agreement]. There is no validated definition of mucosal healing in Crohn's disease. Reporting of endoscopic activity should include accurate descriptions of any abnormalities in each segment, and whenever possible according to validated indices [EL5] [Voting Results: 100% agreement].

In the post-surgical setting measurement of activity relevant to clinical and surgical recurrence at the site of ileocolonic anastomosis can be recorded using the Rutgeerts' score for post-surgical recurrence. The score was developed and validated in order to predict a relevant difference in

prognosis in the post-surgical setting.<sup>59,60</sup> Although the score lacks formal evaluation of inter-observer agreement, it has been widely used across many different clinical trials and clinical series and its prognostic value was confirmed in clinical trials over the past 20 years.<sup>220–224</sup> More specifically, patients with recurrence graded i2 or more were shown to present with a more severe course of disease in terms of clinical and surgical recurrence, while patients with no (i1) or minimal (i1, e.g. less than 5 aphtous recurrent lesions with normal mucosa interposed) endoscopic recurrence are at minimal risk of subsequent recurrence.

In the setting of luminal Crohn's disease, endoscopic activity may reliably be scored with one of the validated endoscopic activity scores, either being the Crohn's disease endoscopic index of severity (CDEIS)<sup>225</sup> or the simple endoscopic score for Crohn's disease (SES-CD).<sup>226</sup> Both scores were shown to be highly reproducible (with excellent inter-observer agreement demonstrated) and they were prospectively validated.<sup>225–228</sup> Nonetheless both scores are rather complicated, and therefore their use is restricted to clinical trials at present and not often used in routine clinical practice. However, reporting of endoscopic activity should always include accurate descriptions of any abnormalities in each segment.

The CDEIS was developed<sup>225</sup> through a selection process involving all endoscopic features of Crohn's disease, then restricting the observation to those with best inter-observer agreement, weighting individual endoscopic variables (by

**Table 9.2** Most commonly used endoscopic scores for CD (CDEIS: Crohn's disease endoscopic index of severity, SES-CD: Simple endoscopic score for Crohn's disease).

| Score                             | Variables included   | Field of applicability   | Strengths and weaknesses   |
|-----------------------------------|--|--|--|
| Rutgeerts' score <sup>59,60</sup> | Aphtous ulcers, ulcers, aphtoid ileitis, erythema, cobblestone, stenosis (all to be evaluated at the anastomotic site or in the afferent ileal limb of an ileocolonic anastomosis)           | Postoperative recurrence (only at the site of an ileo-cecal anastomosis, not suitable for other surgeries) | Strengths:<br>Well known and widely accepted, easy and suitable for routine practice, relevant prognostic value<br>Weaknesses:<br>Potential agreement issues, no formal validation of the score  |
| CDEIS <sup>225</sup>              | Superficial ulcers, deep ulcers, surface affected by ulcers, surface affected by disease, ulcerated stenosis, non-ulcerated stenosis (all to be scored in all ileocolonic segments explored) | Luminal Crohn's disease, useful to measure variations of endoscopic activity (including mucosal healing)   | Strengths:<br>Validated and used in several trials, sensitive to variations in endoscopic activity, allows comparison of different endoscopic examination, prognostic relevance demonstrated<br>Weaknesses:<br>Complex, requires post-procedure time to be scored, not suitable for routine practice   |
| SES-CD <sup>226</sup>             | Ulcer size, surface affected by ulcers, surface affected by disease, type of bowel narrowing (all to be scored in all ileocolonic segments explored)   | Luminal Crohn's disease, useful to measure variations of endoscopic activity (including mucosal healing)   | Strengths:<br>Validated and used in several trials, sensitive to variations in endoscopic activity, allows comparison of different endoscopic examinations, prognostic relevance demonstrated, simplification of some CDEIS variables, results may be linearly derived into CDEIS values<br>Weaknesses:<br>Still complex, requires post-procedure time to be scored, not suitable for routine practice |

means of multivariate regression) against a global evaluation of lesion severity (GELS) scored on a visual-analogue scale by different clinicians observing the same endoscopic pictures. The final score takes into account whether a given segment is explored/available or not, lesions with different relevance (deep/superficial ulcers), surface of colon affected by Crohn's lesions and by ulcers in particular, and finally presence or absence of ulcerated or non-ulcerated narrowing. At least one of the variables, the presence of deep colonic ulcers, is an independent driver of severe prognosis, with patients affected by deep ulcers displaying significant higher rates of colectomies and of new draining fistulae during the long-term follow-up compared to those patients without deep ulcers.<sup>229</sup>

The SES-CD was developed<sup>226</sup> aiming to correlate at best with CDEIS, through a simplification process of the endoscopic variables, which were reduced to hierarchical and categorical and restricted to presence and size of ulcers,

amount of the surface affected by ulcers or by any Crohn's lesion and presence/type of narrowing of the bowel lumen. It was shown to have a close correlation, which enables users to convert SES-CD results into CDEIS and vice-versa using a straight-forward equation:  $CDEIS = 0.76 \square SES-CD + 0.29$ .

During the past few years, there were attempts to define endoscopic remission or minimal activity according to possible CDEIS (lower than 3 points)<sup>230,231</sup> or SES-CD (lower than 5 points)<sup>232</sup> cut-off values, although the best prognosis seemed to be associated to CDEIS or SES-CD scores of 0 points.<sup>231,233</sup> A recently published review outlined the absence of accepted and shared definitions of endoscopic healing.<sup>234</sup> A different endoscopic activity scale, which should be used both for Crohn's disease and ulcerative colitis, is the operative one used in IBSEN study<sup>235</sup>: this score ranges between 0 and 2 points (0 = normal; 1 = light erythema or granularity; 2 = granularity, friability, and bleeding, with or without the addition of

**Table 9.3** Characteristics of the most commonly used scores for UC and CD (CDEIS: Crohn's disease endoscopic index of severity, SES-CD: Simple endoscopic score for Crohn's disease).

| Score                                       | Applicability   | Variable   | Grading  |  |  |
|---|---|--|--|--|--|
| Mayo endoscopic subscore                    | UC  | Mayo 0   | Normal or healed mucosa  |  |  |
|   |   | Mayo 1   | Faded vascular pattern, mild friability, erythema  |  |  |
|   |   | Mayo 2   | Absence of vascular pattern, marked friability, erosions   |  |  |
|   |   | Mayo 3   | Spontaneous bleeding, large ulcers   |  |  |
| Rutgeerts' score                            | Post-operative CD   | i0   | No lesions in neoterminal ileum  |  |  |
|   |   | i1   | ≤5 aftoid ulcers   |  |  |
|   |   | i2   | >5 aftoid ulcers with normal mucosa in-between, or skip areas with larger lesions, or lesions/ulcers (<1 cm) confined to ileocolonic anastomosis |  |  |
|   |   | i3   | Diffuse aftous ileitis with extensively inflamed mucosa  |  |  |
| CDEIS                                       | Luminal CD  | Deep ulcers (in all explored segments)                 | Absent (0 points)<br>Present (12 points)   |  |  |
|   |   | Superficial ulcers (in all explored segments)          | Absent (0 points)<br>Present (6 points)  |  |  |
|   |   | Surface involved by disease (in all explored segments) | 0–10 (as the result of visuoanalogic scale transformation representing a complete ileocolonic segment)   |  |  |
|   |   | Surface involved by ulcers (in all explored segments)  | 0–10 (as the result of visuoanalogic scale transformation representing a complete ileocolonic segment)   |  |  |
|   |   | Ulcerated stenosis (anywhere)                          | Absent (0 points)<br>Present (3 points)  |  |  |
|   |   | Non-ulcerated stenosis (anywhere)                      | Absent (0 points)<br>Present (3 points)  |  |  |
|   |   | SES-CD   | Luminal CD   | Ulcers (in all explored segments)            | Absent (0 points)<br>Aphthous ulcers, 0.1–0.5 cm (1 point)<br>Large ulcers, 0.5–2 cm (2 points)<br>Very large ulcers, >2 cm (3 points) |
|   |   |  |  | Ulcerated surface (in all explored segments) | None (0 points)<br><10% of the segment (1 point)<br>10–30% of the segment (2 points)<br>>30% of the segment (3 points)                 |
| Affected surface (in all explored segments) | None (0 points)<br><50% of the segment (1 point)<br>50–75% of the segment (2 points)<br>>75% of the segment (3 points)                              |  |  |  |  |
| Narrowings (in all explored segments)       | None (0 points)<br>Single, passable by endoscope (1 point)<br>Multiple, passable by endoscope (2 points)<br>Not passable, frank stenosis (3 points) |  |  |  |  |

ulcerations). Score 0 or 1 was regarded as mucosal healing, while all types of ulceration (or of active inflammation) were linked to a score of 2 ("not healed"), both in ulcerative colitis or Crohn's disease patients (Tables 9.2 and 9.3).

## 10. Endoscopic severity and prognosis

### 10.1. Endoscopic activity and prognosis in UC

#### ECCO Statement 10A

Mucosal healing in ulcerative colitis is associated with lower risk of clinical relapse, hospitalisation and colectomy and with lower risk of colitis associated neoplasia [EL2] [Voting Results: 100% agreement]. Mucosal healing is presently assessed with white light endoscopy; this evaluation may be augmented with specific magnified techniques, and may refine prognosis [EL2] [Voting Results: 86% agreement].

Treatment for ulcerative colitis is increasingly directed, as in Crohn's disease, towards mucosal healing as this end point seems to offer better prognosis compared to symptomatic control alone. In a clinical trial setting, "Mucosal healing" can vary from: light erythema, granularity and or friability<sup>47,235</sup> to more stringent definitions: normal mucosal with the absence of all ulceration, both microscopic and macroscopic, providing a sigmoidoscopy score of 0 with no friability.<sup>214</sup>

#### 10.1.1. Endoscopy in predicting outcomes

Endoscopic "mucosal healing" was associated with a lower risk of colectomy at one year in a combined analysis of the ACT 1 and 2 studies in patients who had achieved mucosal healing with infliximab at week 8 (95% colectomy free for Mayo sub score 0–1, 80% for 3,  $p = 0.004$ ).<sup>47</sup> The IBSEN cohort from the pre-biological therapy era demonstrated patients with mucosal healing at one year had a lower risk of colectomy at 5 years (risk ratio 0.22,  $p = 0.02$ ).<sup>235</sup> Mucosal healing defined as Baron score of 0 was associated with lower risks of hospitalisation, colectomy and subsequent immunosuppressive use.<sup>236</sup> Endoscopic "normal colonic appearance" was associated with a lower risk of colitis related neoplasia (odds ratio 0.38,  $p = 0.003$ ), with a cancer risk in those with a normal "healed" colon that was not different to population risk.<sup>237</sup> The prognostic importance of mucosal healing, first suggested by Wight and Truelove in 1966<sup>211,238</sup> seems to be independent of the means to achieve it, being seen in patients treated with or without biological therapies. Increasing colonoscopic inflammation was correlated with the risk of colitis associated neoplasia during surveillance in a univariate analysis, odd ratio 2.5,  $p = 0.001$ .<sup>239</sup> Severe lesions, defined as "extensive deep ulcerations, mucosal detachment at the edge of ulcers, well-like ulcers and large mucosal abrasions", were associated with failure of intensive intravenous treatment with steroids (relative risk 2.32,  $p = 0.007$ ) and the risk of

subsequent colectomy during follow up.<sup>130,132</sup> In a large multi-centre series of patients with acute severe colitis who received cyclosporine as rescue therapy, severe lesions were strongly associated with subsequent colectomy by 6 months (73% versus 42%,  $p < 0.01$ ).<sup>134</sup> Patients with at least one segment of severe inflammation were more likely to have colonic neoplasia during colonoscopic surveillance in a univariate analysis, odds ratio 3.38,  $p = 0.008$ .<sup>237</sup>

#### 10.1.2. Endoscopic severity and QoL

Endoscopic inflammation score (according to Rachmilewitz) had a negative correlation with quality of life (QoL), measured with the inflammatory bowel disease questionnaire, with higher (worse) endoscopic scores having lower QoL,  $r = 0.51$ ,  $p = 0.005$ .<sup>240</sup> A similar relationship between Mayo endoscopic sub score and QoL measurement was seen in the ACT 1 and 2 studies  $r = 0.50$ ,  $p < 0.001$ .<sup>241</sup>

#### 10.1.3. Advanced endoscopy in UC and prognosis

Apparently normal mucosa at endoscopy can be sub-classified by advanced endoscopic imaging techniques. In a prospective study of patients who had achieved clinical and endoscopic remission, crypt opening abnormalities seen with magnifying chromoendoscopy were associated with relapse over 12 months.<sup>242</sup> Recently in another mixed cohort of patients with inflammatory bowel disease in clinical remission with normal mucosa, local barrier dysfunction as assessed by confocal endomicroscopy (cell shedding, microerosions and fluorescein leakage) was associated with a higher risk of relapse.<sup>243</sup>

Although endoscopic severity is associated with worse outcomes, there is as yet no evidence that targeting endoscopic mucosal healing as a treatment outcome will result in better patient outcomes in the short and long term in ulcerative colitis. There remains a need to clearly define endoscopic criteria for both mucosal healing and severe endoscopic lesions.

## 10.2. Endoscopic activity and prognosis in Crohn's disease

#### ECCO Statements 10B

In the absence of a formally validated definition, mucosal healing could be defined either as the absence of mucosal ulceration, or a Crohn's disease endoscopic index of severity (CDEIS) score of 0, or a simple endoscopic score for Crohn's disease (SES-CD) of 0 [EL3] [Voting Results: 100% agreement].

Achieving mucosal healing with Crohn's disease therapy is associated with a short-term decrease in relapse and hospitalisation rates and the need for surgery [EL2] [Voting Results: 100% agreement].

Early post-operative endoscopic recurrence (Rutgeerts' score  $\geq i2$ ) is associated with a higher symptomatic and surgical recurrence rates [EL1]. Therefore medical adaptation should be considered [EL2] [Voting Results: 100% agreement].

### 10.2.1. Mucosal healing and outcomes in CD

An increasing body of evidence suggests that mucosal healing (MH) may change the natural course of CD by decreasing relapse rates, hospitalisation rates and the need for surgery. Unfortunately, a wide variation of definitions of MH has been used in different clinical trials, some evaluating the absence of mucosal ulcerations, others using validated endoscopic activity scores such as the Crohn's disease endoscopic index of severity (CDEIS) or the simple endoscopic score for Crohn's disease (SES-CD).<sup>225,226</sup>

In a single centre cohort study published in 2002, the presence of deep ulcerations at index colonoscopy independently predicted a more aggressive disease course including the development of new fistulae and increased colectomy rates throughout follow-up (risk ratio 5.43).<sup>229</sup> A similar finding was observed in the IBSEN cohort, a Norwegian population-based cohort study including CD patients who underwent index ileocolonoscopy one year after initiation of CD therapy. During follow-up, patients achieving MH (absence of marked granularity and friability, absence of bleeding and ulcerations) one year after initiation of CD therapy showed a trend towards lower surgical resection rates compared to patients not achieving MH (12% vs. 22%,  $p = 0.010$ ).<sup>235</sup> In a 10-year extension of this study, the risk of surgery was significantly reduced among patients who achieved MH compared to patients who did not achieve MH one year after initiation of CD therapy (hazard ratio 0.42).<sup>244,245</sup>

Sub-studies of ACCENT-1 showed that patients who achieved MH (absence of mucosal ulcerations) with infliximab (IFX) had a longer relapse-free survival and required fewer disease-related hospitalisations and surgeries compared to those who did not achieve MH.<sup>246–248</sup> In a sub-study of the SONIC trial, patients achieving MH (absence of mucosal ulcerations) at week 26 were more likely to maintain steroid-free clinical remission (SFCR) at week 50 compared to patients not achieving MH (76% vs. 58%).<sup>249,250</sup> The highest rate for SFCR at week 50 (82%) was achieved among patients with both MH and SFCR at week 26. In a sub-study of the EXTEND trial, achievement of early deep remission (absence of ulcerations and CDAI < 150) 12 weeks after initiation of adalimumab (ADA) therapy was significantly associated with a better quality of life at week 52 and showed a trend towards lower CD related hospitalisation and surgery rates.<sup>49,251</sup>

Also, the long-term follow-up of the step-up/top-down trial showed that, when combining the two treatment arms, patients achieving MH (SES-CD = 0) at year two more frequently remained in SFCR during the following two years compared to patients with persistent endoscopic activity at year two (71% vs. 27%, respectively,  $p = 0.003$ ).<sup>233,252</sup>

Currently, it's not clear what degree of MH is required to avoid disease progression and to change the natural disease course. In a retrospective single centre cohort study reporting the long-term outcome of IFX in 214 patients with CD with a median follow-up of 69 months, patients achieving complete MH (absence of mucosal ulcerations) more frequently experienced a sustained clinical benefit compared to patients who did not achieve MH (64.8% vs. 39.5%,  $p = 0.0004$ ).<sup>252,253</sup> Furthermore, fewer disease-related hospitalisations (42.2% vs. 59.3%,  $p = 0.0018$ ) and a lower need for major abdominal surgery (14.1% vs. 38.4%,  $p < 0.0001$ ) was observed in the group who achieved MH. Interestingly, major abdominal surgery rates were not

significantly different between patients achieving complete and partial MH, the latter defined as clear endoscopic improvement (14.1% vs. 14.0%). Several investigators have tried to define a minimal degree of endoscopic improvement (endoscopic response) which is clinically relevant for improving the long-term outcome, but until now the proposed cut-off values in CDEIS and SES-CD have not been validated.<sup>254,255</sup>

In a placebo-controlled study by the GETAID including 83 patients in clinical remission under azathioprine (AZA), neither presence of ulcerations nor a CDEIS > 0 at ileocolonoscopy before discontinuation of AZA were predictive for clinical relapse.<sup>256</sup> In contrast, in another recent GETAID trial, Louis et al. assessed the risk of clinical relapse after discontinuation of IFX in 109 patients with CD who were in clinical remission under a combined maintenance therapy with IFX and an immunomodulator.<sup>231</sup> In their multivariate analysis, the absence of MH (CDEIS > 0) was among the factors strongly associated with an increased risk of clinical relapse after IFX withdrawal (hazard ratio 2.6). In this study, immunosuppression with AZA or methotrexate was continued after IFX withdrawal.

Finally, within the first year after an ileocolonic resection for CD, the presence of endoscopic lesions at the anastomosis or in the neo-terminal ileum during endoscopy predict postoperative clinical recurrence.<sup>60</sup> Throughout follow-up, symptomatic recurrence occurred less frequently in patients who had no severe endoscopic lesions at one year (Rutgeerts' score i0 or i1) compared to patients with a more severe endoscopic recurrence (Rutgeerts' score  $\geq$  i2).

## 11. Small bowel endoscopy

### 11.1. Small bowel capsule endoscopy (SBCE) in patients with suspected Crohn's disease

#### ECCO Statement 11A

In patients with suspected Crohn's disease and negative ileocolonoscopy, small bowel capsule endoscopy may be the initial diagnostic modality for the evaluation of the small bowel, in the absence of obstructive symptoms or known stenosis. In patients with obstructive features or known stenosis, a cross-sectional imaging modality such as MR enterography or CT enterography should be the method of choice [EL2] [Voting results: 93% agreement].

Crohn's disease frequently involves the terminal ileum, which is accessible to conventional endoscopic evaluation and biopsy at the time of ileocolonoscopy. However, in some patients, Crohn's disease may affect the proximal small bowel out of reach of the colonoscope or terminal ileum intubation may be unsuccessful.<sup>22</sup> In this setting, the diagnostic yield of the capsule for small bowel lesions is higher than ileocolonoscopy, small bowel follow-through and CT enterography.<sup>2,257</sup> Moreover, SBCE may also be superior to MR enterography (MRE), particularly for early mucosal lesions and for proximal small bowel lesions.<sup>258–260</sup> Dionisio et al.<sup>257</sup> conducted a meta-analysis evaluating the diagnostic

yield of SBCE *versus* push enteroscopy (PE), ileocolonoscopy, small bowel follow-through or enteroclysis (SBE/SBFT), computed tomography enterography or enteroclysis (CTE) and MRE. Data on patients with suspected and established Crohn's disease were independently analyzed. A total of 12 trials (n = 428 patients) compared SBCE with SBE/SBFT, eight trials (n = 236) compared SBCE with ileocolonoscopy, four trials (n = 119) compared SBCE with CTE, two trials (n = 102) compared SBCE with PE, and four trials (n = 123) compared SBCE with MRE. In this meta-analysis, SBCE was superior to SBE/SBFT, CTE and ileocolonoscopy, with significant weighted incremental yield (IY) in the evaluation of patients with suspected Crohn's disease (SBCE *versus* SBE/SBFT: 52% *versus* 16% [IY = 32%, P < 0.0001, 95% CI = 16–48%], SBCE *versus* CTE: 68% *versus* 21% [IY = 47%, P < 0.00001, 95% CI = 31–63%], and SBCE *versus* ileocolonoscopy: 47% *versus* 25% [IY = 22%, P = 0.009, 95% CI = 5–39%]. No significant IY was observed when SBCE was compared to MRE: 55% *versus* 45% (IY = 10%, P = 0.43, 95% CI = –14–34%). Recently, Jensen et al.<sup>258</sup> published the results of a prospective, blinded study of multiple small-bowel imaging modalities, comparing SBCE, CTE and MRE performed after ileocolonoscopy in 93 patients with suspected or established Crohn's disease. The sensitivity and specificity for terminal ileum Crohn's disease were 100% and 91% for SBCE, 76% and 85% for CTE, and 81% and 86% for MRE, respectively, while the capsule significantly enhanced the detection of small bowel lesions proximal to the terminal ileum.

Crohn's disease begins with a mucosal inflammatory pattern that over time develops into strictures or fistulas.<sup>8,9</sup> Timely diagnosis and early treatment may lead to better outcomes.<sup>253,261</sup> SBCE has the potential to assume a central role in the early diagnosis of patients with suspected Crohn's disease, as it is the most sensitive diagnostic test to detect early small bowel lesions. In addition, due to the high negative predictive values of a normal examination being consistently reported, small bowel Crohn's disease can possibly be excluded in most patients with a negative capsule study.<sup>262,263</sup>

## 11.2. Diagnostic accuracy

### ECCO Statement 11B

Small bowel capsule endoscopy has a high negative predictive value for small bowel Crohn's disease [EL 4] [Voting results: 100% agreement].

### ECCO Statement 11C

Endoscopic differentiation of small bowel Crohn's disease from drug-induced lesions or other diseases is unreliable [EL3]. Non-steroidal anti-inflammatory drugs (NSAIDs) should be withdrawn at least four weeks prior to small bowel capsule endoscopy in the setting of suspected Crohn's disease [EL4] [Voting results: 100% agreement].

The specificity of minor mucosal lesions on SBCE in suspected Crohn's disease has been debated.<sup>2,264</sup> Indeed, higher diagnostic yield may not correspond to higher diagnostic accuracy, as the small lesions detected by the capsule may not be specific for Crohn's disease as such lesions may be found in a number of other conditions,<sup>265</sup> such as in Behçet's disease, vasculitis, or drug-induced enteropathy, particularly due to non-steroidal anti-inflammatory drugs (NSAIDs).<sup>266–270</sup> Moreover, SBCE has been shown to detect minor mucosal breaks and erosions in about 10% of healthy individuals.<sup>271</sup> In a cohort of 102 patients with suspected Crohn's disease, 37% were initially diagnosed with small bowel ulcerations in SBCE but only in 13% was the diagnosis of Crohn's disease confirmed at one year follow up.<sup>272</sup> In a former prospective study comparing SBCE, CTE, SBFT and ileocolonoscopy using a consensus clinical diagnosis as the reference standard, the sensitivity of SBCE and CTE was identical but the specificity of SBCE was lower.<sup>90</sup>

Some predictive markers of small bowel Crohn's disease have been described to improve specificity, including weight loss,<sup>273</sup> perianal disease,<sup>274</sup> raised inflammatory markers<sup>275–278</sup> and faecal calprotectin,<sup>279–282</sup> although none of these have been validated in prospective trials. Conversely, in patients with abdominal pain or chronic diarrhoea alone, capsule endoscopy rarely results in the detection of clinically relevant lesions in the small bowel.<sup>283–285</sup> The International Conference on Capsule Endoscopy (ICCE)<sup>286</sup> recommended that patients with suspected Crohn's disease should be selected to undergo SBCE if they present with typical symptoms (chronic abdominal pain, chronic diarrhoea, weight loss or growth failure) *plus* either extraintestinal manifestations (fever, arthritis or arthralgia, pyoderma gangrenosum, perianal disease or primary sclerosing cholangitis), inflammatory markers (iron deficiency, erythrocyte sedimentation rate, C-reactive protein, leucocytosis or serology), or abnormal small bowel imaging (small bowel series or CT scan). In a retrospective study of 56 patients with suspected Crohn's disease, SBCE detected significant lesions in 57.9% of those fulfilling two criteria and 77.8% when 3 or more criteria were met but only in 17.8% of those patients who did not meet the ICCE criteria. Furthermore, Crohn's disease was confirmed during follow-up in 21.4%, 52.6% and 77.8% of those patients, respectively.<sup>287</sup>

### ECCO Statement 11D

The pre-test probability of detecting Crohn's disease by small bowel capsule endoscopy can be enhanced by selection of patients based on additional features beyond symptoms, such as typical extraintestinal manifestations, inflammatory markers and/or faecal calprotectin [EL3] [Voting results: 100% agreement].

## 11.3. SBCE in patients with established Crohn's disease

Cross-sectional imaging with MRE or CTE is usually preferable to SBCE for evaluating the small bowel in patients with established Crohn's disease, because of their potential to identify obstructive strictures, assess the transmural nature



of the disease and its anatomical distribution, as well as the presence of extraluminal disease.<sup>2</sup> The risk of cumulative radiation exposure should be taken into account when selecting the cross-sectional imaging modality.

#### ECCO Statement 11E

Cross sectional imaging with MR enterography or CT enterography is usually preferable to small bowel capsule endoscopy in patients with established Crohn's disease as it can identify obstructive lesions, assess the transmural nature of the disease and its anatomical distribution, as well as the presence of extraluminal disease [EL2] [Voting results: 93% agreement].

In a recent meta-analysis,<sup>257</sup> SBCE was superior to push enteroscopy (PE), SBE/SBFT and CTE in the evaluation of patients with established Crohn's disease, with a significant higher yield (SBCE *versus* PE: 66% *versus* 9% (IY = 57%,  $P < 0.00001$ , 95% CI = 43%–71%), SBCE *versus* SBE/SBFT: 71% *versus* 36% (IY = 38%,  $P < 0.00001$ , 95% CI = 22%–54%), and SBCE *versus* CTE: 71% *versus* 39% (IY = 32%,  $P = < 0.0001$ , 95% CI = 16%–47%). Conversely, SBCE diagnostic yield was inferior to MRE: 70% *versus* 79% (IY of –6%,  $P = 0.65$ , 95% CI = –30% to 19%). However, SBCE may enhance the detection of lesions in the proximal small bowel when compared with both CTE and MRE<sup>258,288</sup> and has been shown to detect proximal lesions in up to >50% of patients with previously diagnosed ileal Crohn's disease.<sup>289</sup> The clinical meaning of this incremental yield, mainly for mild and more proximal lesions in patients with previously established Crohn's disease remains to be determined. Currently the use of SBCE in this setting should be reserved for selected clinical scenarios such as patients with unexplained symptoms,<sup>290</sup> iron deficiency anaemia or obscure GI bleeding,<sup>291</sup> when other investigations are inconclusive. SBCE may also be considered in the assessment of postoperative recurrence in those cases where ileocolonoscopy is contraindicated or unsuccessful.<sup>292,293</sup> The potential role of SBCE in the assessment of mucosal healing after drug therapy has also been investigated<sup>294</sup> using quantitative scores such as the Lewis score<sup>295</sup> or the Niv score<sup>296</sup> for clinical and investigational purposes, which are similar to the existing endoscopic scores for ileocolonoscopy, the CDEIS<sup>225</sup> or SES-CD.<sup>226</sup> Finally, some retrospective studies highlighted the potential impact of SBCE on the therapeutic management of patients with established Crohn's disease,<sup>297–300</sup> although prospective controlled data on this topic are lacking.

#### ECCO Statement 11F

The role of small bowel capsule endoscopy in patients with established Crohn's disease should focus on patients with unexplained iron deficiency or obscure GI bleeding or in those with unexplained symptoms, when other investigations are inconclusive [EL 5] [Voting results: 100% agreement].

## 11.4. Scoring systems for capsule endoscopy in CD

The use of a standardised quantitative scoring system to describe the type, location and severity of small bowel lesions has been proposed.<sup>301</sup> The classic threshold of more than 3 ulcers proposed by Mow et al.,<sup>302</sup> which does not assess the distribution or the severity of the inflammatory activity, or take account of oedema or stenosis, has yielded a positive predictive value of only 50% for the diagnosis of Crohn's disease.<sup>272,303</sup> The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) or Niv score has been recently validated in a multicenter prospective trial.<sup>296,304</sup> This scoring index evaluates three parameters: inflammation (A), extent of disease (B) and presence of strictures (C), both for the proximal and distal segments of the small bowel. The final score is calculated by adding the two segmental scores: CECDAI = proximal ( $[A1 \times B1] + C1$ ) + distal ( $[A2 \times B2] + C2$ )—Table 11.1.

When different types of lesions are identified in the same bowel segment, only the more severe is considered to calculate the score.

Another scoring index, the Lewis score,<sup>295,305</sup> is based on the number and distribution of intestinal segments with villous oedema, ulceration and stenosis. Other endoscopic features such as minor mucosal breaks, erythema, villous atrophy or nodularity do not contribute to the score, because of perceived lack of overall clinical significance and/or inability to be judged objectively, resulting in low inter observer agreement.<sup>295</sup> To calculate the score, the small bowel is first divided into equal thirds (tertiles), according to the transit time of the capsule. For each tertile, a numeric subscore is calculated, considering the extension and distribution of oedema, and the number, size and distribution of ulcers. The final score is the sum of the worst affected tertile *plus* the score of stenosis (single/multiple, ulcerated/not ulcerated, traversed/not traversed by the capsule) (Table 11.2).

An intuitive and user-friendly software application is available for the automatic calculation of this score.<sup>305</sup> The Lewis score allows small bowel inflammatory activity to be

**Table 11.1** Capsule Endoscopy Crohn's Disease Activity Index (adapted from Niv Y et al.<sup>296</sup>).

|  |
|--|
| A. Inflammation score  |
| 0 = None   |
| 1 = Mild to moderate edema/ hyperemia/ denudation                              |
| 2 = Severe edema/ hyperemia/ denudation  |
| 3 = Bleeding, exudate, aphthae, erosion, small ulcer (<0,5 cm)                 |
| 4 = Moderate ulcer (0.5–2 cm), pseudopolyp                                     |
| 5 = Large ulcer (>2 cm)  |
| B. Extent of disease score   |
| 0 = No disease   |
| 1 = Focal disease (single segment)   |
| 2 = Patchy disease (2–3 segments)  |
| 3 = Diffuse disease (more than 3 segments)                                     |
| C. Stricture score   |
| 0 = None   |
| 1 = Single-passed  |
| 2 = Multiple-passed  |
| 3 = Obstruction (non-passage)  |
| CECDAI = proximal ( $[A1 \times B1] + C1$ ) + distal ( $[A2 \times B2] + C2$ ) |

**Table 11.2** Lewis Score (adapted from Gralnek et al.<sup>305</sup>).

| Parameters                                     | Number       | Longitudinal extent | Descriptors      |
|--|--------------|---------------------|------------------|
| Villous appearance<br>(worst-affected tertile) | Normal—0     | Short segment—8     | Single—1         |
|  | Oedematous—1 | Long segment—12     | Patchy—14        |
|  |              | Whole tertile—20    | Diffuse—17       |
| Ulcer<br>(worst-affected tertile)              | None—0       | Short segment—5     | <1/4—9           |
|  | Single—3     | Long segment—10     | 1/4–1/2—12       |
|  | Few—5        | Whole tertile—15    | >1/2—18          |
|  | Multiple—10  |                     |                  |
| Stenosis<br>(whole study)                      | None—0       | Ulcerated—24        | Traversed—7      |
|  | Single—14    | Non-ulcerated—2     | Not traversed—10 |
|  | Multiple—20  |                     |                  |

LEWIS SCORE = Score of the worst affected tertile [(villous parameter × extent × descriptor) + (ulcer number × extent × size)] + Stenosis Score (number × ulcerated × traversed).

Longitudinal extent: Short segment: <10% of the tertile; Long segment: 11% to 50% of the tertile; Whole tertile: >50% of the tertile.

Ulcer number: Single: 1; Few: 2–7; Multiple: ≥8.

Ulcer descriptor (size) is determined by how much of the capsule picture is filled by the largest ulcer.

classified into three grades: 1) normal or clinically insignificant mucosal inflammatory change (LS < 135); 2) mild disease (135 ≤ LS ≤ 790); and 3) moderate to severe disease (LS > 790). In a population of patients with suspected Crohn's disease, the diagnosis was confirmed during the follow-up in 82.6% of those with significant inflammatory activity on SBCE (Lewis score ≥ 135), but in only 12.1% of those with a score lower than 135.<sup>287</sup> However, it is important to recognise that inflammatory activity reported by all the scoring systems independently of its etiology<sup>306</sup> and as such SBCE on its own cannot be used to diagnose Crohn's disease, irrespective of the scores.

### 11.5. SBCE in patients with colonic inflammatory bowel disease type unclassified (IBDU)

In up to 10% of adult patients with IBD affecting the colon, it may be impossible to distinguish between Crohn's disease and ulcerative colitis after ileocolonoscopy and small-bowel imaging<sup>307,308</sup> and therefore SBCE may be important to establish a definite diagnosis in these patients with IBDU.<sup>309–311</sup> SBCE has demonstrated small bowel lesions compatible with Crohn's disease in 17%–70% of patients with IBDU or indeterminate colitis, although their clinical significance may be unclear.<sup>309,310</sup> A negative SBCE cannot definitely exclude a future diagnosis of Crohn's disease.<sup>40,312</sup>

### 11.6. Small bowel and colon capsule endoscopy in patients with Ulcerative Colitis

#### ECCO Statement 11G

To date, there is insufficient data to support the use of small bowel or colon capsule endoscopy in the diagnostic work-up or in the surveillance of patients with Ulcerative Colitis [EL5] [Voting results: 100% agreement].

The diagnosis of Ulcerative Colitis relies on a combination of clinical symptoms, laboratorial evaluation and typical

endoscopic and histopathologic features.<sup>76</sup> However, where there is diagnostic difficulty such as in patients with atypical symptoms, rectal sparing, caecal patch or macroscopic backwash ileitis, SBCE may aid diagnosis.<sup>43</sup> Moreover, SBCE may be useful in the investigation of patients with ulcerative colitis and unexplained iron deficiency anaemia.<sup>313</sup> In a study looking at the value of SBCE in patients undergoing pouch surgery<sup>314</sup> no association was observed between the findings of preoperative SBCE and development of pouchitis or Crohn's disease within the pouch over a 12-month period after IPAA. A further study evaluating the role of preoperative SBCE in 20 patients with ulcerative colitis and IBDU<sup>315</sup> suggested that the presence of small bowel lesions prior to colectomy does not predict the outcome after colectomy.<sup>2</sup>

Colon capsule endoscopy (CCE) was compared with conventional colonoscopy in patients with Ulcerative Colitis. In one study of 10 patients with ulcerative colitis, standard colonoscopy was significantly better in assessing disease activity compared to CCE.<sup>316</sup> Another study enrolled 100 patients suspected or known to have UC.<sup>317</sup> The sensitivity of CCE in detecting active colonic inflammation was 89% and the specificity was 75%, with positive and negative predictive values of CCE for colonic inflammation of 93% and 65%, respectively. The authors concluded that although CCE is a safe procedure to monitor mucosal healing in ulcerative colitis, at this stage it cannot be recommended to replace conventional colonoscopy.

### 11.7. Capsule retention in IBD

#### ECCO Statement 11H

In patients with established Crohn's disease, cross-sectional imaging or patency capsule should be performed when small bowel capsule endoscopy is being considered, in order to identify stenosis that may cause capsule retention [EL2] [Voting results: 100% agreement].

The risk of capsule retention in patients with suspected Crohn's disease without obstructive symptoms and without history of small bowel resection or known stenosis is low and comparable to that of obscure GI bleeding.<sup>318–321</sup> Cheifetz et al.<sup>319</sup> reported a retention rate of 13% in patients with established Crohn's disease, but only 1.6% in patients with suspected Crohn's disease. In this setting, routine small bowel imaging or patency capsule prior to capsule endoscopy is not mandatory. The cost-effectiveness of performing SBCE immediately after ileocolonoscopy or only after small bowel imaging has been investigated, with conflicting results.<sup>322,323</sup>

In patients with established Crohn's disease, the risk of small bowel capsule retention is increased, particularly in those with a history of obstructive symptoms or known intestinal stenosis.<sup>318–321,324</sup> Therefore, cross-sectional imaging or a patency capsule should be performed when SBCE is being considered, to identify stenosis that may cause capsule retention.<sup>325</sup> One retrospective study compared the performance of the patency capsule and radiological examinations to detect clinically significant small bowel strictures.<sup>326</sup> Both methods were equivalent, suggesting that if findings show no stricture or the patency capsule is excreted intact, the patient will most likely pass the regular capsule safely. In the event of capsule retention, it can often be managed conservatively. The capsule may be retrieved by device-assisted enteroscopy<sup>327,328</sup> when conservative measures to enable spontaneous passage fail, and only a minority of patients will warrant surgery to retrieve the capsule.<sup>329,330</sup>

## 12. Device-assisted enteroscopy in IBD

### ECCO Statement 12A

In patients with negative endoscopy and suspicion of Crohn's disease on MRI or small bowel capsule endoscopy, device-assisted enteroscopy may be performed if diagnosis needs to be confirmed endoscopically and histologically [EL 3] [Voting results: 100% agreement].

### ECCO Statement 12B

Device-assisted enteroscopy may be performed in expert hands if endoscopic therapy is indicated, including dilatation of strictures, retrieval of impacted capsule, treatment of bleeding [EL 4] [Voting results: 100% agreement].

In 43–60% of patients with established Crohn's disease and suspected small bowel involvement the lesions couldn't be

assessed by means of conventional endoscopy.<sup>331–335</sup> Diagnostic yield of device assisted enteroscopy (DAE) when evaluating patients with suspected Crohn's disease varies between 22% and 70%.<sup>333,336–338</sup> The diagnostic yield is higher if the indication for DAE was based on one or more previous investigations compared to procedures done without prior examinations (77.8% versus 60% respectively).<sup>338</sup> Prospective trials compared DAE to other imaging modalities such as MRE and SBCE. There was an acceptable correlation of 88–75% and 67% respectively although SBCE was not performed when stenosis was suspected.<sup>339,340</sup> Because of the invasive nature of DAE it should only be performed if it alters therapeutic strategy. Step up therapy in Crohn's disease based on a positive DAE has a proven clinical impact as was demonstrated in a prospective trial.<sup>334,335,341</sup> Small bowel inflammation was demonstrated in 75% of the patients with established Crohn's disease and previous negative conventional endoscopy. In 74% of these patients, treatment was adjusted and resulted in clinical remission at 1 year and a significant decrease in CDAl. In another subgroup, endoscopic reevaluation with DAE demonstrated mucosal healing or improvement in the Index score in 90%<sup>335</sup> of patients. Overall, DAE is safe in the assessment of the small bowel in both the adult and paediatric population with (suspected) Crohn's disease.<sup>333,341</sup> The advantages of DAE compared with SBCE include the evaluation of atypical lesions, the ability to obtain biopsies for histopathology, and the potential for therapeutic intervention. Treatment of Crohn's related strictures in experienced hands is reported to be safe and effective.<sup>205,342</sup> Strictures suitable for dilation are: <4 cm, non-inflammatory and non-angulated. See ECCO statement 8A and accompanying text.

## 13. Endoscopy for dysplasia and CRC detection in IBD

### 13.1. Epidemiology

People with longstanding ulcerative colitis (UC) have a higher risk of developing colorectal cancer (CRC) than the general population. Initial estimates were based on the meta analysis by Eaden et al. of 116 studies including population-based and hospital-based cohorts.<sup>343</sup> They found the overall prevalence of UC-CRC to be 3.7%. In a large Swedish population-based study, Ekblom found a standardised incidence ratio (SIR) of 5.7 (95% CI 4.6–7.0).<sup>344</sup> However the magnitude of risk in recent population-based studies appears smaller than in earlier studies: the more recent Swedish population-based study by Soderlund found a SIR of 2.3 (95% CI 2.0–2.6)<sup>345</sup>; Bernstein's population-based study found increased incidence rate ratios in UC patients of 2.75 (95% CI 1.91–3.97).<sup>346</sup> Two studies showed no difference from the general population: Winther's study from Denmark (where the historical colectomy rate is high compared to the rest of the world) had standardised morbidity ratio no different from the general population (SMR, 1.05; 95% CI, .56–1.79).<sup>347</sup> Jess's study from the USA found a SIR of 1.1 (95% confidence interval [CI], 0.4–2.4).<sup>348</sup> A more recent meta-analysis of population-based cohort

studies determined that UC increases the risk of CRC 2.4-fold.<sup>349</sup>

The reasons for the apparent reduced risk of CRC over time is unclear but may include early study selection bias, improved control of mucosal inflammation, more extensive use of 5-ASA compounds, the implementation of surveillance programmes and timely colectomy.<sup>350</sup> Differences in the proportion of patients with proctitis (as opposed to more extensive disease) may also account for some of the variation in CRC incidence.

The CRC risk appears to be the same in Crohn's colitis given the extent of colonic involvement.<sup>351,352</sup> Ekbohm showed that patients with terminal ileal Crohn's had the same risk of CRC as the general population but those with colonic Crohn's had a relative risk (RR) of 5.6 (95% CI 2.1–12.2).<sup>353</sup> Bernstein's Canadian population-based study found a similar risk for CRC in all patients with Crohn's disease (RR 2.64; 95% CI 1.69–4.12) and UC (RR 2.75; 95% CI 1.91–3.97).<sup>346</sup> They found the risk of rectal cancer to be increased in UC (RR 1.90; 95% CI 1.05–3.43) but not in Crohn's colitis (RR 1.08; 95% CI 0.43–2.70). Soderlund found a SIR of 2.1 (95% CI 1.2–3.4) in Crohn's.<sup>345</sup>

### 13.2. Risk factors

#### ECCO Statement 13A

Patients with longstanding ulcerative colitis and Crohn's colitis have an increased risk of colorectal cancer (CRC) compared to the general population [EL2] [Voting results: 93% agreement].

A longer duration of colitis is associated with an increased risk of IBD-CRC. Older reports included in two meta-analyses confirmed an exponential increase in the risk after ten years of UC<sup>343,354</sup>: Eaden showed a cumulative CRC risk of 2% at 10 years, 8% at 20 years, and 18% after 30 years of disease. The mean duration of colitis at the time of IBD-CRC diagnosis was 16.3 years (95% CI 15.0–17.6).

However more recent population based studies have suggested a much lower risk of IBD-CRC. The annual incidence has been found to be as low as 0.06–0.20% and cumulative risk at 30 years to be as low as 2%.<sup>346,347,355–357</sup>

In the largest report of surveillance colonoscopy in patients with extensive UC, the cumulative incidence of CRC by colitis duration showed a linear rather than exponential increase, from 2.5% at 20 years to 10.8% at 40 years of extensive UC.<sup>358</sup> Rutter found the median duration of UC at diagnosis of CRC was 23.5 years (range 11–48). Lakatos's Hungarian population-based study calculated a cumulative risk of 0.6% after 10 years, 5.4% after 20 years and 7.5% after 30 years.

Although IBD-CRC is comparatively rare before 8 years of colitis, Lutgens calculated that 17–22% of patients developed cancer before the starting points for surveillance

(8–10 years from onset of symptoms for extensive colitis and 15–20 years for left-sided disease).<sup>359</sup>

#### ECCO Statement 13B

Colorectal cancer risk is highest in patients with extensive colitis, intermediate in patients with left-sided colitis, and lowest in proctitis [EL2]. Patients with severe inflammation, patients with colitis-associated primary sclerosing cholangitis (PSC), and patients with a family history of CRC may have a particularly increased risk [EL2] [Voting results: 100% agreement].

Several independent factors affect the magnitude of CRC risk. The colonic extent of mucosal inflammation is the best established and has been correlated with CRC risk in several studies, along with a systematic review.<sup>239,344,345,348,354,356,360</sup> Risk is highest in those with pancolitis: Ekbohm calculated a SIR for CRC of 1.7 for proctitis (non significant), 2.8 for left-sided colitis, and 14.8 for pancolitis, as compared with the general population.<sup>344</sup> Again, more recent population-based studies indicate a lower magnitude of increased risk (SIR 5.6 for pancolitis, 2.1 for Crohn's colitis and 1.7 for proctitis [all significant]).<sup>345</sup> It seems reasonable to assume that patients with Crohn's colitis involving only one segment of colo-rectum should not be considered to be at risk of CRC.<sup>361</sup>

How disease extent is measured is important; earliest studies used radiological evidence (barium enemas), more recent studies have used endoscopic or histological evidence. This may in part explain the apparent differing cancer risk over time.

IBD-CRC is thought to occur in the context of inflammation. Although early studies showed no clear association between colitic symptoms and CRC risk, this may be explained by the recognised poor correlation between patients' symptoms and the severity of inflammation. Recent studies have focused on severity of inflammation at a tissue level. Rutter's case-control study found a significant correlation between both colonoscopic (OR = 2.5; P < 0.001) and histological (OR = 5.1; P < 0.001) inflammation and neoplasia risk.<sup>239</sup> Gupta's cohort study also found a significant relationship between histological inflammation over time and progression to advanced neoplasia (hazard ratio 3.0; 95% CI 1.4–6.3).<sup>362</sup> In a further study, Rutter found that mucosal healing may decrease neoplasia risk: macroscopically normal mucosa appears to return the CRC risk to that of the general population.<sup>237</sup>

Post-inflammatory polyps (PIPs) develop during the healing phase of severe inflammation. Their presence has been associated with an increased risk of CRC in two case control studies, probably reflecting the increased risk of previous severe inflammation rather than themselves having malignant potential. Rutter found that cases of CRC were significantly more likely to have PIPs than the controls (OR 2.14; 95% CI 1.24–3.70).<sup>237</sup> Velayos showed the presence of PIPs was associated with double the CRC risk (OR 2.5; 95% CI: 1.4–4.6).<sup>363</sup>

PSC appears to be an independent risk factor for IBD-CRC. Soetikno's meta-analysis of 11 studies concluded that patients with UC-PSC were at increased risk of CRC compared with patients with UC alone (OR 4.09; 95% CI 2.89–5.76).<sup>364</sup> Cancers often occur earlier in a patient's disease; one explanation is that patients with PSC often have milder colonic inflammation and may have had subclinical inflammation for years before colitis diagnosis, however one would also expect the milder inflammation to confer a relatively low risk. Other hypotheses for the increased risk include shared genetic susceptibility to PSC and CRC, and the effect of an altered bile salt pool.

Family history of CRC contributes to the risk of CRC in patients with colitis. Both case control and population-based studies show a 2–3 fold increase.<sup>365</sup> Askling found that a family history of CRC was associated with a 2.5 fold RR of IBD-CRC (95% CI 1.4–4.4) and those with a 1st-degree relative diagnosed with CRC before 50 years of age had a higher risk (RR 9.2; 95% CI 3.7–23).<sup>366</sup> Velayos also found family history of CRC to be an independent risk factor for IBD-CRC in patients with UC (OR 3.7; 95% CI 1.0–13.2).<sup>363</sup>

Young age at diagnosis may be an independent risk factor for IBD-CRC,<sup>349</sup> although data are inconsistent. Interpretation of retrospective studies is complex as children tend to have more extensive and more severe colitis, and those diagnosed at a young age have the potential for longer colitis duration,<sup>367</sup> itself a risk factor. Ekblom found age at diagnosis to be an independent risk factor for CRC.<sup>344</sup> After adjusting for the extent of disease an adjusted SIR of 0.51 was seen for each increase in age group at diagnosis. Other studies have not confirmed this association. In Rutter's 30 year study, patients who developed CRC had a higher median age of onset of disease than those not developing cancer.<sup>358</sup> Greenstein et al. found that the CRC risk was higher in patients diagnosed with IBD above 30–40 years of age compared with those diagnosed below 20 years old.<sup>368</sup> In Eaden's meta-analysis, in adult patients a negative trend (non-significant) between younger age at onset and increased risk of CRC was seen.<sup>343</sup> In children, the cumulative risk of CRC over time was higher than the corresponding rates for adults. Winther found the time between onset of colitis and the development of IBD-CRC to be the same in young and old patients.<sup>347</sup> Karvellas found that patients diagnosed with UC over the age of 40 years developed CRC more quickly than younger patients.<sup>369</sup>

### 13.3. Endoscopy in surveillance

#### ECCO Statement 13C

Surveillance colonoscopy permits detection of dysplasia and earlier detection of CRC, which may lead to improved prognosis [EL4] [Voting results: 100% agreement].

#### 13.3.1. Benefit of surveillance

Surveillance colonoscopy programmes aim to reduce morbidity and mortality due to CRC by detecting cancer at an

earlier stage with better prognosis or by detecting and resecting dysplasia, reducing CRC incidence.

The reduced CRC incidence seen in recent studies may be evidence that surveillance is effective although other potential factors including better disease control may be relevant. The effectiveness of surveillance has been systematically reviewed by the Cochrane collaboration.<sup>354</sup> Limiting their analysis to studies that included a control group, the authors were unable to demonstrate a benefit of surveillance programmes for preventing CRC-related death in UC. However only two studies met their inclusion criteria.<sup>370,371</sup> Lutgen's larger and more recent study showed improved survival from colonoscopic surveillance in IBD patients by detecting CRC at a more favourable tumour stage: 5-year CRC-related survival rate of patients in the surveillance group was 100% compared with 74% in the non-surveillance group (P = 0.042).<sup>372</sup> In the surveillance group, one patient died as a consequence of CRC compared with 29 patients in the control group (P = 0.047). In addition, more early tumour stages were found in the surveillance group (P = 0.004).

Three retrospective case control studies have shown a correlation between the use of surveillance colonoscopy and reduced odds ratio for CRC.<sup>363,373,374</sup> All these studies could be subject to lead-time or selection bias; thus in the absence of a prospective randomised controlled trial, unequivocal evidence for the benefit of these programmes is lacking.

Benefit estimated in years of life saved may be much greater in colitis patients than for general population screening because IBD-CRC tends to occur earlier in life and modelling has evaluated that life saved per case screened ranges from 1.2 to 5 years in UC patients, compared to 1.2 to 4 months in general population screening.<sup>354,375</sup> These issues should be discussed with patients before surveillance commences.

#### 13.3.2. Timing and interval of endoscopic surveillance

#### ECCO Statement 13D

Screening colonoscopy should be offered at estimated 8 years after the onset of colitic symptoms to all patients to reassess disease extent [EL5] [Voting results: 100% agreement].

As duration of disease is a major risk factor for the development of IBD-CRC, it is rational to propose a screening colonoscopy when the risk starts to increase, i.e. after 8–10 years from the onset of disease.<sup>343</sup> This initial colonoscopy also aims to reassess the extent of disease, since this parameter also impacts on the risk of CRC. Nevertheless, the appropriateness of screening colonoscopy as a way of reassessing disease extent and potential risk has not been formally established. It has been proposed in reviews and a prior consensus report,<sup>376</sup> as well as being

agreed during the present consensus conference by the participating experts.

#### ECCO Statement 13E

Ongoing surveillance should be performed in all patients apart from those with proctitis or Crohn's colitis involving only one segment of colorectum [EL4] [Voting results: 100% agreement].

As there is no clear evidence for surveillance intervals, individualising intervals based on risk stratification is recommended [EL5] [Voting results: 100% agreement].

- a) Patients with high risk features (stricture or dysplasia detected within the past 5 years, PSC, extensive colitis with severe active inflammation, or a family history of CRC in a first degree relative at less than 50 years) should have next surveillance colonoscopy scheduled for 1 year [EL4] [Voting results: 93% agreement];
- b) Patients with intermediate risk factors should have their next surveillance colonoscopy 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 CRC in a first degree relative at 50 years and above [EL5] [Voting results: 100% agreement];
- c) Patients with neither intermediate nor high risk features should have their next surveillance colonoscopy scheduled for 5 years [EL4] [Voting results: 93% agreement].

The surveillance schedule should take into account the risk for dysplasia to progress to CRC between two surveillance interventions. However, the timing of dysplasia progression is not known in IBD. Therefore, intervals between repeat surveillance colonoscopy should be prospectively adjusted to each patient according to CRC risk factors and previous colonoscopic findings.<sup>377</sup> Disease extent should be taken as the most extensive histologically-confirmed inflammation from all previous colonoscopies.

There is consistent evidence that individuals who have had high-grade dysplasia (HGD) are at increased risk of CRC.<sup>358,378</sup> The data for low-grade dysplasia (LGD) are less consistent: although most studies show an increased CRC risk, some do not.<sup>379–383</sup> In a recent meta-analysis, LGD was found to be associated with a 12-fold risk of developing advanced neoplasia and a 9-fold increased risk of developing CRC.<sup>384</sup> Thus it seems appropriate that all patients with dysplasia (within the past 5 years) irrespective of grade, should undergo annual colonoscopic surveillance. Since CRC has been observed within 2 years of surveillance colonoscopy, yearly colonoscopy is recommended in patients with high risk features.<sup>383,385</sup> Five-yearly colonoscopy is recommended for patients with extensive colitis with no other risk factor.<sup>237,377</sup> Two to three-yearly colonoscopy is recommended in patients with

intermediate risk.<sup>377</sup> Wherever possible, surveillance colonoscopies should be performed during disease remission to aid discrimination between inflammatory and neoplastic changes. However, surveillance should not be delayed in those with chronic active colitis as these patients have a higher neoplasia risk.<sup>239,362</sup>

#### 13.3.3. Strategies to optimise surveillance

#### ECCO Statement 13F

Effective bowel preparation, meticulous inspection during slow withdrawal and the use of high resolution endoscopic equipment are preferred for optimal neoplasia detection [EL4] [Voting results: 100% agreement].

In recent years, endoscopic equipment, patient preparation and diagnostic technique have advanced considerably. High resolution equipment improves image quality and these instruments may improve dysplasia detection rate. A recent colitis surveillance study showed that high definition colonoscopy improved dysplasia detection compared to standard definition.<sup>386</sup> Achieving optimal colonic preparation is needed for chromoendoscopy and longer withdrawal time yields higher adenoma detection rates in non-IBD patients.<sup>387</sup> In addition longer procedure duration may be associated with increased dysplasia detection<sup>388</sup>.

#### ECCO Statement 13G

Pan-colonic methylene blue or indigo carmine chromoendoscopy should be performed during surveillance colonoscopy, with targeted biopsies of any visible lesion [EL2].

If appropriate expertise for chromoendoscopy is not available, random biopsies (4 every 10 cm) should be performed [EL3]; however this is inferior to chromoendoscopy in the detection rate of neoplastic lesions [EL2] [Voting results: 100% agreement].

The dysplasia yield from surveillance colonoscopy can be improved by spraying dyes that highlight subtle changes in the architecture of the colonic mucosa.<sup>389–395</sup> This holds true for all dysplastic lesions, the proportion of targeted lesions and the proportion of flat lesions detected.

With this method, random biopsies of apparently normal mucosa are of negligible additional value.<sup>394,396</sup> Comparable diagnostic yields from chromoendoscopy have been obtained with both methylene blue and indigo carmine.<sup>389–395</sup>

A meta-analysis including six studies (1277 patients) showed that the difference in dysplasia yield between

chromoendoscopy and white light endoscopy (WLE) was 7% (95% CI 3.2–11.3) on a per patient analysis (NNT 14.3).<sup>397</sup> 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) in favour of chromoendoscopy. Chromoendoscopy also aids discrimination between neoplastic and non-neoplastic changes, based on the surface crypt architecture (pit pattern). Another meta-analysis looked at the diagnostic accuracy of chromoendoscopy compared to histology and reports a sensitivity of 83.3% and specificity 91.3% for chromoendoscopy in detection of intraepithelial neoplasia.<sup>398</sup>

Although chromoendoscopy takes significantly longer than conventional colonoscopy,<sup>398</sup> it not only improves the dysplasia yield but has potential to reduce pathology workload as fewer biopsies are needed.

#### ECCO Statement 13H

Other image enhancement techniques such as narrow band imaging or autofluorescence have not been convincingly demonstrated to be superior to white light endoscopy or chromoendoscopy in the detection of neoplastic lesions, thus they cannot currently be recommended for colitis surveillance [EL2] [Voting results: 93% agreement].

Narrow band imaging (NBI) is a technology which highlights vessel and crypt architecture by altering the light which is emitted to the mucosa. None of the three randomised trials using first generation<sup>399</sup> and second generation<sup>400,401</sup> endoscopes (including high resolution) which analysed the value of NBI compared to WLE<sup>399–401</sup> identified any benefit for NBI detecting colitis associated dysplasia. NBI was also unsatisfactory for differentiating neoplastic from non-neoplastic mucosa. A single cross-over prospective randomised trial comparing narrow-band imaging with chromoendoscopy could not identify a clear benefit for NBI.<sup>402</sup>

A prospective randomised trial analysing the value of Endoscopic tri-modal imaging (ETMI), which incorporates WLE, NBI and autofluorescence imaging (AFI)<sup>403</sup> suggested ETMI was superior to WLE, but further studies are still awaited to confirm this single study.

Endomicroscopy is an emerging technology which provides in vivo histology during ongoing colonoscopy. The technique requires the additional use of contrast agents. Fluorescein-based endomicroscopy is mainly used and proved to be safe and highly accurate analysing intraepithelial neoplasia.<sup>404</sup> Two prospective and randomised trials have evaluated the value of endomicroscopy in addition to chromoendoscopy.<sup>391,405</sup> Here endomicroscopy was able to significantly reduce the number of biopsies while retaining the diagnostic yield of chromoendoscopy.

Endomicroscopy cannot widely screen the colonic mucosa. It is mainly used to analyse colorectal lesions once they have been detected and thus reduces the amount of biopsies.

Endomicroscopy is highly examiner dependent and time consuming and cannot be broadly recommended. Nevertheless endomicroscopy has future potential because it allows functional and molecular imaging.

### 13.4. Diagnosis of dysplasia

#### ECCO Statement 13J

A finding of dysplasia should be confirmed by an independent gastrointestinal specialist pathologist [EL2] [Voting results: 100% agreement].

The grade of dysplasia is important because it impacts on the sensitivity and specificity of the presence or future development of CRC. However histopathological analysis is a qualitative test and interobserver variation for the grading of dysplasia is high, particularly for LGD and where there is background inflammation.<sup>383,406,407</sup> Individual studies do not show an increased risk of malignant transformation in LGD<sup>379,380</sup> or an even higher risk.<sup>408,409</sup> However, in a recent meta-analysis, LGD was found to be associated with a 12-fold risk of developing advanced neoplasia and a 9-fold increased risk of developing CRC.<sup>384</sup> For this reason, dysplasia should be confirmed by an experienced gastrointestinal specialist pathologist.

#### ECCO Statement 13K

A visible lesion with dysplasia should be completely resected by an experienced endoscopist, irrespective of the grade of dysplasia or the localisation relative to the inflamed mucosal areas. In the absence of dysplasia in the surrounding mucosa, ongoing meticulous colonoscopic surveillance is appropriate [EL1]. If endoscopic resection is not possible or if dysplasia is found in the surrounding flat mucosa, proctocolectomy should be recommended [EL4] [Voting results: 100% agreement].

Most dysplasia is visible at colonoscopy,<sup>410–412</sup> even with standard resolution endoscopes. Raised dysplastic lesions on a background of colitis (formerly referred to as DALMs) have until recently been considered an indication for colectomy. In the context of colitis surveillance, the term “flat lesion” has traditionally been used for endoscopically invisible dysplastic lesions diagnosed by random biopsies. Both these terms are confusing and should be abandoned, especially as the term “flat” now has an entirely different endoscopic definition (Paris endoscopic classification).<sup>413</sup> It is preferable to use the terms endoscopically visible and non-visible lesions, since it is increasingly recognised that well-circumscribed visible lesions may be amenable to

complete endoscopic resection<sup>410,414–418</sup> regardless of their location within or outside areas of documented UC and irrespective of the presence of LGD or HGD. This applies also for sporadic adenomas in the context of colitis.<sup>419</sup> If the polypectomy is confirmed complete by histology, biopsies obtained from the flat mucosa immediately adjacent to the polypectomy site show no dysplasia and no dysplasia is found elsewhere in the colon, a careful colonoscopic follow-up preferably with chromoendoscopy at 3 months before reverting to annual surveillance is recommended, because at least half of such patients may develop further lesions.<sup>415–417</sup> However, the risk of developing cancer has not been found to be elevated under careful surveillance,<sup>410,414,416,417,419–421</sup> as confirmed in a recent meta-analysis.<sup>422</sup> If the lesion is not resectable, or is associated with dysplasia in the adjacent mucosa, then colectomy is indicated due to the high risk of concomitant CRC.<sup>410,423</sup>

#### ECCO Statement 13L

Where dysplasia of any grade is found without an associated endoscopically visible lesion, urgent repeat chromoendoscopy should be performed by an experienced endoscopist to determine whether a well-circumscribed lesion exists and to assess for synchronous dysplasia [EL5] [Voting results: 100% agreement]. Adenocarcinoma or HGD without an associated endoscopically visible lesion are indications for surgery [EL3] [Voting results: 100% agreement]. A patient with confirmed LGD detected in mucosa without an associated endoscopically visible lesion should undergo repeat chromoendoscopic colonoscopy with additional random biopsies within 3 months [EL5] [Voting results: 93% agreement].

Once dysplasia is found and cannot be treated endoscopically proctocolectomy should be performed because the risk of CRC is appreciably increased<sup>384</sup> assuming that the biopsies were indeed random biopsies and not targeted biopsies. If LGD is detected, the 9-fold increased risk of developing CRC reported in the most recent meta-analysis<sup>384</sup> may be reasonably be viewed as justification for proctocolectomy as well.<sup>378</sup> However, because some follow-up studies of patients with LGD have shown a low rate of CRC development,<sup>379,380,383</sup> it seems a reasonable alternative to continue intensified colonoscopic surveillance in those who will adhere strictly to the surveillance programme. However, as this remains controversial in the literature<sup>354,379,409</sup> to offer definitive guidance, we recommend multidisciplinary team discussion and also detailed discussion with the patient. When electing for surveillance, we recommend an additional chromoendoscopic procedure to check the resected site and to double-check the remaining colon at around 3 months; in this instance (and for this procedure alone), extensive random biopsy sampling may be prudent.

### 13.5. Pouch surveillance

#### ECCO Statement 13M

Following proctocolectomy, patients with any of the following features are at increased risk of developing rectal cuff or pouch neoplasia [EL3]:

- Previous dysplasia or cancer
- PSC
- Type C mucosa of pouch (persistent atrophy & severe inflammation)

[Voting results: 100% agreement].

Dysplasia following restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is rare but can develop in either the ileal pouch mucosa or any retained anorectal mucosa (the 'anal transition zone'). Cancers reported in the literature occurred over 10 years after the onset of UC.<sup>424</sup> Dysplasia risk factors include previous dysplasia or CRC, longer rectal cuff and PSC.<sup>425,426</sup> Type C pouch mucosa (permanent persistent atrophic mucosa with severe inflammation) has a greater tendency to develop colonic type metaplasia<sup>427,428</sup> and thus both type C mucosa and refractory pouchitis are associated with a higher risk of neoplasia although the absolute risk remains small.<sup>429</sup> The occurrence of neoplasia is extremely rare in the absence of these risk factors.<sup>430</sup> So far no clear evidence that pouch surveillance is beneficial. However if a clinician wishes to offer surveillance, annual pouch surveillance by flexible sigmoidoscopy, taking four proximal and four distal pouch biopsies, would seem reasonable<sup>377</sup> in those with high risk features and every 5 years in those without high risk features.<sup>377</sup>

### Contributors—members of the working parties

#### Diagnosis

Vito Annese (IT), chair  
 Konstantinos H Katsanos (GR)  
 Alessandro Repici (IT)  
 Shaji Sebastian (UK)  
 Endoscopic activity  
 Marco Daperno (IT), chair  
 James East (UK)  
 Marc Ferrante (BE)  
 Ingrid Ordás (ESP)  
 Small bowel endoscopy  
 Rami Eliakim (IS), chair  
 Peter Bossuyt (BE)  
 Torsten Kucharzik (DE)  
 Bruno Rosa (PT)  
 Surveillance  
 Matthew D Rutter (UK), chair  
 Aurelien Amiot (FR)



Martin Götz (DE)  
Ralf Kießlich (DE)

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The following ECCO National Representatives participated in the review process of this consensus: Austria: Gottfried Novacek; Czech Republic: Martin Bortlik, Tomas Douda; Denmark: Jens F. Dahlerup; Finland: Pia Manninen; Germany: Andreas Sturm; Greece: Ioannis Karagiannis; Hungary: Peter Lakatos, Tamas Molnar; Israel: Selwyn Odes; Italy: Anna Kohn, Paolo Gionchetti; Latvia: Juris Pokrotnieks; Norway: Ingrid Prytz Berset; Poland: Edyta Zagorowicz; Romania: Mihai Mircea Diculescu, Adrian Goldis; Russia: Alexander Potapov; Serbia: Njegica Jojic; Spain: Francesc Casellas Jorda; Sweden: Hans Strid; Switzerland: Frank Seibold; Turkey: Aykut Ferhat Celik; UK: Peter Irving.

In addition the following ECCO members, having applied to the consensus, but not included in the working groups, also participated to the revision of statements: Australia: Lawrence Ian; Belgium: Moreels Tom; Croatia: Ivekovic Hrovje, Banić, Marko; Germany: Bokemeyer Bernd; Greece: Mantzaris Gerassimos; Italy: Fiorino Gionata, Papa Alfredo, Pellino, Gianluca; Spain: González Suárez Begoña, Ukraine: Golovchenko Oleksandr; United Kingdom: Beale Amanda. This document has been read and approved by the ECCO Governing Board.

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