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Endoscopic scoring systems for the evaluation and monitoring of disease activity in Crohn's disease

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ABSTRACT

Crohn's disease is a chronic relapsing idiopathic condition that can affect any part of the gastrointestinal tract. It has been shown that mucosal healing is associated with improved clinical outcomes such as reduced risk of surgery, hospitalization and complications. Nowadays mucosal healing is considered the optimal target of medical therapy. To evaluate the mucosa in an objective and standardized manner, it is important to rely on accurate and validated endoscopic scores. The Crohn's disease endoscopic index of severity, the simple endoscopic score for Crohn's disease as well as the Rutgeerts score will be reviewed. Their clinical implications and limitations will be discussed.

Introduction

Crohn's disease (CD) is a condition that can present with different phenotypes, disease locations and severity of inflammation. Although CD may involve any part of the gastrointestinal tract, 20% of patients have isolated colonic disease, 30% have small bowel alone, and 50% of patients have involvement of both the ileum and the colon. Endoscopic findings include mucosal edema, erythema, friability, granularity, cobblestones, ulcers and strictures. It has been well documented that there is a poor correlation between symptoms, as measured by the Crohn's Disease Activity Index (CDAI), and endoscopic disease activity in CD [1,2]. Therefore, endoscopic evaluation is considered a more objective measure of disease activity in both the clinical and research settings.

The management of Crohn's disease has evolved in the past decade with the advent of novel therapeutic agents capable of achieving endoscopic healing [3–5]. Nowadays, clinical remission based on symptom control alone is no longer acceptable. Clinicians need to strive to obtain healing of the gastrointestinal mucosa [6], the definition of which remains to be elucidated. The impact of such a treatment target has been evaluated in multiple studies. Mucosal healing has been associated with a reduced risk of surgery, hospitalization, disease-related complications and with a better long term clinical remission [7,8].

It has been customary for gastroenterologists to describe the diseased segments visualized during endoscopy. However, endoscopists tend to describe lesions very differently, with some giving very detailed accounts and others less so. Given that mucosal healing is the recommended target for medical therapy, it is crucial that there is a standardized assessment of disease activity, including disease severity and extent, to allow for a more objective evaluation of response to therapy. A good endoscopic score must accurately measure the outcome it is intended to evaluate, detect a meaningful change in the disease and provide consistent results in patients with unchanged condition. In addition, it must be easy to use in clinical practice and research settings. Currently, the Crohn's Disease Endoscopic Index of Severity (CDEIS) [9] and the Simple Endoscopic Score for Crohn's Disease (SES-CD) [10] are the most commonly used indices to assess disease activity and response to therapy. The Rutgeerts score is used to assess disease recurrence in the post-operative phase [11].

In both research and clinical practice, endoscopists must recognize endoscopic lesions and their anatomic location accurately, report lesion characteristics correctly, and document disease activity effectively. Therefore in this chapter, we will review the Crohn's disease endoscopic index of severity, the simple endoscopic

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score for Crohn's disease, as well as the Rutgeerts score. Their clinical usage, limitations and unmet needs will be discussed.

Crohn's disease endoscopic index of severity (CDEIS)

In 1987, the GETAID group recognized that, while endoscopy findings were essential to identifying effectiveness of medications, they were not being considered among the primary or secondary endpoints in clinical trials. Therefore, in the first study of its kind, Modigliani and Mary assessed inter-observer variability for ileocolonoscopic lesions in Crohn's disease. They found good to excellent inter-observer agreement for superficial and deep ulcers, stenosis, surface affected by disease and global evaluation of lesion severity (GELS) [9]. Based on these findings, they proceeded to develop and validate the CDEIS in 1989. In the first phase of the study, 2 endoscopists reported findings on 75 colonoscopies (one performing it, and the second observing in real time). The colon was divided into five segments and the endoscopists independently completed a checklist for mucosal lesions (9 in total) for each segment. For each segment, they also scored ulcerated surface and affected surface (surface with mucosal lesions) on a scale of 0–10 cm (representing 0–100% of the surface visible), and recorded their GELS. Multiple linear regression models were used to define the combination of endoscopic lesions that correlated best with the GELS and active disease. This led to the current CDEIS, which was then validated on a different set of test patients [9]. Shortly thereafter, the GETAID group first used the CDEIS in a clinical trial setting to identify that only 13% of patients with colonic Crohn's disease on corticosteroids were actually in endoscopic remission [12].

To calculate the CDEIS, the bowel is divided into 5 segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) and each segment is initially calculated separately. Points are given for presence or absence of deep and superficial ulcers (0 or 12 points for deep, 0 or 6 points for superficial). Surface involved in disease (any type of lesion) and ulcerated surface are each measured in cm from 0 to 10. The total score of all the segments is added together and divided by the number of segments that are visualized. The presence of stenosis anywhere in the ileocolon is given additional points to the total value: 3 points for ulcerated stenosis and an additional 3 points for non-ulcerated stenosis [9]. Score for CDEIS ranges between 0 and 56, however, cut off values for disease severity and responsiveness to therapy have not been properly defined [13]. In clinical trials, for example, a significant decrease in median CDEIS from baseline to a second time point is indicative of an effective therapy [14]. (Table 1, Fig. 1).

Simple Endoscopic Score for Crohn's disease (SES-CD)

It has been well documented that there is a lack of correlation between clinical symptoms and endoscopic findings. Therefore, as clinical trials progressed, it became evident that the end point of therapy should be endoscopic healing of the bowel. However, while the CDEIS was very valuable, it was viewed as time consuming and complicated to use. Therefore, in 2004, Daperno's group developed and validated the simple endoscopic score. The items in the SES-CD were chosen from the GETAID studies for CDEIS, based on the important endoscopic features that contributed to clinical symptomatology and had also been highly reproducible. These variables were ulcer size, ulcerated surface, affected surface (with any lesion) and narrowing. In the study, the colon was again divided into five segments and immediately after the procedure, an endoscopist completed a scoring sheet using the SES-CD and CDEIS. 70 colonoscopies were used in the development phase and an additional 121 in the validation phase. Multiple regression analyses with CDEIS as the dependent variable were highly significant. Although regression modeling created a complex equation that closely correlated the CDEIS to the SES-CD, it was simplified to the sum of the four aforementioned variables. This allowed for a balance between ease of calculating the endoscopy score and a satisfactory correlation of the SES-CD with the CDEIS (pearson correlation coefficient SES-CD to CDEIS 0.887 and spearman rank correlation coefficient SES-CD to CDEIS 0.91). Further, the correlation between the SES-CD and CRP was highly significant (while less so for albumin and CDAI). A second endoscopist reviewed half of the colonoscopies to assess reproducibility, which was found to be very good [10]. The original validation study for SES-CD found a strong correlation with the CDEIS [10]. Since then, other studies have strengthened this finding, with correlation coefficients ranging from 0.86 to 0.92 among central readers [15–17]. Further the change in CDEIS and SES-CD from baseline to follow up colonoscopy correlated well ($r = 0.828$, $p < 0.001$) [15].

To calculate the SES-CD, the bowel is divided into 5 segments: ileum, right colon (ileocecal valve, cecum, and ascending colon to hepatic flexure), transverse colon, left colon (descending colon from splenic flexure, and sigmoid colon) and rectum. Each segment is initially calculated separately, and all values are added together to provide a final score. Points are given from 0 to 3 for each of four variables, and each feature is clearly outlined. Ulcer size is scored as 1 point for aphthous ulcers (0.1–0.5 cm), 2 points for large ulcers (0.5–2 cm) or 3 points for very large ulcers (>2 cm). Ulcerated surface is scored as 1 point for <10%, 2 points for 10–30% or 3 points for >30% ulcerated surface. In other words, if you 'bunched' all the ulcers together, the percent of the surface it would cover is the ulcerated surface. Affected surface (described as surface with any lesions of CD) is scored as 1 point for < 50%, 2 points for 50–75% and 3 points for > 75% affected surface. In other words, when you look at the entire surface of a bowel segment, how much of it has any disease present. Presence of stenosis is scored as 1 point for a single narrowing that can be passed, 2 points for multiple narrowings that can be passed and 3 points for a narrowing that cannot be passed. If any of these four features is not present in a segment, it is scored as 0 (for that feature for that segment). Therefore the maximum score for a segment is 12, and the maximum total score is 56 (as it is not possible to give three points per segment consistently for narrowings; narrowing varies from 0 to 11 points in total). For disease severity, suggested a cut-off value for healed bowel is a score of 0–2, mild disease is 3–6, moderate disease is 7–16 and

Table 1
Features of the Crohn's disease endoscopic index of severity (CDEIS) [14,15].

Features described in the system	Scoring	Division of the ileocolon	Definitions of disease severity
1. Superficial ulcers 2. Deep ulcers 3. Surface involved in disease 4. Ulcerated surface 5. Ulcerated stenosis 6. Non-ulcerated stenosis	Total: 0–44 (all segments added together) Each feature has a different point value	5 segments: terminal ileum; ascending colon; transverse colon; descending and sigmoid colon; rectum	Not clearly defined: Healed: ≤3 Mild: <5 Moderate: 5-15 Severe: >15 Response to therapy: not defined

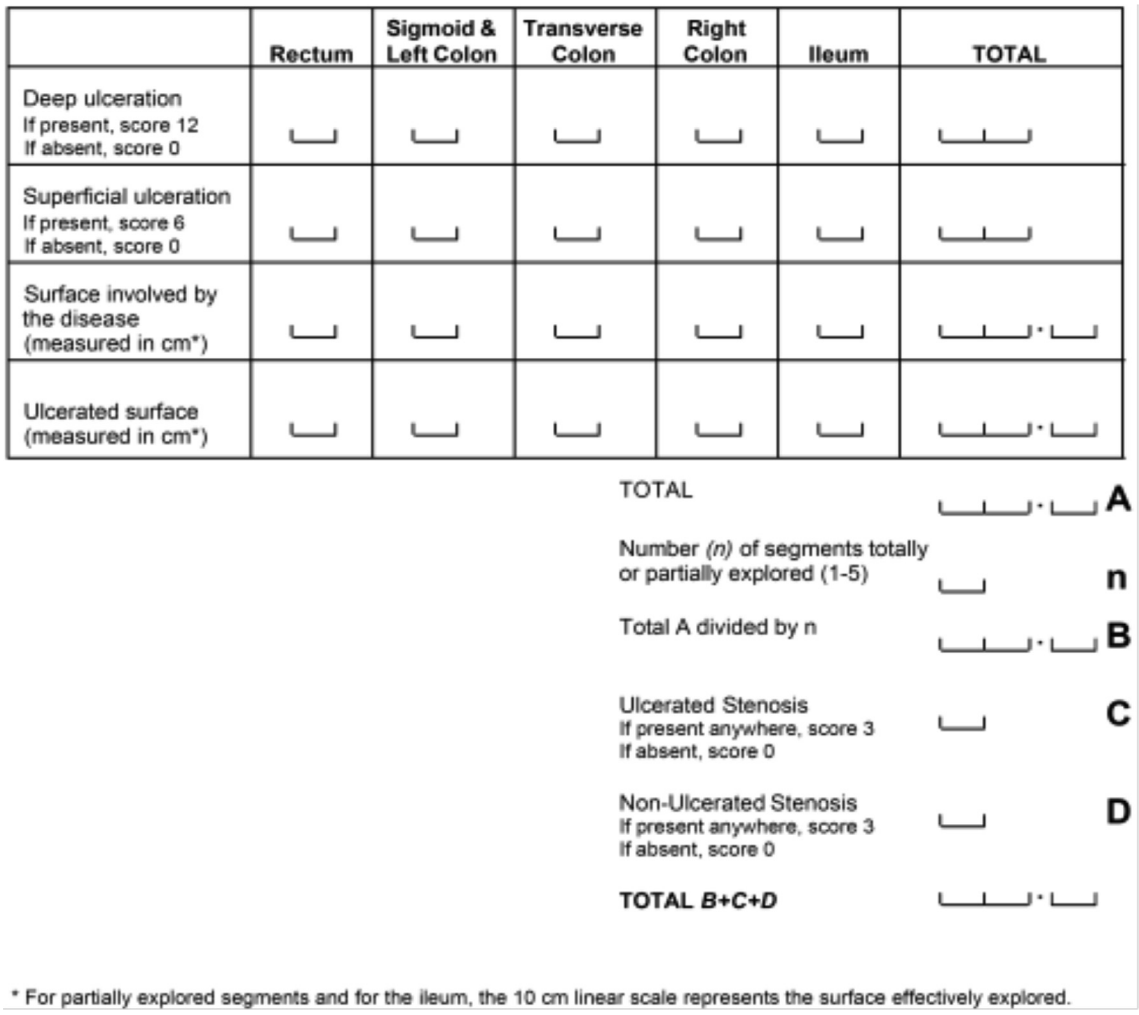

Fig. 1. Calculating the CDEIS.

severe disease is a score >16. The cut-off values for responsiveness to therapy, however, have not been defined [13,17]. (Table 2, Fig. 2).

Reliability of the CDEIS and SES-CD

Outside of clinical trials, a few studies have assessed inter-rater reliability for gastroenterologists who have not been trained to use the scoring systems. In all of these studies the ICC for both SES-CD and CDEIS were consistently good (ICC 0.6–0.8). In the Dubcenco et al.'s study, the ICC improved significantly for the SES-CD after targeted training on areas of weakness (from ICC 0.78 to 0.85) [18]. In Daperno et al.'s study, as expected, the ICC for untrained physicians was significantly lower than for 14 physicians trained to use the scores (ICC SES-CD 0.68 and CDEIS 0.67 for untrained versus ICC SES-CD 0.93 and CDEIS 0.83 for trained) [19]. Notably, for gastroenterologists trained on both scoring systems, the SES-CD has been found to have higher inter-rater reliability than the CDEIS [16,19].

Reliability, validity, responsiveness and feasibility were also assessed for both SES-CD and CDEIS in a recent Cochrane review article [20]. Inter-rater reliability has been found to be good to very good (from 6 studies of CDEIS and 4 studies of SES-CD), while intra-rater reliability data is sparser. Content validity has not been assessed. Both criterion validity and construct validity have ranged from poor to excellent. The scoring systems have most closely correlated with fecal calprotectin and with CDAI. Seven studies demonstrated significant decrease in CDEIS after administration of

Table 2
Features of the simple endoscopic score for Crohn's disease (SES-CD).

Features described in the system	Scoring	Division of the ileocolon	Definitions of disease severity
1. Size of ulcers (aphthous < 0.5 cm, large 0.5–2 cm, very large > 2 cm) 2. Surface ulcerated 3. Surface involved in disease (affected) 4. Presence of narrowing/stenosis	Total: 0–56 (all segments added together) Each feature has a point value of 0–3	5 segments: terminal ileum; right colon; transverse colon; left colon; rectum	Healed: 0-2 Mild: 3-6 Moderate: 7-16 Severe: > 16 Response to therapy: not defined

	SES-CD values			
Variable	0	1	2	3
Ulcers	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%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Fig. 2. Calculating the SES-CD. The same variables are assessed for each of the five segments. Total score: add all values from the five segments.

Grade	Endoscopic findings
i_0	No lesions in the distal ileum
i_1	≤ 5 apthous lesions
i_2	> 5 apthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to ileocolonic anastomosis
i_3	Diffuse apthous ileitis with diffusely inflamed mucosa
i_4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing

Fig. 3. Determining the Rutgeerts score.

treatment (of known efficacy), but minimal data is available on responsiveness for SES-CD. However, there is no standard definition of responsiveness to therapy for either CDEIS or SES-CD. Feasibility has not been formally assessed in any study [20].

Rutgeerts score

In 1984, Rutgeerts et al. assessed the natural history of recurrent Crohn's disease after 'curative' ileocecal resection. The study included 114 patients who had had a resection within ten years. Disease recurrence was based on the presence of ulcers (aphthous – "small, punched out… slightly raised borders" and large - "oval, longitudinal or serpiginous"). The incidence of disease recurrence was 72% at one year, 79% at 1–3 years and 77% at > 3 years. While the incidence rate did not appear to increase over time, the lesions became progressively more severe over time. The disease recurred at the neoterminal ileum in 88%, and did not correlate with the presence of symptoms [21]. In 1990, Rutgeerts et al. assessed 89 patients with ileocecal resections and developed the endoscopic index for grading postoperative recurrence, known as the Rutgeerts score. The score ranges from i0 (no recurrence) to i4 (diffuse inflammation). 3 years post resection, 80% of patients with a score i0 or i1 had no change in endoscopic lesions, while 92% of patients with i3-i4 had disease progression [11].

For the Rutgeerts score, there are five grades of severity of lesions in the neo-terminal ileum. i0 indicates no lesions present. i1 indicates that there are <5 aphthous ulcers present. i2 is when there is > 5 aphthous ulcers (with normal mucosa between them) or skip areas with larger lesions or lesions confined to the ileocolonic anastomosis (<1 cm in length). i3 is the presence of diffuse aphthous ileitis with inflamed mucosa (between ulcers) and i4 is diffuse inflammation with large ulcers, nodules and/or strictures. Post resection ileocolonoscopy is recommended 6–9 months after surgery. At that time, the Rutgeerts score can predict disease recurrence: i0-i1 is considered low risk for disease recurrence (6% at 5 years); i2 is moderate risk (27% risk of recurrence at 5 years) and i3-i4 is high risk of recurrence (63% and 100% respectively at 5 years) [11]. (Table 3, Fig. 3).

Practical challenges and unmet needs

One of the main challenges of the CDEIS is calculating the overall score, as each of the features is calculated separately and weighted differently. For example, ulcers are calculated as present/absent, with deep and superficial ones given different values altogether. Surface measurements use a visual analogue scale (VAS) from 0 to 10 and can be difficult to accurately assess as well [18,22]. Collectively, these values need to be calculated for each segment, and then divided by the number of segments actually visualized. In fact, there are 10 calculations (sums, division, multiplication) required. This can become quite cumbersome, and prone to errors. It can also be very time consuming, which would make it less useful in day-to-day practice. Further, while each endoscopic feature was validated in multiple regression analyses, follow up studies identified a number of features that had poor inter-rater reliability. These features included ulcer depth and assessment of stenosis [10,13,18]. These measures can therefore lead to variability and inaccuracies in the score. (Table 4).

Another practical issue in using the CDEIS is the lack of validated cut off values for inactive, mild, moderate and severe disease. Further, there is also a lack of cut off values for response to therapy. In two studies by Sipponen et al. [17,23], CDEIS below 3 indicated inactive disease, 3–9 was mild disease, 9–12 was moderate disease and ≥12 was severe disease. Another study chose CDEIS less than 5 for mild disease, 5–15 for moderate disease and >15 for severe disease [14]. Few published studies have assessed change in CDEIS in response to treatment, with proposed definitions including a decrease of 5 from baseline or a decrease of 50% from baseline [15]. A post-hoc analysis of SONIC found that the primary end point of steroid free remission at week 50 could be predicted using both mucosal healing (defined as absence of ulcers) and endoscopic response, defined as a decrease in baseline CDEIS by 50% by week 26 (sensitivity 73%, specificity 46%) [15].

While there are significantly fewer calculations in the SES-CD compared to the CDEIS, each segment is still calculated separately, and this can be time consuming (and prone to errors) [24].

Table 3
Features of the Rutgeerts score.

Features described in the system	Scoring	Division of the ileocolon	Definitions of disease severity
Aphthous ulcers, large ulcers, inflamed intervening mucosa, diffuse inflammation	i0 to i4 (with criteria for each)	Neo-terminal ileum examined	Low risk of recurrence: i0-i1 Medium risk: i2 High risk: i3-i4

Table 4
Strengths and limitations of the scoring systems.

Scoring system	Strengths	Limitations
CDEIS	- Takes into account segments that are not visualized - Focuses on features of disease severity that have been correlated with GELS/active disease (ulcerations, surface involved with ulcers or disease) - Prognostic relevance has been demonstrated	- Difficult to use overall and especially in calculating the total at the end - Each feature is scored out of a different denominator - Surface involved and ulcerated is calculated in cm (which can be difficult) - It can be difficult to assess ulcer depth (superficial vs deep)
SES-CD	- Fairly easy to use, as each feature is scored 0–3, with clear definitions of how to determine the score to give - Each feature is very clearly defined (ex large ulcers are 0.5–2 cm, ulcerated surface <10%, 10–30%, >30%) - Surface involved and ulcerated is determined using VAS - Ulcers assessed based on size, not depth - Prognostic relevance has been demonstrated	- If all segments are showing subtle or mild disease activity, it is possible to get a higher score than if there is severe disease in only one segment - Does not take into account segments that are not visualized
Rutgeerts	- Gold standard for evaluation of postoperative recurrence of disease at neo-terminal ileum - Cut off values for disease recurrence have been validated - Easy to use	- Has not been fully validated - Only in post-operative ileo-colonic resection

All segments are added up to provide the final score, but this does not take into account segments that were not visualized or resected surgically. In addition, measurement of ulcer size, and surface ulcerated and affected can be somewhat subjective. Further, if all segments are showing subtle disease activity, it is possible to get a higher score than if there is severe disease in only one segment. However, severe disease in one segment would be considered more significant clinically than subtle diffuse disease and would have greater impact on management [13,17]. Similarly, a patient with isolated ileal or rectal involvement will have a much lower score than a patient with multi-segment colonic disease. The clinical impact of such isolated disease is at least as significant as the colonic disease; therefore, considerations should be made to give more weight to isolated ileal or rectal disease.

Similar to the CDEIS there is a lack of cut-off values for the SES-CD to define response to therapy. In a post-hoc analysis of SONIC, a decrease in baseline SES-CD of 50% at week 26 could predict steroid free remission at week 50 (sensitivity 74%, specificity 48%). Khanna et al. [13] assessed responsiveness of the endoscopic scores to detect clinically meaningful change in disease activity using data from the EXTEND trial (adalimumab). Four gastroenterologists reviewed 122 colonoscopies – at baseline and at week 8–12. The SES-CD showed numerically greater responsiveness to detect change, but a threshold for minimal clinically significant change has not been established. (Table 4).

Notably, neither of the scores takes into account ulcerations at an anastomosis, or disease involving the junction of two segments. Similarly, none of the scores are made to assess disease in remission. There are also several endoscopic features that have prognostic value in terms of risk of colorectal cancer, such as mucosal scarring and pseudopolyps that are not taken into account by either score.

The Rutgeerts score has the advantage of being simple, which makes it user friendly and easily to implement in clinical practice. It also has a strong prognostic relevance which makes is clinically important. However, there are several challenges with this score as well. Despite being used extensively in clinical practice and clinical trials, it has not been formally validated. In addition, it applies to the bowel anastomosis and the pre-anastomotic bowel, but does not take into account new disease development in another part of the bowel. As well, it cannot be used to follow disease improvement over time after initiation of medical therapy. Therefore, it would be advisable to use the CDEIS or SES-CD in addition to the Rutgeerts score in the post-operative endoscopic evaluation. (Table 4).

In view of the above-mentioned practical challenges, there is a clear need for an additional endoscopic score to assess disease activity in CD. In contrast to ulcerative colitis, CD presents in multiple locations and phenotypes, therefore, it is a challenge to develop a comprehensive score that will cover all these variables but also be simple enough to be used in clinical practice. A complex score would be difficult to adopt in busy clinical practice and too simple a score would not be adequate to accurately assess disease activity. There are currently a few international initiatives led by Robarts and the European Crohn's and Colitis Organization to determine the content and the cut-off values of a new validated, reliable and simple endoscopic score.

Summary

With the increased use of biologics, and newer agents being assessed in clinical trials, mucosal healing has become recognized as an important therapeutic end point and predictor of outcomes. The current available scores have allowed some standardization in the endoscopic evaluation, but significant practical challenges still exist. Therefore, there is a strong need for a validated and user-friendly endoscopic score with clear cut-off values that can reliably assess disease activity and remission in Crohn's disease.

Practice points

- Mucosal healing, as assessed through ileocolonoscopy, has become the target end point in therapeutic management of Crohn's disease.
- The Crohn's disease endoscopic index of severity (CDEIS) and the simple endoscopic score for Crohn's disease (SES-CD) are validated measures of Crohn's disease activity, while the Rutgeerts score assesses recurrence of disease after ileocecal resection.
- Currently, the CDEIS and SES-CD are primarily used in research studies, while the Rutgeerts score is also used in clinical practice.

Research agenda

- Further studies are necessary to identify the optimal cut-off values for the endoscopic scoring systems for both Crohn's disease severity and response to therapy.
- Research is underway to develop a more optimal endoscopic scoring system for Crohn's disease (that encompasses both active disease and remission).

Conflicts of interest

The authors have no conflict of interest to declare.

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Nil.

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