



Review Article

Endoscopic scores for inflammatory bowel disease in the era of ‘mucosal healing’: Old problem, new perspectives



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ARTICLE INFO

Article history:

Received 28 January 2016

Accepted 7 March 2016

Available online 14 March 2016

Keywords:

Crohn's disease

Endoscopic score

Inflammatory bowel disease

Mucosal healing

Ulcerative colitis

ABSTRACT

The importance of the endoscopic evaluation in inflammatory bowel disease (IBD) management has been recognized for many years. However, the modalities for reporting endoscopic activity represent an ongoing challenge. To address this, several endoscopic scores have been proposed. Very few have been properly validated, and the use of such tools remains sub-optimal and is mainly restricted to clinical trials. In recent years, a growing emphasis of the concept of ‘mucosal healing’ as a prognostic marker and therapeutic goal has increased the need for a more accurate definition of endoscopic activity in both ulcerative colitis (UC) and Crohn's Disease (CD). In the present review, the evolution of the challenges related to endoscopic scores in IBD has been analyzed, with particular attention paid to the renewed relevance of endoscopic activity in recent years. Currently, despite the growing relevance of endoscopic activity, evaluating this activity in IBD is still a challenge. The implementation of efficacious endoscopic scores and a better definition of the absence of activity (mucosal healing) are needed.

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1. Introduction

Inflammatory bowel disease (IBD) is a pathologic condition that causes chronic inflammation and may involve several tracts of the intestine. The relevance of the endoscopic evaluation in the management of IBD for diagnosis and follow-up is indisputable. This is particularly true for ulcerative colitis (UC), which is characterized by a mucosal inflammation that does not cross the lamina propria and that involves only the colon to varying degrees [1]. By contrast, in Crohn's Disease (CD) the inflammation is typically transmural and may involve several intestinal tracts, including areas not easily accessible by an endoscope [2].

Several scores for the evaluation of endoscopic activity in IBD have been proposed. Although the first attempts to establish a numeric score to evaluate the endoscopic activity of UC date back to the 1950s, the challenge of correctly interpreting and codifying endoscopic features has not been solved, and the issue has become more important over the last decade. The wider utilization of potent therapeutic options for IBD patients, such as biologic drugs, has led to a consistent conceptual modification of the clinical

management, with a subsequent need for the identification of new end-points for the evaluation of therapeutic efficacy. This process has helped move endoscopic activity evaluation toward the more stringent concept of ‘mucosal healing’ (MH). In fact, a growing body of evidence suggests that the complete resolution of evident signs of inflammation during an endoscopic examination is associated with a better long-term outcome in terms of shorter hospital stays, an increase in sustained remission, and a decrease in the need for surgery [3]. The evidence for and limitations of the MH concept are still matter of debate in the literature [4] and are beyond the scope of the present paper. However, MH's growing relevance in the management of IBD has definitely influenced the challenges of endoscopic evaluation of disease activity.

Although different diseases have different issues, on a fundamental level an endoscopic score is needed to codify the different grades of intestinal disease activity observed during an endoscopic examination in a quantitative, simple, reproducible, and acceptable way. An early issue in the development of a scoring system has been the identification of high-risk lesions that are easily recognizable during an endoscopy. In addition, the increased complexity of the evaluation has led to growing disagreement between different operators (inter-observer variability) and even in repeated evaluations by the same operator (intra-observer variability). It is crucial to develop a score that will reduce such variation and standardize the interpretation of results in both trials and clinical practice

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[5]. The gradual shift from a symptom-based to a mucosal-based approach for IBD has led to new interest in the issue of endoscopic scores and reconsideration of the finality of the score itself. There has been a transition from the target to the gradation of endoscopic severity and therefore to the discrimination of patients based on disease severity and identification of the subset of patients meeting the MH criteria, despite MH's variable definition. Such attempts cannot be finalized because no clear definition has been stated for MH in either UC or CD. For the latter disease, clinical trials generally refer to the absence of ulcer, while for UC, most trials refer to a Mayo endoscopic score of 0–1 [6]. The lack of a validated cut-off for endoscopic scores in CD and the limitation of the current Mayo definition of 0–1 in UC further confirm that MH is yet to be clearly defined. In UC in particular, the current belief that endoscopic score of 0 and 1 have the same prognostic relevance has recently been challenged [7,8], and the finding of a relatively higher number of patients with endoscopic healing, as previously defined, than with clinical remission in some trials, such as ULTRA and PURSUIT [9,10], has raised additional questions about the definition of MH. Currently, primary end-points in clinical trials are still represented by clinical parameters and composite indexes, including symptoms, signs and lab tests. The scarce applicability of such parameters in clinical practice is decisively pushing toward the identification and better clarification of appropriate new end-points, and among these, endoscopic disease activity evaluation is one objective parameter that should be included [11].

The relevance of a correct evaluation of disease activity and of agreement among operators has been strongly reinforced by a recent observation that different evaluations of endoscopic reports, such as the evaluation by a 'central reader', may profoundly alter the report of a trial. In a randomized, double-blind, placebo-controlled, multicenter study investigating the safety and efficacy of a delayed-released mesalamine formulation in UC patients, the primary end-point of clinical remission at week 6 was not achieved in the original intention-to-treat analysis (30 vs. 20.6% in the treated vs. placebo group, $p=0.069$). Instead, it was observed after a central reading revision by seven expert readers who independently analyzed sigmoidoscopy recordings (29 vs. 13.8% in the treated vs. placebo group, $p=0.011$) and excluded 87 of 281 patients (31%) from the original population because they did not meet the inclusion criteria [12].

2. Ulcerative colitis

The evolution of the concept of endoscopic score is particularly evident in UC because the role of the endoscopic activity in disease management has long been recognized. Numerous scores have been used for the assessment of endoscopic activity in UC, and a recent systematic review identified 31 scoring systems proposed in the literature [13]. Among these, very few were constantly utilized in clinical trials. Early in 1937, Bargaen et al. described the importance of directly evaluating the mucosa of patients with ulcerative colitis using a rigid proctoscope in conjunction with a magnifying attachment [14], but the first endoscopic score to evaluate disease activity in UC patients in a clinical trial was proposed by Truelove and Witts in 1955 [15]. In 1964, Baron et al. developed a score to evaluate the appearance of rectosigmoid mucosa using a rigid proctoscope, in which disease activity was expressed by severity of bleeding and friability without considering ulcerations [16]. The Baron score was modified by Feagan et al., in 2005, with the removal of the qualitative assessment of different levels of bleeding, and the inclusion of ulceration in the evaluation [17]. Baron score has represented for a long time the most frequently used endoscopic score in clinical trials. Its modified version represents a simple and efficacious tool to evaluate endoscopic activity, but the lack of an

appropriate validation and the unclear definition of MH may limit the utilization of the score in the future.

In 1987, Schroeder et al. described an instrument to measure disease activity called the Mayo score, which included both endoscopic and clinical items [18]. The part of this composite score that evaluate endoscopic activity, namely the Mayo endoscopic subscore (MES), is the scoring system most widely used in clinical trials to describe endoscopic activity as easily reproducible. It is characterized by 4 components and scores range from 0 to 3, with 0 indicating inactive disease with normal mucosa; 1 indicating mild disease (erythema and mild friability); 2 indicating moderate disease (marked erythema, friability, absent vascular pattern and erosions); and 3 indicating severe disease (spontaneous bleeding and diffuse ulceration). MH was defined as a MES of 0 or 1, which predicts a better outcome than a MES of 2 or 3 with an associated reduction in colectomy. MES has been used in multiple clinical trials [13]. Its main limitations are the fact that the definition of MH, although commonly used, has not been validated, and as mentioned above, recent data suggest a difference prognostic relevance between the scores of 0 and 1 [7]. Moreover, the score does not discriminate between superficial and deep ulcerations, and grades 1 and 2 may present significant overlap. Osada et al. found adequate inter- and intra-observer agreement from the experts, but agreement was markedly lower when trainees were involved in the scoring [19]. More recently, the suboptimal agreement of the score was confirmed, and surprisingly, the agreement coefficient was higher among non-expert than expert gastroenterologists ($\kappa=0.71$ vs. 0.53 , respectively) [20].

The need for a better definition of endoscopic activity and the lack of a fully validated tool have recently led to the proposal of new indexes in an attempt to increased inter-observer agreement. In 2012, Travis et al. proposed the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [21], and, in a subsequent study, the authors evaluated the reliability of the UCEIS and validated it with an independent cohort of investigators [22]. The UCEIS score represents a validated index of endoscopic severity of UC, and it is considered a useful tool in clinical practice for reducing variations between different observers. However, it has several limitations. As for other indexes, the definition of MH remains unclear. In addition, the thresholds for mild to moderate and severe disease have not been completely validated. Only the most severely affected part of the mucosa is scored, meaning that disease extension is not evaluated. Most importantly, even though the score offers a detailed description of mucosal inflammation, a real advantage in the inter-observer agreement over simpler scores, such as Baron and MES, has yet to be demonstrated [12].

In an attempt to include disease extension and to increase inter-observer agreement, the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) was recently proposed [23]. The score shows significant correlation with the clinical indexes, laboratory measurement of active disease, and good correlation with patient-defined remission. Therefore, the UCCIS may represent a useful tool based on the evaluation of each colonic segment that provides reproducible results in endoscopic scoring of patients with UC. However, such a score presents some limitations. First, the original study for the development of the score was a single-center study of only 50 patients, and larger studies are needed to validate the usefulness of this index. Second, calculating the score requires a total colonoscopy, which is a more expensive and invasive procedure that is less well tolerated by the patient compared to sigmoidoscopy. Moreover, UCCIS is pretty more complex comparing with other scores and therefore its widespread utilization in every endoscopic center may not be feasible.

Very recently, to conjugate the simplicity of the MES with the need to evaluate disease extension, a Modified Mayo Endoscopic Score (MMES) was proposed [24]. Lobaton et al. calculated this new

Table 1
Most frequently used and more recently proposed endoscopic scores in UC.

Score [year]	Calculation	Pro	Contra
Modified Baron Index [2005]	Stepwise 5 grade scale: Normal mucosa (0) granular with an abnormal vascular pattern (1) friable (2) microulcerations with spontaneous bleeding (3) gross ulceration (4)	Easy in clinical practice Require only rectosigmoidoscopy	Not validated No definition of MH Not considering disease extension Low agreement for granularity and erythema
Mayo endoscopic subscore (MES) [1987]	Stepwise 4 grade scale: Normal (0): no inflammatory signs Mild (1): erythema Moderate (2): friability, erosions Severe (3): spontaneous bleeding, ulcerations	Easy in clinical practice Prospective study Most used in clinical practice and clinical trials Require only rectosigmoidoscopy	Overlap grade 1–2 Low interobserver agreement Not considering disease extension Definition of MH questionable
Ulcerative Colitis Endoscopic Index of severity (UCEIS) [2012]	Total score (3–11) from the sum of 3 components: Vascular pattern: normal (1), patchy obliteration (2), obliterated (3) Bleeding: none (1), mucosal (2), luminal mild (3), luminal moderate-severe (4) Lesions: none (1), erosions (2), superficial ulcer (3), deep ulcer (4)	Validated High interobserver reproducibility Require only rectosigmoidoscopy	No definition of MH Not considering disease extension No established thresholds for mild, moderate and severe disease Definition of superficial vs. deep ulcer
Ulcerative Colitis Colonoscopic Index of severity (UCCIS) [2013]	Total score (0–162) = $3.1 \times (\text{sum of A in 5 tracts}) + 3.6 \times (\text{sum of B}) + 3.5 \times (\text{sum of C}) + 2.5 \times (\text{sum of D})$ (A) Vascular pattern: normal (0), partially visible (1), complete loss (2) (B) Granularity: normal (0), fine (1), coarse (2) (C) Lesions: none (0), erosions or pinpoint ulcers (1), numerous shallow ulcers (2), deep ulcer (3), diffuse ulceration (4) (D) Friability/bleeding: none (0), friability (1), spontaneous bleeding (2)	Consider disease extension Significant correlation with clinical index and laboratory tests Significant interobserver agreement	Not validated in a different casistic Single center study (only 50 patients) Requires total colonoscopy No definition of MH No established thresholds for mild, moderate and severe disease
Modified Mayo Endoscopic Score (MMES) [2015]	Total score = $(\text{sum of MES in 5 tracts}) \times \text{disease extent (dm)} / \text{no. of segment with active inflammation (MES} \geq 1)$	Consider disease extension Easy in clinical practice Significant correlation with clinical index, laboratory tests and histology Complete colonoscopy not essential	Not validated in a different casistic Inter-observer agreement not assessed No established thresholds for mild, moderate and severe disease

Abbreviations: MH = mucosal healing; MES = Mayo endoscopic subscore.

score by multiplying the sum of the MES values of the 5 colonic segments (rectum, sigmoid, descending, transverse, and ascending colon) by the total extension of inflammation (in decimeters – dm) and dividing that by the number of segments with active inflammation ($\text{MES} \geq 1$). The MMES showed significant correlation with fecal calprotectin ($r=0.73$), clinical index ($r=0.54$), and histologic score ($r=0.62$). Because of its simplicity and correlation with different parameters of disease activity, the MMES is a promising and feasible tool not only in trials but even in clinical practice. However, considering that MMES has been just very recently developed, further studies are needed to better assess the validity of the score (i.e., inter-observer agreement was not assessed yet) and its potential application in UC patients.

The most frequently used and more recently developed scores in UC are summarized in Table 1.

The importance of the ongoing problem of endoscopic evaluation of UC is highlighted by the fact that, despite the first scores dating back to the 1950s, new scores have been proposed in the last 2–3 years. On the one hand, this has led to the attempt of a more homogenous definition for patients with inactive disease (mucosal healing) by synthesizing the best features of the most frequently used scores (Mayo and Baron) in the development of the UCEIS score. On the other hand, there is a renewed focus on the

challenge of evaluating disease extension. Most of the currently used scores in UC calculate only the activity of the most inflamed colonic segment (generally rectum/sigma) to enable the calculation of the score from recto-sigmoidoscopy. This could have a concrete advantage of avoiding a complete colonoscopy, which is a more expensive and time-consuming procedure that could be inappropriate in specific situations (i.e., severe flares). However, the extent of mucosal inflammation is clearly one of the most important factors to determine disease course [1], and not including disease extension in the endoscopic score may be a limitation. If the score considers only a segment of colon, patients with completely different clinical situations, such as severe proctitis and severe pancolitis, may have the same endoscopic score. Moreover, a score determined by evaluating only the most affected tract may not reflect the possible progression of the disease in proximal areas (possible in up to 50% of patients [25]) because the numeric score would not change. Finally, the possibility of patchy healing of the colon in treated UC has been highlighted [26,27]. The limitations of an assessment of disease activity based only on a sigmoidoscopy have recently been highlighted by a retrospective analysis of 545 colonoscopic evaluations of UC patients in which the most inflamed segment was found proximal to the splenic flexure in 27% of cases. Severe activity (Mayo endoscopic

Table 2
Most frequently used endoscopic scores in CD.

Score [year]	Calculation	Pro	Contra
CDEIS [1989]	Total score (0–44) = sum of 5 segments score*/no. of explored segments + ulcerated stenosis (yes = 3, no = 0) + non-ulcerated stenosis (yes = 3, no = 0) *segment score from the sum of: deep ulceration (yes = 12, no = 0) superficial ulceration (yes = 6, no = 0) surface involved (0–10) surface ulcerated (0–10)	Gold standard Validated Prospective study Extensively applied in clinical trials	Complexity No definition of MH No correlation with CDAI
SES-CD [2004]	Total score (0–56) = sum of 5 segments score including the sum of: Ulcer: none(0), 0.1–0.5 cm(1), 0.5–2 cm(2), >2 cm(3) Ulcerated surface: none(0), <10%(1), 10–30%(2), >30%(3) Affected surface: none(0), <50%(1), 50–75%(2), >75%(3) Narrowing: none(0), single passable(1), multiple passable(2), unpassable(3)	Validated Prospective study Simpler than CDEIS Correlated with CDEIS	No definition of MH No correlation with CDAI Less applied in clinical trials
Rutgeerts [1990]	Stepwise 5 grade scale: I0 – no lesions in neo-terminal ileum I1 – <5 aphthous lesions in neo-terminal ileum I2 – >5 aphthous lesions with normal mucosa, skip areas with larger lesions, anastomotic lesions I3 – diffuse aphthous ileitis I4 – diffuse inflammation with ulcer, nodules and/or stenosis	Prospective study Extensively applied in clinical trials Strong prognostic relevance	No formal validation Only in post-operative ileo-colonic resection

Abbreviations: MH = mucosal healing; CDAI = Crohn's disease activity index.

score = 3) was more frequently found in proximal than in distal segments, and 40% of patients with inflamed mucosa in the proximal tracts had no inflammation in the rectum-sigmoid colon [28]. Our group has recently reported that the tUCEIS calculated as a sum of 5 colonic segments (total UCEIS – tU) performed better than the regular UCEIS in term of correlation with clinical index and prognostic value [29]. Considering the relevance of the issue, the most recently proposed indexes, namely the UCCIS and the MMES, include the assessment of disease extension in their calculation, but the debate is still open [30]. It is noteworthy that, despite the proposal of different scores, the reproducibility optimization still remains an unmet goal in the evaluation of endoscopic activity in UC patients, probably due to the intrinsic nature of the disease.

3. Crohn's Disease

As previously mentioned, the endoscopic evaluation of CD has many challenges. It is well known that symptoms may not correlate with the activity of disease as measured by endoscopic and cross-sectional imaging techniques [31], and the clinical Crohn's Disease Activity Index (CDAI) still represent the reference parameter in clinical trials for disease activity assessment. However, the need to overcome a simply symptom-based approach and the relevance of intestinal healing as a therapeutic end-point affect the management of CD patients as well, and validated endoscopic scores have been developed for this purpose. A recent systematic review identified 9 endoscopic scores for CD [32]. Among these, two had undergone an appropriate validation process [33,34], and the Rutgeerts score [35], represents a widely used tool in the post-operative setting, despite its lack of formal validation.

The first validated endoscopic evaluative score for CD severity is the Crohn's Disease Endoscopic Index of Severity (CDEIS), presented by the Groupe D'Etudes Therapeutiques Des Affections Inflammatoires du Tube Digestif (GETAID) in 1989 in a

multiphase and prospective study [33]. In the first development phase, two endoscopists simultaneously evaluated colonoscopies from 75 patients, with one endoscopist observing the other during the procedure. The calculation of the total score (range 0–44) was derived from a formula that included the presence of deep or superficial ulceration, the extent of ulcerated and inflamed mucosa, and the presence of ulcerated and non-ulcerated stenosis, in 5 ileo-colonic segments (rectum, sigmoid/left, transverse, right colon and ileum). A limitation of this approach could be fact that the two endoscopists scored the items while physically present in the same procedure room, therefore limiting the independence of the observations. Furthermore, segments that were not evaluated because of technical difficulties, anastomotic narrowing, or surgery were not considered for these calculations even though they could represent important aspects. In terms of the validation phase, a recent study reported that a central reading of the CDEIS to assess CD severity by a group of 4 readers had excellent intra- and inter-observer reliability (intra-observer ICC, 0.89; 95% confidence interval [CI], 0.86–0.93 and inter-observer ICC, 0.71; 95% CI, 0.61–0.79) [32]. Potential limitations include no stated definition of MH and the fact that the CDEIS does not correlate with CDAI [36]. Moreover, the complexity of the calculation is the real limitation to the widespread use of the score. However, the CDEIS still represent the gold standard for endoscopic activity evaluation in CD. In fact, the CDEIS has been used as an inclusion criterion in some studies and as end-point in several clinical trials [32].

In 2004, to simplify the complexity of CDEIS, Daperno et al. used a prospective study to develop the Simple Endoscopic Score in Crohn's Disease (SES-CD) [34]. The four parameters of the CDEIS with high inter-observer agreement were adopted in the SES-CD: ulcer size, proportion of surface covered by the ulcer, proportion of surface covered by other lesions and luminal stenosis. Each descriptor was graded in a stepwise manner, and the total score was calculated as the sum of all the items in each segment, with a range

of 0 to 56. Agreement for the items was again assessed by two endoscopists who graded 71 colonoscopies, resulting in inter-observer ICCs for the SES-CD and CDEIS of 0.98 and 0.90, respectively. As in the CDEIS validation, the agreement phase was determined by two endoscopists who evaluated the same procedure simultaneously. Although the endoscopists scored the colonoscopy without communicating, they may have been influenced by one another. In terms of the validation phase, Khanna et al. reported that a central reading of the SES-CD by a group of 4 readers to assess CD severity had very good intra- and inter-observer reliability (intra-observer ICC, 0.89; 95% CI, 0.86–0.93 and inter-observer ICC, 0.71; 95% CI, 0.63–0.76) [37]. The SES-CD simplified index was highly correlated with the CDEIS (Spearman's $r=0.883$), and this correlation became almost perfect when both scales were scored by a single endoscopist (Spearman's $r=0.938$, $p<0.0001$) [38]. The relationship between score and disease activity has not been clearly defined; however, two studies [39,40] have proposed a correlation between scoring and inflammation [remission (0–2), mild inflammation (3–6), moderate inflammation (7–16) and severe inflammation (>16)]. Because of the high degree of correlation between the CDEIS and the simplicity of its application, the SES-CD has been used in clinical trials [32] and may even be implemented in clinical practice. In the CDEIS, no clear definition for MH has been provided.

One of the most frequently used endoscopic scores is the Rutgeerts score for postoperative CD recurrence. It was formally developed 1990 by examining 89 patients with ileal resection for CD and observing clinical outcomes in patients with early neoterminal ileum lesions. A 5-grade stepwise numeric index was developed for the gradation of endoscopic postoperative recurrence in the neo-terminal ileum. Patients with lower scores had a better prognosis than those with more severe endoscopic lesions [35]. Although the score has been used in both trials and clinical practice, only a few very recent studies have explored intra- and inter-observer agreement, which opens the door to a formal validation [41,42]. For its consistent correlation with prognosis, the Rutgeerts score is the best example of the application of a clinical score to the concrete management of patients, and in the specific subset of post-operative patients, it is probably the most obvious confirmation of the role of MH in disease outcome. For that reason, the score has recently been included in a clinical trial that represent the first treat-to-target study in which endoscopic activity has been considered a primary end-point for decision-making (POCER) [43]. Moreover, it has been used extensively to determine efficacy in clinical trials in post-operative CD patients [32].

Table 2 summarizes the most commonly used endoscopic scores in CD.

4. Conclusion

The challenge of endoscopic evaluation of disease activity in IBD is far from solved. In UC, several different scores have been proposed, but not one has been definitely adopted as the 'gold standard' for endoscopic activity evaluation. In CD, the importance of the endoscopic evaluation has only recently been highlighted. The application of endoscopic scores has been strongly influenced in the last decade by the increasing relevance of the MH as an important end-point for the management of IBD. In addition to the current limitations and the over-estimation of the MH concept, the key relevance of the endoscopic evaluation for IBD assessment and management has been underlined in recent years. Consequently, both old and new challenges relative to the application of endoscopic scores are being considered and evaluated extensively. Available data indicating that the current methods available to evaluate endoscopic disease activity are sub-optimal are

increasing rapidly, and the same MH does not yet have a universally accepted definition. Because the widespread use of central readers to improve the quality and agreement of endoscopic reports is not feasible, a concrete solution appears to be the implementation of efficient scores that may reduce variability and improve the quality of endoscopic reports. To accomplish this, a more intense commitment by scientific societies to implement correct utilization of endoscopic scores is desirable. The education and training of endoscopists could lead to consistent improvements in the inter-observer agreement and reproducibility of the endoscopic reports, as recently shown in the preliminary results of an Italian endoscopic educational program [44]. In the longer term, the progress of available tools (i.e., high-definition endoscopes), may contribute to a more accurate definition of endoscopic activity, as indicated by a preliminary study [45]. Moreover, the wider availability of multimedia tools in the endoscopic room will probably lead to the utilization and transfer of video for a more complete evaluation of endoscopic activity in IBD patients.

Conflict of interest

None declared.

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