



ECCO Guideline/Consensus Paper

## 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.<sup>1,2</sup> Although somewhat limited by subjective definitions, their strength lies in the potential to monitor patient progress over time.<sup>1</sup>

The **Simple Colitis Clinical Activity Index [SCCAI]**<sup>2,3</sup> [Table 1] and the **Paediatric Ulcerative Colitis Activity Index [PUCAI]**<sup>4</sup> [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

**Table 1.** Clinical scoring system for the Simple Clinical Colitis Activity Index.<sup>3</sup>

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

**Table 2.** Mayo score for ulcerative colitis.<sup>6</sup>

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

and 19 points and include nocturnal bowel movements and faecal urgency, which affect patient quality of life [QoL].<sup>3</sup> An SCCAI score <2 indicates clinical remission, and a decrease of >1.5 points from baseline correlates with patient-defined significant improvement.<sup>5</sup>

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].<sup>6,7</sup> 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.<sup>8</sup> 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.<sup>6–8</sup> A **Partial Mayo Score [PMS]** <1 indicates remission.<sup>1</sup> The PMS has been shown to correlate well with the full scoring system.<sup>9,10</sup>

The **Truelove and Witts Severity Index** was described in 1955.<sup>11</sup> Its elements reflect levels of systemic toxicity and provide objective criteria for assessment of acute severe colitis, need for hospitalisation, and corticosteroid therapy<sup>2</sup> [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.<sup>12</sup>

The **Pouchitis Disease Activity Index** was developed to provide a standard definition of pouchitis, including histological subscores.<sup>13</sup> 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].

#### 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.<sup>12,14,15</sup> These systems are also increasingly used in clinical practice to guide treatment decisions with the aim of achieving mucosal healing [MH] [Table 4].<sup>16–19</sup>

The first attempt to classify endoscopic UC severity was performed by Truelove and Witts.<sup>11</sup> 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.<sup>20</sup> 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**

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

The **Powell-Tuck Index** [also known as St Mark's Index]<sup>23</sup> 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]<sup>7</sup> 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.<sup>11</sup>

	Mild	Moderate <sup>a</sup> between mild and severe <sup>b</sup>	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**<sup>24</sup> 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]<sup>6</sup> 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.<sup>8</sup> 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.<sup>18</sup> Clinical remission is defined as an MCS ≤2 and no individual subscore >1. MH has been defined as a subscore of 0 to 1.<sup>18</sup> Interobserver agreement can vary markedly.<sup>18</sup> 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,<sup>25</sup> 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 Annesse V *et al.*<sup>14</sup>

Score	Endoscopic variables	Strengths	Weaknesses	Proposed remission score
Truelove and Witts <sup>11</sup>	No endoscopic descriptor definitions	----	----	----
Sigmoidoscopic assessment Baron Score <sup>[20]</sup>	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] <sup>23</sup>	Bleeding [non-haemorrhagic vs haemorrhagic mucosa]	-----	Only evaluates bleeding Subjective interpretation	Not defined
Sutherland Index <sup>7</sup>	Friability, exudation, spontaneous haemorrhage	-----	Does not evaluate ulcers Not accurate in discriminating between mild to moderate friability	0
Mayo Endoscopic Subscore <sup>6</sup>	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 <sup>24</sup>	Vascular pattern, granularity, mucosal damage [mucus, fibrin, exudate, erosions, ulcers, bleeding]	Easy to calculate	Subjective interpretation of mucosal damage and bleeding	0–4
Modified Baron Score <sup>21</sup>	Vascular pattern, granularity, hyperaemia, friability, ulceration, bleeding	Easy to calculate Used in clinical trials	No discrimination between superficial and deep ulceration	0
UCEIS <sup>26</sup>	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 <sup>33</sup>	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 [ $\kappa$  0.5].<sup>26</sup> 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.<sup>27,28</sup> The remission target is a score  $\leq 1$ . The UCEIS shows strong correlation with patient-reported outcomes.<sup>29–31</sup> Both UCEIS and MCS have demonstrated a high degree of correlation for UC [Supplementary Table 4, available as Supplementary data at ECCO-JCC online].<sup>32</sup>

The Ulcerative Colitis Colonoscopic Index of Severity [UCCIS] has recently been prospectively validated.<sup>33</sup> 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.<sup>34</sup> 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].<sup>35</sup> Measuring clinical activity is important but no longer sufficient, and both CDAI and HBI are limited by subjective interpretation [Table 5].<sup>36,37</sup>

The CDAI<sup>36</sup> 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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>40</sup> Patients with CD who have an HBI score  $\leq 3$  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 L mann 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 L mann score is expected to represent a patient's disease course and to assess the effect of various medical therapies.<sup>41</sup>

Irvine developed the PDAI.<sup>42</sup> 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.*<sup>43</sup> 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],<sup>44</sup> the Simple Endoscopic Score for Crohn's Disease [SES-CD],<sup>45</sup> and the Rutgeerts endoscopic grading scale for postoperative recurrence [Supplementary Tables 6 and 6a, available as Supplementary data at ECCO-JCC online].<sup>14,46</sup>

The CDEIS scores CD activity [from 0 to 44] in five bowel segments [terminal ileum, right colon, left colon and sigmoid, rectum] and considers specific mucosal lesions [such as ulcers and stenosis] and extent of disease.<sup>44,47</sup> 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 <sup>3</sup>	CDAI	0–600 [ $< 150$ ]	Calculation based on a 7-day diary; difficulty in assessment of perianal disease activity
Harvey - Bradshaw Index <sup>37</sup>	HBI	0–50 [ $\leq 4$ ]	Simple and more practical
Perianal Crohn's Disease Activity Index <sup>42</sup>	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.<sup>45</sup> 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.<sup>46</sup> 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].<sup>48</sup> 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.<sup>49</sup> 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.<sup>47</sup>

## 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.<sup>2,50,51</sup> The European Society of Pathology [ESP] and the European Crohn's and Colitis Organisation [ECCO] published a consensus document.<sup>52,53</sup> 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.<sup>54,55</sup>

#### 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.<sup>52,53</sup> 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.<sup>56</sup> Ultimately basal plasmacytosis decreases, resulting in normal cellularity, and remission may result in a complete normalisation of the mucosa in approximately 24% of cases.<sup>57,58</sup> 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.<sup>59</sup> 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<sup>60–62</sup> 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.<sup>63–65</sup> 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.*<sup>59</sup> 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<sup>66</sup> and the Geboes<sup>67</sup> 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,<sup>55</sup> 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.<sup>67</sup> Mosli *et al.* recently developed an alternative instrument using some component items of the Geboes Index [Supplementary Table 9].<sup>68</sup>

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.<sup>36</sup> 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.*<sup>68</sup>] are fully validated; the Geboes Index is only partially [not formally] validated but is widely used.<sup>68</sup>

### 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.<sup>69</sup> 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].<sup>70</sup>

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 [ $r = 0.83$ ].<sup>71,72</sup> A MaRIA subscore of  $\geq 7$  is indicative of bowel segments with active CD, and a subscore of  $\geq 11$  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.<sup>73</sup> The MaRIA score closely correlated with the SES-CD in the small bowel [ $r = 0.808$ ;  $p < 0.001$ ]. A MaRIA score of  $\geq 11$  had high sensitivity, specificity, and diagnostic accuracy for ulcerative lesions [sensitivity, 78.3%; specificity, 98.0%]. Similarly, a MaRIA score of  $\geq 7$  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.<sup>71</sup> MaRIA showed high accuracy for detecting ulcer healing [accuracy 0.9] and MH [accuracy 0.83] in CD patients following medical therapeutic intervention.<sup>74,75</sup>

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].<sup>76</sup>

Comparative studies using ileocolonoscopy as the reference standard have validated both indexes.<sup>77,78</sup> 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.<sup>77</sup>

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**.<sup>79</sup> To derive and validate the DWI-MaRIA score, the same MR enterography [MaRIA] was considered as the reference standard.<sup>80</sup> 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.<sup>81</sup>

The **Sailer Index** was developed specifically for assessing postoperative recurrence at the anastomotic site using MR enteroclysis.<sup>82,83</sup>

The most frequently used MRI index for perianal disease is the **Van Assche Index**.<sup>84</sup> 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.<sup>84–86</sup> This index has only been partially validated.<sup>87,88</sup> 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.<sup>89</sup>

#### 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.<sup>90</sup> 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,<sup>91</sup> further studies demonstrated that up to 60% of patients had a reduction in score 1 year after starting anti-tumour necrosis factor [TNF] therapy.<sup>92–94</sup>

In conclusion, there are different available indexes for grading luminal disease using MR enterography. MaRIA<sup>111–112</sup> 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.<sup>95,96</sup>

### 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.<sup>97,98</sup> QoL is now a key measure in clinical trials in IBD.<sup>99</sup> This corresponds to the WHO statement that 'health is not merely an absence of disease' but rather 'complete physical, mental and social well-being',<sup>200</sup> which underpins the importance of improving HRQoL as a treatment objective.<sup>201</sup>

HRQoL in IBD may be an indirect indicator of disease activity<sup>202,203</sup> and an outcome measure when assessing the efficacy of treatment.

There is reasonable expectation that effective treatment should improve QoL.<sup>204</sup>

However, QoL is just one report from patients<sup>1</sup> in a continuum with general QoL measures at one end,<sup>205</sup> disease [IBD]-specific HRQoL measurements<sup>206</sup> in the centre, and instruments that measure specific variables such as continence,<sup>207</sup> sexual dysfunction,<sup>208</sup> food-related QoL,<sup>209</sup> fatigue,<sup>210</sup> and disability<sup>211</sup> 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].<sup>99</sup> Disease-specific measures may be more sensitive to variable disease activity,<sup>212</sup> whereas generic QoL instruments permit comparison of different patient populations.<sup>1,213</sup> These instruments are not only used in adults and children alike; the process has also been extended to parents,<sup>214–216</sup> families, and carers.<sup>102</sup>

The **Inflammatory Bowel Diseases Questionnaire** [IBDQ] is the foremost<sup>106</sup> and the most widely used tool. The IBDQ has up to 36 items and has been purported to represent the gold standard.<sup>217</sup> 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.<sup>99,112,113,118</sup>

Two recent systematic<sup>98,119</sup> analysed IBD-specific tools. Another review has highlighted the fragmented approach to the use of QoL in this population.<sup>113</sup> 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.<sup>120,121</sup> Some questions exist about its retest reliability.<sup>122</sup> English,<sup>120</sup> Danish, and Korean versions have been also developed.<sup>121</sup> Additionally, the scale has been studied in children with IBD.<sup>123</sup> 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.<sup>124</sup>

The **Short-Form 36** health survey [SF-36] is the generic instrument for IBD patients<sup>125,126</sup> and is used for both clinical and research purposes.<sup>112</sup> 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.<sup>113</sup>

The **EQ-5D** is a shorter generic tool that has also been validated in IBD<sup>127</sup> 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.<sup>128</sup>

## 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.<sup>129</sup> 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.<sup>130</sup> 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.<sup>131</sup> A retrospective analysis of 5282 patients who underwent an outpatient colonoscopy associated the previous diagnosis of IBD with higher demand of sedation.<sup>132,133</sup> 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.<sup>133–136</sup> Besides deep sedation, the use of CO<sub>2</sub> has been shown to improve patient comfort and satisfaction and should be implemented if possible.<sup>137</sup>

#### 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.<sup>14,129,138</sup> 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).<sup>139</sup> Martel *et al.* obtained similar results in an analysis of 47 trials, including split doses of all available preparations [OR 2.5].<sup>140</sup> 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.<sup>138,141–143</sup> Patients who have undergone many colonoscopies may have a personal preference for their bowel preparation, which should be taken into consideration.<sup>138</sup> 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.<sup>138,143</sup>

#### 5.1.3 Technical requirements and training

High-definition technology is preferred over standard colonoscopy, especially when performing dysplasia surveillance.<sup>14,144</sup> 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.<sup>14</sup>

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.<sup>145</sup>

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.<sup>146,147</sup>

#### 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<sub>2</sub> 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.<sup>148</sup> 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.<sup>148,149</sup> 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.<sup>150</sup>

### 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.<sup>151</sup> 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.<sup>49,151,152</sup>

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.<sup>153</sup>

### 5.2.3 Training

Capsule endoscopy should be performed by a gastroenterologist experienced in conducting, interpreting, and reporting capsule endoscopy procedures.<sup>151</sup> 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.<sup>154</sup> 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.<sup>155</sup>

### 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.<sup>156</sup>

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.<sup>155,157</sup> The use of CO<sub>2</sub> 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.<sup>158,159</sup>

## 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.<sup>160</sup> Pneumocolon



requires retrograde insufflation of gas [e.g. room air or CO<sub>2</sub>] into the terminal ileum via a rectal tube, and requires bowel preparation to remove intraluminal material before the procedure.<sup>161</sup>

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.<sup>162</sup> 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.<sup>163,164</sup> 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 should be constantly adjusted to obtain uniform distension 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.<sup>162</sup> 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.<sup>165</sup> Although the radiation exposure for barium studies is lower than for CT, it is nevertheless a significant exposure for adults<sup>166</sup> and children,<sup>167</sup> particularly when repeated examinations are performed. Moreover, excessive fluoroscopy time and frequent abdominal radiographs can result in doses that are equivalent to CT.<sup>167</sup>

#### 5.4.4 Training

SBFT and SBE are highly operator-dependent, and patient radiation doses are influenced by the radiologist's technique.<sup>168,169</sup> 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.<sup>170</sup>

### 5.4 MRI and CT

#### 5.5.1 Equipment

MR enterography and MR enteroclysis should be performed at  $\geq 1.5T$ . No evidence supports the superiority of one platform over another.<sup>171,172</sup> Phased-array coils should be used routinely. For perianal fistula MRI, phased-array surface coils are preferred to endo-coils, given their larger field view and greater patient acceptance.<sup>173</sup> 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.<sup>174,175</sup> 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.<sup>176</sup> These include mannitol, PEG, sorbitol, or combinations thereof.<sup>177–182</sup> 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.<sup>183</sup> Oral contrast agents should be ingested 45 min before the examination.<sup>184</sup> Volumes over 1000 mL may give better distension,<sup>179</sup> although it is possible to acquire diagnostically acceptable images with ingested volumes of 450 mL.<sup>185</sup> 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,<sup>186</sup> but may provide superior distension of the proximal small bowel in particular.<sup>187</sup> 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.<sup>170</sup>

Diagnostic accuracy for colonic inflammation is improved with colonic filling, either by prolonged oral contrast administration<sup>188,189</sup> or via a rectal liquid enema.<sup>190</sup> 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.<sup>191</sup>

#### 5.5.4 Technical parameters

CT images should be acquired following intravenous contrast agent administration in the enteric or portal venous phase only.<sup>192</sup> 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.<sup>193</sup>

Radiation exposure is the major limiting factor for the use of CT in IBD.<sup>194,195</sup> 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.<sup>196</sup> It is therefore imperative that dose exposure is minimised by optimising tube voltage and current.<sup>197,198</sup> The use of automated tube current modulation reduces dose while maintaining image quality.<sup>199</sup> Furthermore, there are good data demonstrating that iterative reconstruction techniques significantly reduce dose while producing diagnostically acceptable images<sup>200–204</sup>; 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.<sup>170</sup> 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,<sup>205</sup> administration of these agents improves bowel distension<sup>199</sup> and use is currently recommended.<sup>170</sup> Hyoscine butylbromide [butylscopolamine] is the spasmolytic agent of choice, although glucagon is an acceptable alternative.<sup>206</sup> 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.<sup>207,208</sup> However, recent studies have reported long-term retention of gadolinium in the brain of exposed patients,<sup>209–212</sup> and protocols omitting gadolinium contrast may have similar diagnostic accuracy.<sup>213,214</sup> Administration of gadolinium should therefore be considered on a case-by-case basis. There are increasing data supporting the use of diffusion-weighted imaging<sup>214–217</sup> and cine motility sequences,<sup>218–221</sup> in both disease detection and activity assessment. Pending further research, these sequences are currently considered optional.<sup>170</sup>

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.<sup>222,223</sup> The use of gadolinium enhancement on T1-weighted imaging is useful for differentiating granulation tissue from fluid, for gauging fistula activity,<sup>85</sup> and may increase staging accuracy.<sup>224</sup>

### 5.5.5 Training

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

#### 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 preceded 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,<sup>231</sup> 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.<sup>232</sup>

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.<sup>233</sup> 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.<sup>234–236</sup>

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.<sup>237</sup> There are several ways of interpreting contrast enhancement in the bowel wall. These include pattern of enhancement,<sup>238,239</sup> contrast quantification at peak intensity,<sup>240</sup> and dynamic contrast-enhanced ultrasound where intensity changes over time are analysed.<sup>241</sup>

### 5.6.2 Contrast-enhanced ultrasound

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

### 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.<sup>244</sup> 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.<sup>245</sup>

### 5.6.4 Ultrasound elastography

Gut fibrosis develops in up to 50% of Crohn's disease [CD] patients and is a major challenge.<sup>246</sup> Clinically suspected fibrostenotic disease is currently mainly investigated by contrast-enhanced CT,<sup>247</sup> or MR<sup>247,248</sup> enterography, or MR enteroclysis, or native ultrasound and CEUS [see above]. Novel MRI sequences [such as magnetisation transfer] also show promise,<sup>249,250</sup> 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<sup>251</sup> 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.<sup>252,253</sup>

### 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.<sup>254</sup> 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.<sup>254,255</sup> 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.<sup>256</sup>

#### 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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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

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WG4: Endoscopic and clinical scoring systems in IBD: CDAI, CDEIS, May -Score, Life quality indexes, Cross-sectional imaging

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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.

## References

1. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al.* Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE]: determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;110:1324–38.
2. Dignass A, Eliakim R, Magro F, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis. Part 1: definitions and diagnosis. *J Crohns Colitis* 2012;6:965–90.
3. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998;43:29–32.
4. Turner D, Otley AR, Mack D, *et al.* Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
5. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005;54:782–8.
6. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625–9.
7. Sutherland LR, Martin F, Greer S, *et al.* 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987;92:1894–8.
8. D'Haens G, Sandborn WJ, Feagan BG, *et al.* A review of activity indexes and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;132:763–86.
9. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008;14:1660–6.
10. Turner D, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A systematic prospective comparison of noninvasive disease activity indexes in ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:1081–8.
11. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955;2:1041–8.

12. Lichtiger S, Present DH, Kornbluth A, *et al.* Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841–5.
13. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc* 1994;69:409–15.
14. Annese V, Daperno M, Rutter MD, *et al.*; European Crohn's and Colitis Organisation. European evidence-based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013;7:982–1018.
15. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012;61:1619–35.
16. Frøslie KF, Jahnsen J, Moum BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007;133:412–22.
17. Ardizzone S, Maconi G, Russo A, Imbisi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006;55:47–53.
18. Colombel JF, Rutgeerts P, Reinisch W, *et al.* Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011;141:1194–201.
19. Rutter M, Saunders B, Wilkinson K, *et al.* Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126:451–9.
20. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964;1:89–92.
21. Feagan BG, Greenberg GR, Wild G, *et al.* Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. *N Engl J Med* 2005;352:2499–507.
22. Feagan BG, Sandborn WJ, D'Haens G, *et al.* The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. *Gastroenterology* 2013;145:149–57.e2.
23. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol* 1978;13:833–7.
24. Rachmilewitz D. Coated mesalazine [5-aminosalicylic acid] versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989;298:82–6.
25. Lobatón T, Bessisow T, De Hertogh G, *et al.* The Modified Mayo Endoscopic Score [MMES]: a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. *J Crohns Colitis* 2015;9:846–52.
26. Travis SP, Schnell D, Krzeski P, *et al.* Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013;145:987–95.
27. Ikeya K, Hanai H, Sugimoto K, *et al.* The ulcerative colitis endoscopic index of severity more accurately reflects clinical outcomes and long-term prognosis than the Mayo Endoscopic Score. *J Crohns Colitis* 2016;10:286–95.
28. Saigusa K, Matsuoka K, Sugimoto S, *et al.* Ulcerative colitis endoscopic index of severity is associated with long-term prognosis in ulcerative colitis patients treated with infliximab. *Dig Endosc* 2016;28:665–70.
29. Corte C, Fernandopulle N, Catuneanu AM, *et al.* Association between the ulcerative colitis endoscopic index of severity [UCEIS] and outcomes in acute severe ulcerative colitis. *J Crohns Colitis* 2015;9:376–81.
30. Arai M, Naganuma M, Sugimoto S, *et al.* The Ulcerative Colitis Endoscopic Index Of Severity is useful to predict medium- to long-term prognosis in ulcerative colitis patients with clinical remission. *J Crohns Colitis* 2016;10:1303–9.
31. Travis SP, Schnell D, Feagan BG, *et al.* The impact of clinical information on the assessment of endoscopic activity: characteristics of the Ulcerative Colitis Endoscopic Index of Severity [UCEIS]. *J Crohns Colitis* 2015;9:607–16.
32. Colombel JF, Ordás I, Ullman T, *et al.* Agreement between rectosigmoidoscopy and colonoscopy analyses of disease activity and healing in patients with ulcerative colitis. *Gastroenterology* 2016;150:389–95.e3.
33. Samuel S, Bruining DH, Loftus EV Jr, *et al.* Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol* 2013;11:49–54.e1.
34. D'Inca R, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol* 2014;7:151–61.
35. Gomollón F, Dignass A, Annese V, *et al.*; ECCO. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016. Part 1: diagnosis and medical management. *J Crohns Colitis* 2017;11:3–25.
36. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National cooperative Crohn's disease study. *Gastroenterology* 1976;70:439–44.
37. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;1:514.
38. Papay P, Ignjatovic A, Karmiris K, *et al.* Optimising monitoring in the management of Crohn's disease: a physician's perspective. *J Crohns Colitis* 2013;7:653–69.
39. Sostegni R, Daperno M, Scaglione N, Lavagna A, Rocca R, Pera A. Review article: Crohn's disease: monitoring disease activity. *Aliment Pharmacol Ther* 2003;17[Suppl 2]:11–7.
40. Solem CA, Loftus EV Jr, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:707–12.
41. Pariente B, Cosnes J, Danese S, *et al.* Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis* 2011;17:1415–22.
42. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. *J Clin Gastroenterol* 1995;20:27–32.
43. Pikarsky AJ, Gervaz P, Wexner SD. Perianal Crohn disease: a new scoring system to evaluate and predict outcome of surgical intervention. *Arch Surg* 2002;137:774–7; discussion 778.
44. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif [GETAID]. *Gut* 1989;30:983–9.
45. Daperno M, D'Haens G, Van Assche G, *et al.* Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;60:505–12.
46. Rutgeerts P, Geboes K, Vantrappen G, Beys J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;99:956–63.
47. De Cruz P, Kamm MA, Prideaux L, Allen PB, Moore G. Mucosal healing in Crohn's disease: a systematic review. *Inflamm Bowel Dis* 2013;19:429–44.
48. Niv Y, Ilani S, Levi Z, *et al.* Validation of the Capsule Endoscopy Crohn's Disease Activity Index [CECDAI or Niv score]: a multicenter prospective study. *Endoscopy* 2012;44:21–6.
49. Galnek IM, Defranich R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008;27:146–54.
50. Stange EF, Travis SP, Vermeire S, *et al.*; European Crohn's and Colitis Organisation [ECCO]. European evidence-based consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. *J Crohns Colitis* 2008;2:1–23.
51. Van Assche G, Dignass A, Panes J, *et al.*; European Crohn's and Colitis Organisation [ECCO]. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010;4:7–27.
52. Langner C, Magro F, Driessen A, *et al.*; European Society of Pathology; European Crohn's and Colitis Foundation. The histopathological approach to inflammatory bowel disease: a practice guide. *Virchows Arch* 2014;464:511–27.
53. Magro F, Langner C, Driessen A, *et al.*; European Society of Pathology [ESP]; European Crohn's and Colitis Organisation [ECCO]. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013;7:827–51.
54. Bryant RV, Burger DC, Delo J, *et al.* Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. *Gut* 2016;65:408–14.

55. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut* 2017;66:43–9.
56. Price AB, Morson BC. Inflammatory bowel disease: the surgical pathology of Crohn's disease and ulcerative colitis. *Hum Pathol* 1975;6:7–29.
57. Moum B, Ekblom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol* 1999;94:1564–9.
58. Levine TS, Tzardi M, Mitchell S, Sowter C, Price AB. Diagnostic difficulty arising from rectal recovery in ulcerative colitis. *J Clin Pathol* 1996;49:319–23.
59. Bryant RV, Winer S, Travis SP, Riddell RH. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. *J Crohns Colitis* 2014;8:1582–97.
60. Hefti MM, Chessin DB, Harpaz NH, Steinhagen RM, Ullman TA. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. *Dis Colon Rectum* 2009;52:193–7.
61. Rubin D, Huo D, Hetzel J, Bunnag A, Sedrak M, Hart J. Increased degree of histological inflammation predicts colectomy and hospitalization in patients with ulcerative colitis. *Gastroenterology* 2012;132(S1):A19.
62. Lichtenstein GR, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2010;16:338–46.
63. Bryant RV, Winer S, Travis SP, Riddell RH. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. *J Crohns Colitis* 2014;8:1582–97.
64. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? *Clin Gastroenterol Hepatol* 2014;12:929–34.e2.
65. Mosli MH, Feagan BG, Sandborn WJ, et al. Histologic evaluation of ulcerative colitis: a systematic review of disease activity indexes. *Inflamm Bowel Dis* 2014;20:564–75.
66. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991;32:174–8.
67. Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000;47:404–9.
68. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. *Gut* 2017;66:50–8.
69. Panés J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther* 2011;34:125–45.
70. Rimola J, Ordás I, Rodríguez S, Ricart E, Panés J. Imaging indexes of activity and severity for Crohn's disease: current status and future trends. *Abdom Imaging* 2012;37:958–66.
71. Coimbra AJ, Rimola J, O'Byrne S, et al. Magnetic resonance enterography is feasible and reliable in multicenter clinical trials in patients with Crohn's disease, and may help select subjects with active inflammation. *Aliment Pharmacol Ther* 2016;43:61–72.
72. Ordás I, Rimola J, Rodríguez S, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. *Gastroenterology* 2014;146:374–82.e1.
73. Takenaka K, Ohtsuka K, Kitazume Y, et al. Correlation of the endoscopic and magnetic resonance scoring systems in the deep small intestine in Crohn's disease. *Inflamm Bowel Dis* 2015;21:1832–8.
74. Ordás I, Rimola J, Rodríguez S, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. *Gastroenterology* 2014;146:374–82.e1.
75. Stoppino LP, Della Valle N, Rizzi S, et al. Magnetic resonance enterography changes after antibody to tumor necrosis factor [anti-TNF] alpha therapy in Crohn's disease: correlation with SES-CD and clinical-biological markers. *BMC Med Imaging* 2016;16:37.
76. Steward MJ, Punwani S, Proctor I, et al. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *Eur J Radiol* 2012;81:2080–8.
77. Tielbeek JA, Makanyanga JC, Bipat S, et al. Grading Crohn disease activity with MRI: interobserver variability of MRI features, MRI scoring of severity, and correlation with Crohn disease endoscopic index of severity. *AJR Am J Roentgenol* 2013;201:1220–8.
78. Rimola J, Alvarez-Cofiño A, Pérez-Jeldres T, et al. Comparison of three magnetic resonance enterography indexes for grading activity in Crohn's disease. *J Gastroenterol* 2017;52:585–93.
79. Buisson A, Joubert A, Montoriol PF, et al. Diffusion-weighted magnetic resonance imaging for detecting and assessing ileal inflammation in Crohn's disease. *Aliment Pharmacol Ther* 2013;37:537–45.
80. Hordonneau C, Buisson A, Scanzì J, et al. Diffusion-weighted magnetic resonance imaging in ileocolonic Crohn's disease: validation of quantitative index of activity. *Am J Gastroenterol* 2014;109:89–98.
81. Rimola J, Rodríguez S, García-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. *Gut* 2009;58:1113–20.
82. Sailer J, Peloschek P, Reinisch W, Vogelsang H, Turetschek K, Schima W. Anastomotic recurrence of Crohn's disease after ileocolic resection: comparison of MR enteroclysis with endoscopy. *Eur Radiol* 2008;18:2512–21.
83. Dohan A, Taylor S, Hoeffel C, et al. Diffusion-weighted MRI in Crohn's disease: Current status and recommendations. *J Magn Reson Imaging* 2016;44:1381–96.
84. Van Assche G, Vanbeckevoort D, Bielen D, et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *Am J Gastroenterol* 2003;98:332–9.
85. Horsthuis K, Lavini C, Bipat S, Stokkers PC, Stoker J. Perianal Crohn disease: evaluation of dynamic contrast-enhanced MR imaging as an indicator of disease activity. *Radiology* 2009;251:380–7.
86. Karmiris K, Bielen D, Vanbeckevoort D, et al. Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging. *Clin Gastroenterol Hepatol* 2011;9:130–6.
87. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. *Am J Gastroenterol* 2009;104:2973–86.
88. Horsthuis K, Ziech ML, Bipat S, et al. Evaluation of an MRI-based score of disease activity in perianal fistulizing Crohn's disease. *Clin Imaging* 2011;35:360–5.
89. Samaan MA, Puylaert CAJ, Levesque BG, et al. The development of a magnetic resonance imaging index for fistulizing Crohn's disease. *Aliment Pharmacol Ther* 2017;46:516–28.
90. Savoye-Collet C, Savoye G, Koning E, Dacher JN, Lerebours E. Fistulizing perianal Crohn's disease: contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy. *Inflamm Bowel Dis* 2011;17:1751–8.
91. Pariente B, Mary JY, Danese S, et al. Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology* 2015;148:52–63.e3.
92. Fiorino G, Bonifacio C, Allocca M, et al. Bowel damage as assessed by the Lémann index is reversible on anti-TNF therapy for Crohn's disease. *J Crohns Colitis* 2015;9:633–9.
93. Gilletta C, Lewin M, Bourrier A, et al. Changes in the Lémann index values during the first years of Crohn's disease. *Clin Gastroenterol Hepatol* 2015;13:1633–40.e3.
94. Rispo A, Imperatore N, Testa A, et al. Bowel damage in Crohn's disease: direct comparison of ultrasonography-based and magnetic resonance-based Lemann index. *Inflamm Bowel Dis* 2017;23:143–51.
95. Rimola J, Ordás I, Rodríguez S, et al. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. *Inflamm Bowel Dis* 2011;17:1759–68.
96. Steward MJ, Punwani S, Proctor I, et al. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *Eur J Radiol* 2012;81:2080–8.
97. Becker HM, Grigat D, Ghosh S, et al. Living with inflammatory bowel disease: a Crohn's and Colitis Canada survey. *Can J Gastroenterol Hepatol* 2015;29:77–84.
98. Alrubaiy L, Rikaby I, Dodds P, Hutchings HA, Williams JG. Systematic review of health-related quality of life measures for inflammatory bowel disease. *J Crohns Colitis* 2015;9:284–92.

99. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014;12:1246–56.e6.
100. Grad FP. The Preamble of the Constitution of the World Health Organization. *Bull World Health Organ* 2002;80:981–4.
101. El-Matary W. Patient-reported outcome measures in inflammatory bowel disease. *Can J Gastroenterol Hepatol* 2014;28:536–42.
102. Zand A, van Deen WK, Inserra EK, et al. Presenteeism in inflammatory bowel diseases: a hidden problem with significant economic impact. *Inflamm Bowel Dis* 2015;21:1623–30.
103. Zahn A, Hinz U, Karner M, Ehehalt R, Stremmel W. Health-related quality of life correlates with clinical and endoscopic activity indexes but not with demographic features in patients with ulcerative colitis. *Inflamm Bowel Dis* 2006;12:1058–67.
104. Øresland T, Bemelman WA, Sampietro GM, et al.; European Crohn's and Colitis Organisation [ECCO]. European evidence-based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015;9:4–25.
105. Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. *J Crohns Colitis* 2017;11:165–74.
106. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;96:804–10.
107. Dibley L, Norton C, Cotterill N, Bassett P. Development and initial validation of a disease-specific bowel continence questionnaire for inflammatory bowel disease patients: the ICIQ-IBD. *Eur J Gastroenterol Hepatol* 2016;28:233–9.
108. Mantzouranis G, Faffiora E, Glantzounis G, Christodoulou DK, Katsanos KH. Inflammatory bowel disease and sexual function in male and female patients: an update on evidence in the past 10 years. *J Crohns Colitis* 2015;9:1160–8.
109. Hughes LD, King L, Morgan M, et al. Food-related quality of life in inflammatory bowel disease: development and validation of a questionnaire. *J Crohns Colitis* 2016;10:194–201.
110. Huppertz-Hauss G, Hoivik ML, Jelsness-Jørgensen LP, et al. Fatigue in a population-based cohort of patients with inflammatory bowel disease 20 years after diagnosis: the IBSen study. *Scand J Gastroenterol* 2017;52:351–8.
111. Gower-Rousseau C, Sarter H, Savoye G, et al.; International Programme to Develop New Indexes for Crohn's Disease [IPNIC] group. Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. *Gut* 2017;66:588–96.
112. Bernklev T, Jahnsen J, Lygren I, Henriksen M, Vatn M, Moum B. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. *Inflamm Bowel Dis* 2005;11:909–18.
113. Hoivik ML, Bernklev T, Moum B. Need for standardization in population-based quality of life studies: a review of the current literature. *Inflamm Bowel Dis* 2010;16:525–36.
114. Ravens-Sieberer U, Gosch A, Rajmil L, et al. KIDSCREEN-52 quality-of-life measure for children and adolescents. *Expert Rev Pharmacoecon Outcomes Res* 2005;5:353–64.
115. Griffiths AM, Nicholas D, Smith C, et al. Development of a quality-of-life index for pediatric inflammatory bowel disease: dealing with differences related to age and IBD type. *J Pediatr Gastroenterol Nutr* 1999;28:546–52.
116. Kunz JH, Greenley RN, Howard M. Maternal, paternal, and family health-related quality of life in the context of pediatric inflammatory bowel disease. *Qual Life Res* 2011;20:1197–204.
117. Maunder RG, Cohen Z, McLeod RS, Greenberg GR. Effect of intervention in inflammatory bowel disease on health-related quality of life: a critical review. *Dis Colon Rectum* 1995;38:1147–61.
118. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators: Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol* 1996;91:1571–8.
119. Chen XL, Zhong LH, Wen Y, et al. Inflammatory bowel disease-specific health-related quality of life instruments: a systematic review of measurement properties. *Health Qual Life Outcomes* 2017;15:177.
120. McDermott E, Keegan D, Byrne K, Doherty GA, Mulcahy HE. The Short Health Scale: a valid and reliable measure of health-related quality of life in English-speaking inflammatory bowel disease patients. *J Crohns Colitis* 2013;7:616–21.
121. Park SK, Ko BM, Goong HJ, et al. Short health scale: A valid measure of health-related quality of life in Korean-speaking patients with inflammatory bowel disease. *World J Gastroenterol* 2017;23:3530–7.
122. Jelsness-Jørgensen LP, Bernklev T, Moum B. Quality of life in patients with inflammatory bowel disease: translation, validity, reliability and sensitivity to change of the Norwegian version of the short health scale [SHS]. *Qual Life Res* 2012;21:1671–6.
123. Abdovic S, Pavic AM, Milosevic M, Persic M, Senecic-Cala I, Kolacek S. Short health scale: a valid, reliable, and responsive measure of health-related quality of life in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:818–23.
124. Krarup AL, Peterson E, Ringström G, Törnblom H, Hjortswang H, Simrén M. The short health scale: a simple, valid, reliable, and responsive way of measuring subjective health in patients with irritable bowel syndrome. *J Clin Gastroenterol* 2015;49:565–70.
125. Feagan BG, Coteur G, Tan S, Keininger DL, Schreiber S. Clinically meaningful improvement in health-related quality of life in a randomized controlled trial of certolizumab pegol maintenance therapy for Crohn's disease. *Am J Gastroenterol* 2009;104:1976–83.
126. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indexes and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;132:763–86.
127. Stark RG, Reitmeir P, Leidl R, König HH. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. *Inflamm Bowel Dis* 2010;16:42–51.
128. Alrubaiy L, Cheung WY, Dodds P, et al. Development of a short questionnaire to assess the quality of life in Crohn's disease and ulcerative colitis. *J Crohns Colitis* 2015;9:66–76.
129. Kaminski MF, Thomas-Gibson S, Bugajski M, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy [ESGE] quality improvement initiative. *United European Gastroenterol J* 2017;5:309–34.
130. Panes J, Jairath V, Levesque BG. Advances in use of endoscopy, radiology, and biomarkers to monitor inflammatory bowel diseases. *Gastroenterology* 2017;152:362–73.e3.
131. Terheggen G, Lanyi B, Schanz S, et al. Safety, feasibility, and tolerability of ileocolonoscopy in inflammatory bowel disease. *Endoscopy* 2008;40:656–63.
132. Shingina A, Ou G, Takach O, et al. Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience. *World J Gastrointest Endosc* 2016;8:770–6.
133. Igea F, Casellas JA, González-Huix F, et al.; Spanish Society of Digestive Endoscopy. Sedation for gastrointestinal endoscopy. *Endoscopy* 2014;46:720–31.
134. Ferreira AO, Cravo M. Sedation in gastrointestinal endoscopy: Where are we at in 2014? *World J Gastrointest Endosc* 2015;7:102–9.
135. Conigliaro R, Fanti L, Manno M, Brosolo P; Italian Society of Digestive Endoscopy [SIED] Sedation Group. Italian Society of Digestive Endoscopy [SIED] position paper on the non-anaesthesiologist administration of propofol for gastrointestinal endoscopy. *Dig Liver Dis* 2017;49:1185–90.
136. Dumonceau JM, Riphaut A, Schreiber F, et al. Non-anesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline—Updated June 2015. *Endoscopy* 2015;47:1175–89.
137. Memon MA, Memon B, Yunus RM, Khan S. Carbon dioxide versus air insufflation for elective colonoscopy: a meta-analysis and systematic review of randomized controlled trials. *Surg Laparosc Endosc Percutan Tech* 2016;26:102–16.
138. Mathus-Vliegen E, Pellisé M, Heresbach D, et al. Consensus guidelines for the use of bowel preparation prior to colonic diagnostic procedures:

- colonoscopy and small bowel video capsule endoscopy. *Curr Med Res Opin* 2013;29:931–45.
139. Kilgore TW, Abdinoor AA, Szary NM, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc* 2011;73:1240–5.
  140. Martel M, Barkun AN, Menard C, Restellini S, Kherad O, Vanasse A. Split-dose preparations are superior to day-before bowel cleansing regimens: a meta-analysis. *Gastroenterology* 2015;149:79–88.
  141. Nett A, Velayos F, McQuaid K. Quality bowel preparation for surveillance colonoscopy in patients with inflammatory bowel disease is a must. *Gastrointest Endosc Clin N Am* 2014;24:379–92.
  142. Manes G, Fontana P, de Nucci G, Radaelli F, Hassan C, Ardizzone S. Colon cleansing for colonoscopy in patients with ulcerative colitis: efficacy and acceptability of a 2-L PEG plus Bisacodyl versus 4-L PEG. *Inflamm Bowel Dis* 2015;21:2137–44.
  143. Hassan C, Bretthauer M, Kaminski MF, et al.; European Society of Gastrointestinal Endoscopy. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy [ESGE] guideline. *Endoscopy* 2013;45:142–50.
  144. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endosc* 2015;81:489–501. e26.
  145. Chen M, Shen B. Endoscopic therapy in Crohn's disease: principle, preparation, and technique. *Inflamm Bowel Dis* 2015;21:2222–40.
  146. Marion JF, Wayne JD, Present DH, et al.; Chromoendoscopy Study Group at Mount Sinai School of Medicine. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. *Am J Gastroenterol* 2008;103:2342–9.
  147. Har-Noy O, Katz L, Avni T, et al. Chromoendoscopy, narrow-band imaging or white light endoscopy for neoplasia detection in inflammatory bowel diseases. *Dig Dis Sci* 2017;62:2982–90.
  148. Collins PD. Video capsule endoscopy in inflammatory bowel disease. *World J Gastrointest Endosc* 2016;8:477–88.
  149. Han YM, Im JP. Colon capsule endoscopy: where are we and where are we going. *Clin Endosc* 2016;49:449–53.
  150. Boal Carvalho P, Rosa B, Dias de Castro F, Moreira MJ, Cotter J. PillCam COLON 2 in Crohn's disease: a new concept of pan-enteric mucosal healing assessment. *World J Gastroenterol* 2015;21:7233–41.
  151. Enns RA, Hookey L, Armstrong D, et al. Clinical practice guidelines for the use of video capsule endoscopy. *Gastroenterology* 2017;152:497–514.
  152. Gal E, Geller A, Fraser G, Levi Z, Niv Y. Assessment and validation of the new capsule endoscopy Crohn's disease activity index [CECDAI]. *Dig Dis Sci* 2008;53:1933–7.
  153. Rezapour M, Amadi C, Gerson LB. Retention associated with video capsule endoscopy: systematic review and meta-analysis. *Gastrointest Endosc* 2017;85:1157–68. e2.
  154. Perez-Cuadrado E, Macenlle R, Iglesias J, Fabra R, Lamas D. Usefulness or oral video push enteroscopy in Crohn's disease. *Endoscopy* 1997;29:745–7.
  155. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy [ESGE] Clinical Guideline. *Endoscopy* 2015;47:352–76.
  156. Saygili F, Saygili SM, Oztas E. Examining the whole bowel, double balloon enteroscopy: Indications, diagnostic yield and complications. *World J Gastrointest Endosc* 2015;7:247–52.
  157. Arulanandan A, Dulai PS, Singh S, Sandborn WJ, Kalmaz D. Systematic review: safety of balloon assisted enteroscopy in Crohn's disease. *World J Gastroenterol* 2016;22:8999–9011.
  158. Li X, Zhao YJ, Dai J, et al. Carbon dioxide insufflation improves the intubation depth and total enteroscopy rate in single-balloon enteroscopy: a randomised, controlled, double-blind trial. *Gut* 2014;63:1560–5.
  159. Lenz P, Meister T, Manno M, et al. CO<sub>2</sub> insufflation during single-balloon enteroscopy: a multicenter randomized controlled trial. *Endoscopy* 2014;46:53–8.
  160. Marshall JK, Cawdron R, Zealley I, Riddell RH, Somers S, Irvine EJ. Prospective comparison of small bowel meal with pneumocolon versus ileo-colonoscopy for the diagnosis of ileal Crohn's disease. *Am J Gastroenterol* 2004;99:1321–9.
  161. Pickhardt PJ. The peroral pneumocolon revisited: a valuable fluoroscopic and CT technique for ileocecal evaluation. *Abdom Imaging* 2012;37:313–25.
  162. Maglinte DD, Lappas JC, Kelvin FM, Rex D, Chernish SM. Small bowel radiography: how, when, and why? *Radiology* 1987;163:297–305.
  163. Sellink JL. Radiologic examination of the small intestine by duodenal intubation. *Acta Radiol Diagn [Stockh]* 1974;15:318–32.
  164. Herlinger H. A modified technique for the double-contrast small bowel enema. *Gastrointest Radiol* 1978;3:201–7.
  165. Thoeni RF, Gould RG. Enteroclysis and small bowel series: comparison of radiation dose and examination time. *Radiology* 1991;178:659–62.
  166. Jaffe TA, Gaca AM, Delaney S, et al. Radiation doses from small-bowel follow-through and abdominopelvic MDCT in Crohn's disease. *AJR Am J Roentgenol* 2007;189:1015–22.
  167. Gaca AM, Jaffe TA, Delaney S, et al. Radiation doses from small-bowel follow-through and abdomen/pelvis MDCT in pediatric Crohn disease. *Pediatr Radiol* 2008;38:285–91.
  168. Frederick-Dyer KC, Faulkner AR, Chang TT, Heidel RE, Pasciak AS. Online training on the safe use of fluoroscopy can result in a significant decrease in patient dose. *Acad Radiol* 2013;20:1272–7.
  169. Bibbo G, Balman D, Linke R. Diagnostic reference levels for common paediatric fluoroscopic examinations performed at a dedicated paediatric Australian hospital. *J Med Imaging Radiat Oncol* 2016;60:469–74.
  170. Taylor SA, Avni F, Cronin CG, et al. The first joint ESGAR/ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging. *Eur Radiol* 2017;27:2570–82.
  171. Fiorino G, Bonifacio C, Padrenostro M, et al. Comparison between 1.5 and 3.0 Tesla magnetic resonance enterography for the assessment of disease activity and complications in ileo-colonic Crohn's disease. *Dig Dis Sci* 2013;58:3246–55.
  172. Jiang X, Asbach P, Hamm B, Xu K, Banzer J. MR imaging of distal ileal and colorectal chronic inflammatory bowel disease—diagnostic accuracy of 1.5 T and 3 T MRI compared to colonoscopy. *Int J Colorectal Dis* 2014;29:1541–50.
  173. Halligan S, Stoker J. Imaging of fistula in ano. *Radiology* 2006;239:18–33.
  174. Jesuratnam-Nielsen K, Løgager VB, Munkholm P, Thomsen HS. Diagnostic accuracy of three different MRI protocols in patients with inflammatory bowel disease. *Acta Radiol Open* 2015;4:2058460115588099.
  175. Jesuratnam-Nielsen K, Løgager VB, Rezanavaz-Gheshlagh B, Munkholm P, Thomsen HS. Plain magnetic resonance imaging as an alternative in evaluating inflammation and bowel damage in inflammatory bowel disease—a prospective comparison with conventional magnetic resonance follow-through. *Scand J Gastroenterol* 2015;50:519–27.
  176. Borthne AS, Abdelnoor M, Storaas T, Pierre-Jerome C, Kløw NE. Osmolarity: a decisive parameter of bowel agents in intestinal magnetic resonance imaging. *Eur Radiol* 2006;16:1331–6.
  177. Ippolito D, Invernizzi F, Galimberti S, Panelli MR, Sironi S. MR enterography with polyethylene glycol as oral contrast medium in the follow-up of patients with Crohn disease: comparison with CT enterography. *Abdom Imaging* 2010;35:563–70.
  178. Ajaj W, Goehde SC, Schneemann H, Ruehm SG, Debatin JF, Lauenstein TC. Oral contrast agents for small bowel MRI: comparison of different additives to optimize bowel distension. *Eur Radiol* 2004;14:458–64.
  179. Ajaj W, Goehde SC, Schneemann H, Ruehm SG, Debatin JF, Lauenstein TC. Dose optimization of mannitol solution for small bowel distension in MRI. *J Magn Reson Imaging* 2004;20:648–53.
  180. Maccioni F, Viscido A, Marini M, Caprilli R. MRI evaluation of Crohn's disease of the small and large bowel with the use of negative superparamagnetic oral contrast agents. *Abdom Imaging* 2002;27:384–93.
  181. Laghi A, Paolantonio P, Iafrate F, et al. MR of the small bowel with a biphasic oral contrast agent [polyethylene glycol]: technical aspects and findings in patients affected by Crohn's disease. *Radiol Med* 2003;106:18–27.
  182. Evrimler S, Algin O. MR enterography with oral contrast agent composed of methylcellulose, low-dose barium sulfate, sorbitol, and



- lactulose: assessment of diagnostic performance, reliability, image quality, and patient tolerance. *Clin Imaging* 2016;40:523–30.
183. Maccioni F. Double-contrast magnetic resonance imaging of the small and large bowel: effectiveness in the evaluation of inflammatory bowel disease. *Abdom Imaging* 2010;35:31–40.
  184. Bekendam MIJ, Puylaert CAJ, Phoa SKSS, Nio CY, Stoker J. Shortened oral contrast preparation for improved small bowel distension at MR enterography. *Abdom Radiol [NY]* 2017;42:2225–32.
  185. Kuehle CA, Ajaj W, Ladd SC, Massing S, Barkhausen J, Lauenstein TC. Hydro-MRI of the small bowel: effect of contrast volume, timing of contrast administration, and data acquisition on bowel distention. *AJR Am J Roentgenol* 2006;187:W375–85.
  186. Negaard A, Sandvik L, Berstad AE, et al. MRI of the small bowel with oral contrast or nasojejunal intubation in Crohn's disease: randomized comparison of patient acceptance. *Scand J Gastroenterol* 2008;43:44–51.
  187. Minordi LM, Vecchioli A, Mirk P, Bonomo L. CT enterography with polyethylene glycol solution vs CT enteroclysis in small bowel disease. *Br J Radiol* 2011;84:112–9.
  188. Minordi LM, Scalfaferrì F, Marra RS, et al. Enterography CT without and with water enema in patients with Crohn's disease: Results from a comparative observational study in comparison with endoscopy. *Eur J Radiol* 2016;85:404–13.
  189. Cronin CG, Lohan DG, Browne AM, Roche C, Murphy JM. Does MRI with oral contrast medium allow single-study depiction of inflammatory bowel disease enteritis and colitis? *Eur Radiol* 2010;20:1667–74.
  190. Friedrich C, Fajfar A, Pawlik M, et al. Magnetic resonance enterography with and without biphasic contrast agent enema compared to conventional ileocolonoscopy in patients with Crohn's disease. *Inflamm Bowel Dis* 2012;18:1842–8.
  191. Cronin CG, Lohan DG, Mhuirheartaigh JN, et al. MRI small-bowel follow-through: prone versus supine patient positioning for best small-bowel distention and lesion detection. *AJR Am J Roentgenol* 2008;191:502–6.
  192. Vandenbroucke F, Mortelé KJ, Tatli S, et al. Noninvasive multidetector computed tomography enterography in patients with small-bowel Crohn's disease: is a 40-second delay better than 70 seconds? *Acta Radiol* 2007;48:1052–60.
  193. Huprich JE, Fletcher JG. CT enterography: principles, technique and utility in Crohn's disease. *Eur J Radiol* 2009;69:393–7.
  194. Baker ME, Hara AK, Platt JF, Maglente DD, Fletcher JG. CT enterography for Crohn's disease: optimal technique and imaging issues. *Abdom Imaging* 2015;40:938–52.
  195. Young W, Hyman N, Osler T. Predictors of excessive CT scan use in a surgical cohort of patients with Crohn's disease. *Postgrad Med* 2013;125:94–9.
  196. Desmond AN, O'Regan K, Curran C, et al. Crohn's disease: factors associated with exposure to high levels of diagnostic radiation. *Gut* 2008;57:1524–9.
  197. Guimarães LS, Fletcher JG, Yu L, et al. Feasibility of dose reduction using novel denoising techniques for low kV [80 kV] CT enterography: optimization and validation. *Acad Radiol* 2010;17:1203–10.
  198. Camera L, Liccardo I, Romano F, et al. Diagnostic efficacy of single-pass abdominal multidetector-row CT: prospective evaluation of a low dose protocol. *Br J Radiol* 2017;90:20160612.
  199. Lee S, Yoon SW, Yoo SM, et al. Comparison of image quality and radiation dose between combined automatic tube current modulation and fixed tube current technique in CT of abdomen and pelvis. *Acta Radiol* 2011;52:1101–6.
  200. Gandhi NS, Baker ME, Goenka AH, et al. Diagnostic accuracy of CT enterography for active inflammatory terminal ileal Crohn disease: comparison of full-dose and half-dose images reconstructed with FBP and half-dose images with SAFIRE. *Radiology* 2016;280:436–45.
  201. Murphy KP, Crush L, Twomey M, et al. Model-based iterative reconstruction in CT enterography. *AJR Am J Roentgenol* 2015;205:1173–81.
  202. Murphy KP, Crush L, McLaughlin PD, et al. The role of pure iterative reconstruction in conventional dose CT enterography. *Abdom Imaging* 2015;40:251–7.
  203. McLaughlin PD, Murphy KP, Twomey M, et al. Pure iterative reconstruction improves image quality in computed tomography of the abdomen and pelvis acquired at substantially reduced radiation doses in patients with active Crohn disease. *J Comput Assist Tomogr* 2016;40:225–33.
  204. Kaza RK, Platt JF, Al-Hawary MM, Wasnik A, Liu PS, Pandya A. CT enterography at 80 kVp with adaptive statistical iterative reconstruction versus at 120 kVp with standard reconstruction: image quality, diagnostic adequacy, and dose reduction. *AJR Am J Roentgenol* 2012;198:1084–92.
  205. Grand DJ, Beland MD, Machan JT, Mayo-Smith WW. Detection of Crohn's disease: Comparison of CT and MR enterography without anti-peristaltic agents performed on the same day. *Eur J Radiol* 2012;81:1735–41.
  206. Gutzeit A, Binkert CA, Koh DM, et al. Evaluation of the anti-peristaltic effect of glucagon and hyoscine on the small bowel: comparison of intravenous and intramuscular drug administration. *Eur Radiol* 2012;22:1186–94.
  207. Maccioni F, Bruni A, Viscido A, et al. MR imaging in patients with Crohn disease: value of T2- versus T1-weighted gadolinium-enhanced MR sequences with use of an oral superparamagnetic contrast agent. *Radiology* 2006;238:517–30.
  208. Low RN, Sebrechts CP, Politoske DA, et al. Crohn disease with endoscopic correlation: single-shot fast spin-echo and gadolinium-enhanced fat-suppressed spoiled gradient-echo MR imaging. *Radiology* 2002;222:652–60.
  209. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology* 2015;275:783–91.
  210. Roberts DR, Chatterjee AR, Yazdani M, et al. Pediatric patients demonstrate progressive T1-weighted hyperintensity in the dentate nucleus following multiple doses of gadolinium-based contrast agent. *AJNR Am J Neuroradiol* 2016;37:2340–7.
  211. Kanda T, Oba H, Toyoda K, Furui S. Recent advances in understanding gadolinium retention in the brain. *AJNR Am J Neuroradiol* 2016;37:E1–2.
  212. Kahn J, Posch H, Steffen IG, et al. Is there long-term signal intensity increase in the central nervous system on T1-weighted images after MR imaging with the hepatospecific contrast agent gadoxetic acid? A cross-sectional study in 91 patients. *Radiology* 2017;282:708–16.
  213. Quaiá E, Sozzi M, Gennari AG, Pontello M, Angileri R, Cova MA. Impact of gadolinium-based contrast agent in the assessment of Crohn's disease activity: Is contrast agent injection necessary? *J Magn Reson Imaging* 2016;43:688–97.
  214. Seo N, Park SH, Kim KJ, et al. MR enterography for the evaluation of small-bowel inflammation in Crohn disease by using diffusion-weighted imaging without intravenous contrast material: a prospective noninferiority study. *Radiology* 2016;278:762–72.
  215. Kim KJ, Lee Y, Park SH, et al. Diffusion-weighted MR enterography for evaluating Crohn's disease: how does it add diagnostically to conventional MR enterography? *Inflamm Bowel Dis* 2015;21:101–9.
  216. Sirin S, Kathemann S, Schweiger B, et al. Magnetic resonance colonography including diffusion-weighted imaging in children and adolescents with inflammatory bowel disease: do we really need intravenous contrast? *Invest Radiol* 2015;50:32–9.
  217. Shenoy-Bhangle AS, Nimkin K, Aranson T, Gee MS. Value of diffusion-weighted imaging when added to magnetic resonance enterographic evaluation of Crohn disease in children. *Pediatr Radiol* 2016;46:34–42.
  218. Menys A, Helbren E, Makanyanga J, et al. Small bowel strictures in Crohn's disease: a quantitative investigation of intestinal motility using MR enterography. *Neurogastroenterol Motil* 2013;25:967.
  219. Plumb AA, Menys A, Russo E, et al. Magnetic resonance imaging-quantified small bowel motility is a sensitive marker of response to medical therapy in Crohn's disease. *Aliment Pharmacol Ther* 2015;42:343–55.
  220. Hahnemann ML, Nensa F, Kinner S, et al. Quantitative assessment of small bowel motility in patients with Crohn's disease using dynamic MRI. *Neurogastroenterol Motil* 2015;27:841–8.

221. Hahne ML, Nensa F, Kinner S, et al. Improved detection of inflammatory bowel disease by additional automated motility analysis in magnetic resonance imaging. *Invest Radiol* 2015;50:67–72.
222. Tolan DJ. Magnetic resonance imaging for perianal fistula. *Semin Ultrasound CT MR* 2016;37:313–22.
223. Lo Re G, Tudisca C, Vernuccio F, et al. MR imaging of perianal fistulas in Crohn's disease: sensitivity and specificity of STIR sequences. *Radiol Med* 2016;121:243–51.
224. Torkzad MR, Ahlström H, Karlbom U. Comparison of different magnetic resonance imaging sequences for assessment of fistula-in-ano. *World J Radiol* 2014;6:203–9.
225. Tielbeek JA, Bipat S, Boellaard TN, Nio CY, Stoker J. Training readers to improve their accuracy in grading Crohn's disease activity on MRI. *Eur Radiol* 2014;24:1059–67.
226. Puylaert CA, Tielbeek JA, Bipat S, Boellaard TN, Nio CY, Stoker J. Long-term performance of readers trained in grading Crohn disease activity using MRI. *Acad Radiol* 2016;23:1539–44.
227. AlSabban Z, Church P, Moineddin R, et al. Accuracy and interobserver agreement of diffusion-weighted imaging in pediatric inflammatory bowel disease. *Clin Imaging* 2017;41:14–22.
228. Horvat N, Tavares CC, Andrade AR, et al. Inter- and intraobserver agreement in computed tomography enterography in inflammatory bowel disease. *World J Gastroenterol* 2016;22:10002–8.
229. Jensen MD, Ormstrup T, Vagn-Hansen C, Østergaard L, Rafaelsen SR. Interobserver and intermodality agreement for detection of small bowel Crohn's disease with MR enterography and CT enterography. *Inflamm Bowel Dis* 2011;17:1081–8.
230. Buchanan GN, Halligan S, Taylor S, Williams A, Cohen R, Bartram C. MRI of fistula in ano: inter- and intraobserver agreement and effects of directed education. *AJR Am J Roentgenol* 2004;183:135–40.
231. Fraquelli M, Colli A, Casazza G, et al. Role of US in detection of Crohn disease: meta-analysis. *Radiology* 2005;236:95–101.
232. Rompel O, Huelss B, Bodenschatz K, Reutter G, Darge K. Harmonic US imaging of appendicitis in children. *Pediatr Radiol* 2006;36:1257–64.
233. Ruess L, Blask AR, Bulas DI, et al. Inflammatory bowel disease in children and young adults: correlation of sonographic and clinical parameters during treatment. *AJR Am J Roentgenol* 2000;175:79–84.
234. Ripollés T, Simó L, Martínez-Pérez MJ, Pastor MR, Igual A, López A. Sonographic findings in ischemic colitis in 58 patients. *AJR Am J Roentgenol* 2005;184:777–85.
235. Drews BH, Barth TF, Hänle MM, et al. Comparison of sonographically measured bowel wall vascularity, histology, and disease activity in Crohn's disease. *Eur Radiol* 2009;19:1379–86.
236. Neye H, Voderholzer W, Rickes S, Weber J, Wermke W, Lochs H. Evaluation of criteria for the activity of Crohn's disease by power Doppler sonography. *Dig Dis* 2004;22:67–72.
237. Wilson SR, Burns PN. Microbubble-enhanced US in body imaging: what role? *Radiology* 2010;257:24–39.
238. Migaleddu V, Scanu AM, Quaia E, et al. Contrast-enhanced ultrasonographic evaluation of inflammatory activity in Crohn's disease. *Gastroenterology* 2009;137:43–52.
239. Medellin A, Merrill C, Wilson SR. Role of contrast-enhanced ultrasound in evaluation of the bowel. *Abdom Radiol [NY]* 2018;43:918–33.
240. Kratzer W, Schmidt SA, Mittrach C, et al. Contrast-enhanced wide-band harmonic imaging ultrasound [SonoVue]: a new technique for quantifying bowel wall vascularity in Crohn's disease. *Scand J Gastroenterol* 2005;40:985–91.
241. Nylund K, Jirik R, Mezl M, et al. Quantitative contrast-enhanced ultrasound comparison between inflammatory and fibrotic lesions in patients with Crohn's disease. *Ultrasound Med Biol* 2013;39:1197–206.
242. Romanini L, Passamonti M, Navarria M, et al. Quantitative analysis of contrast-enhanced ultrasonography of the bowel wall can predict disease activity in inflammatory bowel disease. *Eur J Radiol* 2014;83:1317–23.
243. Ripollés T, Martínez-Pérez MJ, Paredes JM, Vizuete J, García-Martínez E, Jiménez-Restrepo DH. Contrast-enhanced ultrasound in the differentiation between phlegmon and abscess in Crohn's disease and other abdominal conditions. *Eur J Radiol* 2013;82:e525–31.
244. Calabrese E, Zorzi F, Pallone F. Ultrasound in Crohn's disease. *Curr Drug Targets* 2012;13:1224–33.
245. Calabrese E, Zorzi F, Onali S, et al. Accuracy of small-intestine contrast ultrasonography, compared with computed tomography enteroclysis, in characterizing lesions in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2013;11:950–5.
246. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut* 2013;62:1072–84.
247. Quencer KB, Nimkin K, Mino-Kenudson M, Gee MS. Detecting active inflammation and fibrosis in pediatric Crohn's disease: prospective evaluation of MR-E and CT-E. *Abdom Imaging* 2013;38:705–13.
248. Ha CY, Kumar N, Raptis CA, Narra VR, Ciorba MA. Magnetic resonance enterography: safe and effective imaging for stricturing Crohn's disease. *Dig Dis Sci* 2011;56:2906–13.
249. Ripollés T, Rausell N, Paredes JM, Grau E, Martínez MJ, Vizuete J. Effectiveness of contrast-enhanced ultrasound for characterisation of intestinal inflammation in Crohn's disease: a comparison with surgical histopathology analysis. *J Crohns Colitis* 2013;7:120–8.
250. Quaia E, De Paoli L, Stocca T, Cabibbo B, Casagrande F, Cova MA. The value of small bowel wall contrast enhancement after sulfur hexafluoride-filled microbubble injection to differentiate inflammatory from fibrotic strictures in patients with Crohn's disease. *Ultrasound Med Biol* 2012;38:1324–32.
251. Ophir J, Céspedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 1991;13:111–34.
252. Baumgart DC, Müller HP, Grittner U, et al. US-based real-time elastography for the detection of fibrotic gut tissue in patients with stricturing Crohn disease. *Radiology* 2015;275:889–99.
253. Fraquelli M, Branchi F, Cribiù FM, et al. The role of ultrasound elasticity imaging in predicting ileal fibrosis in Crohn's disease patients. *Inflamm Bowel Dis* 2015;21:2605–12.
254. Nylund K, Maconi G, Hollerweger A, et al. EFSUMB recommendations and guidelines for gastrointestinal ultrasound. *Ultraschall Med* 2017;38:e1–e15.
255. Atkinson NS, Bryant RV, Dong Y, et al. WFUMB position paper. Learning gastrointestinal ultrasound: theory and practice. *Ultrasound Med Biol* 2016;42:2732–42.
256. Fraquelli M, Sarno A, Girelli C, et al. Reproducibility of bowel ultrasonography in the evaluation of Crohn's disease. *Dig Liver Dis* 2008;40:860–6.