## Title:

Current best practice for disease activity assessment in IBD

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# Current best practice for disease activity assessment in IBD

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Abstract | Therapeutic advances in the management of IBD have led to a paradigm shift in the assessment of IBD disease activity. Beyond clinical remission, objective assessment of inflammation is now critical to guiding subsequent therapy as part of a 'treat to target' strategy. Multiple domains of disease activity assessment in IBD exist, each of which has its merits, although none are perfect. The aim of this Review is to comprehensively evaluate measures of disease activity in both ulcerative colitis and Crohn's disease, including clinical, endoscopic, histological and radiological assessment tools, as well as the use of biomarkers and quality of life evaluation. A subjective appraisal of the best indices for use in clinical practice is provided, based on index validation, responsiveness and experience in clinical trials, international specialist opinion, and practicality and suitability for use in clinical practice. This Review aims to enable the reader to gain confidence in IBD disease activity assessment and to give ready access to the necessary tools.

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Management of IBD is guided by the anatomical distribution of disease, symptom severity, response to medical therapy and the ability of the patient to accept and tolerate treatment[1,2]. Disease severity indices help to guide clinical decisions and are particularly helpful for patients who fail to show adequate response to therapy, as they clearly demonstrate (in a quantitative manner) that they have not met the desired target (TABLE 1,2). Advances such as increased availability and use of biologic agents for the treatment of IBD have led to a paradigm shift in the assessment of disease activity, as we are now better able to achieve remission targets. Beyond clinical remission, ongoing treatment strategies require guidance from objective assessment of disease activity. IBD disease activity comprises multiple domains that can be assessed; each of these domains has its merits, although none are perfect (FIG. 1).

The aim of this Review is to evaluate measures of disease activity assessment in both ulcerative colitis and Crohn's disease. Formal evaluation of disease activity in IBD is associated with many challenges, including confusing terminology, different names or abbreviations for the same index, and the tendency to use composite indices that combine symptom assessment with objective measures of inflammation or quality of life (QOL).

To make this summary clinically useful, we have divided the paper into sections on ulcerative colitis and Crohn's disease; in each we will discuss clinical, endoscopic, histological and radiological assessment, as well as biomarkers and QOL. A subjective evaluation of the best disease activity indices for use in clinical practice is provided. Remission thresholds for disease activity indices are also provided when possible. The indices were selected after several considerations: extent of validation; responsiveness and experience in clinical trials; international expert opinion[3]; active comparison between all indices in clinical practice[4]; and ease of use in clinical practice. Although to some extent the choice of indices was that of the authors, the selection is informed by our extensive involvement in index development, evaluation, formal guideline development, clinical trials and clinical practice[3–9]. This Review aims to give the reader ready access to appropriate assessment tools, and to enable the reader to gain confidence in IBD disease activity assessment. A comprehensive list of relevant disease activity indices is provided as a supplementary table for both ulcerative colitis and Crohn's disease (see Supplementary information S1 (tables 1, 2, respectively)). A good case can be made (and one that we advocate) for separating the components of disease activity assessment, using distinct and independently validated clinical, endoscopic, histological and QOL indices. We recognize that this might as yet represent a minority view, but we believe it will gain ground, particularly as QOL becomes an important outcome measure for care.

## Ulcerative colitis

***Clinical assessment of disease activity.*** There are 17 ulcerative colitis indices that evaluate symptoms, eight of which do so independently of endoscopic scoring or

**Key points**

- Objective assessment of disease activity in IBD is important for guiding subsequent therapy as part of a 'treat to target' strategy
- Multiple domains of disease activity assessment exist in IBD (symptoms, endoscopy, histology, radiology, biomarkers and quality of life), and targets should be recognized as goals for therapy within each domain
- Confusing terminology and the use of composite indices (combining symptom assessment with objective measurements of quality of life or inflammation) confound the formal evaluation of disease activity
- Biomarkers are useful adjuncts to monitor disease activity in both ulcerative colitis and Crohn's disease
- Assessment of quality of life is an important aspect of medical decision-making, as improving quality of life is a major goal of therapy

biochemical markers (see Supplementary information S1 (table 1)). For assessment of mild to moderate ulcerative colitis we recommend the Simple Colitis Clinical Activity index (SCCAI)[10], the Partial Mayo Clinic Index[11,12] and the Pediatric Ulcerative Colitis Activity Index (PUCAI)[13]. For severe disease, we recommend Truelove and Witts' criteria[14].

The SCCAI (see Supplementary information S2 (table 1) online) is one of the eight indices that exclude endoscopic assessment and biochemical markers. Importantly, it includes nocturnal bowel movements and urgency of defecation[10]. These symptoms are of vital importance to patients due to their effect on QOL, but are neglected by other indices. Scores in this index range from 0 to 19 points. The SCCAI has been compared prospectively with the multiple other ulcerative colitis indices and, along with the PUCAI, performed best of all noninvasive indices for validity, reliability, responsiveness (ability to measure the change in disease activity) and feasibility. This index was sufficiently able to discriminate remission from active disease[15]. As the SCCAI does not include a Physician Global Assessment or biochemical markers, it can readily be completed by patients. The remission target is a SCCAI total score of <1 (REF. 3).

The Partial Mayo Clinic Index (see Supplementary information S2 (table 2)) is currently the most widely used index in trial design[11,12]. The full Mayo Clinic Index (Partial Mayo Clinic Index plus endoscopic subscore) has become the standard for assessing disease activity in adult clinical trials in which endoscopic assessment is mandated by the FDA[16]. Rectal bleeding and frequency of bowel motions are the only two symptoms assessed. Although readily criticized because it is an unvalidated derivation of an unvalidated index, when the Partial Mayo Index was compared with other noninvasive indices, it performed well for discriminating remission from active disease, showed responsiveness and had good construct validity. However, insufficient test–retest validity was shown[15]. A Physician Global Assessment is necessary for the Partial Mayo Index, therefore making it less feasible for clinical use as it does not allow independent use by patients. The remission target is a Partial Mayo total score of ≤1 (REF. 3).

The PUCAI (see Supplementary information S2 (table 3)) was devised by paediatric gastroenterologists as a noninvasive instrument to assess disease activity in children; repeated endoscopy in this setting is less tolerable to both patients and parents[13]. This index comprises six descriptors, each with different levels, creating a total score ranging from 0 to 85: abdominal pain, degree of rectal bleeding, average stool consistency, number of stools in 24 h, presence of nocturnal stools and patient activity level are assessed. The PUCAI was rigorously developed and validated in children[13], and has also been shown to be valid, reliable and responsive in adults[15]. This index permits less frequent endoscopic assessment for all patients with ulcerative colitis, both in clinical practice and clinical trials[15]. The remission target is a PUCAI total score of <10 (REF. 3).

For severe disease assessment and management we encourage the use of the Truelove and Witts' criteria (see Supplementary information S2 (table 4))[14]. This index provides objective criteria to identify acute severe colitis, and has been widely used to define the need for hospital admission and intravenous steroids[17]. The criteria for acute severe colitis are ≥6 stools per day, with frequent blood in the stool, with at least one of the following features: body temperature >37.8 °C; heart rate >90 bpm, haemoglobin levels <10.5 g/dl and erythrocyte sedimentation rate >30 mm/h. Patients with more of these criteria present at admission have a greater chance of needing a colectomy on that admission[18].

***Endoscopic assessment of disease activity.*** Mucosal healing is the remission target when assessing IBD disease activity endoscopically. Simply stated, mucosal healing should imply the absence of ulceration and erosions. Nevertheless, there is currently no validated definition of mucosal healing in IBD[16,19,20].

Mucosal healing should be recognized as the ultimate therapeutic goal for ulcerative colitis, as the disease is limited to the mucosa[19]. Thus, endoscopic assessment of patients with ulcerative colitis is increasingly used in clinical practice to guide treatment decision-making. Mucosal healing in ulcerative colitis has been associated with decreased need for corticosteroids[21], decreased hospitalization rates[22–24], sustained clinical remission[25], decreased colectomy[21,22,24,25] and decreased risk of colorectal cancer[26].

Many different endoscopic indices for ulcerative colitis have been used in clinical trials (see Supplementary information S1 (table 1)). This Review focuses on the endoscopic indices that we, the authors, feel are best used in clinical practice: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[8,9] and the Mayo Clinic endoscopy subscore[11].

The UCEIS is the only validated endoscopic index in ulcerative colitis (see Supplementary information S2 (table 5))[8,9], and was developed because of wide inter-observer variation in endoscopic assessment of disease activity when using previously published endoscopic indices[4]. The UCEIS is simple to use in clinical practice, as all it requires is the endoscopist to grade vascular pattern, bleeding and erosions or ulceration, which

then enables a total score from 0 to 8 to be calculated. Disadvantages of the UCEIS are that extent of disease is not documented (as only the worst affected area is scored), there is no definition of mucosal healing, and there are no validated thresholds for mild, moderate or severe disease. Use of the UCEIS has been shown to reduce interobserver variation[8,27], and its responsiveness will be defined by its use in clinical trials of ulcerative colitis that are currently in progress[28]. We encourage its use in clinical practice so that there is a uniform language for describing disease activity. The remission target is a UCEIS total score of ≤1 (REF. 3).

The Mayo Clinic endoscopy subscore has not been formally validated, however, it has been the standard for assessing disease activity in adult clinical trials where endoscopic assessment is mandated by the FDA[16]. The subscore has four components, each with a maximum score of 3 (see Supplementary information S2 (table 6))[2]. Overlap in the features of the different levels contributes to interobserver variation; moreover, the index does not take into account extent of disease and there is no validated definition of mucosal healing. The value of using the Mayo Clinic Score in clinical practice simply lies infamiliarity among practitioners. The remission target is a Mayo Clinic endoscopy subscore of ≤1, reflecting the use of this threshold as an outcome measure in clinical trials, its association with a lower colectomy rate during follow-up and recommendation by a group of international specialists[3].

***Histological assessment of disease activity.*** Substantial disparity exists between histological and endoscopic disease activity assessment in ulcerative colitis[5]. Microscopic inflammation can persist despite the appearance of endoscopically healed colonic mucosa, representing a harbinger of residual active disease[29,30]. Accordingly, observational studies have shown that persistent histological inflammation in ulcerative colitis is associated with an increased risk of clinical relapse, hospitalization, colectomy and colorectal neoplasia[30–33]. Histological remission is not yet recommended as a target of treatment in either clinical trials or practice[3], however the FDA are considering documentation of patient histological disease activity at trial inclusion and as an outcome measure in clinical trials[5]. Histological healing represents 'complete' remission in ulcerative colitis, and given its association with improved patient outcomes and reduced disease-related complications, is likely to be a future therapeutic target in clinical practice[5].

There are 26 histological activity indices in ulcerative colitis, only two of which are validated (see Supplementary information S1 (table 1))[6,34]. As a consequence, no gold standard exists for assessing histological disease activity, or for defining histological remission, in patients with ulcerative colitis. The operating characteristics of any histological scoring system in ulcerative colitis depend on the number, quality and distribution of colonic biopsy samples taken, as well as the histological features incorporated[5,35,36]. Histological features with the highest intraobserver and interobserver agreement are erosion or ulceration, and the presence and density of lamina propria neutrophil infiltrates[36,37]. Basal plasmacytosis has been associated with increased risk of ulcerative colitis relapse[30], but concordance between reporting histopathologists is poor[36,37].

Until 2015, the Riley Score (see Supplementary information S2 (table 7))[38], and the Geboes Score (see Supplementary information S2 (table 8)) were the most useful histological indices in patients with ulcerative colitis[39]. These scoring systems are widely used and each has been shown to predict clinical relapse in patients with endoscopically quiescent disease[30,38,40]. However, the operating characteristics of the scores in assessing the intended histological parameters are only partially validated and each includes histological features, such as crypt destruction, crypt architectural changes and lamina propria eosinophils, that lack reproducibility[36,37]. Two new, validated indices have been developed for use in patients with ulcerative colitis: the Nancy Index (see Supplementary information S2 (table 9))[6], and the Robarts Histopathology Index (RHI; see Supplementary information S2 (table 10))[34]. Of these indices, the Nancy Index is our recommendation for use in clinical practice, because of its simplicity, reproducibility and ease of use, whereas the RHI will probably be preferred for clinical trials, owing to well-defined responsiveness.

The Nancy Index and the RHI are validated, reproducible and responsive[6,34]. The Nancy Index has three histological descriptors (the presence of ulceration, the severity of acute inflammatory infiltrate and the severity of chronic inflammatory infiltrate) defining five grades of activity (grade 0, least severe disease, to grade 4, most severe disease) in a weighted scoring algorithm (presence of ulceration defines the most severe disease)[6]. The RHI incorporates four histological descriptors (severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium and the severity of erosions or ulceration), each of which is objectively graded between 0 and 3. Using data from a phase II trial of vedolizumab, this index has been shown to be responsive to disease activity change, and is probably a useful tool for clinical trials[41].

***Radiological assessment of disease activity.*** Imaging techniques are adjunctive to endoscopic assessment of disease activity in ulcerative colitis, and resolution of radiological abnormalities in ulcerative colitis is not considered a treatment target in clinical practice[3,42].

Abdominal radiography is indicated in patients with severe ulcerative colitis to assess the extent of faecal residue, colonic dilatation or mucosal islands (areas of preserved colonic mucosa amidst denuded ulcerated mucosa)[42]. Features on plain abdominal radiography, in particular toxic megacolon (colonic dilatation >5.5 cm), assist with prognostication of patients with severe colitis, and can guide management toward colectomy[42,43]. Plain abdominal radiography has no role in ulcerative colitis disease activity assessment outside of the acute setting, as it lacks sensitivity in evaluating mild–moderate grades of disease severity, but might identify proximal constipation as a cause of refractory distal disease[42,44].

Table 1 | **Ulcerative colitis disease activity assessment indices in clinical practice**

| Index name | Abbreviation | Range (remission threshold) | Strengths | Weaknesses | Suppl. table no. |
|---|---|---|---|---|---|
| ***Clinical*** | | | | | |
| Simple Clinical Colitis Activity Index[10] | SCCAI | 0–19 (≤2) | • Can be completed by patient<br>• Includes important factors such as urgency, incontinence and nocturnal bowel movements<br>• Reliable, valid, responsive and feasible | Not validated | 1 |
| Partial Mayo Index[11,12] | NA | 0–9 (≤1) | • Most widely used<br>• Discriminates remission from active disease | • Not validated<br>• Relies on subjective Physician Global Assessment | 2 |
| Pediatric Ulcerative Colitis Activity Index[13] | PUCAI | 0–85 (<10) | • Validated<br>• Reliable and responsive in adults<br>• Might permit less frequent endoscopic assessment | Has not been widely adopted in the adult population | 3 |
| Truelove and Witts' Severity Index[14] | TWC | | • Objective criteria for acute severe colitis<br>• Useful for prognosis | Not validated, although widely used | 4 |
| ***Endoscopic*** | | | | | |
| Ulcerative Colitis Endoscopic Index of Severity[8,9] | UCEIS | 0–8 (≤1) | • Validated<br>• Easy to use<br>• High interobserver reproducibility<br>• Accounts for 88% of variation between observers<br>• Now used in clinical trials | • No validated definition of mucosal healing or response<br>• Does not consider disease extent<br>• No thresholds for mild, moderate and severe disease | 5 |
| Mayo Clinic Index: endoscopic sub-score[11] | | 0–3 (≤1) | • Easy to use<br>• Commonly used in clinical trials and clinical practice | • Overlap of the different levels results in low interobserver agreement<br>• No validated definition of mucosal healing<br>• Subjective terms (minimal or slight friability) reduce concordance<br>• Does not consider disease extent | 6 |
| ***Histological*** | | | | | |
| Riley Score[38] | NA | 0–18 | Widely used, simple, predictive value in outcomes in ulcerative colitis | Partially validated, includes items with poor reproducibility | 7 |
| Geboes Score[39] | NA | 0.0–5.4 (<3.1) | Widely used, predictive value in outcomes in ulcerative colitis | Partially validated, includes items with poor reproducibility | 8 |
| Nancy Histological Index[6] | NA | 0–4 (0) | • Validated, responsive, good intraobserver and interobserver agreement<br>• Reliable, simple, and easy to use | Lacks data on predictive value in outcomes in ulcerative colitis | 9 |
| Robarts histopathological index[34] | RHI | 0–12 (≤6) | Validated and responsive (compared with endoscopic and QOL indices) | Lack data on predictive value in outcomes in ulcerative colitis | 10 |
| ***Radiological*** | | | | | |
| Magnetic resonance colonography simplified index[47] | MRC-S | 0–4 (0) | Simple and correlates well with endoscopic disease activity | • Not validated<br>• Cost and availability of MRI and requirement for bowel preparation | 11 |
| Segmental magnetic resonance score[48] | MR-score-S | 0–6 (0) | • Good reproducibility and interobserver agreement, correlates well with endoscopic features<br>• No need for bowel preparation | • Not validated<br>• Cost and availability of MRI | 12 |
| Bowel Ultrasound Severity Score[49] | NA | 0–3 (0) | • High concordance between US score and endoscopic disease activity<br>• Bowel US score predictive of outcomes in ulcerative colitis | • Not validated<br>• Dependent on expert and experienced ultrasonographer | 13 |
| ***Biomarkers*** | | | | | |
| C-Reactive protein | CRP | 0 to >200 mg/l (≤5 mg/l) | • Predictive of outcomes in acute severe colitis (Oxford criteria*)<br>• Widely available | • Less useful in mild disease<br>• Poor correlation with endoscopic disease activity | 14 |
| Faecal calprotectin | FC | 0 to >1,000 μg/g (<50 to <250 μg/g) | Useful for monitoring disease activity in ulcerative colitis (using ΔFC) | • Wide range of cutoff values for determining active versus inactive disease | NA |

Table 1 (cont.) | **Ulcerative colitis disease activity assessment indices in clinical practice**

| Index name | Abbreviation | Range (remission threshold) | Strengths | Weaknesses | Suppl. table no. |
|---|---|---|---|---|---|
| *Quality of life* | | | | | |
| IBD-Control 8 | NA | 0–16 (16 = best QOL) | • Easy to use<br>• No licensing fee<br>• Captures disease control from patient's perspective | Calculating total score requires the answers to be translated | 15 |
| Short Inflammatory Bowel Disease Questionnaire[77] | SIBDQ | 10–70 (70 = best QOL) | • Easy to use<br>• Results correlate to the longer 32-item IBDQ<br>• Widely accepted<br>• Validated<br>• Reproducible and responsive | Licensing fee required for use | 16 |
| Crohn's Ulcerative Colitis Questionnaire-8 (REF. 77) | CUCQ-8 | 0–8 (0 = best QOL) | • Easy to use<br>• Results correlate with longer 32-item questionnaire<br>• Validated<br>• No licensing fee | Calculating total score requires each question to be translated into a subscore out of 1 | 17 |

For a full list of identified indices, please see Supplementary information S1 (table 1). *Oxford criteria defined as more than eight stools per day or 3–8 stools per day and plasma CRP concentration >45 mg/l. FC, faecal calprotectin; NA, not applicable; QOL, quality of life; US, ultrasonography.

Cross-sectional imaging in ulcerative colitis is predominantly performed to assess complications of disease, to exclude small bowel inflammation and Crohn's disease as a differential diagnosis, and to assess colonic disease when stenosis or severe comorbidities limit the utility of colonoscopy[17,42]. CT is associated with radiation exposure and has little role in assessing disease activity in ulcerative colitis; inflammation as assessed by CT correlates only moderately with endoscopic colonic inflammation (sensitivity 74%)[45], and use of CT infrequently leads to a change in clinical management[46].

MRI and bowel ultrasonography demonstrate good sensitivity for evaluating disease activity and extent in ulcerative colitis without associated ionizing radiation, and represent the most useful techniques for assessing luminal disease activity in ulcerative colitis when patient or disease-related factors render endoscopic examination infeasible[42] (see Supplementary information S1 (table 1)). Two scoring systems have been described for the assessment of colonic inflammation in ulcerative colitis with MRI, one with bowel preparation and one without[47,48]. A simplified magnetic resonance colonography index (MRC-S), based on four radiological features (gadolinium contrast uptake, presence of oedema, lymphadenopathy, and presence of the comb sign (hypervascularity of the mesentery)), correlates significantly with endoscopy as a reference standard ($r = 0.81$, $P < 0.001$) (see Supplementary information S2 (table 11))[47]. The presence of one of these features (MRC-S ≥1) has high sensitivity and specificity for active disease (87% and 88%, respectively). Using MRI and diffusion-weighted imaging (a technique used to evaluate cellular movement within a tissue voxel) without bowel preparation, a segmental MRI score (MR-score-S) of >1 demonstrated a sensitivity and specificity of 89% and 86%, respectively, for active disease (see Supplementary information S2 (table 12))[48]. The MR-score-S is calculated from six radiological features, including the presence of intestinal ulceration, parietal oedema and differentiation between bowel wall layers. The MRC-S might be a simpler score to use in clinical practice as it includes fewer variables, however the MR-score-S is benefited by not requiring bowel preparation.

Disease assessment by bowel ultrasonography has been shown to correlate with colonic inflammation in ulcerative colitis, although performance is operator-dependent and might not be generalizable[42]. An ultrasonography scoring system proposed by Parente *et al.*[49] is useful in clinical practice and incorporates measurement of colonic wall thickness with the degree of intramural blood flow (Supplementary information S2 (table 13))[49,50]. This score is concordant with the severity of endoscopically assessed inflammation in moderate-to-severe ulcerative colitis (weighted kappa 0.76–0.90), and is responsive to disease activity change after steroid therapy, predicting disease outcomes at 15 months[49]. Bowel ultrasonography is a helpful adjunct to endoscopy in ulcerative colitis, as it is a cheap, non-invasive and non-irradiating means of monitoring disease activity and extent, and is convenient to patients given that it can be readily performed in the clinical setting[51]. However, expertise in bowel ultrasonography might be limited in many centres and MRI might be the preferred imaging modality.

***Biomarkers to assess disease activity.*** Biomarkers are a useful adjunct to endoscopy for assessing disease activity in ulcerative colitis[3], in that they are noninvasive and yet provide objective evidence of inflammation beyond clinical assessment alone. The most useful biomarkers in ulcerative colitis are plasma levels of C-reactive protein (CRP) and faecal calprotectin.

CRP is a useful marker in clinical practice for predicting disease outcomes at the time of diagnosis of ulcerative colitis, and in patients with severe ulcerative colitis. Plasma CRP levels have been shown to

Table 2 | **Crohn's disease activity assessment indices in clinical practice**

| Index name | Abbreviation | Range (remission threshold) | Strengths | Weaknesses | Suppl. table no. |
|---|---|---|---|---|---|
| ***Clinical*** | | | | | |
| Crohn's Disease Activity Index[81] | CDAI | 0–600 (<150) | Widely used | • Complex calculation involving a 7-day diary<br>• High variability<br>• Low contribution to total score for perianal disease | 18 |
| Harvey-Bradshaw Index[83] | HBI | 0–50 (≤4) | • Simpler, less cumbersome<br>• Does not require a 7-day diary<br>• Correlates well with CDAI | Low contribution to total score for perianal disease | 19 |
| Perianal Crohn's Disease Activity Index[85] | PDAI | 0–19 | Easy to use | Does not allow documentation of fistula severity | 20 |
| ***Endoscopic*** | | | | | |
| Crohn's Disease Endoscopic Index of Severity[88] | CDEIS | 0–44 (<3) | • Current gold-standard<br>• Reproducible and validated<br>• Extensively used in clinical trials | • Complex<br>• Cumbersome to use in clinical practice<br>• Needs experience and training<br>• No validated definition of mucosal healing<br>• No correlation with CDAI | 21 |
| Simple Endoscopic Score for Crohn's disease[89] | SES-CD | 0–56 | • Simplified version of the CDEIS<br>• Validated<br>• Performance correlates well with CDEIS | • Only slightly less complex than CDEIS<br>• Validated against CDEIS in only one study<br>• No validated definition of mucosal healing<br>• No correlation with CDAI<br>• Less frequently used in clinical trials | 22 |
| Rutgeerts' Post-operative Endoscopic Index[90,91] | NA | i0 to i4 (<i2) | • Standard for evaluating post-operative recurrence<br>• Strong prognostic relevance<br>• Widely used in clinical practice and trials | • Discriminative ability unclear, especially of the i2 domain<br>• Only for use after ileocolic resection | 23 |
| ***Histology*** | | | | | |
| Colonic and Ileal Global Histologic Disease Activity Score[92,96] | CGHAS<br>IGHAS | 0–16 | Takes into account patchy disease activity | • Not validated<br>• No data on reproducibility<br>• Inherent issues with histological scoring in Crohn's disease | 24 |
| ***Radiology*** | | | | | |
| Magnetic Resonance Index of Activity[100–102] | MaRIA | • Segmental mucosal healing <7<br>• Segmental ulcer healing <11 | • Validated<br>• Good intraobserver and interobserver concordance<br>• Correlates well with endoscopy<br>• Responsive index | Might be best used in clinical trials rather than clinical practice | 25 |
| Van Assche MRI-Based Score for Severity of Perianal Crohn's Disease[104] | NA | 0–24 | • Validated<br>• Good interobserver concordance | Utility in clinical practice might be limited due to complexity | 26 |
| Limberg scoring system for bowel ultrasonography[109] | Limberg Score | 0–4 | Widely used | Not validated | 27 |
| ***Biomarkers*** | | | | | |
| C-Reactive protein | CRP | 0 to >200 mg/l (≤5 mg/l) | • Useful for monitoring disease activity in Crohn's disease<br>• Predictive of relapse whilst on therapy and following withdrawal | Modest correlation with endoscopic disease activity (especially ileal disease) | NA |
| Faecal calprotectin | FC | 0 to >1,000 μg/g (<50 to <250 μg/g) | Useful for monitoring disease activity in Crohn's disease (using ΔFC) | • Wide range of cutoff values for determining active versus inactive disease<br>• Lacks sensitivity and specificity for endoscopy disease activity (especially ileal disease) | NA |

Table 2 (cont.) | **Crohn's disease activity assessment indices in clinical practice**

| Index name | Abbreviation | Range (remission threshold) | Strengths | Weaknesses | Suppl. table no. |
|---|---|---|---|---|---|
| *Quality of life* | | | | | |
| IBD-Control 8 | NA | 0–16 (16 = best QOL) | • Easy to use<br>• No licensing fee<br>• Captures disease control from patient's perspective | Calculating total score requires the answers to be translated | 15 |
| Short Inflammatory Bowel Disease Questionnaire[77] | SIBDQ | 10–70 (70 = best QOL) | • Easy to calculate total score<br>• Results correlate to the longer 32-item IBDQ<br>• Widely accepted<br>• Validated<br>• Reproducible and responsive | Licensing fee required for use | 16 |
| Crohn's Ulcerative Colitis Questionnaire-8 (REF. 77) | CUCQ-8 | 0–8 (0 = best QOL) | • Easy to use<br>• Results correlate with longer 32-item questionnaire<br>• Validated<br>• No licensing fee | Calculating total score requires each question to be translated into a subscore out of 1 | 17 |

For a full list of identified indices, please see Supplementary information S1 (table 2). FC, faecal calprotectin; NA, not applicable; QOL, quality of life.

predict the risk of colectomy in patients with ulcerative colitis[52–57]. The Oxford criteria (more than eight stools per day or 3–8 stools per day and plasma CRP concentration >45 mg/l (>428.6 nmol/l)) predicts an 85% risk of colectomy during the period of that hospital admission after 3 days of intravenous corticosteroid therapy for acute severe colitis (Supplementary information S2 (table 14))[55]. These criteria provide an indication of the need for medical rescue therapy, either surgical or medical, such as cyclosporine or infliximab[1]. A scoring system involving plasma CRP levels, extent of disease and serum haemoglobin levels at the time of diagnosis of ulcerative colitis has been shown to predict the risk of acute severe colitis within 3 years[58,59]. Although a reduction in plasma CRP level has been shown to correlate with treatment response, CRP concentration is less useful in quiescent, mild, or moderately active ulcerative colitis, as it correlates weakly with endoscopic disease activity[60].

Faecal calprotectin level is a useful noninvasive tool for monitoring disease activity over time. This biomarker has been shown to predict persistent inflammation[61–63] and risk of relapse[64–68] in patients with ulcerative colitis, and is responsive to up-titration of therapy[69]. However, a single faecal calprotectin cutoff value to predict endoscopically assessed disease remission is not credible, because a broad range of cutoff values have been described (ranging from <50 µg/g to <250 µg/g), mostly with only moderate sensitivity and specificity for disease activity[70,71]. Faecal calprotectin level varies widely between stools on a daily basis in patients with active ulcerative colitis[72], and readings can be influenced by variability inherent in the assay[73]. The clinical utility of faecal calprotectin levels for an individual patient lies in monitoring the change of this biomarker over time (Δfaecal calprotectin); rising faecal calprotectin levels prompt endoscopic evaluation and guide therapy. No useful disease activity scoring system based upon faecal calprotectin levels exists.

***QOL in ulcerative colitis.*** Measurement of QOL is important in the assessment of IBD because it evaluates the patient's social and emotional well-being, behaviour and attitudes, and (to some extent) physical disease-related symptoms. QOL assessments are now an important component of medical decision-making, as improving QOL is the ultimate goal of therapy and value-based health care[74]. An international working group (ICHOM; International Consortium for Health Outcomes Measurement) is developing a standard set of measures in IBD, and are due to report in late 2016. Nevertheless, most disease-specific QOL indices for IBD (such as the IBDQ[75]) are lengthy and time-consuming, often precluding their use in clinical settings. The challenge is to find a measure of QOL that is fast to complete, valid, internally reliable, reproducible, responsive and acceptable to patients.

The questionnaire that we recommend for use in clinical practice is the IBD-Control (Supplementary information S2 (table 15))[76]. IBD-Control is the first patient-related outcome measure to capture disease control from the patient's perspective, using a simple set of generic terms applicable to both ulcerative colitis and Crohn's disease. Summary scores show strong validity versus more complex QOL questionnaires, disease activity scores and Physician Global Assessment[76]. A limited version, IBD-Control 8, includes the questionnaire elements 1a, 1b and 3a–3f, with the total score being calculated as follows: the 'worst' response is scored 0 (being either a 'Yes' or 'No' depending on the question), 'not sure' is scored 1, and the 'best' response (being either a 'Yes' or 'No' depending on the question) is scored 2. For IBD-Control 8, if all responses are favourable, the maximum score is 16, equating to the best disease control. This questionnaire is free to use and (unlike the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)) not subject to license. Its simplicity, the fact that it is completed by patients and its adoption by international groups (ICHOM and the UK IBD Registry) are other advantages.

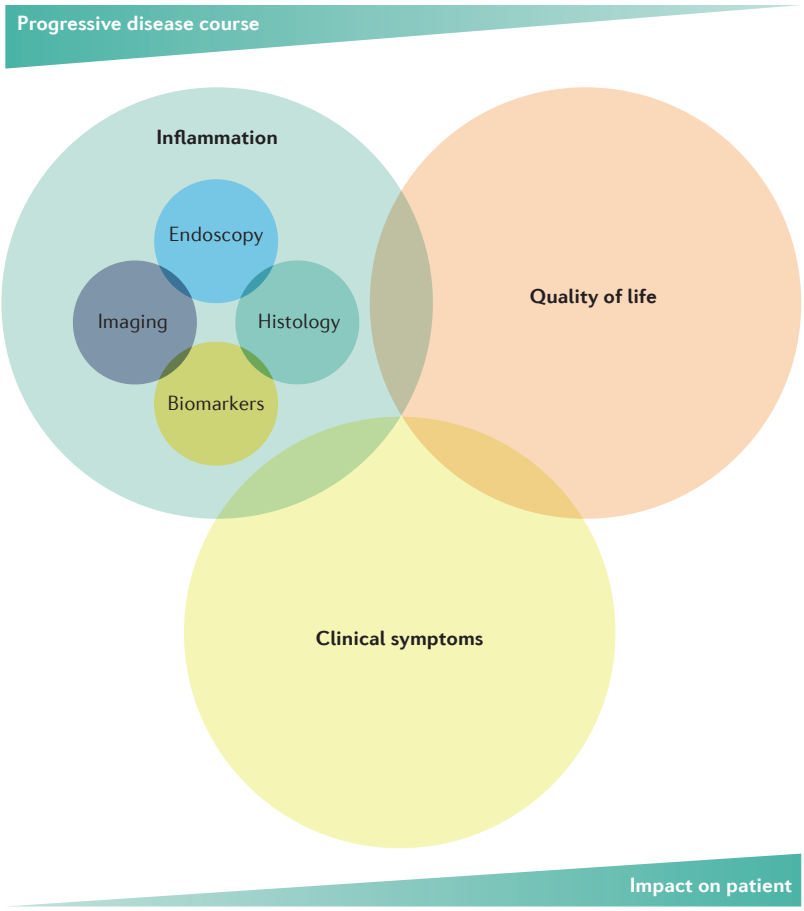


Figure 1 | **Domains of disease activity assessment.** Overlapping domains of disease activity assessment in IBD: inflammation, clinical symptoms, and quality of life. Inflammation can be assessed by endoscopy, histology, imaging, and/or biomarkers.

Other QOL questionnaires used in clinical practice include the SIBDQ[77] (see Supplementary information S2 (table 16)) and the Crohn's Ulcerative Colitis Questionnaire-8 (CUCQ-8)[78] (see Supplementary information S2 (table 17)). These short questionnaires (the SIBDQ has 10 questions and the CUCQ-8 has eight questions) explain >95% of the variance of their respective 32 question versions (the IBDQ and the CUCQ-32).

The SIBDQ gives results similar to the full 32-item IBDQ[75], is widely accepted and has been validated in different populations[77]. Scores generated by this index range from 10–70, which correspond to poor-to-good QOL, respectively. This questionnaire is reproducible and responsive to changes in disease severity[79], but there is a licensing fee attached to its use.

The CUCQ-8, developed from the CUCQ-32, was designed for use in clinical practice, both for patients with stable disease as well as those with acute IBD. Scores range from 0–8, which correspond to good-to-poor QOL, notably the opposite way around to the SIBDQ and IBD-Control. The CUCQ-8 requires no licensing fee for its use and is the only QOL index that has been used as a primary end-point in a randomized clinical trial (CONSTRUCT) in ulcerative colitis[80].

## Crohn's disease

***Clinical assessment of disease activity.*** The Crohn's Disease Activity Index (CDAI, see Supplementary information S2 (table 18)) is the most commonly used tool for assessing disease response to treatment in Crohn's disease clinical trials[81]. However, calculation of the CDAI is complex and involves eight items, including haematocrit, physical examination (abdominal examination and weight measurement) and a 7-day patient diary (to record number of soft stools, abdominal pain and general well-being), so it is rarely used in clinical practice. Interobserver variability between CDAI scores is high, even among experienced physicians[82]. The remission target is a CDAI <150 (REF. 3).

The Harvey–Bradshaw Index (HBI)[83] (see Supplementary information S2 (table 19)) is simpler to use than the CDAI, making data collection easier[84]; moreover, scores from this index have been shown to correlate closely with CDAI scores[84]. The HBI has five variables (including general well-being, severity of abdominal pain, number of liquid stools, presence of abdominal mass and presence of complications) and items are scored based upon the previous day, so it does not require prospective 7-day data collection. The remission target for this index is an HBI score ≤4 (REF. 3).

The CDAI is not an accurate instrument to assess the activity of perianal Crohn's disease or Crohn's disease with other fistulae, because the presence of perianal disease or other fistulae (which can be terribly disabling for the patient) only accounts for a small proportion of the total score. The perianal Crohn's disease activity index (PDAI)[85] is currently the gold standard for evaluating the severity of perianal disease (see Supplementary information S2 (table 20)). This index comprises five items: discharge; pain; restriction of sexual activity; type of perianal disease; and degree of induration. Discharge, pain and degree of induration seem to be more commonly used in clinical practice.

***Endoscopic assessment of disease activity.*** In contrast to ulcerative colitis, mucosal healing in Crohn's disease might reasonably be considered a minimal (rather than the ultimate) therapeutic goal, because Crohn's disease is transmural. The benefits of achieving mucosal healing include decreased need for corticosteroids, decreased hospitalization, sustained clinical remission and decreased need for surgery[21,23,24].

Complete resolution of all endoscopically visible ulcers is a simple definition of mucosal healing for clinical practice and has been recommended by international consensus bodies[86]. Nevertheless, the binomial definition (presence or absence of ulcers) is currently unvalidated, difficult to achieve and crude, because it does not allow quantification of improvement of mucosal inflammation[87].

Validated endoscopic indices have been developed for the assessment of Crohn's disease activity (see Supplementary information S1 (table 2)). The Crohn's Disease Activity Index of Severity (CDEIS)[88] is the most commonly used tool in clinical trials, whereas the Simple Endoscopic Score for Crohn's Disease (SES-CD)[89]

is a slightly simplified version of the same index. Rutgeerts' Post-operative Endoscopic Index[90] is used for estimating the risk of disease recurrence after ileocolic resection for Crohn's disease.

The CDEIS examines four endoscopic variables (the presence of deep ulceration, superficial ulceration, the length of ulcerated mucosa and the length of diseased mucosa) in each of the following locations: rectum, sigmoid and left colon, transverse colon, right colon and ileum (see Supplementary information S2 (table 21)). Although the CDEIS is a reproducible and validated index, it is complex, requiring over 30 entries to reach the final score[88]. As with all indices, implementation requires both training and experience, but the complexity of the CDEIS makes it cumbersome to use in clinical practice. The remission target is a total CDEIS score of <3 (REF. 3).

The SES-CD (see Supplementary information S2 (table 22)) correlates well with the CDEIS, but is only slightly less complex, requiring over 20 entries to complete the total score, and therefore also being difficult to complete in routine clinical practice[89]. Endoscopic features (ulcer size, extent of ulcerated surfaces, extent of surfaces with any other lesions and stenosis) are scored from 0 to 3 depending on severity or extent in each of the five colorectal locations assessed by the CDEIS. An SES-CD score of 0 equates to absence of ulcers.

Rutgeerts' Post-operative Endoscopic Index (see Supplementary information S2 (table 23)) determines the severity of endoscopic disease recurrence at the anastomosis and in the neoterminal ileum after ileocolic resection[90,91]. This index consists of five grades of increasing disease recurrence severity, between i0 and i4, as assessed by the number and nature of ulcers in the distal ileum. The Post-operative Endoscopic Index has gained popularity because its assessment of disease recurrence predicts symptom recurrence. The remission target is a grade <i2 (REF. 3).

For endoscopic reporting of Crohn's disease activity in clinical practice, we recommend using the SES-CD, or at the very least reporting, for each bowel section, the presence or absence of ulcers, stenosis and the proportion of surface area affected. For postoperative assessment of disease recurrence following ileocolic resection, we recommend Rutgeerts' score.

***Histological assessment of disease activity.*** Histological disease activity assessment in Crohn's disease is difficult because inflammation is discontinuous, transmural and can exist beyond the reach of the endoscope[5,35]. Targeted mucosal biopsies can be used in an attempt to limit sampling error, but transmural inflammation can only be assessed in specimens obtained during surgical resection. Thus, histological scoring systems for mucosal biopsy samples are challenging to develop and to use in practice[92]. Nevertheless, microscopic inflammation can persist in biopsy samples from tissue that appears quiescent when observed endoscopically[29,93,94], and some limited evidence suggests that presence of microscopic inflammation is associated with increased rates of clinical relapse, stricture formation and surgery[29].

Several histological scoring systems have been proposed for assessing Crohn's disease activity (see Supplementary information S1 (table 2)), the best known of which are the Colonic and Ileal Global Histologic Disease Activity Scores (CGHAS and IGHAS) (see Supplementary information S2 (table 24))[92,95,96]. Due to the complexity of these scoring systems and lack of evidence correlating histological disease activity with disease outcomes in Crohn's disease, we do not recommend routine use of such scoring in clinical practice. Rather, the presence of histological inflammation in endoscopically quiescent disease should caution against de-escalation of therapy[5].

***Radiological assessment of disease activity.*** Given that transmural inflammation in Crohn's disease can extend beyond the reach of endoscopy, imaging has an important role in assessing disease activity[42]. Imaging also enables evaluation of the complications of Crohn's disease, including stricturing disease, fistulae and abscesses[97]. MRI is the preferred modality for assessing complex complications of Crohn's disease and the presence and severity of perianal fistulae in particular. MRI and ultrasonography are the preferred modalities for assessing luminal disease activity and strictures in Crohn's disease[42].

Although the overall accuracy of CT, ultrasonography and MRI for assessing luminal disease activity in Crohn's disease is similar[42,97], radiation exposure limits the use of CT, which is particularly relevant to younger patients who might be exposed to a substantial cumulative radiation dose over their disease course. CT is therefore not the first-choice imaging technique for assessing disease activity in Crohn's disease; when MRI and ultrasonography are unavailable, low-dose CT can be an alternative[98]. Plain film radiography and barium contrast studies now have little role in Crohn's disease, due to their limited sensitivity for assessing activity in comparison to MRI, CT and ultrasonography[42].

Intestinal MRI requires rapid image acquisition and luminal distension for accurate assessment of disease distribution and activity, which can be achieved with a neutral contrast agent delivered via enterography or enteroclysis[99]. Among the available scoring systems (see Supplementary information S1 (table 2)), the Magnetic Resonance Index of Activity (MaRIA) is best-validated for assessment of disease activity in Crohn's disease and we recommend its use in clinical practice (see Supplementary information S2 (table 25))[100,101]. The MaRIA correlates well with CDEIS scores assessed by ileocolonoscopy ($r = 0.83$, $P < 0.001$)[100], and has been shown to be reliable in assessing disease response to therapy in Crohn's disease (90% accuracy for detecting ulcer healing and 83% accuracy for detecting endoscopic remission as assessed using CDEIS)[102]. Although MRI is expensive in comparison to other imaging modalities, the technique is cost-effective compared with CT in patients younger than 50 years old, based on quality-adjusted life-year data factoring in radiation exposure[103].

MRI is a widely used and accurate tool to assess the presence and severity of perianal fistulizing disease[42]. The Van Assche MRI-based score for assessing

the severity of perianal Crohn's disease[104], based on the classification of perianal fistulae developed at St. Mark's Hospital, Harrow, UK[105], is useful for formal assessment of response of fistulizing disease to therapy (see Supplementary information S2 (table 26)). The score incorporates criteria relating to the local extension of fistulae, as well as active inflammation, and it demonstrates good interobserver agreement and responsiveness following anti-TNF therapy[104]. The score is useful for clinical trials, but has less utility in clinical practice due to its relative complexity compared with other scores.

Doppler ultrasonography is helpful in assessing disease activity, based on intestinal wall thickness and intensity of blood flow[106–108]. Although there are several scoring systems for ultrasonographic assessment of disease activity (see Supplementary information S1 (table 2)), the most widely used of which is the Limberg Score (see Supplementary information S2 (table 27))[109], none of these indices have been validated. Small studies ($n = 24–110$) have shown that ultrasonography is responsive to improvements in disease activity following therapy[110–113], and might be useful for disease monitoring after surgical resection[114,115]. Point-of-care ultrasonography has also been shown to influence clinical decision-making, particularly when patients are asymptomatic but ultrasonography reveals evidence of active disease[116]. Despite promising data, the use of ultrasonography remains limited by the availability of an experienced bowel sonographer. Outside Europe, ultrasonography has been less commonly used, with cross-sectional imaging (CT and MRI) favoured for its reproducible protocols and capacity for archival images. However, as clinician awareness of the imperative for close monitoring of IBD disease activity as a part of a 'treat to target' management strategy grows, ultrasonography is becoming increasingly appealing as a cheap and noninvasive tool, and its use is burgeoning in countries such as Australia[51].

***Biomarkers to assess disease activity.*** Biomarkers are a noninvasive adjunct to endoscopy and cross-sectional imaging for monitoring disease activity in Crohn's disease[3]. Plasma levels of CRP and faecal calprotectin are the most useful biomarkers in clinical practice.

An improvement in plasma CRP levels (that is, a reduced plasma concentration of CRP) has been shown to correlate with a clinical therapeutic response in Crohn's disease[117–123]. An elevated plasma CRP level predicts clinical relapse in Crohn's disease[124,125], in both asymptomatic patients[126] as well as following withdrawal of therapy[127–129]. Higher plasma CRP levels before treatment have been shown to predict an increased likelihood of maintenance of remission following anti-TNF therapy[130]. However, CRP level correlates only modestly with endoscopic disease activity in Crohn's disease[70,71,131–134], and a normal plasma CRP concentration has been reported in patients with active disease, particularly those with predominantly ileal rather than predominantly colonic pathology[135–137]. The converse is also true, as an elevated CRP level does not always correlate with active disease[131]. Plasma CRP concentration is therefore not a target of therapy, but rather a tool to monitor inflammation to guide the necessity of radiological or endoscopic activity assessment.

Faecal calprotectin level has been shown to correlate with endoscopic and MRI-based assessment of disease activity in Crohn's disease[132,138–140], and to predict disease relapse[65,68,141,142]. Levels of faecal calprotectin are also useful in monitoring disease activity following initiation of therapy[123], as well as in the postoperative Crohn's disease setting[137,143]. However, faecal calprotectin concentration is less accurate for ileal than colonic disease, and can be normal even in the presence of large ulcers[144]. Faecal calprotectin level cutoff values for predicting remission vary widely between studies (from <50 μg/g to <250 μg/g) and are only moderately predictive for individual patients[71] unless a stringent cutoff value is used (such as <50 μg/g), which comes at the expense of sensitivity or unnecessary investigations. Thus, as for ulcerative colitis, it seems that the change in faecal calprotectin level, rather than the absolute level in an individual patient, is best used in clinical practice to aid treatment decision-making.

***QOL.*** The three QOL questionnaires that we recommend for use in clinical practice and the rationale behind these choices are the same as those used in ulcerative colitis: either IBD-Control[76] (see Supplementary information S2 (table 15)), the SIBDQ[77] (see Supplementary information S2 (table 16)) or the CUCQ-8 (REF. 77) (see Supplementary information S2 (table 17)).

## Conclusions

The overarching goal of therapy in IBD is to modify the disease course to improve QOL and avoid disability, whilst balancing the risks associated with therapy[145,146]. To reach this goal, therapy must be directed to achieve resolution of both objective inflammation and clinical symptoms, as well as normalization of QOL. This 'treat to target' approach requires a clinician to look beyond clinical symptoms and to assess disease activity as objectively as possible. This method enables a composite appraisal of the measurable burden of inflammation, the burden of disease on the patient and the cumulative complications of disease over its course[146].

Despite the disparity between clinical and objective measures of inflammation in IBD, both are important when assessing disease activity. The objective burden of inflammation denotes risk of negative disease outcomes in IBD, whereas clinicians realize that symptoms and QOL are most important to patients. Among the confusing myriad of disease activity indices within each domain of assessment, this Review has collected and appraised the most practical and relevant indices for clinical practice, augmented by supplementary tables to provide a comprehensive overview. Current indices need to be validated according to well-established statistical criteria. The metrics will help with clinical decision-making and encourage physicians to strive for appropriate treatment targets that can be expected to improve outcomes for patients with IBD.

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**Author contributions**
All authors contributed equally to this article.

**Competing interests statement**
A.J.W. has served as an advisory board member for AbbVie, Ferring, Janssen-Cilag, Hospira and Takeda. She has received honoraria for speaking from AbbVie, Ferring, Janssen-Cilag and Shire, and has received grants for support of research from AbbVie, Ferring, Janssen-Cilag and Shire. R.V.B. has received conference attendance support from Ferring, Janssen, and Takeda, and honoraria for speaking from Abbvie, Janssen-Cilag and Shire, and S.P.L.T. has received grants for research support from AbbVie, Lilly, Norman Collison Foundation, UCB and Vifor. He has received consulting and/or speaker fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cosmo, Ferring, Giuliani SpA, GlaxoSmithKline, Lilly, MSD, Neovacs, Novartis, Norman Collison Foundation, Novo Nordisk, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, TopiVert, UCB, VHsquared, Vifor, and Warner Chilcott.

**Review criteria**
A literature search was performed to evaluate available disease activity assessment indices within each of the prescribed domains; clinical, endoscopic, histologic and radiologic assessment, biomarkers and quality of life (see Supplementary information S3 (box) online).

**FURTHER INFORMATION**
**ICHOM:** http://www.ichom.org

**SUPPLEMENTARY INFORMATION**
**See online article:** S1 (tables) | S2 (tables) | S3 (box)
**ALL LINKS ARE ACTIVE IN THE ONLINE PDF**