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EDITORIAL

Fecal calprotectin and endoscopic scores: The cornerstones in clinical practice for evaluating mucosal healing in inflammatory bowel disease

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Abstract

Managing inflammatory bowel disease (IBD) is becoming increasingly complex and personalized, considering the advent of new advanced therapies with distinct mechanisms of action. Achieving mucosal healing (MH) is a pivotal therapeutic goal in IBD management and can prevent IBD progression and reduce flares, hospitalization, surgery, intestinal damage, and colorectal cancer. Employing proactive disease and therapy assessment is essential to achieve better control of intestinal inflammation, even if subclinical, to alter the natural course of IBD. Periodic monitoring of fecal calprotectin (FC) levels and interval endoscopic evaluations are cornerstones for evaluating response/remission to advanced therapies targeting IBD, assessing MH, and detecting subclinical recurrence. Here, we comment on the article by Ishida *et al* Moreover, this editorial aimed to review the role of FC and endoscopic scores in predicting MH in patients with IBD. Furthermore, we intend to present some evidence on the role of these markers in future targets, such as histological and transmural healing. Additional prospective multicenter studies with a stricter MH criterion, standardized endoscopic and histopathological analyses, and virtual chromoscopy, potentially including artificial intelligence and other biomarkers, are desired.

Key Words: Fecal calprotectin; Endoscopic scores; Mucosal healing; Histological healing; Ulcerative colitis; Inflammatory bowel diseases

Core Tip: Mucosal healing (MH) is a pivotal goal in inflammatory bowel disease (IBD) management and can prevent IBD relapse. However, assessing MH is challenging due to the poor correlation between symptoms and intestinal inflammation. Fecal calprotectin (FC) levels and interval endoscopic evaluation are cornerstones for achieving this goal. The editorial updates the best predictor tools of IBD relapse in 12 mo concerning FC and endoscopic scores (ESs). In the retrospective single-center study, all three ESs and FC were useful in predicting ulcerative colitis relapse, suggesting the Ulcerative Colitis Endoscopic Index of Severity as the preferred choice for combining feasibility and accuracy.

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INTRODUCTION

The management of inflammatory bowel disease (IBD) is becoming more complex and personalized, given the numerous advanced therapies recently incorporated into the therapeutic arsenal for controlling IBD. Achieving mucosal healing (MH) is a pivotal therapeutic goal in IBD management, and it can prevent IBD progression and reduce disease flares, hospitalization rates, the need for surgery, irreversible intestinal damage, and colorectal cancer development[1,2]. However, evaluating an individual therapy-induced MH is difficult. For example, the relapse of intestinal symptoms is usually non-specific and cannot confirm disease activity or a late event indicating persistent or recurrent intestinal inflammation[3]. A critical point is to not rely solely on symptoms to assess therapy-induced MH. Consequently, employing proactive disease and therapy assessment is essential to better control intestinal inflammation, even if subclinical, to alter the natural course of IBD[4]. Furthermore, the periodic monitoring of fecal calprotectin (FC) levels and interval endoscopic evaluation are cornerstones for evaluating response/remission to advanced therapies targeting IBD, assessing MH, and detecting subclinical recurrence[5]

Therefore, in this editorial, we comment on the article by Ishida *et al*[6], published in a recent issue of the *World Journal of Gastroenterology* in 2023. They studied the usefulness of FC and endoscopic scores for predicting clinical relapse within 12 mo in 75 patients with ulcerative colitis (UC) in clinical remission. The endoscopic scores studied were the Mayo Endoscopic Subscore (MES), UC Endoscopic Index of Severity (UCEIS), and UC Colonoscopic Index of Severity (UCCIS). In total, 18 patients (24%) experienced clinical relapse during the 12 mo. The cutoff values for predicting relapse were an FC and UCCIS score of ≥ 323 mg/kg and ≥ 10.2, respectively. In summary, the accuracy of the endoscopic scores and biomarkers for predicting relapse was 86.7%, 85.3%, 76.0%, and 73.3% for UCCIS, UCEIS, FC, and MES, respectively. Therefore, the authors concluded that the endoscopic scores studied and FC may predict disease relapse in 12 mo among patients with UC in clinical remission.

In their article[6], the authors included patients with UC in clinical remission measured using the Rachmilewitz score [clinical activity index (CAI ≤ 4)][7]. However, the criteria used to define MH were not overly strict and included patients with mild endoscopic activity, as shown by the MES, UCEIS score, and UCEIS score of 1 (42.7%), 2 (17.3%), and 3 (8.0%), respectively. Furthermore, the criteria used to define clinical relapse, which was the primary outcome, were simply an increase in CAI above baseline, determined by the worsening of diarrhea, abdominal pain, or bloody stools requiring modification or the addition of treatment. To the best of our knowledge and in accord with the consensus and guidelines on IBD[8], the best definition for disease activity, disease remission, or relapse should be based on clinical parameters and endoscopic evaluation or even with the use of the FC, which was not reported in the article. This could underestimate or overestimate the association between the scores and disease activity as the correlation between the presence of symptoms and endoscopic activity is not 100%. Moreover, the authors did not assess FC levels during clinical relapse. Other important comments can be highlighted. First, as a retrospective study, it is crucial to determine whether the scores were explicitly provided in the report or were calculated based on the descriptive findings or image review. Therefore, information regarding the experience of the endoscopists with IBD scores should be considered as significant interobserver variability exists in scoring IBD activity[9]. Lastly, an observation regarding the timing of stool sampling should be considered as some samples were collected the day after the endoscopic procedure (colonic preparation and possible biopsies), which could have influenced the FC results[10].

Despite these limitations, the article by Ishida *et al*[6] provides important information regarding the association between endoscopic scores and FC for predicting clinical relapse in patients with UC. These findings should encourage disease monitoring, especially in patients with evidence of residual disease activity, such as FC values > 150 mg/kg and mild activity on endoscopy. Another relevant point of the study was the evaluation of the relationship between FC, UCEIS score, and UCCIS score. The data were strengthened by the fact that the researchers analyzed FC and endoscopic scores simultaneously[6].

This editorial aimed to review the role of FC and endoscopic scores in predicting MH in patients with IBD, given the importance of MH as a target in IBD, following the recommendation of the Selecting Therapeutic Targets in IBD II

(STRIDE-II) consensus[11]. Furthermore, we intend to present some evidence on the role of these markers in future targets, such as histological and transmural healing (TH).

FECAL BIOMARKERS AND MUCOSAL HEALING IN PATIENTS WITH IBD

FC is a calcium-binding protein comprising a complex of two proteins, S100A8 and S100A9[12], primarily derived from the cytoplasm of neutrophils. It has antibacterial activity and a role in the innate immune response[13]. It is also expressed by monocytes, dendritic cells, activated macrophages, keratinocytes, and some mucosal epithelial cells[14]. FC is an early marker of neutrophil degranulation and appears to be the most sensitive marker of intestinal inflammation in IBD, with concentrations correlated with the extent of mucosal inflammation. This biomarker is closely correlated with endoscopy score and MH[8] and can be measured with several commercially available assays. According to the European Crohn's and Colitis Organization (ECCO) guidelines[8], FC is indicated for the initial diagnosis of IBD, to differentiate between IBD flare and irritable bowel syndrome (IBS) symptoms, confirm an IBD relapse, and monitor IBD treatment, and is closely associated with MH[15-17] and histological healing[8,11].

In IBD assessment, a recent systematic review and meta-analysis showed that FC was a validated biomarker to distinguish between IBD and IBS with a sensitivity of 85.8% and a specificity of 91.7% . A cutoff value of ≤ 50 μg/g had better sensitivity than a cutoff of > 50 μg/g (87% *vs* 79%)[18]. Another meta-analysis concluded that the probability of having IBD when the FC value was ≤ 40 μg/g was relatively low (≤ 1%)[19].

FC can also be used to monitor IBD flares in patients in clinical and biochemical remission[8]. Therefore, repeated monitoring of the patient every 3-4 mo is indicated when the FC value is in the estimated target. However, the therapeutic plan must be discussed if the FC exceeds the desired value, and the FC should be remeasured within 1 mo to confirm the previous result. Moreover, repeating the test is recommended to confirm the value before optimizing therapy in case of doubt[8].

Recently, the American Gastroenterological Association (AGA) published guidelines on the role of biomarkers, including C-reactive protein (CRP) and FC, and endoscopy, in the management of Crohn's Disease (CD)[20] and UC[21]. In CD, monitoring based on biomarkers may be performed every 6-12 mo in patients in symptomatic remission[20].

Despite the recommendation of using FC as a reliable marker, no consensus exists on the ideal cutoff value for IBD monitoring[8]. A meta-analysis published in 2015 included 744 UC patients and 727 CD patients from 13 studies. The FC cutoff value ranged from 30 to 274 μg/g for clinical disease activity[22]. The pooled sensitivity and specificity were 0.92 (0.90-0.94) and 0.60 (0.52-0.67), respectively, for a cutoff value of 50 μg/g, and 0.80 (0.76-0.84) and 0.82 (0.77-0.86), respectively, for a cutoff value of 250 μg/g[22]. Some studies have shown that FC can predict IBD recurrence. A systematic review by Heida *et al*[23] published in 2017 revealed that an increase in FC level in patients in clinical remission was associated with a 53%-83% likelihood of recurrence within 2-3 mo. Conversely, patients with consecutive normal FC levels had a 67%-94% probability of maintaining clinical remission over the next 2-3 mo[23]. A cutoff value of 150 μg/g was associated with the risk of disease recurrence in both UC and CD. Specifically, patients with an FC of ≥ 150 μg/g had 14-fold and 2-fold increased risks of UC recurrence and CD relapse, respectively, compared with levels below the threshold[24]. A prospective study involving 164 patients with UC with MH observed that an FC cutoff value of 115 μg/g had a sensitivity and specificity of 83% and 81%, respectively, to predict endoscopic relapse within 12 mo and lactoferrin, another possible biomarker, had a sensitivity and specificity of 70% and 79%, respectively at a threshold of 145 μg/g[25]. For patients with UC, the AGA recommends monitoring asymptomatic patients with FC every 6-12 mo. An FC value of < 150 μg/g in patients in symptomatic remission may rule out active inflammation and prevent routine endoscopic assessment of the disease. In contrast, an FC value of < 50 μg/g may be preferred over < 150 μg/g to detect endoscopic improvement in patients with UC who have recently achieved symptomatic remission after treatment adjustment. Repeating the examination within 3-6 mo or performing endoscopic assessment to confirm disease activity is recommended in asymptomatic patients with an FC value of > 150 μg/g. However, for symptomatic patients with UC and with moderate-to-severe symptoms suggestive of a flare-up, an FC value of > 150 μg/g indicates disease activity, and endoscopic assessment can be avoided. An endoscopic assessment is recommended before treatment adjustment in patients with mild symptoms and an FC value of > 150 μg/g[21].

For patients with CD, the AGA recommends using an FC value of < 150 μg/g in patients in symptomatic remission (with recent endoscopic remission) to rule out active inflammation and avoid endoscopic assessment of disease activity. The AGA suggests confirming disease activity in patients without recent confirmation of endoscopic remission by endoscopic evaluation. An endoscopic assessment of disease activity rather than empiric treatment adjustment is recommended in patients presenting with an FC value of > 150 μg/g. Similarly, in patients with CD symptoms and a normal FC value of < 150 μg/g, the AGA suggests endoscopic assessment of disease activity rather than empiric treatment adjustment. This similar approach is suggested for symptomatic patients with CD with a normal FC value of < 150 μg/g[20].

Despite the lack of a published established cutoff value for disease activity in IBD, FC is a more sensitive marker of disease activity than hemoglobin, CRP, and albumin[26,27] for in colonic and small bowel diseases[28,29]. FC, in symptomatic patients, has a good correlation (r > 0.8) with endoscopic disease activity in CD and UC[30,31]. Additionally, FC can predict treatment responses in patients with UC[32,33] and with CD[34]. An FC value of ≤ 168 μg/g was associated with a sustained clinical response at 1 year (sensitivity and specificity of 83% and 74%. respectively), and a value of ≤ 121 μg/g was associated with MH (sensitivity and specificity of 79% and 57%, respectively) in patients with UC after 1 year of treatment with anti-tumor necrosis factor agents[32].

The ECCO consensus recommends the use of FC as a marker of MH in patients with UC who clinically respond to medical therapy approximately 3-6 mo after treatment initiation[8]. Regarding the ideal FC value associated with MH, a systemic review including nine studies showed that the cutoff values of FC ranged between 58 μg/g (sensitivity and specificity of 89.7% and 93.3%, respectively) and 490 μg/g (sensitivity and specificity of 100% and 62%, respectively) for MH detection in patients with UC[35]. In contrast, the cutoff values of FC in patients with CD ranged from 71 μg/g (sensitivity and specificity of 95.9% and 52.3%, respectively) to 918 μg/g (sensitivity and specificity of 50% and 100%, respectively) for MH detection[35]. According to the STRIDE-II guidelines, an FC cutoff value of 150 μg/g can be used to identify MH, and an FC value of < 600 μg/g is associated with minimal inflammation in patients with CD[11]. A meta-analysis published in 2021 included 17 colonic CD and 49 UC studies[36]. In the CD studies, the authors observed a sensitivity and specificity of 0.828 (0.769-0.874) and 0.759 (0.683-0.821), respectively, for FC in MH diagnosis. In the analysis of the receiver operating characteristic (ROC) curve, the area under the ROC curve (AUC) was 0.829. In contrast, the sensitivity and specificity were 0.804 (0.757-0.843) and 0.817 (0.780-0.848), respectively, in the UC studies, and the analysis of the ROC curve showed an AUC of 0.858. Therefore, the authors concluded that FC was a reliable biomarker of MH in IBD with good diagnostic accuracy. Notably, the included studies used various FC cutoff values to correspond to MH (13.9-251 μg/g) in UC, although the most common values were between 150 and 250 μg/g. Similarly, no universal cutoff value for FC in CD was identified, with the reported range relatively wide, ranging from 54-918 μg/g, with a mean cutoff of 205 μg/g[36].

Another meta-analysis that included 1682 and 221 patients with UC and CD, respectively, investigated the optimal FC range for predicting MH[37]. The optimal performance in UC was at a cutoff range of 60-75 μg/g, with high sensitivity (0.87, 95%CI: 0.80-0.91) and specificity (0.81, 95%CI: 0.76-0.85). Among the 221 patients with CD, an FC value of 180-250 μg/g had moderate sensitivity (0.67, 95%CI: 0.41-0.86) and high specificity (0.76, 95%CI: 0.65-0.85). The authors evaluated seven different ranges of FC cutoff values according to the included studies but only one cutoff in CD as follows: 25-50, 60-75, 96-125, 150-180, 192-201, 170-200, and 250-259 μg/g[37]. Recently, another meta-analysis that included 33 studies showed that both FC and fecal lactoferrin were highly sensitive and specific for distinguishing endoscopic activity from MH in patients with CD[38]. Regarding endoscopic activity, FC had pooled sensitivity, specificity, and AUC of 81% (77%-84%), 74% (70%-80%), and 0.85, respectively. The diagnostic odds ratio (DOR) was 13.93 (10.89-17.81). For MH, FC had a sensitivity, specificity, AUC, and DOR of 88% (84%-90%), 72% (64%-79%), 0.88, and 18.17 (11.08-29.82), respectively. Fecal lactoferrin had a sensitivity, specificity, AUC, and DOR of 75% (65%-83%), 80% (57%-92%), 0.81, and 13.41 (5.74-31.32), respectively, for endoscopic activity. Furthermore, the authors noted that 15 of the 25 studies (60%) reported FC values of > 200 μg/g as the optimal cutoff when discriminating between endoscopically active and inactive disease[38].

In small bowel CD, a study that included 165 patients showed that the optimal cutoff value of FC for predicting MH was 76.99 μg/g (sensitivity, specificity, and AUC of 79.45%, 84.21%, and 0.877, respectively). FC was also strongly correlated with the Simplified Endoscopic Score for CD (SES-CD) in these patients (r = 0.753, P < 0.001)[39]. Histological healing in UC has been associated with better prognosis, reduction in clinical recurrence rates, need for steroid use, hospitalization, and surgery, in addition to reducing the risk of dysplasia and colonic neoplasia[40]. Although histological healing is recognized as an important outcome, it is not yet considered a treatment target in UC or CD[11]. However, it could be implemented as an additional target in the UC scenario, combined with MH, to achieve a deeper level of healing. A systematic review published in 2020 that included 12 studies and 1,168 patients with UC found a correlation between FC and histological activity. Eleven different FC cutoff points were identified to distinguish histological remission, ranging from 40.5-200 μg/g, and cutoff values indicating histologic activity varied from 72-250 μg/g[41].

A recent study aimed to determine the optimal FC cutoff value for predicting histological healing in patients with UC in clinical and endoscopic remission (partial Mayo score of ≤ 2 points and MES of 0-1)[42]. The authors included 76 patients, and the FC value in patients with histological healing was 56.2 μg/g compared with 118.1 μg/g in those with histological activity (P = 0.002). Therefore, the optimal cutoff value for predicting histological healing was 82.7 μg/g (sensitivity, specificity, and AUC of 73%, 64%, and 0.71, respectively), and FC values increased with to the histological grade of severity. FC value was also lower in patients with MES of 0 (53.4 μg/g) than in those with MES of 1 (171.8 μg/g; P < 0.001)[42]. Similar FC values were observed in a study published in 2020, which included 185 patients with UC. An FC value of ≥ 135 μg/g predicted histological activity [Geboes score (GS) of ≥ 3.1] with a sensitivity, specificity, and AUC of 54%, 69%, and 0.627, respectively[43]. Patients in histological remission had a median FC of 79.5 μg/g compared with a median FC of 148.5 μg/g for GS of ≥ 3.1 (P = 0.003)[43]. Another study found that an FC value of < 100 μg/g had a high sensitivity to identify endoscopic (81.5%), histological (91.7%), and deep (82.4%) remissions[44]. Cannatelli *et al*[45] in 2021 published results from a group of patients with CD, where they found that the value of FC for predicting endoscopic healing measured as an SES-CD of ≤ 2 was 96 μg/g (sensitivity, specificity, accuracy, and AUC of 75.0%, 84.4%, 82.9%, and 75.0, respectively). In this study, the optimal cutoff of FC for predicting histological remission assessed with modified Riley = 0 was 225 μg/g (sensitivity, specificity, accuracy, and AUC of 88.9%, 71.9%, 75.6%, and 80.9, respectively)[45].

A recent study evaluated the accuracy of FC for predicting clinical, endoscopic, and histological remission in patients with UC treated with biological therapy[46]. When comparing FC values of < 250 and > 250 μg/g, the group with FC levels of ≤ 250 μg/g had a higher probability of achieving clinical [odds ratio (OR): 4.03; 95%CI: 2.78-5.85], endoscopic (OR: 4.26; 95%CI: 2.83-6.40), and histologic (OR: 6.42; 95%CI: 4.02-10.26) remission at week 52 compared with the group with FC levels of ≥ 250 μg/g. The study also observed a reduced probability of risk of colectomy and hospitalization[46].

A study evaluated the association between FC and TH using intestinal ultrasound[47]. The study included 118 patients with CD treated with biological therapy for 2 years. Specifically, the clinical remission rate, MH, and TH were 62.7%, 44.1%, and 32.2%, respectively. Mean FC concentration decreased from 307.5 ± 248.2 to 45.4 ± 31.3 μg/g (P < 0.001) and from 384.5 ± 355.8 to 44.9 ± 27.82 μg/g (P < 0.001) in patients with TH and those with MH, respectively. An FC cutoff value of 94 μg/g was associated with MH (sensitivity, specificity, and AUC of 94.2%, 84.8%, and 0.95, respectively) and TH (sensitivity, specificity, and AUC of 92.1%, 70%, and 0.88, respectively)[47].

FC can also identify postoperative recurrence in patients with CD who underwent ileocecal resection[48]. A meta-analysis including 10 articles and 613 postoperative patients reported sensitivity and specificity values of 0.82 and 0.61 for FC, respectively[49]. In a prospective study, an FC level of > 100 μg/g was associated with a sensitivity, specificity, and accuracy of 95%, 54%, and 77%, respectively, for predicting endoscopic recurrence[50]. Considering patients with CD in surgically induced remission in the first 12 mo, the AGA recommends an FC value of < 150 μg/g to avoid endoscopic assessment of disease activity in patients at low risk of postoperative disease recurrence. However, for patients at high risk of postoperative disease recurrence, the AGA recommends endoscopic evaluation for assessing endoscopic recurrence rather than relying only on biomarkers[20].

Studies have also shown that FC values were significantly elevated in pouchitis[51]. A retrospective study that included 26 patients with and 40 patients without pouchitis, found that the optimal FC value for predicting a high risk of pouchitis was 143.25 μg/g (AUC: 0.876)[51]. In contrast, a prospective study that included 170 patients (72 with pouchitis) found that the FC cutoff value associated with the presence of pouchitis was 246 μg/g (sensitivity, specificity, and AUC of 83.9%, 71.0%, and 0.85, respectively). Furthermore, the authors reported a good correlation coefficient between calprotectin and the modified pouchitis disease activity index (r^2 = 0.279, P < 0.001)[52]. An FC value of < 125 μg/g (sensitivity and specificity of 35.29 and 83.33, respectively) or < 100 μg/g (sensitivity and specificity of 29.41 and 94.44, respectively) was associated with endoscopic remission in patients with ileal pouch-anal anastomosis[53]. A systematic clinical review published in 2020 included 117 studies that enrolled 256 patients (100 with pouchitis) and reported an FC cutoff value ranging from 56 to 494 μg/g among the studies[54].

Although FC is an easy, non-invasive, cost-effective, and reliable biomarker, it has some limitations that should be mentioned. Some factors can affect FC levels, by increasing the concentration[55,56]. Specifically, some factors should be highlighted, particularly variability with age, lifestyle, obesity[55], and the influence of some medications, such as non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and proton pump inhibitors[56]. As FC levels are a measure of mucosal inflammation, elevated FC concentrations can also be found in other disorders with an inflammatory component, such as infectious enteritis, ischemic colitis, diverticulitis, or colorectal cancer[14]. Therefore, when evaluating FC levels, the patient's clinical characteristics should be considered to interpret the test accurately.

Notably, for the optimal use of this inflammatory biomarker in clinical practice, care should be taken in the pre-analytical and analytical phases of FC measurement. The stool sample should be collected at home and in a minimum quantity of 100 mg. If possible, the sample should be collected from the first bowel movement of the day, and formed or semi-formed stools are preferable. Preventing contamination of the fecal sample with urine or toilet water is important. Analysis of only one stool sample is necessary and limiting storage at 4 °C and 2-3 d is preferable. When possible, taking non-steroidal anti-inflammatory drugs and proton-pump inhibitors, which could induce an increase in FC levels, should be discontinued at least 2 wk before performing the assay. In the laboratory, the samples should be processed within 3 d and no later than 1 wk. An enzyme-linked immunosorbent assay should be used to conduct quantitative FC measurements, as well as choosing the same laboratory and technique to perform serial FC measurements, but point-of-care tests and home-based measurements are valid alternatives[10,57].

In addition to FC, other fecal markers have been studied in IBD. These, include alpha-1-antitrypsin, beta-glucuronidase, chitinase 3-like-1, fecal eosinophil proteins, fecal hemoglobin, high-mobility group box 1 (HMGB1), human beta-defensin-2, human neutrophil peptides, lysozyme, M2-pyruvate kinase, matrix metalloproteinase 9, myeloperoxidase, neopterin, neutrophil gelatinase-associated lipocalin, polymorphonuclear neutrophil elastase, and S100A12[58]. S100A12 is a protein released during granulocyte activation and is associated with clinical activity, while HMGB1 has a good correlation with clinical and endoscopic activity[58]. However, future studies are needed to validate these fecal biomarkers and for their use in the clinical management of patients with IBD.

In conclusion, FC is a reliable biomarker that could be used in clinical practice for patients with IBD, from diagnosis to monitoring therapy and predicting relapse. Despite its well-established role in the literature, some limitations exist on its use, particularly within the range of 100-250 μg/g, where a combination or confirmation with other methods to assess disease activity is needed. Therefore, new fecal biomarkers require further study to validate their use as substitute or complementary tests for FC.

ENDOSCOPIC SCORES AND MH IN PATIENTS WITH IBD

Endoscopy has a fundamental role in the journey of patients with IBD. It is indicated for the diagnosis, management, prognosis, surveillance of dysplasia, and even treatment of some IBD complications, such as fistulae and strictures[59]. Table 1 outlines the recommendations for the use of FC and endoscopy in patients with IBD. Table 2 lists the advantages and limitations of these procedures in this clinical setting. The availability of biologics and small molecules in the therapeutic arsenal of IBD brought a new prospective with more ambitious goals that could genuinely alter the natural course of the disease[60]. Endoscopic healing, recently proposed by the STRIDE-II consensus as the therapeutic target for IBD, is associated with improved long-term outcomes[11]. The presence of mucosal inflammation, even in the absence of symptoms, can lead to bowel damage, complications, and higher rates of hospitalization and surgery[61]. Therefore, the greatest challenge lies in determining the criteria for defining endoscopic and/or MH and to what extent we should prioritize it, given the limited pipeline of drugs.

Endoscopic activity assessment is crucial in IBD management, and many scores have been proposed to evaluate mucosal improvement. The most used scores in clinical practice for CD are the CD Endoscopic Index of Severity[62] and the SES-CD[63]. Each has advantages and disadvantages, and the simplified score is more suitable for routine use. Several endoscopic scoring systems are currently in use for UC. Two of the most routinely used scoring systems are the MES[64]

Table 1 Main indications for the use of fecal calprotectin and endoscopy in patients with inflammatory bowel disease

Fecal calprotectin	Endoscopy
Differential diagnosis of IBD and irritable bowel syndrome	Differential diagnosis with mimics
Monitoring therapeutic response	Evaluation of disease extension
Monitoring mucosal healing	Monitoring therapeutic response
Monitoring histological healing	Monitoring mucosal healing
Prediction of disease activity and postoperative recurrence	Monitoring histological healing
	Prediction of disease activity and postoperative recurrence
	Dysplasia surveillance
	Treatment of some complications (*e.g.*, strictures)

IBD: Inflammatory bowel disease.

Table 2 Advantages and limitations of fecal calprotectin and endoscopy in patients with inflammatory bowel disease

	Fecal calprotectin	Endoscopy
Advantages	Noninvasive	Direct evaluation of the mucosa
	Low-cost, cost-effective	Gold standard method to evaluate the goal of IBD treatment (mucosal healing)
	Easy collection and storage	Possibility of obtaining samples (biopsies)
	Validated in UC and CD	Validated in IBD diagnostic, monitoring, and prediction of disease activity
	Validated in both colonic and small bowel disease	Validated in adults and pediatric population
	Validated in IBD diagnostic, monitoring, and prediction of disease activity	Validated scores for both UC and CD
	Validated in adults and pediatric population	
	Distinguish patients with IBD from those with IBS	
Limitations	Not specific for IBD	Invasive
	Not differentiated UC from CD	Cost
	No validated cutoff to define disease activity	Availability
	Presence of a "gray zone" level between 100 and 250 μg/g, which is difficult to interpret	Inter-observer variability
	Lower accuracy in detecting inflammatory activity in patients with CD of the small intestine or of the upper gastrointestinal tract compared to predominant or extensive colonic involvement	
	Variation depending on patient age, presence of obesity, and lifestyle	
	The presence of mucus and blood can interfere with FC result	
	High day-to-day variability	
	Despite the low cost, it is not available in some locations	

CD: Crohn's disease; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; UC: Ulcerative colitis.

and UCEIS[65]. In a study by Ishida *et al*[6], only patients with MES 0 or 1 were enrolled because is no clear definition of endoscopic remission by UCEIS[6]. MES is a simple score used in large-scale clinical trials and daily practice, but it has some limitations in the description of both active and inactive UC. Despite some similarities with MES, the UCEIS considers the depth of ulcers. The more detailed description of the ulcers by UCEIS makes it slightly more laborious. This might explain the better performance of UCEIS compared with MES in most published studies, with higher reliability and a potential prognostic role[66]. UCEIS is not as complicated a score to measure and can reveal the most severe colitis area better and more precisely than the MES[67]. However, both scores described above solely focus on the most active area of inflammation and do not consider the entire colon. Therefore, the UCCIS score was developed to fill this gap and include the evaluation of disease progression. It provides more detailed information about the inflammatory condition of the entire colonic mucosa[68]. This is relevant as patients with UC undergoing treatment can have erratic mucosal healing

with "patchy" inflammation or histologic rectal sparing[69]. The UCCIS score evaluates the vascular pattern, granularity, friability, and erosions/ulcers in the five segments of the colon (ascendant, transverse, descendent, colon, and rectum). Subsequently, they are applied to a formula that, unfortunately, is difficult to use. Therefore, calculating the UCCIS score requires time, effort, and a complete colonoscopy, making its daily use almost impractical[70]. A recent study by Ishida *et al*[6] determined the cutoff values of the UCCIS score for predicting a 5-year clinical relapse in patients with UC. Relapse rates were significantly lower in patients with a UCCIS score of ≥ 9.8 than in those with a UCCIS score of < 9.8 (log-rank test, $P < 0.001$). Therefore, prospective multicenter studies are needed to compare the UCCIS score with biomarkers or histological indices and evaluate its potential prognostic role[71].

A significant challenge concerning the assessment of endoscopic disease activity is the relative subjectivity of the evaluated parameters, which may lead to lower rates of interobserver agreement, particularly among unexperienced endoscopists[9]. To minimize these variabilities, a central endoscopy reading of the recorded examinations by trained readers has been proposed and adopted, at least in most clinical trials[72]. Recently, artificial intelligence has been added to the endoscopic arsenal to improve the quality and definition of images, aiding a better assessment of disease activity, mainly in UC. The use of a computer-aided diagnostic system can overcome the subjectivity of the scores and overcome the bias of interobserver variability[73]. A computerized system, developed by Maeda *et al*[74], which analyzed approximately 13000 images from 87 patients, determined active histological inflammation with a sensitivity, specificity, and accuracy of 74%, 97%, and 91%, respectively[74]. Other computer-assisted diagnostic systems have also been developed. Ozawa *et al*[75] used a convolutional neural network that had an AUROC of 0.86 and 0.98 to identify MES of 0 and 1, respectively[75]. Takenaka *et al*[76] used another deep neural network system and reported accuracies of 90.1% and 92.9% in rating endoscopic remission and histologic healing, respectively[76].

MH, defined as MES of ≤ 1, has been the treatment target in UC for many years. However, in observational studies and *post hoc* analysis of the infliximab trials, when patients with MES of 0 and 1 were subdivided, the group with MES of 0 at week 8 showed a higher steroid-free remission rate at week 54 than those with MES of 1 (63% and 46%, respectively)[77]. Carvalho *et al*[78] evaluated 138 patients with UC in steroid-free remission, and patients with MES of 1 had a significant three-fold increased risk of relapse compared with those with MES of 0[78]. In a meta-analysis published in 2020, including 2608 patients with UC in clinical remission from 17 studies, MES of 0 was associated with a 52% lower risk of relapse than MES of 1 (relative risk: 0.48, 95%CI: 0.37-0.62)[79]. Currently, there is a trend toward considering endoscopic remission and improvement in UC as MES of 0 and ≤ 1, respectively, representing MH[64]. Based on these findings, the 2021 update of the STRIDE-II guidelines began considering endoscopic healing in CD as SES-CD score of < 3 points or the absence of ulcerations, while in UC, a MES of 0 or UCEIS score of ≤ 1[11].

In the previous year, a study by George *et al*[80], including 445 patients with UC, aimed to evaluate the risk of relapse among patients with MES of 0 or 1 and determine if the Robarts Histopathologic Index (RHI) was predictive of clinical relapse. Most patients (95%) with MES of 0 were in histologic remission based on the RHI compared with only 35% with MES of 1. Within 1 year of colonoscopy, 26% of patients experienced a clinical relapse. Patients with MES of 1 or RHI of > 3 were significantly more likely to relapse ($P < 0.01$) than those with MES of 0 or RHI of ≤ 3. When stratified into four groups by MES and histologic activity, defined by an RHI of > 3 (MES of 0, RHI of ≤ 3; MES of 0, RHI of > 3; MES of 1, RHI of ≤ 3; and MES of 1, RHI of > 3), an RHI of > 3 was the better predictor of clinical relapse ($P = 0.008$)[80].

The histological index, RHI, used in the previous study assesses four characteristics of mucosal activity, including inflammatory infiltration, neutrophils in the lamina propria or the epithelium, and erosion or ulcers. Each of these items is rated on a scale from 0 to 3, depending on their intensity. Additionally, each parameter has a different weight and is multiplied by 1, 2, 3, and 5 to in a total possible score ranging from 0 (inactive) to 33 (severely active disease)[81]. RHI is not the only histopathological index used to evaluate the activity of patients with UC. The Nancy Index (NI) and GS are also studied for this purpose. The NI was the first validated index to assess histological disease activity in UC. The first criteria are the presence of mucosal ulceration (loss of colonic crypts with "immature" granulation tissue with disorganized blood vessels and extravasated neutrophils) or the presence of fibrinopurulent exudate. The second criterion is the acute inflammatory cells infiltrate (presence of neutrophils in the lamina propria or epithelium). The last criterion is evaluation of the presence and intensity of chronic inflammatory infiltrate (presence of lymphocytes and/or plasmocytes and/or eosinophils in the lamina propria)[82]. In a phase III clinical trial of adalimumab, a moderate ($r \geq 0.3$) positive correlation between NI and MES ($r = 0.39$ for the endoscopy subscore) was reported by Peyrin-Biroulet *et al*[83] at week 8. In the same study, this correlation increased ($r = 0.53$) when evaluated in week 52[83]. GS is a complex and difficult score that assesses features relevant to histological inflammation in UC to distinguish among quiescent disease (inactive disease or grade 1), mildly active disease (presence of polymorphonuclear cells or neutrophils or grades 2 and 3), and moderate to severely active disease (epithelial cell damage or grades 4 and 5)[84]. In the abovementioned adalimumab, study, comparing the three histological indices found significant differences among the mean scores of all three indices observed across the known groups based on MESs and full Mayo scores at weeks 8 and 52 ($P < 0.001$)[83].

For CD, TH is an ambitious and powerful treatment goal and appears to be associated with improvement in all clinical outcomes, with better long-term results even after the discontinuation of biologics; however, we still do not have sufficient data to support optimizing therapy when TH is not achieved[85]. The evolution of endoscopic equipment with the advent of virtual chromoendoscopy (VCE) brought an improvement in endoscopic image analyzing mucosal and vascular components. This new technique enabled the development of the Paddington International VCE ScOre (PICaSSO score), a validated score that showed optimal performance in defining deep remission, a strong correlation with histological activity, and a high interobserver agreement and reliability[86]. Most previous studies showed a relatively strong correlation between PICaSSO and UCEIS, with similar short-term prognostic performance. However, data comparing with UCCIS are scarce. A comparison among a modified PICaSSO, MES, and a probe-based confocal laser endomicroscopy in the prediction of histological healing (RHI of ≤ 3) was conducted in a prospective study by Iacucci *et al*[87] and published in 2020. The modified PICaSSO simplified and structured by thresholds of severity from

Table 3 Endoscopic indices of ulcerative colitis activity with their strengths and limitations

Indices	Endoscopic technique	Validation	Strengths	Limitations
MES	WLE	No	The easiest to use	Subjectivity
			Used in clinical trials and daily practice	Moderate reproducibility
				Not appropriate description of inflammation and severity
				Ambiguous definition of endoscopic remission
UCEIS	WLE	Yes	Easy to use	No thresholds for mild, moderate and severe disease
			Good reproducibility and agreement	No definition of superficial or deep ulcer
			High correlation with clinical, and histological indices and biomarkers	
			Clear definition or ER/MH	
			Clinically relevant outcomes	
UCCIS	WLE	Yes	Good reproducibility and agreement	No definition of MH
			Provides details about the status of inflammation of the entire colonic mucosa	No thresholds for mild, moderate and severe disease
				Few evidence
PICaSSO	VCE-iSCAN	Yes	High reproducibility and agreement	Endoscopy experience and training required.
			Strong accuracy discriminating quiescent from mild disease.	No long-term clinical outcome
			Highest correlation with MH	

Adapted from Ruscio *et al*[89]. ER: Endoscopic remission; HH: Histological healing; MES: Mayo endoscopic subscore; MH: Mucosal healing; PICaSSO: Paddington international virtual chromoendoscopy score; UCCIS: Ulcerative colitis colonoscopic index of severity; UCEIS: Ulcerative colitis endoscopic index of severity; WLE: White-light endoscopy; VCE: Virtual chromoendoscopy.

the original score, had optimal performances (AUROC: 0.96, accuracy: 91.5%) with a cutoff threshold of 4[87].

Preliminary unpublished reports suggest that the score, originally validated using the iSCAN platform, appeared to be reproducible when used with other VCE techniques, such as the narrow-band imaging near focus (Olympus) or blue-light imaging (Fujifilm) platforms[88]. Despite their weaknesses, mostly due to poor use in practice, the UCEIS, UCCIS, and PICaSSO have been described as useful and reliable endoscopic scores with superior strength to the MES. Table 3 summarizes the endoscopic indices for UC activity, highlighting their strengths and limitations[89].

Although endoscopy is an invasive tool for monitoring UC, it remains cost-effective. However, it is the gold standard method for evaluating MH, which is the desired target of IBD treatment. In this context, the use of endoscopy scores is essential to standardize reports, allowing a comparison of examinations before and after treatment. Endoscopic findings in patients with UC in clinical remission can also predict the risk of relapse, which can be improved by rigorous remission definitions of endoscopic (MES of 0/UCEIS score of ≤ 1) and histologic remission. In the analysis of Ishida *et al*[6], all three endoscopic indices and FC were useful in predicting disease relapse[6]. Despite the better results with UCCIS, its complexity makes routine use difficult and impractical. Therefore, UCEIS appears to be the scoring system that combines simplicity with better accuracy in the prediction of clinical relapse for clinical practice. The PICaSSO score shows promise; however, the equipment required and the need for endoscopist training are some gaps in most centers.

CONCLUSION

Achieving MH is a pivotal therapeutic goal in the management of IBD. Employing proactive disease and therapy assessment is crucial to achieve better control of intestinal inflammation, even if subclinical, to alter the natural history of the disease. Furthermore, periodic monitoring of FC levels and interval endoscopic evaluations are cornerstones for evaluating response and remission to advanced therapies targeting IBD and detecting subclinical recurrence. Therefore, this editorial aimed to review the role of FC and endoscopic scores in predicting MH in patients with IBD. In addition, Tables 4 and 5 present practical tips to assist the clinician caring for patients with IBD in interpreting and optimizing the use of FC in patients with CD and UC. Despite the UCEIS being more reliable than the MES for assessing endoscopic healing, the widespread use and simplicity of MES justify its routine use in predicting UC relapse. Even with excellent

Table 4 Practical pearls for the use of fecal calprotectin in Crohn's disease

FC is a reliable test in distinguishing patients with IBD from those with IBS. A cutoff of ≤50 μg/g appears to have a better sensitivity and a negative predictive value of > 95% for IBD in Western countries[18]
FC should be measured before starting or optimizing any therapy for CD, at the end of the induction phase, every 2–4 mo in patients being treated for active disease, and every 6–12 mo during the maintenance therapy in those in symptomatic remission; and in case of clinical relapse of disease[14,20]
In patients with CD in symptomatic remission with confirmation of endoscopic remission within the last 3 years, an FC of < 150 μg/g can reliably rule out active inflammation and avoid routine endoscopic reassessment with relatively low false negatives[20]
Where there is a symptom-biomarker disconnect, or in patients with mild symptoms, an FC value of > 150 μg/g is insufficient to identify endoscopically active inflammation. In this context, endoscopic or radiologic assessment is necessary to truly define the presence of active disease before making empiric treatment adjustments[20]
In the presence of moderate to severe symptoms, an elevated FC strongly suggests endoscopically active disease and can be used to make decisions regarding most changes in therapy. However, normal FC is insufficient to dismiss inflammation, and endoscopic or radiologic assessment is important in this setting[20]
In small bowel CD, where only a short segment of involvement may exist, as well as in relatively proximal disease (upper gastrointestinal, stomach, and esophagus), the FC concentrations may not be elevated to that degree and produce false negatives[57]
Many times, FC is highly effective in detecting endoscopic ulcerations regardless of the CD location. A cutoff value of > 200 μg/g in patients with isolated ileal involvement and > 250 μg/g for ileocolonic or colonic disease may be the optimal threshold to detect endoscopic ulcerations[90]
Normalization of FC (*e.g.*, < 250 μg/g) within 12 mo of starting therapy is associated with a reduced risk of CD progression[91]
In patients with CD in surgically induced remission within the past 12 mo at a low risk of postoperative recurrence, an FC value of < 50 μg/g reliably rules out postoperative recurrence. In patients at high risk (*e.g.*, smokers, more than one intestinal resection, surgery due to penetrating disease, perianal disease, and long segments of small bowel resection), FC cannot be used to rule out or confirm endoscopic recurrence[20]
After ileocecal resection, an FC cutoff value of > 150 μg/g is likely to have the best overall accuracy in predicting postoperative endoscopic recurrence, with a sensitivity of approximately 70%[92]
FC concentration from an ileostomy effluent can be used for assessing and monitoring small bowel inflammation and disease recurrence. An FC level of > 60 μg/g is strongly suggestive of the presence of small bowel inflammation[93]

Adapted from Dajti *et al*[18], Kapel *et al*[14], Ananthakrishnan *et al*[20], D'Amico *et al*[57], Buisson *et al*[90], Plevris *et al*[91], Tham *et al*[92], and Daoud *et al*[93]. CD: Crohn's disease; FC: Fecal calprotectin; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome.

Table 5 Practical pearls to the use of fecal calprotectin in ulcerative colitis

FC should be measured before starting or optimizing any therapy for UC, at the end of induction therapy, every 2–4 mo in patients being treated for active disease, and every 6–12 mo during the maintenance therapy in patients in symptomatic remission; and in case of clinical relapse of disease[94]
FC values of < 150 μg/g typically reflect remission, FC values ranging from 150–250 μg/g are a grey zone, and cutoff values of > 200–300 μg/g suggest the presence of active disease[11]
Prior to symptoms based on the diagnosis of a flare, FC is reported to be elevated approximately 8 wk in advance. Conversely, patients who maintain remission usually present FC concentrations persistently < 60 μg/g[95]
FC is a reliable biomarker to evaluate the response to treatment. A post-induction FC concentration of ≤ 250 μg/g *vs* > 250 μg/g is associated with a substantially higher probability of achieving clinical, endoscopic, and histologic remission[46]
FC is a valuable marker of endoscopic inflammation, being useful in distinguishing Mayo endoscopic subscores of 0 from 1–3 using the FC cutoff of 60 μg/g[96]
Persistent high values of FC are an important predictor of disease flare in asymptomatic patients[94]
In patients with mild-to-moderate UC who achieve complete endoscopic healing, a FC cutoff value between 75 and 100 μg/g can be used to discriminate patients with ongoing microscopic inflammation from those with histologic remission[97]
In patients with ileal pouch-anal anastomosis, FC values of > 100 μg/g are suggestive of endoscopic or histological inflammation of the pouch (*e.g.*, pouchitis)[57]

Adapted from D'Amico *et al*[94], Turner *et al*[11], Yamamoto *et al*[95], D'Amico *et al*[57], Dulai *et al*[46], Suttichaimongkol *et al*[96], D'Amico *et al*[94], and Stevens *et al*[97]. FC: Fecal calprotectin; UC: Ulcerative colitis.

prediction rates of relapse, the value of histological healing and TH as a therapeutic target in IBD continue to evolve and need further study. Data to support treatment intensification based only on histologic and transmural activity remains insufficient, and these patients at least require a closer follow-up.

FOOTNOTES

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