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Endoscopy and cross-sectional imaging for assessing Crohn's disease activity

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Abstract

Crohn's disease (CD) is principally characterized by chronic and recurrent inflammation of the gastrointestinal tract, most commonly found in the ileo-colonic region. The chronicity and severity of intestinal inflammation together contribute to progressive, cumulative, deep, transmural intestinal damage, including stricturing, obstruction, abscesses, and fistulae. Both intestinal inflammation and its chronic complications result in a range of symptoms subsequently leading to patient presentations with diarrhea, abdominal pain, and anemia related to intestinal blood loss. Measuring disease activity and severity are essential for decision of treatment intensity early in the disease course and longitudinal monitoring of therapeutic efficacy. This review will summarize the transition from subjective symptoms driving disease activity indices, into increasingly objective and quantitative measures of intestinal injury by direct mucosal assessment (endoscopy), cross-sectional imaging, and surrogate biomarkers. Specific commentary on intestinal stricture and perianal fistula assessment and management are presented in accompanying sections of this series.

Keywords

Crohn's disease; disease activity; therapeutic monitoring; MR-enterography; CT-enterography; CDEIS; SES-CD; CDAI; MaRIA

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The Emergence of Mucosal Injury Assessment

Historically, disease severity was assessed by patient reported symptoms, formalized in the 1970s as the Crohn's disease activity index (CDAI)¹. The CDAI is a weighted score of the number of bowel movements, use of anti-diarrheals, degree of abdominal pain, overall well-being, extra-intestinal manifestations, also including an exam for an abdominal mass and a hematocrit measurement. Clinical remission is defined by a CDAI of <150, while clinical response is defined as a reduction of 70–100 points following treatment². The Harvey Bradshaw index (HBI) is a simplified symptom assessment that is strongly correlated to the CDAI^{3,4}. Despite being used by governmental medical authorities for over 30 years as the primary end point of therapeutic trials, the CDAI fails to predict disease behavior and key clinical outcomes in CD. Treating to an endpoint of symptom relief and CDAI improvement resulted in no reduction in the incidence of surgery between 1950 and 2000^{5,6}. In addition, D'Haens and colleagues showed that interval development of structural intestinal damage often occurs in asymptomatic patients⁷. Despite their immediate impact on quality of life, it became clear that symptom-centered activity measures were insufficient to predict disease course and a therapeutic response that improves disease natural history.

Mucosal injury provides an excellent summative reflection of CD activity. While now intuitive, successive studies over 20 years established that the degree of mucosal injury is directly correlated with the future need for corticosteroids, hospitalization, and major abdominal surgery^{8–10}. Perhaps the cornerstone in establishing mucosal injury and healing as the dominant measure of CD activity are studies demonstrating that resolution of mucosal injury indeed improves clinical outcomes. In a study of 214 patients using infliximab, patients achieving mucosal healing less frequently required hospitalization or surgery compared to those with persistent mucosal injury (59% vs. 42%, $p=0.0018$)¹¹. The CDAI is poorly correlated with mucosal injury assessed by ileocolonoscopy and other surrogate markers of inflammation in CD (Modigliani 1990). In the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial of combined thiopurine and anti-TNF therapy in CD, post-hoc analysis revealed that remission by CDAI (<150) poorly predicted mucosal healing, with a PPV of 0.53 and NPV of 0.65¹². Considering the poor prognostic performance and capabilities to evaluate therapeutic effects, the use of the CDAI and symptom-based assessments are very likely to be replaced by direct or surrogate measures of mucosal injury as primary treatment endpoints in future CD clinical trials.

Ileocolonoscopy as a Disease Activity Assessment in Crohn's Disease

Our most familiar method for assessing mucosal injury is by direct inspection using ileocolonoscopy. Several endoscopic features are associated with CD activity. Mild mucosal injury is characterized by frank mucosal erythema and edema, with increasing activity demonstrated by progressive damage from aphthous ulcers, to shallow ulcers, and ultimately to deep ulcerative lesions. The degree of surface involvement and the presence of intestinal stenosis must also be considered in determining total disease burden. Standardized reporting of qualitative endoscopic disease severity features resulted in the Crohn's Disease Endoscopic Index of Activity (CDEIS)¹³. The CDEIS divides the colon and ileum into 5 segments: rectum, sigmoid and left colon, transverse colon, right colon, and ileum. In a

development study of 133 colonoscopies with a separate validation set of 103 patients, logistic regression identified the presence of deep ulceration (12 points), shallow ulceration (6 points), and the percentage of the diseased surface in each segment to best model the global evaluation of lesion severity. The range of the CDEIS is 0 (no evidence of activity) to 44 (deep ulceration present in all surfaces). An alternative tool, Simple Endoscopic Score for Crohn's disease (SES-CD), was developed as a less complex instrument that reduced inter-observer variation and the number of calculations needed to encourage more routine use (Figure 1)¹⁴. Total SES-CD score range is 0 to 56, with each section ranging from 0–12 points. The SES-CD and CDEIS are near perfectly correlated with each other with a correlation coefficient of $r=0.938$ ($p<0.0001$), which is expected as the SES-CD was developed using the CDEIS as a reference¹⁵. Other scoring systems have been proposed, including the Frosli score which grades mucosal appearance on a 0–2 scale based on the degree of erythema, granularity, friability, and frank bleeding, though this has not gained wide use¹⁶.

The score ranges and criteria defining CD severity grades are often arbitrarily defined in clinical studies. Suggestions of cut-off values defining “sufficient” endoscopic response using the CDEIS included reductions of 3, 4, or 5 points, or the percent reduction from the baseline score^{17–19}. SES-CD score definitions also vary, though typically including remission as 0–2, mild 3–6, moderate 7–15, and severe as 16, though the presented reference values have not been validated (Table 1)^{7,20}. The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) recently sponsored a 14-member expert panel to review existing data on endoscopic outcome measurements and cutoffs²¹. Using a Delphi-voting process on each potential criteria, the highest ranking consensus criteria for endoscopic remission criteria was an SES-CD of 0–2, with endoscopic response defined as a >50% reduction of baseline SES-CD or CDEIS. The capacity to pair visual and histologic assessments are a key strength of ileocolonoscopy; however the usefulness of histologic grading of disease severity remains debated in Crohn's disease^{12,22}. The Geboes system, along with other histologic assessment indices, has been used in clinical studies (mostly ulcerative colitis); however reliable incremental histologic changes have not been reliably linked with clinical outcomes. At this juncture, histology is not a key therapeutic endpoint in clinical practice²³.

CDEIS and SES-CD scores have also been shown to predict clinical outcomes in CD. A post-hoc analysis of SONIC found a reduction from baseline CDEIS or SES-CD of >50% after 26 weeks of treatment was more predictive of steroid-free remission at 1 year compared to all other endoscopic score cut-off values tested¹². Additionally, a >50% reduction in CDEIS or SES-CD predicted steroid-free remission at 1 year as well as complete mucosal healing (sensitivity and specificity 74% and 48% vs. 56% and 65%, respectively). Supporting similar clinical outcomes resulting from partial and complete healing, a retrospective study found that future need for bowel resection was lower in patients achieving at least partial mucosal healing compared to those without change (14.0% vs. 38.4%). However, rates of bowel resection was not significantly different in those achieving complete healing versus partial healing (14.0% vs. 14.1%, respectively)⁸. These studies both support the concept that at least partial mucosal healing is associated with

improved clinical outcomes and calls into question whether achieving complete mucosal healing provides added clinical benefit.

Endoscopic Evaluation of Post-Operative Disease Recurrence

Seminal work connecting mucosal injury to clinical outcomes stemmed from examinations of postoperative CD behavior by Rutgeerts and colleagues in the 1980s. In what came to be known as the Rutgeerts' score, the extent of ulceration proximal to the anastomosis at one year following resection was found to be predictive of symptomatic recurrence and need for future surgery²⁴. Post-operative symptoms recurrence was 8.6% in those with 5 or less aphthous ulcers (i0–i1), 27% in those with >5 aphthous ulcers (i2), 75% in those with diffuse ileal ulceration (i3), and 100% in those with diffuse ulceration with nodules and luminal narrowing (i4) over the 8 year prospective follow up period (Figure 2). The Rutgeerts' score has been used in the majority of clinical trials examining post-operative patients. However, similar to the CDEIS and SES-CD, there is no agreement on what constitutes sufficient mucosal injury to denote clinically meaningful recurrence. Most studies have used i2 to denote meaningful disease recurrence, though cut-offs of i3, i4, or >i0 have also been used^{25–27}. Debate continues regarding whether i2 lesions at the anastomosis itself compared to those proximal to anastomosis are equally predictive of clinical outcomes²⁸. The IOIBD expert consensus panel voted unanimously to define post-operative remission as Rutgeerts' score of i1²¹.

Limitations of Ileocolonoscopy for Disease Activity Assessment

Ileocolonoscopy provides excellent mucosal injury assessment, yet its invasiveness, cost, and inability to survey lesions proximal to the distal most portions of the ileum are core limitations. Further, endoscopic scoring systems are based on qualitative and potentially subjective elements, raising concerns over reproducibility²⁰. As a result, it has become commonplace to use expert central readers to grade activity in therapeutic clinical trials. Khanna and colleagues compared the endoscopic scores of 50 colonoscopies between 4 expert blinded central readers to determine the reliability of these measures²⁹. Intra-observer agreement as very good with both SES-CD and CDEIS with intraclass correlation coefficients (ICC) of 0.91 (95%CI 0.89, 0.95) and 0.89 (95%CI 0.86, 0.93), respectively; inter-observer ICCs were 0.83 (95%CI 0.75, 0.88) and 0.71 (95%CI 0.63, 0.76). Examination of individual factors revealed that stenosis and superficial ulceration grading had low inter-rater (0.48, 0.65) and intra-rater agreement (0.63, 0.78), respectively. Reproducibility of the Rutgeerts' score has also been questioned, as a recent study of 14 IBD specialists found a Rutgeerts' score agreement to be marginal, $\kappa=0.57$ ³⁰.

Capsule Endoscopy and Deep Enteroscopy

Video capsule endoscopy (VCE) and deep enteroscopy allow direct inspection of proximal small bowel mucosa out of the reach of standard ileocolonoscopy. The Lewis score was developed to quantify small bowel mucosal injury using a 0–3 graded severity of edema, erythema, and ulceration, the length of disease, and presence of stenosis as captured by VCE³¹. A Lewis score of ≥ 135 was diagnostic for active Crohn's disease in 82.6% of

patients with known active small bowel disease by endoscopy or imaging³². A 93 patient prospective observational study comparing diagnostic capabilities of VCE, CTE, and MRE for terminal ileal disease found similar accuracy of VCE to MRE and superiority over CTE, with a reported sensitivity and specificity of VCE of 100 and 91%³³. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) is an alternative scoring system that dichotomizes disease location into proximal and distal small bowel with gradation of ulcer size, degree of involved surface, and degree of luminal narrowing due to strictures³⁴. The CECDAI has good correlation with the Lewis score ($r=0.767$)³⁵. In a small study, Hall and colleagues showed that CECDAI was able to demonstrate mucosal healing of 27% and 62% of subjects initiating thiopurines or anti-TNF therapy based on a post-treatment score of $<3-5$ ³⁶. The principle limitation of VCE is the potential for capsule retention due to stricturing disease, which despite the use of a patency capsule is reported to occur in 1.5–7.5% of all studies³⁷. Further, without confirmative histology some lesions detected by VCE may be the result of alternative diagnoses such as non-steroidal-induced enteropathy. As a result, a recent ECCO position statement suggested that a diagnosis of CD should not be based on capsule study alone³⁸.

Deep enteroscopy, including single balloon (SBE) and double balloon (DBE) techniques are frequently deployed in the setting of suspicious disease activity identified by other modalities (cross-sectional imaging or VCE studies) where verification of the etiology of the segment of active inflammation is needed (e.g. CD, lymphoma, malignancy, medication-related mucosal injury). In a retrospective multicenter study examining the management impact of DBE in patients with suspected Crohn's disease, 40% (17/43) were given new diagnoses of Crohn's disease, 28% (12/43) had a normal study, and 14% (6/43) were given an alternative diagnosis following DBE³⁹. Risks of perforation during DBE are greater than standard colonoscopy⁴⁰. DBE is also a prolonged procedure with a longer duration of deep sedation, often requiring mechanical ventilation, which is associated with an increased risk of sedation-related complications⁴¹. While diagnostically helpful, the risks and complexity of DBE procedures have tempered its use in routine longitudinal disease activity monitoring. In a study of 110 patients undergoing paired examinations, balloon enteroscopy (SES-CD) and MRE (MaRIA) disease activity scores were strongly correlated ($r=0.806$, $p<0.001$) in the proximal ileum and jejunum⁴². This suggests that cross sectional imaging, often more convenient for patient and provider, may have comparable performance to deep endoscopy for proximal small bowel lesions.

Imaging and CT-Enterography in Crohn's Disease

While a proven sensitive method to measure mucosal injury, routine ileocolonoscopy is limited by its maximal extent, inability to assess deep bowel wall activity, and poor sensitivity for describing and detecting transmural complications⁴³. Several imaging methods, including computed tomography (CT), magnetic resonance (MR), and ultrasound (US) imaging are essential complimentary tests for assessing structural and extra-intestinal disease complications. Additionally, the ability of modern imaging to detect and quantify mucosal injury has improved, approaching a performance comparable to ileocolonoscopy.

CT-enterography (CTE) protocols are optimized to detect and measure intestinal damage and inflammation. Standard CT protocols use positive oral contrast, which obscures mucosal detail, rendering it insensitive to all but the most severe mucosal injury⁴⁴. The use of low density, negative, non-absorbable oral contrast in conjunction with improvements in multi-detector scan technology (MDCT) together provide reliable small bowel resolution with millimeter-level detail sufficient to appreciate even subtle mucosal injury⁴⁵. Several features on CTE are correlated with disease activity when using endoscopic scoring as the reference. Bowel wall thickening (usually >3 mm), mural stratification and enhancement, mesenteric lymphadenopathy and vascular engorgement (Comb sign) are correlated with both endoscopic and histologic findings in CD^{46,47} (Figure 3). Peri-intestinal mesenteric (creeping) fat is an additional feature associated with the degree of endoscopic activity⁴⁸. CTE has a demonstrated ability to detect penetrating complications with excellent sensitivity and specificity, including small bowel stricturing (92% and 100%), intra-abdominal fistulas (77.8% and 86.8%), and abscesses (85.0% and 95.1%)⁴⁹. In addition, CTE has the capacity to detect some extra-intestinal features of IBD including nephrolithiasis, PSC, sacroileitis and perianal disease.

CTE results have been shown to impact medical management and are capable of tracking therapeutic response. Several studies have shown that CTE results altered therapeutic decision making in approximately 50% of CD cases, with clinically unsuspected strictures found in 16–61% of CD patients^{50,51}. Outside of merely detecting disease, in a retrospective study of 63 CD patients receiving infliximab, 49.5% of lesions demonstrated radiographic improvement, 40.0% worsened, and 10.5% were unchanged over a mean follow up period of 365 days (IQR 215–630)⁵². While this study demonstrates the capability of CTE to trend CD activity changes after initiating therapy, the agreement with endoscopy was fair to poor ($\kappa=0.30$), conflicting with prior studies that reported higher sensitivity and specificity of 81% and 88% for detecting terminal ileal disease compared to an endoscopic gold standard⁵³. CTE parameters of CD activity may capture complimentary features not directly reported by endoscopic methods. Chiorean and colleagues developed a CTE index of activity using graded histopathology from resected specimens as reference⁴⁷. Including parameters of bowel wall thickness, mucosal hyperenhancement, mural stratification, the Comb sign, and regional lymphadenopathy, they demonstrated good correlation between histopathology and CTE in the grade of inflammation ($r=0.70$, $p<.0001$) and moderate correlation with the grade of fibrosis ($r=0.60$, $p<.0001$). Minordi and colleagues developed a CT-index of post-operative CD recurrence⁵⁴. Using the parameters discussed above, high, intermediate, and low CT-activity scores were compared to Rutgeerts' scores of i3–i4, i2, and i0–i1, respectively. In 34 consecutive patients, they demonstrated a sensitivity and specificity of 100% and 96.9% in differentiating Rutgeerts' i0–1 vs. i2 endoscopic activity at the anastomosis. Despite excellent spatial resolution and wide availability, radiation exposure from CTE has influenced the expanded use and development of non-ionizing imaging methods, principally MRI and ultrasound.

MR-Enterography for Assessing Disease Activity

Compared to CT, MRI is a more sophisticated imaging method. MRI stabilizes protons within a magnetic field and then detects energy emissions following radio pulses. Post-

contrast T1-weighted and T2-weighted sequences provide multiple means of tissue contrast based on water and fat signal. Past barriers of using MRI for assessment of the intestine included difficulty achieving adequate intestinal distension and motility during data acquisition. Using biphasic non-absorbable oral contrast agents, anti-motility agents like glucagon, and high-speed MR technology with adjustment for respiratory variation, MR-enterography (MRE) became a feasible, radiation-free modality for CD assessment⁵⁵. CTE and MRE have similar capabilities to identify features of disease activity including bowel wall thickening, enhancement, and mesenteric adenopathy, with reported sensitivities and specificities of 85% and 91%, respectively^{33,56,57}. MRE has also been shown to accurately detect proximal small bowel disease, with a sensitivity and specificity of 74% and 91% compared to capsule endoscopy and very good correlation to DBE ($r=0.88$)⁵⁸. The correlation between MR-detected structural features and the need for surgery was shown in a retrospective study of 112 CD subjects where 59% of subjects with MRE-detected stenosis underwent surgery compared to 23% without stenosis over a mean follow up of 49 months, $p<.0001$ ^{59,60}. The presence of an intestinal stricture or intra-abdominal fistulas detected by MRI carried an OR of 3.4 (95% CI 1, 11) and OR 10.5 (95% CI 2, 46) for future surgery. While access and expertise previously limited use of MRE compared to CTE, increasing experience and comfort with MRE interpretation and the absence of ionizing radiation have resulted in a marked increase in use, especially in pediatric populations.

A more concerted effort on operationalizing MRE CD activity indices is reflected by the numerous indices and scoring systems proposed (Table 2). In a detailed systematic review of 14 MR-activity indices, all included wall thickness (using between 3–4 mm as a pathologic cut-off) and post-contrast enhancement in their scores⁶¹. Of MRI scores available, the Magnetic Resonance Index of Activity (MaRIA) has received particular attention⁶². Rimola and colleagues compared imaging features to CDEIS scores in a 50-patient study of paired ileocolonoscopy and MRE. The weighted sum of bowel wall thickness ($\times 1.5$), relative contrast enhancement (RCE, $\times 0.02$), and the presence of wall edema ($\times 5$) and mucosal ulceration ($\times 10$) were determined by logistic regression against the CDEIS and comprised the final MaRIA score. The MaRIA score exhibited excellent sensitivity and specificity for detecting active disease (0.81 and 0.89, respectively) with very good per-segment correlation with the CDEIS ($r=0.82$, $p<0.001$). In follow up validation studies, MaRIA has demonstrated excellent reproducibility with kappa values of $\kappa=0.91$, 0.93, 0.87, and 0.96 for wall thickness, RCE, edema, and ulceration, $p<0.001$ ⁶³. The MaRIA score has sufficient sensitivity to changes in CD activity following modifications in therapy. In a prospective study of 48 patients with active CD undergoing paired MRE and ileocolonoscopy, therapeutic responders exhibited a mean MaRIA score decline from 18.86 ± 9.50 (baseline) to 8.73 ± 5.88 after 12 weeks⁶⁴. The MaRIA score did not significantly differ from CDEIS scores ($p=0.42$) and was moderately correlated with the degree of endoscopic change ($r=0.51$, $p<0.001$). Additional MR activity indices have been developed, including the Crohn's Disease MRI Index (CDMI) which uses histology as a reference, and the Clermont score which employs diffusion-weighted imaging to quantify inflammation and replace the need for IV gadolinium^{65,66}. Finally, a post-operative disease severity assessment using MRE can detect Rutgeerts' i2 endoscopic recurrence with a sensitivity and specificity of 100 and 89%, respectively⁶⁷.

Ultrasound for Crohn's Disease

Considering its lack of ionizing radiation, low cost, and bedside availability, transabdominal ultrasound utilization in CD assessment has expanded further in Europe with increasing adoption in North America. In a systematic review, Panes and colleagues found that traditional ultrasound can identify CD with a sensitivity and specificity of 86% and 94%, respectively, compared to both endoscopy and cross sectional imaging⁵⁶. However, standard ultrasound assessment parameters (principally bowel wall thickness and Power-Doppler blood flow) may be insufficiently dynamic and reproducible to accurately grade CD activity⁶⁸. Additionally, poor performance proximal to the ileum, and lack of sensitivity to more mild disease activity (aphthous ulcerations) to date have tempered enthusiasm for use of ultrasound to graded inflammation and assess for complications in patients with CD in the US⁶⁹. The use of non-absorbable oral contrasts for proximal bowel distension have improved accuracy of disease localization, extent, complications, and inter-observer agreement but increase the duration of the exam⁷⁰. The use of intravenous microbubble, contrast-enhanced ultrasound (CEUS) offers a quantitative measure of bowel perfusion data that may correlate to disease activity and potentially therapeutic response. A meta-analysis of CEUS revealed a pooled sensitivity and specificity of 0.94 (95% CI 0.87–0.97) and 0.79 (95% CI 0.67–0.88) for detecting active vs. inactive CD based on endoscopic gold standards⁷¹. A pilot study in 39 CD subjects used CEUS image analysis to quantify bowel perfusion kinetics, showing that higher perfusion rates, standardized to bowel thickness, predicted medically responsive vs. surgical disease with a sensitivity and specificity of 0.82 and 0.94 respectively (AUROC 0.92)⁷². Ultrasound disease activity scoring systems have been developed and may have promise for measuring therapeutic response, though index comparison to endoscopic standards are pending^{73,74}. A major limitation is that ultrasound requires significant training and has yet to prove itself sufficiently sensitive and dynamic to disease activity changes or capable of locating and comparing diseased segments over time. However, continued technologic improvements combined with its lack of ionizing radiation, convenience, and low cost, position ultrasound to become a likely future modality of routine longitudinal assessment in CD.

Modality Choice for Activity Assessment in CD

Choice of modality for longitudinal disease activity monitoring considers factors of disease distribution, known disease severity, surgical history, stricturing and penetrating complications, clinical or therapeutic changes, and local technology access and expertise. While accumulating data suggests that imaging modalities may have similar capabilities, endoscopy is more established and remains the favored primary measure of disease activity and therapeutic response for CD patients with ileocolonic disease location. When proximal small bowel disease is present, the risks, costs, and patient burden are factored into choice of monitoring modality. While VCE can be used, cross-sectional imaging techniques are more frequently employed for proximal small bowel activity assessments due to their convenience, accuracy, and the potential for capsule retention with use of VCE. Concerns of ionizing radiation exposure have resulted in recommendations to use MRE (or ultrasound, where expertise is available) over CTE, which traditionally delivers between 10–25mSv per scan. MRE is preferred over CTE for elective studies, especially in those 35 years of age or

younger who have the greatest risk for malignancy secondary to long-term, cumulative diagnostic radiation exposure⁷⁵. However, implementation of automated tube current modulation and iterative image reconstruction techniques have substantially reduced radiation exposure from CTE to 1–5mSv without loss of diagnostic accuracy^{76,77}. Considering much greater access, lower cost (especially in the United States), and good agreement compared to MRE, low-radiation CTE continues to have a strong presence in CD assessment, especially in urgent and emergent settings. Of course ultrasound, especially in combination with oral and IV contrast, has good performance as discussed above, but limited experience and challenges in efficiently surveying the entire bowel have restricted widespread use, notably in North America.

As treatment endpoints increasingly rely on the objective resolution of intestinal inflammation (“treat to target”), the frequency and sequence of disease activity assessments differ based on the clinical scenario. While few formal guidelines exist, we propose the following timing suggestions for objective interrogation of CD activity. After major therapeutic changes, we recommend ileocolonoscopy, or small bowel assessment by MRE or VCE when needed, at 6–9 months using a standardized scoring index; this is in agreement with Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-expert committee suggested intervals⁷⁸. Additionally, the STRIDE committee endorses reassessment of anastomotic disease activity by ileocolonoscopy at 6–12 months after bowel resection using an activity threshold of ≥ 2 to denote significant disease recurrence. The necessary frequency of disease activity assessment is less certain in asymptomatic patients with documented objective evidence of resolution or improvement in disease activity. For patients with no history of severe structural disease or surgery, who were in remission by previous objective studies, our approach is to alternate endoscopy and cross-sectional imaging assessments (to screen for interval structural changes) every 2–3 years. In patients with improvement but not resolution of disease activity, we recommend repeat assessment in 6–9 months if changes in therapy are initiated or 1–2 years if no changes in therapy are made to document stabilization of disease. Patients with complex CD phenotypes and a history of prior surgery undergo annual assessment, alternating between endoscopy and imaging (preferably MRE). Providers can consider adjusting these intervals if there is no objective evidence of active inflammation on repeated exams. In addition, “diagnostic surveillance” can be personalized if patients are reticent to change therapy based on findings, if medical co-morbid conditions exist, or if patients are of advanced age.

Non-invasive biomarkers, such as C-reactive protein (CRP) and fecal calprotectin and lactoferrin, while limited by accuracy and reproducibility, may be used as a convenient screen for significant changes in disease activity at shorter intervals and/or as an alternative to endoscopic assessment, though the value of such practices are debated. Elevated CRP levels >0.6 – 0.8 mg/L have been associated with future clinical relapse and increased risk of surgical resection in several prognostic and therapeutic trials^{79–81}. Fecal calprotectin (FCP), a more specific marker of intestinal inflammation, has a 99% negative predictive value (NPV) for distinguishing IBD from functional diarrhea, an accuracy of 87% for identifying a SES-CD ≥ 3 , and a NPV of 93% for Rutgeerts’ score of ≥ 2 disease in post-operative CD patients^{82,83}. A recent excellent comprehensive review of biomarker performance with

strategies for integrating CRP and FCP into routine CD activity monitoring between more involved assessments has been published⁸⁴.

Evolving concepts of disease activity in CD

As multimodal indices continue development towards quantitative, objective, reproducible activity measures, they remain focused on the inflammatory aspects of CD. Progressive intestinal fibrosis and related structural complications are equally important, though poorly measured, elements of disease course. Available therapies principally target inflammation, however the degree of existing structural complications and irreversible intestinal fibrosis present are likely to impact therapeutic efficacy. While most endoscopic and image-based activity assessments include some qualitative assessment of stricturing disease, these lack the necessary descriptive resolution needed to account for their clinical and therapeutic impact. The Lémann index represents efforts to measure cumulative structural bowel damage, combining endoscopy, cross-sectional imaging, and clinical history⁸⁵. The Lémann index appears to capture progressive bowel damage, with mean scores increasing with disease duration: 6.3 for durations <2 years and 19 for durations of >10 years. In addition, a prospective study of 30 patients initiating anti-TNF therapy showed reductions in the Lémann index among therapeutic responders, reflecting the potential to reverse some aspects of damage attributed to CD⁸⁶. Emerging technologies to measure fibrosis including magnetization-transfer MRI, ultrasound elastography, and photo-acoustics, represent future methods to more directly quantify fibrosis and distinguish it from inflammation^{87–89}. In place of a unified, all encompassing, disease assessment, indices for therapeutic response (using inflammatory parameters) and expected disease course (incorporating structural and fibrotic cumulative damage) are likely to be separated. Finally, while the correlation between objective mucosal healing and reduction in corticosteroid use, hospitalization, and surgery is strong, at this juncture there is no direct evidence that treating exclusively to an objective measure of disease activity results in optimized benefit and risk for the patient. Patient comorbidities (e.g. age, chronic infectious diseases), disease experience, and individual, as well as societal fiscal costs incurred, are together incorporated with objective disease descriptions for treatment decisions. Despite the reduced emphasis on subjective symptoms, capturing the patient experience of disease will continue to be a cornerstone of assessment. Systematic descriptions of patient experience using patient reported outcomes (PROs) will be elements in the evaluation of therapeutic efficacy in years to come. PRO instruments will reclaim the individual experience of disease, while objective assessments by endoscopy and imaging will more accurately and reproducibly determine the physiologic response to therapy.

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ABBREVIATIONS

CDAI	Crohn's disease activity index
HBI	Harvey-Bradshaw index

CDEIS	Crohn's disease endoscopic index of severity
SES-CD	Simple Endoscopic Score, Crohn's disease
CTE	Computed tomographic enterography
MRE	Magnetic resonance enterography
CECDAI	Capsule endoscopy Crohn's disease activity index
CEUS	Contrast enhanced ultrasound
PPV	Positive predictive value
NPV	Negative predictive value
CD	Crohn's disease
IBD	Inflammatory bowel disease
VCE	video capsule endoscopy

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SES-CD Score Key				
	0	1	2	3
Size of Ulcers	None	Aphthous Ulcers 0-5mm	Large Ulcers 5-20mm	Very Large Ulcers >20mm
Ulcerated Surface	None	<10%	10-30%	>30%
Affected Surface	Unaffected Segment	<50%	50-75%	>75%
Narrowing	None	Single Stricture, can be passed	Multiple Strictures, can be passed	Stricture(s) cannot be passed

SES-CD Segmental Score						
	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Terminal Ileum	Total
Size of Ulcers	0	2	0	0	2	4
Ulcerated Surface	0	2	0	0	1	3
Affected Surface	0	3	0	0	1	4
Narrowing	0	0	0	0	1	1
Total 1 + 2 + 3 + 4=						12

Total 1
 Total 2
 Total 3
 Total 4
 SES-CD Score

Figure 1. The SES-CD Endoscopic Index of Activity

In this simplified version of the CDEIS, individual segments are scored using the score key.

In this example a patient has disease noted in the terminal ileum with a single passable stricture and more severe disease activity with large ulcers over 10–30% of the surface area.

Figure 2.

Rutgeerts' post-operative endoscopic recurrence score. Significant endoscopic recurrence is often defined as $\geq i2$ disease, though some studies use alternative definitions.

Figure 3.

Cross Sectional Imaging Features of Disease Activity. In comparison to traditional positive contrast studies (panel A), enterography protocols better reveal intestinal features of disease activity. Bowel wall thickening of $>3\text{--}4\text{mm}$, mural stratification, mucosal hyper-enhancement (panel B) and peri-intestinal features, including mesenteric hyper-vascularity (Comb sign) and fat stranding (panel C) are strongly correlated with endoscopic CD activity. MR-enterography, which spares exposure to ionizing radiation, exhibits excellent agreement with CTE findings, here demonstrating mural stratification, with mucosal hyper-enhancement and surrounding mesenteric fat stranding on T2-weighted fat-saturation imaging (panel D).

Table 1

Endoscopic disease activity indices in Crohn’s disease. The CDEIS and SES-CD represent the most commonly used endoscopic disease activity indices. Note, for CDEIS and SES-CD, severity ranges are based on the most typical values used in published clinical trials. In addition, the Capsule Endoscopy Crohn’s disease Activity Index (CECDAD) is an alternative VCE scoring method that is strongly correlated with the Lewis score ($r=0.767$).

Scoring System	Parameters Included	Reference Standard	Remission	Mild	Moderate	Severe
CDEIS (1989)	Segmental assessment of colon and ileum. Presence of deep ulceration, superficial ulceration, ulcerated stenosis and percent frank and superficial ulceration	Global evaluation of lesion severity by endoscopist (0–10 linear analogue scale)	0–3	3–9	9–12	>12
SES-CD (2004)	Segmental assessment of colon and ileum. Classification of ulcer size, stenosis, and percent ulcerated and affected surface.	Multiple linear regression with CDEIS scores in each segment were used in development	0–2	3–6	7–15	>16
Lewis Score (2008)	Segmental Assessment of Small Bowel Termites. Villious Appearance and Extent. Ulceation (Number and Extent), Stenosis (Number, Ulceration, Traversed).	Expert global evaluation of severity was matched to <i>a priori</i> criteria dem med relivant to systematic capsule	<135	135–790		>790

Table 2

Image-based Crohn's disease activity indices. The Clermont score is notable to include similar features to the MaRIA but using diffusion-weighted imaging (ADC) to better quantify inflammation signal without the use of gadolinium IV contrast. The Crohn's disease MR Index (CDMI) is notable as a score developed against a reference of histologic inflammation.

Scoring System	Assessment Detail	Sensitivity	Specificity	Correlation to Reference
MaRIA (2009)	Endoscopic Segment Activity (MaRIA >7.3)	0.81	0.89	r= 0.78, p<.001 vs. CDEIS
	Detect Endoscopic Ulceration (MaRIA >9.6)	0.95	0.91	
	Detect Endoscopic Mucosal Healing (MaRIA <7)	0.85	0.78	r= 0.71, p<.001 vs. CDEIS
	Endoscopic Segment Activity (MaRIA >7)	1.00	0.83	r= 0.80, p<.001 vs. CDEIS
Clermont (2013)	Detect Ulceration (Clermont >18.9)	0.77	0.71	r= 0.63 vs. CDEIS
	Deep Ulceration (ADC >1.42)	0.91	0.83	r=-0.44 vs. CDEIS
	Superficial Ulceration (ADC >1.90)	0.64	0.75	
	Active vs. Inactive by MaRIA (ADC > 1.90)	0.97	0.98	r= 0.99 ileum, 0.80 colon vs. MaRIA
CDMI (2012)	Acute Inflammation by Histology (CDMI >4.1)	0.81	0.70	r= 0.48, p=0.002 vs. Histology