



CONSENSUS/GUIDELINES

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

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**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 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 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 Subjective interpretation of friability and bleeding 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 Subjective interpretation	Not defined
Sutherland Index <sup>214</sup>	Friability, exudation, spontaneous haemorrhage	–	Do not evaluate ulcers 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 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 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 Developed following rigorous methodology 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 Developed and validated following rigorous methodology 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: Well known and widely accepted, easy and suitable for routine practice, relevant prognostic value Weaknesses: 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: Validated and used in several trials, sensitive to variations in endoscopic activity, allows comparison of different endoscopic examination, prognostic relevance demonstrated Weaknesses: 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: 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 Weaknesses: 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) Present (12 points)		
		Superficial ulcers (in all explored segments)	Absent (0 points) 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) Present (3 points)		
		Non-ulcerated stenosis (anywhere)	Absent (0 points) Present (3 points)		
		SES-CD	Luminal CD	Ulcers (in all explored segments)	Absent (0 points) Aphthous ulcers, 0.1–0.5 cm (1 point) Large ulcers, 0.5–2 cm (2 points) Very large ulcers, >2 cm (3 points)
				Ulcerated surface (in all explored segments)	None (0 points) <10% of the segment (1 point) 10–30% of the segment (2 points) >30% of the segment (3 points)
Affected surface (in all explored segments)	None (0 points) <50% of the segment (1 point) 50–75% of the segment (2 points) >75% of the segment (3 points)				
Narrowings (in all explored segments)	None (0 points) Single, passable by endoscope (1 point) Multiple, passable by endoscope (2 points) 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 (worst-affected tertile)	Normal—0	Short segment—8	Single—1
	Oedematous—1	Long segment—12	Patchy—14
		Whole tertile—20	Diffuse—17
Ulcer (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 (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, Ekbohm 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>

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## References

1. Leighton JA, Shen B, Baron TH, Adler DG, Davila R, Egan JV, et al. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointest Endosc* 2006;**63**:558–65.
2. Bourreille A, Ignjatovic A, Aabakken L, Loftus Jr EV, Eliakim R, Pennazio M, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009;**41**:618–37.
3. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. *Am J Public Health* 1984;**74**:979–83.
4. [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).
5. Manes G, Imbesi V, Ardizzone S, Cassinotti A, Bosani M, Massari A, et al. Appropriateness and diagnostic yield of colonoscopy in the management of patients with ulcerative colitis: a prospective study in an open access endoscopy service. *Inflamm Bowel Dis* 2008;**14**:1133–8.
6. Markowitz J, Kahn E, Grancher K, Hyams J, Treem W, Daum F. Atypical rectosigmoid histology in children with newly diagnosed ulcerative colitis. *Am J Gastroenterol* 1993;**88**:2034–7.
7. Robert ME, Skacel M, Ullman T, Bernstein CN, Easley K, Goldblum JR. Patterns of colonic involvement at initial presentation in ulcerative colitis: a retrospective study of 46 newly diagnosed cases. *Am J Clin Pathol* 2004;**122**:94–9.
8. Robert ME, Tang L, Hao LM, Reyes-Mugica M. Patterns of inflammation in mucosal biopsies of ulcerative colitis: perceived differences in pediatric populations are limited to children younger than 10 years. *Am J Surg Pathol* 2004;**28**:183–9.
9. Rajwal SR, Puntis JW, McClean P, Davison SM, Newell SJ, Sugarman I, et al. Endoscopic rectal sparing in children with untreated ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2004;**38**:66–9.
10. Odze R, Antonioli D, Peppercorn M, Goldman H. Effect of topical 5-aminosalicylic acid (5-ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. *Am J Surg Pathol* 1993;**17**:869–75.
11. D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study. *Am J Gastroenterol* 1997;**92**:1275–9.
12. Mutinga ML, Odze RD, Wang HH, Hornick JL, Farraye FA. The clinical significance of right-sided colonic inflammation in patients with left-sided chronic ulcerative colitis. *Inflamm Bowel Dis* 2004;**10**:215–9.
13. Kim B, Barnett JL, Kleer CG, Appelman HD. Endoscopic and histological patchiness in treated ulcerative colitis. *Am J Gastroenterol* 1999;**94**:3258–62.
14. Byeon JS, Yang SK, Myung SJ, Pyo SI, Park HJ, Kim YM, et al. Clinical course of distal ulcerative colitis in relation to appendiceal orifice inflammation status. *Inflamm Bowel Dis* 2005;**11**:366–71.
15. Ladefoged K, Munck LK, Jorgensen F, Engel P. Skip inflammation of the appendiceal orifice: a prospective endoscopic study. *Scand J Gastroenterol* 2005;**40**:1192–6.
16. Yang SK, Jung HY, Kang GH, Kim YM, Myung SJ, Shim KN, et al. Appendiceal orifice inflammation as a skip lesion in ulcerative colitis: an analysis in relation to medical therapy and disease extent. *Gastrointest Endosc* 1999;**49**:743–7.
17. Matsumoto T, Nakamura S, Shimizu M, Iida M. Significance of appendiceal involvement in patients with ulcerative colitis. *Gastrointest Endosc* 2002;**55**:180–5.
18. Haskell H, Andrews Jr CW, Reddy SI, Dendrinos K, Farraye FA, Stucchi AF, et al. Pathologic features and clinical significance of “backwash” ileitis in ulcerative colitis. *Am J Surg Pathol* 2005;**29**:1472–81.
19. Goldstein N, Dulai M. Contemporary morphologic definition of backwash ileitis in ulcerative colitis and features that distinguish it from Crohn disease. *Am J Clin Pathol* 2006;**126**:365–76.
20. Abdelrazeq AS, Wilson TR, Leitch DL, Lund JN, Leveson SH. Ileitis in ulcerative colitis: is it a backwash? *Dis Colon Rectum* 2005;**48**:2038–46.
21. Geboes K, Ectors N, D'Haens G, Rutgeerts P. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease? *Am J Gastroenterol* 1998;**93**:201–6.
22. Van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *J Crohns Colitis* 2010;**4**:7–27.
23. Navaneethan U, Parasa S, Venkatesh PG, Trikudanathan G, Shen B. Prevalence and risk factors for colonic perforation during colonoscopy in hospitalized inflammatory bowel disease patients. *J Crohns Colitis* 2011;**5**:189–95.
24. Navaneethan U, Kochhar G, Phull H, Venkatesh PG, Remzi FH, Kiran RP, et al. Severe disease on endoscopy and steroid use increase the risk for bowel perforation during colonoscopy in inflammatory bowel disease patients. *J Crohns Colitis* 2012;**6**:470–5.

25. Buisson A, Chevaux JB, Hudziak H, Bresler L, Bigard MA, Peyrin-Biroulet L. Colonoscopic perforations in inflammatory bowel disease: a retrospective study in a French referral centre. *Dig Liver Dis* 2013;45:569–72.
26. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;17:1314–21.
27. Castellaneta SP, Afzal NA, Greenberg M, Deere H, Davies S, Murch SH, et al. Diagnostic role of upper gastrointestinal endoscopy in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2004;39:257–61.
28. Crocco S, Martellosi S, Giurici N, Villanacci V, Ventura A. Upper gastrointestinal involvement in paediatric onset Crohn's disease: prevalence and clinical implications. *J Crohns Colitis* 2012;6:51–5.
29. Annunziata ML, Caviglia R, Papparella LG, Cicala M. Upper gastrointestinal involvement of Crohn's disease: a prospective study on the role of upper endoscopy in the diagnostic work-up. *Dig Dis Sci* 2012;57:1618–23.
30. Rutgeerts P, Onette E, Vantrappen G, Geboes K, Broeckaert L, Talloen L. Crohn's disease of the stomach and duodenum: a clinical study with emphasis on the value of endoscopy and endoscopic biopsies. *Endoscopy* 1980;12:288–94.
31. Turner D, Griffiths AM. Esophageal, gastric, and duodenal manifestations of IBD and the role of upper endoscopy in IBD diagnosis. *Curr Gastroenterol Rep* 2007;9:475–8.
32. Casella G, D'Inca R, Oliva L, Daperno M, Saladino V, Zoli G, et al. Prevalence of celiac disease in inflammatory bowel diseases: an IG-IBD multicentre study. *Dig Liver Dis* 2010;42:175–8.
33. Altschuler A, Collins B, Lewis JD, Velayos F, Allison JE, Hutfless S, et al. Gastroenterologists' attitudes and self-reported practices regarding inflammatory bowel disease. *Inflamm Bowel Dis* 2008;14:992–9.
34. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012;61:535–42.
35. Thia KT, Loftus Jr EV, Pardi DS, Kane SV, Faubion WA, Tremaine WJ, et al. Measurement of disease activity in ulcerative colitis: interobserver agreement and predictors of severity. *Inflamm Bowel Dis* 2011;17:1257–64.
36. Feagan BG, Greenberg GR, Wild G, Fedorak RN, Pare P, McDonald JW, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med* 2005;352:2499–507.
37. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Reliability and initial validation of the Ulcerative Colitis Endoscopic Index of Severity. *Gastroenterology* Jul 25 2013 <http://dx.doi.org/10.1053/j.gastro.2013.07.024> pii: S0016-5085(13)01075-5 (Epub ahead of print).
38. Dillon M, Brown S, Casey W, Walsh D, Durnin M, Abubaker K, et al. Colonoscopy under general anesthesia in children. *Pediatrics* 1998;102:381–3.
39. Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, et al. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013;7:827–51.
40. Henriksen M, Jahnsen J, Lygren I, Sauar J, Schulz T, Stray N, et al. Change of diagnosis during the first five years after onset of inflammatory bowel disease: results of a prospective follow-up study (the IBSEN Study). *Scand J Gastroenterol* 2006;41:1037–43.
41. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19(Suppl A):5–36.
42. Meucci G, Bortoli A, Riccioli FA, Girelli CM, Radaelli F, Rivolta R, et al. Frequency and clinical evolution of indeterminate colitis: a retrospective multi-centre study in northern Italy. GSMII (Gruppo di Studio per le Malattie Infiammatorie Intestinali). *Eur J Gastroenterol Hepatol* 1999;11:909–13.
43. Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012;6:965–90.
44. Jarnerot G. How to judge the response to treatment in ulcerative colitis? *Inflamm Bowel Dis* 2008;14(Suppl 2):S222–3.
45. Rutgeerts P, Vermeire S, Van Assche G. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? *Gut* 2007;56:453–5.
46. Lopez-Palacios N, Mendoza JL, Taxonera C, Lana R, Lopez-Jamar JM, Diaz-Rubio M. Mucosal healing for predicting clinical outcome in patients with ulcerative colitis using thiopurines in monotherapy. *Eur J Intern Med* 2011;22:621–5.
47. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011;141:1194–201.
48. Peyrin-Biroulet L, Ferrante M, Magro F, Campbell S, Franchimont D, Fidder H, et al. Results from the 2nd Scientific Workshop of the ECCO I: impact of mucosal healing on the course of inflammatory bowel disease. *J Crohns Colitis* 2011;5:477–83.
49. Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;142(1102-1111): e1102.
50. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. *Clin Gastroenterol Hepatol* 2005;3:11–24.
51. Sipponen T, Savilahti E, Karkkainen P, Kolho KL, Nuutinen H, Turunen U, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflamm Bowel Dis* 2008;14:1392–8.
52. Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008;14:40–6.
53. af Bjorkesten CG, Nieminen U, Turunen U, Arkkila P, Sipponen T, Farkkila M. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. *Scand J Gastroenterol* 2012;47:528–37.
54. D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;18:2218–24.
55. Gisbert JP, Bermejo F, Perez-Calle JL, Taxonera C, Vera I, McNicholl AG, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. *Inflamm Bowel Dis* 2009;15:1190–8.
56. Schoepfer AM, Beglinger C, Straumann A, Trummel M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009;15:1851–8.
57. Meucci G, Fasoli R, Saibeni S, Valpiani D, Gullotta R, Colombo E, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. *Inflamm Bowel Dis* 2012;18:1006–10.

58. Thakkar K, Lucia CJ, Ferry GD, McDuffie A, Watson K, Tsou M, et al. Repeat endoscopy affects patient management in pediatric inflammatory bowel disease. *Am J Gastroenterol* 2009;**104**:722–7.
59. Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984;**25**:665–72.
60. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956–63.
61. Amiot A, Gornet JM, Baudry C, Munoz-Bongrand N, Auger M, Simon M, et al. Crohn's disease recurrence after total proctocolectomy with definitive ileostomy. *Dig Liver Dis* 2011;**43**:698–702.
62. Kurer MA, Stamou KM, Wilson TR, Bradford IM, Leveson SH. Early symptomatic recurrence after intestinal resection in Crohn's disease is unpredictable. *Colorectal Dis* 2007;**9**:567–71.
63. Leal-Valdivieso C, Marin I, Manosa M, Naves JE, Zabana Y, Pinol M, et al. Should we monitor Crohn's disease patients for postoperative recurrence after permanent ileostomy? *Inflamm Bowel Dis* 2012;**18**:E196.
64. Cappell MS. Risks versus benefits of gastrointestinal endoscopy during pregnancy. *Nat Rev Gastroenterol Hepatol* 2011;**8**:610–34.
65. Nikolaus S, Schreiber S. Diagnostics of inflammatory bowel disease. *Gastroenterology* 2007;**133**:1670–89.
66. Simpson P, Papadakis KA. Endoscopic evaluation of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2008;**14**:1287–97.
67. Shen B. Endoscopic, imaging and histologic evaluation of Crohn's disease and ulcerative colitis. *Am J Gastroenterol* 2007;**102**:S41–5.
68. Stange EF, Travis SP, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, et al. European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. *J Crohns Colitis* 2008;**2**:1–23.
69. Bousvaros A, Antonioli DA, Colletti RB, Dubinsky MC, Glickman JN, Gold BD, et al. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr* 2007;**44**:653–74.
70. Ben-Horin S, Margalit M, Bossuyt P, Maul J, Shapira Y, Bojic D, et al. Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection. *J Crohns Colitis* 2010;**4**:194–8.
71. Shanahan F, Targan S, Anton P, Duerr R. Colonoscopy during an attack of severe ulcerative colitis. *Am J Gastroenterol* 1991;**86**:1278.
72. Oberhuber G, Puspok A, Oesterreicher C, Novacek G, Zauner C, Burghuber M, et al. Focally enhanced gastritis: a frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997;**112**:698–706.
73. Sharif F, McDermott M, Dillon M, Drumm B, Rowland M, Imrie C, et al. Focally enhanced gastritis in children with Crohn's disease and ulcerative colitis. *Am J Gastroenterol* 2002;**97**:1415–20.
74. Valdez R, Appelman HD, Bronner MP, Greenson JK. Diffuse duodenitis associated with ulcerative colitis. *Am J Surg Pathol* 2000;**24**:1407–13.
75. Chutkan RK, Scherl E, Wayne JD. Colonoscopy in inflammatory bowel disease. *Gastrointest Endosc Clin N Am* 2002;**12**:463–83 [viii].
76. Pera A, Bellando P, Caldera D, Ponti V, Astegiano M, Barletti C, et al. Colonoscopy in inflammatory bowel disease: diagnostic accuracy and proposal of an endoscopic score. *Gastroenterology* 1987;**92**:181–5.
77. Tedesco FJ, Hardin RD, Harper RN, Edwards BH. Infectious colitis endoscopically simulating inflammatory bowel disease: a prospective evaluation. *Gastrointest Endosc* 1983;**29**:195–7.
78. Rameshshanker R, Arebi N. Endoscopy in inflammatory bowel disease when and why. *World J Gastrointest Endosc* 2012;**4**:201–11.
79. Wilcox CM, Chalasani N, Lazenby A, Schwartz DA. Cytomegalovirus colitis in acquired immunodeficiency syndrome: a clinical and endoscopic study. *Gastrointest Endosc* 1998;**48**:39–43.
80. Battaglino MP, Rockey DC. Cytomegalovirus colitis presenting with the endoscopic appearance of pseudomembranous colitis. *Gastrointest Endosc* 1999;**50**:697–700.
81. Roskell DE, Hyde GM, Campbell AP, Jewell DP, Gray W. HIV associated cytomegalovirus colitis as a mimic of inflammatory bowel disease. *Gut* 1995;**37**:148–50.
82. Osawa R, Singh N. Cytomegalovirus infection in critically ill patients: a systematic review. *Crit Care* 2009;**13**:R68.
83. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. *Dig Dis Sci* 2005;**50**:609–16.
84. Nishimoto Y, Matsumoto T, Suekane H, Shimizu M, Mikami Y, Iida M. Cytomegalovirus infection in a patient with ulcerative colitis: colonoscopic findings. *Gastrointest Endosc* 2001;**53**:816–8.
85. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002;**34**:1094–7.
86. Kim JJ, Simpson N, Klipfel N, Debose R, Barr N, Laine L. Cytomegalovirus infection in patients with active inflammatory bowel disease. *Dig Dis Sci* 2010;**55**:1059–65.
87. Maconi G, Colombo E, Zerbi P, Sampietro GM, Fociani P, Bosani M, et al. Prevalence, detection rate and outcome of cytomegalovirus infection in ulcerative colitis patients requiring colonic resection. *Dig Liver Dis* 2005;**37**:418–23.
88. Suzuki H, Kato J, Kuriyama M, Hiraoka S, Kuwaki K, Yamamoto K. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection. *World J Gastroenterol* 2010;**16**:1245–51.
89. Almadi MA, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *Am J Gastroenterol* 2009;**104**:1003–12.
90. Solem CA, Loftus Jr EV, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. *Gastrointest Endosc* 2008;**68**:255–66.
91. Jeong SH, Lee KJ, Kim YB, Kwon HC, Sin SJ, Chung JY. Diagnostic value of terminal ileum intubation during colonoscopy. *J Gastroenterol Hepatol* 2008;**23**:51–5.
92. Stahlberg D, Veress B, Tribukait B, Broome U. Atrophy and neoplastic transformation of the ileal pouch mucosa in patients with ulcerative colitis and primary sclerosing cholangitis: a case control study. *Dis Colon Rectum* 2003;**46**:770–8.
93. Shen B, Wu H, Remzi F, Lopez R, Shen L, Fazio V. Diagnostic value of esophagogastroduodenoscopy in patients with ileal pouch-anal anastomosis. *Inflamm Bowel Dis* 2009;**15**:395–401.
94. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**:289–97.
95. Kim KM, Lee A, Choi KY, Lee KY, Kwak JJ. Intestinal tuberculosis: clinicopathologic analysis and diagnosis by endoscopic biopsy. *Am J Gastroenterol* 1998;**93**:606–9.
96. Alvares JF, Devarbhavi H, Makhija P, Rao S, Kottoor R. Clinical, colonoscopic, and histological profile of colonic tuberculosis in a tertiary hospital. *Endoscopy* 2005;**37**:351–6.

97. Gilinsky NH, Marks IN, Kottler RE, Price SK. Abdominal tuberculosis. A 10-year review. *S Afr Med J* 1983;64:849–57.
98. Lee YJ, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, et al. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. *Endoscopy* 2006;38:592–7.
99. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, et al. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am J Gastroenterol* 2010;105:642–51.
100. Epstein D, Watermeyer G, Kirsch R. Review article: the diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. *Aliment Pharmacol Ther* 2007;25:1373–88.
101. Pulimood AB, Amarapurkar DN, Ghoshal U, Phillip M, Pai CG, Reddy DN, et al. Differentiation of Crohn's disease from intestinal tuberculosis in India in 2010. *World J Gastroenterol* 2011;17:433–43.
102. Tursi A, Inchingolo CD, Nenna R, Stoppino G, Zotti M, Panella C, et al. Pattern of mucosal tumor necrosis factor-alpha expression in segmental colitis associated with diverticula suggests a truly autonomous clinical entity. *Inflamm Bowel Dis* 2008;14:1315–7.
103. Mann NS, Hoda KK. Segmental colitis associated with diverticulosis: systematic evaluation of 486 cases with meta-analysis. *Hepatogastroenterology* 2012;59:2119–21.
104. Imperiali G, Meucci G, Alvisi C, Fasoli R, Ferrara A, Girelli CM, et al. Segmental colitis associated with diverticula: a prospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). *Am J Gastroenterol* 2000;95:1014–6.
105. Hadithi M, Cazemier M, Meijer GA, Bloemena E, Felt-Bersma RJ, Mulder CJ, et al. Retrospective analysis of old-age colitis in the Dutch inflammatory bowel disease population. *World J Gastroenterol* 2008;14:3183–7.
106. Rispo A, Pasquale L, Cozzolino A, Di Girolamo E, De Palma GD, Grassia R, et al. Lower prevalence of diverticulosis in patients with ulcerative colitis. *Dis Colon Rectum* 2007;50:1164–8.
107. Lamps LW, Knapple WL. Diverticular disease-associated segmental colitis. *Clin Gastroenterol Hepatol* 2007;5:27–31.
108. Tursi A, Elisei W, Brandimarte G, Giorgetti GM, Lecca PG, Di Cesare L, et al. The endoscopic spectrum of segmental colitis associated with diverticulosis. *Colorectal Dis* 2010;12:464–70.
109. Tursi A, Elisei W, Giorgetti GM, Aiello F, Brandimarte G. Inflammatory manifestations at colonoscopy in patients with colonic diverticular disease. *Aliment Pharmacol Ther* 2011;33:358–65.
110. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia American Gastrointestinal Association. *Gastroenterol* 2000;118:954–68.
111. Zou X, Cao J, Yao Y, Liu W, Chen L. Endoscopic findings and clinicopathologic characteristics of ischemic colitis: a report of 85 cases. *Dig Dis Sci* 2009;54:2009–15.
112. Beppu K, Osada T, Nagahara A, Matsumoto K, Shibuya T, Sakamoto N, et al. Relationship between endoscopic findings and clinical severity in ischemic colitis. *Intern Med* 2011;50:2263–7.
113. Habu Y, Tahashi Y, Kiyota K, Matsumura K, Hirota M, Inokuchi H, et al. Reevaluation of clinical features of ischemic colitis. Analysis of 68 consecutive cases diagnosed by early colonoscopy. *Scand J Gastroenterol* 1996;31:881–6.
114. Scowcroft CW, Sanowski RA, Kozarek RA. Colonoscopy in ischemic colitis. *Gastrointest Endosc* 1981;27:156–61.
115. Mantzaris GJ, Hatzis A, Archavlis E, Petraki K, Lazou A, Ladas S, et al. The role of colonoscopy in the differential diagnosis of acute, severe hemorrhagic colitis. *Endoscopy* 1995;27:645–53.
116. Dejaco C, Oesterreicher C, Angelberger S, Puspok A, Birner P, Poetzi R, et al. Diagnosing colitis: a prospective study on essential parameters for reaching a diagnosis. *Endoscopy* 2003;35:1004–8.
117. Surawicz CM, Haggitt RC, Husseman M, McFarland LV. Mucosal biopsy diagnosis of colitis: acute self-limited colitis and idiopathic inflammatory bowel disease. *Gastroenterology* 1994;107:755–63.
118. Schumacher G, Sandstedt B, Kollberg B. A prospective study of first attacks of inflammatory bowel disease and infectious colitis. Clinical findings and early diagnosis. *Scand J Gastroenterol* 1994;29:265–74.
119. Schumacher G. First attack of inflammatory bowel disease and infectious colitis. A clinical, histological and microbiological study with special reference to early diagnosis. *Scand J Gastroenterol Suppl* 1993;198:1–24.
120. Schumacher G, Kollberg B, Sandstedt B, Jorup C, Grillner L, Ljungh A, et al. A prospective study of first attacks of inflammatory bowel disease and non-relapsing colitis. Microbiologic findings. *Scand J Gastroenterol* 1993;28:1077–85.
121. Surawicz CM. What's the best way to differentiate infectious colitis (acute self-limited colitis) from IBD? *Inflamm Bowel Dis* 2008;14(Suppl 2):S157–8.
122. Nahon S, Bouhnik Y, Lavergne-Slove A, Bitoun A, Panis Y, Valleur P, et al. Colonoscopy accurately predicts the anatomical severity of colonic Crohn's disease attacks: correlation with findings from colectomy specimens. *Am J Gastroenterol* 2002;97:3102–7.
123. Alemayehu G, Jarnerot G. Colonoscopy during an attack of severe ulcerative colitis is a safe procedure and of great value in clinical decision making. *Am J Gastroenterol* 1991;86:187–90.
124. Higgins PD, Schwartz M, Mapili J, Zimmermann EM. Is endoscopy necessary for the measurement of disease activity in ulcerative colitis? *Am J Gastroenterol* 2005;100:355–61.
125. Regueiro M, Rodemann J, Kip KE, Saul M, Swoger J, Baidoo L, et al. Physician assessment of ulcerative colitis activity correlates poorly with endoscopic disease activity. *Inflamm Bowel Dis* 2011;17:1008–14.
126. Mirpour S, Rabie R, Mirpour K, Gholamrezanezhad A. Evaluation of relationship between clinical and colonoscopic features in patients with active ulcerative colitis. *Indian J Gastroenterol* 2007;26:74–6.
127. D'Amato M, Pompili M, Marra G, Rapaccini GL, Anti M. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel diseases. *Gut* 1986;27:1228.
128. Buckell NA, Williams GT, Bartram CI, Lennard-Jones JE. Depth of ulceration in acute colitis: correlation with outcome and clinical and radiologic features. *Gastroenterology* 1980;79:19–25.
129. Hefti MM, Chessin DB, Harpaz NH, Steinhagen RM, Ullman TA. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. *Dis Colon Rectum* 2009;52:193–7.
130. Carbonnel F, Lavergne A, Lemann M, Bitoun A, Valleur P, Hautefeuille P, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994;39:1550–7.
131. Seo M, Okada M, Yao T, Mataka H, Maeda K. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *J Gastroenterol* 2002;37:29–34.
132. Carbonnel F, Gargouri D, Lemann M, Beaugerie L, Cattan S, Cosnes J, et al. Predictive factors of outcome of intensive intravenous treatment for attacks of ulcerative colitis. *Aliment Pharmacol Ther* 2000;14:273–9.
133. Bernal I, Manosa M, Domenech E, Garcia-Planella E, Navarro M, Lorenzo-Zuniga V, et al. Predictors of clinical response to systemic steroids in active ulcerative colitis. *Dig Dis Sci* 2006;51:1434–8.
134. Cacheux W, Seksik P, Lemann M, Marteau P, Nion-Larmurier I, Afchain P, et al. Predictive factors of response to cyclosporine

- in steroid-refractory ulcerative colitis. *Am J Gastroenterol* 2008;**103**:637–42.
135. Aratari A, Papi C, Clemente V, Moretti A, Luchetti R, Koch M, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. *Dig Liver Dis* 2008;**40**:821–6.
  136. Navarro-Llavat M, Domenech E, Bernal I, Sanchez-Delgado J, Manterola JM, Garcia-Planella E, et al. Prospective, observational, cross-sectional study of intestinal infections among acutely active inflammatory bowel disease patients. *Digestion* 2009;**80**:25–9.
  137. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47–91.
  138. Rodemann JF, Dubberke ER, Reske KA, Seo da H, Stone CD. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;**5**:339–44.
  139. Bossuyt P, Verhaegen J, Van Assche G, Rutgeerts P, Vermeire S. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:4–7.
  140. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;**6**:991–1030.
  141. Huetting WE, Buskens E, van der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. *Dig Surg* 2005;**22**:69–79.
  142. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. *Ann Surg* 1995;**222**:120–7.
  143. McLaughlin SD, Clark SK, Thomas-Gibson S, Tekkis PP, Ciclitira PJ, Nicholls RJ. Guide to endoscopy of the ileo-anal pouch following restorative proctocolectomy with ileal pouch-anal anastomosis; indications, technique, and management of common findings. *Inflamm Bowel Dis* 2009;**15**:1256–63.
  144. Shen B, Fazio VW, Remzi FH, Lashner BA. Clinical approach to diseases of ileal pouch-anal anastomosis. *Am J Gastroenterol* 2005;**100**:2796–807.
  145. Shen B, Fazio VW, Remzi FH, Delaney CP, Bennett AE, Achkar JP, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. *Am J Gastroenterol* 2005;**100**:93–101.
  146. Ghali P, Bittton A. The role of endoscopy in the evaluation of pouches and ostomies. *Gastrointest Endosc Clin N Am* 2002;**12**:605–19.
  147. Shen B. Diagnosis and management of postoperative ileal pouch disorders. *Clin Colon Rectal Surg* 2010;**23**:259–68.
  148. Shen B, Achkar JP, Lashner BA, Ormsby AH, Remzi FH, Bevins CL, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001;**121**:261–7.
  149. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. *Int J Colorectal Dis* 1986;**1**:167–74.
  150. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc* 1994;**69**:409–15.
  151. Shen B, Remzi FH, Lavery IC, Lashner BA, Fazio VW. A proposed classification of ileal pouch disorders and associated complications after restorative proctocolectomy. *Clin Gastroenterol Hepatol* 2008;**6**:145–58 [quiz 124].
  152. Shen B. Diagnosis and treatment of patients with pouchitis. *Drugs* 2003;**63**:453–61.
  153. Nicholls RJ. Review article: ulcerative colitis—surgical indications and treatment. *Aliment Pharmacol Ther* 2002;**16**(Suppl 4):25–8.
  154. Shen B, Plesec TP, Remer E, Kiran P, Remzi FH, Lopez R, et al. Asymmetric endoscopic inflammation of the ileal pouch: a sign of ischemic pouchitis? *Inflamm Bowel Dis* 2010;**16**:836–46.
  155. Moonka D, Furth EE, MacDermott RP, Lichtenstein GR. Pouchitis associated with primary cytomegalovirus infection. *Am J Gastroenterol* 1998;**93**:264–6.
  156. Shen B. Crohn's disease of the ileal pouch: reality, diagnosis, and management. *Inflamm Bowel Dis* 2009;**15**:284–94.
  157. Shen B, Fazio VW, Remzi FH, Delaney CP, Achkar JP, Bennett A, et al. Endoscopic balloon dilation of ileal pouch strictures. *Am J Gastroenterol* 2004;**99**:2340–7.
  158. Shen B, Lian L, Kiran RP, Queener E, Lavery IC, Fazio VW, et al. Efficacy and safety of endoscopic treatment of ileal pouch strictures. *Inflamm Bowel Dis* 2011;**17**:2527–35.
  159. Kuiper T, Vlug MS, van den Broek FJ, Tytgat KM, van Eeden S, Fockens P, et al. The prevalence of dysplasia in the ileoanal pouch following restorative proctocolectomy for ulcerative colitis with associated dysplasia. *Colorectal Dis* 2012;**14**:469–73.
  160. Kariv R, Remzi FH, Lian L, Bennett AE, Kiran RP, Kariv Y, et al. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. *Gastroenterology* 2010;**139**:806–12 [812 e801-802].
  161. Das P, Johnson MW, Tekkis PP, Nicholls RJ. Risk of dysplasia and adenocarcinoma following restorative proctocolectomy for ulcerative colitis. *Colorectal Dis* 2007;**9**:15–27.
  162. Ault GT, Nunoo-Mensah JW, Johnson L, Vukasin P, Kaiser A, Beart Jr RW. Adenocarcinoma arising in the middle of ileoanal pouches: report of five cases. *Dis Colon Rectum* 2009;**52**:538–41.
  163. Scarpa M, van Koperen PJ, Ubbink DT, Hommes DW, Ten Kate FJ, Bemelman WA. Systematic review of dysplasia after restorative proctocolectomy for ulcerative colitis. *Br J Surg* 2007;**94**:534–45.
  164. Herline AJ, Meisinger LL, Rusin LC, Roberts PL, Murray JJ, Collier JA, et al. Is routine pouch surveillance for dysplasia indicated for ileoanal pouches? *Dis Colon Rectum* 2003;**46**:156–9.
  165. Hernandez JD, Jimenez-Huyke C, Rosado K, Gonzalez-Keelan C, Lojo JJ, Torres EA. Surveillance for dysplasia in patients with ileal pouch-anal anastomosis for ulcerative colitis: an interim analysis. *Dig Dis Sci* 2010;**55**:2332–6.
  166. Knupper N, Straub E, Terpe HJ, Vestweber KH. Adenocarcinoma of the ileoanal pouch for ulcerative colitis—a complication of severe chronic atrophic pouchitis? *Int J Colorectal Dis* 2006;**21**:478–82.
  167. Ozuner G, Fazio VW, Lavery IC, Milsom JW, Strong SA. Reoperative rates for Crohn's disease following strictureplasty. Long-term analysis. *Dis Colon Rectum* 1996;**39**:1199–203.
  168. Hassan C, Zullo A, De Francesco V, Ierardi E, Giustini M, Pitidis A, et al. Systematic review: endoscopic dilatation in Crohn's disease. *Aliment Pharmacol Ther* 2007;**26**:1457–64.
  169. Singh VV, Draganov P, Valentine J. Efficacy and safety of endoscopic balloon dilation of symptomatic upper and lower gastrointestinal Crohn's disease strictures. *J Clin Gastroenterol* 2005;**39**:284–90.
  170. Morini S, Hassan C, Lorenzetti R, Zullo A, Cerro P, Winn S, et al. Long-term outcome of endoscopic pneumatic dilatation in Crohn's disease. *Dig Liver Dis* 2003;**35**:893–7.
  171. Stienecker K, Gleichmann D, Neumayer U, Glaser HJ, Tonus C. Long-term results of endoscopic balloon dilatation of lower gastrointestinal tract strictures in Crohn's disease: a prospective study. *World J Gastroenterol* 2009;**15**:2623–7.
  172. Ajlouni Y, Iser JH, Gibson PR. Endoscopic balloon dilatation of intestinal strictures in Crohn's disease: safe alternative to surgery. *J Gastroenterol Hepatol* 2007;**22**:486–90.
  173. Foster EN, Quiros JA, Prindiville TP. Long-term follow-up of the endoscopic treatment of strictures in pediatric and adult

- patients with inflammatory bowel disease. *J Clin Gastroenterol* 2008;**42**:880–5.
174. Ferlitsch A, Reinisch W, Puspok A, Dejaco C, Schillinger M, Schofl R, et al. Safety and efficacy of endoscopic balloon dilation for treatment of Crohn's disease strictures. *Endoscopy* 2006;**38**:483–7.
  175. Sabate JM, Villarejo J, Bouhnik Y, Allez M, Gornet JM, Vahedi K, et al. Hydrostatic balloon dilatation of Crohn's strictures. *Aliment Pharmacol Ther* 2003;**18**:409–13.
  176. Breysem Y, Janssens JF, Coremans G, Vantrappen G, Hendrickx G, Rutgeerts P. Endoscopic balloon dilation of colonic and ileo-colonic Crohn's strictures: long-term results. *Gastrointest Endosc* 1992;**38**:142–7.
  177. Williams AJ, Palmer KR. Endoscopic balloon dilatation as a therapeutic option in the management of intestinal strictures resulting from Crohn's disease. *Br J Surg* 1991;**78**:453–4.
  178. Thomas-Gibson S, Brooker JC, Hayward CM, Shah SG, Williams CB, Saunders BP. Colonoscopic balloon dilation of Crohn's strictures: a review of long-term outcomes. *Eur J Gastroenterol Hepatol* 2003;**15**:485–8.
  179. Blomberg B, Rolny P, Jarnerot G. Endoscopic treatment of anastomotic strictures in Crohn's disease. *Endoscopy* 1991;**23**:195–8.
  180. Hoffmann JC, Heller F, Faiss S, von Lampe B, Kroesen AJ, Wahnschaffe U, et al. Through the endoscope balloon dilation of ileocolonic strictures: prognostic factors, complications, and effectiveness. *Int J Colorectal Dis* 2008;**23**:689–96.
  181. Scimeca D, Mocciaro F, Cottone M, Montalbano LM, D'Amico G, Olivo M, et al. Efficacy and safety of endoscopic balloon dilation of symptomatic intestinal Crohn's disease strictures. *Dig Liver Dis* 2011;**43**:121–5.
  182. Mueller T, Rieder B, Bechtner G, Pfeiffer A. The response of Crohn's strictures to endoscopic balloon dilation. *Aliment Pharmacol Ther* 2010;**31**:634–9.
  183. Couckuyt H, Gevers AM, Coremans G, Hiele M, Rutgeerts P. Efficacy and safety of hydrostatic balloon dilatation of ileocolonic Crohn's strictures: a prospective long-term analysis. *Gut* 1995;**36**:577–80.
  184. Gevers AM, Couckuyt H, Coremans G, Hiele M, Rutgeerts P. Efficacy and safety of hydrostatic balloon dilation of ileocolonic Crohn's strictures. A prospective long-term analysis. *Acta Gastroenterol Belg* 1994;**57**:320–2.
  185. Nomura E, Takagi S, Kikuchi T, Negoro K, Takahashi S, Kinouchi Y, et al. Efficacy and safety of endoscopic balloon dilation for Crohn's strictures. *Dis Colon Rectum* 2006;**49**:S59–67.
  186. Saunders BP, Brown GJ, Lemann M, Rutgeerts P. Balloon dilation of ileocolonic strictures in Crohn's disease. *Endoscopy* 2004;**36**:1001–7.
  187. Gustavsson A, Magnuson A, Blomberg B, Andersson M, Halfvarson J, Tysk C. Endoscopic dilation is an efficacious and safe treatment of intestinal strictures in Crohn's disease. *Aliment Pharmacol Ther* 2012;**36**:151–8.
  188. Van Assche G. Is endoscopic balloon therapy an effective treatment for patients with Crohn's disease strictures? *Nat Clin Pract Gastroenterol Hepatol* 2005;**2**:298–9.
  189. Coffey MJ, Wright RA. Efficacy and safety of hydrostatic balloon dilatation of ileocolonic Crohn's strictures: a prospective long-term analysis. *Gastrointest Endosc* 1996;**43**:89–90.
  190. Nguyen-Tang T, Huber O, Gervaz P, Dumonceau JM. Long-term quality of life after endoscopic dilation of strictured colorectal or colocolonic anastomoses. *Surg Endosc* 2008;**22**:1660–6.
  191. Wibmer AG, Kroesen AJ, Grone J, Buhr HJ, Ritz JP. Comparison of strictureplasty and endoscopic balloon dilatation for stricturing Crohn's disease—review of the literature. *Int J Colorectal Dis* 2010;**25**:1149–57.
  192. Kirtley DW, Willis M, Thomas E. Balloon dilation of recurrent terminal ileal Crohn's stricture. *Gastrointest Endosc* 1987;**33**:399–400.
  193. Matsui T, Hatakeyama S, Ikeda K, Yao T, Takenaka K, Sakurai T. Long-term outcome of endoscopic balloon dilation in obstructive gastroduodenal Crohn's disease. *Endoscopy* 1997;**29**:640–5.
  194. Kelly SM, Hunter JO. Endoscopic balloon dilatation of duodenal strictures in Crohn's disease. *Postgrad Med J* 1995;**71**:623–4.
  195. Matsui T, Ikeda K, Tsuda S, Yao K, Sou S, Satoh S, et al. Long-term outcome of endoscopic balloon dilation in obstructive gastrointestinal Crohn's disease: a prospective long-term study. *Diagn Ther Endosc* 2000;**6**:67–75.
  196. Thienpont C, D'Hoore A, Vermeire S, Demedts I, Bisschops R, Coremans G, et al. Long-term outcome of endoscopic dilatation in patients with Crohn's disease is not affected by disease activity or medical therapy. *Gut* 2010;**59**:320–4.
  197. Honzawa Y, Nakase H, Matsuura M, Higuchi H, Toyonaga T, Matsumura K, et al. Prior use of immunomodulatory drugs improves the clinical outcome of endoscopic balloon dilation for intestinal stricture in patients with Crohn's disease. *Dig Endosc* Jan 29 2013 <http://dx.doi.org/10.1111/den.12029> [Epub ahead of print].
  198. Gustavsson A, Magnuson A, Blomberg B, Andersson M, Halfvarson J, Tysk C. Smoking is a risk factor for recurrence of intestinal stricture after endoscopic dilation in Crohn's disease. *Aliment Pharmacol Ther* 2013;**37**:430–7.
  199. East JE, Brooker JC, Rutter MD, Saunders BP. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. *Clin Gastroenterol Hepatol* 2007;**5**:1065–9.
  200. Brooker JC, Beckett CG, Saunders BP, Benson MJ. Long-acting steroid injection after endoscopic dilation of anastomotic Crohn's strictures may improve the outcome: a retrospective case series. *Endoscopy* 2003;**35**:333–7.
  201. Lavy A. Triamcinolone improves outcome in Crohn's disease strictures. *Dis Colon Rectum* 1997;**40**:184–6.
  202. Van Assche G. Intramural steroid injection and endoscopic dilation for Crohn's disease. *Clin Gastroenterol Hepatol* 2007;**5**:1027–8.
  203. Di Nardo G, Oliva S, Passariello M, Pallotta N, Civitelli F, Frediani S, et al. Intralesional steroid injection after endoscopic balloon dilation in pediatric Crohn's disease with stricture: a prospective, randomized, double-blind, controlled trial. *Gastrointest Endosc* 2010;**72**:1201–8.
  204. Swaminath A, Lichtiger S. Dilation of colonic strictures by intralesional injection of infliximab in patients with Crohn's colitis. *Inflamm Bowel Dis* 2008;**14**:213–6.
  205. Pohl J, May A, Nachbar L, Ell C. Diagnostic and therapeutic yield of push-and-pull enteroscopy for symptomatic small bowel Crohn's disease strictures. *Eur J Gastroenterol Hepatol* 2007;**19**:529–34.
  206. Fukumoto A, Tanaka S, Yamamoto H, Yao T, Matsui T, Iida M, et al. Diagnosis and treatment of small-bowel stricture by double balloon endoscopy. *Gastrointest Endosc* 2007;**66**:S108–12.
  207. Hirai F, Beppu T, Sou S, Seki T, Yao K, Matsui T. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010;**22**:200–4.
  208. Perez-Cuadrado E, Molina Perez E. Multiple strictures in jejunal Crohn's disease: push enteroscopy dilation. *Endoscopy* 2001;**33**:194.
  209. Matsushashi N, Nakajima A, Suzuki A, Yazaki Y, Takazoe M. Long-term outcome of non-surgical strictureplasty using metallic stents for intestinal strictures in Crohn's disease. *Gastrointest Endosc* 2000;**51**:343–5.
  210. Loras C, Perez-Roldan F, Gornals JB, Barrio J, Igea F, Gonzalez-Huix F, et al. Endoscopic treatment with self-expanding metal stents for Crohn's disease strictures. *Aliment Pharmacol Ther* 2012;**36**:833–9.
  211. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955;**2**:1041–8.

212. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964;1:89–92.
213. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol* 1978;13:833–7.
214. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987;92:1894–8.
215. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625–9.
216. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
217. Van Assche G, Sandborn WJ, Feagan BG, Salzberg BA, Silvers D, Monroe PS, et al. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. *Gut* 2006;55:1568–74.
218. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989;298:82–6.
219. Samuel S, Bruining DH, Loftus Jr EV, Thia KT, Schroeder KW, Tremaine WJ, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013;11(49-54):e41.
220. Marteau P, Lemann M, Seksik P, Laharie D, Colombel JF, Bouhnik Y, et al. Ineffectiveness of *Lactobacillus johnsonii* LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut* 2006;55:842–7.
221. Calabrese E, Petruzzello C, Onali S, Condino G, Zorzi F, Pallone F, et al. Severity of postoperative recurrence in Crohn's disease: correlation between endoscopic and sonographic findings. *Inflamm Bowel Dis* 2009;15:1635–42.
222. Hanauer SB, KORELITZ BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004;127:723–9.
223. Reinisch W, Angelberger S, Petritsch W, Shonova O, Lukas M, Bar-Meir S, et al. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. *Gut* 2010;59:752–9.
224. Sailer J, Peloschek P, Reinisch W, Vogelsang H, Turetschek K, Schima W. Anastomotic recurrence of Crohn's disease after ileocolic resection: comparison of MR enteroclysis with endoscopy. *Eur Radiol* 2008;18:2512–21.
225. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989;30:983–9.
226. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;60:505–12.
227. Cellier C, Sahnoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gut* 1994;35:231–5.
228. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. *Gastroenterology* 1990;98:811–8.
229. Allez M, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. *Am J Gastroenterol* 2002;97:947–53.
230. Colombel JF, Hebuterne X. Endoscopic mucosal improvement in patients with active Crohn's disease treated with certolizumab Pegol: first results of the MUSIC clinical trial. *Am J Gastroenterol* 2008;103:1107 (A).
231. Louis E, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012;142(63–70):e65 (quiz e31).
232. Reinisch W, Rutgeerts P, Panaccione R, D'Haens G, Thakkar R, Yu A. Identifying appropriate dichotomizing points for SES-CD to predict long-term clinical remission for adalimumab-treated patients with Crohn's disease. *J Crohns Colitis* 2010;4:P045.
233. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010;138:463–8 [quiz e410-461].
234. Daperno M, Castiglione F, de Ridder L, Dotan I, Farkkila M, Florholmen J, et al. Results of the 2nd part Scientific Workshop of the ECCO. II: Measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. *J Crohns Colitis* 2011;5:484–98.
235. Frosliø KF, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007;133:412–22.
236. Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol* 2011;9(483–489):e483.
237. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, et al. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut* 2004;53:1813–6.
238. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. *Am J Dig Dis* 1966;11:847–57.
239. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126:451–9.
240. Zahn A, Hinz U, Karner M, Ehehalt R, Stremmel W. Health-related quality of life correlates with clinical and endoscopic activity indexes but not with demographic features in patients with ulcerative colitis. *Inflamm Bowel Dis* 2006;12:1058–67.
241. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol* 2007;102:794–802.
242. Nishio Y, Ando T, Maeda O, Ishiguro K, Watanabe O, Ohmiya N, et al. Pit patterns in rectal mucosa assessed by magnifying colonoscopy are predictive of relapse in patients with quiescent ulcerative colitis. *Gut* 2006;55:1768–73.
243. Kiesslich R, Duckworth CA, Moussata D, Gloeckner A, Lim LG, Goetz M, et al. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. *Gut* 2012;61:1146–53.
244. Solberg IC, Lygren I, Jahnsen J, Aadland E, Hoie O, Cvancarova M, et al. Clinical course during the first 10 years of ulcerative

- colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009;**44**:431–40.
245. Solberg IC, Lygren I, Jahnsen J, Vatn M, Moum B. Mucosal healing after initial treatment may be a prognostic marker for long-term outcome in inflammatory bowel disease. *Gut* 2008;**57**:A15.
246. D'Haens GR, Noman M, Baert F, et al. Endoscopic healing after infliximab treatment for Crohn's disease provides a longer time to relapse. *Gastroenterology* 2002;**122**:A100.
247. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
248. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;**126**:402–13.
249. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
250. Reinisch W, Rutgeerts P, Colombel JF, et al. Association of steroid-free clinical remission and complete mucosal healing at 6 months with clinical outcome at 1 year: a post-hoc analysis of SONIC trial data. *Gastroenterology* 2011;**140**:S261–2.
251. Colombel JF, Rutgeerts P, Sandborn WJ, et al. Achievement of early deep remission predicts better long-term outcomes for adalimumab-treated patients with Crohn's disease: data from EXTEND. *Am J Gastroenterol* 2010;**105**:S434–5.
252. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**:660–7.
253. Schnitzler F, Fidler H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1295–301.
254. Mary JY, Lemann M, Colombel JF, et al. Endoscopic remission and response in Crohn's disease: an objective definition using the CDEIS. *Gut* 2005;**54**:A50.
255. Ferrante M, Colombel JF, Sandborn WJ, et al. Evolution of endoscopic activity scores in patients with Crohn's disease under azathioprine and/or infliximab: a post-hoc analysis of the SONIC data. *Gastroenterology* 2011;**140**:S422.
256. Lemann M, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;**128**:1812–8.
257. Dionisio PM, Gurudu SR, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2010;**105**:1240–8 [quiz 1249].
258. Jensen MD, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. *Clin Gastroenterol Hepatol* 2011;**9**:124–9.
259. Toth E, Nemeth A, Nielsen J, Wurm Johansson G, Ekberg O, Thorlacius H. Capsule endoscopy is superior to magnetic resonance enterography for detection of Crohn's lesions in the small bowel. *Gut* 2011;**60**:A404.
260. Pica R, Cassieri C, Avallone EV, Crispino P, Rivera M, Paoluzi P. Small bowel involvement in Crohn's disease: a prospective study comparing wireless capsule endoscopy and magnetic resonance enteroclysis. *Gut* 2012;**61**:A398.
261. Pineton de Chambrun G, Peyrin-Biroulet L, Lemann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol* 2010;**7**:15–29.
262. Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy* 2005;**37**:960–5.
263. Leighton JA. The role of endoscopic imaging of the small bowel in clinical practice. *Am J Gastroenterol* 2011;**106**:27–36 [quiz 37].
264. Mehdizadeh S, Chen GC, Barkodar L, Enayati PJ, Pirouz S, Yadegari M, et al. Capsule endoscopy in patients with Crohn's disease: diagnostic yield and safety. *Gastrointest Endosc* 2010;**71**:121–7.
265. Doherty GA, Moss AC, Cheifetz AS. Capsule endoscopy for small-bowel evaluation in Crohn's disease. *Gastrointest Endosc* 2011;**74**:167–75.
266. Levesque BG. Yield to diagnostic accuracy: capsule endoscopy in Crohn's disease. *Gastrointest Endosc* 2010;**71**:128–30.
267. Maiden L, Thjodleifsson B, Seigal A, Bjarnason II, Scott D, Birgisson S, et al. Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a cross-sectional capsule enteroscopy study. *Clin Gastroenterol Hepatol* 2007;**5**:1040–5.
268. Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005;**3**:55–9.
269. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin Gastroenterol Hepatol* 2005;**3**:133–41.
270. Maiden L, Thjodleifsson B, Theodoros A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. *Gastroenterology* 2005;**128**:1172–8.
271. Lewis JR, Pashinsky Y, Tinsley A, Lewis BS. Capsule endoscopy in healthy individuals. *Gastroenterology* 2012;**142**:S52–3.
272. Tukey M, Pleskow D, Legnani P, Cheifetz AS, Moss AC. The utility of capsule endoscopy in patients with suspected Crohn's disease. *Am J Gastroenterol* 2009;**104**:2734–9.
273. Shim KN, Kim YS, Kim KJ, Kim YH, Kim TI, Do JH, et al. Abdominal pain accompanied by weight loss may increase the diagnostic yield of capsule endoscopy: a Korean multicenter study. *Scand J Gastroenterol* 2006;**41**:983–8.
274. Adler SN, Yoav M, Eitan S, Yehuda C, Eliakim R. Does capsule endoscopy have an added value in patients with perianal disease and a negative work up for Crohn's disease? *World J Gastrointest Endosc* 2012;**4**:185–8.
275. De Bona M, Bellumat A, Cian E, Valiante F, Moschini A, De Boni M. Capsule endoscopy findings in patients with suspected Crohn's disease and biochemical markers of inflammation. *Dig Liver Dis* 2006;**38**:331–5.
276. Valle J, Alcantara M, Perez-Gruoso MJ, Navajas J, Munoz-Rosas C, Legaz ML, et al. Clinical features of patients with negative results from traditional diagnostic work-up and Crohn's disease findings from capsule endoscopy. *J Clin Gastroenterol* 2006;**40**:692–6.
277. Rosa B, Moreira MJ, Rodrigues S, Cardoso H, Rebelo A, Marques M, et al. Lewis Score and capsule endoscopy findings in Crohn's disease. *Gut* 2011;**60**:A402.
278. Rodrigues S, Magro F, Cardoso H, Rosa B, Moreira MJ, Marques M, et al. Role of capsule endoscopy in the evaluation of different segments of the small bowel in Crohn's disease: correlation of biomarkers, endoscopy, and Lewis score. *Endoscopy* 2011;**43**:A130.
279. Sipponen T, Haapamaki J, Savilahti E, Alfthan H, Hamalainen E, Rautiainen H, et al. Fecal calprotectin and S100A12 have low utility in prediction of small bowel Crohn's disease detected by wireless capsule endoscopy. *Scand J Gastroenterol* 2012;**47**:778–84.
280. Koulaouzidis A, Douglas S, Rogers MA, Arnott ID, Plevris JN. Fecal calprotectin: a selection tool for small bowel capsule



- endoscopy in suspected IBD with prior negative bi-directional endoscopy. *Scand J Gastroenterol* 2011;**46**:561–6.
281. Aggarwal V, Day AS, Connor SJ, Leach ST, Grimm MC, Craig PI. Capsule endoscopy findings in small bowel Crohn's disease patients in clinical remission: correlation with the Crohn's disease activity index, faecal calprotectin and S100A12. *Gastroenterology* 2010;**138**:S114:S114.
  282. Koulaouzidis A, Douglas S, Plevris JN. Lewis score correlates more closely with fecal calprotectin than Capsule Endoscopy Crohn's Disease Activity Index. *Dig Dis Sci* 2012;**57**:987–93.
  283. May A, Manner H, Schneider M, Ipsen A, Ell C. Prospective multicenter trial of capsule endoscopy in patients with chronic abdominal pain, diarrhea and other signs and symptoms (CEDAP-Plus Study). *Endoscopy* 2007;**39**:606–12.
  284. Bardan E, Nadler M, Chowers Y, Fidder H, Bar-Meir S. Capsule endoscopy for the evaluation of patients with chronic abdominal pain. *Endoscopy* 2003;**35**:688–9.
  285. Viazis N, Zacharakis G, Saprikis E, Anastasopoulos H, Kechagias G, Markoutsaki T, et al. A single center experience of 2300 consecutive patients undergoing capsule endoscopy: indications and diagnostic yield. *Endoscopy* 2011;**43**:A129.
  286. Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, et al. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy* 2007;**39**:895–909.
  287. Rosa B, Moreira MJ, Rebelo A, Cotter J. Lewis Score: a useful clinical tool for patients with suspected Crohn's Disease submitted to capsule endoscopy. *J Crohns Colitis* 2012;**6**:692–7.
  288. Voderholzer WA, Beinhoelzl J, Rogalla P, Murrer S, Schachschal G, Lochs H, et al. Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut* 2005;**54**:369–73.
  289. Petruzzello C, Onali S, Calabrese E, Zorzi F, Ascolani M, Condino G, et al. Wireless capsule endoscopy and proximal small bowel lesions in Crohn's disease. *World J Gastroenterol* 2010;**16**:3299–304.
  290. Niv Y. Diagnostic value of capsule endoscopy during relapse in co-morbid irritable bowel syndrome and Crohn's disease. *Eur J Gastroenterol Hepatol* 2004;**16**:1073–4.
  291. Leighton JA, Triester SL, Sharma VK. Capsule endoscopy: a meta-analysis for use with obscure gastrointestinal bleeding and Crohn's disease. *Gastrointest Endosc Clin N Am* 2006;**16**:229–50.
  292. Pons Beltran V, Nos P, Bastida G, Beltran B, Arguello L, Aguas M, et al. Evaluation of postsurgical recurrence in Crohn's disease: a new indication for capsule endoscopy? *Gastrointest Endosc* 2007;**66**:533–40.
  293. Bourreille A, Jarry M, D'Halluin PN, Ben-Soussan E, Maunoury V, Bulois P, et al. Wireless capsule endoscopy versus ileocolonoscopy for the diagnosis of postoperative recurrence of Crohn's disease: a prospective study. *Gut* 2006;**55**:978–83.
  294. Efthymiou A, Viazis N, Mantzaris G, Papadimitriou N, Tzourmakliotis D, Raptis S, et al. Does clinical response correlate with mucosal healing in patients with Crohn's disease of the small bowel? A prospective, case-series study using wireless capsule endoscopy. *Inflamm Bowel Dis* 2008;**14**:1542–7.
  295. Lewis BS. Expanding role of capsule endoscopy in inflammatory bowel disease. *World J Gastroenterol* 2008;**14**:4137–41.
  296. Niv Y, Ilani S, Levi Z, Hershkowitz M, Niv E, Fireman Z, et al. Validation of the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score): a multicenter prospective study. *Endoscopy* 2012;**44**:21–6.
  297. Castro FD, Rosa B, Moreira MJ, Cotter J. Impact of capsule endoscopy on management of Crohn's disease: a single center experience. *Gastrointest Endosc* 2012;**75**:AB254.
  298. Long MD, Barnes E, Isaacs K, Morgan D, Herfarth HH. Impact of capsule endoscopy on management of inflammatory bowel disease: a single tertiary care center experience. *Inflamm Bowel Dis* 2011;**17**:1855–62.
  299. Lorenzo-Zuniga V, de Vega VM, Domenech E, Cabre E, Manosa M, Boix J. Impact of capsule endoscopy findings in the management of Crohn's Disease. *Dig Dis Sci* 2010;**55**:411–4.
  300. Sidhu R, McAlindon ME, Drew K, Hardcastle S, Cameron IC, Sanders DS. Evaluating the role of small-bowel endoscopy in clinical practice: the largest single-centre experience. *Eur J Gastroenterol Hepatol* 2012;**24**:513–9.
  301. Gurudu SR, Leighton JA. Correlation of two capsule endoscopy scoring systems with fecal calprotectin: does it really matter? *Dig Dis Sci* 2012;**57**:827–9.
  302. Mow WS, Lo SK, Targan SR, Dubinsky MC, Treyzon L, Abreu-Martin MT, et al. Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2004;**2**:31–40.
  303. Jensen MD, Nathan T, Kjeldsen J. Inter-observer agreement for detection of small bowel Crohn's disease with capsule endoscopy. *Scand J Gastroenterol* 2010;**45**:878–84.
  304. Gal E, Geller A, Fraser G, Levi Z, Niv Y. Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). *Dig Dis Sci* 2008;**53**:1933–7.
  305. Gralnek IM, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008;**27**:146–54.
  306. Swaminath A, Legnani P, Kornbluth A. Video capsule endoscopy in inflammatory bowel disease: past, present, and future redux. *Inflamm Bowel Dis* 2010;**16**:1254–62.
  307. Vind I, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006;**101**:1274–82.
  308. Stewenius J, Adnerhill I, Ekelund G, Floren CH, Fork FT, Janzon L, et al. Ulcerative colitis and indeterminate colitis in the city of Malmo, Sweden. A 25-year incidence study. *Scand J Gastroenterol* 1995;**30**:38–43.
  309. Maunoury V, Savoye G, Bourreille A, Bouhnik Y, Jarry M, Sacher-Huvelin S, et al. Value of wireless capsule endoscopy in patients with indeterminate colitis (inflammatory bowel disease type unclassified). *Inflamm Bowel Dis* 2007;**13**:152–5.
  310. Mehdizadeh S, Chen G, Enayati PJ, Cheng DW, Han NJ, Shaye OA, et al. Diagnostic yield of capsule endoscopy in ulcerative colitis and inflammatory bowel disease of unclassified type (IBDU). *Endoscopy* 2008;**40**:30–5.
  311. Di Nardo G, Oliva S, Ferrari F, Riccioni ME, Staiano A, Lombardi G, et al. Usefulness of wireless capsule endoscopy in paediatric inflammatory bowel disease. *Dig Liver Dis* 2011;**43**:220–4.
  312. Joossens S, Reinisch W, Vermeire S, Sendid B, Poulain D, Peeters M, et al. The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002;**122**:1242–7.
  313. Shen B, Remzi FH, Santisi J, Lashner BA, Brzezinski A, Fazio VW. Application of wireless capsule endoscopy for the evaluation of iron deficiency anemia in patients with ileal pouches. *J Clin Gastroenterol* 2008;**42**:897–902.
  314. Murrell Z, Vasiliauskas E, Melmed G, Lo S, Targan S, Fleshner P. Preoperative wireless capsule endoscopy does not predict outcome after ileal pouch-anal anastomosis. *Dis Colon Rectum* 2010;**53**:293–300.
  315. Schluender SJ, Mehdizadeh S, Vasiliauskas EA, Dubinsky M, Papadakis KA, Ippoliti A, et al. Does preoperative wireless endoscopic capsule predict long-term outcome after ileal pouch-anal anastomosis (IPAA)? *Gastroenterology* 2006:130.

316. Meister T, Heinzow H, Dortgolz A, Lenze F, Ross M, Domagk D, et al. Colon capsule endoscopy versus standard colonoscopy in assessing disease activity in patients with ulcerative colitis: a prospective trial. *Gastrointest Endosc* 2012;75:AB475.
317. Sung J, Ho KY, Chiu HM, Ching J, Travis S, Peled R. The use of Pillcam Colon in assessing mucosal inflammation in ulcerative colitis: a multicenter study. *Endoscopy* 2012;44:754–8.
318. Postgate AJ, Burling D, Gupta A, Fitzpatrick A, Fraser C. Safety, reliability and limitations of the given patency capsule in patients at risk of capsule retention: a 3-year technical review. *Dig Dis Sci* 2008;53:2732–8.
319. Cheifetz AS, Kornbluth AA, Legnani P, Schmelkin I, Brown A, Lichtiger S, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. *Am J Gastroenterol* 2006;101:2218–22.
320. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010;71:280–6.
321. Hoog CM, Bark LA, Arkanj J, Gorsetman J, Brostrom O, Sjoqvist U. Capsule retentions and incomplete capsule endoscopy examinations: an analysis of 2300 examinations. *Gastroenterol Res Pract* 2012;2012:518718.
322. Levesque BG, Cipriano LE, Chang SL, Lee KK, Owens DK, Garber AM. Cost effectiveness of alternative imaging strategies for the diagnosis of small-bowel Crohn's disease. *Clin Gastroenterol Hepatol* 2010;8:261–7 [267 e261–264].
323. Leighton JA, Gralnek IM, Richner RE, Lacey MJ, Papatheofanis FJ. Capsule endoscopy in suspected small bowel Crohn's disease: economic impact of disease diagnosis and treatment. *World J Gastroenterol* 2009;15:5685–92.
324. Rondonotti E, Soncini M, Girelli C, Ballardini G, Bianchi G, Brunati S, et al. Small bowel capsule endoscopy in clinical practice: a multicenter 7-year survey. *Eur J Gastroenterol Hepatol* 2010;22:1380–6.
325. Herrerias JM, Leighton JA, Costamagna G, Infantolino A, Eliakim R, Fischer D, et al. Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. *Gastrointest Endosc* 2008;67:902–9.
326. Yadav A, Heigh RI, Hara AK, Decker GA, Crowell MD, Gurudu SR, et al. Performance of the patency capsule compared with nonenteroclysis radiologic examinations in patients with known or suspected intestinal strictures. *Gastrointest Endosc* 2011;74:834–9.
327. Tanaka S, Mitsui K, Shirakawa K, Tatsuguchi A, Nakamura T, Hayashi Y, et al. Successful retrieval of video capsule endoscopy retained at ileal stenosis of Crohn's disease using double-balloon endoscopy. *J Gastroenterol Hepatol* 2006;21:922–3.
328. Van Weyenberg SJ, Van Turenhout ST, Bouma G, Van Waesberghe JH, Van der Peet DL, Mulder CJ, et al. Double-balloon endoscopy as the primary method for small-bowel video capsule endoscope retrieval. *Gastrointest Endosc* 2010;71:535–41.
329. Bai Y, Gao J, Song B, Zhou YQ, Zou DW, Li ZS. Surgical intervention for capsule endoscopy retained at ileal stricture. *Endoscopy* 2007;39(Suppl 1):E268–9.
330. Magdeburg R, Riestler T, Hummel F, Lohr M, Post S, Sturm J. Ileus secondary to wireless capsule enteroscopy. *Int J Colorectal Dis* 2006;21:610–3.
331. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;135:1106–13.
332. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140:1785–94.
333. de Ridder L, Mensink PB, Lequin MH, Aktas H, de Krijger RR, van der Woude CJ, et al. Single-balloon enteroscopy, magnetic resonance enterography, and abdominal US useful for evaluation of small-bowel disease in children with (suspected) Crohn's disease. *Gastrointest Endosc* 2012;75:87–94.
334. Mensink PB, Groenen MJ, van Buuren HR, Kuipers EJ, van der Woude CJ. Double-balloon enteroscopy in Crohn's disease patients suspected of small bowel activity: findings and clinical impact. *J Gastroenterol* 2009;44:271–6.
335. Mensink PB, Aktas H, Zelinkova Z, West RL, Kuipers EJ, van der Woude CJ. Impact of double-balloon enteroscopy findings on the management of Crohn's disease. *Scand J Gastroenterol* 2010;45:483–9.
336. Heine GD, Hadithi M, Groenen MJ, Kuipers EJ, Jacobs MA, Mulder CJ. Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. *Endoscopy* 2006;38:42–8.
337. Gay G, Delvaux M. Double balloon enteroscopy in Crohn's disease and related disorders: our experience. *Gastrointest Endosc* 2007;66:582–90.
338. Manes G, Imbesi V, Ardizzone S, Cassinotti A, Pallotta S, Porro GB. Use of double-balloon enteroscopy in the management of patients with Crohn's disease: feasibility and diagnostic yield in a high-volume centre for inflammatory bowel disease. *Surg Endosc* 2009;23:2790–5.
339. Wiarda BM, Heine DG, Mensink P, Stolk M, Dees J, Hazenberg HJ, et al. Comparison of magnetic resonance enteroclysis and capsule endoscopy with balloon-assisted enteroscopy in patients with obscure gastrointestinal bleeding. *Endoscopy* 2012;44:668–73.
340. Seiderer J, Herrmann K, Diepolder H, Schoenberg SO, Wagner AC, Goke B, et al. Double-balloon enteroscopy versus magnetic resonance enteroclysis in diagnosing suspected small-bowel Crohn's disease: results of a pilot study. *Scand J Gastroenterol* 2007;42:1376–85.
341. Di Nardo G, Oliva S, Aloia M, Rossi P, Casciani E, Masselli G, et al. Usefulness of single-balloon enteroscopy in pediatric Crohn's disease. *Gastrointest Endosc* 2012;75:80–6.
342. Despott EJ, Gupta A, Burling D, Tripoli E, Konieczko K, Hart A, et al. Effective dilation of small-bowel strictures by double-balloon enteroscopy in patients with symptomatic Crohn's disease (with video). *Gastrointest Endosc* 2009;70:1030–6.
343. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526–35.
344. Ekblom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990;323:1228–33.
345. Soderlund S, Brandt L, Lapidus A, Karlen P, Brostrom O, Lofberg R, et al. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009;136:1561–7.
346. Bernstein CN, Blanchard JF, Kliever E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer* 2001;91:854–62.
347. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004;2:1088–95.
348. Jess T, Loftus Jr EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted county Minnesota. *Gastroenterology* 2006;130:1039–46.
349. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012;10:639–45.
350. Loftus Jr EV. Epidemiology and risk factors for colorectal dysplasia and cancer in ulcerative colitis. *Gastroenterol Clin North Am* 2006;35:517–31.
351. Friedman S, Rubin PH, Bodian C, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's

- colitis: results of a surveillance program spanning 25 years. *Clin Gastroenterol Hepatol* 2008;**6**:993–8.
352. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut* 1994;**35**:1590–2 [see comments].
  353. Ekbohm A, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990;**336**:357–9.
  354. Collins PD, Mpofu C, Watson AJ, Rhodes JM. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. *Cochrane Database Syst Rev* 2006:CD000279.
  355. Palli D, Trallori G, Saieva C, Tarantino O, Edili E, d'Albasio G, et al. General and cancer specific mortality of a population based cohort of patients with inflammatory bowel disease: the Florence Study. *Gut* 1998;**42**:175–9.
  356. Lakatos L, Mester G, Erdelyi Z, David G, Pandur T, Balogh M, et al. Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. *Inflamm Bowel Dis* 2006;**12**:205–11.
  357. Jess T, Loftus Jr EV, Velayos FS, Winther KV, Tremaine WJ, Zinsmeister AR, et al. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterol* 2007;**102**:829–36.
  358. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;**130**:1030–8.
  359. Lutgens MW, Vleggaar FP, Schipper ME, Stokkers PC, van der WJ, Hommes DW, et al. High frequency of early colorectal cancer in inflammatory bowel disease. *Gut* 2008;**57**:1246–51.
  360. Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams CB. Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. *Gut* 1990;**31**:800–6.
  361. Itzkowitz SH, Present DH. Consensus conference: colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;**11**:314–21.
  362. Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007;**133**:1099–105.
  363. Velayos FS, Loftus Jr EV, Jess T, Harmsen WS, Bida J, Zinsmeister AR, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology* 2006;**130**:1941–9.
  364. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002;**56**:48–54.
  365. Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM. Familial predisposition for colorectal cancer in chronic ulcerative colitis: a case-control study. *Gastroenterology* 1998;**115**:1079–83.
  366. Askling J, Dickman PW, Karlen P, Brostrom O, Lapidus A, Lofberg R, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology* 2001;**120**:1356–62.
  367. Jess T, Simonsen J, Jorgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012;**143**:375–81 [e371; quiz e313–374].
  368. Greenstein AJ, Sachar DB, Smith H, Pucillo A, Papatestas AE, Kreef I, et al. Cancer in universal and left-sided ulcerative colitis: factors determining risk. *Gastroenterology* 1979;**77**:290–4.
  369. Karvellas CJ, Fedorak RN, Hanson J, Wong CK. Increased risk of colorectal cancer in ulcerative colitis patients diagnosed after 40 years of age. *Can J Gastroenterol* 2007;**21**:443–6.
  370. Lashner BA, Kane SV, Hanauer SB. Colon cancer surveillance in chronic ulcerative colitis: historical cohort study. *Am J Gastroenterol* 1990;**85**:1083–7.
  371. Choi PM, Nugent FW, Schoetz Jr DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. *Gastroenterology* 1993;**105**:418–24.
  372. Lutgens MW, Oldenburg B, Siersema PD, van Bodegraven AA, Dijkstra G, Hommes DW, et al. Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. *Br J Cancer* 2009;**101**:1671–5.
  373. Karlen P, Kornfeld D, Brostrom O, Lofberg R, Persson PG, Ekbohm A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. *Gut* 1998;**42**:711–4.
  374. Eaden J, Abrams K, Ekbohm A, Jackson E, Mayberry J. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther* 2000;**14**:145–53.
  375. Provenzale D, Wong JB, Onken JE, Lipscomb J. Performing a cost-effectiveness analysis: surveillance of patients with ulcerative colitis. *Am J Gastroenterol* 1998;**93**:872–80.
  376. Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis* 2013;**7**:1–33.
  377. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;**59**:666–89.
  378. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994;**343**:71–4.
  379. Jess T, Loftus Jr EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, et al. Incidence and prognosis of colorectal dysplasia in inflammatory bowel disease: a population-based study from Olmsted County Minnesota. *Inflamm Bowel Dis* 2006;**12**:669–76.
  380. Befrits R, Ljung T, Jaramillo E, Rubio C. Low-grade dysplasia in extensive, long-standing inflammatory bowel disease: a follow-up study. *Dis Colon Rectum* 2002;**45**:615–20.
  381. Leidenius M, Kellokumpu I, Husa A, Riihela M, Sipponen P. Dysplasia and carcinoma in longstanding ulcerative colitis: an endoscopic and histological surveillance programme. *Gut* 1991;**32**:1521–5.
  382. Rutegard J, Ahsgren L, Stenling R, Janunger KG. Ulcerative colitis. Cancer surveillance in an unselected population. *Scand J Gastroenterol* 1988;**23**:139–45.
  383. Lim CH, Dixon MF, Vail A, Forman D, Lynch DA, Axon AT. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. *Gut* 2003;**52**:1127–32.
  384. Thomas T, Abrams KA, Robinson RJ, Mayberry JF. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. *Aliment Pharmacol Ther* 2007;**25**:657–68.
  385. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology* 1994;**107**:934–44.
  386. Subramanian V, Ramappa V, Telakis E, Mannath J, Jawhari AU, Hawkey CJ, et al. Comparison of high definition with standard white light endoscopy for detection of dysplastic lesions during surveillance colonoscopy in patients with colonic inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**19**:350–5.
  387. Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med* 2006;**355**:2533–41.

388. Toruner M, Harewood GC, Loftus Jr EV, Sandborn WJ, Tremaine WJ, Faubion WA, et al. Endoscopic factors in the diagnosis of colorectal dysplasia in chronic inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:428–34.
389. Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003;124:880–8.
390. Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. *Endoscopy* 2005;37:1186–92.
391. Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterology* 2007;132:874–82.
392. Marion JF, Wayne JD, Present DH, Israel Y, Bodian C, Harpaz N, et al. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. *Am J Gastroenterol* 2008;103:2342–9.
393. Matsumoto T, Nakamura S, Jo Y, Yao T, Iida M. Chromoscopy might improve diagnostic accuracy in cancer surveillance for ulcerative colitis. *Am J Gastroenterol* 2003;98:1827–33.
394. Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonial indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004;53:256–60.
395. Hlavaty T, Huorka M, Koller T, Zita P, Kresanova E, Rychly B, et al. Colorectal cancer screening in patients with ulcerative and Crohn's colitis with use of colonoscopy, chromoendoscopy and confocal endomicroscopy. *Eur J Gastroenterol Hepatol* 2011;23:680–9.
396. van den Broek FJ, Stokkers PC, Reitsma JB, Boltjes RP, Ponsioen CY, Fockens P, et al. Random biopsies taken during colonoscopic surveillance of patients with longstanding ulcerative colitis: low yield and absence of clinical consequences. *Am J Gastroenterol* Mar 22 2011 [Epub ahead of print].
397. Subramanian V, Mannath J, Raguath K, Hawkey CJ. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;33:304–12.
398. Wu L, Li P, Wu J, Cao Y, Gao F. The diagnostic accuracy of chromoendoscopy for dysplasia in ulcerative colitis: meta-analysis of six randomized controlled trials. *Colorectal Dis* 2012;14:416–20.
399. Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, van Deventer SJ, et al. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. *Endoscopy* 2007;39:216–21.
400. van den Broek FJ, Fockens P, van Eeden S, Stokkers PC, Ponsioen CY, Reitsma JB, et al. Narrow-band imaging versus high-definition endoscopy for the diagnosis of neoplasia in ulcerative colitis. *Endoscopy* 2011;43:108–15.
401. Ignjatovic A, East JE, Subramanian V, Suzuki N, Guenther T, Palmer N, et al. Narrow band imaging for detection of dysplasia in colitis: a randomized controlled trial. *Am J Gastroenterol* 2012;107:885–90.
402. Pellisé M, López-Cerón M, Rodríguez de Miguel C, Jimeno M, Zabalza M, Ricart E, et al. Narrow-band imaging as an alternative to chromoendoscopy for the detection of dysplasia in long-standing inflammatory bowel disease: a prospective, randomized, crossover study. *Gastrointest Endosc* 2011;74:840–8.
403. van den Broek FJ, Fockens P, van Eeden S, Reitsma JB, Hardwick JC, Stokkers PC, et al. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. *Gut* 2008;57:1083–9.
404. Wallace MB, Meining A, Canto MI, Fockens P, Miehlke S, Roesch T, et al. The safety of intravenous fluorescein for confocal laser endomicroscopy in the gastrointestinal tract. *Aliment Pharmacol Ther* 2010;31:548–52.
405. Gunther U, Kusch D, Heller F, Burgel N, Leonhardt S, Daum S, et al. Surveillance colonoscopy in patients with inflammatory bowel disease: comparison of random biopsy vs. targeted biopsy protocols. *Int J Colorectal Dis* 2011;26:667–72.
406. Odze RD, Tomaszewski JE, Furth EE, Feldman MD, Diallo R, Poremba C, et al. Variability in the diagnosis of dysplasia in ulcerative colitis by dynamic telepathology. *Oncol Rep* 2006;16:1123–9.
407. Odze RD, Goldblum J, Noffsinger A, Alsaigh N, Rybicki LA, Fogt F. Interobserver variability in the diagnosis of ulcerative colitis-associated dysplasia by telepathology. *Mod Pathol* 2002;15:379–86.
408. Taylor BA, Pemberton JH, Carpenter HA, Levin KE, Schroeder KW, Welling DR, et al. Dysplasia in chronic ulcerative colitis: implications for colonoscopic surveillance. *Dis Colon Rectum* 1992;35:950–6.
409. Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology* 2003;125:1311–9.
410. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. *Gastrointest Endosc* 2004;60:334–9.
411. Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? *Gastrointest Endosc* 2007;65:998–1004.
412. Blonski W, Kundu R, Lewis J, Aberra F, Osterman M, Lichtenstein GR. Is dysplasia visible during surveillance colonoscopy in patients with ulcerative colitis? *Scand J Gastroenterol* 2008;43:698–703.
413. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;58:S3–S43.
414. Blonski W, Kundu R, Furth EF, Lewis J, Aberra F, Lichtenstein GR. High-grade dysplastic adenoma-like mass lesions are not an indication for colectomy in patients with ulcerative colitis. *Scand J Gastroenterol* 2008;43:817–20.
415. Odze RD, Farraye FA, Hecht JL, Hornick JL. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. *Clin Gastroenterol Hepatol* 2004;2:534–41.
416. Rubin PH, Friedman S, Harpaz N, Goldstein E, Weiser J, Schiller J, et al. Colonoscopic polypectomy in chronic colitis: conservative management after endoscopic resection of dysplastic polyps. *Gastroenterology* 1999;117:1295–300.
417. Engelskjerd M, Farraye FA, Odze RD. Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. [see comments] *Gastroenterology* 1999;117:1288–94 [Discussion].
418. Smith LA, Baraza W, Tiffin N, Cross SS, Hurlstone DP. Endoscopic resection of adenoma-like mass in chronic ulcerative colitis using a combined endoscopic mucosal resection and cap assisted submucosal dissection technique. *Inflamm Bowel Dis* 2008;14:1380–6.
419. Vieth M, Behrens H, Stolte M. Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. *Gut* 2006;55:1151–5.
420. Kisiel JB, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. Outcome of sporadic adenomas and adenoma-like

- dysplasia in patients with ulcerative colitis undergoing polypectomy. *Inflamm Bowel Dis* 2012;**18**:226–35.
421. Torres C, Antonioli D, Odze RD. Polypoid dysplasia and adenomas in inflammatory bowel disease: a clinical, pathologic, and follow-up study of 89 polyps from 59 patients. *Am J Surg Pathol* 1998;**22**:275–84.
422. Wanders LK, Dekker E, Pullens B, Bassett P, Travis SP, East JE. Cancer risk following resection of polypoid dysplasia in patients with long-standing ulcerative colitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2013 [in press].
423. Blackstone MO, Riddell RH, Rogers BH, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. *Gastroenterology* 1981;**80**:366–74.
424. Borjesson L, Willen R, Haboubi N, Duff SE, Hulten L. The risk of dysplasia and cancer in the ileal pouch mucosa after restorative proctocolectomy for ulcerative proctocolitis is low: a long-term follow-up study. *Colorectal Dis* 2004;**6**:494–8.
425. O'Riordain MG, Fazio VW, Lavery IC, Remzi F, Fabbri N, Meneu J, et al. Incidence and natural history of dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of a five-year to ten-year follow-up. *Dis Colon Rectum* 2000;**43**:1660–5.
426. Gorgun E, Remzi FH, Manilich E, Preen M, Shen B, Fazio VW. Surgical outcome in patients with primary sclerosing cholangitis undergoing ileal pouch-anal anastomosis: a case-control study. *Surgery* 2005;**138**:631–7 [discussion 637–639].
427. Setti C, Talbot IC, Nicholls RJ. Longterm appraisal of the histological appearances of the ileal reservoir mucosa after restorative proctocolectomy for ulcerative colitis. *Gut* 1994;**35**:1721–7.
428. Veress B, Reinholt FP, Lindquist K, Lofberg R, Liljeqvist L. Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. *Gastroenterology* 1995;**109**:1090–7.
429. Gullberg K, Stahlberg D, Liljeqvist L, Tribukait B, Reinholt FP, Veress B, et al. Neoplastic transformation of the pelvic pouch mucosa in patients with ulcerative colitis. *Gastroenterology* 1997;**112**:1487–92.
430. Coull DB, Lee FD, Henderson AP, Anderson JH, McKee RF, Finlay IG. Risk of dysplasia in the columnar cuff after stapled restorative proctocolectomy. *Br J Surg* 2003;**90**:72–5.