Journal of Crohn's and Colitis, 2019, 144–164K
doi:10.1093/ecco-jcc/jjy113
Advance Access publication August 23, 2018
ECCO Guideline/Consensus Paper

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ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications

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Introduction

This new diagnostic consensus guideline is a joint project of the European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR] that now merges the former ECCO-ESGAR Imaging Guideline and the former ECCO Endoscopy Guideline, also including laboratory parameters. It has been drafted by 30 ECCO and ESGAR members from 17 European countries. All the authors recognise the work of and are grateful to previous ECCO and ESGAR members who contributed to creating the earlier consensus guidelines on imaging and endoscopy.

The former guidelines have been condensed into this new diagnostic consensus guideline which consists of two papers: the first detailing assessment at initial diagnosis, to monitor treatment and for the detection of complications; the second dealing with the available scoring systems and general considerations regarding the different diagnostic tools.

The strategy to define consensus was similar to that previously described in other ECCO consensus guidelines [available at: www.ecco-ibd.eu]. Briefly, an open call for participants was made, with ECCO participants selected by the Guidelines' Committee of ECCO [known as GuiCom] on the basis of their publication record and a personal statement, and ESGAR participants nominated by ESGAR. The following working parties were established: diagnostics at initial diagnosis, diagnostics for monitoring treatment in patients with known IBD, diagnostics for the detection of complications, scores for IBD, and general principles and technical aspects.

Provisional guideline statements and supporting text were written following a comprehensive literature review, then refined following two voting rounds. The first voting round introduced a more comprehensive voting procedure, in which each guidelines participant voted on all statements by explicitly reviewing those statements together with their respective supporting text and references.

The second voting round included optional national representative participation of ECCO's 36 member countries and ESGAR's 28 member countries. The level of evidence was graded according to the Oxford Centre for Evidence-Based Medicine [www.cebm.net]. The ECCO statements were finalised by the authors at a face-to-face meeting in Barcelona in October 2017, and represent consensus with agreement of at least 80% of the present participants. Consensus statements are intended to be read in context with their qualifying comments, and not in isolation. The supporting text was then finalised under the direction of each working group leader [SV, TK, GF, VA, EC], before being integrated by the consensus leaders [CM, JS, AS].

Chapter 1: Initial diagnosis

Statement 1.1. ECCO-ESGAR Diagnostics GL [2018]

A single reference standard for the diagnosis of Crohn's disease [CD] or ulcerative colitis [UC] does not exist. The diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations [EL5]

A single reference standard for the diagnosis of Crohn's disease [CD] or ulcerative colitis [UC] does not exist. At a minimum, the diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, and histological investigations. When CD is suspected, it may be necessary to visualise [radiologically] the small intestine. Infectious colitis, including *Clostridium difficile*, should be excluded.

Statement 1.2. ECCO-ESGAR Diagnostics GL [2018]

Genetic or serological testing is currently not recommended for routine diagnosis of CD or UC [EL3]

Statement 1.3. ECCO-ESGAR Diagnostics GL [2018]

On diagnosis, complementary investigations should focus on markers of disease activity [EL2], malnutrition, or malabsorption [EL5]. Immunisation status should be assessed. Consider screening for latent tuberculosis [EL5]

At diagnosis, every patient should have a biochemical assessment with full blood count, inflammatory markers (C-reactive protein [CRP]), electrolytes, liver enzymes, and a stool sample for microbiological analysis, including *C. difficile*.[1,2] The full blood count may reveal thrombocytosis [due to an inflammatory response], anaemia, and leukocytosis. The presence of raised inflammatory markers [CRP] broadly correlates with clinical severity in CD[1] but less so in UC except in the case of acute severe colitis.[2] However, laboratory markers of chronic inflammation may be normal in both UC and CD.[3,4] As raised CRP, leukocytosis, or both are not IBD-specific, their presence cannot differentiate IBD from infectious [or other causes of] colitis. Apart from biochemical evidence of malnutrition, hypoalbuminaemia can reflect severe inflammation; however this is not superior to CRP.[4]

Faecal calprotectin [FC], a neutrophil-derived protein, appears to be the most sensitive marker of intestinal inflammation in IBD. Other neutrophil-derived proteins are elastase, lysozyme, and lactoferrin.[3,5–10] Calprotectin values correlate well with endoscopic indices of disease activity and are thus important in various clinical settings, including initial diagnosis, diagnosis of relapse, and response to treatment.[11–15]

In the initial investigations of a patient with gastrointestinal symptoms and a raised stool marker of inflammation, an ileocolonoscopy should be performed. An exact cut-off value that distinguishes between IBD and functional bowel diseases does not exist.[16,17] However, good diagnostic accuracy can potentially be obtained at a cut-off value of 150 µg/g, as recently suggested in a meta-analysis.[18] However, FC lacks the specificity to discriminate between IBD and other causes of intestinal inflammation.[7]

During the diagnostic process of IBD, gastrointestinal infections should always be excluded.[1,2] Loose stools for more than 6 weeks usually discriminate IBD-associated colitis from most cases of infectious diarrhoea.[19] Stool specimens should be obtained to exclude common pathogens and specifically assayed for *C difficile* toxin. Additional tests may be tailored according to medical history, such as for those who have travelled abroad. This may include assessment for ova, cysts, and parasites.[20]

Serological markers may be used to support a diagnosis, though the accuracy of the best available tests [pANCA and ASCAs] is rather limited and hence ineffective at differentiating colonic CD from UC.[21,22] Similarly, the additional diagnostic value of antiglycan and antimicrobial antibodies, such as anti-OmpC and CBir1, is small.[3,4,23,24] Likewise, although more than 250 IBD-associated susceptibility single nucleotide polymorphisms [SNPs] have been identified, genetic testing for common variants does not allow diagnosis of IBD.[25]

Some infections are preventable, and the risk for severe infections during immunosuppression can be decreased or eliminated if the patient is adequately vaccinated. Vaccination is best given before initiating immunomodulatory therapy. The following should be assessed before vaccination: hepatitis B surface antibody, hepatitis B antigen, hepatitis B core antibody, hepatitis A IgG, measles serology, and varicella serology. Additional baseline tests recommended at diagnosis include hepatitis C serology, EpsteinBarr serology and human immunodeficiency virus serology, after appropriate counselling.[26]

Statement 1.4. ECCO-ESGAR Diagnostics GL [2018]

[ECCO Anaemia Guideline: statement 1D in Dignass *et al.*] Diagnostic criteria for iron deficiency depend on the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin <30 μg/L is an appropriate criterion [EL2]. In the presence of inflammation, serum ferritin up to 100 μg/L may still be consistent with iron deficiency [EL4]

Statement 1.5. ECCO-ESGAR Diagnostics GL [2018]

[ECCO Anaemia Guideline: statement 1E in Dignass *et al.*] In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anaemia of chronic disease are serum ferritin >100 μg/L and transferrin saturation <20%. If the serum ferritin level is between 30 and 100 μg/L, a combination of true iron deficiency and anaemia of chronic disease is likely [EL2]

One of the most frequent complications of IBD is anaemia (haemoglobin [Hb] <13 g/dL for men and <12 g/dL for women), which may affect patients' quality of life and should hence be evaluated at initial diagnosis.[27–29] In cases of documented anaemia, further workup should start from the evaluation of mean corpuscular volume [MCV]. Microcytic anaemia is usually the most common type of anaemia in IBD, which usually indicates iron deficiency anaemia.[30] Macrocytosis may indicate vitamin B12 or folate deficiency and is also commonly seen during thiopurine therapy, whereas normocytosis may suggest anaemia of chronic disease [ACD].[31] The distinction between iron deficiency anaemia and ACD or a mixed picture of micro- and macrocytosis is important, as treatment is different between these conditions.

The diagnosis of iron deficiency depends on the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, the diagnosis is made when serum ferritin is <30 μg/L.[32,33] In the presence of inflammation, serum ferritin up to 100 μg/L may still be compatible with iron deficiency.[34,35] Other markers suggestive of iron deficiency anaemia are low mean corpuscular volume [MCV], raised red cell distribution width [RDW], microcytic hypochromic pencil red cells on blood film, low serum iron, raised total iron-binding capacity, and transferrin saturation of <16%.[36]

Statement 1.6. ECCO-ESGAR Diagnostics GL [2018]

For suspected IBD, ileocolonoscopy with biopsies from inflamed and uninflamed segments are required to establish diagnosis [EL1], except in the case of acute severe colitis in which sigmoidoscopy may be sufficient [EL3]

Statement 1.7. ECCO-ESGAR Diagnostics GL [2018]

No endoscopic feature is specific for CD or UC. The most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation and rectal involvement [EL2]. The most useful endoscopic features in CD are discontinuous lesions, presence of strictures and fistulae, and perianal involvement [EL2]

For a reliable diagnosis of UC and CD, ileocolonoscopy with a minimum of two biopsies from the inflamed regions should be obtained.[37–40] Additional biopsies from uninflamed regions and every colonic segment [including the rectum, especially in UC] may be helpful in the diagnostic process and to diagnose microscopic pathology. The distinction of infectious colitis from IBD is usually characterised by preserved crypt architecture and acute inflammation.[41] However, in very early disease the architecture can be preserved. Other differential diagnoses include segmental colitis associated with diverticulitis [SCAD] and ischaemic colitis.[42–45]

Granulomas and focal crypt architectural abnormalities, in conjunction with focal or patchy chronic inflammation [defined by the presence of lymphocytes and plasma cells], or mucin preservation at active sites, are CD-related histological features. The patchy nature of the inflammation is only diagnostic in untreated adult patients.[46–50] One single feature is not considered to be diagnostic, though there are no data available as to how many features must be present in an endoscopically derived biopsy before a firm diagnosis can be made.[40] On surgical samples, a diagnosis of CD should be made when at least three histological features suggestive of CD [segmental crypt architectural abnormalities and mucin depletion, mucin preservation at the active sites, and focal chronic inflammation without crypt atrophy] are present in the absence of granulomas, or when an epithelioid granuloma is present with one other feature.[39,40]

Focal or diffuse basal plasmacytosis has been recognised as the earliest feature with the highest predictive value for UC diagnosis. This can be identified in 38% of patients within 2 weeks after symptom presentation. During this period, the distribution pattern of basal plasmacytosis is focal but may eventually change into a diffuse pattern throughout the disease course. Only about 20% of patients show crypt distortion within 2 weeks of the first symptoms of colitis. The distinction from infectious colitis is therefore a major concern. Widespread mucosal or crypt architectural distortion, mucosal atrophy, and an irregular or villous mucosal surface appear later, at least 4 weeks after presentation.[41,51] Not all microscopic features found in UC are observed in early disease. A correct diagnosis of UC is reached in approximately 75% of cases where two or three features are present. However, the exact number of features needed for UC diagnosis has not been established.[37]

Due to the increased risk of bowel perforation, complete ileocolonoscopy is not usually recommended in case of acute severe colitis.[52] However, a study by Terheggen *et al.* demonstrated that there was no relationship between complication rate and disease activity.[53]

Flexible sigmoidoscopy can be safely performed to establish the diagnosis of UC. Phosphate enema preparation before flexible sigmoidoscopy has been reported to be safe in this setting,[54] though it is generally advised to avoid purgatives, especially fleet enemas and oral sodium phosphate preparations.[55]

Statement 1.8. ECCO-ESGAR Diagnostics GL [2018]

Patients with clinical suspicion of CD and with normal endoscopy should be considered for small bowel capsule endoscopy [SBCE] evaluation or cross-sectional imaging [EL2]. If stenotic disease is suspected, risk of retention should be assessed [EL2]

Small bowel capsule endoscopy [SBCE] is a sensitive tool to detect mucosal abnormalities in the small bowel. There are currently two validated indexes available, namely the Capsule Endoscopy Crohn's Disease Activity Index [CECDAI] and the Lewis Score, which assess the disease location and activity of small bowel involvement. Both will be discussed further in part 2. The diagnostic yield of SBCE is comparable to other modalities (MR enterography, small intestine contrast ultrasound [SICUS]), apart from proximal small bowel involvement for which SBCE seems superior.[56] As proximal small bowel involvement is associated with a higher risk of surgery,[57] this superior accuracy might have prognostic value.[56] Data from small, prospective cohorts suggest that the diagnostic yield of SBCE is highest in patients with suggestive CD symptoms and increased inflammatory markers,[58,59] although this was not replicated in larger retrospective cohorts.[60,61] However, the likelihood of positive diagnosis is very low in patients with suspected CD with FC <50 µg/g.[62] Additionally, all patients with unclassified IBD at diagnosis could also be considered for SBCE.

Similarly, as normal imaging tests such as intestinal ultrasound [IUS] and MR enterography of the small bowel cannot entirely exclude small bowel involvement, CD patients with normal radiological tests can be considered for additional SBCE, for example in patients with clinical signs suspicious of small bowel Crohn´s disease and elevated calprotectin and/or otherwise unexplained iron deficiency anaemia. Contraindications for SBCE include gastrointestinal obstruction, strictures, and swallowing disorders.[63–65] The risk of capsule retention in patients with suspected CD without obstructive symptoms and without history of small bowel resection or known stenosis is low and comparable to that of obscure gastrointestinal [GI] bleeding.[66–69] Data on retention rates in patients with CD varies from 2% to 13% in patients with established CD, to approximately 1.5% in patients with suspected CD.[70] If small bowel stenosis is not firmly excluded, a patency capsule can be used to confirm small bowel patency before performing SBCE. All patency capsules are dissolved within 72 h. SBCE is considered safe if the patency capsule is excreted before 30 h, an intact capsule is excreted after 30 h, or passage to the colon of an intact patency capsule has been radiologically confirmed.[71] Yadav *et al.* demonstrated that the negative predictive value [NPV] for patency capsules and radiological tests were not significantly different.[72] Thus, if either test is negative before SBCE, the patient will most likely pass the capsule without incident. Radiological tests have the advantage of eliminating false-positive results, as they do not depend on intestinal motility. However, cross-sectional imaging is significantly less accurate in the evaluation of functional small bowel patency, frequently overestimating the risk of obstruction. In a recent study evaluating the accuracy of MRI for prediction of patency capsule retention in patients with established small bowel CD, the sensitivity and specificity of MR enterography were 92.3% and 59%, respectively. Thus, if the decision to administer SBCE was based on imaging and not on patency capsule results, at least 40% of the patients would not have undergone SBCE.[57] Questions about optimal bowel preparation, selection of patients, and the optimal reading protocol remain to be clarified[73] and are discussed in more detail later in part 2.

Statement 1.9. ECCO-ESGAR Diagnostics GL [2018]

Upper GI endoscopy is recommended in patients with CD with upper GI symptoms, but not for asymptomatic newly diagnosed adult IBD patients [EL5]

CD involving the upper GI tract [oesophagus, stomach, and duodenum] is almost invariably accompanied by small or large bowel involvement.[74–76] Patients who have upper gastrointestinal symptoms such as nausea, dyspepsia, and vomiting will benefit from upper GI endoscopy.[77] Whether asymptomatic adult CD patients should routinely undergo oesophago-gastroduodenoscopy is still debated. However, a prospective registry reported a higher prevalence of upper GI involvement in asymptomatic CD patients than initially expected,[77] suggesting a place for a standard gastroscopy at CD diagnosis to correctly evaluate disease extent. When it is difficult to obtain a histological diagnosis of CD, upper GI endoscopy may support the diagnosis, as focal gastritis may be a feature of CD.[74] Finally, upper GI endoscopy is mandatory in patients with suspected concomitant coeliac disease.[78]

The sensitivity and specificity of radiological imaging techniques in the assessment of upper GI CD are unclear, with publications limited to case reports and small series. Radiological assessment of patients should be reserved only for those patients with CD and upper GI symptoms in whom endoscopic assessment has failed or is incomplete. Radiological assessment of the upper GI tract should not form part of routine diagnostic workup.

Statement 1.10. ECCO-ESGAR Diagnostics GL [2018]

All newly diagnosed CD patients should undergo small bowel assessment [intestinal ultrasound, MR enterography and/or capsule endoscopy] [EL2]

The ileocaecal region is usually visualised adequately endoscopically. The proximal ileum and jejunum can be more difficult to assess. A study by Samuel *et al.* evaluated CD patients with computed tomography [CT] enterography and ileocolonoscopy. Among the group of patients with normal results from ileoscopy, 53.7% had active, small bowel CD. Ileoscopic examination can thus miss CD of the terminal ileum, as the disease can skip the distal ileum or may be confined to the intramural portion of the bowel wall and mesentery.[79]

CT and MRI are both used to assess the small intestine. Both techniques can establish disease extent and activity based on wall thickness and increased intravenous contrast enhancement.[80] A direct comparison of CT and MRI for the diagnosis of a variety of small intestinal lesions demonstrates high sensitivity and specificity, similar for both techniques.[81–83] Due to the absence of radiation, MRI should be preferred over CT, particularly in young patients.[81]

A study by Messaris *et al.* demonstrated that routine use of MR enterography can alter the management of patients with ileal or ileocolonic CD. In this study, 64 [53%] of patients had additional medical management for active inflammation, and 16% underwent an operation for complicated CD or medical intractability. The intraoperative findings were consistent with the MRI diagnosis in all surgically treated patients.[84] Similarly, Mendoza *et al.* demonstrated

that MRI influenced a change in treatment [medical or surgical] in 83 [55.3%] patients. The change in management even affected those patients who were already diagnosed with ileal or ileocolonic CD.[85]

A direct comparison of intestinal ultrasound [IUS] and MRI performed in 234 consecutive suspected CD patients showed a similar diagnostic accuracy in detecting small bowel CD. Sensitivity, specificity, positive predictive value [PPV], and NPV for CD diagnosis were 94%, 97%, 97%, and 94% for IUS and 96%, 94%, 94%, and 96% for MR enterography, respectively. IUS was less accurate than MR enterography in defining CD extent [r = 0.69], whereas the concordance in terms of CD location between the two procedures was high [κ = 0.81]. MR enterography also showed a fair concordance with IUS regarding strictures [κ = 0.82] and abscesses [κ = 0.88], with better detection of enteroenteric fistulas [κ = 0.67].[86]

A UK multicentre trial of 284 newly diagnosed or suspected relapsed Crohn's disease patients showed that MRE had significantly greater sensitivity for small bowel disease extent [presence and location] compared with IUS [80% versus 70%, respectively]. MRE also had significantly greater specificity than IUS [95% versus 81%, respectively]. For detecting the presence of small bowel disease irrespective of location, IUS sensitivity was 92%, compared with 97% for MRE. Sensitivity for active small bowel [SB] disease was significantly greater for MRE than IUS (96% versus 90% [82 to 95]).[87]

A review by Calabrese *et al.* reported that IUS had a 79.7% sensitivity and 96.7% specificity for the diagnosis of suspected CD, and an 89% sensitivity and 94.3% specificity in assessment of patients with known CD with lower accuracy for detecting proximal small bowel lesions. Administration of an oral contrast agent improved the sensitivity and specificity in determining CD lesions.[88]

In a systematic review, the diagnostic yield of SBCE is comparable to MR enterography and IUS, apart from proximal small bowel involvement for which SBCE seems to be superior. The odds ratio [OR] for diagnosis via SBCE versus MR enterography was 0.56 (95% confidence interval [CI] 0.28–1.13; p = 0.1] and the OR for SBCE had superior diagnostic yield for proximal small bowel disease with an OR of 2.62 [95% CI 1.10–6.53; p = 0.03].[56]

A range of factors, including local availability and expertise, determines the choice of small bowel imaging modality. For initial assessment and exclusion of CD, SBCE, IUS, MR enterography, and CT enterography are superior to small bowel follow-through [SBFT].[83,89] Cross-sectional imaging of the small bowel should be performed in preference to SBCE where clinical symptoms indicate obstructive or stricturing small bowel CD.

Statement 1.11. ECCO-ESGAR Diagnostics GL [2018]

The presence of at least three small intestine ulcers in SBCE highly suggests a diagnosis of CD, provided the patient has not been using non-steroidal anti-inflammatory drugs [NSAIDs] for at least 1 month before the test [EL4]

Statement 1.12. ECCO-ESGAR Diagnostics GL [2018]

In patients with negative endoscopy and suspicion of CD on MRI or small bowel capsule endoscopy, device-assisted enteroscopy may be performed if diagnosis needs to be confirmed endoscopically and histologically [EL3]

Several small studies have evaluated the utility of SBCE for reclassification of patients with UC and with unclassified IBD, and reported varying reclassification rates. Although a normal SBCE cannot exclude CD, the presence of small bowel pathology that is consistent with CD enables reclassification.[90–95] In a study by Mow *et al.*, multiple ulcerations [≥3 ulcerations] were considered diagnostic for CD and were observed in 26% of cases.[90] Similar data have been reported by Monteiro *et al.*; 25% of patients with unclassified IBD were found to have small bowel involvement consistent with CD. Still, 37% of patients remained IBD unclassified during further follow-up.[95]

Statement 1.13. ECCO-ESGAR Diagnostics GL [2018]

Patients with unexplained perianal abscesses or complex fistulae should be investigated for CD [EL4]

Perianal manifestations result in fistula and abscess formation in 21% to 54% of CD patients[96–99] and more frequently [up to 41%] in patients with isolated colonic involvement compared with isolated ileal disease [12%].[97] A thorough baseline clinical examination of the perianal area should to be performed in all newly diagnosed patients at ileocolonoscopy, as symptoms can be initially very mild.

Diagnosis and classification of perianal disease are usually achieved via a combination of both clinical and imaging findings.[100] Fistulae can be considered 'simple' if they are low [of superficial or low intersphincteric or low transsphincteric origin], have a single external opening, and lack evidence of abscesses, rectovaginal fistulas, or anorectal strictures. 'Complex' fistulas are high [of high intersphincteric or high trans-sphincteric or extrasphincteric or suprasphincteric origin], may have multiple external openings, and can be associated with the presence of abscesses, rectovaginal fistulae, or anorectal strictures.[101]

A perianal abscess may be the first presentation of CD in a healthy individual.[102] Patients with an unexplained fistula and suspicion of CD should therefore undergo ileocolonoscopy to assess mucosal inflammation in the ileum or colon that may indicate CD.[103] In case of a negative conventional workup including ileocolonoscopy, capsule endoscopy can provide an incremental diagnostic yield of 24%.[104]

Proctosigmoidoscopy or ileocolonoscopy [if the proximal colon also needs evaluation] should be performed routinely in all patients with perianal CD to assess disease extent, severity of luminal inflammation, and presence of internal openings, and to exclude complications such as strictures and cancer.[103,105] Proctitis is a known risk factor of persistent non-healing fistula tracts and increased proctectomy rates,[106] and often indicates complex fistulae and associated complications such as abscesses.[100] Undiagnosed extensions and abscesses are major causes of recurrent disease after attempted surgical cure.[100]

Chapter 2: Monitoring known IBD

2.1. Monitoring therapeutic success

Statement 2.1.1. ECCO-ESGAR Diagnostics GL [2018]

Response to treatment in active ulcerative colitis [UC] should be determined by a combination of clinical parameters, endoscopy, and laboratory markers such as C-reactive protein [CRP] and faecal calprotectin [EL1]

Statement 2.1.2. ECCO-ESGAR Diagnostics GL [2018]

In patients with UC who clinically respond to medical therapy, mucosal healing [MH] should be determined endoscopically or by faecal calprotectin [FC] approximately 3 to 6 months after treatment initiation [EL5]

Statement 2.1.3. ECCO-ESGAR Diagnostics GL [2018]

Endoscopic reassessment in UC should be considered in case of severe relapse, persistent disease activity, new unexplained symptoms, and before switch of therapy [EL5]. Sigmoidoscopy might be sufficient in most patients [EL5]

There is no gold standard in determination of therapeutic success in ulcerative colitis [UC]. For follow-up of active disease in UC, endoscopy remains the reference standard. As UC involves the mucosa continuously from the rectum, colonoscopy with biopsies is still the reference standard for assessment of disease extent. However, flexible sigmoidoscopy is adequate for assessment of disease activity in most patients.

Several studies determined the benefit of mucosal healing [MH] in patients with UC. In a prospective Norwegian cohort, MH was associated with reduced risk of colectomy in UC and lower inflammation at 5 years.[107] These findings could be confirmed by a recent meta-analysis.[108] In this meta-analysis, patients with MH had a pooled odds ratio of 4.50 for achieving long-term [after at least 52 weeks] clinical remission (95% confidence interval [CI] 2.12–9.52), 4.15 for remaining free of colectomy [95% CI 2.53–6.81], 8.40 for achieving long-term MH [95% CI 3.13–22.53], and 9.70 for achieving long-term corticosteroid-free clinical remission [95% CI 0.94–99.67], compared with patients without MH. In accordance with these findings, an international consensus panel recently recommended MH as an important therapeutic goal for UC.[109]

There is no evidence-based consensus of when best to reassess disease activity after a change in therapy. However, in most induction studies MH has been determined approximately 2 to 3 months after starting treatment.[110] Although this appears to be an appropriate time point to reassess, the exact timing will depend upon clinical necessity and the chosen therapy.

There is a growing need to replace invasive diagnostics by surrogate non-invasive markers. Blood parameters are convenient. However, C-reactive protein [CRP] has low sensitivity in determining active mucosal disease in UC, with serum levels frequently within normal limits even in active disease.[111] The exception is in patients with elevated CRP levels during disease flare, for whom CRP might be used as a suitable follow-up. A more accurate surrogate marker of MH is faecal calprotectin [FC]. There is a strong correlation between endoscopic inflammation and FC in UC. In a study with 52 patients, FC correlated with clinical Mayo score [r = 0.63; $p < 0.0001$].[112] This correlation was strengthened by adding the endoscopic subscore [r = 0.90; $p < 0.0001$]. The endoscopic subscore also correlated independently with FC [r = 0.96; $p < 0.0001$]. The use of FC as a surrogate marker for MH in UC has also been demonstrated in several other studies.[113,114]

Another potential non-invasive alternative for monitoring active UC is intestinal ultrasound [IUS]. In four studies that assessed the diagnostic accuracy of IUS in a total of 74 patients, sensitivities ranged from 48% to 100% and specificities ranged from 82% to 90%. Current evidence indicates that the diagnostic accuracy of IUS in UC is also related to disease site, as sensitivity is high for sigmoid or descending colonic disease [reaching 97%][115] but low for rectal disease.[116] The utility of IUS for assessing activity has been assessed in a study including 38 IBD patients [12 UC] and six controls.[117] The mean colonic wall thickness was 3.2 mm in both Crohn's disease [CD] and UC, being higher in moderately [$n = 46$; $p < 0.001$] or severely inflamed bowels [$n = 20$; $p < 0.001$] compared with normal segments [$n = 58$]. There are only few studies that address the use of IUS for follow-up of patients with active UC under treatment. In a recent study of 83 patients with moderate-to-severe UC, endoscopic and IUS severity were graded 0 to 3 at entry according to validated scores.[116] Of the recruited patients, 74 patients who were clinically responsive to steroids were followed up with repeated colonoscopy and IUS at 3, 9, and 15 months from recruitment. A high and consistent concordance was demonstrated between endoscopic and IUS scores [weighted κ between 0.76 and 0.90]. Thus, IUS may be a potential alternative to endoscopy to assess response to treatment of severe UC.

As IUS has significant limitations in detecting rectal disease, proctitis cannot be assessed by IUS as an alternative to sigmoidoscopy. Whereas FC has been shown to be useful for follow-up of proctitis during treatment with mesalamine suppositories 8 weeks after treatment, the absolute levels of FC in ulcerative proctitis are low.[118] Transrectal endosonography studies show that mucosal thickness correlates with endoscopic disease activity and a decline in bowel wall thickness, which can be determined a few weeks after treatment in patients with active UC.[119]

No study has compared the combination of different parameters such as IUS plus FC in active UC, even though it is conceivable that combinations might enhance sensitivity. MR colonography [MRC] can also assess inflammation with relatively high accuracy. In the largest series of 50 patients who underwent both MRC and endoscopy, the segmental simplified MRC index strongly correlated with the modified Baron score [r = 0.81, $p < 0.001$]. MRC was also able to detect endoscopic inflammation and severe lesions with high diagnostic accuracy [sensitivity 87% and 83%, specificity 88% and 82%, area under the curve 0.95 and 0.91, $p < 0.001$, respectively]. MRI may provide useful information on wall thickening, oedema, polyps, and extraluminal complications.[120–122] MRI, especially when implemented with diffusion-weighted sequences, has high diagnostic accuracy in detecting active inflammation. Oussalah *et al*. investigated 35 patients with UC, and reported a sensitivity and specificity of 89.47% and 86.67%, respectively.[123] Moreover, the accuracy of the diffusion-weighted imaging hyperintensity for detecting colonic inflammation was greater in UC than in CD [$p = 0.004$].

Statement 2.1.4. ECCO-ESGAR Diagnostics GL [2018]

Clinical and biochemical response to treatment of Crohn's disease [CD] should be determined within 12 weeks following initiation of therapy [EL2]. Endoscopic or transmural response to therapy should be evaluated within 6 months following initiation of therapy [EL5]

Statement 2.1.5. ECCO-ESGAR Diagnostics GL [2018]

Endoscopic or cross-sectional reassessment in CD should be considered in cases of relapse, persistent disease activity, new unexplained symptoms, and prior to switch of therapy [EL5]

Mucosal healing

There is no reference standard for determining therapeutic success in CD. Clinical symptoms as scored by the CD Activity Index [CDAI] are not a reliable measure of the underlying inflammation. An increasing body of evidence suggests that MH may change the natural course of CD by decreasing relapse rates, hospitalisation rates, and the need for surgery[124–126]; as such, evaluation should be aimed at detecting this

endpoint, or at least at assessing a reliable surrogate marker of MH. MH can be directly visualised endoscopically. Cross-sectional imaging and non-invasive serological and faecal surrogate markers may however provide an indication, especially important when assessing parts of the bowel that are difficult to reach endoscopically.

The time interval of when to evaluate MH endoscopically can be inferred somewhat from trial data. However, studies have seldom been designed to directly evaluate the best point for reassessment and, as such, inferences regarding optimal timing for re-evaluation must be taken with care. Any recent change in therapy must also be considered. For example, it is recognised that the anti-integrin antibody vedolizumab takes longer than steroids or anti-TNFs for MH to occur. A sub-study of the SONIC trial demonstrated that MH along with steroid-free clinical remission at Week 26 was strongly predictive of steroid-free clinical remission at Week 50 [82%].[127] The EXTEND trial demonstrated that MH at 12 weeks correlated well with MH at 52 weeks.[126] Thus, it appears that 12 to 24 weeks is a sensible time scale for re-evaluation of MH.

The degree of mucosal inflammation may differ between segments of the digestive tract[128]; the need for panenteric evaluation remains to be determined. In a retrospective analysis of the SONIC trial, CDAI scores and CRP values at baseline and at Week 26 were analysed from 188 CD patients who had evaluable ileocolonoscopy with evidence of mucosal ulceration at baseline.[129] Half of the patients treated with azathioprine or infliximab [or both] in clinical remission had endoscopic or CRP evidence [or both] of residual active CD, whereas other patients with endoscopic and CRP normalisation had persistent clinical symptoms. In a retrospective study of 201 patients with CD, the predictors of medium-term clinical efficacy and MH during adalimumab therapy were evaluated.[130] Clinical efficacy and normalised CRP at Week 12 were associated with medium-term clinical efficacy and mucosal healing during adalimumab therapy, whereas need for combined immunosuppression at induction and smoking status were predictors for non-response. Thus, correlation between CRP and MH is variable. Several studies indicate that FC correlates well with colonic inflammation in CD and might therefore be used as a surrogate marker.[62,112] Importantly, although initial studies suggested that FC may be less sensitive in isolated small bowel disease, a recent meta-analysis demonstrated that the diagnostic yield of FC is significant for detection of active disease in the small bowel, with a negative predictive value [NPV] of 90% for the cut-off value of 50 µg/mL.[62]

Transmural healing – Role of MRI, CT, and IUS

There is no reference standard for CD activity, and any kind of diagnostic modality [including endoscopy, MRI, laboratory parameters, or IUS] can only be used as a surrogate marker in this situation. CD is a transmural process; thus full-thickness bowel healing or remodelling could be important endpoints.

Various studies have assessed the value of cross-sectional imaging techniques for therapeutic monitoring in CD affecting the small and large bowel. These studies assessed IUS,[131–136] CT,[137] or MRI.[138–140]

The role of IUS as a non-invasive and inexpensive imaging modality for determining the treatment response of transmural inflammation in CD has been evaluated in different studies. The utility of IUS for assessing activity and drug response has been compared with colonoscopy,[116] with high concordance [weighted κ between 0.76 and 0.90]. For example, a prospective study performed on 24 consecutive patients with CD used IUS to assess changes induced by anti-TNF therapy and its relationship with clinical and biological response.[141] Parameters were measured 1 week before induction treatment and 2 weeks thereafter. Anti-TNF therapy led to a significant reduction in bowel wall thickness [$p = 0.005$] and Doppler flow [$p = 0.02$], leading to the disappearance of IUS changes in 50% of the patients. However, sonographic normality was only achieved in five out of 17 patients [29%] with a clinical and biological response, and could not differentiate between those with and without clinical and biological response [$p = 0.27$]. A more recent prospective trial evaluated IUS features in patients with CD after treatment with biologics, using ileocolonoscopy as a reference standard.[142] In this trial, normalisation of the IUS parameters could be observed in 62.8% of the patients, with a significant correlation compared with ileocolonoscopy [$\kappa = 0.76$; $p < 0.001$]. Some authors suggest that Contrast-enhanced ultrasound (CEUS) might be useful to determine treatment outcome shortly after initiating treatment with biologics.[133] In a study on 133 CD patients, transmural healing could be observed in approximately 25% of patients.[134] Most of the patients received anti-TNF therapy. In a paediatric CD study, 32 patients were included and followed up by IUS and ileocolonoscopy 9 to 12 months after treatment initiation. Patients with MH showed a significant decrease of bowel wall thickness and disease extension.[135] In a prospective multicentre longitudinal study of 51 patients with active CD, all patients underwent a clinical assessment and sonographic examination at baseline, 12 weeks after treatment initiation, and after 1 year of treatment.[136] Improvement at 52 weeks was more frequent in patients with improvement at the end of induction [12 weeks] compared with patients who did not improve [85% versus 28%; $p < 0.0001$]. The authors concluded that sonographic response after 12 weeks of therapy predicts 1-year sonographic response. A large multicentre trial including 243 patients from 50 centres in Germany has recently been conducted to determine the role of IUS for monitoring treatment response.[132] In this trial, CD patients with an acute disease flare received anti-inflammatory treatment. Almost all sonographic parameters determined during IUS [including bowel wall thickness, vascularisation parameters, fibro-fatty proliferation] showed a highly significant decrease [$p < 0.001$ in all groups] at different sites. Interestingly, reduction of bowel wall thickness was more pronounced in the colon compared with the ileum. Improvement of ultrasound parameters correlated with laboratory parameters such as CRP.[132] Based on current studies, IUS seems to be a valuable method to determine transmural healing in CD, with bowel wall thickness and vascularisation appearing to be the most relevant parameters.[143]

The value of CT was assessed in a retrospective North American study on 63 infliximab-treated patients with CD.[137] Of 105 lesions, 21 [20%] were colonic. Poor-to-fair correlation was found between CT enterography features of response and improved clinical symptoms [κ 0.26], improved endoscopic appearance [κ 0.07], and reduction of CRP [κ 0.30]. When comparing responders [complete and partial] with non-responders, only the presence of the 'comb sign' on the index CT enterography was predictive of radiological response [$p = 0.024$]. Even though CT in principle might be a suitable method to determine disease activity in CD, it should be noted that CT, due to radiation safety, should not usually be used for monitoring disease activity if MRI or IUS is available.

In terms of responsiveness and reliability, different studies have shown that MRI has a high accuracy for monitoring therapeutic responses using endoscopy as a reference standard.[138–140] In a recent study, 48 patients with ileocolonic CD were prospectively evaluated with MR enterography in comparison with ileocolonoscopy.[138] MR enterography determined ulcer healing with 90% accuracy and endoscopic remission with 83% accuracy. The mean CD Endoscopic Index Of Severity [CDEIS] and Magnetic Resonance Index Of Activity

[MaRIA] scores significantly changed at Week 12 in segments with ulcer healing, based on endoscopic examination [CDEIS, 21.28 ± 9.10 at baseline versus 2.73 ± 4.12 at 12 weeks; $p < 0.001$; and MaRIA, 18.86 ± 9.50 at baseline versus 8.73 ± 5.88 at 12 weeks; $p < 0.001$]. The authors concluded that the MaRIA score is a valid, responsive, and reliable index assessing response to therapy in patients with CD. In a retrospective study with 50 patients, MRI inflammation scores during anti-TNF therapy improved in 29 of 64 lesions [45.3%], remained unchanged in 18 of 64 lesions [28.1%], or deteriorated in 17 of 64 lesions [26.6%] over time. In the anti-TNF responder group, the mean intestinal inflammation score of all lesions improved from 5.19 to 3.12 [$p < 0.0001$]. The mean inflammation scores in stenotic lesions in anti-TNF responders also improved significantly, from 6.33 to 4.58 [$p = 0.01$]. In contrast, the mean inflammation scores did not change significantly [5.55–5.92; $p = 0.49$] in non-responders. Diagnostic accuracy of anti-TNF response on MRI was 68%.[139] The authors conclude that MRI can be used to guide the optimal use of TNF antagonists in daily clinical practice. In a prospective single-centre trial with 27 patients treated with anti-TNF [infliximab or adalimumab], the mean SES-CD and MaRIA scores significantly changed at Week 26 [SES-CD: 14.7 ± 8.9 at baseline versus 4.4 ± 4.6 at 26 weeks; $p < 0.001$; MaRIA: 41.1 ± 14.8 at baseline versus. 32.8 ± 11.7 at 26 weeks; $p < 0.001$]. The overall MaRIA correlated with endoscopic score and with clinical activity [CDAI] both at baseline and at Week 26 [$p < 0.05$]. The authors conclude that the MaRIA has a good correlation with SES-CD, a high accuracy for prediction of endoscopic mucosal healing, and is a reliable indicator to monitor the use of TNF antagonists in patients with CD.[140]

In a systematic review and analysis to identify MRE variables used to describe inflammation and damage wall enhancement, mucosal lesions and wall T2 hyperintensity were the most consistently useful for inflammation [most sensitivities >80% and specificities >90%].[144]

In addition, in a retrospective analysis of 150 CD patients, having either had a pre- and post-therapy CTE or MRE radiological response to medical therapy was associated with significant reductions in long-term risk of hospitalisation, surgery, or corticosteroid usage among small bowel CD patients.[145]

As MR enterography and IUS appear to be of similar value for monitoring transmural healing in CD during treatment, which imaging modality to use depends on local availability and expertise.

Video-capsule endoscopy

As endoscopic access of the small bowel is more difficult, response to treatment should either be determined by IUS or MR enterography or by capsule endoscopy. The superiority of small bowel capsule endoscopy [SBCE] compared with other imaging modalities to determine small bowel disease in CD has been described in different studies.[146]

Recent clinical trials have evaluated the potential role of SBCE for assessment of MH in the small bowel.[147–149] These trials used quantitative scores such as the Lewis Score[150] or the Capsule Endoscopy CD Activity Index [CECDAI], analogous to the application to ileocolonoscopy of the CDEIS or the simple endoscopic score for CD. In a case-control study, 40 patients with known or suspected CD were included and underwent SBCE.[147] When patients achieved clinical response [after at least 1 month of treatment] they underwent a second SBCE, with evaluation of the same parameters. The numbers (mean ± standard error of the mean [SEM]) of large ulcers before and after treatment were 8.3 ± 1.4 and 5 ± 0.8, respectively (mean difference 3.3 ± 1.2, 95% confidence interval [CI] 0.8–5.9; $p = 0.01$). The other variables did not improve significantly. In another study, the CECDAI index was used to assess ileitis severity. All parameters were reassessed at Week 52. In total, 108 capsule procedures were performed on 43 patients. Based on the CECDAI, 39 patients [90%] exhibited active small bowel CD at baseline, with 28 patients [65%] undergoing assessment at 52 weeks. In total, 12 patients [42%] achieved complete MH and deep remission at the 52-week assessment [95% CI -0.62 to -0.22; $p < 0.0001$].[148] SBCE has a significant impact on disease management; in the largest retrospective series of patients with established CD that were evaluated with SBCE, a change in management was suggested in 52% of 187 patients.[60]

Statement 2.1.6. ECCO-ESGAR Diagnostics GL [2018]

In the absence of credible evidence to support the best modality to assess response to treatment in upper GI disease of CD, endoscopy is recommended as the preferred method [EL5]

Data on imaging in upper GI CD and in particular on monitoring disease are sparse and sizeable series are unavailable, with essentially absent data for the stomach. Cross-sectional imaging may reveal ulcers or strictures in oesophageal CD, but superficial lesions are difficult to detect, underscoring the importance of endoscopy in the diagnosis of oesophageal CD. Endoscopy with tissue biopsy is useful to exclude other common oesophageal disorders. The most commonly described findings on endoscopy include aphthous ulcers, superficial erosions, and late-stage stricture development and cobblestoning of the mucosa.[151,152] One study discussed the application of various methods to diagnose various inflammatory conditions of the oesophagus.[153]

Although IUS and MRI seem to be feasible tools to determine disease activity of CD in the duodenum and stomach, there are no convincing data that prove their value in disease monitoring. Upper GI involvement should therefore be primarily monitored by the reference standard endoscopy.

Statement 2.1.7. ECCO-ESGAR Diagnostics GL [2018]

Extramural complications in CD [such as fistulae and abscesses] should be monitored by cross-sectional imaging, including intestinal ultrasound [IUS] [EL2] or MRI [EL2] [or both] in combination with clinical and laboratory parameters [EL5]

Whereas a variety of studies have shown good sensitivity and specificity of cross-sectional imaging to assess fistulae and abscesses, there are only few studies that address the follow-up of these extramural complications after treatment. The sensitivity of cross-sectional imaging modalities such as MRI, IUS, and CT to determine extramural complications has been shown to be high in a recent meta-analysis, with sensitivity between 84% and 93% and specificity between 90% and 93%, as discussed above.[81,154] Although CT is accurate for follow-up of mural and extramural complications in CD patients, CT is not recommended for monitoring patients with active disease under treatment, due to radiation safety.[155] Although the dose can be reduced substantially with state-of-the-art low-radiation-dose CT scanners, the use of non-ionizing radiation techniques is preferable, considering the usually young age of these patients. Thus, CT should be used judiciously, ideally only in the emergency setting and if IUS and MRI are unavailable.

Statement 2.1.8. ECCO-ESGAR Diagnostics GL [2018]

Perianal CD should be reassessed by clinical evaluation in combination with endoscopic examination of the rectum plus MRI [EL1]. Transrectal ultrasonography [TRUS] in the absence of anal stenosis [EL1] or transperineal ultrasonography [TPUS] [EL2] might be used instead of MRI

Evaluation of perianal CD and fistula closure is primarily achieved with clinical evaluation. The definition of fistula healing varies in the literature and there is no consensus on when a first or definitive evaluation of fistula healing should be performed.[156] The Perianal Disease Activity Index [PDAI][157] is a clinical scoring system that has been used and validated in clinical studies both at diagnosis and to measure treatment response. Fistula drainage assessment has been used in several clinical trials of medical therapy,[158–160] but is very much investigator-dependent and has not been validated in large studies. A single retrospective study has evaluated the PDAI scoring system, where high scores predicted short-term surgical outcome, but this has not since been validated.[161]

MRI classifications of fistula severity have been proposed, such as the system published by Van Assche *et al.*[162] Thus far, this system is of limited use outside clinical trials. MRI is increasingly used to assess fistula healing, particularly during medical therapies.[162–164] Various MRI classifications have been proposed, including the Van Assche Score,[162] which considers the number of fistulae, localisation, extensions, T2 hyperintensity, abscesses, and rectal involvement. Assessment of dynamic contrast enhancement has also been proposed as a means to monitor fistula activity.[165] It has been shown that fistulae may reopen after therapy cessation, and studies using MRI findings as a more stringent endpoint of deep fistula healing suggest that MRI[162,164,166] and endo-anal ultrasound[167,168] may be useful for identification of fistulae that show external closure but retain an internal fistula tract. This suggests that imaging assessment of deep healing is superior to simple clinical evaluation, although long-term comparative studies are lacking.

Despite the lack of relevant studies evaluating the role of MRI for the specific assessment of patients during and after therapy, several comparative studies have been performed evaluating ultrasound and MRI in perianal fistula diagnosis in CD. In most of these studies, MRI seems to be the method of choice. Schwartz *et al*. compared examination under anaesthesia [EUA], MRI, and transrectal ultrasonography [TRUS], and demonstrated a diagnostic accuracy of 91%, 87%, and 91%, respectively.[169] Buchanan *et al*. performed a large prospective clinical trial comparing preoperative digital rectal examination, endoscopic ultrasound, and body-coil MRI for the preoperative assessment of anal fistulae. According to their results, MRI was superior to both methods for abscess detection and accuracy in fistula classification [90% of patients correctly classified by MRI, 81% by TRUS, and 61% by EUA].[170] In a recent meta-analysis, the sensitivity of MRI and of TRUS to determine perianal CD was 87% for both imaging modalities, and specificity was 69% versus 43%, respectively.[171] A recent consensus suggested a combination of different imaging modalities for diagnostic use during perianal CD.[172]

MRI may therefore be slightly superior to TRUS for determining perianal disease activity. However, use of the adequate imaging modality also depends on local availability and expertise.

If MRI is not available and TRUS is either not available or unfeasible due to pain, transperineal ultrasonography [TPUS] is an alternative, although its sensitivity is lower than TRUS. In a recent study investigating 46 patients with perianal CD, 53 fistulae detected by TRUS were correctly classified by TPUS in 45 cases, reaching a sensitivity of 84.9%.[173]

Statement 2.1.9. ECCO-ESGAR Diagnostics GL [2018]

Therapeutic drug monitoring might be beneficial in CD and UC in patients with non-response to thiopurines [EL3] or anti-TNF therapy [EL2]. Drug level monitoring is mandatory during treatment with calcineurin inhibitors [EL2]

Primary non-response and secondary loss of response are common problems during anti-TNF therapy. Loss of response [LOR] to anti-TNF has been shown to be as high as 20% to 40% after the first year of treatment[174] and about 10% in the following years.

In a recent study on 247 patients, it was shown that therapeutic drug monitoring by measurement of anti-TNF trough levels and antidrug antibodies in IBD patients with secondary LOR may lead to therapeutic changes in more than 70% of patients.[175] Several studies have demonstrated that low trough levels and detectable antidrug antibodies are associated with LOR.[176–178] In a recent meta-analysis of 22 trials with 3483 patients, it was shown that high infliximab trough levels correlate with good clinical response and low CRP levels.[179] Similar results have been shown for golimumab[180] and adalimumab.[181] Even though the primary endpoint of the TAXIT trial [treatment guidance via infliximab trough level concentration measurements] was not achieved, it was shown that dose escalation in patients with sub-therapeutic levels improved clinical response.[182] The optimal trough level concentration in this study was defined as 3–7 µg/mL. A cohort of 60 CD patients treated with adalimumab has been investigated retrospectively.[183] Higher adalimumab trough levels were significantly associated with MH [median 14.7 µg/mL in those with MH versus 3.4 µg/mL in those without; $p < 0.001$]. This study suggests that attaining MH alone or a combined outcome of clinical and endoscopic remission is more likely to occur in those patients who achieve an adalimumab trough level of at least 8.14 µg/mL.

In a recent study, primary non-response to anti-TNF therapy in patients with severe UC was associated with faecal loss of infliximab.[184] However, the optimal time points and cut-off levels for trough level measurements to determine primary non-response must still be determined.

Different studies have shown that measurement of thiopurine metabolites, such as 6-mercaptopurine [6-MMP] and 6-thioguanine [6-TGN], might be beneficial in patients with suboptimal response to thiopurines. In a recent study, determination of 6-TGN and 6-MMP levels identified patients with reduced compliance in 11% and raised 6-MMP levels in 10%. Treatment improvement could be achieved in 87% of patients after optimising thiopurine usage.[185]

It is likely that as vedolizumab and ustekinumab drug monitoring becomes more easily available, this will also form part of management strategies when treating patients with these agents.

2.2. Monitoring clinically asymptomatic patients

Statement 2.2.1. ECCO-ESGAR Diagnostics GL [2018]

In patients with IBD who have reached clinical and biochemical remission, monitoring is aimed at early recognition of a disease flare [EL5]. The interval of monitoring should be between 3 to 6 months depending upon duration of remission and current therapy [EL5]. Relapse can be detected with FC before clinical symptoms [EL2]

Figure 1 shows a simplified disease progression pathway in IBD from risk factors to irreversible intestinal fibrosis. The practicality of a given test for IBD monitoring decreases further downstream in the pathway, as the disease becomes more resistant to standard therapy. The ideal monitoring test is non-invasive, simple to conduct, and easily interpretable. Such a test should detect an imminent disease flare [often undetectable by symptom-based reporting alone] and make provision for proactive treatment optimisation [Table 1].

Faecal calprotectin

The utility of FC monitoring in patients with quiescent disease was evaluated in a recently published systematic review.[186] Electronic searches up to April 2016 identified six prospective studies [mostly in UC patients] that met the selection criteria. Since then, an additional five prospective studies in both UC and CD patients were published.[118,187–190]

Two consecutively elevated FC levels were the best predictor for clinical relapse, but this was investigated systematically in only one study.[191] In one of the more recently published studies, patients with both UC and CD provided faecal samples every third month and were prospectively followed until the first clinical relapse.[188] This study revealed that FC levels start rising approximately 3 months before a relapse becomes clinically apparent, and confirmed the observations of the aforementioned systematic review. These findings support the biological implausibility that a single FC measurement at baseline can predict the clinical course over a 12-month period, as suggested in a meta-analysis[192] and more recently by Theede *et al*.[193]

Currently, there is no consensus on the ideal cut-off point for FC monitoring. In clinical trials where response to a new treatment is monitored, a low cut-off point [e.g. 100 µg/g] is frequently used to demarcate the upper limit of the normal FC range. Conversely, in real-life studies, a higher cut-off point is advocated [e.g. 250 µg/g] as an action threshold for adjusting treatment.[194–197] A prospective evaluation of a monitoring strategy is needed, namely a planned and organised system of repeated FC assessments and subsequent decisions about starting, modifying, or de-escalating therapy, as has been part of the recently published CALM study.[198]

A general construct for FC-based disease monitoring in patients with IBD is shown in Figure 2, which illustrates the four phases of disease monitoring.[199,200] Repeated FC measures are used to longitudinally track changes in a patient's condition over time. In phase I, IBD is suspected but is neither endoscopically confirmed nor treated. In phase II, induction therapy is introduced to achieve disease control, resulting in patient response. Phase III begins with disease remission with continuation of maintenance therapy. The goal of monitoring in this phase is to detect deviations from the target range, indicating the start of phase IV. In phase IV, therapy is adjusted to re-establish disease control and bring FC levels back to the target range.

When the FC concentration is in the target range, the patient is reassured and advised to retest in 3 months. When the FC concentration is in the action range, the treatment plan is adjusted and re-testing is advised for the next month. In the uncertain range, a test interval of 1 month is advised before progressing to a treatment decision.

C-reactive protein

Serum CRP is an acute-phase reactant that has been used in clinical practice for many years as a general measure of inflammation. In a meta-analysis of cohort and case-control studies that compared the diagnostic accuracy of CRP [index test] with endoscopy [reference standard] in patients with symptomatic IBD, a CRP concentration of ≥5 mg/L appeared to have a high specificity for detecting endoscopic disease activity.[111] However, the sensitivity was very poor and a negative test does not exclude the presence of a flare. Almost two-thirds of the asymptomatic patients with normalised CRP still had active endoscopic lesions, and consequently an isolated fall in CRP was insufficient reassurance of endoscopic remission.[201] Repeated CRP measurements in the detection of early postoperative recurrence of CD,[202] or in the follow-up of small bowel CD,[203] are inferior to repeated FC measurements.

Statement 2.2.2. ECCO-ESGAR Diagnostics GL [2018]

Asymptomatic patients with abnormal biochemical parameters may have an imminent disease flare. After excluding infection, endoscopic or cross-sectional imaging [or both] should be performed [EL5]

Capsule endoscopy

Recent prospective studies have shown that stool markers such as FC are useful in monitoring inflammation in the small bowel. Increased FC levels with negative findings on conventional endoscopy should trigger further investigations into the presence of active small bowel disease.[204] Small bowel CD is in many cases located proximal to the terminal ileum and is therefore inaccessible to conventional ileocolonoscopy. In a considerable proportion of asymptomatic patients with CD, previously unknown new proximal involvement and progression to stricturing or penetrating disease were demonstrated with capsule endoscopy,[61] leading to modifications in the original Montreal classification and consequently to treatment escalation.[205] In a prospective

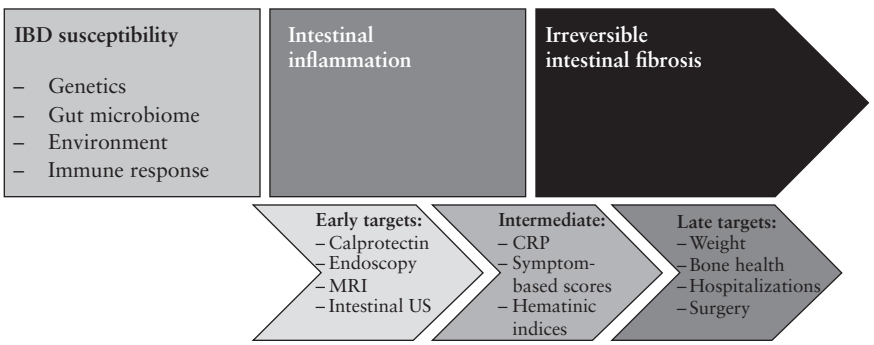

Figure 1. Targets along the disease progression pathway in IBD.

observational cohort of patients with asymptomatic or mildly active small bowel CD, tolerance and preference to MR enterography versus capsule endoscopy were compared. Pre-examination and procedural discomfort was perceived more favourable in capsule endoscopy. The superior tolerability of capsule endoscopy, along with diagnostic features, should be considered when choosing between these two modalities for long-term follow-up.[205] A negative FC result in an asymptomatic CD patient should deter the clinician from using additional small bowel imaging techniques.[204]

MR enterography

MR enterography is not a suitable technique for early recognition of disease recurrence, since aphthoid ulcerations cannot be assessed. As disease severity progresses, MR enterography manifestations become more apparent. Several studies have evaluated the ability of MR enterography to quantify therapeutic response to immunosuppressive therapy, especially in children.[206]

Intestinal ultrasound

IUS is a non-invasive, widely available technique that does not use ionising radiation and is well accepted and tolerated by patients. Most parts of the large bowel [with the exception of the rectum] and major parts of the small bowel [with the exception of the proximal jejunum] can be visualised by IUS. The advantages of IUS include rapid evaluation of bowel wall thickness and direct visualisation of bowel vascularisation and motility.[88,207,208] The role of this technique in monitoring patients with asymptomatic CD or UC is not yet clear. More is known about the role of IUS in monitoring response to treatment in CD patients. In a prospective trial that followed 234 CD patients with bowel wall alterations in the terminal ileum or in the colon, follow-up every 3 months showed significant improvements in nearly all ultrasound parameters.[132] There is good concordance between ultrasound and MR enterography for disease location and activity, and fewer technical difficulties with IUS.[209]

Statement 2.2.3. ECCO-ESGAR Diagnostics GL [2018]

Before de-escalation or withdrawal of maintenance IBD therapy, it is necessary to assess disease activity using a combination of clinical and biochemical markers and endoscopic and/or cross-sectional imaging, balancing the risks and benefits of withdrawal [EL5]

In a recent meta-analysis of 18 studies, stopping immunomodulatory monotherapy after a period of remission was associated with approximately 75% of patients experiencing a relapse within 5 years after therapy discontinuation.[210] Approximately 50% of patients who discontinued anti-TNF therapy after combination therapy in this systematic review maintained remission 24 months later, but the proportion decreased over time.[210] Similar results have been reported in other meta-analyses.[211,212] The factors that predict relapse after discontinuation of therapy remain controversial.

In a placebo-controlled study by the GETAID group, which included 83 patients in clinical remission under azathioprine, neither the presence of ulcerations nor a CDEIS >0 at ileocolonoscopy before azathioprine discontinuation was predictive of clinical relapse.[213] In contrast, in another GETAID trial, Louis *et al.* assessed the risk of clinical relapse after discontinuation of infliximab in 109 patients with CD who were in clinical remission under combined maintenance therapy with infliximab and an immunomodulatory agent.[214] In their multivariate analysis, the absence of MH was among the factors strongly associated with an increased risk of clinical relapse after infliximab withdrawal [hazard ratio 2.6]. In this study, immunosuppression with azathioprine or methotrexate was continued after infliximab withdrawal. In a recent meta-analysis, the relapse rate 1 year after discontinuation of anti-TNF therapy was 42%, which decreased to 26% when endoscopic remission was also required.[211] Assessment of endoscopic activity in patients with quiescent CD is recommended before discontinuation of treatment is considered.

Table 1. Markers of disease activity for monitoring asymptomatic IBD patients.

	Validity [correlation with gold standard]	Responsiveness to changes in condition	Signal-to-noise ratio [ability to differentiate changes in condition from background variability]	Practicality
Endoscopy	Gold standard	Gold standard	Gold standard	Low Requires bowel preparation and general anaesthesia in children
Faecal calprotectin	Good	Good Rises quickly in case of relapse; falls rapidly with successful treatment	Moderate Risk of false-positive results	High Possible reluctance of patients for repeated stool collection
C-reactive protein	Moderate	Moderate Late position in disease progression pathway	Moderate Risk of false-positive results [acute infections and other inflammatory conditions] and false-negative results [normal CRP despite active disease]	High Quick result; but requires venepuncture
Capsule endoscopy	Good	Good	Moderate Potential over-interpretation of insignificant mucosal lesions	Moderate Requires bowel preparation, but is generally well tolerated
MR enterography	Moderate	Moderate Late position in disease progression pathway	Unknown	Moderate Requires oral preparation for bowel distention, and in children preparation through a nasoduodenal tube
Intestinal ultrasound	Unknown	Good	Unknown	High Non-invasive, widely available, and well tolerated

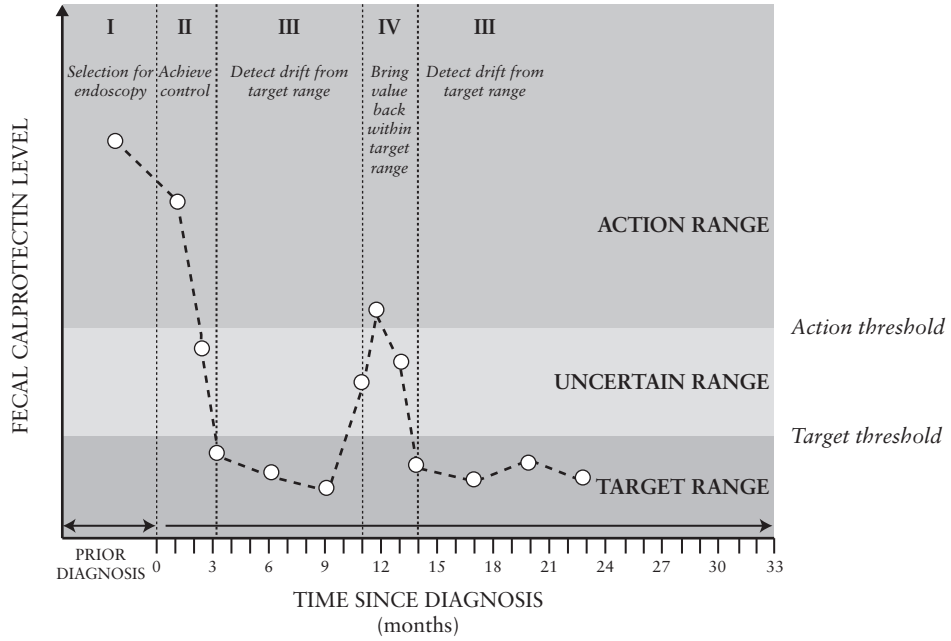

Figure 2. Conceptual model of FC-based monitoring in IBD patients [Copyright 2017 by the Wolters Kluwer Health, Inc. Used with permission].

2.3. Monitoring clinically symptomatic patients

Statement 2.3.1. ECCO-ESGAR Diagnostics GL [2018]

All patients with a suspected new flare of IBD should be investigated for infection, including exclusion of *Clostridium difficile* infection [EL3]

Bacterial infection and *Clostridium difficile* should be excluded in all patients. Diagnostic workup is recommended according to test availability and local practice. Available tests include glutamate dehydrogenase antigen and toxin A/B enzyme immunoassays, bacterial cultures, cytotoxicity assay, and nucleic acid amplification technology tests.

This is particularly important in patients with colonic disease where the diagnostic yield is higher; in one series of paediatric patients with UC [n = 354 stool tests], 1.8% of tests were positive for *Salmonella* serotype typhi and 13.6% were positive for *C. difficile* toxin.[215] Patients with CD have comparatively lower rates of *C. difficile* infection.[216]

In UC, *C difficile* is associated with poorer outcome, including increased colectomy rates[217] and increased postoperative complications[218,219]; detection is thus of direct clinical relevance. Additional interrogation of faeces with polymerase chain reaction [PCR] should not be performed routinely as there is a high rate of detection of bacteria that may not be of clinical significance, even in healthy controls.[220]

Parasitic infections are found in about 12% of patients with UC who reside in endemic areas.[221] If travel history is suggestive, stool examination for ova cysts and parasites and *Strongyloides* serology should be performed before therapy is escalated. Local protocols regarding testing and transport of stool samples should be followed. Further guidance on management of opportunistic infection can be found in the second European evidence-based consensus on the prevention, diagnosis, and management of opportunistic infections in inflammatory bowel disease.[26]

A recent meta-analysis revealed that cytomegalovirus [CMV] infection in IBD may be associated with longer disease duration, reduced efficacy of corticosteroid therapy, and increased colectomy rate.[222] Corticosteroid and thiopurine exposure are associated with reactivation of latent CMV.[223] However, tissue damage following exposure to immunomodulators is rare.[224] Anti-TNF agents and cyclosporine also do not appear to be associated with adverse outcomes in CMV-positive patients.[225] Therefore, the ECCO guidance on opportunistic infections recommends that testing for CMV should be reserved for steroid-resistant disease.[26]

Statement 2.3.2. ECCO-ESGAR Diagnostics GL [2018]

Cytomegalovirus [CMV] should be tested in immunosuppressant-resistant UC as CMV is associated with adverse outcomes, including reduced efficacy of therapy and increased colectomy rates [EL3]

CMV disease is most commonly assessed via detection of CMV DNA through PCR or immunohistochemistry of tissue biopsies and blood. The second European evidence-based consensus on opportunistic infection in IBD provides more detailed information on the diagnosis and management of CMV infection.[26]

Statement 2.3.3. ECCO-ESGAR Diagnostics GL [2018]

Colonoscopy is the modality of choice to assess disease activity of symptomatic colonic CD or UC [EL5]. Cross-sectional imaging is complementary to assess phenotype [EL2], and may be used as an alternative to evaluate disease activity. Sigmoidoscopy should be considered in UC if symptoms suggest an acute severe flare

Ileocolonoscopy provides direct mucosal visualisation of the colon and terminal ileum and allows histological assessment and therapeutic intervention. As such it is the gold standard investigation of large bowel disease.

If assessment of disease location or behaviour is not necessary, FC can be used to evaluate activity from the colon to the small bowel.[62,204,226–229] Studies have shown good correlation [r > 0.8] with endoscopic disease activity in both CD and UC.[230,231]

If acute severe UC is suspected, endoscopic evaluation should be limited to flexible sigmoidoscopy, as discussed previously in this guideline.

MR enterography[232–237] of the colon, capsule endoscopy,[238–240] and IUS[115] can also be considered for assessment of disease extent and phenotype in individuals reluctant to undergo endoscopic evaluation. In a UK multicentre trial, IUS had superior sensitivity compared with MRE for colonic disease presence in newly diagnosed patients [67% versus 47%, respectively].[87]

Statement 2.3.4. ECCO-ESGAR Diagnostics GL [2018]

Symptomatic small bowel disease can be investigated with MR enterography, IUS, and/or small bowel capsule endoscopy [SBCE] [EL2]

MR enterography, IUS, and SBCE are all sensitive and specific investigations of symptomatic small bowel disease. The decision on which investigation is 'first line' is based upon local availability and expertise.

MR enterography allows assessment of the small bowel without radiation exposure.[241] The presence of wall oedema, contraction frequency,[242] ulcers, and extramural signs such as fat stranding and lymphadenopathy, make MR enterography somewhat informative of whether the abnormalities detected are more inflammatory or fibrotic.[242–245] However, it should be noted that no imaging modality can fully assess whether a stricture is inflammatory or fibrotic in nature. MR enterography is also safe and well tolerated in paediatric populations.[246–248] A recent meta-analysis of 27 studies [19 included in pooled analysis] showed MRI to have a sensitivity of 0.88 [95% CI 0.86–0.91] and a specificity of 0.88 [95% CI 0.84–0.91].[249] The studies included both MR with oral contrast solution [MR enterography] or contrast administered by nasojejunal tube insertion [MR enteroclysis]. MRI is perhaps superior to IUS in assessing disease extent[86] and leads to changes in clinical management following investigation[250]; MRI increases scores of disease location [L] and disease behaviour [B] of the Montreal classification in over 20% of patients.[251]

MR enteroclysis is not significantly more sensitive or specific than MR enterography.[252] MR enteroclysis is also less well tolerated than MR enterography[253] and requires minimal radiation exposure for fluoroscopic nasojejunal placement.[254] Accordingly, MR enteroclysis is not routinely recommended.

IUS may be available immediately within the clinical setting; if this investigation is sufficient to confirm active disease it may preclude the need for further investigation. The sensitivity and specificity of IUS can be enhanced with contrast studies. Small intestine contrast ultrasound [SICUS] entails administering oral contrast and enables a greater rate of detection of small bowel lesions than by standard IUS,[255,256] and in particular enables greater detection of strictures and associated dilatation. SICUS shows sensitivity and specificity comparable to MR enterography and CT enterography.[257–259] In one study, SICUS was shown to be more sensitive in the proximal small bowel [92% versus 75%], similar within the proximal and mid ileum, and less specific within the terminal ileum.[260] One study showed SICUS to be more sensitive and specific than CT enteroclysis.[261] The rates of detection of small bowel complications [such as strictures] are comparable to MR enterography.[258] CEUS may facilitate differentiation between inflammatory and fibrotic strictures.[262] In the recently published METRIC trial, both MRE and IUS had a high sensitivity for detecting small bowel disease presence. However, the sensitivity of MRE for small bowel disease extent (80% [95% CI 72–86]) and presence [97%[91–99]] were significantly greater than that of IUS [70%[62–78] for disease extent, 92%[84–96] for disease presence]: a 10% [95% CI 1–18; $p = 0{\cdot}027$] difference for extent, and 5% [1–9; $p = 0{\cdot}025$] difference for presence.[87]

Most studies show the diagnostic accuracy of SBCE to be comparable to MR enterography, CT enterography, and IUS in CD,[56,263–267] although a 2017 meta-analysis demonstrated superior detection of proximal small bowel disease compared with MR enterography (odds ratio [OR] 2.79, 95% CI 1.2–6.48).[56] This is in comparison with MR enterography, CT enterography, barium studies, and IUS.[89] Clinically, the use of SBCE is associated with earlier escalation of therapy.[268] However, the benefits of this investigation are somewhat offset by a small risk of capsule retention; even with use of patency capsule in patients deemed to be at risk, the rates of capsule retention range from 1.5% to 2.1%.[60] The outcome of the retained capsule varies between studies; approximately 85% are asymptomatic and 15% result in partial or complete small bowel obstruction. The latter generally requires surgical management. The former can sometimes be retrieved with small bowel enteroscopy or managed conservatively.[269] Routine use of a patency capsule has not been shown to reduce the risk of retention in the absence of risk factors. Patients who benefit from patency capsules include those with stricturing or penetrating disease phenotypes.[270] Cost analyses suggest that SBCE is cost-effective[271] and frequently leads to changes in therapy.[272]

Barium studies, in particular barium follow-through, are still used in some centres for suspected active small bowel CD.[273,274] However, sensitivity and specificity are less than those of MR enterography, IUS, or SBCE. Furthermore, radiation exposure also makes barium studies less appealing.[275] This is particularly true in paediatric assessment.[276] Accordingly, ECCO-ESGAR discourages barium studies unless local facilities preclude alternatives.

CT should largely be reserved for the emergency setting due to radiation exposure. However, low-radiation CT enterography yields results comparable to full-dose CT when evaluating CD. Accordingly, low-radiation CT enterography may be an alternative when local resources preclude alternatives or in older patients where radiation exposure is of less concern. When considering the efficacy of CT, the diagnostic yield of CT enterography is similar to that of MR enterography.[80,277,278] Indeed, several studies comment that CT yields images of higher spatial resolution[279–281] and that there is greater agreement between radiologists when interpreting CT.[277] CT is often the only cross-sectional abdominal imaging modality available outside standard working hours, and as such is widely used in the emergency setting. CT has a high detection rate of complications, including perforation, strictures, and abscesses.[281]

Studies of positron emission topography [PET] are limited. At present, PET does not appear to detect significantly more lesions than CT enterography[282] or MR enterography alone.[283] Leukocyte scintigraphy has been shown to detect inflammatory lesions not otherwise shown prior to laparotomy. However, there is insufficient evidence to routinely include this test in clinical practice.[284]

Non-invasive evaluation of symptomatic IBD includes measurement of blood and stool inflammatory markers and measurement of parameters indicative of malabsorption. The use of non-invasive markers to assess disease activity is largely covered elsewhere. In brief, FC is a more sensitive marker of disease activity than haemoglobin, CRP, or albumin.[285,286] In symptomatic disease, FC can be used to evaluate activity from the colon to the small bowel.[62,204,226–229] Studies have shown good correlation [$r > 0.8$] with endoscopic disease activity in both CD and UC.[230,231] One of the main drawbacks of indirect markers is their limited information on disease phenotype and potential complications.

Statement 2.3.5. ECCO-ESGAR Diagnostics GL [2018]

Balloon-assisted enteroscopy can be used for diagnostic evaluation or endoscopic intervention [or both] throughout the small bowel [EL3]

Balloon-assisted enteroscopy allows direct mucosal visualisation of the entire small bowel. Unlike other imaging modalities, balloon-assisted enteroscopy also enables the taking of biopsies, therapeutic intervention throughout the small bowel,[287–289] and interventions to manage bleeding. One study showed a change in management in 75% of patients who underwent this investigation.[290] However, this examination is time-consuming and requires patient sedation. The risk of perforation is 0.12% without therapeutic intervention but 1.74% with therapeutic intervention, the majority of which occurred after stricture dilatation.[291] Bleeding occurs in approximately 2.5%,[292] although one series demonstrated four out of six significant bleeds occurring following polypectomy.[293] It is worth noting that real-world data on both the benefits and complications are skewed by selection bias, as at present this test is usually reserved for patients where other imaging modalities have been inconclusive or in scenarios when therapeutic intervention is a key aim.

Statement 2.3.6. ECCO-ESGAR Diagnostics GL [2018]

Malabsorption parameters should be assessed at regular intervals in all patients with IBD [EL5]

Nutritional deficiencies are frequently associated with symptomatic IBD. The reason for this is 2-fold. First, the discomfort and anorexia associated with disease flares preclude adequate intake. Second, inflammatory or fibrotic change to the bowel directly hinders absorption.

In all patients with IBD, weight should be recorded at each clinic review with the aim of early dietetic support when unintentional weight loss is noted. Anaemia is common and should be screened for in all IBD patients; this topic is covered in full in Chapter 1 of this guideline. Patients with symptoms suggestive of active disease should be screened for anaemia every 3 months. Initial screening should include complete blood count, ferritin, and CRP. There is no evidence on optimal screening intervals for any of the parameters used for malabsorption. Common practice in patients with small bowel disease or previous resection is to measure vitamin B12 and folic acid every 3 to 6 months. Judicious care must be taken when interpreting ferritin results in symptomatic patients; the ECCO anaemia guideline recommends ferritin values of up to 100 µg/L may still be consistent with iron deficiency in active disease, especially with a transferrin saturation of <20%. If low haemoglobin is confirmed, a more extensive workup should be undertaken as per the anaemia guideline.

Low albumin is common in active IBD, as it is an acute phase protein. Active IBD itself may lead to malabsorption, and low albumin in IBD may correlate with nutritional status. However, the use of albumin as a direct marker of malabsorption is tenuous. In a meta-analysis of 63 studies, albumin did not correlate with nutritional status in calorie-restricted but otherwise healthy individuals.[294] Longitudinal follow-up of serum albumin in patients with anorexia nervosa and in healthy controls also failed to yield significant differences.[295] As such, albumin is not an appropriate test for malabsorption and ECCO does not recommend albumin measurements for this reason.

Low vitamin D has been observed in between 16% to 95% of IBD patients, depending upon the study.[296,297] Deficiency is associated with active disease, female gender, and non-Caucasian ethnicity, with one recent study suggesting higher prevalence in CD.[298] A retrospective analysis has also linked low vitamin D with more frequent flares and lower quality-of-life scores.[299] Unfortunately, prospective follow-up after supplementation does not show a clear beneficial impact in disease course.[300] Nevertheless, ECCO suggests measuring vitamin D in symptomatic patients, then re-evaluating after treatment to verify that levels are replete.

Other micronutrient deficiencies to be considered in IBD patients include vitamin K, selenium, vitamin A, vitamin C, zinc, vitamin B6, and vitamin B1.[301,302] All patients with symptomatic IBD do not routinely require evaluation of all of the above. However, testing should be considered in patients with small bowel CD, in those who have undergone resection, and in those receiving nutritional supplementation [in particular parenteral nutrition] or if the specific clinical scenario lends suspicion to a deficiency [such as poor wound healing].

2.4. Imaging after surgery [including ileo-anal pouch]

Statement 2.4.1 ECCO-ESGAR Diagnostics GL [2018]

Ileocolonoscopy is the reference standard in the diagnosis of postoperative recurrence after ileocolonic resection. Endoscopy is recommended within the first 6 to 12 months after surgery [EL3]

Statement 2.4.2. ECCO-ESGAR Diagnostics GL [2018]

FC, IUS, MR enterography, and SBCE can be considered as non-invasive alternatives to detect postoperative recurrence, in particular after small bowel resection [EL2]

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 ileocaecal disease have shown that in the absence of treatment, the postoperative endoscopic recurrence rate is approximately 65% to 90% within 12 months and 80% to 100% within 3 years of the operation.[303,304] The rates of recurrence are also significant in patients after total proctocolectomy and permanent ileostomy. In a recent meta-analysis of 18 cohort studies, the risk of clinical recurrence was 28.0%, with a 5-year and 10-year median cumulative rate of 23.5%.[305] Identification and treatment of early mucosal recurrence may therefore prevent clinical recurrence.

Ileocolonoscopy is the reference standard in the diagnosis of postoperative recurrence by defining the presence and severity of morphological recurrence. Data from endoscopic follow-up of patients after resection of ileocaecal disease have shown that in the absence of treatment, the postoperative recurrence rate is approximately 65% to 90% within 12 months.[303,304] Ileocolonoscopy is therefore recommended within the first year after surgery where treatment decisions may be affected. The Rutgeert´s score may be used for detailed description [see Chapter 4 of this guideline].

Non-invasive modalities may also be accurate and efficient in detection of postoperative recurrence.

FC can accurately identify postoperative recurrence.[306,307] In a meta-analysis of 10 studies that evaluated the accuracy of FC for detection of endoscopic recurrence, the pooled sensitivity and specificity values for assessing suspected endoscopic recurrence were 0.82 and 0.61, respectively.[308] In a more recent prospective study, FC levels >100 µg/g indicated endoscopic recurrence [defined as Rutgeerts

score ≥i2] with 89% sensitivity and 58% specificity and an NPV of 91%; the authors suggested that colonoscopy could have been avoided in 47% of patients. In an additional prospective study from the GETAID group, FC levels >100 µg/g were associated with a positive predictive value and NPV of 93% and 77%, respectively, for prediction of endoscopic recurrence.[309]

Several imaging modalities are available to reliably diagnose post-surgical recurrence, including IUS, small bowel follow-through, CT enteroclysis or CT enterography including virtual colonoscopy, MR enteroclysis or MR enterography, SBCE, and white blood cell scintigraphy.

Several authors have previously emphasised the value of IUS in postoperative follow-up, and confirmed the observation of bowel wall thickening as an indicator for recurrence.[310–312] SICUS has shown an excellent correlation with the endoscopic Rutgeerts score [r = 0.67; p = 0.0001], reaching 87.5% accuracy for detecting CD recurrence.[313] SICUS is also considered to be superior to standard IUS in detecting postoperative CD recurrence after ileocaecal resection.[314] Bowel wall thickening was defined by thickness of >3.5 mm. SICUS prediction of recurrence was found to be correct in 100% of cases and confirmed by endoscopy.[314] In a recent retrospective series from Italy, the absolute incidence of new surgical intervention is 13% in patients with bowel thickness of 3 mm and 40% in patients with bowel thickness >6 mm.[315]

CT enterography or CT enteroclysis are alternatives to endoscopy for assessing postoperative recurrence of CD activity.[316] In a prospective series that included 32 postoperative patients from China, a significant correlation between endoscopic and CT recurrence [r = 0.782; p < 0.0001] was demonstrated.[317] Due to false-negative findings, CT colonography has been tested for assessing the postoperative recurrence of CD with inconclusive results. However, CT colonography represents an alternative to conventional colonoscopy in non-compliant post-surgical patients with a rigid stenosis that does not allow passage of the endoscope.[318] However, due to concerns regarding cumulative radiation exposure, imaging modalities not associated with radiation [such as MR enterography or IUS] are preferable to CT enterography.

MR enterography may be an alternative to endoscopy as a diagnostic tool in postoperative recurrence evaluation in CD patients. Similar to the endoscopic Rutgeerts score for assessing postoperative recurrence, one study showed an objective evaluation using an MRI-based index of activity and severity for postoperative recurrence. This score achieved a high correlation with the endoscopic index, which allowed differentiation between mild and severe lesions[319] and prediction of the risk of clinical postoperative recurrence in CD patients.[320]

Although the Rutgeerts score has been used to evaluate the efficacy of several drugs, there is a lack of information on whether mural healing changes seen by cross-sectional imaging techniques are in parallel to endoscopic MH.

Capsule endoscopy can also be used to access postoperative recurrence.[321,322] A fair correlation between the modalities [r^2 = 0.54–0.64; p < 0.05] was observed in a small pilot study that compared the Rutgeerts score calculated by capsule endoscopy and ileocolonoscopy.[322] An important advantage of capsule endoscopy is the ability to detect proximal small bowel recurrence. However, data on the use of capsule endoscopy for this indication are currently very limited, and patency capsule evaluation should be recommended before capsule endoscopy to minimize the risk of retention.

In a recent meta-analysis, MR enterography, IUS, and SBCE had excellent accuracy [area under the curve >0.9 for all modalities] for detection of endoscopic recurrence as defined by a Rutgeerts score ≥2.[323]

Statement 2.4.3. ECCO-ESGAR Diagnostics GL [2018]

Endoscopy with biopsies should be performed in the assessment of pouch-related symptoms [EL2]

The ileo-anal pouch is a well-established option for patients who require surgery for chronic UC. Despite excellent functional results, the short-term and long-term outcome of ileal pouch with anal anastomosis [IPAA] are determined by the occurrence of complications. These may be directly related to the surgery or may occur over the long term. Immediate postoperative complications include leakage, abscess formation, pelvic sepsis, and fistula formation. More chronic disorders following IPAA are pouchitis, cuffitis, irritable pouch syndrome, pouch stricture, pouch sinus, afferent loop syndrome, or small bowel obstruction.[324] Following surgery, up to 40% of patients have a single episode of pouchitis [a non-specific inflammatory condition at the ileal pouch reservoir][325] within 12 months, whereas 19% and 5% experience intermittent episodes and chronic pouchitis, respectively.[326–328] The incidence of pouch failure is up to 7% at 3 years and 9% at 5 years.[329,330]

Endoscopy plays a significant role in diagnosing and guiding therapy in patients with pouch complications.[324,331–334] Importantly, the severity of symptoms does not always correlate with endoscopic or histological findings.[335,336] Therefore, a cumulative clinical, endoscopic, and histological assessment is needed. Several diagnostic criteria are available and the most common in clinical use is the Pouch Disease Activity Index.[337] Furthermore, it is valuable to classify the phenotype of pouchitis before initiating therapy, to provide guidance regarding treatment modalities and duration of treatment.[338] In case of antibiotic-refractory pouchitis, endoscopic evaluation can facilitate exclusion of contributory factors such as ischaemic pouchitis and infections.[339] Pouch endoscopy is essential in the diagnosis of CD of the pouch and prepouch ileitis.[324,334,335]

FC levels are significantly elevated in cases of pouchitis. In a study that included 56 pouch patients, FC concentrations correlated closely with the objective pouchitis score, the Pouch Disease Activity Index, and endoscopic and histological inflammatory scores [Spearman rank test, p-values < 0.0001]; FC levels ≥92.5 µg/g had a sensitivity of 90% and a specificity of 76.5% for detection of pouch inflammation.[340] Other potential biomarkers of pouch inflammation, such as faecal matrix metalloprotease-9[341] and serum alpha-1 antitrypsin,[342] are also being evaluated but are currently not in routine clinical practice.

Chapter 3: Detection of complications

3.1. Detection of strictures

Statement 3.1.1. ECCO-ESGAR Diagnostics GL [2018]

Cross-sectional imaging should be used to detect small bowel strictures [EL2]. Due to radiation exposure with CT, the preferred methods are MRI and/or intestinal ultrasound [IUS]. No imaging technique is currently able to determine the degree of fibrosis [EL3]

Despite wide heterogeneity in the definitions for strictures, the accuracy of intestinal ultrasound [IUS], CT enterography, and MR enterography is high for diagnosis of stenosis affecting the small bowel.[81] IUS is an accurate technique for detection of small bowel stenosis.

Based on pooled data using surgery as a reference standard, the sensitivity and specificity of IUS are 79% and 92%, respectively.[81] Use of oral contrast agents, such as small intestine contrast ultrasound [SICUS], can improve the accuracy of IUS in detecting the presence and number of small bowel stenosis; sensitivity increased from 74% to 89% in one study.[131] The sensitivity of CT enterography for stenosis detection was 92% and specificity was 100% when CT was compared with ileocolonoscopy.[343–345] Studies using endoscopy and surgery as a reference standard reported a sensitivity of 85% and 90%, respectively, with a specificity of 100%.[82,346] MRI studies with an adequate reference standard [endoscopy, surgery, or both] for diagnosis of stenosis showed a sensitivity of 89% and a specificity of 94%.[81] The accuracy had a tendency to improve using enteroclysis [i.e. enteric contrast introduced via nasojejunal intubation rather than oral] as compared with enterography [sensitivity of 100% versus 86% and specificity of 100% versus 93%, respectively].[253] Direct comparison of CT and MRI for diagnosis of stenosis indicated a similar sensitivity [85% versus 92%] and specificity [100% versus 90%].[82] The use of luminal contrast and anti-peristaltic agents is recommended for CT enterography and MR enterography.[347]

Strictures in Crohn's disease [CD] are transmural and contain variable proportions of inflammatory and fibrotic tissue.[348] Quantification of active inflammation versus fibrosis is challenging. With regards to current techniques used in clinical practice, no technique is sufficiently accurate to assess the degree of fibrosis in a stricture with adequate precision to guide clinical decisions. The stratified echo pattern of the different layers of the intestinal wall components of a stricture has been associated with collagen deposition, but this approach lacks consistency.[349] On CT enterography, the presence of fibrosis was linked to stenotic lesions, but could not distinguish inflammation from fibrosis.[350] Conventional-sequence MR enterography revealed conflicting results for fibrosis characterisation.[351,352] Rimola *et al*. developed a technique using gadolinium enhancement between 70 s and 7 min on MR enterography. This approach was able to distinguish mild or moderate fibrosis from severe fibrosis irrespective of the degree of inflammation.[353] This approach awaits external validation.

Although several novel imaging techniques have been proposed, data are limited, acquisition methods are unstandardised, and there is limited evidence to support external validity. These techniques include MR with dynamic contrast-enhanced technique,[354] magnetisation-transfer MR,[355,356] ultrasound elastography,[357,358] or contrast-enhanced ultrasound [CEUS].[359,360] While stenosis can be detected by endoscopy, most investigators use the ability to pass the endoscope as a measure of stenosis. The proportion of fibrosis cannot be evaluated precisely by biomarkers, endoscopy, or histology. There is no consistent approach regarding strategy for monitoring strictures over time or with which method.

Although not the preferred technique, ileocolonoscopy can be used for stricture diagnosis. The commonly used definition is a narrowing that cannot be passed with an endoscope.[361] An ileocolonoscopy is not necessary in all cases after a stricture has been detected on cross-sectional imaging, but should be considered if endoscopic therapy through endoscopic balloon dilatation is a valid therapeutic approach[362] and in case of colonic strictures when malignancy cannot be excluded.

Statement 3.1.2. ECCO-ESGAR Diagnostics GL [2018]

Any colonic stricture should be carefully surveyed due to risk of carcinoma [EL4]; surgery should be considered

Consistent with the observation that patients with ulcerative colitis [UC] and patients with colonic CD are at an increased risk of developing colorectal cancer [CRC],[363–365] detection of a new colonic stricture should lead to a careful diagnostic workup to exclude malignancy. A recently published population-based study suggested that colonic strictures at diagnosis or during follow-up are associated with a 3.6% and 4.9% probability of CRC at 5 and 10 years, respectively.[366] According to the ECCO evidence-based consensus for endoscopy in IBD, patients with strictures detected within 5 years should be considered 'high risk' and receive surveillance colonoscopy yearly. Malignancy is more frequent in the CD-affected colon and the incidence is comparable to UC.[367,368] In a GETAID study, dysplasia or cancer was detected in 3.5% of patients with IBD who underwent surgery for colonic strictures.[369] In addition, small bowel adenocarcinoma is rare but can be fatal if overlooked.[370] The endoscopist should therefore have a low threshold for taking a biopsy before endoscopic balloon dilatation.[370] In addition, the use of paediatric endoscopes with a smaller diameter may permit stricture traversal. Cross-sectional imaging should be considered as a complementary diagnostic modality. Currently, there is no method [including histology] that can definitively rule out malignancy in a patient with IBD and colonic strictures.

3.2. Detection of fistulae and abscesses

3.2.1. Detection of intra-abdominal fistulae and abscesses

Statement 3.2.1. ECCO-ESGAR Diagnostics GL [2018]

Cross-sectional imaging [IUS, MRI, and CT] can detect internal penetrating disease and intra-abdominal abscesses with varying accuracy [EL1]. MRI is preferable to ultrasound for deep-seated fistulae or abscesses or pelvic fistulae [EL4]

In a systematic review for the diagnosis of intra-abdominal fistulising lesions, cross-sectional imaging showed the following accuracy: for CT with surgery and endoscopy as reference standard, the sensitivity was 70% and specificity 97%; MRI with surgery or endoscopy as the reference standard showed a sensitivity of 76% and specificity of 96% for fistula diagnosis; IUS with surgery, barium studies, and colonoscopy as the reference standard showed a sensitivity of 74% and specificity of 95%.[81] Oral contrast agents do not improve accuracy of IUS for detection of internal fistulae.[131] If available, CT or MRI is preferable for detection of intra-abdominal or pelvic fistulae over ultrasound; MRI has the advantage of no radiation exposure.[80,81] Cross-sectional imaging has a pivotal role in the assessment of penetrating complications of CD. In one study, there was no clinical fistula or abscess suspicion from pre-CT examination in half of patients with penetrating CD complications. Cross-sectional imaging changed management in more than three-quarters of these patients.[371] White blood cell scintigraphy is not indicated for diagnosis and characterisation of fistulae.

A systematic review revealed the following point estimates for diagnosis of abscesses: using surgery as a reference standard, IUS had a sensitivity of 84% and a specificity of 93%, which was dependent on disease location in CD.[81] Detection of intra-abdominal abscesses via CT, with surgery as the reference standard, revealed a sensitivity of 86% and a specificity of 88%.[350] One prospective study showed a sensitivity of 85% and specificity of 95% of CT for intra-abdominal abscesses.[372] CT and ultrasound showed an overall high and comparable accuracy in the detection of intra-abdominal abscesses, although CT showed a slightly greater positive predictive value than ultrasound.

CEUS has been shown to differentiate between an intra-abdominal phlegmon and abscess with high accuracy.[373] The accuracy of MRI for abscess detection, using surgery as the reference standard, showed sensitivities ranging from 86% to 100% and specificities from 93% to 100%.[352,374,375] A systematic review of these three studies showed a sensitivity of 86% and a specificity of 93% for MRI detection of abscesses.[81] Endoscopy is not used for evaluation of internal penetrating disease, due to an inability to image extramural structures.

3.2.2 Detection of fistulae and abscesses

Statement 3.2.2. ECCO-ESGAR Diagnostics GL [2018]

MRI is the most accurate imaging modality for diagnosis and classification of perianal CD and is the recommended first-line test [EL1]. Transrectal ultrasonography [TRUS] is superior to clinical examination and is an alternative to MRI [EL2]. Combining any modality of MRI, examination under anaesthesia [EUA], or TRUS improves accuracy [EL2]

Statement 3.2.3. ECCO-ESGAR Diagnostics GL [2018]

Examination under anaesthesia [EUA] with drainage is recommended if a perianal abscess is suspected, and should not be postponed if pelvic imaging is not immediately available [EL2]

Statement 3.2.4. ECCO-ESGAR Diagnostics GL [2018]

Endoscopic evaluation of the rectum is essential to determine the most appropriate management strategy for perianal CD [EL2]

Three diagnostic tests are commonly used alone or in combination for the diagnosis and classification of perianal disease, namely examination under anaesthesia [EUA], MRI, or transrectal ultrasonography [TRUS]. Both TRUS [with and without hydrogen peroxide] and MRI can identify and classify fistulous tracts with a diagnostic accuracy for MRI ranging from 80% to 100% in most reported studies. The diagnostic accuracy of TRUS is more variable and ranges from 50% to 100%.[165,170,376–385] MRI is the recommended first-line test, as TRUS is hindered by patient discomfort, cannot be performed in the presence of stenosis, and has a smaller field of view. EUA by an experienced surgeon has long been considered the reference standard for assessment of perianal CD. However, a prospective blinded study comparing EUA, MRI, and TRUS found diagnostic accuracies of 91%, 87%, and 91%, respectively, with 100% accuracy when any two of the tests were combined.[169] A larger prospective clinical trial compared preoperative digital rectal examination [33% sensitivity], TRUS [75% sensitivity], and body-coil MRI [85% sensitivity]. MRI may change management in patients with perianal CD by detecting an abscess not suspected clinically,[376,386] and should therefore precede EUA unless there is a need for immediate drainage of sepsis. Although the use of EUA may be limited by luminal stenosis, dilatations during the procedure can be performed.

Undiagnosed fistula extensions and abscesses are major causes of recurrent disease after attempted surgical cure.[377] Furthermore, full knowledge of the presence and extent of these secondary tracts is required for appropriate medical therapy, particularly with anti-TNF agents.[166] Accurate classification of perianal fistulae is thus essential before starting therapy. Two prospective studies evaluated the effect of preoperative MRI on clinical outcome after surgical treatment for perianal fistulising disease.[376,377] Both studies showed that MRI revealed additional and clinically relevant information to the surgeon performing EUA. A prospective comparison of modalities using a robust outcome-based reference standard found MRI superior to TRUS for fistula classification and detecting abscesses.[170] In general, MRI is preferred in CD, especially in recurrent or suspected complex disease.

Endoscopy can facilitate detection of perianal disease and has a role in assessing the degree of inflammation in the rectum, which may affect management.[105] Endoscopy has not been shown to be useful in monitoring perianal disease or assessing response to fistula therapy.

Transperineal ultrasound [TPUS] has been evaluated in small studies for the documentation of perianal disease and may have clinical utility.[387,388]

3.3 Detection of pouch complications

Statement 3.3.1. ECCO-ESGAR Diagnostics GL [2018]

Cross-sectional imaging and endoscopy are complementary methods for assessing suspected structural complications after ileal pouch anal anastomosis [IPAA] [EL4]. Pouchography can be used additionally to assess functional disorders and other complications [EL3]

Inflammatory and non-inflammatory complications of the ileal pouch anal anastomosis [IPAA] are common and include strictures, abscesses, fistulae, and sinus tracts culminating in pouch failure in up to 9% of cases at 5 years.[329,330,332,389] These complications can be immediately postoperative or long-term. In the cases of IPAA stenosis, fistulae, abscesses, and sinuses, EUA by an experienced IBD surgeon is important for diagnosis and timely treatment of most pathologies. The choice of diagnostic modality depends on the clinically suspected disorder, local expertise, and availability. Endoscopy is essential to obtain information on mucosal status and for diagnosis of intraluminal or anastomotic complications, such as strictures. Endoscopic balloon dilatation can be used to treat pouch stricture.[390,391] For suspected extraluminal complications, such as abscesses, fistulae, or sinus tracts,[392,393] pelvic CT, MRI, and TRUS or TPUS are sensitive methods that allow the identification and characterisation of septic problems[170]; use of these modalities depends on local availability and experience level. Unfortunately, the proportion of fibrosis versus inflammation cannot be assessed precisely by any currently available diagnostic tool.[394–396] Contrast pouchography can assist in assessment of pouch strictures, pouch fistulae, and leakage[100] but is only used in a limited number of centres. A correlation of pelvic CT, MRI, pouch endoscopy, and retrograde pouchography findings with clinical outcome revealed a reasonable accuracy for diagnosis of strictures, fistulae, sinuses, and pouch leaks, with all methods.[397] CT had the lowest accuracy for small bowel strictures [74%]; MRI had the lowest accuracy for pouch sinuses [68%]. A combination of two imaging tests increased diagnostic accuracy to 100%. In the acute postoperative setting, complications of IPAA include anastomotic leaks and abscesses. Leaks from the tip of the J-pouch and the pouch-anal anastomosis often result in pelvic abscesses. Detection of anastomotic dehiscence after IPAA is possible using transanal ultrasound and TPUS, although pelvic CT or MRI scanning is usually required to outline the full extent of the complication and guide drainage.[396,398] Complications of the pouch should be discussed in a multidisciplinary team setting to individualise management.

3.4 Detection of emergency complications

Statement 3.4.1. ECCO-ESGAR Diagnostics GL [2018]

In acute severe colitis, a plain abdominal radiograph is an acceptable first study to detect toxic megacolon. In selected cases, CT could be indicated as an initial method to screen for complications [EL3]

Diagnosis of toxic megacolon is usually made by clinical signs of systemic toxicity supported by imaging confirmation. Detection of transverse colonic dilatation >5.5 cm by means of plain abdominal X-ray is still the most established radiological definition of toxic megacolon.[399] Some case series have shown that in patients with toxic megacolon, CT scan and IUS can be promising alternatives that provide additional information.[400,401] A CT scan is an important tool for diagnosis of associated perforation or ascending pylephlebitis. A study observed that among 18 patients with toxic megacolon [four with underlying UC], CT scans revealed abdominal complications in four patients, missed clinically and on plain abdominal films.[400] Larger clinical studies are warranted to assess the diagnostic benefit of cross-sectional radiological studies in the assessment of toxic megacolon.

Statement 3.4.2. ECCO-ESGAR Diagnostics GL [2018]

When a perforation is suspected, CT should be performed in all patients with acute abdominal pain and established diagnosis of IBD [EL2]

Spontaneous free perforation is a rare but serious event in CD, but can be more common in acute severe colitis. Spontaneous free perforation may result from severe inflammation or superimposed malignancy. It is estimated that approximately 1% to 2% of patients with CD will present with a free perforation initially or at some time over their disease course.[402,403]

In IBD patients, intestinal perforation frequently presents as a peri-intestinal abscess that may be detected by cross-sectional imaging methods such as IUS, MRI, or CT. A systematic review showed that in this context the three techniques have a high accuracy for identification of fistulae, abscesses, and stenoses [sensitivities and specificities of 0.80], although IUS yields more false-positive results for abscesses.[81]

3.5. Detection of postoperative complications

Statement 3.5.1. ECCO-ESGAR Diagnostics GL [2018]

Acute postoperative complications in IBD patients [mainly anastomotic leaks and abscesses] should be initially investigated by CT [EL3]. Ultrasound may be an alternative first-line investigation, but should be followed by immediate CT, if negative or equivocal. [EL4]

Anastomotic leaks after intestinal surgery may be promptly diagnosed clinically, due to specific clinical presentation in the postoperative period. However, when anastomotic leaks are suspected in cases of atypical clinical manifestations, correct and rapid radiological diagnosis is necessary for successful management. Few studies have been designed to assess detection of these complications in CD,[81] and most are derived from the surgical literature.[404–406] A prospective database populated over a 10-year period showed that anastomotic leaks are frequently diagnosed late in the postoperative period and often after initial hospital discharge [median time 12.7 days, range 1–38].[404] In this study, CT was the preferred imaging modality.[404] In contrast, other studies showed that most postoperative CT features overlap between patients with or without clinically important anastomotic leaks, and that CT studies performed on patients shortly after abdominal surgery are not definitive. A negative CT does not exclude postoperative lower gastrointestinal tract leaks.[405,406] A combination of CT, laboratory examinations, and clinical signs and symptoms will optimise diagnosis of such complications.

There is no evidence that the addition of intraluminal contrast is more sensitive for detection of anastomotic dehiscence in IBD, as peri-anastomotic located fluid-containing gas is the most prevalent sign of anastomotic insufficiency.[406] Selected use of intraluminal contrast can be individualised according to physician preference.

3.6. Surveillance for colorectal cancer in IBD patients with colonic inflammation

Statement 3.6.1. ECCO-ESGAR Diagnostics GL [2018]

[ECCO UC Guideline: statement 8D in Magro F *et al.*]
Screening colonoscopy should be offered 8 years after onset of symptoms to all patients to reassess disease extent and exclude dysplasia [EL5]

Statement 3.6.2. ECCO-ESGAR Diagnostics GL [2018]

[ECCO UC Guideline: statement 8E in Magro F *et al.*]
When disease activity is limited to the rectum without evidence of previous or current endoscopic or microscopic inflammation [or both] proximal to the rectum, inclusion in a regular surveillance colonoscopy programme is not necessary [EL2]

Statement 3.6.3. ECCO-ESGAR Diagnostics GL [2018]

[ECCO UC Guideline: statement 8F in Magro F *et al.*]
In patients with concurrent primary sclerosing cholangitis [PSC], annual surveillance colonoscopy should be performed following the diagnosis of PSC, irrespective of disease activity, extent, and duration [EL3]

Statement 3.6.4. ECCO-ESGAR Diagnostics GL [2018]

[ECCO UC Guideline: statement 8G in Magro F *et al.*]
Ongoing surveillance should be performed in all patients apart from those with proctitis [EL3]. Patients with high-risk features [e.g. stricture or dysplasia detected within the past 5 years, PSC, extensive colitis with severe active inflammation] should have their next surveillance colonoscopy scheduled for 1 year [EL4]. Patients with intermediate risk factors should have their next surveillance scheduled for 2 to 3 years. Intermediate risk factors include extensive colitis with mild or moderate active inflammation, post-inflammatory polyps, or a family history of colorectal cancer [CRC] in a first-degree relative diagnosed at age 50 years and above [EL5]. Patients with neither intermediate nor high-risk features should have their next surveillance colonoscopy scheduled for 5 years [EL5]

Statement 3.6.5. ECCO-ESGAR Diagnostics GL [2018]

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

Statement 3.6.6. ECCO-ESGAR Diagnostics GL [2018]

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

Statement 3.6.7. ECCO-ESGAR Diagnostics GL [2018]

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]. A patient with confirmed low-grade dysplasia detected in mucosa without an associated endoscopically visible lesion should undergo repeat chromoendoscopic colonoscopy with additional random biopsies within 3 months [EL5]

Statement 3.6.8. ECCO-ESGAR Diagnostics GL [2018]

[ECCO UC Guideline: statement 8K in Magro F *et al.*]
Presence of low-grade or high-grade dysplasia should be confirmed by an independent gastrointestinal specialist pathologist [EL5]

Longstanding UC and CD with colonic inflammation are associated with an increased risk of CRC, with a variable estimate between studies.[363–365] However, the risk of CRC seems to decline over time.[407–409] Possible reasons are the emergence of effective surveillance strategies, better control of inflammation with drugs, and a modified approach to maintenance therapy or colectomy, as stated in previous guidelines.[410]

On the basis of systematic endoscopic assessment, together with medical and family history of the patient, surveillance colonoscopy programmes have been developed to reduce CRC-associated morbidity and mortality.[363] At the onset of these programmes, an initial screening colonoscopy is performed to reassess disease extent and confirm the absence of dysplastic lesions.[363] The timing of surveillance colonoscopies should be based on the level of risk of the patient, as extensively discussed in the recent ECCO consensus[363] [Table 2]. The suggested timeline for surveillance in Crohn's colitis, though scientific data are more limited, should be applied as for UC.

Good bowel preparation is essential for an efficient surveillance colonoscopy, since the quality of the preparation in UC patients significantly affects the lesion detection rate.[411]

A recent colitis surveillance study demonstrated that high-definition colonoscopy improves dysplasia detection in comparison with standard definition.[363,412] Targeted biopsies have been shown to be not inferior to random biopsies for neoplasia detection rate per colonoscopy in a randomized controlled trial.[363,413] Spraying dyes, such as methylene blue or indigo carmine,[414–416] highlight subtle changes in the colonic mucosa architecture and can improve the detection rate of dysplasia.[417] There is abundant evidence from clinical trials and real-life studies that chromoendoscopy is superior to white-light endoscopy for dysplasia detection,[418–426] independent of operator familiarity or from the availability of high-resolution endoscopy. Narrow-band imaging and endomicroscopy cannot currently be recommended for dysplasia screening in IBD.[363]

3.7. Diagnostic and monitoring techniques during pregnancy

Statement 3.7.1. ECCO-ESGAR Diagnostics GL [2018]

IUS and abdominal MRI without intravenous gadolinium are the safest techniques to examine pregnant women in whom IBD is known or suspected, regardless of the trimester [EL5]

Statement 3.7.2. ECCO-ESGAR Diagnostics GL [2018]

Endoscopy is generally considered to be safe in pregnancy; however, procedures should only be performed when there is a strong indication and clear clinical benefit [EL3]

Data are scarce concerning the medical imaging of pregnant women in whom IBD is known or suspected. Recent guidelines by the American College of Obstetricians and Gynecologists state that

Table 2. Timeline of endoscopic surveillance according to risk factors after screening colonoscopy.

Risk level	Risk factors	Surveillance
Lower risk	Extensive colitis with mild endoscopic or histological inflammation Colitis affecting <50% of the colon	Every 5 years
Intermediate risk	Extensive colitis with mild endoscopic or histological inflammation [or both] CRC in a first-degree relative older than 50 years	Every 2–3 years
Higher risk	Extensive colitis with moderate-to-severe endoscopic or histological inflammation [or both] CRC in a first-degree relative younger than 50 years History of PSC [included post-OLT] Stricture in past 5 years Dysplasia in the past 5 years in a patient who declines surgery	Yearly

CRC, colorectal cancer; PSC, primary sclerosing cholangitis; OLT, orthoptic liver transplantation.

ultrasound, MRI, CT, and nuclear medicine imaging techniques are theoretically safe if used prudently.[427] The main concerns regarding these techniques are increased fetal temperature caused by application of high-frequency ultrasound, or a magnetic field and fetal radiation exposure, either via X-ray or radio-isotopes.

Ultrasound and MRI are the best choice for pregnant women, but application of either can theoretically increase the temperature of maternal and fetal tissues.[428,429] The Food and Drug Administration limits the spatial-peak temporal average intensity of ultrasound transducers to 720 mW/cm^2.[427] Ultrasound examination should be performed according to the 'as low as reasonably achievable' principle,[430] accounting for exposure time related to the thermal index generated during the procedure [keeping this value <1].[431,432] No specific data apply to IBD populations.

Regarding MRI, a recent retrospective survey of 1 424 105 deliveries from the province of Ontario compared those with first-trimester MRI [*n* = 1737] with no MRI [*n* = 1 418 451]. MRI did not confer additional risk of congenital anomalies, neoplasms, or vision or hearing loss. No additional risk of nephrogenic systemic fibrosis was found when gadolinium-enhanced MRI [n = 397] was compared with no MRI [*n* = 1 418 451]. Gadolinium-enhanced MRI at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions [adjusted hazard ratio 1.36; 95% CI 1.09–1.69] and for stillbirth or neonatal death [adjusted relative risk 3.70; 95% CI 1.55–0.85].[433] Another retrospective study of 751 neonates exposed to 1.5T MRI in utero, compared with 10 042 unexposed neonates, found no difference between groups regarding birthweight or incidence of hearing impairment or deafness.[434]

Specific data on MRI in pregnant women with IBD are limited. Stern *et al.* reported nine pregnant women [seven with established CD] who underwent unenhanced MRI. Features typical of active CD were identified with their protocol [mural thickening ≥3 mm, ulcers, mural oedema, 'comb sign', phlegmon, abscesses, and fistulae]. MRI detected complications in four women and was sufficiently accurate to inform medical management.[435] One case report described MR colonography used safely to examine a pregnant woman of 20 weeks gestational age with acute severe colitis, indicating conservative therapy that avoided colectomy.[436] Another case report described a pregnant woman of 26 weeks gestational age who underwent unenhanced MRI to diagnose adhesions following ileo-anal pouch surgery, with no adverse events.[437] Another case report did not reveal any safety concerns in a pregnant woman with fistulising CD.[438]

X-ray exposure is associated with an increased risk of congenital malformation[439,440] and childhood cancer,[441] estimated at 6% per Gy.[440] However, exposure at ≤50 mGy is considered safe at any trimester.[440] In the absence of data for IBD patients, Hurwitz *et al.* showed that multidetector row CT to investigate suspected appendicitis conferred a dose of 1.52 to 1.68 cGy and 2 to 4 cGy at Months 0 and 3, respectively.[442] Unless potential risks are outweighed by clinical need, current data do not support the use of CT or any other X-ray technique. Due to the absence of specific data regarding use of radio-isotopes in pregnant women with suspected or diagnosed IBD, radio-isotopes should be avoided in this patient population.

Limited evidence exists regarding the utility and safety of endoscopy in pregnant women with IBD. Due to potential complications described in the recent ECCO pregnancy and reproduction consensus,[443] endoscopy in pregnancy should be reserved for strong indications. To avoid vena cava compression, pregnant patients should be placed in the left pelvic tilt or left lateral position before, during, and after the endoscopic procedure. Close attention should be paid to appropriate drug selection, using drugs appropriate for pregnancy and using the minimum dose possible to achieve the desired effect. Sedative drugs should be administered to provide patient comfort; over-sedation should be avoided.

3.8. Diagnostics for biliary extra-intestinal manifestations of IBD

Statement 3.8.1. ECCO-ESGAR Diagnostics GL [2018]

Ultrasound is the first-line non-invasive imaging procedure in the workup of elevated liver enzymes, cholestasis, or both [EL1]. Magnetic resonance cholangiopancreatography should be considered if ultrasound and serology are inconclusive [EL1]

Statement 3.8.2. ECCO-ESGAR Diagnostics GL [2018]

[ECCO-EIM Guidelines: statement 7B in M. Harbord *et al.*] If high-quality magnetic resonance cholangiography is normal in a patient with IBD and suspected PSC, an ultrasound-guided liver biopsy should be considered to diagnose small-duct PSC [EL2]

Statement 3.8.3. ECCO-ESGAR Diagnostics GL [2018]

[ECCO EIM Guidelines: statement 7H in M. Harbord *et al.*] There is no evidence-based follow up regimen proven to detect biliary neoplasia earlier in PSC. Annual ultrasonography to detect gallbladder mass lesions is recommended [EL4]. Additional imaging (MRI/MRC, CT, or endoscopic retrograde cholangiography [ERC]) should be performed without delay if cholangiocarcinoma is suspected [EL1]

Statement 3.8.4. ECCO-ESGAR Diagnostics GL [2018]

[ECCO EIM Guidelines: statement 7E in M. Harbord *et al.*] In PSC patients with clinical or radiological suspicion of significant strictures or cholangiocarcinoma, ERC is recommended to diagnose strictures that may be amenable to endoscopic dilatation [with or without stenting] and for brush cytology specimen evaluation [EL2]. Prophylactic antibiotic therapy is recommended [EL1]

The statements above have been included in this ECCO diagnostic guideline for completion of endoscopic or cross-sectional imaging diagnostics of extra-intestinal biliary involvement in patients with IBD. For detailed explanation and references, please refer to the ECCO EIM guideline.[244]

Conflict of Interest Statement

ECCO and ESGAR have diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of *JCC* but also is 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 authors.

The ECCO-ESGAR Consensus Guidelines are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO-ESGAR Consensus Guidelines. The European Crohn´s and Colitis Organisation, the European Society of Gastrointestinal and Abdominal Radiology, and/or any of their staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO-ESGAR Consensus Guidelines.

Acknowledgments

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WG2: Imaging techniques in regard to clinical situations: Monitoring therapeutic success [inclusive calpro], Monitoring clinically asymptomatic patients, Monitoring clinically symptomatic patients, Imaging after surgery including ileoanal pouch
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Member – Uri Kopylov
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WG3: Detecting [suspected] complications [stricture, fistula, abscess, anastomotic insufficiency, toxic megacolon, perforation]: Endoscopic and non-medical, non-surgical interventions [stricture, abscess, bleeding], Cancer surveillance, Imaging during pregnancy
Leader – Gionata Fiorino
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WG5: General principles and technical aspects of: endoscopy including enteroscopy, capsule endoscopy, ultrasound, CT, MRI, SBE/SBFT
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Journal of Crohn's and Colitis, 2018, 273–290
doi:10.1093/ecco-jcc/jjy114
Advance Access publication August 24, 2018
ECCO Guideline/Consensus Paper

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ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects

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Chapter 4: Scores for Inflammatory Bowel Disease

4.1 Clinical and endoscopic scoring systems in inflammatory bowel disease

Statement 4.1. ECCO-ESGAR Diagnostics GL [2018]

Clinical indexes are useful for standardising disease activity. However, despite widespread use, no score has been validated in clinical practice [EL5]

4.1.1 Clinical and endoscopic scoring systems in ulcerative colitis

There are several scoring systems presently available to classify disease severity in ulcerative colitis [UC] within the multiple domains of disease activity, which aid objective assessment of disease and guide therapeutic and monitoring strategies.[1,2] Although somewhat limited by subjective definitions, their strength lies in the potential to monitor patient progress over time.[1]

The **Simple Colitis Clinical Activity Index** [SCCAI][2,3] [Table 1] and the **Paediatric Ulcerative Colitis Activity Index** [PUCAI][4] [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online] are reliable and responsive scores with clear definitions for clinical response and remission. SCCAI scores range between 0 and 19 points and include nocturnal bowel movements and faecal urgency, which affect patient quality of life [QoL].[3] An SCCAI score <2 indicates clinical remission, and a decrease of >1.5 points from baseline correlates with patient-defined significant improvement.[5]

The **Mayo Clinic Score [or Index]** [Partial Mayo Clinic Index and endoscopic subscore] and **Ulcerative Colitis Disease Activity Index** [UCDAI] are a composite assessment of clinical symptoms [stool frequency and rectal bleeding] and endoscopic severity [Table 2].[6,7] Whereas these indexes are not validated, the Mayo Clinic Score is easy to apply and has been used for assessing therapeutic endpoints in adult clinical trials.[8] Clinical improvement is defined as the reduction of baseline scores by ≥3 points and clinical remission as an overall score ≤2 [and no individual subscore >1] or UCDAI ≤1.[6–8] A **Partial Mayo Score** [PMS] <1 indicates remission.[1] The PMS has been shown to correlate well with the full scoring system.[9,10]

The **Truelove and Witts Severity Index** was described in 1955.[11] Its elements reflect levels of systemic toxicity and provide objective criteria for assessment of acute severe colitis, need for hospitalisation, and corticosteroid therapy[2] [Table 3]. The **Lichtiger Index** is a modification of the Truelove and Witts Index and was used in the cyclosporine trial for steroid-refractory UC.[12]

The **Pouchitis Disease Activity Index** was developed to provide a standard definition of pouchitis, including histological subscores.[13] A Pouchitis Disease Activity Index score ≥7 indicates acute pouchitis, and remission is defined as a score ≤2 including endoscopic subscores ≤1 [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online].

Table 1. Clinical scoring system for the Simple Clinical Colitis Activity Index.[3]

Symptom	Score
Bowel frequency [day]	
1–3	0
4–6	1
7–9	2
>9	3
Bowel frequency [night]	
1–3	1
4–6	2
Urgency of defaecation	
Hurry	1
Immediately	2
Incontinence	3
Blood in stool	
Trace	1
Occasionally frank	2
Usually frank	3
General well-being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extracolonic features [joints, eyes, mouth, skin, perianal]	1 per manifestation

Statement 4.1.1. ECCO-ESGAR Diagnostics GL [2018]

Endoscopic scores in ulcerative colitis [UC] should be used for standardisation of care [EL5]. The Mayo Clinic Subscore [MCS] is accepted and extensively used, and the UC Endoscopic Index of Severity [UCEIS] and the UC Colonoscopic Index of Severity [UCCIS] are formally validated [EL2]. The Pouchitis Disease Activity Index provides a standard definition of pouchitis [EL4]

Endoscopic scoring systems in ulcerative colitis

A plethora of UC endoscopic scoring systems have been developed over the years.[1,2,14,15] These systems are also increasingly used in clinical practice to guide treatment decisions with the aim of achieving mucosal healing [MH] [Table 4].[16–19]

The first attempt to classify endoscopic UC severity was performed by Truelove and Witts.[11] Mucosal appearance is classified into the following three categories: [1] normal or near normal; [2] improved; or [3] no change or worse. This classification lacks well-defined endoscopic descriptors.

Baron *et al.* subsequently evaluated interobserver agreement using rigid sigmoidoscopy.[20] The degree of disease activity is based on a 4-point scale [0–3] mainly according to bleeding severity. The presence of ulceration is not taken into account. A **Baron Score** ≤1 [0, normal mucosa; 1, abnormal mucosa but non-haemorrhagic] is defined as endoscopic remission. The Baron Score has not been formally validated. Feagan *et al.* described the **Modified Baron Score**

Table 2. Mayo score for ulcerative colitis.[6]

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

[MBS] in a placebo-controlled trial.[21,22] Endoscopic activity is categorised according to a 5-point scale [0–4].

The **Powell-Tuck Index** [also known as St Mark's Index][23] grades the severity of inflammation using a 3-point scale [0–2], focusing on mucosal bleeding as the predominant variable [Supplementary Table 3, available as Supplementary data at *ECCO-JCC* online].

The **Sutherland Index** [UC Disease Activity Index, UCDAI][7] was developed during a placebo-controlled trial. Mucosal appearance is described on a 4-point scale [0–3] evaluating the following three endoscopic findings: [1] friability; [2] exudation; and [3] spontaneous haemorrhage.

Table 3. Disease activity in ulcerative colitis, adapted from Truelove and Witts.[11]

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

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

The **Rachmilewitz Endoscopic Index**[24] was developed during a controlled trial. The index includes the following four variables: [1] vascular pattern; [2] granularity; [3] mucosal damage [mucus, fibrin, exudate, erosions, ulcers]; and [4] bleeding. The cut-off for endoscopic remission is ≤4 points.

The endoscopic component of the **Mayo Clinic Score** [MCS][6] assesses inflammation based on a 4-point scale [0–3] as follows: [0] normal; [1] erythema; decreased vascular pattern, mild friability; [2] marked erythema, absent vascular pattern, friability, erosions; and [3] ulceration, spontaneous bleeding. The MCS is most commonly used in clinical trials.[8] Clinical response is defined as reduction from baseline MCS by ≥3 points and a decrease of 30% from the baseline score with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.[18] Clinical remission is defined as an MCS ≤2 and no individual subscore >1. MH has been defined as a subscore of 0 to 1.[18] Interobserver agreement can vary markedly.[18] For the MCS, the most inflamed part determines the overall score.

The **Modified Mayo Score** [MMES] divides the colon into five segments and the score for each segment is added to give a modified score,[25] which is multiplied by the maximal extent of inflammation and divided by the number of segments with active inflammation to give the final MMES.

The **Ulcerative Colitis Endoscopic Index of Severity** [UCEIS] is a validated endoscopic index that was developed due to wide interobserver variation [Supplementary Table 4, available as Supplementary data at *ECCO-JCC* online]. UCEIS grades three endoscopic findings in the

Table 4. Comparison of endoscopic scoring indexes in ulcerative colitis. Adapted from Annese V *et al.*[14]

Score	Endoscopic variables	Strengths	Weaknesses	Proposed remission score
Truelove and Witts[11] Sigmoidoscopic assessment	No endoscopic descriptor definitions	-----	-----	-----
Baron Score[20]	Vascular pattern, friability, bleeding	Easy to calculate	Does not evaluate ulcers Subjective interpretation of friability and bleeding Poor interobserver agreement	0–1
Powell-Tuck Index [St Mark's Index][23]	Bleeding [non-haemorrhagic vs haemorrhagic mucosa]	-------	Only evaluates bleeding Subjective interpretation	Not defined
Sutherland Index[7]	Friability, exudation, spontaneous haemorrhage	-------	Does not evaluate ulcers Not accurate in discriminating between mild to moderate friability	0
Mayo Endoscopic Subscore[6]	Erythema, vascular pattern, friability, erosions, ulcers, bleeding	Easy to calculate Widely used in clinical trials	Not accurate in discriminating between mild to moderate friability	0–1
Rachmilewitz Index[24]	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[21]	Vascular pattern, granularity, hyperaemia, friability, ulceration, bleeding	Easy to calculate Used in clinical trials	No discrimination between superficial and deep ulceration	0
UCEIS[26]	Vascular pattern, bleeding, erosions, ulcers	Accurate for the assessment of disease severity Developed following rigorous methodology	Low agreement for normal appearance of the mucosa	Validated
UCCIS[33]	Vascular pattern, granularity, ulceration, bleeding, friability	Accurate, easy scoring as based on only four different parameters Developed and validated following rigorous methodology Covers the entire colon	Single-centre development, high expertise required Broader validation needed	Validated

most severely affected part of the colon, namely vascular pattern, bleeding, and erosions and ulcers. Initially developed as an 11-point score, UCEIS was simplified to an 8-point tool scoring erosions and ulcers [0–2], vascular pattern [0–2], and bleeding [1–4], with a satisfactory interobserver agreement [κ 0.5].[26] Friability has been excluded from this index. The extent of disease is not relevant in this score. Although this score appears more responsive to change following treatment than the MCS, UCEIS is still not extensively used due to lack of familiarity.[27,28] The remission target is a score ≤1. The UCEIS shows strong correlation with patient-reported outcomes.[29–31] Both UCEIS and MCS have demonstrated a high degree of correlation for UC [Supplementary Table 4, available as Supplementary data at *ECCO-JCC* online].[32]

The **Ulcerative Colitis Colonoscopic Index of Severity** [UCCIS] has recently been prospectively validated.[33] The UCCIS includes the following six variables: [1] vascular pattern; [2] granularity; [3] ulceration; [4] bleeding and 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 visual analogue scale [VAS] scale. The UCCIS has good-to-excellent interobserver agreement, but a cut-off level for endoscopic response and remission is currently lacking.

4.1.2 Clinical and endoscopic scoring systems in Crohn's disease

Numerous tools are available for assessing disease activity in Crohn's disease [CD] patients.[34] The most commonly used clinical activity indexes are the **Harvey-Bradshaw Index** [HBI], the **Crohn's Disease Activity Index** [CDAI], and the **Perianal Disease Activity Index** [PDAI] [Table 5].[35] Measuring clinical activity is important but no longer sufficient, and both CDAI and HBI are limited by subjective interpretation [Table 5].[36,37]

The CDAI[36] was developed by Best *et al.* in 1976. The CDAI consists of eight factors, each summed after adjustment with a weighting factor. Remission is defined as CDAI <150, and a value >450 represents severe disease. Most major research studies on medications in CD define response as decrease in CDAI of >70 points; however, in some studies a drop of 100 points is required for response.[38] The CDAI system has some limitations. These include: interobserver variability; relevant weight for scores of 'general well-being' and 'intensity of abdominal pain' items, which are subjective and reflect patients' perceptions of their disease; and the calculation of the CDAI is based on a diary completed by the patient for 7 days before evaluation. This requirement precludes the use of the CDAI in everyday practice. Furthermore, the CDAI is not accurate in patients with fistulising or stenotic behaviour and it is not useful in patients with previous extensive ileocolonic resections or stoma. Currently, however, the CDAI is the most frequently used index for clinical trials.[39] However, exploratory and until now unvalidated patient-related outcomes scores [PRO] are asked by the authorities.

The **Harvey-Bradshaw Index** [HBI] was developed in 1980 as a simpler version of CDAI. The HBI consists of only clinical parameters; the first three items are scored from the previous day. These items include general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications. The HBI relies primarily on assessment of patient symptoms with scattered use of objective parameters. It correlates poorly with biological evidence of active disease, including endoscopic assessments and C-reactive protein levels. Furthermore, the HBI has the limitation of overestimating disease activity in the setting of concomitant functional bowel symptoms while underestimating disease in a subset of patients who may have subclinical stricturing or penetrating luminal complications.[40] Patients with CD who have an HBI score ≤3 are very likely to be in remission according to the CDAI. Patients with a score of 8 to 9 or higher are considered to have severe disease.

The **Crohn's Disease Digestive Damage Score** [the Lémann score] [Supplementary Table 5, available as Supplementary data at *ECCO-JCC* online] considers damage location, severity, extent, progression, and reversibility as measured by diagnostic imaging modalities and history of surgical resection [see section 4.3]. The Lémann score is expected to represent a patient's disease course and to assess the effect of various medical therapies.[41]

Irvine developed the PDAI.[42] Each of the five elements identified was graded on a 5-point Likert scale. Correlation between the PDAI [maximum 20 points] and the physician and patient global assessment is good. A more recent scoring system proposed by Pikarsky *et al.*[43] attempts to predict the outcome following surgical intervention in patients with perianal CD. However, the lack of a validated clinical outcome measure in CD seems to be most obvious in perianal Crohn's disease.

Statement 4.1.2. ECCO-ESGAR Diagnostics GL [2018]

The Crohn's Disease Endoscopic Index Of Severity [CDEIS] and the Simple Endoscopic Score for Crohn's disease [SES-CD] are validated and reproducible scoring systems measuring luminal endoscopic activity [EL2]. There is no validated definition of or score for mucosal healing [MH] in Crohn's disease [CD]. The severity of postoperative CD recurrence in the neo-terminal ileum should be stratified using the Rutgeerts score [EL2]

There are currently three endoscopic scoring systems for CD, namely the **Crohn's Disease Endoscopic Index of Severity** [CDEIS],[44] the **Simple Endoscopic Score for Crohn's Disease** [SES-CD],[45] and the **Rutgeerts** endoscopic grading scale for postoperative recurrence [Supplementary Tables 6 and 6a, available as Supplementary data at *ECCO-JCC* online].[14,46]

The CDEIS scores CD activity [from 0 to 44] in five bowel segments [terminal ileum, right colon, transverse, left colon and sigmoid, rectum] and considers specific mucosal lesions [such as ulcers and stenosis] and extent of disease.[44,47] The CDEIS is complicated to use, and requires training and experience in estimating the extent of ulcerated or diseased mucosal surfaces and expertise in distinguishing deep from superficial ulcerations. The CDEIS is also time-consuming. It has consequently not become routine in clinical practice and is used mainly in clinical trials.

Table 5. Non-endoscopic Crohn's disease activity indexes in clinical practice.

Activity index	Acronym	Range and [remission] values	Comments for clinical practice
Crohn's Disease Activity Index[3]	CDAI	0–600 [<150]	Calculation based on a 7-day diary; difficulty in assessment of perianal disease activity
Harvey - Bradshaw Index[37]	HBI	0–50 [≤4]	Simple and more practical
Perianal Crohn's Disease Activity Index[42]	PDAI	0–19	Problematic fistula severity assessment

The SES-CD was developed to simplify the CDEIS. The SES-CD includes four variables, each considered in five bowel segments [ulcer size, extent of ulcerated surface, extent of affected surface, and stenosis]. Scores range from 0 to 6. The SES-CD correlates highly with CDEIS. Defining SES-CD cut-offs must take into account endoscopically meaningful changes.[45] However, as the SES-CD do not define MH, this score is currently not much used in clinical practice.

Rutgeerts *et al.* developed a score for grading lesions in the neo-terminal ileum and anastomosis.[46] This score is considered the gold standard for establishing the prognosis in cases of postoperative recurrence; scores of 3 and 4 are validated cut-offs for predicting clinical relapse. The **Modified Rutgeerts Score** refers to a more refined definition of grade i2, which includes lesions confined to the ileocolonic anastomosis [i2a] or moderate lesions on the neo-terminal ileum [i2b].

4.1.3 Capsule endoscopy scores

The **Capsule Endoscopy CD Activity Index** [CECDAI or Niv Score] was validated in a multicentre prospective study of patients with isolated small bowel CD [Supplementary Table 7, available as Supplementary data at *ECCO-JCC* online].[48] The CECDAI evaluates the following three endoscopic parameters: inflammation [A, 0 to 5 points], extent of disease [B, 0 to 3 points], and strictures [C, 0 to 3 points], for both the proximal and the distal segments of the small bowel, based on the transit time of the capsule [Supplementary Table 7].

The **Lewis Score** assesses villous oedema, ulcers, and stenosis, and classifies CD activity from mild to severe.[49] The small bowel is first divided into three equal parts [tertiles] based on capsule transit time from the first duodenal image to the first caecal image. For each tertile, a subscore is determined based on the extent and distribution of oedema and on the number, size, and distribution of ulcers. The Lewis Score is the sum of the worst affected tertile plus the stenosis score [Supplementary Table 8, available as Supplementary data at *ECCO-JCC* online]. These small bowel capsule endoscopy scoring systems have been developed only recently, and their usefulness in clinical trials and clinical practice remains to be seen.[47]

4.2 Histological scoring systems in IBD

Statement 4.2. ECCO-ESGAR Diagnostics GL [2018]

A validated histological score should be used in clinical practice for UC [EL3]. There are no scores validated in clinical practice for CD [EL5]

The histological examination of endoscopic biopsies is not only a crucial element in the diagnostic workup but also in the evaluation of therapeutic effect and in identification of dysplasia.[2,50,51] The European Society of Pathology [ESP] and the European Crohn's and Colitis Organisation [ECCO] published a consensus document.[52,53] Since the publication of these guidelines, significant recent literature on histological healing and new histological scoring systems have added to our understanding of the assessment of disease activity, influencing the paradigms around grading and assessment of disease activity.[54,55]

4.2.1 Histological remission in IBD

In UC, histological remission should be defined as evidence of normalisation of the bowel mucosa. Active disease is defined by the presence of neutrophils within the crypt epithelium and crypt lumen [cryptitis and crypt abscesses] and ultimately by erosions and ulcers.[52,53] Histologically, MH is characterised by partial resolution of the crypt architectural distortion and of the inflammatory infiltrate, although the mucosa may still show some features of sustained damage, such as a decreased crypt density with branching and shortening of the crypts.[56] Ultimately basal plasmacytosis decreases, resulting in normal cellularity, and remission may result in a complete normalisation of the mucosa in approximately 24% of cases.[57,58] According to ECCO-ESP, active inflammation is usually absent in quiescent disease. There is no consensus on the acceptable number of eosinophils or lymphoid aggregates, nor on residual basal plasmacytosis. Although endoscopic MH is associated with better outcomes in IBD, less is known about the significance of achieving histological remission.[59] However, recent data suggest that histological remission, defined as minimal residual microscopic disease and absence of epithelial damage, is highly reproducible in multiple UC cohorts. Histological remitters are also more likely to achieve endoscopic and clinical response or remission and to remain symptom-free at 12 months after a course of corticosteroids. Reduced hospitalisation or colectomy rates[60–62] have also been observed when histological remission is achieved.

There is a need for a clear definition of 'complete' histological MH or 'histological remission', and to have a reproducible, standardised, and validated histological scoring system for biopsy evaluation. A histological endpoint is likely to be more relevant in UC than CD, as the diffuse mucosal inflammation in UC is less subject to biopsy bias than the patchy transmural inflammation of CD.

4.2.2 Histological scoring systems

A unique standard system for grading histological activity does not exist.[63–65] Numerous methods of classification of histological activity have been proposed and some are widely used, with only a few validated and proven to be reproducible [Supplementary Tables 9 and 10, available as Supplementary data at *ECCO-JCC* online]. Most the published systems were developed for UC [Supplementary Table 9]. Bryant *et al.*[59] published the results of a systematic bibliographic search that retrieved 22 different histological scoring systems for IBD. The most widely used in UC are the Riley Index[66] and the Geboes[67] Index. Some [such as the Riley Index] are difficult to reproduce, as the criteria for separating grades are not provided. The Geboes Index is subjective for chronic inflammation [grade 1] and eosinophils and neutrophils in the lamina propria [grade 2], but acute inflammation is well defined. The Geboes Index also includes the requisites to grade architecture and can be modified to include the evaluation of basal plasmacytosis. The recently published Nancy Score,[55] a three-descriptor histological index, has been validated for use in clinical practice and clinical trials. The relationship between the Nancy Score and Geboes Index was assessed with good responsiveness and correlation between them.[67] Mosli *et al.* recently developed an alternative instrument using some component items of the Geboes Index [Supplementary Table 9].[68]

Few scores were designed specifically for CD [Supplementary Table 10, available as Supplementary data at *ECCO-JCC* online]. The **Colonic and Ileal Global Histologic Disease Activity Score** [CGHAS or IGHAS] is probably the most widely used. This system is subjective and has not been validated, and its role is currently undefined [Supplementary Table 10].

4.2.3 Practice points and future directions

There is a clear need for a standard definition of histological MH and for a standard and fully validated system of histological disease activity. Histology may be more effective in predicting clinical relapses or

in evaluating benefit from therapy.[36] Meanwhile, pathologists should use a simple and validated scoring system to complement endoscopic scores. At present, the Nancy Score and Robarts histopathology [referenced in Mosli *et al.*[68]] are fully validated; the Geboes Index is only partially [not formally] validated but is widely used.[68]

4.3 Cross-sectional imaging scoring systems in IBD

Statement 4.3. ECCO-ESGAR Diagnostics GL [2018]

Magnetic resonance [MR] enterography-based indexes have high accuracy for assessing luminal CD activity and can be used in clinical trials for measuring activity and response to pharmacological interventions [EL3]. There are no validated scores for grading luminal activity based on ultrasound and computed enterography. Scoring of perianal fistula activity by MR imaging in CD allows evaluation of disease severity and changes after therapy [EL3]

Cross-sectional imaging has an established role in clinical practice for evaluation of the small and large bowel in patients with CD.[69] Assessments based on cross-sectional imaging may have use in clinical trials, with the added potential for validated indexes as surrogates for therapeutic response.

4.3.1 Cross-sectional index for luminal Crohn's disease

There are no formally validated indexes on luminal activity based on ultrasonography or CT enterography. Among the different indexes published based on MR enterography, only a few have been derived using valid external reference standards [i.e. endoscopy or histology] and use descriptors identified in multivariate analyses as independent predictors for detecting activity and severity [Supplementary Table 1].[70]

The **Magnetic Resonance Index of Activity** [MaRIA] is a composite index that takes into account bowel wall thickness, quantifies bowel enhancement after gadolinium injection, and identifies ulceration and bowel oedema [Supplementary Table 2]. A subscore is calculated for five colonic segments and for the terminal ileum. The global score is computed as the sum total of the subscores. The MaRIA score has good correlation with CDEIS [r = 0.83].[71,72] A MaRIA subscore of ≥7 is indicative of bowel segments with active CD, and a subscore of ≥11 units identifies segments with severe activity [ulcers at endoscopy].

In a study by Takenaka *et al.*, single-balloon enteroscopy was compared with MR enterography in patients with ileal CD.[73] The MaRIA score closely correlated with the SES-CD in the small bowel [r = 0.808; $p < 0.001$]. A MaRIA score of ≥11 had high sensitivity, specificity, and diagnostic accuracy for ulcerative lesions [sensitivity, 78.3%; specificity, 98.0%]. Similarly, a MaRIA score of ≥7 had high sensitivity, specificity, and diagnostic accuracy for all mucosal lesions [sensitivity, 87.0%; specificity, 86.0%].

The main limitation of the MaRIA index is that it was developed using both oral contrast and active colonic distension with water enema. It is still uncertain if diagnostic accuracy will remain similar without colonic distension.[71] MaRIA showed high accuracy for detecting ulcer healing [accuracy 0.9] and MH [accuracy 0.83] in CD patients following medical therapeutic intervention.[74,75]

The **Acute Inflammation Score** [AIS] is another MR enterography index and is a composite of two descriptors [mural thickness and mural T2 signal] that are evaluated in a semiquantitative fashion. A cut-off of 4.1 units defines the presence of active disease with an area under the curve [AUC] of 0.77, and demonstrated a moderate degree of correlation with histopathological inflammation [Kendall's tau = 0.40].[76]

Comparative studies using ileocolonoscopy as the reference standard have validated both indexes.[77,78] Reproducibility is critical to be considered as a useful instrument in practice. Specifically, moderate-to-good degrees of interobserver agreement [0.42–0.69] among expert readers has been reported.[77]

A recent index very similar to MaRIA but using diffusion-weighted imaging [DWI] sequence instead of contrast enhancement has been recently developed. This index is called the **DWI-MaRIA** score or **Clermont Score**.[79] To derive and validate the DWI-MaRIA score, the same MR enterography [MaRIA] was considered as the reference standard.[80] The correlation between the MaRIA and Clermont scores in the terminal ileum was almost perfect [r = 0.99] but was significantly lower in the colon.[81]

The **Sailer Index** was developed specifically for assessing postoperative recurrence at the anastomotic site using MR enteroclysis.[82,83]

The most frequently used MRI index for perianal disease is the **Van Assche Index**.[84] This score combines both the anatomical and complexity of fistula characteristics together with MRI findings linked to the inflammation observed. Changes in the Van Assche Index have good correlation with clinical response to treatment.[84–86] This index has only been partially validated.[87,88] However, certain aspects of the index need to be elucidated further, such as the responsiveness of each individual item of the index and the definition of a clinically relevant change in score.[89]

4.3.2 Bowel damage index

The real potential for acute and chronic inflammation to cause bowel destruction through fibrosis and penetrating disease led the development of scoring systems for bowel damage.[90] The Lémann Index was designed to measure damage severity in all segments of the digestive tract, based on the assessment of stricturing and penetrating lesions using MR or CT and endoscopy together with previous surgery [Supplementary Table 3]. After an initial study,[91] further studies demonstrated that up to 60% of patients had a reduction in score 1 year after starting anti-tumour necrosis factor [TNF] therapy.[92–94]

In conclusion, there are different available indexes for grading luminal disease using MR enterography. MaRIA[111–112] is the best-characterised among these indexes. For perianal disease, there is need for an improved validated index for measuring response which overcomes the current limitations.[95,96]

4.4 Quality of life scoring systems for IBD

Statement 4.4. ECCO-ESGAR Diagnostics GL [2018]

The Inflammatory Bowel Diseases Questionnaire [IBDQ] is considered the gold standard for use in clinical trials, but is lengthy and thus impractical in clinical practice [EL3]. At present, there is insufficient evidence to recommend a specific quality of life [QoL] score in clinical practice [EL5]

Due to the wider appreciation that the nature of IBD often has a negative impact on patients' lives, emphasis on health-related quality of life [HRQoL] and its assessment are integral to the holistic care of patients with IBD.[97,98] QoL is now a key measure in clinical trials in IBD.[99] This corresponds to the WHO statement that 'health is not merely an absence of disease' but rather 'complete physical, mental and social well-being',[200] which underpins the importance of improving HRQoL as a treatment objective.[201]

HRQoL in IBD may be an indirect indicator of disease activity[202,203] and an outcome measure when assessing the efficacy of treatment.

There is reasonable expectation that effective treatment should improve QoL.[204]

However, QoL is just one report from patients[1] in a continuum with general QoL measures at one end,[205] disease [IBD]-specific HRQoL measurements[206] in the centre, and instruments that measure specific variables such as continence,[207] sexual dysfunction,[208] food-related QoL,[209] fatigue,[210] and disability[211] at the other end [Supplementary Table 13, available as Supplementary data at *ECCO-JCC* online]. Some are specific for IBD and others can be used across all medical fields [Supplementary Table 14, available as Supplementary data at *ECCO-JCC* online].[99] Disease-specific measures may be more sensitive to variable disease activity,[212] whereas generic QoL instruments permit comparison of different patient populations.[1,213] These instruments are not only used in adults and children alike; the process has also been extended to parents,[214–216] families, and carers.[102]

The **Inflammatory Bowel Diseases Questionnaire** [IBDQ] is the foremost[106] and the most widely used tool. The IBDQ has up to 36 items and has been purported to represent the gold standard.[217] Short questionnaires may be more appropriate when time for completion is limited. In contrast, in the research setting, the need for more information may necessitate the use of longer questionnaires or even a combination of generic and disease-specific questionnaires.[99,112,113,118]

Two recent systematic[98,119] analysed IBD-specific tools. Another review has highlighted the fragmented approach to the use of QoL in this population.[113] Some of the limitations are summarised in the Supplementary table 14.

The **Short Health Scale** [SHS] deserves a mention as it consists of only four questions. Developed in Sweden, the SHS showed good reliability, validity, and responsiveness in both patients with UC and those with CD.[120,121] Some questions exist about its retest reliability.[122] English,[120] Danish, and Korean versions have been also developed.[121] Additionally, the scale has been studied in children with IBD.[123] However, the SHS showed similar properties in patients with irritable bowel syndrome, thus indicating that this scale is a more generic and not a disease-specific instrument.[124]

The **Short-Form 36** health survey [SF-36] is the generic instrument for IBD patients[125,126] and is used for both clinical and research purposes.[112] The SF-36 has eight dimensions, which are combined into two summary scores that reflect physical and mental components. Individual domain scores should be reported, to allow comparison across different nationalities.[113]

The **EQ-5D** is a shorter generic tool that has also been validated in IBD[127] but is less frequently used. The EQ-5D has five questions or domains that have the same set of answers and are combined with a standardised VAS.

The **CUCQ-8** is a validated IBD-specific and QoL-specific 32-item short questionnaire that has the potential to be an efficient tool for assessing the QoL of all IBD patients.[128]

Chapter 5 General principles and technical aspects of endoscopy including enteroscopy, capsule endoscopy, ultrasound, CT, MRI, and small bowel enteroclysis/small bowel follow-through [SBE/SBFT]

5.1 Principles of conventional endoscopy

5.1.1 Sedation

Colonoscopy is generally perceived as unpleasant by patients. As stated by the European quality improvement initiative for lower gastrointestinal endoscopy, patient experience should be routinely measured and its improvement is crucial for acceptance.[129] Colonoscopy is an essential tool for diagnosing and monitoring IBD; biopsy and culture sampling are often needed. Although research on the development of different non-invasive surrogates is under way, current therapeutic goals include endoscopically assessed mucosal healing [MH]. IBD patients undergo endoscopic procedures [mostly for surveillance] more often than the general population.[130] Hence, acceptance of the procedure is crucial for adequate management of the disease. Furthermore, endoscopy in IBD can be more demanding than in the general population; a prospective study on 558 colonoscopies in IBD patients showed a mean procedure time of 21 min. The current European quality initiative established a minimum standard of 6 min and a target standard mean of 10 min of withdrawal time.[131] A retrospective analysis of 5282 patients who underwent an outpatient colonoscopy associated the previous diagnosis of IBD with higher demand of sedation.[132,133] Therefore, endoscopic procedures in IBD patients should be performed under deep sedation instead of conscious sedation or no sedation. Propofol-based sedation is currently the best option for deep sedation in most cases, and should be administered by an endoscopist, anaesthesiologist, or trained nurse according to country-specific regulation.[133–136] Besides deep sedation, the use of CO_2 has been shown to improve patient comfort and satisfaction and should be implemented if possible.[137]

5.1.2 Bowel preparation

Bowel preparation quality is important for the efficacy of colonoscopy and correlates with diagnostic yield and caecal intubation rate. Bowel preparation quality should be routinely measured according to validated scales.[14,129,138] Generally, patients with IBD do not have less successful bowel preparation outcomes but may have decreased preparation tolerance, which affects adherence. Regardless of the kind or the volume of the bowel preparation used, split-dose administration has demonstrated better quality and acceptance of the preparation in many studies. These results have been validated in two meta-analyses. Kilgore *et al*. included five trials and found that split-dose polyethylene glycol [PEG] was associated with satisfactory bowel cleansing and patient tolerability (odds ratio [OR] 3.7).[139] Martel *et al*. obtained similar results in an analysis of 47 trials, including split doses of all available preparations [OR 2.5].[140] Hence, split-dose administration of a low-volume PEG-based purgative should be recommended, especially in patients with previous preparation intolerance, intestinal hypomotility, or stenosis.[138,141–143] Patients who have undergone many colonoscopies may have a personal preference for their bowel preparation, which should be taken into consideration.[138] IBD could be considered as a relative contraindication for the use of sodium phosphate-based agents, which may also cause mucosal abnormalities that mimic IBD.[138,143]

5.1.3 Technical requirements and training

High-definition technology is preferred over standard colonoscopy, especially when performing dysplasia surveillance.[14,144] Regardless of diagnostic or therapeutic intent, endoscopy in IBD is technically demanding and a thorough knowledge of the disease is also required. Moreover, some clinical scenarios [including severely active disease or endoscopic dilation] appear to be associated with higher risk of perforation.[14]

To optimise diagnostic yield and impact of clinical management, IBD endoscopists should be experienced in both endoscopic and clinical management of the disease. Therefore, endoscopy in IBD should be considered as part of the specific training in IBD.[145]

Colonoscopic surveillance of chronic colitis patients using methylene blue dye-spray targeted biopsies results in improved dysplasia yield compared with conventional random and targeted biopsy methods. Accordingly, this technique warrants incorporation into clinical practice in this setting and consideration as a standard of care for these patients.[146,147]

Statement 5.1.1. ECCO-ESGAR Diagnostics GL [2018]

Conventional endoscopy is essential for diagnosis and monitoring of IBD; patient experience and acceptance must be considered. Propofol-based deep sedation [EL5] and CO_2 insufflation [EL5] should be offered. IBD endoscopy should be performed preferably by an endoscopist who is experienced in IBD endoscopy and also in IBD clinical management [EL5]. Bowel preparation with a split-dose polyethylene glycol [PEG]-based purgative is recommended [EL1]

5.2 Capsule endoscopy

Wireless video-capsule endoscopy is a method of endoluminal mucosal examination of the bowel. This form of endoscopy is based on a pill-sized camera tool that is swallowed by the patient and travels through the patients' luminal digestive tract through its intrinsic motor activity. The capsule continuously captures images that are wirelessly transmitted to a data recorder worn by the patient. Images are downloaded, processed, and examined by a trained gastroenterologist on a workstation.

5.2.1 Equipment

All currently available small bowel video capsules are appropriate for IBD.[148] Advances in technology have enabled wireless capsule endoscopy systems to examine the colonic mucosa. Despite substantial agreement shown in different endoscopic disease activity indexes between capsule and conventional colonoscopy, there are insufficient data to recommend colon capsule studies in the evaluation of IBD.[148,149] Recently, a new capsule endoscopy system has been developed that evaluates both the intestinal and colonic mucosa; however, data regarding its usefulness in IBD remain scarce.[150]

5.2.2 Patient preparation and basic technique

Patients should fast for at least 12 h prior to capsule ingestion. The use of bowel preparation is recommended, as this has been shown to improve the visualisation and the diagnostic yield. Although there are not enough data to recommend any specific type of preparation, PEG in half dose [1 L], low volume [2 L], or high volume [4 L] has been shown to be beneficial.[151] As recommended for any other indication, following capsule ingestion with water, clear liquids may be taken after 2 h and food and medications may be taken after 4 h. Appropriate documentation of the procedure and its findings in IBD patients undergoing capsule endoscopy should include standardised items. Use of IBD-specific scales such as the Lewis Score and the capsule endoscopy Crohn's Disease Activity Index is encouraged.[49,151,152]

On the basis of a recent meta-analysis, the capsule retention rate in patients with suspected or known IBD is approximately between 4% and 8%. These rates decreased by half in studies that used either a patency capsule or a cross-sectional imaging technique [such as MR enterography or CT enterography] to assess patency before performing capsule endoscopy.[153]

5.2.3 Training

Capsule endoscopy should be performed by a gastroenterologist experienced in conducting, interpreting, and reporting capsule endoscopy procedures.[151] Moreover, capsule endoscopy in IBD patients should be evaluated by gastroenterologists with experience in conventional endoscopy in IBD patients.

Statement 5.1.2. ECCO-ESGAR Diagnostics GL [2018]

Capsule endoscopy is appropriate to evaluate small bowel Crohn's disease [CD]. The use of bowel preparation [EL1] and simeticone [EL2] is recommended for capsule endoscopy

5.3 Enteroscopy

5.3.1 Equipment

Enteroscopy enables live assessment, treatment, and tissue sampling of the small bowel. Conventional push enteroscopy is intended to access only the proximal small bowel, but the median insertion typically does not exceed 100 cm from the angle of Treitz.[154] In patients with IBD, it may be necessary to reach deeper beyond the limits of ileocolonoscopy and push enteroscopy. Therefore, in IBD patients undergoing direct endoscopic assessment of the small bowel, device-assisted enteroscopy should be performed. There are not enough data to recommend any modality of device-assisted deep enteroscopy, either single, double-balloon, or spiral enteroscopy, or balloon-guided endoscopy.[155]

5.3.2 Patient preparation and basic technique

Fasting for at least 12 h and avoidance of liquid consumption for 4 h is generally sufficient for patients undergoing oral device-assisted enteroscopy. However, standard colonoscopy preparation is required for retrograde examination.[156]

Device-assisted enteroscopy is clinically challenging and requires deep sedation or general anaesthesia. This procedure seems to be as safe in IBD patients as in other populations: the general rate of major complications is estimated at 0.7%. Accordingly, this procedure should only be performed if indicated and change of clinical management is intended or expected.[155,157] The use of CO_2 insufflation instead of room air is highly recommended in device-assisted enteroscopy procedures, as it may improve the intubation depth and reduce post-procedural discomfort.[158,159]

5.4. Small bowel follow-through and enteroclysis

5.4.1 Equipment

Small-bowel follow through [SBFT] and small-bowel enteroclysis [SBE] are performed using conventional X-ray equipment imaging. Digital fluoroscope technology is now widely available and allows real-time image projection and storage of image 'loops'. Digital technology facilitates better radiation dose control in the generally young IBD patient population. Equipment to compress, move, and separate the opacified small bowel should be available. SBFT and SBE have high accuracy for mucosal abnormalities [including ulcerations and strictures] and can possibly identify extramural complications, such as internal fistulas.

5.4.2 Patient preparation and basic technique

For both investigations, patients should have 'nil by mouth' for 6 h before the procedure. SBFT may be augmented by pneumocolon to produce double-contrast imaging of the distal ileum, which enhances the sensitivity for detecting subtle mucosal changes.[160] Pneumocolon

requires retrograde insufflation of gas [e.g. room air or CO_2] into the terminal ileum via a rectal tube, and requires bowel preparation to remove intraluminal material before the procedure.[161]

SBFT consists of oral administration of 400 mL to 600 mL barium sulphate suspension, typically 30% to 50% weight/volume over a specific period of time.[162] Ingested volumes should be individualised for each patient. This is followed by serial fluoroscopic interrogation of the small bowel and spot filming at intervals of 20 to 30 min, tracking passage of the contrast agent through the bowel. Targeted compression views of the small bowel are mandatory to ensure that the whole small bowel is visualised as far as possible. Magnified compression views also facilitate detailed evaluation of the small bowel mucosa.

SBE requires placement of a nasojejunal catheter under fluoroscopic guidance and insufflating the small bowel with barium and air or methylcellulose, to create a double-contrast distended view of the small bowel.[163,164] Automated pump infusion is preferred over hand injection. SBE in general provides better distension of the small bowel than SBFT and has been suggested to improve evaluation of the bowel mucosa. However, any diagnostic superiority over SBFT remains unproven. Furthermore, conscious sedation is sometimes necessary due to the discomfort the procedure can cause.

5.4.3 Technical parameters

During SBE, infusion rates of should be constantly adjusted to obtain uniform distention of the entire small intestine, without overwhelming peristaltic capacity. All accessible segments of the small bowel should be manually or mechanically compressed during the course of infusion. This includes using rotation and palpation and special manoeuvres used to isolate pelvic small bowel loops.[162] Large-format images should be obtained when the entire small bowel is adequately filled and distended. Similarly, segments of the small bowel should be manually or mechanically compressed to ensure adequate visualisation during SBFT.

Barium sulphate is non-toxic and is normally passed in stool. SBE is inherently more invasive, with tube placement under fluoroscopic guidance resulting in a higher radiation exposure than that from SBFT.[165] Although the radiation exposure for barium studies is lower than for CT, it is nevertheless a significant exposure for adults[166] and children,[167] particularly when repeated examinations are performed. Moreover, excessive fluoroscopy time and frequent abdominal radiographs can result in doses that are equivalent to CT.[167]

5.4.4 Training

SBFT and SBE are highly operator-dependent, and patient radiation doses are influenced by the radiologist's technique.[168,169] Consequently, dedicated gastrointestinal radiologists who are experienced in conducting and interpreting them should perform both procedures.

> **Statement 5.2.1. ECCO-ESGAR Diagnostics GL [2018]**
>
> Small-bowel follow through [SBFT] and small-bowel enteroclysis [SBE] have a diminishing role and are largely now replaced by cross-sectional techniques. However, they may have a role in specific clinical circumstances [EL5]

5.5 Cross-sectional imaging techniques

Reference should be made to the ESGAR/ESPR guidelines for the technical performance of cross-sectional small-bowel and colonic imaging.[170]

5.4 MRI and CT

5.5.1 Equipment

MR enterography and MR enteroclysis should be performed at ≥ 1.5T. No evidence supports the superiority of one platform over another.[171,172] Phased-array coils should be used routinely. For perianal fistula MRI, phased-array surface coils are preferred to endocoils, given their larger field view and greater patient acceptance.[173] Due to the propulsive motor action of the gut, CT requires rapid acquisition of high-resolution images of the bowel. Although there are no comparative studies comparing different CT platforms, CT enterography and CT enteroclysis in general should be performed on scanners with at least 16 slices [ideally 64 or greater].

5.5.2 Patient preparation and basic technique

Patient preparation regimens are similar to MR enterography and CT enterography. Due to insufficient distension of the bowel, there is evidence that studies performed without oral contrast preparation have inferior diagnostic accuracy when compared with those performed after administration of oral contrast.[174,175] Patients should fast from solids for 4–6 h before MR enterography or CT enterography. Liquids should also be restricted, although water is permissible. There are ranges of suitable oral agents available to distend the small bowel, usually with hyperosmolar properties.[176] These include mannitol, PEG, sorbitol, or combinations thereof.[177–182] There is currently no evidence that favours one preparation over another. Although use is not widespread, negative-contrast agents containing paramagnetic iron reduce luminal signal on both T1-weighted and T2-weighted images.[183] Oral contrast agents should be ingested 45 min before the examination.[184] Volumes over 1000 mL may give better distension,[179] although it is possible to acquire diagnostically acceptable images with ingested volumes of 450 mL.[185] Patients should be warned that they might experience cramping and diarrhoea after ingesting hyperosmolar oral contrast agents.

Enteroclysis is more invasive than enterography and is less well tolerated by patients,[186] but may provide superior distension of the proximal small bowel in particular.[187] MR enteroclysis and CT enteroclysis should be performed with similar distension agents as MR enterography and CT enterography, which should be infused via an 8F or 10F nasojejunal tube placed under fluoroscopic guidance. Automated pump infusion [at a rate of 80–120 mL/min] is preferred over hand injection, although both are acceptable. On-table monitoring of small bowel distension should be performed during both MR enteroclysis and CT enteroclysis, and infused volumes should be individualised for each patient.[170]

Diagnostic accuracy for colonic inflammation is improved with colonic filling, either by prolonged oral contrast administration[188,189] or via a rectal liquid enema.[190] However, additional colonic preparation is not required for routine MR enterography or CT enterography. Superior bowel distension may be achieved by placing the patient prone, but there is no evidence that this translates into superior diagnostic accuracy compared with the supine position.[191]

5.5.4 Technical parameters

CT images should be acquired following intravenous contrast agent administration in the enteric or portal venous phase only.[192] Iodinated contrast administration facilitates assessment of the bowel wall enhancement pattern and mesenteric vascularity. The use of multiplanar reformats is mandatory during CT evaluation, and these should be reconstructed at 3 mm or less.[193]

Radiation exposure is the major limiting factor for the use of CT in IBD.[194,195] Exposure to high radiation doses can occur [primarily

due to repeated CT] and particularly in those with young age of disease onset and complicated disease.[196] It is therefore imperative that dose exposure is minimised by optimising tube voltage and current.[197,198] The use of automated tube current modulation reduces dose while maintaining image quality.[199] Furthermore, there are good data demonstrating that iterative reconstruction techniques significantly reduce dose while producing diagnostically acceptable images[200–204]; these techniques should be applied routinely when available. It is good practice to maintain a log of radiation exposure for patients with IBD undergoing repeat medical imaging.[170] Due to the risks from repeated radiation exposure, given the chronic nature of the disease and need for repeated imaging, MRI is generally the preferred modality in IBD patients.

Although diagnostically acceptable MR enterography images can be acquired without use of spasmolytic agents,[205] administration of these agents improves bowel distension[199] and use is currently recommended.[170] Hyoscine butylbromide [butylscopolamine] is the spasmolytic agent of choice, although glucagon is an acceptable alternative.[206] High-quality MR enterography and MR enteroclysis require fast breath-hold sequences to minimise breathing and peristaltic artefacts. A typical protocol should include a combination of T2-weighted and steady-state free precession gradient echo [SSFP GE] sequences. T1-weighted images acquired in the enteric or portal venous phase following intravenous gadolinium contrast administration facilitate assessment of the bowel wall enhancement pattern and mesenteric vascularity, with some evidence that they increase diagnostic accuracy.[207,208] However, recent studies have reported long-term retention of gadolinium in the brain of exposed patients,[209–212] and protocols omitting gadolinium contrast may have similar diagnostic accuracy.[213,214] Administration of gadolinium should therefore be considered on a case-by-case basis. There are increasing data supporting the use of diffusion-weighted imaging[214–217] and cine motility sequences,[218–221] in both disease detection and activity assessment. Pending further research, these sequences are currently considered optional.[170]

Sequence selection in perianal fistula imaging should include high-resolution T2-weighted images with and without fat saturation angled to the plane of the anal canal. Short T1 inversion recovery [STIR] sequences are an alternative to fat-saturated T2-weighted sequences.[222,223] The use of gadolinium enhancement on T1-weighted imaging is useful for differentiating granulation tissue from fluid, for gauging fistula activity,[85] and may increase staging accuracy.[224]

5.5.5 Training

There is evidence of a learning curve in the interpretation of MR enterograpy. Initial data suggest that feedback on 100 cases is required to achieve diagnostic accuracy equivalent to that of experienced radiologists.[225] However, once trained, radiologists tend to maintain their interpretation skills long term.[226] Moderate-to-good interobserver agreement has been reported for MR enterography[77,226,227] and CT enterography,[228] with one study suggesting higher reader agreement for CT enterography over MR enterography.[229] There are also data that confirmed a learning curve in the interpretation of MRI perianal fistula imaging, with improvement in accuracy after dedicated training.[230]

Statement 5.3.1.1. ECCO-ESGAR Diagnostics GL [2018]

CT enterography and CT enteroclysis should be performed on CT scanners with at least 16 slices. MR enterography and MR enteroclysis can be performed at 1.5T or 3T [EL2]

Statement 5.3.1.2. ECCO-ESGAR Diagnostics GL [2018]

A suitable oral contrast agent should be administered 45 min before MRI and CT enterography or infused via nasojejunal tube before MR enteroclysis or CT enteroclysis [EL2]

Statement 5.3.1.3. ECCO-ESGAR Diagnostics GL [2018]

Dedicated colonic preparation is not part of routine protocols but can be achieved either by prolonged oral contrast or administration of a liquid rectal enema [EL2]

Statement 5.3.1.4. ECCO-ESGAR Diagnostics GL [2018]

Radiation exposure is a limitation of CT and should only be used if MRI or ultrasound is not available. Dose exposure must be minimised by optimising acquisition parameters, use of tube current modulation, and iterative reconstruction techniques when available [EL2]. Cumulative radiation exposure of IBD patients should be monitored [EL5]

Statement 5.3.1.5. ECCO-ESGAR Diagnostics GL [2018]

MR enterography and MR enteroclysis should be performed with fast breath-hold sequences to minimise breathing and peristaltic artefacts [EL2]. Consideration should be precede the routine use of intravenous gadolinium in all patients, weighing the risks and benefits [EL4]

Statement 5.3.1.6. ECCO-ESGAR Diagnostics GL [2018]

Radiologists interpreting cross-sectional imaging in IBD require appropriate training, with initial evidence suggesting that radiologists should review at least 100 cases [EL2]

5.6 Ultrasonography

5.6.1 Equipment

Modern ultrasound devices have sufficient quality and screen resolution to delineate the structure of the gastrointestinal wall. The resolution of an ultrasound transducer is dependent on the frequency, the speed of sound in tissue, and the number of cycles in the ultrasound pulse. Since the thickness of the bowel wall layer is usually < 3 mm,[231] the frequency of the transducer must be at least 5 MHz for wall layers to be well discriminated. No head-to-head studies have been published comparing the diagnostic performance of regular low-frequency, mid-frequency, or high-frequency probes for detection of the normal small bowel and pathological findings. Harmonic imaging should be activated when available, as this may improve delineation of the bowel wall.[232]

Doppler ultrasound can assess both blood flow in the visceral vessels that supply the gastrointestinal tract and the smaller vessels of the intestinal wall. Doppler ultrasound cannot detect capillary flow. Colour Doppler or power Doppler can both be used to evaluate bowel wall vascularity.[233] Flow parameters should be optimised to maximise the sensitivity for the detection of vessels with low-velocity flow in the bowel wall. The information obtained from colour

Doppler images is semi-quantitative. It is recommended to measure bowel wall vascularity according to the number of vessels detected per square centimetre.[234–236]

Increased vascularity of the diseased bowel wall is a marker of disease activity. To improve the sensitivity of Doppler ultrasound, intravenous ultrasound contrast agents have been introduced. For example, the second-generation echo-signal enhancer SonoVue is injected as a bolus in units of 1.2–4.5 mL into an antecubital vein, immediately followed by injection of 10 mL of normal saline solution [0.9% NaCl] flush. For each examination, a recording is initiated a few seconds before the intravenous administration of the agent, and continuous imaging is performed for 40 s.[237] There are several ways of interpreting contrast enhancement in the bowel wall. These include pattern of enhancement,[238,239] contrast quantification at peak intensity,[240] and dynamic contrast-enhanced ultrasound where intensity changes over time are analysed.[241]

5.6.2 Contrast-enhanced ultrasound

Contrast-enhanced ultrasound [CEUS] can be used to quantify vascularity[242] but can also be used to separate vascular from avascular tissue, which is particularly useful when trying to differentiate a phlegmon from an abscess.[243]

5.6.3 Small intestine contrast ultrasonography

In recent years, the use of oral contrast agents [such as PEG solution] has been introduced to distend the bowel for better characterisation of the bowel wall and increased disease detection. The use of an oral contrast agent does not alter the procedure greatly; the same equipment is used with the addition of 375–800 mL of oral contrast fluid. However, the procedure duration increases, ranging from 25 to 60 min.[244] The accuracy for assessing lesions in the proximal small bowel and for defining the extent of diseased ileal walls can be significantly improved using small intestine contrast ultrasonography.[245]

5.6.4 Ultrasound elastography

Gut fibrosis develops in up to 50% of Crohn's disease [CD] patients and is a major challenge.[246] Clinically suspected fibrostenotic disease is currently mainly investigated by contrast-enhanced CT,[247] or MR[247,248] enterography, or MR enteroclysis, or native ultrasound and CEUS [see above]. Novel MRI sequences [such as magnetisation transfer] also show promise,[249,250] although detection and characterisation of fibrotic disease by imaging remains suboptimal. Whereas MR elastography is being studied for staging several diseases [such as liver fibrosis], it has not been studied in fibrotic bowel disease. Ultrasound elasticity imaging based on strain under deformation and elastic modulus[251] is an evolving technique. Recent studies suggest that ultrasound elastography can differentiate between fibrotic and inflammatory stenosis independent of wall thickness and blood flow in CD.[252,253]

5.6.5 Patient preparation and basic technique

Abdominal ultrasound is most successful in non-obese patients, due to its basic technical principles as discussed above. The small bowel and colon should be carefully and systematically interrogated, using gentle graded compression. No patient preparation is needed to perform bowel ultrasound. However, to reduce the amount of food and bowel gas, a fasting period of at least 4–6 hours is recommended, although there are no rigorous studies confirming this approach.[254] Administration of a spasmolytic agent is not required and indeed may interfere with the real-time assessment of bowel peristalsis by the operator. Colonic preparation or liquid enemas are also not required. As noted above, use of colour Doppler should be routine. Although both CEUS and elastography are highly promising evolving techniques, they are not yet routinely used outside specialist centres.

5.6.6 Training

The interobserver agreement between operators with various degrees of experience in bowel ultrasound and its learning curve needs to be investigated further. Dedicated training in bowel ultrasound is necessary and should preferably be performed following training in general abdominal ultrasound.[254,255] Preliminary data suggest that signs of CD in bowel ultrasound can be standardized and have shown fair-to-good reproducibility. In particular, bowel wall thickness shows excellent reproducibility.[256]

Statement 5.3.2.1. ECCO-ESGAR Diagnostics GL [2018]

For a complete examination of the bowel with ultrasound, low-resolution and high-resolution probes should be used [EL5]

Statement 5.3.2.2. ECCO-ESGAR Diagnostics GL [2018]

The use of intraluminal orally administered contrast agents improves the overall accuracy in diagnosing small-bowel CD [EL2]

Statement 5.3.2.3. ECCO-ESGAR Diagnostics GL [2018]

Contrast-enhanced ultrasound [CEUS] of the bowel can be used to differentiate vascular from avascular intestinal or peri-intestinal lesions, including abscesses [EL3]

Statement 5.3.2.4. ECCO-ESGAR Diagnostics GL [2018]

A standard ultrasound examination of the intestine does not require specific patient preparation, although fasting is recommended before the examination [EL4]

Statement 5.3.2.5. ECCO-ESGAR Diagnostics GL [2018]

Dedicated training in bowel ultrasound is necessary and should be performed following training in general abdominal ultrasound [EL5]

Conflict of Interest

ECCO and ESGAR have diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of *JCC*, but also is 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 authors. The ECCO-ESGAR Consensus Guidelines are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO-ESGAR Consensus Guidelines.

The European Crohn´s and Colitis Organisation, the European Society of Gastrointestinal and Abdominal Radiology, and/or any of its staff members, and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO-ESGAR Consensus Guidelines.

Acknowledgements

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WG2: Imaging techniques in regard to clinical situations: Monitoring therapeutic success [inclusive calpro], Monitoring clinically asymptomatic patients, Monitoring clinically symptomatic patients, Imaging after surgery including ileoanal pouch
Leader – Torsten Kucharzik
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Member – Uri Kopylov
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WG3: Detecting [suspected] complications [stricture, fistula, abscess, anastomotic insufficiency, toxic megacolon, perforation]: Endoscopic and non-medical, non-surgical interventions [stricture, abscess, bleeding], Cancer surveillance, Imaging during pregnancy
Leader – Gionata Fiorino
Member – Florian Rieder
Member – Paulo Kotze
Member – Abraham Eliakim
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WG4: Endoscopic and clinical scoring systems in IBD: CDAI, CDEIS, May -Score, Life quality indexes, Cross-sectional imaging
Leader – Vito Annese
Member – Jimmy Limdi
Member – Konstantinos Katsanos
Y-ECCO – Eduards Krustiņš
ESGAR – Jordi Rimola
WG5: General principles and technical aspects of: endoscopy including enteroscopy, capsule endoscopy, ultrasound, CT, MRI, SBE/SBFT
Important note: The idea of your role is to help colleagues to set up standards at their institutions, e.g. what is mandatory for MR enteroclysis, requirements for endoscopy, ultrasonography, etc.
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Supplementary Data

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

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