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Assessment of Mucosal Healing in Inflammatory Bowel Disease

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Abstract

In recent decades, the advent of biological therapy has changed the treatment of inflammatory bowel disease (IBD) and has opened new therapeutic endpoints such as mucosal healing (MH). MH incorporated with clinical remission presents a new concept: deep remission, which correlates with a decrease in hospitalization and surgery and improvement in the patient's quality of life. Several techniques can be used to assess mucosal healing such as endoscopy which remains the gold standard. But considerable variations may exist in the interpretation of the definition of mucosal healing which may also be histological or evaluated by radiological or biological methods. Thus, it is important to study mucosal inflammation by endoscopic scores and by new, more sensitive techniques such as videocapsule endoscopy (VCE), magnetic resonance enterography (MRE), chromoendoscopy and confocal laser endomicroscopy (CLE). Biomarkers, such as fecal calprotectin (FC) were also studied in the evaluation of MH and showed positive results. These methods are currently the subject of validation studies.

Keywords: Endoscopy; Biomarkers; Histological healing

Abbreviations

Anti-TNF: Anti-Tumoral Necrosis Factor; AIS: Histopathological Scoring of Acute Inflammation; CD: Crohn's Disease; CDAS: Crohn's Disease Activity Score; CDEAS: Crohn's Disease Endomicroscopy Activity Score; CDEIS: Crohn's Disease Endoscopic Index of Severity; CECDAl: Capsule Endoscopy Crohn's Disease Activity Index; CE: NBI Narrow Banding Imaging Coupled with Endocytoscopy; CLE: Confocal Laser

Endomicroscopy; CRP: C-Reactive Protein; ECSS: Endocytoscopy System Score; FC: Fecal Calprotectin; FICE: Fuji Intelligent Chromo Endoscopy; IBD: Inflammatory Bowel Disease; MARIA: Magnetic Resonance Index Of Activity; MH: Mucosal Healing; MRE: Magnetic Resonance Enterography; NBI: Narrow Banding Imaging; NPV: Negative Predictive Value; Se: Sensitivity; SES-CD: Simplified Endoscopic Score For Crohn's Disease; Spe: Specificity; PPV: Positive Predictive Value; UC: Ulcerative Colitis; UCEIS: Ulcerative Colitis Endoscopic Index Of Severity; UEGW: United European Gastroenterology Week; VCE: Video-capsule Endoscopy

Introduction

The history of IBD is characterized by recurrent episodes of intestinal inflammation followed by complications such as strictures abscesses or fistulas leading to repeated hospitalizations, treatment intensification and surgery. Despite increased use of immune-modulators and biologic therapy, surgical resection is still required in 60% of patients with Crohn's Disease (CD) and 10% of patients with ulcerative colitis (UC) during the first 10 years following diagnosis [1,2].

Conventional management strategies based on clinical symptoms correlate poorly with mucosal inflammation which could be responsible for this data. A post-hoc analysis of the SONIC trial showed that approximately half of patients in clinical remission had endoscopic lesions [3]. Thus, with the advent of anti-tumoral necrosis factor (anti-TNF), emerged the concept of mucosal healing (MH) [4]. Now integrated in the majority of clinical trials, MH has become a fundamental key therapeutic endpoint in the management of IBD [5]. Indeed, accumulated evidence indicates that the complete resolution of evident signs of inflammation during an endoscopic examination is associated with better long-term outcome in terms of sustained clinical remission [6], a decrease in the need for hospitalizations and surgery and a reduced risk of colorectal cancer [7]. Several methods are available for the

evaluation of MH, such as imaging (Magnetic Resonance Enterography (MRE)), histology and biomarkers. This review considers each technique in relation to the definition and evaluation of MH.

Endoscopic Mucosal Healing

There is no consensus about the definition of endoscopic mucosal healing. Furthermore, among existing endoscopic scores, the score that corresponds with MH differs between studies. This lack of a validated cut-off for endoscopic scores confirms that MH is yet to be clearly defined. In clinical practice, we consider endoscopic MH to correspond with the absence of friability (for UC), ulcerations and erosions (UC and CD) [3].

Regarding CD, a panel of experts recently proposed the threshold for endoscopic remission to be defined as a SES-CD score (Simplified Endoscopic Score for Crohn's Disease) of between 0 and 2 [8]. In current practice, Rutgeert's score is used to evaluate the endoscopic postoperative recurrence commonly defined as a score ≥ 2 (5 or more aphthous ulcers at

the site of anastomosis). This index predicts post-operative recurrence [9].

Regarding UC, the majority of clinical trials define endoscopic mucosal healing as a Mayo score equal to 0 or 1. A new endoscopic score, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), has been developed and recently validated. However, the cut-off corresponding to endoscopic MH remains to be determined [10].

These definitions highlight the ambiguity of this concept which does not hide the reality that some inflammatory lesions persist. The current belief that an endoscopic score of 0 and 1 has the same prognostic relevance has recently been challenged. The risk of relapse has been shown to be significantly higher in patients with a Mayo score equal to 1 compared with those with a Mayo score of 0 [11,12]. These results highlight the importance of determining a standardized definition of mucosal healing, which may also be histological. Advantages and disadvantages of each score are available in (Table 1) [8,10,13-17].

Table 1 Advantages and disadvantages of scores defining endoscopic MH.

Scores	Definition of MH	Advantages	Disadvantages
CDEIS [8,13,14]	CDEIS <4?	The only score validated for CD	Complexity
		Reproducible	Learning curve
		Gold standard	No cut-off
SES CD [8,15]	SES CD 0-2	Good reproducibility	No distinction between superficial or deep ulceration
		Well correlated with CDEIS	Complexity
Mayo [10,16]	Mayo=0 or 1	Easy in clinical practice	No cut-off
			Subjective parameters
			(friability)
			Low reproducibility
UCEIS [17]	UCEIS=3?	Better reproducibility than Mayo Score and Validated score	No cut-off

Histological Mucosal Healing

Histological inflammation is common even when the mucosa appears normal [18]. Accumulated evidence indicates that persistent histological disease is associated with an increased risk of hospitalization, colectomy, relapse, and colorectal neoplasia [19-21]. Thus, some authors have suggested that histological healing may be the ultimate therapeutic goal especially in UC [22].

Recently, Bressenot et al. developed and validated the first histological index for UC, the Nancy index [23]. This score is composed of three histological items defining five grades of disease activity (0 to 5). These histological parameters are the

presence of mucosal ulceration, neutrophils in lamina propria and/or epithelial cells and presence of lymphocytes and/or plasmocytes and/or eosinophils in lamina propria. A grade 0 corresponding to the absence of significant histological disease could define histological healing. In this study, this index was easy to use and reproducible.

A sub-analysis of PURSUIT trial presented as an abstract showed that an absence of ulceration and erosion as well as an absence of crypt destruction and minimal neutrophil infiltration of the epithelia (<5%) could constitute histological healing in UC [24]. However, clinical trials will be required to define the predictive value of these criteria in assessing outcomes in UC and correlating it with endoscopic scoring.

In CD, disease activity is not generally assessed by a pathologist. This is mainly attributable to the discontinued topography of the disease inducing sample error. Moreover, the benefits of achieving histological remission are unclear.

The incorporation of histological healing in establishing remission in IBD goes beyond deep remission. The term of complete remission proposed by Bryan et al. should be preferred as it implies concordance between clinical, endoscopic and histological remission and may be the ultimate treatment endpoint [25].

Overall, histological evaluation of IBD activity requires multiple samples that are why alternative techniques could be of interest.

Evaluation Methods

Endoscopy plays an essential role in the diagnosis, follow up and management of IBD, and remains the « gold standard » in order to evaluate the activity of the disease and treatment response. However, due to limited agreement of endoscopic scores, other endoscopic techniques, such as chromoendoscopy and confocal laser endomicroscopy have also been evaluated. In addition, endoscopy could be an invasive procedure so a range of non-invasive methods for the evaluation of IBD have been assessed including fecal calprotectin (FC), videocapsule endoscopy, ultrasound and MRE. The advantages and disadvantages of each method are available in (Table 2) [19,23,24,26-49].

Table 2 Advantages and disadvantages of the different methods for assessment of MH.

Methods	Advantages	Disadvantages	Criteria
White light endoscopy	Accessible	Invasive	Vascularization
	Gold standard	Low inter-observer agreement	Ulcers
	Topography		Erosions
			Erythema
		Bleeding	
Histological analysis [18,19,23,24]	Gold Standard	Sampling bias	Crypt morphology
	Validated score (Nancy Index)	Many classifications	Erosions, ulcers
		No threshold of MH	Basal plasmocytosis
Predictive of relapse		Inflammatory infiltrate of lamina propria	
Chromoendoscopy [27-29]	High association with histology (84.5%)	Time consuming (for indigo carmine)	Vessel architecture Pit pattern
	Biopsies Predictive of inflammation (92%) and extent of disease (90%) accessible	Few studies available Requires specific training	
Confocal endomicroscopy [30-34] and Endocytoscopy [35,36]	Study mucosa at a microscopic level	Accessibility	Crypt morphology
		Expensive	Vascularization
	CDEAS score	Invasive	Fluorescein leakage Microerosions
	Se 84%	Requires specific training	Lamina propria infiltration
	Spe 100%		
	PPV 87%	Reduction of the field of view that requires a chromoendoscopy before.	
	NPV 100%		
	High correlation with histology standard (r=0.871 p<0.01)		
Videocapsule [37-39]	Small intestine exploration	No biopsy	Ulcers
	Non invasive	Weak specificity	Aphthous ulcerations
			Erythema
			Erosions
		Stenosis	

			Bleeding
Ultrasound [40,41]	Accessible	Accessibility of segments	Parietal thickness
	Low cost	Intestinal gas	Doppler vascularization
	No radiation	Low inter-observer agreement	Parietal enhancement after contrast
	Well correlated with endoscopy (k=0.63)	No biopsy	
	Se 86.8% Spe 86.8% PPV 97.1% NPV 83.3%		
MRE [42-44]	Small intestine exploration	Low Spe 78% and	Parietal thickness
		NPV 63%	Parietal enhancement
	Non invasive Se 85%	No biopsy	T2 hyper-intensity
		Low number of studies	Ulcers
	High correlation between score MaRIA and CDEIS (r=0.82)		
			Mesenteric congestion
Fecal calprotectin [45-49]	Se 89%	Low Spe 35%	Threshold: 200-250 µg/g
	Non invasive Accessible	No validated cut-off	
	Good reproducibility		

Chromoendoscopy

Chromoendoscopy is a technique requiring a dye, such as indigo carmine or methylene blue, or virtual dye based on light filters (Narrow Banding Imaging, NBI, from Olympus, I-scan from Pentax and FICE from Fuji), to study the architecture of crypts and the vascular pattern, in order to detect and better characterize intestinal lesions. These techniques are efficient for neoplasia or dysplasia detection but few studies have focused on their ability to detect and grade inflammation.

Methylene blue chromoendoscopy correlate better with histology than white light for detecting inflammation (84.5% versus 37%, $p < 0.0001$) [27]. In this study, the areas of inflamed mucosa were graded according to the degree of mucosal destruction. A reticular surface pattern with scattered erosions was defined as a mild inflammatory change, whereas multiple erosive changes with partially preserved mucosa were classified as moderate inflammatory changes. An ulcerated mucosal surface was classified as a severe inflammatory change. Mucosal healing was defined as an intact mucosa with regularly distributed pits. A recent study compared white light endoscopy with i-scan to detect and quantify the extent of inflammation in 78 patients with IBD. Histological disease was classified according to Riley scoring system. The measure of the extent and severity of inflammation was significantly improved when using i-scan (92% versus 49% and 90% versus 54%, $p = .0009$ and $p = .066$ respectively) [28]. Mild inflammatory changes, moderate inflammatory changes and severe inflammatory changes were described as a decreased vascular pattern, an absent vascular pattern and ulcerations,

respectively. Mucosal healing was defined as an intact mucosa with a normal aspect of vascular pattern.

Electronic virtual chromoendoscopy is easy to use and it could be useful in assessing inflammation in patients with IBD. Danese et al demonstrated that the use of NBI detected increased angiogenesis (defined by an increased microvessel density in colonic biopsy) in areas that appeared normal with white light endoscopy. Mucosal healing was defined as a normal capillary vascular pattern with white light endoscopy (any irregularities) and with NBI (milder or regular capillary vascular pattern). Monitoring of the vascular pattern visualized in NBI might identify early signs of residual disease activity in otherwise normal appearing mucosa and could predict intestinal inflammation [29]. A normal vascular pattern could help to define mucosal healing more precisely.

Confocal Laser Endomicroscopy and Endocytoscopy

Confocal laser endomicroscopy (CLE) is a novel method that enables *in-vivo* real-time imaging of mucosa at a microscopic level revealing mucosal changes otherwise undetectable by white light endoscopy. This method has shown significant agreement with conventional histology [30-32]. Inflammatory activity can be detected by CLE, even when the mucosa appears normal macroscopically under white light endoscopy. Inflammation is therefore characterized by a modification in crypt architecture, micro-vascularization anomalies and infiltration of the lamina propria with fluorescein leakage into the intestinal lumen [50]. These parameters are well correlated with standard histology and can be used to predict

clinical relapse in UC [32]. Li et al. showed that the rate of relapse was significantly higher in patients with active inflammation detected by CLE (64% versus 18% $p < 0.001$) [32]. Stemming from this work, several scores and classifications have been proposed to measure inflammatory activity. CDEAS score (Crohn's Disease Endomicroscopy Activity Score), for example, correlates well with histology and is based on 6 parameters including crypt morphology (number of colonic crypts, crypt tortuosity, crypt lumen), presence of microerosions, vascularity, cellular infiltrate within the lamina propria and number of goblet cells [30]. Kiesslich et al. have also shown that in patients with UC or CD in clinical remission, leakage of fluorescein within epithelial cells demonstrated a local barrier dysfunction and was associated with relapse within 12 months of CLE examination [33]. Recently, Kartensen et al. have shown that a defective ileal barrier as measured by fluorescein leakage and microerosions could predict relapse in patients with Crohn's Disease, who were otherwise in clinical and endoscopic remission [51]. So, MH could be defined in CLE by an intact intestinal barrier function corresponding to the absence of fluorescein leakage and microerosions.

Endocytoscopy also allows for histological examination. This technique consists of a contact light microscope which enables real-time visualization of cellular structures of the superficial epithelial layer. Bessho et al. proposed a scoring system based on the sum of graduated criteria including shave of the crypts graduated (0-3), distance between crypts (0-2) and the visibility of superficial microvessels (0-1). The Endocytoscopy System Score (ECSS) shows a strong correlation with histology and good agreement for distinguishing between active and inactive US [35]. These results were confirmed by Maeda et al. who evaluated the performance of virtual chromoendoscopy coupled with endocytoscopy (CE-NBI) compared to standard endoscopy in UC [36]. The presence of easily visible and dilated microvessels within the intestinal mucosa identified by CE-NBI was predictive of acute intestinal inflammation (sensitivity (Se) 84%, specificity (Spe) 100%, positive predictive value (PPV) 87% and negative predictive value (NPV) 100%). This is significantly higher than classical endoscopy (Mayo score) and correlates highly with standard histology (Geboes score). This method could also enable us to differentiate easily between active and quiescent UC and evaluate histological healing in real time.

Videocapsule Endoscopy

VCE is recommended when CD is suspected, in the absence of lesions detected by colonoscopy and gastroscopy [52]. VCE is highly sensitive in the detection of superficial lesions of the mucosa and several studies have demonstrated it to be superior to MRE and enteroscanner for diagnosis in patients suspected of CD (Se 100%, Spe 91% versus 81% and 86% versus 76% and 85%, respectively) [37]. Disease activity is currently characterized using two scoring systems: the Lewis score, recently validated 53 and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) [53,54]. The Lewis score analyses 3 mucosal parameters (villous appearance, ulcerations and stenosis) in each of the 4 segments of the

small intestine (duodenum, jejunum, proximal and distal ileum). CECDAI was developed by simplifying the evaluation of the jejunal and ileal segments and limiting it to 3 parameters per segment: inflammation, extent and structuring. A Lewis score of < 135 indicates inactive disease and appears to correspond with a CECDAI score of < 3.8 . However, there is no gold standard for the definition of MH and further studies are necessary to evaluate these scores [38].

In UC, colon capsule endoscopy (PillCam Colon 2, PCC2, and Given Imaging) was evaluated for the detection of inflammation in 96 patients. The results were modest compared to colonoscopy (Se 89%, Spe 75%, and NPV 65%) [39]. Another study showed that the colon capsule underestimated both the severity and the extension of lesions compared to colonoscopy [55]. Thus, this technique is not recommended in this case.

Ultrasound

Recent progress in technology (Doppler, Contrast Agent, Image Quality), as well as the numerous advantages it presents (easy to use, absence of irradiation, easily repeatable and inexpensive), make ultrasound an attractive tool in the management and treatment of IBDs. Ultrasound is traditionally used for the detection of complications (abscesses and fistulas), and its performance has recently been assessed for the evaluation of response to treatment and the achievement of mucosal healing in patients with CD.

Castiglione et al. showed that the presence of transmural healing upon ultrasound, defined by a parietal thickness of less than 3 mm, was well correlated with endoscopic remission (SES-CD 0-2) ($k=0.63$, $p < 0.001$) [40]. These results were confirmed in a study by Moreno et al., in which normal ultrasound (parietal thickness < 3 mm, color Doppler grade 0-1, increase of parietal enhancement after contrast injection $< 46\%$) was predictive of endoscopic mucosal healing (Se 83.3%, Spe 91.7%) [41]. In this work, transmural healing was the best criteria for the prediction of endoscopic remission (Se 86.8%, Spe 96.2%, PPV 97.1% and NPV 83.3%) [41]. Ultrasound is an attractive and reliable technique for evaluating mucosal healing under the guidance of an experienced operator.

Magnetic Resonance Enterography (MRE)

MRE is important for evaluating the degree and the extent of intestinal inflammation throughout the small intestine, as well as the detection of complications, such as stenoses, fistulas or abscesses. Several studies have examined the role of MRE in monitoring treatment response and have shown a significant correlation between response to treatment and signal intensity [43]. MRI changes associated with the presence of inflammation include parietal thickness > 3 mm, T2 hyperintensity, mesenteric congestion, ulcers, contrast enhancement and positive restricted diffusion. Based on these parameters, several inflammation scores have been proposed to measure disease activity. The best known and commonly

used is the MaRIA (Magnetic Resonance Index of Activity) score, developed by the Barcelona group [42]. Although the majority of scoring systems allow for the distinction between active and inactive disease, only the MaRIA score and CDAS

(Crohn's Disease Activity Score) have been evaluated for the identification of mucosal healing, defined by a MaRIA score of lower than 7 and a CDAS inferior to [41,43,44] (Table 3).

Table 3 Principal MRE scores.

Scores	Patients	Reference	Results	Predictive factors of active disease
MaRIA (Crohn) [42,43]	Prospective study of 48 patients with active CD and reevaluated at 12 weeks after treatment (corticoids, anti-TNF)	Ileocolonoscopy CDEIS <3.5	Prediction of mucosal healing per segments	Ulcers (P=0.003)
				Edema (P=0.02)
			MaRIA score <7	Parietal enhancement (P=0.01)
			Se : 85%	
			Spe : 78%	
PNV : 63%	Parietal thickness (P=0.007)			
CDAS (Crohn) [44]	16 patients with operated CD	Histopathological scoring of acute inflammation (AIS) ≤ 2: Inactive disease	Prediction of mucosal healing	Parietal thickness (P=0.007)
			CDAS Score <4.1	T2 hyperintensity (P=0.06)
			Se : 81%	
			Spe : 70%	
ROC : .77				

Biomarkers

Despite ongoing progress, most imaging techniques remain invasive. Therefore, it is interesting to highlight potential biomarkers which could play a role in predicting intestinal inflammation. The most commonly used biomarker is C-reactive protein (CRP). Several studies have shown that early CRP normalization correlates with long-term clinical and endoscopic remission. A concentration of CRP greater than or equal to 5 mg/L allows us to identify the presence of intestinal inflammation with good Spe (73%) but weak Se (49%). Nonetheless, an increase in CRP is not specific to inflammatory illness and can also be observed in cases of sepsis or systemic inflammation. In addition, it is estimated that 30% of patients suffering from IBD flare have normal levels of CRP. These fallbacks have encouraged the development of alternative biomarker tests, such as FC. A high correlation between the level of FC and endoscopic lesion severity, with a threshold greater than 250 µg/g of feces, was reported as optimal threshold to discriminate between active and quiescent disease. D'Haens et al. reported that, for patients with CD, a level of FC <250 µg/g was predictive of mucosal healing (defined by CDEIS<3) with a Se of 94% and a Spe of 62% [45]. Data suggests an increased potential for FC to detect mucosal inflammation in the colon making this marker more sensitive than isolated ileal location in both RCH and colonic Crohn's disease. A recent study showed that at the threshold of 150 µg/g, for patients with UC disease, FC had a Se of 79% and Spe of 75% to define patients who had achieved endoscopic remission (subscore of Mayo=0). However, the correlation between FC concentration and endoscopic measures was very moderate at an individual level (k=0.38). In this case, FC could reflect persistence microscopic inflammation with a better Se than endoscopy [46].

A sub-analysis of the STORI study by GETAID, showed that at the threshold concentration of 200 µg/g, for 85 patients with CD in remission, FC level had a Se of 89% and a Spe of 35% to define patients in healing endoscopy determination (CDEIS=0) [47]. A combination of FC and CRP dosage allowed the identification of patients with a CDEIS score <3 with a Se of 72% and Spe of 74 [47]. Recently, two studies evaluated the role of FC in assessing post-operative recurrence in CD patients [48,49]. A cut-off of FC>100 µg/g identified patients with endoscopic recurrence with high Se (>90%) and a Spe around 50% and high NPV (91% to 93%).

Thus, FC could avoid repeated invasive techniques on selected patients and it could also help therapeutic decision.

Conclusions and Future Prospects

Recently, MH has become an important therapeutic target in IBD management. However, it remains a secondary treatment endpoint, most likely due to a lack of consensus on the definition of MH. The different methods detailed in this review hold several advantages and disadvantages when compared to histologic healing, which remains the gold standard despite its limitations. Depending on pathology and topography, standard endoscopy should be complemented with other techniques. A combination of these techniques would allow us to better define MH and thus integrate global remission with clinical and biological remission.

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