

Assessment of mucosal healing in inflammatory bowel disease: review CME

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Background and Aims: Mucosal healing is an important treatment end-point in inflammatory bowel disease, and achieving mucosal healing has been demonstrated to improve disease-related outcomes. Considerable uncertainty exists, however, regarding the optimal approach for the assessment of mucosal healing. Aims: to compare currently available diagnostic tools for the assessment of mucosal healing and outline the ideal approach to integrating these tools into clinical trials and clinical practice.

Methods: Review article.

Results: Endoscopy represents the criterion standard for the assessment of mucosal healing, and frequent endoscopic assessment is associated with a higher rate of achieving mucosal healing. The use of mucosal biopsy allows for the identification of persistent histologic disease activity, but the incremental clinical benefit of achieving histologic healing is yet to be determined. Magnetic resonance enterography has a high sensitivity for ulcer healing in endoscopically inaccessible disease activity. However, the presence of mucosal lesions cannot be reliably excluded based on this modality alone, and further small-bowel endoscopy should be considered in symptomatic patients. Video capsule endoscopy or device-assisted enteroscopy can be used, with device-assisted enteroscopy being preferred in stricturing Crohn's disease because of the risk of capsule retention or in patients in whom small-bowel malignancy is a possibility.

Conclusions: Endoscopy remains the criterion standard for the assessment of mucosal healing. Several alternative diagnostic modalities have become available that can be of value in specific clinical circumstances, particularly in patients with small-bowel involvement. (Gastrointest Endosc 2015;82:246-55.)

Abbreviations: CD, Crohn's disease; CDEIS, Crohn's disease endoscopic index of severity; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index; DAE, device-assisted enteroscopy; IBD, inflammatory bowel disease; MaRIA, Magnetic Resonance Index of Activity; MH, mucosal healing; MRE, magnetic resonance enterography; NBI, narrow-band imaging; SES-CD, Simplified Endoscopic Score in Crohn's Disease; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; VCE, video capsule endoscopy.

DISCLOSURE: P. Dulai is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (grant 5T32DK007202-39). P. Dulai received research support from Alpc and Polymedco. B. Levesque has served as a consultant for Takeda, Abbvie, and Nestle Health Sciences. B. Feagan received research support from, participated on scientific advisory boards for, and served as a consultant for Abbott/Abbvie, Amgen, Astra Zeneca, Bristol-Myers Squibb, Janssen, Pfizer, Tillotts, and UCB Pharma. He has participated on scientific advisory boards and served as a consultant for Avaxia Biologics Inc, Celgene, Biogen, Ferring, Merck, Novonordisk, Prometbeus, Protagonist, Salix, Takeda, TiGenix, and Teva. He has received research support from and served as a consultant for Roche/Genentech, Millennium, and Receptos. He has received research support from Santarus and Sanofi. He has served on scientific advisory boards for Novartis, has served as a consultant for Actogenix, Albireo Pharma, Avir Pharma, Axcan, Baxter Healthcare Corp, Boehringer-Ingelheim, Calypso Biotech, EnGene, GiCare Pharma, Gilead, Given Imaging Inc, GSK, Ironwood Pharma, Kyowa Kakko Kirin Co Ltd, Lexicon, Lilly, Nektar,

Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc, Vertex Pharma, VHSquared Ltd, Warner-Chilcott, Wyeth, Zealand, and Zyngenia. He has participated in speakers bureaus for Abbott/Abbvie, Jnj/Janssen, Takeda, Warner-Chilcott, and UCB Pharma and is on the board of directors for Roberts Clinical Trials. G. D'Haens received research support and lecture fees from, and served as a consultant for, Abbvie, Janssen and Takeda. G. D'Haens has served as a consultant for and received lecture fees from Centocor, Ferring, Giuliani SpA, Merck, Otsuka, Shire, Schering-Plough, Tillotts, UCB, and Vifor and has received research support from Given Imaging, MSD, Dr Falk Pharma, and Photopill and has served as a consultant for Ablynx, ActoGenix, AM Pharma, Boehringer Ingelheim GmbH, ChemoCentryx, Cosmo Technologies, Elan Pharmaceuticals, Engene, Dr Falk Pharma, Galapagos, Given Imaging, GlaxoSmithKline, Mitsubishi Tanabe Pharma, Neovacs, Novonordisk, PDL Biopharma, Pfizer, Receptos, Salix, Sandoz, Setpoint, Sigma, and Versant and has received lecture fees from Norgine, and Tramedico. W. Sandborn received research support from Janssen, Abbvie, and Western University London Ontario (owner of Roberts Clinical Trials) and has served as a consultant for Janssen, Abbvie, UCB Pharma, Shire, Salix, and Takeda.

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0016-5107/\$36.00

<http://dx.doi.org/10.1016/j.gie.2015.03.1974>

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Ulcerative colitis (UC) and Crohn's disease (CD) are idiopathic inflammatory bowel diseases (IBD) characterized by recurrent episodes of intestinal inflammation and mucosal ulceration.¹⁻³ Management strategies traditionally have been aimed at the nonspecific inhibition of inflammation with the intent of reducing disease-related symptoms such as diarrhea, abdominal pain, and fatigue. Accordingly, treatment end-points largely have focused on subjective measures of symptom severity.⁴ Symptom-based measures, however, correlate poorly with mucosal inflammation, are difficult to apply in clinical practice, and have little value in predicting disease-related morbidity and mortality.⁵⁻⁸ Recent advances in biologic therapy have transitioned treatment goals toward targeting specific inflammatory mechanisms with the intent of modifying long-term outcomes such as disease-related adverse events, hospitalizations, and surgery. Thus, efforts have now focused on identifying well-defined, reliable, and readily measurable end-points that accurately predict treatment response and long-term outcomes.⁶

Central to the pathogenesis of IBD is mucosal barrier dysfunction, which leads to an aberrant host response to commensal microorganisms and, ultimately, to loss of intestinal immune homeostasis. The end result of this uncontrolled immune reaction is intestinal inflammation, erosions, friability, and mucosal ulceration.¹⁻³ Thus, restoration of barrier function through mucosal healing (MH) has the potential to be a key treatment target in IBD. In support of this concept, data from both clinical trials and prospective cohort studies have demonstrated that the presence of MH after treatment is associated with better short-term and long-term disease-related outcomes.⁹⁻¹¹ The optimal approach to assessing and integrating this new treatment target into clinical practice remains to be determined. In this review, we will highlight the modalities currently available for the assessment of MH and outline a pragmatic approach to integrating these tools into clinical practice. We anticipate this will allow providers to better understand the changing role of MH in IBD and the optimal approach to using this end-point in clinical practice.

MH: CLINICAL RELEVANCE AND CURRENT DEFINITIONS

A fundamental principle regarding the importance of MH as a treatment target for IBD is that restoration of mucosal integrity is critical to re-establishing the barrier function of gut epithelium. An intact mucosal barrier prevents the translocation of commensal bacteria into the mucosa and submucosa, thereby down-regulating the pathologic immune response, which in turn, ameliorates clinical manifestations of the disease.¹¹ Although symptom-based metrics such as resolution of pain, bleeding, and diarrhea hypothetically might be adequate surrogates for MH, a strong correlation

has not been demonstrated between these methods of assessment.^{5,6,12,13} A key feature of IBD is the repetitive nature in which epithelial damage occurs, often before clinical signs manifest.^{14,15} Thus, the chronicity of damage often is well-established at the time of presentation, and healing often lags behind symptomatic improvement.⁵ Logically, this would suggest that symptom-based assessments may be neither sensitive nor specific enough, when used in isolation, to adequately manage patients. Given the clinical impact of continued mucosal inflammation on short-term and long-term disease-related adverse events and the clear impact improving endoscopic disease activity and achieving MH has on reducing these risks¹⁶⁻²² (Table 1), an impetus has developed to include MH as a primary treatment target in both clinical trials and clinical practice.⁶

The greatest experience with the use of MH as a treatment target has been in the setting of randomized controlled trials (Table 2). Within these trials, however, definitions have varied considerably for both UC and CD. Hence, it is not surprising that no well-validated and widely accepted definitions exist in clinical practice. This deficiency has created considerable uncertainty regarding the optimal approach to integrating MH as a treatment target.^{12,13,23} In UC, disease activity is limited to the mucosa, and thus it seems plausible that MH represents the ultimate therapeutic goal. Therefore, absence of friability, blood, erosions, or ulcerations in all examined segments, with restoration of a normal vascular pattern, seems to be a valid definition.⁷ The definition of MH in CD is less easily defined, given the transmural nature of the disease and wide variability in lesion characteristics. The International Organization for Inflammatory Bowel Disease has proposed defining MH in CD as the absence of all visible ulcers.⁸ Although this dichotomous definition is simple to apply in clinical practice, it is relatively insensitive to change and does not allow for a quantification of overall improvement or improvement beyond ulcer healing. It is important though to recognize that the importance of complete MH beyond healing of ulcerations and erosions is yet to be determined.²⁴ Accordingly, for practical purposes, providers should consider the term *MH* to represent the absence of friability (UC), ulcerations, and erosions (UC and CD).

PERFORMANCE CHARACTERISTICS OF AVAILABLE DIAGNOSTIC TOOLS

Endoscopy

Endoscopy plays an integral role in the diagnosis, monitoring, and management of IBD and IBD-related adverse events. One of the most important roles for endoscopy remains its ability to assess and stratify disease activity, which in turn influences medical decisions.^{25,26} In the past few years, this role has been given greater prominence, and a new role has emerged in the assessment and monitoring

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