Mucosal Healing As a Target of Therapy for Colonic Inflammatory Bowel Disease and Methods to Score Disease Activity

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KEYWORDS

• Mucosal healing • Ulcerative colitis • Crohn's disease • Inflammatory bowel disease

KEY POINTS

- Mucosal healing is an important end point in clinical trials.
- Mucosal healing predicts the following:
  - Less corticosteroid use
  - Lower hospitalization rates
  - Increased sustained clinical remission
  - Lower colectomy and bowel resection rates
- Mucosal healing decreases the risk of colorectal cancer in ulcerative colitis (UC).
- Mucosal healing should be recognized by clinicians and health care providers as a goal for inflammatory bowel disease (IBD) therapy.

INTRODUCTION

UC and Crohn's disease are characterized by the presence of gut inflammation accompanied by areas of ulceration (**Fig. 1**). Mucosal healing is becoming increasingly important in the clinical management of UC and Crohn's disease, as well as being used as an end point in clinical trials. Achieving mucosal healing has unequivocally been associated with better outcomes, and for these reasons, it has become an important treatment goal. There are, however, multiple methods to score endoscopic disease activity in both UC and Crohn's disease. This article therefore focuses on

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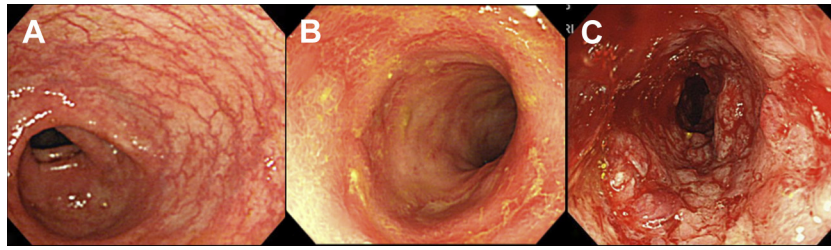

Fig. 1. Assessment of mucosal healing using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) with descriptors of vascular pattern (V), bleeding (B), and erosions/ulcers (E). (*A*) UCEIS 0 (V0 B0 E0), (*B*) UCEIS 5 (V2 B1 E0), and (*C*) UCEIS 8 (V2 B3 E3).

those used most frequently or that have been validated: the Mayo endoscopic score and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) for UC and the Crohn's Disease Endoscopic Index of Severity (CDEIS), the Simple Endoscopic Score for Crohn's Disease (SES-CD), and the Rutgeerts Postoperative Endoscopic Index for Crohn's disease. Because indices are complex and potentially confusing, the article follows a standard approach describing the indices in this order.

DEFINITION OF MUCOSAL HEALING

Mucosal healing in the context of IBD refers to the endoscopic assessment of disease activity. Simply stated, mucosal healing should imply the absence of ulceration and erosions. Nevertheless, there is currently no validated definition of mucosal healing in IBD.[1–3]

Ulcerative Colitis

In patients with UC, mucosal healing may represent the ultimate therapeutic goal, because the disease is limited to the mucosa. The pattern of inflammation in UC is associated with several mucosal changes, initially vascular congestion, erythema, and granularity. As inflammation becomes more severe, friability (bleeding to light touch), spontaneous bleeding, and erosions and ulcers develop. An International Organization of Inflammatory Bowel Disease (IOIBD) task force defined mucosal healing in UC as the absence of friability, blood, erosions, and ulcers in all visualized segments of the colonic mucosa.[2] However, some studies allow erythema and friability in the definition of mucosal healing.[4] Many different endoscopic indices for UC have been used in clinical trials, although none have been fully validated in prospective studies; this creates problems when comparing trials.[5]

Crohn's Disease

In contrast to UC, mucosal healing in Crohn's disease might reasonably be considered a minimum (rather than the ultimate) therapeutic goal, because the disease is transmural. Even this therapeutic goal, however, is not routine clinical practice in most centers. The pattern of inflammation in Crohn's disease is characterized by several mucosal features that include patchy erythema, nodularity, aphthoid, and then deeper, serpiginous ulceration, strictures, and, in severe cases, penetrating ulcers. The complete resolution of all visible ulcers is a simple definition of mucosal healing for clinical practice, and this is what has been suggested by IOIBD task force.[6] Nevertheless, this binomial definition (presence or absence of ulcers) is currently unvalidated, is difficult to achieve, and is rather crude for use in therapeutic trials because it does not allow quantification of improvement of mucosal inflammation.[7] The largest trials that have

used mucosal healing as a primary or major secondary end point have used the definition of absence of ulcers rather than the prespecified cut-off values on the CDEIS or SES-CD. Studies have yet to determine the minimum degree of endoscopic improvement associated with improved clinical outcomes.

BENEFITS OF MUCOSAL HEALING

Mucosal healing in IBD has been associated with the following:

- Decreased need for corticosteroids[8]
- Decreased hospitalization rates[9–11]
- Sustained clinical remission[11,12]
- Decreased colectomy and bowel resection[5,8,9,11,12]
- Decreased risk of colorectal cancer[13]

Multivariate analysis of data from a case-controlled study of patients with longstanding, extensive UC showed that those with endoscopically normal mucosa at surveillance colonoscopy had the same 5-year cancer risk as the general population.[13] The presence of persisting histologic inflammation was, however, a determinant of risk for colorectal cancer.[14] In the same surveillance population, evidence of postinflammatory polyps or strictures was associated with a significantly increased colorectal cancer risk. For Crohn's disease, there has been no demonstrable reduction in colorectal cancer in those with mucosal healing.

Before monoclonal antibodies against tumor necrosis factor (anti-TNF) were introduced for Crohn's disease, a symptom-oriented management approach was common. This approach was largely used because of the failure to demonstrate a correlation between endoscopic remission (mucosal healing) and decrease in relapse rates in patients treated with steroids compared with clinical remission (symptom control). Steroids, however, do not heal the ileal or colonic mucosa. In contrast, both azathioprine and anti-TNF therapy have now been shown to achieve and then maintain mucosal healing, thereby influencing the course of Crohn's disease.[8,10]

For these reasons, mucosal healing has emerged since 2012 as an important therapeutic goal for both UC and Crohn's disease. Moreover, because trials in IBD have traditionally had a high placebo response rate, there is a move to include mucosal healing as an end point in trials to drive down placebo rates.[15,16] For most patients, mucosal healing is only maintained with continued therapy. Current treatments do not cure the disease, and therefore, cessation of therapy almost invariably leads to disease recurrence.[17] If mucosal healing influences the subsequent course of disease, logic suggests that its presence should be confirmed or therapy augmented if it has not been achieved. For these reasons, endoscopic assessment is increasingly used in clinical practice to guide decision making in the management of IBD, but augmenting treatment in the absence of symptoms just because endoscopic lesions are present remains a challenge to many clinicians. On the other hand, most are persuaded that mucosal healing is an appropriate therapeutic goal when starting, stepping up, switching, or stopping expensive biologic therapy.

LIMITATIONS OF MUCOSAL HEALING

Although colonoscopy is considered to be a low-risk invasive procedure, it still carries a risk of perforation, bleeding, or sedation. Furthermore, colonoscopy is an investment of time and resources both for the patient and the community.

Even when using validated indices such as the UCEIS and CDEIS, further research is needed to determine what degree of improvement, measured by endoscopy, is

clinically meaningful. In addition, although disease may seem inactive at endoscopy, microscopic disease activity may persist. Persistent histologic activity is associated with a shorter time to relapse in UC,[18,19] so endoscopic mucosal healing alone may be an insufficient therapeutic goal.[20] Surrogate, noninvasive markers of mucosal healing are therefore needed, but biomarkers such as fecal calprotectin have yet to demonstrate sufficient specificity for mucosal healing to replace endoscopic assessment.[17]

METHODS TO SCORE DISEASE ACTIVITY

Ulcerative Colitis

Truelove and Witts[21] were the first to comment on mucosal appearance as a measure of disease activity, using rigid sigmoidoscopy in the first placebo-controlled trial of cortisone for UC in 1955. Since 1956, it has been recognized that endoscopic and histologic microscopic changes can persist despite symptom resolution.[22] Endoscopic indices evolved from the Baron score,[23] initially developed for rigid proctoscopy in ambulatory patients with mild to moderate disease, which rated vascular pattern, mucosal bleeding, and friability. Subsequent endoscopic indices of increasing complexity incorporated the presence of ulcers, mucopus, granularity, and appearance of light scattering, in addition to bleeding and friability. Such modifications were intended to improve the capture of disease activity, but they invariably increased the subjectivity of the scoring system. **Table 1** summarizes commonly used endoscopic indices for UC, none of which have been validated with the exception of the UCEIS.[31] Nonetheless, there is no agreed threshold for defining either mucosal healing or endoscopic remission, which makes it almost impossible to compare mucosal healing rates between studies.[33]

Space does not allow a review of all indices, so this article focuses on the Mayo Clinic endoscopy subscore, because this is commonly used in clinical trials, and the UCEIS, which has been validated.

The Mayo Clinic endoscopy subscore has 4 components, with a maximum total score of 3 (**Table 2**).[26] There is overlap in the features of the different levels of this endoscopic index, which causes high interobserver variation. The most troublesome component of this index is friability, as this is subjective and leads to inconsistent results.[34] This inconsistency has lead to an adaptation of the index to remove friability from level 1.[35]

The value of this index lies with its widespread use in clinical trials. In trials of infliximab and adalimumab, mucosal healing was defined as a Mayo subscore of 0 or 1 or a decrease from the baseline subscores of 2 or 3. In Active Ulcerative Colitis Trials, patients with a posttreatment Mayo score of grade 1 were no more likely to undergo a colectomy than those with a score of 0.[36]

The UCEIS (**Table 3**) was developed because of wide interobserver variation in endoscopic assessment of disease activity.[31] There was only 76% agreement for severe and 27% agreement for normal endoscopic mucosal appearances between 10 experienced investigators and a central reader. Thirty different investigators then rated 25/60 different videos for 10 descriptors and assessed overall severity on a 0 to 100 visual analog scale. Kappa statistics tested interobserver and intraobserver variability for each descriptor. Different models to predict the overall assessment of severity as judged by a visual analog scale were developed using general linear mixed regression. The final model incorporated just 3 descriptors, each with precise definitions. A third validation phase used another 25 different investigators from North America and Europe, who assessed in a randomly selected subset of 28/60 videos, including

Table 1
Endoscopic disease activity indices[a] for ulcerative colitis

Index[a]	Validated	Variables	Strengths	Weaknesses
Truelove and Witts Endoscopy Index[21]	No	Granularity, hyperemia	Precedence (first reported index), but no other merit	No description of endoscopic lesions, so interobserver variability is high
Baron Index[23]	No	Bleeding, vascular pattern, friability	Easy to use	Ulcerations not included in score, no definition of mucosal healing
Powell-Tuck Index[24]	No	Bleeding	Easy to use	Ulceration not included, no definition of mucosal healing
Sutherland Index[25]	No	Friability, bleeding, exudation	Easy to use; overlap in descriptive terms used for different levels of activity	Subjective, no definition of mucosal healing
Mayo Clinic Index: endoscopic subscore[26]	No	Vascular pattern, erythema, friability, erosions and ulcerations, bleeding	Easy to use, commonly used in clinical trials; overlap in descriptive terms used for different levels of activity	No validated definition of mucosal healing The term minimal or slight friability is subjective and leads to inconsistent results
Rachmilewitz Index[27]	No	Granulation, mucosal damage, vascular pattern, vulnerability of mucosa (bleeding)	None reported	Complex and subjective descriptive terms
Modified Baron Index[28]	No	Vascular pattern, granularity, friability, bleeding, ulceration	Easy to use	No validated definition of mucosal healing
Endoscopic Activity Index[29]	No	Size of ulcers (4 levels), depth of ulcers (4 levels), redness (3 levels), Bleeding (4 levels), mucosal edema (4 levels), mucosal exudate (3 levels)	Closely correlated with clinical activity. Comparable to other indices. Useful in severe disease	
Matts Index[30]	No	Granularity, bleeding, edema, ulceration	Easy to use	
Ulcerative Colitis Endoscopic Index or Severity[31]	Preliminary[32]	Vascular pattern (3 levels), bleeding (4 levels), ulceration (4 levels)	Easy to use Independent of clinical symptoms, accounts for 88% of variation between observers	Sensitivity to change, and mucosal healing remain undefined

[a] The word index is best used for an instrument designed to assess activity and score for the level of activity assigned by the index.[31]

Table 2
Mayo endoscopic score

Score	Disease Activity	Endoscopic Features (Descriptors)
0	Normal or inactive	None
1	Mild	Erythema, decreased vascular pattern, mild friability[a]
2	Moderate	Marked erythema, absent vascular pattern, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

[a] Endoscopic assessment in the mesalamine MMX trials removed friability from level 1 (see text).
Adapted from Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–9; with permission.

2 duplicated videos to assess test-retest reliability. Intraobserver kappa values were 0.82, 0.72, and 0.78 for vascular pattern, bleeding, and erosion and ulcer descriptors, and interobserver kappa values were 0.83, 0.56, and 0.77, respectively. The correlation coefficient (r^2) between UCEIS and overall severity evaluation was 0.94 ($P<.0001$), meaning that it accounted for 88% (0.94^2) of the variation between observers in the overall assessment of endoscopic activity.[32]

The term friability invariably needs explanation. The UCEIS dispensed with the term mucosal friability, because the model including friability as a descriptor did not

Table 3
The Ulcerative Colitis Endoscopic Index of Severity

Descriptor (Score Most Severe Lesions)	Likert Scale Anchor Points	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 ($\leq$5 mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

Adapted from Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012;61:1619–35.

perform significantly better than one including bleeding. In practical terms, the most severely affected part of the mucosa is scored. There are, however, still limitations; thresholds for remission and mild, moderate, and severe disease have yet to be set. The extent to which full colonoscopy may influence the score compared with the flexible sigmoidoscopy on which it was based, has only started to be evaluated.[37] Knowledge of symptoms does not materially influence the score, and a comparison with the Mayo Clinic endoscopy subscore shows that the UCEIS is less subject to variation by a central reader.[38] Nevertheless, the UCEIS is simple enough to use in clinical practice and should achieve its goal of reducing variation in endoscopic assessment of activity between observers. Clinicians are beginning to use the UCEIS in clinical practice, and a preliminary study in patients admitted with acute severe colitis shows that a score of 7 or 8 (out of 8) on admission predicted an inadequate response to intravenous steroids and the need for rescue therapy with cyclosporine or infliximab.[39] The UCEIS is now being used in clinical trials of UC that are in progress.

Crohn's Disease

There are validated endoscopic indices for the assessment of Crohn's disease activity (**Table 4**). The CDEIS is the standard, whereas the SES-CD is a simplified version. The Rutgeerts Postoperative Endoscopic Index is used for estimating the risk of recurrence after ileocolic resection for Crohn's disease.

The CDEIS[40] is a prospectively developed instrument constructed to detect changes in disease activity and examines 4 endoscopic variables (deep ulceration, superficial ulceration, length of ulcerated mucosa, and length of diseased mucosa) in each of the following locations: rectum, sigmoid and left colon, transverse colon, and right colon and ileum (**Table 5**). The total score is then divided by the number

Table 4
Endoscopic indices for Crohn's disease

Index	Validated	Variables	Strengths	Weaknesses
Crohn's Disease Endoscopic Index of Severity (CDEIS)[40]	Yes	Superficial and deep ulceration, ulcerated and nonulcerated stenosis, surface area of ulcerated and disease segments	Standard, reproducible, gold standard	Complex, need experience/ training, difficult for beginners and daily routine, no validated definition of mucosal healing
Simple Endoscopic Score for Crohn's Disease (SES-CD)[41]	Yes	Ulcer size, ulcerated surface, affected surface, presence of stenosis	Simplified index; performance correlates with CDEIS	Validated against CDEIS in only one study, less frequently used than CDEIS, no validated definition of mucosal healing
Rutgeerts Postoperative Endoscopic Index[42]	No	Aphthous ulcerations, inflammation, ulcers, nodules, narrowing	Standard for evaluating postoperative recurrence, validated levels for predicting relapse	Only for use after ileocolic resection

Table 5
Example of the CDEIS scoring form

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	Total	
Deep ulcerations (12 present, 0 absent)	0	12	0	12	N/A	24	Total 1
Superficial ulceration (6 present, 0 absent)	6	6	6	6	N/A	24	Total 2
Surface involved by the disease (per 10 cm)[a]	5.6	4.9	3.4	5.6	N/A	19.5	Total 3
Ulcerated surface (per 10 cm)[a]	0.7	0.5	0.9	0.4	N/A	22	Total 4
Total 1 + Total 2 + Total 3 + Total 4						89.5	Total A
Number (*n*) of segments totally or partially examined (1–5)						4	*n*
Total A divided by *n*						22.4	Total B
Quote 3 if ulcerated stenosis anywhere, 0 if not						3	C
Quote 3 if nonulcerated stenosis anywhere, 0 if not						0	D
Total B + C + D						25.4	CDEIS

[a] Analog scales to be converted to numeric values.

Adapted from Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989;30:983–9; with permission.

of locations explored (1–5). An additional 3 points is given if an ulcerated stenosis is present, and a further 3 points if a nonulcerated stenosis is present. CDEIS scores range from 0 to 44.

- Deep ulcerations: score 0 if absent or 12 if present
- Superficial ulcerations: score 0 if absent or 6 if present
- Length of ulcerated mucosa (0–10 cm): score 0 to 10 according to length in centimeters
- Length of diseased mucosa (0–10 cm): score 0 to 10 according to length in centimeters

Although CDEIS is the standard index and is reproducible, it is also complex. It requires training and experience, especially for estimating ulcerated or diseased mucosal surfaces and distinguishing between superficial and deep ulceration. It is cumbersome to use in clinical practice. The CDEIS has appropriate sensitivity to measure changes in the mucosal appearance. Endoscopic remission (minor or no lesions) is defined as a CDEIS score less than or equal to 6 or less than or equal to 7, and complete endoscopic remission (mucosal healing, ie, no lesions at all or scarred lesions only) is defined as a CDEIS score less than or equal to 3 or less than or equal to 4. An endoscopic response is a decrease from baseline CDEIS score of at least 4 or 5 points. The CDEIS has been used in trials of corticosteroids, thiopurines, and TNF antagonists.

In the MUSIC (Endoscopic Mucosal Improvement in Patients With Active Crohn's Disease Treated With Certolizumab Pegol) study of certolizumab pegol in Crohn's disease, maintenance of improvement between weeks 10 and 54, based on individual patient data, was found in 70% of those who responded (decline in CDEIS >5) and those with complete remission (CDEIS<3), and in more than 40% of those with remission (CDEIS<6).[43]

The SES-CD (**Table 6**) correlates well with the CDEIS, with a correlation coefficient $r = 0.920$ and excellent interobserver reliability (k coefficients 0.791–1.000). This score

Table 6
Simple Endoscopic Score for Crohn's Disease

Variable	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1–0.5 cm)	Large ulcers (diameter 0.5–2 cm)	Very large ulcers (diameter >2 cm)
Ulcerated surface (%)	None	<10	10–30	>30
Affected surface (%)	Unaffected segment	<50	50–75	>75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment.

Adapted from Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505–12; with permission.

was developed to meet the need for a reliable, easy-to-use endoscopic scoring instrument for Crohn's disease, one that by contrast would be less complex than the CDEIS. Selected endoscopic parameters (ulcer size, ulcerated and affected surfaces, stenosis) were scored from 0 to 3, whereby SES-CD = 0 equates to absence of ulcers.[41] No cutoff values have been determined for the SES-CD, and there is no definition of mucosal healing.

The Rutgeerts Postoperative Endoscopic Index (**Table 7**) determines the severity of endoscopic disease recurrence at the anastomosis and in the neoterminal ileum after ileocolic resection.[42,44] The severity of endoscopic recurrence predicts clinical recurrence, so it has gained popularity.[42] In the year after ileocolic resection, patients with a Rutgeerts score of 0 or 1 have a low risk of clinical recurrence (20% at 3 years follow-up) compared with those patients who have a score of grade 3 or 4 (92% at 3 years follow-up). Level 2 is associated with an intermediate risk of clinical recurrence, but the definition of grade 2 is more subjective and is exposed to variability.

This index has also been incorporated into a randomized clinical trial. In the Post Operative Crohn's Endoscopic Recurrence study, it was shown that treating according to the risk of recurrence with a 6-month postoperative colonoscopy and treatment

Table 7
Rutgeerts Postoperative Endoscopic Index

	Distal Ileum
Grade 0	Nil
Grade 1	≤5 Aphthous ulcers
Grade 2	>5 Aphthous ulcers with normal intervening mucosa, or skip areas of larger lesions or lesions confined to the ileocolic anastomosis (ie, <1 cm in length)
Grade 3	Diffuse aphthous ulceration with diffusely inflamed mucosa
Grade 4	Diffuse inflammation with large ulcers, nodules, and/or narrowing

An endoscopic scoring system for postoperative disease recurrence in Crohn's disease. The original paper uses the term grade rather than level, and as with other tables, the descriptions are precisely those used in the original paper.

Adapted from Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956–63; with permission.

step up for those who had a Rutgeerts score ≥i2, is significantly superior to drug therapy alone in preventing postoperative recurrence.[45]

SUMMARY

The colonoscopic assessment of mucosal healing has proved increasingly important in the management of both UC and Crohn's disease. All clinicians should strive for this goal. There is evidence for a decrease in corticosteroid use, decreased hospitalization, an increase in sustained remission, and a decrease in the need for surgery. Further advancements with surrogate noninvasive markers for mucosal healing may help to overcome existing limitations and need for colonoscopy. Multiple endoscopic indices exist for UC; however, the only validated index is the UCEIS, and its use in both clinical practice and clinical trials is encouraged. The CDEIS and the SES-CD are both validated for Crohn's disease. The Rutgeerts Postoperative Endoscopic Index is useful for the prediction of postoperative recurrence in those patients who have had an ileocolic resection.

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