Curr Gastroenterol Rep (2016) 18: 5
DOI 10.1007/s11894-015-0477-6

Understanding Endoscopic Disease Activity in IBD: How to Incorporate It into Practice

Britt Christensen[1,2] · **David T. Rubin**[1]

Published online: 12 January 2016

Abstract Endoscopic assessment of disease activity is an essential part of clinical practice in inflammatory bowel disease (IBD) and is used for diagnosis, prognosis, monitoring for dysplasia and increasingly for the evaluation of mucosal or endoscopic response to therapy. Recently, mucosal or endoscopic healing has emerged as a key goal of therapy as it has been found that patients who achieve endoscopic remission have improved outcomes compared to those who do not, and this may be independent of their clinical disease activity. However, there is currently no validated definition of mucosal healing and there are numerous endoscopic scoring systems proposed to define endoscopic activity and response to therapy in both ulcerative colitis and Crohn's disease. This article will discuss the most common endoscopic scores used to measure endoscopic disease activity in IBD, the pros and cons of each of these scoring systems and proposed definitions for endoscopic response or remission that exist for each. In addition, the role of endoscopy in prognosticating the disease course is discussed and how endoscopy can be utilized as part of a "treat-to-target" treatment strategy where endoscopy results direct decisions regarding medical strategies in clinical practice is highlighted.

Keywords Crohn's disease · Colonoscopy · Disease activity indices · Endoscopic disease activity · Inflammatory bowel disease · Mucosal activity · Mucosal healing · Ulcerative colitis

Topical Collection on *Inflammatory Bowel Disease*

✉ David T. Rubin
drubin@medicine.bsd.uchicago.edu

[1] University of Chicago Medicine Inflammatory Bowel Disease Center, 5841 S. Maryland Ave., MC4076, Room M410, Chicago, IL 60637, USA

[2] Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Australia

Introduction

Endoscopy in IBD is used to diagnose ulcerative colitis (UC) and Crohn's disease (CD), prognosticate disease severity, obtain biopsies of intestinal mucosa for histological examination, monitor for dysplasia and risk of colorectal cancer and more recently to evaluate mucosal or endoscopic response to therapy. Historically, the aim of treatment for patients with inflammatory bowel disease (IBD) has been to induce and maintain clinical (symptomatic) remission. However, increasingly, there has been a paradigmatic shift in therapeutic approach with a push toward aiming for endoscopic remission or mucosal healing as a primary treatment goal. This is in recognition of the fact that treating to induce clinical remission is unreliable as IBD symptoms are subjective, with patients in clinical remission having significant endoscopic disease activity [1–5] and patients who feel unwell having no endoscopic findings of disease activity [3]. This puts a significant proportion of patients at risk of either disease progression due to inadequate treatment or at risk of over treatment with unnecessary medications if we rely on clinical symptoms alone to determine our anti-inflammatory treatment strategy. Furthermore, patients who do achieve endoscopic remission have improved outcomes compared to those who do not, with patients who achieve mucosal healing being found to have a decreased risk of clinical relapse, hospitalizations, surgery and colorectal neoplasia [1, 3, 6••, 7–14].

Therefore, in order to accurately assess disease activity and determine and quantify response to therapy, endoscopic assessment is required and is increasingly becoming the standard of care. This article will discuss the most common endoscopic scores used to measure endoscopic disease activity in IBD and their role in predicting the course of these diseases and their impact on decisions regarding medical strategies. We also provide a brief review of emerging non-invasive markers

of mucosal healing that are increasingly being incorporated into the real world setting and discuss how the assessment of endoscopic disease activity should be incorporated into routine clinical practice.

Endoscopic Disease Activity Indices for Ulcerative Colitis

Endoscopic findings of mucosal inflammation in UC typically include erythema, edema with vascular congestion or loss of fine vascular pattern, and granularity [15]. As the disease progresses in severity, friability, spontaneous bleeding and macroscopic ulceration can also occur [15]. Truelove and Witts developed the initial mucosal scoring system for UC in 1955 [16]. They reported endoscopic lesions as normal or near normal, improved or no change/worse on sigmoidoscopy during a placebo-controlled trial of cortisone for the treatment of active disease. Since then, many endoscopic scoring systems for UC have been developed to measure endoscopic disease activity (Table 1).

As there are many scoring systems available, this review will focus on the most common scoring system used in clinical trials of UC, the Mayo Clinic endoscopy subscore, and the newest scoring system that is currently undergoing validation and is likely to be increasingly adopted in the future, the ulcerative colitis endoscopic index of severity (UCEIS).

The most common endoscopic score used in clinical trials to measure endoscopic disease activity in UC is the Mayo Clinic endoscopy sub-score [26]. This score has four components: erythema, friability, vascular pattern and erosions/ulceration with a maximum total score of 3 (Fig. 1). Although not formally validated, mucosal healing has generally been defined as a Mayo score of either 0 or 1 [29]. This definition has since been found to be fitting with a post hoc analysis of the active ulcerative colitis trials (ACT)-1 establishing that patients who achieve a post-treatment Mayo endoscopic score of 0 or 1 have equivalent rates of colectomy on follow-up and are significantly less likely to undergo colectomy over the subsequent year than those with higher Mayo endoscopic sub-scores [30]. However, of note, patients who achieved a score of 0 were found to have higher rates of steroid-free remission at 1 year compared to those who only achieved a score of 1 [30]. The strengths of the Mayo endoscopic sub-score lie in the frequency of its use in clinical trials and its ease of use. Its weakness lies in its lack of validation, the fact that it does not distinguish between deep and superficial ulceration [31•] and that the score only reflects the most severely affected segment of the bowel visualized without giving any indication of the extent or distribution of mucosal inflammation and setting no minimal insertion length. In addition, the original score includes variable degrees of friability in the score of 1 and 2, which results in high inter-observer discrepancy and inconsistent results [32]. In fact, because of this concern, some studies have used a modified Mayo scoring system that classifies the presence of any degree of friability as an automatic Mayo endoscopic sub-score of 2 [33–35]. This modified Mayo Clinic Endoscopic Score (MMCS) has been found on initial review to have excellent intra-observer and inter-observer reliability (intra and inter-class correlation coefficient and 95 % confident interval [95 % CI] 0.89 [0.85–0.92] and 0.79 [0.72–0.95], respectively) and is responsive to change [36].

Due to the need for a prospectively validated endoscopic assessment tool that can assess mucosal healing in UC and be applied to clinical practice, the ulcerative colitis endoscopic index of severity (UCEIS) [37] and the ulcerative colitis colonoscopic index of severity (UCCIS) [27] have recently been developed and undergone initial validation. The UCEIS (Table 2) is the most cited of these tools and was prospectively developed using multiple validated steps with the final tool evaluating vascular pattern, bleeding and erosions and ulcers with the worst segment of the colon scored for each variable on a 0–2 or 0–3 scale giving a total score of 0–8 [37]. The final scoring system is easy to use and has a high intra and inter-observer agreement with an intra-observer kappa value of 0.82, 0.72 and 0.78 and inter-observer kappa values of 0.83, 0.56 and 0.77, respectively, for three main descriptor domains of vascular pattern, bleeding and erosion/ulcers [28•]. The correlation coefficient (r^2) between the UCEIS and overall severity evaluation was 0.94 ($p < 0.0001$), meaning it accounts for 88 % of the variance in overall assessment of severity between observers [28•]. The main limitation of this score currently is that there is still no threshold set for remission, mild, moderate and severe disease although these are anticipated in the near future. A preliminary study has shown that in patients admitted with acute severe colitis, a score of 7 or 8 out of 8 at the time of admission predicts inadequate response to intravenous steroids and need for rescue therapy with cyclosporine or infliximab [38]. This scoring system is currently being adopted in clinical trials and will likely be adapted for clinical practice in the future.

Endoscopic Disease Activity Indices for Crohn's Disease

Endoscopic findings in CD consist of edema, erythema, apthoid ulceration, cobblestone appearance and strictures [15]. There are currently three major endoscopic indices for evaluating CD disease activity (Table 3). The two validated endoscopic activity scores for CD are the Crohn's disease endoscopic index of severity (CDEIS) [39] and the simple

Table 1 Endoscopic disease activity scoring systems in ulcerative colitis

Endoscopic scores	Variables	Score range	Definition of remission and response	Strengths	Weaknesses
Truelove and Witts sigmoidoscopic assessment [16]	Hyperemia, granularity and change in overall appearance of the mucosa	No description	Not defined	Able to stratify patients by their disease severity	Not validated High inter-observer variability No definition of mucosal healing
Baron score [17]	Severity of mucosal bleeding and friability	0–3	Remission: 0–1 (NV) Response: Not defined	Easy to use Good inter-observer correlation	Not validated No assessment of ulcers No definition of mucosal healing
Modified Baron score [18]	Friability, vascular pattern, granularity, bleeding and ulceration	0–4	Remission: 0–1 (NV) Response: Not defined	Easy to use Good inter-observer correlation	Not validated No definition of mucosal healing
Powell-Tuck sigmoidoscopic assessment [19, 20]	Severity of mucosal bleeding and friability	0–2	Not defined	Easy to use	Not validated No definition of mucosal healing Ulceration not included
Rachmilewitz endoscopic index [20]	Granulation, vascular pattern, vulnerability of mucosa, mucosal damage	4 items rated 0–3. Total of 0–12 points	Remission: 0–4 (NV) Response: Not defined		Not validated Complex and subjective descriptive terms
Sigmoidoscopic index [21]	Erythema, friability, ulceration, mucous, vascular pattern	5 items rated 0–3. Total 0–16 points	Remission: 0–4 (NV) Response: Not defined		Not validated Complex
Sigmoidoscopic inflammation grade score [22]	Edema, vascular pattern Granularity, friability, bleeding, ulcers	0–4	Not defined		Not validated No definition of mucosal healing
Sutherland mucosal appearance assessment [23]	Friability, exudation, bleeding	0–3	Not defined		Not validated Subjective No definition of mucosal healing Easy to use
Endoscopic activity index [24]	Ulcers (size and depth), erythema, bleeding, mucosal edema, mucosal exudate	0–3	Not defined		Complex Not validated No definition of mucosal healing Closely correlated with clinical activity
Matts Index [25]	Granularity, bleeding, edema Ulceration	1–4	Not defined		Not validated No definition of mucosal healing Easy to use Good inter and intra-observer agreement
Mayo endoscopic sub-score [26]	Erythema, vascular pattern, friability, bleeding, erosions, ulcerations	0–3	Remission: 0 or 0–1 (PV) Response: Not defined		Not validated Extensive use in clinical trials and RCTs
Ulcerative colitis colonoscopy index of severity (UCCIS) [27]	Vascular pattern, granularity, ulceration, bleeding/friability	4 items rated 0–2 for vascular pattern, granularity, bleeding/ friability and 0–4 for ulcerations. To total 0–10 points	Not defined	Preliminary validation Based on rigorous methodology Provides pan-colonic assessment	Includes subjective parameters and complex scale No definition of mucosal healing Requires post-procedure time to be scored

Table 1 (continued)

Endoscopic scores	Variables	Score range	Definition of remission and response	Strengths	Weaknesses
Ulcerative colitis endoscopic index of severity (UCEIS) [28•]	Vascular pattern, bleeding, erosions/ulceration	3 items rated 0–3 for vascular pattern and 0–4 for bleeding and ulceration. Total of 0–11 points	Not defined	Preliminary validation Easy to use Based on rigorous methodology Accounts for 94 % of variance between endoscopists for the overall assessment of severity Independent of clinical symptoms	Limited to rectosigmoid Low agreement for normal appearing mucosa Sensitivity to change and mucosal healing remain undefined

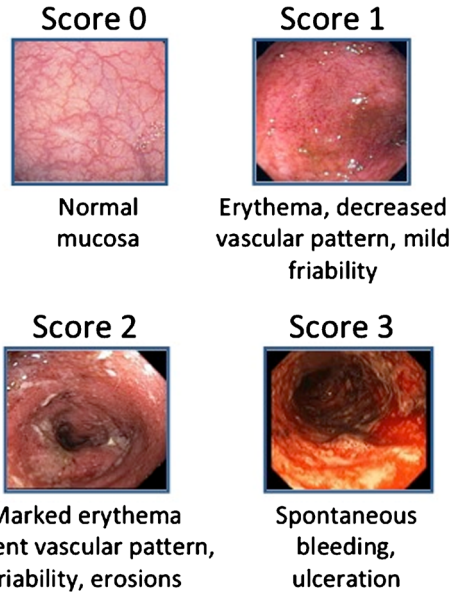

Fig. 1 Mayo endoscopic sub-score

endoscopic score for Crohn's disease (SES-CD) [40]. Both tools have been prospectively validated and shown to be reproducible and have good inter-observer agreement [42–44].

The CDEIS is often considered the gold standard for classifying endoscopic disease activity in CD. The endoscopic parameters of (1) presence or absence of ulcers, distinguished as superficial or deep, (2) percentage of surface ulcerated and/or affected, and (3) presence of stenosis, classified as ulcerated or non-ulcerated stenosis in the five bowel segments (terminal ileum, right colon, transverse colon and sigmoid, and rectum) are evaluated to give a total score of 0–44 [39]. It has good correlation with the Crohn's disease activity index (CDAI), is highly reproducible and is sensitive to changes in endoscopic mucosal appearance and healing [30]. The CDEIS is the most commonly used endoscopic tool to assess disease activity in clinical trials although there is no agreement or formal validation regarding cut-off values for defining endoscopic response to treatment, endoscopic remission or mucosal healing and no data available on long-term clinical outcomes. In the available trials, endoscopic response has previously been defined as a decrease from the baseline score of at least 3 or 5 points [43, 45] although more recently, a post hoc analysis of the SONIC trial by Ferrante et al. [46], showed that defining endoscopic response as a decrease from baseline of the CDEIS score of at least 50 %, was most predictive of corticosteroid-free clinical remission by week 50, including that of a decrease in score of 3 or 5 points. In trials utilizing the CDEIS, endoscopic remission has been defined as "partial" using a cut-off of <6 [40, 45, 47], and "complete" using a cut-off of <3 [40, 45], <4 [48], ≤4 [49] or 0 [50]. The main limitation of the CDEIS is the fact that it is a

Table 2 The ulcerative colitis endoscopic index of severity (UCEIS) [28•]

Descriptor	Score	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa no visible erosions or ulcers
	Erosions (1)	Tiny defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa which are discrete fibrin-covered ulcers when compared with erosion, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slightly raised edge

The three descriptors are scored for the worst affected area of the colon to give a score of 0–8

[Adapted from. Travis S et al. Reliability and Initial Validation of the Ulcerative Colitis Endoscopic Index of Severity. Gastroenterology. 2013; 145:987–995] [28•]

complex tool that requires training and experience to utilize, resulting in a 2002 expert consensus statement that the CDEIS should be reserved for use in clinical trials only due to its complexity [51].

To overcome these limitations, a simplified index, the simple endoscopic score for CD (SES-CD) was developed. The SES-CD is reliable and correlates well with the CDEIS (correlation coefficient $r^2 = 0.920$) [40]. The endoscopic parameters of (1) ulcer size, (2) ulcerated and affected surfaces, and (3) stenosis are scored from 0 to 3 in each of the five bowel segments (terminal ileum, right colon, transverse colon and sigmoid, and rectum) to give a total score of 0–60 [40]. However, despite it being much simpler than the CDEIS, the SES-CD is still a complex index with limited use in clinical practice. In addition, as with the CDEIS, there is a lack of consensus on the definition of endoscopic response and remission. In previous clinical trials, a SES-CD score of <3 [49, 52–54] or equal to 0 [13, 50, 55–57] has been used to define endoscopic remission or minimal endoscopic activity and, more recently, Moskovitz et al. [58] validated the cut-off values for the SES-CD as 0–2 for endoscopic remission, 3–6 for mild endoscopic disease, 7–15 for moderate endoscopic disease activity and ≥16 for severe endoscopic disease activity. In regard to defining endoscopic response to treatment, as with the CDEIS, Ferrante et al. [46] demonstrated that a decrease from baseline of the SES-CD score of at least 50 % was most predictive of improved outcomes. With this evidence in mind, the International Organization for the Study of Inflammatory Bowel Disease is preparing an expert opinion publication stating that endoscopic response to therapy should be defined as a >50 % decrease in the SES-CD and that remission should be defined as an SES-CD of 0–2 [59].

The final endoscopic activity scoring system commonly used in CD is the Rutgeert's score [41] (Fig. 2). The Rutgeert's score assesses and quantifies endoscopic disease recurrence in the neo-terminal ileum after ileal or ileocolonic resection [41, 60] and is the most commonly used tool used to assess recurrence in postoperative CD trials. The numerical score ranges from 0 to 4; (0) normal mucosa; (1) <5 apthous lesions; (2) >5 apthous ulcers with normal intervening tissue; (3) diffuse inflammation with diffuse ulcers; (4) nodules and/or narrowing. Although it has not been fully prospectively validated, the severity of the Rutgeert's score on endoscopy in an asymptomatic patient within 12 months of the ileocolonic resection has been shown to predict the risk of clinical recurrence with Rutgeert's score of grade 0 or 1 being associated with a very low risk of clinical recurrence (80–85 % asymptomatic at 3 years follow-up) compared to those who have a score of 3 or 4 (<10 % asymptomatic

Table 3 Crohn's disease endoscopic disease activity scoring systems

Score	Variables	Score range	Definition response/remission	Strengths	Weakness
Crohn's disease endoscopic index of severity (CDEIS) [39]	Deep ulceration, superficial ulceration, inflammation, ulcerated stenosis, non-ulcerated stenosis	0–44	Complete remission 0, <3, <4, or <6 (NV) Response: decrease from baseline of 50 % (PV) to 75 % or decrease from baseline of 3–5 points (NV)	Validated Reproducible Extensive use in clinical trials	Complex Many variables Requires training and experience No validated definition of mucosal healing or response
Simple endoscopic score for Crohn's disease (SES-CD) [40]	Ulcer size, ulcerated surface, inflammation, stenosis	0–60	Remission 0 or <3 points (NV) Response: decrease from baseline of 50 % (PV) or decrease from baseline of ≥5 points (NV)	Validated Score correlates well with CDEIS Reproducible	Complex Not practical for clinical setting Validated against CDEIS in only one study No validated definition of mucosal healing or response
Rutgeerts score [41]	Apthoid lesions, ulcers, inflammation, nodules and stenosis	i0–i4	Score of i0–i1 low risk of clinical recurrence Score of i2 = intermediate risk of clinical recurrence Score of i3 = high risk of clinical recurrence (PV)	Gold Standard for assessment of postoperative recurrence Extensive use in clinical trials Validated cut-off values for clinical recurrence	No formal validation Only useful for ileal or ileal-colonic surgery

NV not validated, *PV* partially validated

at 3 years follow-up) [41]. Therefore, ileocolonoscopy is recommended within 1 year following surgical resection to determine if postoperative treatment is effective or if additional treatment is required.

Endoscopic Assessment Can Predict Disease Severity

Endoscopic severity may predict the future clinical course of IBD. In both UC and CD, severe endoscopic lesions predict an increased risk of colectomy. In CD, severe endoscopic ulceration increases the risk of colectomy to 31 % from a baseline of 6 % at 12 months in those without severe endoscopic lesions [61] and in UC, the odds ratio of colectomy when a patient is admitted for a severe attack is 41 in those with severe lesions on endoscopy compared to those without severe lesions [62]. In addition, it has been shown that only 34 % of patients who respond to medical therapy in severe colitis have severe endoscopic lesions compared to 91 % in those who do not respond to medical therapy (OR >20) [40].

Importance of Achieving Mucosal Healing in IBD

In recent years, mucosal healing has increasingly emerged as a major aim of therapeutic interventions in IBD. This is secondary to the growing evidence that demonstrates improved clinical outcomes in those achieving mucosal healing compared to those who do not.

Improved clinical outcomes in patients who achieve mucosal healing compared to clinical remission alone was first reported back in 1966 by Wright et al. [63] who found that UC patients not achieving mucosal healing when treated with steroids relapsed more frequently during a follow-up period of 1 year compared to patients who did (40 vs. 18 %, respectively). Since then, a plethora of studies have confirmed this finding and demonstrated that in both UC and CD, mucosal healing is associated with prolonged remission, fewer hospitalizations and surgical procedures, less bowel damage (fistulas) in CD, less immunosuppression therapy, a lower risk of colorectal cancer, and improved quality of life [1, 3, 6••, 7–14, 30, 62, 64–66].

Recently, it has also been demonstrated that the severity and chronicity of inflammation in the colon is associated with the risk of colorectal neoplasia [67–70]. The degree of endoscopic and histologic inflammation has been found to correlate with the risk of developing colorectal neoplasia on univariate analysis with more severe disease being associated with higher cancer risk [67, 68]. Despite the fact that on multivariate analysis only histological inflammation was an independent predictor of risk, a follow-up study of colorectal surveillance did find that UC patients who have mucosal healing

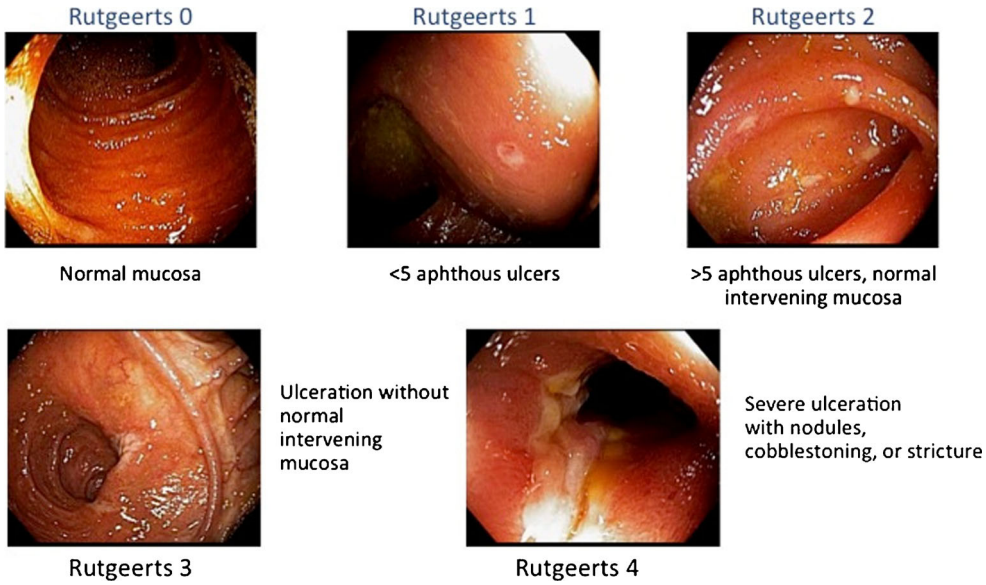

Fig. 2 Rutgeerts' score for postoperative endoscopic recurrence

or a macroscopically normal colon have a colorectal cancer risk similar to that of the general population on 5-year follow-up [68].

Endoscopic Assessment in Clinical Practice

Clinical disease activity is subjective and not a reliable indicator of endoscopic disease activity. It has been found that up to half of patients who are in clinical remission will still have endoscopic evidence of active disease [71]. In addition, a high prevalence of clinical symptoms has been noted in patients who actually have achieved mucosal healing [3, 72]. This leads to a situation in which patients may be either under- or over-treated in relation to their symptoms and disease activity if endoscopic assessment does not occur, and is the reason that assessment of endoscopic disease activity is increasingly being applied to treatment algorithms.

When to Look

In regard to timing of endoscopic assessment, due to the prognostic value of endoscopy in regard to long-term outcomes, patients who have a significant increase in clinical symptoms or are first presenting with symptoms should undergo a baseline endoscopy. This allows an appropriate treatment plan to be initiated that is titrated to the patient's disease severity. Once therapy has commenced, it is now increasingly accepted that a follow-up colonoscopy should occur to assess for mucosal healing or endoscopic response to therapy. The timing of this is still controversial but should likely occur between 3 and 6 months (earlier if the faster acting anti-TNF therapies are utilized and later if the slower acting anti-metabolite or anti-integrin medications are used).

How to Document Endoscopic Activity and Mucosal Healing

The routine use of endoscopic scoring systems is currently limited to trial settings. The reason for this is secondary to the fact that currently there is no one accepted tool that has been standardized for this setting in either CD or UC, often the scoring systems are too complex and time-consuming to be used in clinical practice and many suffer from high inter-observer variability. In addition, the existing scoring systems do not have well-defined and validated thresholds for mucosal response or healing and there is no consensus on degree of mucosal healing that is required to limit future disability or change the natural history of the disease.

However, despite their limitations, the use of an endoscopic scoring system can aid in the reporting of endoscopic findings and allow easy comparison between a patient's current and previous colonoscopy result. If it is feasible, we recommend the use of the Mayo subscore for UC and the SES-CD score for CD. However, in clinical practice, generally documentation of endoscopic disease activity remains subjective. If the endoscopic scoring systems are not used, it is important to report in each segment of the bowel on the following:

- The extent and location of inflammation
- If the bowel involvement is continuous or involves skip areas
- The presence of erythema, loss of vascular pattern, bleeding (contact or spontaneous), presence of erosions or ulceration (superficial or deep) and the presence of strictures or fistulas.

We also recommend specific language in the impressions to distinguish "clinical remission" from "endoscopic remission" from other end points (like histologic remission). Such examples include the following:

> IMPRESSION: Endoscopically moderately active left-sided ulcerative colitis.
> IMPRESSION: Endoscopically quiescent panulcerative colitis and clinical remission (deep remission).
> IMPRESSION: Endoscopically mildly active patchy Crohn's ileitis and proximal colitis.

In addition, on follow-up, ileocolonoscopy is important to note if the endoscopic disease activity has improved, worsened or is stable.

Although not yet suitable for adoption in the clinical setting, currently newer endoscopic scoring systems are being developed and future studies are likely to validate these scoring systems in the clinical setting and demonstrate their role in the day-to-day management of IBD patients. This will help with the comparison between drug efficacies and optimize a treat-to-target treatment algorithm in our patients.

How to Achieve Mucosal Healing

If a patient is symptomatic and has not achieved mucosal healing, then escalation of medical therapies should occur. If a patient who is in clinical remission is found to have unexpected mucosal inflammation, an open dialogue should occur about the goals of treatment. Symptom control and the side effects of therapy should be acknowledged but a discussion about the risks of uncontrolled inflammation and resulting progressive disease should also occur and short and long-term goals recognized. It is now thought that achieving mucosal healing will improve the long-term outcomes of inducing sustained clinical remission and reducing hospitalizations and surgery in patients with IBD and reduce or prevent progressive disease and disability. Therefore, adopting a "treat-to-target" approach is increasingly being accepted with the target being that of mucosal healing. After discussing the pros and cons of escalation of therapy with the patient, techniques to treat to mucosal healing include confirming adherence to medication and overcoming barriers to adherence, optimization of current medical therapies including assessment of medication metabolites or therapeutic monitoring of anti-TNF therapy and adjusting therapy as needed and if required consideration given to switching therapy to another drug within the same class or outside the class depending on the clinical context [73].

Preliminary retrospective data suggest that repeated assessment of endoscopic disease activity with adjustment of medical therapy to the target of mucosal healing is feasible in clinical practice and seems to be of benefit [74••, 75••]. However, although it is thought that mucosal healing will improve long-term outcomes, there are still many unresolved challenges in regard to incorporating endoscopic assessment and the target of mucosal healing into routine clinical practice (Table 4). It is still unclear just how much healing is required and it is yet to be demonstrated prospectively that mucosal healing can prevent disease progression or change the natural history of IBD [73]. Therefore, before any medication adjustment takes place, the risks of medical escalation must be weighed against the benefits of achieving mucosal healing as this escalation of therapy is likely to increase the associated risks of the medication [73, 76••]. For targets of healing, a recent expert statement from the International Organization for the study of Inflammatory Bowel Diseases (IOIBD) has recommended selecting a Mayo endoscopic sub-score of 0–1 to define endoscopic remission in UC and the resolution of ulceration at ileocolonoscopy in CD [77••].

Conclusion

Ileocolonoscopy is now considered the gold standard to assess disease severity, prognosticate a patient's future disease course and quantify mucosal response and healing following treatment in inflammatory bowel disease and is more reliable in determining disease activity than relying on clinical symptoms alone. Numerous endoscopic scoring systems exist however most are limited due to their complexity and a lack of formal validation. In addition, there is currently limited consensus on the value or percentage improvement in these scores that should be used to define mucosal improvement and healing and there is limited data on how these scores can be utilized to predict long term improved clinical outcomes and therapeutic management strategies in regard to continuing or stopping therapy or changing the type of therapy completely. Despite these limitations, the assessment of disease activity and mucosal healing by endoscopy is increasingly becoming standard of care and should now be routinely implemented into clinical practice as part of a treat-to-target strategy.

Table 4 Unresolved challenges to the incorporation of routine endoscopic assessment and mucosal healing in IBD management

How much healing is really needed to impact outcomes?
Can mucosal healing be achieved in most patients?
What is the incremental benefit achieved by dose escalation or switching therapies?
What is the optimal time interval between changes in therapy and subsequent endoscopic re-assessment?
How accurate are the existing less invasive measures of mucosal injury?
Can de-escalation occur after deep remission is sustained for some time?
Will patients agree to therapy changes based only on endoscopic findings?
Will insurers pay for these tests?

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Colombel JF et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141(4):1194–201.
2. Modigliani R et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des affections Inflammatoires digestives. Gastroenterology. 1990;98(4):811–8.
3. Rutgeerts P et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76.
4. Baars JE et al. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflamm Bowel Dis. 2012;18(9):1634–40.
5. Gomes P et al. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986;27(1):92–5.
6. •• Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619–35. **Excellent review on role of mucosal healing in IBD and how this involves incorportating endoscopy into clinical practice**.
7. Sandborn WJ et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009;137(4):1250–60.
8. Froslie KF et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412–22.
9. Feagan BG et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol. 2007;102(4):794–802.
10. Meucci G et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. Inflamm Bowel Dis. 2012;18(6):1006–10.
11. Ardizzone S et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9(6):483–9. e3.
12. Solem CA et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(8):707–12.
13. Baert F et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138(2):463–8. quiz e10-1.
14. D'Haens G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371(9613):660–7.
15. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. Clin Gastroenterol Hepatol. 2005;3(1):11–24.
16. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041–8.
17. Baron JH et al. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J. 1964;1(5375):89–92.
18. Feagan BG et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med. 2005;352(24):2499–507.
19. Powell-Tuck J et al. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand J Gastroenterol. 1978;13(7):833–7.
20. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298(6666):82–6.
21. Hanauer S et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial Pentasa study group. Am J Gastroenterol. 1993;88(8):1188–97.
22. Hanauer SB et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. Gastroenterology. 1998;115(3):525–32.
23. Sutherland LR et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987;92(6):1894–8.
24. Naganuma M et al. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. J Gastroenterol. 2010;45(9):936–43.
25. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med. 1961;30:393–407.
26. Schroeder KW et al. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9.
27. Samuel S et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol. 2013;11(1):49–54.
28. • Travis SP et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145(5):987–95. **Validation study of the newest and validated endoscopy score for UC that is likely to be increasingly incorporated into clinical practice and trials in the future**.
29. D'Haens G et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132(2):763–86.
30. Rutgeerts P et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63(3):433–42. quiz 64.
31. • Mazzuoli S et al. Definition and evaluation of mucosal healing in clinical practice. Dig Liver Dis. 2013;45(12):969–77. **Good review article on mucosal healing and endoscopic outcomes in IBD**.
32. Walsh A et al. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. Gastrointest Endosc Clin N Am. 2014;24(3):367–78. **Good review article on endoscopic indices to quanitfy mcuosal healing**.
33. D'Haens G et al. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. Gastroenterology. 2012;143(6):1461–9.
34. Kamm MA et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132(1):66–75. quiz 432–3.
35. Feagan BG et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145(1):149–57. e2.

36. Levesque B et al. Responsiveness of central endoscopic assessment of disease activity using the modified mayo clinic score in ulcerative colitis. Gastroenterology. 2014;144(5):S-767.
37. Travis SP et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). Gut. 2012;61(4):535–42.
38. Corte C et al. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. J Crohns Colitis. 2015;9(5):376–81.
39. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des affections Inflammatoires du tube Digestif (GETAID). Gut. 1989;30(7):983–9.
40. Daperno M et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505–12.
41. Rutgeerts P et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956–63.
42. Annese V et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982–1018.
43. Daperno M et al. Results of the 2nd part scientific workshop of the ECCO. II: measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. J Crohns Colitis. 2011;5(5):484–98.
44. Tontini GE et al. Endoscopic scoring systems for inflammatory bowel disease: pros and cons. Expert Rev Gastroenterol Hepatol. 2014;8(5):543–54.
45. Hebuterne X et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. 2013;62(2):201–8.
46. Ferrante M et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. Gastroenterology. 2013;145(5):978–86. e5.
47. Colombel JF et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3):423–31. e1.
48. Laharie D et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Aliment Pharmacol Ther. 2011;33(6):714–21.
49. Rutgeerts P et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology. 2012;142(5):1102–11. e2.
50. Lemann M et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology. 2005;128(7):1812–8.
51. Sandborn WJ et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology. 2002;122(2):512–30.
52. Colombel JF et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(3):414–22. e5.
53. Sipponen T et al. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scand J Gastroenterol. 2010;45(3):325–31.
54. Sipponen T et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther. 2008;28(10):1221–9.
55. Louis E et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012;142(1):63–70. e5; quiz e31.
56. Aomatsu T et al. Fecal calprotectin is a useful marker for disease activity in pediatric patients with inflammatory bowel disease. Dig Dis Sci. 2011;56(8):2372–7.
57. Dignass A et al. Once versus three times daily dosing of oral budesonide for active Crohn's disease: a double-blind, double-dummy, randomised trial. J Crohns Colitis. 2014;8(9):970–80.
58. Moskovitz D et al. Defining and validating cut-offs for the simple endosocpic score for Crohn's disease. Gastroenterology. 2007;132(4):A173–S1097.
59. Columbel JF. Measuring severity of disease and defining treatment benefit using the simple endoscopic activity score (SES-CD). US Food and Drug Administration's gastroenterology regulatory endpoints and the advancement of therapeutics (GREAT) 3 workshop; Silver Spring, MD 2015.
60. Rutgeerts P et al. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut. 1984;25(6):665–72.
61. Allez M et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97(4):947–53.
62. Carbonnel F et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. Dig Dis Sci. 1994;39(7):1550–7.
63. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis. 1966;11(11):847–57.
64. Schnitzler F et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15(9):1295–301.
65. Rutgeerts P et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004;126(2):402–13.
66. Solberg IC et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431–40.
67. Rutter M et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451–9.
68. Rutter MD et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006;130(4):1030–8.
69. Gupta RB et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007;133(4):1099–105.
70. Rubin DT et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case–control study. Clin Gastroenterol Hepatol. 2013;11(12):1601–8 e1-4.
71. Peyrin-Biroulet L et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut. 2014;63(1):88–95.
72. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2012;107(10):1474–82.
73. Bouguen G, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13(6):1042–1050.
74.•• Bouguen G et al. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20(2):231–9. **Nice retrospective study that looks at the use of endoscopic assessment and treating to mucosal healing to improve outcomes in UC**.
75.•• Bouguen G et al. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(6):978–85. **Nice retrospective study that demonstrates improved outcomes in CD with the use of routine endoscopic assesment and treating to mucosal healing**.
76.•• De Cruz P et al. Mucosal healing in Crohn's disease: a systematic review. Inflamm Bowel Dis. 2013;19(2):429–44. **Nice review**

article looking at how mucosal healing improves outcomes and markers of mucosal healing in CD.

77.•• Peyrin-Biroulet L et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110:1324–28. **Expert opinion on new therapeutic goals in IBD that incorporates endoscopic assessment and healing**.