

# Implementation of the Simple Endoscopic Activity Score in Crohn's Disease

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## ABSTRACT

Simple Endoscopic Score for Crohn's Disease (SES-CD) was developed as an attempt to simplify Crohn's Disease Endoscopic Index of Severity (CDEIS). Since it was constructed from CDEIS, SES-CD performs comparably but also carries similar limitations. Several studies have utilized SES-CD scoring to describe disease severity or response to therapy. Some of them used SES-CD score as a continuous variable while others utilized certain cutoff values to define severity grades. All SES-CD cutoff values reported in published clinical trials were empirically selected by experts. Although in most of the studies that used SEC-CD scoring to define disease severity, a score <3 reflected inactive disease, no study is using score 0 to predefine inactivity. Studies applying SES-CD to define response to treatment used score 0. There is no optimal SES-CD cut-off for endoscopic remission. The quantification of mucosal healing using SES-CD scoring has not been standardized yet. As the definition of mucosal healing by SES-CD is unset, the concept of deep remission is also still evolving. Serum and fecal biomarkers as well as new radiologic imaging techniques are complementary to SES-CD. Current practice as well as important changes in endoscopy should be taken into consideration when defining SES-CD cutoffs. The optimal timing of SES-CD scoring to assess mucosal healing is not defined yet. To conclude, SES-CD represents a valuable tool. However, a consensus agreement on its optimal use is required.

**Key Words:** Crohn's disease, Crohn's disease severity, endoscopy, mucosal healing, remission, response, SES-CD, simple endoscopic activity score for Crohn's disease

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The complex nature of Crohn's disease (CD) mandates that scoring systems incorporate a wide array of endoscopic and imaging findings, adjusted for specific age groups, to properly describe disease phenotypes and its complications.<sup>[1]</sup> Endoscopic features of CD vary broadly and precise description of endoscopic lesions should include the type, location, depth, and the extent of the lesion. Many efforts toward the quantification of these characteristics have been made utilizing various endoscopic scoring tools. Required qualities of an accurate scoring system include reliability, validity, and sensitivity-to-change. CD Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score

for CD (SES-CD) are two scoring systems that have shown promising results. Endoscopic scores are being used more frequently by clinical trials to assess the efficacy of various treatment agents on inducing and maintaining mucosal healing. In fact, they are considered by some the gold standard tool indicating the presence or absence of active bowel inflammation.<sup>[2]</sup>

CDEIS is a validated scoring system in which six endoscopic variables (presence of deep ulcers, superficial ulcers, nonulcerated stenosis, ulcerated stenosis, proportion of ulcerated surface, and proportion of surface affected by disease) are assessed in each of the five ileocolonic segments: Rectum, sigmoid and left colon, transverse colon, right colon, and ileum. For these five segments, the percentage

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of ulcerated colonic surface and the percentage of surface “affected by any Crohn’s disease lesion” are indicated on a 10 cm visual analogue scale. CDEIS scores range from 0 to 44 and higher scores indicate more severe disease. Although CDEIS is often considered the standard for evaluating endoscopic disease severity in CD, its calculation is complex and its use has revealed several limitations. The major weakness of CDEIS lies in its apparent lack of practicality. More than that, there have been concerns that CDEIS may underestimate disease severity when only 1 out of 5 segments is involved, and especially the ileum. Finally, the absence of validated score cutoffs associated with specific prognostic values, response to treatment, and endoscopic healing, represents another limitation.<sup>[3]</sup> It is therefore argued that CDEIS is not the ideal index to define endoscopic remission.

SES-CD was developed in 2004 by a European multicenter prospective study as an attempt to simplify CDEIS. It was based on the importance and reproducibility of the most relevant endoscopic characteristics of CD.<sup>[4]</sup> The aim of the present review was to describe SES-CD scoring and evaluate its impact on defining CD severity, response to treatment, and remission after treatment based on the most recent literature.

## METHODS

A literature review was performed using MEDLINE and PUBMED. Clinical trials using SES-CD scoring to define disease severity, response to treatment, and remission after treatment were abstracted. Furthermore, case-controlled studies, cohort studies, as well as clinical reviews on the topic studied were considered. Finally, case reports, editorials, letters to the editors, and commentaries were also reviewed. All articles included in the present review were written in English language. The full text publications of all relevant articles were retrieved.

## CONSTRUCTION AND VALIDATION OF THE SES-CD

SES-CD is simpler than CDEIS scoring system that is based on four endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis). It is also assessed in the five ileocolonic segments. The variables included in SES-CD originate from a careful review of the Groupe d’Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) studies in France with regard to the importance and the reproducibility of the most relevant endoscopic characteristics of Crohn’s disease. Only those characteristics that were considered to contribute

to clinical symptomatology and were shown to have good reproducibility in the GETAID studies were incorporated in the SES-CD. Each of the four SES-CD variables is scored from 0 to 3, with the sum of the scores for each variable ranging from 0 to 15, except for the presence and extent of stenosis, which ranges from 0 to 11, yielding a total SES-CD score of 0–56. More specifically, ileocolonoscopy findings can be scored according to SES-CD as following: The four endoscopic variables are scored from 0 to 3 in each bowel segment (ileum, right/transverse/left colon, and rectum): presence and size of ulcers (none = score 0; diameter 0.1–0.5 cm = score 1; 0.5–2 cm = score 2; >2 cm = score 3); extent of ulcerated surface (none = 0; <10% = 1; 10%–30% = 2; >30% = 3); extent of affected surface (none = 0; <50% = 1; 50–75% = 2; >75% = 3); and presence and type of narrowings (none = 0; single, can be passed = 1; multiple, can be passed = 2; cannot be passed = 3). As with CDEIS, higher SES-CD scores indicate more severe disease.<sup>[4]</sup>

SES-CD construction and subsequent validation was based on a multicenter study from three countries. For the development phase of the study, 191 consecutive patients, with an established diagnosis of CD, were enrolled. The endoscopist completed an endoscopic scoring sheet immediately after colonoscopy. A second endoscopist observed the colonoscopy on the video monitor in some of the examinations (35/70 in the development phase and 36/121 in the validation phase) and recorded the lesions independently. Endoscopic lesions as defined above were shown to be reproducible in a sample of 71 paired examinations. Subsequently, in the first 70 consecutive patients (60 colonoscopies reaching the ileum), data of one of the endoscopists was randomly selected out of the 35 examinations performed by pairs. The new index was constructed by multiple linear regressions as a linear combination of independent variables showing the highest correlation with CDEIS, which was the dependent variable. The final SES-CD was based on a balance between simplicity of variable calculation and high correlation with CDEIS, and was defined as the simple sum of the four lesions across the observed segments. SES-CD was then validated on a sample of 121 additional patients (103 endoscopies reaching the ileum), with data from one endoscopist being selected at random out of the 36 examinations performed by pairs. A SES-CD value can be converted into a CDEIS value by the formula:  $CDEIS = 0.76 \text{ SES-CD} + 0.29$ .<sup>[4]</sup>

ES-CD was significantly correlated with CDEIS (Pearson’s correlation coefficient of 0.88,  $n = 70$ ) and this significant correlation was confirmed in subsequent studies.<sup>[5–7]</sup> However, it should be noted that SES-CD overestimates severity in inactive and mild CD when compared with CDEIS.<sup>[7]</sup>

## STRENGTHS AND WEAKNESSES OF SES-CD

Compared with CDEIS, SES-CD is easier and faster to calculate, and it gives reproducible results. Furthermore, it reliably correlates with CDEIS, which currently is the most widely accepted score.<sup>[8]</sup> Indeed, the size of ulcers and the extent of ulcerated surface are the most reproducible endoscopic parameters in the SES-CD system. Additionally SES-CD also evaluates luminal stenosis. Interestingly, instead of counting the sum of one SES-CD variable of all segments, the authors of a recent study counted the sum of the four variables of each segment, thus providing the option of calculating ileal and colonic SES-CD as two separate scores, which is not possible with CDEIS.<sup>[7]</sup>

Since it is derived from CDEIS, many SES-CD weaknesses are similar to those of CDEIS. One major limitation of SES-CD is that it mainly converts continuous into binary values of equal weight using cutoffs that have been empirically decided by experts. As a result, it fails to capture synergistic effects based on the interactions of interdependent systems. Of note is that the two indices evaluate ulcers in different ways, based on the size in SES-CD and based on the depth in CDEIS. Another limitation of SES-CD is that it does not take into account the number of segments explored by the endoscopist. It assumes that unexplored segments do not contain lesions, even when the reason of an unexplored segment is a nonpassable stenosis.

None of the endoscopic scores succeeded so far to precisely match with the underlying clinical symptoms, correlate with laboratory indices, or reflect patients' perception of their bowel disease. A possible explanation for these suboptimal correlations between endoscopic appearance and symptomatology could lie in the multiple systemic manifestations of the inflammatory process that result in symptoms, which are not necessarily reflected by the appearance of the bowel mucosa. Another explanation could be the difference between the time needed to observe the clinical evolution of the disease and the time to observe mucosa healing. In addition, discrepancies between SES-CD and clinical indices could be attributed to potential involvement of proximal segments of the gut that are not assessed in colonoscopy.

Finally, the reproducibility of endoscopic scores in CD remains suboptimal. Regardless of the scoring method used, endoscopic assessment of disease activity can be subjective and the resulting interobserver variation is another limitation of endoscopic scores. This variation is largely attributed to the existence of cutoff values defining CD severity and response to therapy.<sup>[9,10]</sup>

## STUDIES USING SES-CD SCORING WITHOUT CUTOFFS

In addition to the SES-CD introducing study,<sup>[4]</sup> there are more studies using SES-CD scoring as a continuous value (without applying SES-CD cutoffs) to describe disease severity or response to therapy [Table 1].<sup>[11-26]</sup>

Of note, radiological approaches aiming to detect and assess inflammatory activity of thickened ileal walls by using either contrast-enhanced ultrasonography<sup>[13]</sup> or diffusion-weighted magnetic resonance entero-colonography<sup>[27]</sup> demonstrated good correlations with SES-CD scoring.

A median SES-CD score decrease from  $15 \pm 2.7$  to  $8 \pm 1.6$  was described as significant in a study of anti-TNF $\alpha$  therapy.<sup>[21]</sup> It still remains unexplored whether these SES-CD score changes do always represent clinically meaningful outcomes and a real step-down/step-up from prior disease activity status.

## STUDIES USING SES-CD CUTOFFS TO DEFINE DISEASE SEVERITY

Several studies attempted to define CD severity based on a variety of SES-CD predefined cutoffs. Although selected cutoff values are similar between some of those studies, they differ significantly in others [Table 2]. In total, 11 studies used cutoff values to determine disease severity and six different cutoffs were used.

In the majority of studies, CD severity was defined as inactive when SES-CD was 0–2; mild when 3–6; moderate

**Table 1: Trials in Crohn's disease using the simple endoscopic activity score without cutoff values**

Authors	Year	Using SES-CD without cutoffs
Daperno <i>et al.</i> <sup>[4]</sup>	2004	Introducing study of SES-CD
D'Haens <i>et al.</i> <sup>[11]</sup>	2008	Not using SES-CD cutoffs
Gallego <i>et al.</i> <sup>[12]</sup>	2011	Only SES-CD for the terminal ileum without cutoffs
De Franco <i>et al.</i> <sup>[13]</sup>	2012	Only SES-CD for the terminal ileum without cutoffs
Rutgeerts <i>et al.</i> (EXTEND trial) <sup>[14]</sup>	2012	SES-CD to assess a minimal level of inflammation to inclusion in the study
D'Haens <i>et al.</i> <sup>[15]</sup>	2012	Not using SES-CD cutoffs
Ozeki <i>et al.</i> <sup>[16]</sup>	2012	Not using SES-CD cutoffs
Bessissow <i>et al.</i> <sup>[17]</sup>	2013	Not using SES-CD cutoffs
Palone <i>et al.</i> <sup>[18]</sup>	2014	Not using SES-CD cutoffs
Yang <i>et al.</i> <sup>[19]</sup>	2014	Not using SES-CD cutoffs
Eder <i>et al.</i> <sup>[20]</sup>	2014	Not using SES-CD cutoffs
Hashiguchi <i>et al.</i> <sup>[21]</sup>	2014	Not using SES-CD cutoffs
Kierkuś <i>et al.</i> <sup>[22]</sup>	2015	Not using SES-CD cutoffs

SES-CD: Simple endoscopic activity score

7–15; and severe >16.<sup>[7,25,28,30,33]</sup> Additional classifications used are as follows: inactive 0–2; mild 3–6; moderate 7–16; severe >16<sup>[32,34]</sup> or remitting 0–2, mild 3–6, moderate 7–9, severe >9.<sup>[35]</sup> In this group of studies, inactive disease scoring ranges from 0 to 2 and the differences in scoring are mainly noted in moderate/severe groups with the most frequent cutoff being 16.

In the remaining studies, CD severity was defined as inactive: 0–3; mild: 4–9; moderate: 10–17; severe:  $\geq 18$ <sup>[36]</sup> or inactive 0–3; mild or moderate 4–14; severe  $\geq 15$ <sup>[29]</sup> or inactive 0–3; mild 4–10; moderate 11–19; and high  $\geq 20$ .<sup>[31]</sup> In one study,<sup>[34]</sup> scores of SES-CD  $\geq 3$  were defined as endoscopically active and in another SES-CD score >7 was defined as severe CD activity.<sup>[37]</sup> In this group of studies, inactive disease scoring ranges from 0 to 3 and the differences in scoring are varying significantly in all the remaining categories of disease activity (mild, moderate, and severe).

A critical overview of all studies using SES-CD scoring to define disease severity suggests that a score up to 3 is an acceptable cutoff value for inactive disease and that no study is using the SES-CD score 0 to predefine inactivity.

## STUDIES USING SES-CD CUTOFFS TO DEFINE RESPONSE TO TREATMENT

Initially, SES-CD was used empirically to quantify response to therapy in CD patients as follows: complete (no endoscopic lesions), near complete, partial healing (large ulcers with >33% reduction in size) and no healing.<sup>[38]</sup>

Subsequently, studies using several SES-CD cutoffs to define response to therapy were published [Table 3]. For example, in the *post hoc* analysis of the SONIC trial,<sup>[23]</sup> response was defined as a decrease in SES-CD of at least 50% from baseline.<sup>[39]</sup> In another study,<sup>[40]</sup> early good endoscopic response (complete or near complete mucosal healing) was defined as SES-CD 0–3. Additionally, in the same study, early good endoscopic response was associated with reduced endoscopically confirmed relapse, anti-TNF use and hospitalization at 1 year.

Based on another study,<sup>[30]</sup> partial response was defined as a one-class change in the SES-CD, that is, from endoscopically moderately active disease to mild disease, or from endoscopically severely active disease to moderate disease, whereas nonresponse was defined as no change or worsening of the SES-CD score.

## STUDIES USING SES-CD CUTOFFS TO DEFINE REMISSION

There is no general consensus on the optimal SES-CD cutoff level for endoscopic remission. Studies defining remission

**Table 2: Trials in Crohn's disease using the simple endoscopic activity score to define disease severity**

Author	Year	Severity (with SES-CD cutoffs)
Moskovitz <i>et al.</i> <sup>[28]</sup>	2007	Inactive 0-2; mild 3-6; moderate 7-15; severe $\geq 16$
Sipponen <i>et al.</i> <sup>[29]</sup>	2008	Inactive 0-3; mild or moderate 4-14; severe $\geq 15$
Sipponen <i>et al.</i> <sup>[7]</sup>	2010	Inactive 0-2; mild 3-6; moderate 7-15; severe $\geq 16$
Sipponen <i>et al.</i> <sup>[30]</sup>	2010	Inactive 0-2; mild 3-6; moderate 7-15; severe $\geq 16$
Schoepfer <i>et al.</i> <sup>[31]</sup>	2010	Inactive: 0-3; mild: 4-9; moderate: 10-7; severe: $\geq 18$
af Björkesten <i>et al.</i> <sup>[32]</sup>	2012	Inactive 0-2; mild 3-6; moderate 7-16; severe >16
Algaba <i>et al.</i> <sup>[25]</sup>	2013	Inactive 0-2; mild 3-6; moderate 7-16; severe >16
Molander <i>et al.</i> <sup>[33]</sup>	2013	Inactive 0-2; mild 3-6; moderate 7-15; severe $\geq 16$
Sasaki <i>et al.</i> <sup>[34]</sup>	2014	Endoscopically active $\geq 3$
Yüksel <i>et al.</i> <sup>[35]</sup>	2014	Remission 0-2, mild 3-6, moderate 7-9, severe >9
Schaffer <i>et al.</i> <sup>[36]</sup>	2014	Inactive: 0-3 points; mild: 4-9; moderate: 10-17; severe: $\geq 18$

SES-CD: Simple endoscopic activity score

**Table 3: Trials in Crohn's disease using the simple endoscopic activity score to define response to treatment**

Authors	Journal	Response (with SES-CD cutoffs)
Sipponen <i>et al.</i> <sup>[29]</sup>	2010	A partial response as a one-class change in the SES-CD (inactive 0-2; mild 3-6; moderate 7-15; severe $\geq 16$ ) A nonresponse as no change or worsening of the SES-CD score
Ferrante <i>et al.</i> <sup>[39]</sup>	2013	Decrease from baseline in SES-CD of at least 50%
Grover <i>et al.</i> <sup>[40]</sup>	2014	Early good endoscopic response SES-CD 0-3 (complete MH, or near-complete MH)

SES-CD: Simple endoscopic activity score

with SES-CD scoring are distributed in several groups based on the cutoffs used [Table 4].

In total, 14 studies used SES-CD to determine remission or mucosal healing and four different definitions of endoscopic remission were used. Among them, 8/14 studies used 0 as the definition of endoscopic remission and 6/14 studies used 0–2 instead. In the remaining two studies, endoscopic remission was defined as a SES-CD score of 0–3.

The majority of studies used score 0 to define absence of colonic lesions,<sup>[42,43]</sup> or complete mucosal healing.<sup>[26,28,41,44-46]</sup> One of these studies<sup>[26]</sup> used SES-CD ulcer score of 0



**Table 4: Trials in Crohn's disease using the simple endoscopic activity score to define remission after treatment**

Authors	Year	Remission (with SES-CD cutoffs, MH = mucosal healing)
Moskovitz <i>et al.</i> <sup>[28]</sup>	2007	Score 0 [MH]
Sipponen <i>et al.</i> <sup>[29]</sup>	2008	SES-CD cutoff value 3 for inactive disease
Baert <i>et al.</i> <sup>[41]</sup>	2010	Score 0 [MH]
Sipponen <i>et al.</i> <sup>[30]</sup>	2010	Score 0-2 [mh] or a two- or three-class decrease in the SES-CD from the baseline score (ie, change from endoscopically severely active disease to mildly active or inactive or from moderately active to inactive)
Aomatsu <i>et al.</i> <sup>[42]</sup>	2011	Score 0 (no colonic lesions) Score ≥1 in presence of mucosal lesions
Aomatsu <i>et al.</i> <sup>[43]</sup>	2011	Score 0 (no colonic lesions) Score ≥1 in presence of mucosal lesions
af Björkstén <i>et al.</i> <sup>[32]</sup>	2013	Score 0-2
Molander <i>et al.</i> <sup>[33]</sup>	2013	Score 0-2 (deep remission)
Beigel <i>et al.</i> <sup>[44]</sup>	2014	Score 0 [MH]
Fukuchi <i>et al.</i> <sup>[45]</sup>	2014	Score 0 [MH]
Yüksel <i>et al.</i> <sup>[35]</sup>	2014	Score 0-2
Yu <i>et al.</i> <sup>[46]</sup>	2014	Score 0 [MH], complete MH
Schaffer <i>et al.</i> <sup>[36]</sup>	2014	Score 0-3
Dignass <i>et al.</i> <sup>[26]</sup>	2014	Score 0 [MH] SES-CD ulcer score of 0, "deep remission" (complete MH, in all bowel segments)

SES-CD: Simple endoscopic activity score

to define "deep remission". The remaining studies used SES-CD score 0 to define CD remission.<sup>[7,9,32,33,35]</sup> In two of these studies,<sup>[7,9]</sup> authors defined remission either as a SES-CD score of 0–2 (mucosal healing) or as a two- or three-class decrease in the SES-CD from the baseline score, that is, change from endoscopically severely active disease to mildly active or inactive or from moderately active to inactive.<sup>[7]</sup> The third group included studies using the SES-CD score 0–3 to define remission.<sup>[29,31,36]</sup> In all these studies, there was a general agreement that SES-CD of 0 was strongly related to mucosal healing and absence of ulcers in any part of the examined bowel.

## SES-CD AND MUCOSAL HEALING

The need for objective documentation of the mucosal healing was an important trigger of searching new "treat-to-target" drugs in inflammatory bowel disease (IBD).<sup>[47]</sup> Mucosal healing has been correlated to short- and long-term prognosis in CD. Mucosal healing has also emerged as a desirable treatment goal in clinical practice in patients with CD. The growing interest in mucosal healing especially in trials of new biologics has made endoscopic monitoring of CD essential.<sup>[48]</sup> On the other hand, whether mucosal healing is always "essential" in practice remains the subject

of discussion with individual IBD patients and their expectations. Furthermore, CD is a transmural disease not fully appreciated by endoscopy and there is still no validated or consistent definition of mucosal healing in CD.

A precise definition of mucosal healing has not been established yet, although in clinical trials it was defined as the "complete absence of all inflammatory and ulcerative lesions in all segments of gut" in endoscopy. This definition does not include mucosal improvement and does not distinguish among grades of mucosal healing.<sup>[6]</sup>

In the SONIC study<sup>[23]</sup> and in a validation of endoscopic activity scores using data from SONIC, mucosal healing was defined as absence of ulcers at week 26.<sup>[39]</sup> In the EXTEND trial, mucosal healing was the primary endpoint defined as absence of mucosal ulceration at week 12.<sup>[14]</sup>

It would be expected that SES-CD scoring for mucosal healing would correspond to Mayo score for mucosal healing in UC where a Mayo score of 0 is practically associated with absence of colonic lesions. However, this review clearly demonstrates that SES-CD cutoffs used to define mucosal healing in CD vary among studies.

In the majority of studies,<sup>[26,41,42,44-46]</sup> an SES-CD score of 0 means no colonic lesions or mucosal healing, and SES-CD >1 indicates the presence of mucosal lesions. In the first of these studies,<sup>[26]</sup> complete mucosal healing at week 8 was defined as an SES-CD score of 0 on the subscore for size of ulcer in all bowel segments (SES-CD, ulcer 0). In the last of these studies,<sup>[46]</sup> near-complete healing was defined as a marked endoscopic improvement but aphthous ulcers (<0.5 cm) or erosions, in the absence of stenosis, and the affected segment being less than 50% (SES-CD = 3). Partial mucosal healing was defined as <50% affected areas and the size of the biggest ulcer being <2 cm. Considerable number of ulcers could still persist and single luminal narrowing could be observed but was passable by DBE (SES-CD = 4–5). Unchanged or worse condition was defined as lesions that were similar to or more severe than the baseline findings and unimproved short-segment stenosis (SESCD ≥ 6). Finally, two studies defined mucosal healing as an SES-CD <2<sup>[30]</sup> or an SES-CD 0–3 points.<sup>[36]</sup> From the above studies, it becomes evident that the quantification of mucosal healing using SES-CD scoring has not been standardized yet.

## SES-CD AND DEEP REMISSION

Deep remission is a new target for therapy in IBD. As the definition of mucosal healing by SES-CD is unset, the concept of deep remission is still evolving and a consensus on its definition has not been reached yet. In one study, deep remission was defined as SES-CD <2 and

CDAI <150.<sup>[29]</sup> According to the authors, achievement of endoscopic remission (defined as SES-CD <2) seems to induce deep remission in most patients. In other studies “deep remission” was defined as mucosal healing with SES-CD 0 and clinical remission at week 8<sup>[26]</sup> or absence of clinical symptoms with concomitant endoscopic remission and SES-CD 0–2.<sup>[33]</sup>

### SES-CD USED AS PREDICTOR OF CD EVOLUTION

Endoscopic remission, defined as SES-CD ≤2, predicted long-term prognosis even in patients with clinical remission. This tendency was observed in both patients treated or not treated with biologics.<sup>[29,32]</sup> The 3-month SES-CD <3 had a sensitivity of 88%, and specificity of 64%, to predict 1-year endoscopic remission in patients who received anti-TNF maintenance therapy. This was confirmed by a subsequent study where the cumulative nonrelapse rate was 33% in patients with SES-CD ≥3 compared with 88% in patients with SES-CD ≤2. SES-CD ≤2 was found to be an independent determinant of nonrelapse.<sup>[9]</sup> In the SONIC study, a decrease in SES-CD of at least 50% from baseline predicted midterm corticosteroid-free remission at week 50.<sup>[39]</sup> In another study,<sup>[46]</sup> no patient with moderate small-bowel CD and a baseline SES-CD of 7–9 achieved complete healing after 24 months of azathioprine treatment. In contrast, a higher mucosal healing rate was observed especially in patients with duration of disease less than 12 months and a baseline SES-CD of 5 or 6.

### SES-CD CORRELATIONS WITH FECAL, SERUM, RADIOLOGIC, AND OTHER MARKERS

Endoscopic evaluations of disease severity are invasive, relatively expensive, and unpleasant to the patients. Accurate tests that are less invasive and inexpensive would be ideal. A number of promising serum and fecal biomarkers as well as new radiologic imaging techniques have emerged aiming to determine severity.

SES-CD scoring of endoscopic activity has been significantly correlated with fecal calprotectin,<sup>[15,29,31,32,36,37,42]</sup> fecal lactoferrin,<sup>[30]</sup> fecal chitinase 3-like-1,<sup>[43]</sup> and fecal HMGB1 levels.<sup>[18]</sup> In two of these studies,<sup>[29,31]</sup> fecal calprotectin levels were significantly correlated with SES-CD scores with coefficients ranging from 0.47 to 0.73, sensitivities ranging from 81% to 91%, and specificities ranging from 58% to 100%.

A significant association between calprotectin and both macroscopic and microscopic disease extension in IBD has been demonstrated in children. More specifically, fecal markers were significantly lower in patients with an SES-CD <3 than in those with a higher endoscopic score.<sup>[29]</sup> However, for ileal CD, existing data are conflicting; it has

been shown that even in the presence of large or very large ulcers, patients with ileal CD may not have markedly elevated fecal calprotectin levels.<sup>[49]</sup> Also, of note is that in pediatric IBD patients with endoscopic remission (SES-CD 0), a weak but significant FC elevation was detectable.<sup>[42]</sup>

SES-CD scoring of endoscopic activity has also been significantly correlated with C-reactive protein (CRP) levels,<sup>[7,20,32,37]</sup> platelet count,<sup>[20]</sup> as well as serum angiopoietin 1,<sup>[25]</sup> serum ficolin-2,<sup>[36]</sup> and interleukin-6 concentrations.<sup>[37]</sup> Of note, serum highly sensitive CRP and interleukin-6 concentrations were significantly higher in patients with more severe endoscopic disease activity and an SES-CD score >7 points.<sup>[37]</sup> SES-CD scoring of endoscopic activity has been demonstrated to moderately or poorly correlate with Crohn’s disease activity index (CDAI) and Harvey–Bradshaw index (HBI).<sup>[7,31]</sup> In addition, changes between baseline and follow-up endoscopic scores correlated significantly with delta-SES-CD, but failed to correlate with delta-CDAI or delta-CRP.<sup>[7]</sup>

Magnetic resonance enterography (MRE) overall correlation with SES-CD score is considered moderate to strong.<sup>[12]</sup> The wall thickness in MRI correlates with both CDAI and SES-CD.<sup>[19]</sup> Furthermore, Simple Enterographic Activity Score for CD (SEAS-CD) has been proposed as a useful tool in the quantification of small-bowel CD activity in MRE.<sup>[20]</sup> MRE cannot be used alone, and it is rather a complementary technique to endoscopy, especially valuable for patients with extraluminal disease.<sup>[10,35]</sup> Of interest, SES-CD was also linked to anxiety prior to endoscopy and to a higher GI-specific anxiety.<sup>[17]</sup>

To summarize, emerging serum and fecal biomarkers as well as new radiologic imaging techniques are not always reliable *per se* at identifying endoscopic remission and SES-CD scoring seems to be mandatory for precise estimations of disease activity. In addition, all these studies clearly demonstrated that timing should be different for SES-CD and biomarker(s) assessment, and delta score changes during followup need careful interpretation.

### DEFINING OPTIMAL SES-CD CUTOFFS

The thresholds of SES-CD to define remission or response to therapy remain unvalidated in clinical practice. Empirical thresholds using different indices have been proposed in various clinical trials. Logistic regression models incorporating various combinations of biomarkers and other indices have been examined and their corresponding receiver operating characteristic (ROC) curves have been generated from the predicted probabilities for SES-CD.<sup>[39]</sup> Optimal cutoff scores have been determined by maximizing the sum of sensitivity and specificity based on logistic models that

pre-define a minimum specificity in which approximately equal penalty between false positives and false negatives is achieved.<sup>[50]</sup>

The current practice in endoscopy and important endoscopic changes need to be taken into consideration when defining SES-CD cutoffs. For example, detecting very small ulcers as well as measuring the exact size of ulcers (i.e., with biopsy forceps) especially if <5 mm or >2 cm is mandatory for appropriate scoring.<sup>[15]</sup> Indeed, large IBD trials used “absence of ulcers” or complete mucosal healing (defined as SES-CD zero) as the main endoscopic endpoint and as a rather stable predictor of response to therapy. Although “absence of ulcers” is an easy and convenient endpoint for the endoscopists and the clinical trials, this should not represent the only clinically meaningful treatment goal, as the reduction of the “ulcer load” by 50% may be also clinically relevant and a good predictor of the efficacy of therapy.

There are some points here that merit special interest. First, patients with suboptimal bowel cleansing or incomplete endoscopic evaluation of their five bowel segments should be excluded from SES-CD scoring assessment.<sup>[42]</sup> Special precautions should always be taken in ileal disease as the total SES-CD can underestimate disease activity. In such cases a separate ileal score has been suggested.<sup>[29]</sup> Secondly, decimals in a cutoff value may hide important prognostic outcomes. For example, in a recent study ROC curve analysis to determine the cutoff value of SES-CD indicated that sensitivity and specificity for clinical relapse was 84% and 75%, respectively, when SES-CD cut-off value was 2.5 (AUC 0.84).<sup>[9]</sup> Thirdly, during initiation of a new therapy, timing of SES-CD scoring is important. SES-CD scoring may require different cutoff values depending on the different time points and the targeted endpoint. For example, in the EXTEND study an SES-CD score of 5.0 at week 12 represented an optimal dichotomizing point for predicting week-52 clinical remission in CD patients.<sup>[50]</sup>

## DEFINING OPTIMAL TIME FOR SES-CD SCORING

The use of endoscopic activity scores in CD has currently no role outside clinical trials and is not calculated in routine clinical examinations. To date, CDEIS and SES-CD have the most data regarding operating properties; however, further validation is required.<sup>[4,51]</sup>

SES-CD scoring at baseline (week 0) and within the first three months after initiation of treatment has been studied in many reports and more specifically after 6,<sup>[45]</sup> 8,<sup>[26]</sup> 10,<sup>[16,22,39]</sup> and 12<sup>[32,50]</sup> weeks of treatment. Furthermore, SES-CD scoring following the first 3 months until one year after the initiation of treatment has been also performed in some

studies, including score calculations in 6 months<sup>[21,29]</sup> and 1 year<sup>[22]</sup> after anti-TNF $\alpha$  therapy.

The optimal timing of SES-CD scoring to assess mucosal healing is not defined yet but a 6-month followup seems to represent the minimal observation period for SES-CD scoring. In one study, SES-CD scoring has been calculated every 4 weeks revealing insignificant changes in the first trimester<sup>[42]</sup> while in a different study SES-CD change from baseline to the 3-month followup did not show any association with 1-year endoscopic remission.<sup>[29]</sup> In addition, in the *post hoc* analysis of SONIC trial, (<http://www.ncbi.nlm.nih.gov/pubmed/?term=23954314>) mucosal healing assessed by SES-CD at week 26 was associated with corticosteroid free remission at week 50. In another study,<sup>[39]</sup> the difference in the mucosal healing ratio as described by SES-CD was only significant between 6 and 52 weeks.<sup>[45]</sup> Finally, in a double-balloon endoscopy study, SES-CD scoring was performed after 12 and 24 months of low-dose azathioprine therapy, respectively.<sup>[46]</sup>

## CONCLUSIONS

During diagnosis and followup of patients with CD, clinical decision making should be driven by disease activity monitoring, with the aim of optimizing treatment for tight disease control. However, limited data exist to guide the selection of the appropriate monitoring tools and the frequency with which they should be used. An accurate monitoring tool could additionally guide the selection of patients for clinical trials and also for routine assessments.

A global assessment of Crohn's disease activity, comprising clinical, endoscopic, biochemical, and pathological indices is not available yet and perhaps exists only in theory. All existing indices are rather complex and time-consuming, therefore their use is limited to clinical trials. In everyday clinical practice, most gastroenterologists rely on their clinical judgment, which is less reproducible, but simpler for decision making.

SES-CD was developed to meet the clinical need for a reliable, easy-to-use endoscopic scoring instrument, and also for its need in research for endoscopic endpoints in trials evaluating new agents for CD in the era of mucosal healing and central endoscopy reading.

The importance of measuring and recording SES-CD in a standardized fashion to enable longitudinal evaluation of disease activity is highlighted. However, it is clear that further studies are needed to validate SES-CD cutoff points used for endoscopic remission and response. Furthermore, future research should focus on exploring the predictive power of SES-CD for subclinical disease relapse, as a marker of

response to therapy and as a means to justify escalation of medical therapy in symptomatic patients.

To conclude, in patients with Crohn's disease, SES-CD scoring represents a valuable tool. However, a consensus agreement on its optimal use is required.

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### Conflicts of interest

None of the authors have any potential conflicts (financial, professional, or personal) that are relevant to the manuscript.

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