Published in final edited form as:

Curr Treat Options Gastroenterol. 2014 March ; 12(1): 103–117. doi:10.1007/s11938-013-0008-1.

The Role of Mucosal Healing in the Treatment of Patients with Inflammatory Bowel Disease

Byron P. Vaughn, MD, Sveta Shah, MD, and Adam S. Cheifetz, MD

Beth-Israel Deaconess Medical Center, Center for Inflammatory Bowel Disease, 330 Brookline Ave. Boston, MA 02215, Phone: 617-667-2136, Fax: 617-667-5826

Introduction

Classically, the goals of care when treating a patient with inflammatory bowel disease (IBD) were inducing and maintaining clinical remission and improving the patient's quality of life [1, 2]. Unfortunately, many of the therapies for IBD have rare but potentially serious side effects [3–7]. Thus, when managing a patient with IBD, physicians must balance the benefits and risks of the various medications with the risk of untreated, or undertreated, disease [8]. A new treatment paradigm is emerging that focuses on “mucosal healing” (MH) in addition to the alleviation of symptoms [9, 10]. Some physicians are now advocating “deep remission,” or clinical plus endoscopic remission, as the goal for the treatment of IBD in the hope that attaining deep remission will improve the natural history of IBD. However, while this concept is intuitively appealing, not all patients will achieve MH, despite aggressive therapy, and in some cases it may expose patients to unnecessary risk from medications without an increased benefit. Changing the treatment paradigm for IBD to include deep remission requires quality data that MH healing is both attainable and improves clinical outcomes for patients with IBD.

Definition of mucosal healing

There is currently no singular validated definition for MH. For some, mucosal healing means a normal-appearing mucosa devoid of any inflammatory changes, although this can be quite difficult to attain. Practically, MH may be considered the absence of ulceration, which is potentially a more realistic goal. MH may also be defined as significant improvement in the appearance of the mucosa, but such a definition is notably more subjective. For the purposes of this review, we specify the definition of MH as noted in individual studies when discussing specific results.

Crohn's disease

There are numerous endoscopic scoring systems for Crohn's disease (CD), most of which are typically utilized only in the research setting. The Crohn's Disease Endoscopic Activity Index (CDEIS) and the Simple Endoscopic Score for Crohn's disease (SES-CD) are the most commonly used. The Rutgeerts score for CD is utilized in the postoperative setting, both clinically and in research trials. The CDEIS defines MH as a score of <6, with complete endoscopic remission being a score of <3 (which precludes any ulcerations).

Correspondence to: Byron P. Vaughn.

Conflict of Interest

Sveta Shah declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

However, while often considered the gold standard, this system is not perfect. The CDEIS requires a complicated computation involving multiple measurements in various segments, thus limiting its practicality in the non-research setting [11]. Although the CDEIS can be laborious and time-consuming, it demonstrates good inter-observer correlation ($r = 0.72$) [11, 12]. Additionally, the CDEIS does not correlate with symptoms in the Crohn's Disease Activity Index (CDAI) [13, 14]. The SES-CD was devised as an alternative to the CDEIS, and while reliable and reproducible, it is still cumbersome for routine use [15]. The Rutgeerts score is a validated tool to assess CD recurrence after ileocecal resection that is simple to use and an excellent predictor of symptomatic postoperative recurrence [16]. However, its use is limited to the postoperative setting. It is also important to emphasize that CD is a transmural process that may involve any segment of the GI tract, thus limiting the ability of endoscopy to accurately assess MH in every clinical situation. New scoring systems such as the Lemann score for CD are designed to incorporate transmural inflammation and allow assessment of the entire bowel [17].

Ulcerative colitis

There are more than 10 indices used to assess ulcerative colitis, none of which have been validated [11, 16, 18, 19]. The Mayo score is the most commonly utilized. For UC, it has been suggested that a Mayo endoscopic score of 0–1 be used as a cutoff for MH, with 0 being normal or inactive disease and 1 being mild erythema, decreased vascular pattern, or mild friability [20]. Other endoscopic scores in UC include the Baron endoscopic score or the endoscopic component of the UC Disease Activity Index (UCDAI) [21, 22]. In a consensus statement, D'Haens et al. propose that MH be defined as absence of all “friability, blood, erosions, and ulcers in all visualized segments” [23]. Additionally, they argue that due to a lag time in healing, histologic remission should not be a primary endpoint in a research protocol, although it is of significant interest and should be viewed as a secondary outcome. These scores are quite helpful, especially in the research setting, although the definition of MH can differ between trials and, historically, none of the tools have been validated. A new endoscopic scoring system, the Ulcerative Colitis Endoscopy Index of Severity (UCEIS) was recently developed [24] as a tool to measure endoscopic severity of UC based on flexible sigmoidoscopy. It consists of 3 descriptors (vascular pattern, bleeding, erosions/ulcers), each with a score ranging from 0–8. While there is no fully validated test for endoscopic severity of UC, the UCEIS has undergone an initial validation and demonstrated satisfactory reliability. This test promises to be advantageous as the first validated tool to measure endoscopic activity in UC and will likely become used in clinical trials.

How often is MH achieved with various medications?

In order to be able to recommend MH as a goal of therapy for patients with IBD, it is critical to understand how often that goal is attainable and to select a therapy that has the highest probability of attaining this objective. The following section will address the data regarding the ability of various medications to achieve MH. Table 1 shows the rates of MH seen with specific medications for CD, and Table 2 shows the same for UC.

Crohn's Disease

Steroids—Steroids have long been used to induce clinical remission with CD, although the data demonstrating the effect of steroids on MH are limited. In a study of 8 patients with prior ileocecal or ileocolonic resections, oral prednisolone was unable to achieve endoscopic remission after 6–9 weeks of treatment despite clinical improvement [25]. In another cohort of patients who achieved clinical remission on steroids, only 29% had subsequent endoscopic remission (defined as absence of mucosal lesions or scarred lesions only) at 3–7

weeks [13]. A recent systematic review suggested that despite the effectiveness of second-generation corticosteroids for induction of remission, the data for mucosal healing are limited [26].

Thiopurines—Until recently, data for endoscopic healing with thiopurines in Crohn's disease have been limited. In the 1990's, only a few small trials included MH as an outcome [27–29]. More recent studies have used MH as an endpoint, and the results have been variable. In 2005, the GETAID group demonstrated that in patients in clinical remission on azathioprine for at least 42 months, only 36% had a CDEIS of 0 (complete MH) [30]. A subsequent randomized trial of MH, where MH was defined as a CDEIS score of less than 6, compared azathioprine to budesonide. Azathioprine demonstrated MH rates as high as 83% at 1 year, compared to 24% with budesonide alone [31]. However, when considering only complete MH (CDEIS of 0) and on intention-to-treat analysis, the rate of MH dropped to 58%. In the SONIC trial, treatment-naïve patients randomized to the azathioprine arm had a 6-month MH rate of 16.5% [32]. The SONIC trial defined MH as no ulcers among those who had ulceration at baseline. In addition to the follow-up time differences, this definition of MH is more stringent than a CDEIS score of <6 and thus may account for some of the variations seen in MH rates with azathioprine.

Methotrexate—Data regarding MH rates with methotrexate are also limited and quite variable. In a small study from 1989 that evaluated the efficacy of methotrexate for refractory IBD [33], 5 of 14 patients with Crohn's colitis demonstrated mucosal and histologic healing after 12 weeks of methotrexate. Notably, none of the patients with UC had MH. Another small but more recent case series noted that up to 50% of CD patients with a clinical response will achieve MH [34]. Neither of these studies included a control arm, making the results difficult to interpret. A prospective observational study of patients in clinical remission defined MH as absence of mucosal ulcerations in all segments, and found MH rates of 11% with methotrexate versus 50% with azathioprine and 60% with infliximab [35]. However, the overall number of patients was small and each group had variable follow-up.

Anti-TNF—Unlike the therapies discussed thus far, many more studies have been done within the last decade to directly evaluate the effect of anti-TNF inhibitors on mucosal healing. In an ACCENT I substudy, MH (defined as the absence of mucosal ulcerations at follow-up in patients who had ulcerations at baseline) was achieved in 31% of patients at 10 weeks who received scheduled infliximab (IFX) and in 50% of patients at 54 weeks. Placebo rates of healing were 0% at week 10 and 7% at week 54 [36]. A second study of MH with IFX, where MH was similarly defined as disappearance of mucosal ulcerations, found that 45% of patients had complete healing after a median of 6.7 months (interquartile range 1.4–24.6 months) with sustained infliximab treatment [37].

The SONIC trial assessed MH in treatment-naïve patients who received azathioprine, infliximab, or the combination of azathioprine and infliximab. MH was defined as disappearance of mucosal ulcerations after presence of ulcerations at baseline [32]. At 6 months, the rates of MH were 43.9% on combination therapy, 30.1% on infliximab alone, and 16.5% on azathioprine alone. In the “Step Up versus Top Down” trial, patients were randomized to induction therapy with 3 infusions of infliximab and maintenance therapy with azathioprine versus traditional “step up” therapy with multiple courses of corticosteroids before institution of a thiopurine [38]. This longer-term study found a MH rate, defined as no ulceration, of 73.1% in the early combination treatment arm versus 30.4% in the traditional therapy arm at 2 years' time.

Adalimumab has also been shown to induce MH. In the EXTEND trial, adalimumab had a MH rate of 27% versus 13% at week 12 ($p = 0.56$) and a MH rate of 24% versus 0% in placebo at 1 year ($p < 0.001$) [39]. MH was defined as no ulcerations present in any of the 5 examined segments used in the CDEIS. There is also some data for certolizumab pegol and MH, although the numbers are less impressive [39,40]. In the MUSIC trial, the primary outcome was a mean change in CDEIS score at week 10, while secondary outcomes included MH at weeks 10 and 54. The mean CDEIS was 14.5 (standard deviation of 5.3) at baseline, with mean decrease of 5.7 at week (95% CI 4.6 to 6.8, $p < 0.0001$) [40]. MH, defined as the absence of ulcerations, occurred in 4% of patients at week 10 and 8% of patients at week 54. The rate of complete endoscopic remission (or CDEIS score of < 3) was only 10% at week 10 and 14% at week 54. The authors argue that the rates of complete MH were low given the severity of baseline ulcerations.

Anti-integrin inhibitors—A small retrospective study of MH with natalizumab in patients who had previously failed immunomodulators and anti-TNF agents demonstrated a MH rate of 42.3% after treatment for a mean duration of 14.1 months [41]. MH was defined as a decrease of the SES-CD of $> 70\%$, which are less stringent criteria than studies defining MH as complete absence of ulceration. MH was not an endpoint in the recent trial of vedolizumab for CD [42].

Ulcerative colitis

Given that the inflamed mucosa is easier to assess in UC, MH has been used as an endpoint in multiple landmark studies of the treatment of UC. However, interpretation of these studies is complicated by heterogeneity in the definition of MH, severity of disease in patients studied, extent of disease, and time points assessed. The ranges of rates of MH for various therapies in UC are presented in Table 2.

Mesalamine—The ASCEND I and II trials assessed the use of delayed-release mesalamine (Asacol) for the treatment of mild–moderate UC [43, 44]. In these trials, MH was defined as a Mayo endoscopy score of 0 or 1. A post hoc analysis determined that 80% of patients with moderately active UC achieved MH on mesalamine 4.8 g/day and 68% achieved MH on mesalamine 2.4 g/day ($p = 0.012$). Higher rates of MH were achieved in those with mild UC, with 84% achieving MH on mesalamine 4.8 g/day and 88% on mesalamine 2.4 g/day ($p = 0.765$) [45]. It is important to note that the definition of MH did include a Mayo score of 1, which includes mild erythema and friability [20].

Two large studies evaluating the efficacy of MMX mesalamine (Lialda) for the treatment of mild–moderate UC used a stringent definition of MH that only allowed minimal erythema, granularity, and decreased vascular patterns [46,47]. Lichtenstein et al. found that the combined endpoint of clinical and endoscopic remission by week 8 was achieved in 34.1% of patients on MMX mesalamine 2.4 g BID, 29.2% of patients on 4.8 g/day, and 12.9% of patients on placebo, with both therapy arms achieving significance versus placebo [46]. Improvement in endoscopic score by week 8 was seen in 61.4% of patients on MMX mesalamine 2.4 g BID, 69.7% of patients on 4.8 g/day, and 35.3% of patients on placebo [46]. Kamm et al. found clinical and endoscopic remission by week 8 in 40.5% of patients on MMX mesalamine 2.4 g/day, 41.2% of patients on 4.8 g/day, 32.6% of patients on Asacol 2.4 g/day, and 22.1% of patients on placebo [47]. Improvement in endoscopic score by week 8 was seen in 69% of patients on MMX mesalamine 2.4 g/day, 76.5% of patients on 4.8 g/day, 58.1% of patients on Asacol 2.4 g/day, and 41.9% of patients given placebo. A post hoc analysis of these studies determined that the combined rate of MH in these studies was 32% on MMX mesalamine 2.4 g/day, 32.2% on 4.8 g/day, and 15.8% on placebo [48]. The addition of topical mesalamine to oral mesalamine may improve the proportion of

patients achieving MH. This was assessed in a prospective trial of 6 weeks of combined oral (4 g/day) and rectal (2 g/day) mesalamine[49]. By week 6, 69.1% of patients on this regimen achieved MH (defined as Mayo endoscopic subscore of 0– or 1).

A recent meta-analysis of patients with mild–moderate disease found MH rates in a range of 35–49% on oral mesalamine agents and 46–62% on topical mesalamine[50]. The higher rates of MH with oral mesalamine in the ASCEND I and II studies may be due to the definition of MH used. In the combined ASCEND I and II trials, if MH healing was defined as an endoscopic score of 0, it was achieved in only 32% of moderately active patients on mesalamine 4.8 g/day and 24% of patients on 2.4 g/day ($p=0.125$). Using the more stringent definition of MH in those with mild UC, the rate of MH decreased to 44% in patients on mesalamine 4.8 g/day and 42% in patients on mesalamine 2.4 g/day at 6 weeks ($p=0.640$) [45].

Steroids—In 1955, Truelove et al. described the effects of cortisone in ulcerative colitis. In this study, 30% of patients had “normal” or “near-normal” endoscopic appearance on sigmoidoscopy following cortisone 100 mg/day for 2 to 6 weeks (versus 11% in the control group) [51]. In a more recent cohort of UC patients receiving steroids, 38% were able to achieve MH at three months, where MH was defined as a Baron score of 0 (i.e., normal mucosa or mild erythema) [52]. Others, however, noted less impressive results. In a study comparing budesonide to prednisolone, only 11.8% of patients who received budesonide and 15.8% of patients who received prednisolone achieved endoscopic remission (defined as normal or non-inflamed mucosa at 4 weeks) [53].

Thiopurines—There are few studies in UC assessing the effect of thiopurines on MH. A study by Ardizzone et al. measured rates of MH after 6 months on azathioprine 2 mg/kg/day versus 5-ASA 3.2 g/day [54]. This trial randomized corticosteroid-dependent patients to azathioprine 2 mg/kg/day or mesalamine 3.2 g/day and utilized the Baron endoscopic score of 0 or 1 (range 0–3) as the definition endoscopic remission. A Baron score of 0 is normal mucosa, while a Baron score of 1 represents granular or edematous mucosa with loss of vascular pattern [21, 54]. The authors noted a MH rate of 53% on azathioprine and 19% on mesalamine at 6 months[54]. Thus, it is reasonable to conclude that thiopurines for steroid-dependent UC do achieve MH, and likely at a higher rate than mesalamine.

Anti-TNF—Anti-TNF medications including infliximab, adalimumab, and golimumab are approved for the treatment of moderate–severe UC [20, 55–57]. In the ACT 1 and 2 studies, MH was defined as Mayo endoscopy subscore of 0 or 1. At week 8, MH occurred in 59–62% of patients on infliximab and 30.9–33.9% of patients on placebo. At week 54, MH occurred in 45.5–46.7% of patients on infliximab and 18.2% of patients on placebo [20]. The ULTRA 1 and 2 studies evaluated adalimumab for moderate–severe UC and similarly defined MH as a Mayo endoscopic subscore of 0 or 1 [55, 57]. In ULTRA 1, 37.7–46.9% of patients who underwent induction followed by maintenance achieved MH at 8 weeks [55]. However, this was not significant compared to the placebo rate of MH of 41.5%. In ULTRA 2, the MH on adalimumab was 41.1% versus the placebo MH rate of 31.7% by week eight ($p<0.05$) [57]. By week 52, 25% had MH on adalimumab versus 15.4% on placebo ($p<0.05$). This effect appeared to be driven by patients who were anti-TNF-naïve. The PURSUIT-SC trial was a large phase 2/3 trial of golimumab for moderate–severe UC. MH was a major secondary endpoint defined as Mayo endoscopic subscore of 0 or 1. MH was achieved in 43.2–45.3% of patients on golimumab compared to 28.5% of patients on placebo ($p<0.05$) [56]. MH was achieved in 41.7–42.4% of patients at 30 and 54 weeks (versus 26.6% on placebo) [58].

Anti-integrin inhibitors—Unlike the trial for CD, the phase 3 trial of vedolizumab in UC did have MH as a study endpoint [59]. MH was defined as Mayo endoscopic subscore of 0 or 1. The vedolizumab arm had a MH rate at 52 weeks of 51.6–56% versus 19.8% in the placebo arm ($p < 0.001$) [59].

Why is mucosal healing important?

Using MH as clinical endpoint is helpful for multiple reasons. First, it allows the clinician to distinguish symptoms due to underlying inflammation from other etiologies such as irritable bowel syndrome and bile salt malabsorption, as symptom scores and endoscopic scores do not correlate [13]. One study documented that patients with IBS had higher CDAI scores than patients with CD [60]. This was driven by the subjective subcomponents of the CDAI. There is also a considerable overlap of IBS symptoms in patients with IBD [61]. As our medical therapies have rare but significant adverse events, it is important to confirm objective evidence of active IBD before stepping up therapy. This can help guide therapy and potentially prevent inappropriate “step-up” therapy when MH is already achieved. Additionally, MH has been associated with a number of improved outcomes in both CD and UC. Although the current data (discussed below) are limited, there appears to be a consistent association between MH and fewer disease-related complications such as surgery and hospitalizations. Additionally, the severity of endoscopic lesions can also help to predict the course of IBD. Studies have shown that patients with severe ulcerations have a worse clinical course, and other studies have demonstrated that MH tends to predict a sustained clinical response. Finally, for research purposes, MH is a more objective endpoint than clinical indices.

Crohn's disease

Several studies have noted improved outcomes in patients with MH. Studies suggest that patients with MH are at lower risk of flaring, of developing complications of CD, and of requiring hospitalization or surgery. A single-center prospective cohort of patients with CD receiving IFX noted that patients who achieved MH had significantly fewer hospitalizations and abdominal surgeries than patients who did not achieve MH [62]. In the same study, patients who achieved partial MH (clear endoscopic improvement although ulcerations were still present) had similar surgical rates to those who achieved complete MH (absence of ulceration). Similar results were noted in a substudy of ACCENT I patients. Patients achieving MH had fewer hospitalizations, although the results were not statistically significant [36].

MH also appears to be associated with fewer flares of CD. Patients who achieved MH as part of the “Step Up versus Top Down Study” had fewer flares over a 2 year follow-up period compared to the group that did not achieve MH [38, 63]. In fact, complete MH (SES-CD of 0) was the only predictor of steroid-free remission in the 2-year follow-up period. Similarly, in a prospective study comparing the MH rates of methotrexate to thiopurines and infliximab, patients who achieved MH (defined as CDEIS < 4), regardless of the specific therapy, had fewer flares over the 2-year follow-up time [35]. Thus, while data are still limited to subsets of patients in prior studies and observational cohorts, achieving MH appears to confer a long-term benefit [64].

Achieving MH also predicts a better clinical course. For example, healing early on in the course of therapy with IFX predicts MH at 1 year. Although the number of patients in the trial was small, a prospective observational study noted that patients who achieved MH at 3 months predicted MH at 1 year [65]. The rate of MH at 3 months was only 24%, but significantly more of these patients with early MH still had MH at 12 months (70% versus

17% of patients without early MH, $p = 0.01$). Thus the patients who achieve MH may represent a lower-risk group of patients.

Additionally, MH may also predict longer-term outcomes. In the IBSEN cohort, achieving MH at 1 year was found to be predictive of less inflammation seen on endoscopy at a 5-year follow-up ($p = 0.02$) [66]. Among patients who were on steroids at 1 year, those who achieved MH at 1 year were less likely to still be requiring steroids at 5 years ($p = 0.02$). Total steroid use, however, was the same at 5 years regardless of MH status at 1 year ($p = 0.4$). While there was a trend towards fewer surgeries ($p = 0.1$), there was no association with MH at 1 year. And while the cohort was large, the number of patients with 5 year MH data was smaller (124 patients). The study also had several limitations. First, it was spread out over many sites, increasing the potential variability in treatment decisions such as use of steroids or validation of a flare, and the definition of MH for this cohort did not use a validated endoscopic scoring system. Although less inflammation was seen at 5 years for those who achieved early MH, improvement in other clinical outcomes requires more evaluation. To summarize, there is ample evidence that MH healing in CD is associated with better outcomes – specifically, fewer hospitalizations and surgeries and potentially fewer flares.

In addition, MH may have a role in predicting the course of disease. Patients with severe endoscopic disease are at higher risk for flaring and developing complications, such as surgery. Retrospective analysis suggests that patients with CD who have severe ulceration on endoscopy have an increased risk of colectomy compared to those who do not. Endoscopy can thus be used to help risk-stratify patients and identify those who may be more appropriate for early aggressive treatment with biologics.

Ulcerative colitis

Similar to CD, MH in UC is associated with improved outcomes and can help predict disease course. In a post hoc analysis of ACT 1 and ACT 2, patients who had a lower endoscopic subscore at week 8 were more likely to be colectomy-free at week 54 [67]. Interestingly however, there was no difference in outcomes in patients who achieved a subscore of 0 vs. 1. While it may be that complete MH healing (Mayo endoscopic score of 0) does not provide benefit beyond that of near-complete MH (Mayo endoscopic score of 1), it is possible that the study was underpowered to detect a difference between those groups. Another retrospective analysis found similar results, where patients achieving an endoscopic score of 0 or 1 had significantly fewer colectomies at 48 months [68]. The IBSEN cohort demonstrated that those who achieved MH at 1 year had significantly fewer colectomies reported at 5 years ($p = 0.02$) [66]. Given the small overall number of colectomies, only a limited analysis could be performed, but MH was consistently protective against colectomy at 5 years, with a RR of 0.22 (95% CI: 0.06–0.79). However, MH was not able to predict patient-reported disease course at 5 years. Unlike the CD arm, MH in UC at 1 year was not associated with less inflammation at 5 years. Notably, no patients in this cohort were given biologics, and drug maintenance data is not reported. Given other data suggesting that maintenance medication is required for maintenance of MH, it is possible that variations in treatment among these patients over 5 years accounted for the lack of additional long-term benefit [36].

In patients with less severe UC, a prospective trial of combined oral and topical mesalamine for mild–moderately active UC found that patients who achieved MH had a significantly lower relapse rate, at 23%, as opposed to 80% in patients who only achieved clinical remission ($p < 0.0001$) [49]. However, the majority of patients in this study who achieved clinical remission also achieved endoscopic remission. In Milan, another cohort of patients with UC who were followed for 5 years demonstrated that those with MH required less

immunosuppressive therapy and experienced fewer hospitalizations and colectomies than those who did not achieve MH 3 months after steroids [52]. While only 60 patients achieved MH, on a multivariate analysis, the lack of MH after corticosteroid use was the only predictor of more aggressive disease (defined as need for immunosuppressive medications, hospitalizations, or surgery) at 5 years.

MH in UC is not only associated with improved outcomes but is also predictive of disease course. Using endoscopic lesions to predict the course in UC is not a novel concept. In 1996, for example, in developing a prediction tool for outcomes of severe UC, Travis et al. noted that the presence of severe rectal inflammation was more common in the group of patients that went to colectomy [69]. Additionally, in patients with severe UC who require rescue therapy with cyclosporine, those without severe lesions seen on endoscopy are more likely to avoid colectomy than those with severe lesions ($p < 0.001$) [70]. This finding has also been demonstrated in patients with refractory UC receiving IFX. In a multivariate analysis, Laharie et al. found the absence of MH to be the only predictor of colectomy, with an OR of 18.01 (95% CI: 1.58–204.92; $p = 0.02$) [68].

To summarize, while the data for UC are still somewhat limited, patients who achieve MH appear to have improved outcomes, including fewer flares and fewer colectomies. However, based on the available data, it is not clear that MH in UC is associated with fewer hospitalizations.

Prevention of cancer

In IBD, MH may provide an additional benefit by reducing the incidence of colorectal neoplasia. Severe inflammation on histology is a risk factor for colorectal cancer in UC [71,72]. Similarly, it has also been suggested that endoscopic evidence of inflammation increases the risk of progression to neoplasia and that an endoscopically normal colon in a patient with UC has a similar risk of cancer as the general population [73]. Unfortunately, demonstrating this effect in a prospective controlled trial would require following a large number of patients over a long period of time. Thus far, evaluation of large data repositories has been unable to show a decrease of colorectal cancer with mesalamine over a short period of time [74]. However, a recently published case-control study demonstrated a protective effect of mesalamine and thiopurines against colorectal neoplasia in UC [75]. This study was large enough to stratify for degree of histologic inflammation and while mesalamine agents were not significantly associated with a decreased risk of colorectal neoplasia after adjustment ($p = 0.56$), an association was present with thiopurines ($p = 0.011$). If MH does have a chemoprotective effect, it is likely more relevant in UC than CD.

Limitations of mucosal healing

MH, despite its many advantages, is not a perfect endpoint. First, there is no single universally agreed-upon definition of MH. This makes it difficult to translate MH into practice as a clinically relevant endpoint. The majority of recent studies for UC use the Mayo endoscopic subscore of 0 or 1, which should be relatively easy to use clinically. There is no simple correlate in CD, however, and more comprehensive assessments such as the Lemann score may be required. A second limitation of MH as an endpoint is that it is not always achievable and may expose patients to unnecessary risk, particularly when it leads to escalation of therapy for a patient already in clinical remission. A more reasonable approach may involve a trial of escalated therapy for 6–12 months, with a plan to scale back treatment if endoscopic improvement is not achieved. A third limitation, more specific to Crohn's disease, is that MH may be difficult to assess and may not be accessible by routine ileocolonoscopy, as in more proximal small-bowel Crohn's disease. As such, other surrogate markers such as fecal calprotectin or cross-sectional imaging are likely to be required in this

setting to assess for healing. Additionally, the majority of endoscopic scores are difficult to calculate in practice, thus limiting their use. Simply assessing for the presence of any ulceration is usually feasible and is potentially the best outcome of MH. Finally, the current evidence that MH is associated with better outcomes is largely of an indirect nature, and more data is necessary regarding long-term outcomes of MH in order to appropriately advise patients. To truly demonstrate that achieving MH is superior to clinical remission requires a large comparative-effectiveness trial randomizing patients to treatment to clinical remission or increasing therapies until MH is achieved.

Conclusion

In conclusion, MH is an appealing endpoint for IBD for a variety of reasons. Current data suggest that MH, when achieved, in both CD and UC, is associated with fewer disease flares, hospitalizations, and surgeries. Thus it is reasonable to educate patients on the potential benefits of MH and to discuss this option of as a goal of care. However, MH may not be an achievable endpoint for all patients. If therapy is escalated for the sole purpose of achieving MH, then reassessment within a year is recommended to ensure benefit. In the research setting, MH should continue to be utilized as a major variable, as it provides a more objective assessment tool than current clinical indices. The authors view MH as an important clinical endpoint. We routinely discuss MH with our patients and often strive to achieve it as a goal of care.

Acknowledgments

Byron P Vaughn is supported by the training grant NIH training grant 5T32DK007760-14.

Adam S. Cheifetz has received consultancy fees from AbbVie, Janssen, Pfizer, Given Imaging, Prometheus, UCB, and Warner Chilcott.

References

Papers of particular interest, published recently, have been highlighted as

• Of importance

•• Of major importance

1. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006 Mar 1; 130(3):940–987. [PubMed: 16530532]
2. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009 Nov 19; 361(21):2066–2078. [PubMed: 19923578]
3. Singh JA, Wells GA, Christensen R, TanjongGhogu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011; (2):CD008794. [PubMed: 21328309]
4. Stanbury RM, Graham EM. Systemic corticosteroid therapy--side effects and their management. *Br J Ophthalmol*. 1998 Jun; 82(6):704–708. [PubMed: 9797677]
5. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. 2005 Aug 1; 41(Suppl 3):S194–S198.
6. Vaughn BP, Doherty GA, Gautam S, Moss AC, Cheifetz AS. Screening for tuberculosis and hepatitis B prior to the initiation of anti-tumor necrosis therapy. *Inflamm Bowel Dis*. 2012 Jun; 18(6):1057–1063. [PubMed: 21953829]

7. Bucher C, Degen L, Dirnhofer S, Pless M, Herrmann R, Schraml P, et al. Biologics in inflammatory disease: infliximab associated risk of lymphoma development. *Gut*. 2005 May; 54(5):732–733. [PubMed: 15831931]
8. Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. *Gastroenterology*. 2000 Jun; 118(6):1018–1024. [PubMed: 10833475]
9. Neurath MF, Travis SPL. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut*. 2012 Sep 28; 61(11):1619–1635. [PubMed: 22842618] A recent systematic review detailing the role of mucosal healing in IBD
10. Neurath MF. New targets for mucosal healing and therapy in inflammatory bowel diseases. *Mucosal Immunol*. 2013 Oct. [Epub ahead of print].
11. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Grouped"EtudesThérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut*. 1989 Jul; 30(7):983–989. [PubMed: 2668130]
12. Landi B, Anh TN, Cortot A, Soule JC, Rene E, Gendre JP, et al. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Grouped"EtudesThérapeutiques des Affections Inflammatoires Digestives. *Gastroenterology*. 1992 May; 102(5):1647–1653. [PubMed: 1568574]
13. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone.Grouped"EtudeThérapeutique des Affections Inflammatoires Digestives. *Gastroenterology*. 1990 Apr; 98(4):811–818. [PubMed: 2179031]
14. Cellier C, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Grouped"EtudesThérapeutiques des Affections Inflammatoires Digestives. *Gut*. 1994 Feb; 35(2):231–235. [PubMed: 7508411]
15. Sostegni R, Daperno M, Scaglione N, Lavagna A, Rocca R, Pera A. Review article: Crohn's disease: monitoring disease activity. *Aliment Pharmacol Ther*. 2003 Jun; 17(Suppl 2):11–17. [PubMed: 12786607]
16. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990 Oct; 99(4):956–963. [PubMed: 2394349]
17. Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, et al. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis*. 2011 Jun; 17(6):1415–1422. [PubMed: 21560202]
18. Daperno M, D'Haens G, van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004 Oct; 60(4):505–512. [PubMed: 15472670]
19. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987 Dec; 317(26):1625–1629. [PubMed: 3317057]
20. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005 Dec; 353(23):2462–2476. [PubMed: 16339095]
21. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J*. 1964 Jan; 1(5375):89–92. [PubMed: 14075156]
22. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, et al. 5- Aminosalicic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology*. 1987 Jun; 92(6):1894–1898. [PubMed: 3569765]
23. D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, et al. A Review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology*. 2007 Feb; 132(2):763–786. [PubMed: 17258735]

24. Travis SPL, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel J-F, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology*. 2013 Nov; 145(5):987–995. [PubMed: 23891974]
25. Olaison G, Sjö Dahl R, Tagesson C. Glucocorticoid treatment in ileal Crohn's disease: relief of symptoms but not of endoscopically viewed inflammation. *Gut*. 1990 Mar; 31(3):325–328. [PubMed: 2323598]
26. De Cassan C, Fiorino G, Danese S. Second-generation corticosteroids for the treatment of Crohn's disease and ulcerative colitis: more effective and less side effects? *Dig Dis*. 2012; 30(4):368–375. [PubMed: 22796798]
27. D'Haens G, Geboes K, Ponette E, Penninckx F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology*. 1997 May; 112(5):1475–1481. [PubMed: 9136824]
28. D'Haens G, Van Deventer S, Van Hogezaand R, Chalmers D, Kothe C, Baert F, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology*. 1999 May; 116(5):1029–1034. [PubMed: 10220494]
29. D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc*. 1999 Nov; 50(5):667–671. [PubMed: 10536324]
30. Lemann M, Mary J-Y, Colombel J-F, Duclos B, Soule J-C, Lerebours E, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology*. 2005 Jun; 128(7):1812–1818. [PubMed: 15940616]
31. Mantzaris GJ, Christidou A, Sfakianakis M, Roussos A, Koilakou S, Petraki K, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. *Inflamm Bowel Dis*. 2009 Mar; 15(3):375–382. [PubMed: 19009634]
32. Colombel J-F, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010 Apr; 362(15):1383–1395. [PubMed: 20393175] Data supporting the use of combination therapy for Crohn's disease with improved outcomes including mucosal healing
33. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med*. 1989 Mar; 110(5):353–356. [PubMed: 2492786]
34. Mañosa M, Naves JE, Leal C, Cabré E, Moreno V, Lorenzo-Zuñiga V, et al. Does methotrexate induce mucosal healing in Crohn's disease? *Inflamm Bowel Dis*. 2010 Mar; 16(3):377–378. [PubMed: 19575354]
35. Laharie D, Reffet A, Belleannée G, Chabrun E, Subtil C, Razaire S, et al. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. *Aliment Pharmacol Ther*. 2011 Jan 16; 33(6):714–721. [PubMed: 21235604]
36. Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc*. 2006 Mar; 63(3):433–442. [PubMed: 16500392]
37. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijis I, Van Assche G, et al. Longterm outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut*. 2009 Apr; 58(4):492–500. [PubMed: 18832518]
38. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008 Feb; 371(9613):660–667. [PubMed: 18295023]
39. Rutgeerts P, van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel J-F, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012 May; 142(5):1102–1102. [PubMed: 22326435] Data supporting adalimumab and mucosal healing

40. Hebuterne X, Lémann M, Bouhnik Y, Dewit O, Dupas JL, Mross M, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. *Gut*. 2013 Jan; 62(2):201–208. [PubMed: 22525883]
41. Sakuraba A, Annunziata ML, Cohen RD, Hanauer SB, Rubin DT. Mucosal Healing is associated with improved long-term outcome of maintenance therapy with natalizumab in Crohn's disease. *Inflamm Bowel Dis*. 2013 Nov; 19(12):2577–2583. [PubMed: 24132161] An important study looking at first generation anti-integrin inhibitors and their role in mucosal healing
42. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel J-F, Sands BE, et al. Vedolizumab as induction and maintenance therapy for crohn's disease. *N Engl J Med*. 2013 Aug 22; 369(8):711–721. [PubMed: 23964933]
43. Hanauer SB, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: The ASCEND II trial. *Am J Gastroenterol*. 2005 Nov; 100(11):2478–2485. [PubMed: 16279903]
44. Hanauer SB, Sandborn WJ, Dallaire C, Archambault A, Yacyshyn B, Yeh C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol*. 2007 Dec; 21(12):827–834. [PubMed: 18080055]
45. Lichtenstein GR, Ramsey D, Rubin DT. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing--ASCEND I and II combined analysis. *Aliment Pharmacol Ther*. 2011 Mar; 33(6):672–678. [PubMed: 21255059]
46. Lichtenstein GR, Kamm MA, Boddu P, Gubergits N, Lyne A, Butler T, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol*. 2007 Jan; 5(1):95–102. [PubMed: 17234558]
47. Kamm MA, Lichtenstein GR, Sandborn WJ, Schreiber S, Lees K, Barrett K, et al. Effect of extended MMX mesalamine therapy for acute, mild-to-moderate ulcerative colitis. *Inflamm Bowel Dis*. 2009 Jan; 15(1):1–8. [PubMed: 18671232]
48. Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T, Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther*. 2007 Jul; 26(2):205–215. [PubMed: 17593066]
49. Meucci G, Fasoli R, Saibeni S, Valpiani D, Gullotta R, Colombo E, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. *Inflamm Bowel Dis*. 2012 Jun; 18(6):1006–1010. [PubMed: 21830282]
50. Römkens TEH, Kampschreur MT, Drenth JPH, van Oijen MGH, de Jong DJ. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. *Inflamm Bowel Dis*. 2012 Nov; 18(11):2190–2198. [PubMed: 22419617] Meta-analysis of mucosal healing rates with mesalamine agents
51. Truelove S. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. *Gastroenterologia*. 1954 Feb; 81(2):86–90. [PubMed: 13151358]
52. Ardizzone S, Cassinotti A, Duca P, Mazzali C, Penati C, Manes G, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol*. 2011 Jun; 9(6):483–483. [PubMed: 21195796]
53. Lofberg R, Danielsson A, Suhr O, Nilsson A, Schioler R, Nyberg A, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology*. 1996 Jun; 110(6):1713–1718. [PubMed: 8964395]
54. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut*. 2006 Jan; 55(1):47–53. [PubMed: 15972298]
55. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut*. 2011 May; 60(6):780–787. [PubMed: 21209123]

56. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johannis J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2013 Jun. [Epub ahead of print].
57. Sandborn WJ, Van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis. *Gastroenterology*. 2012 Feb; 142(2):257–265. [PubMed: 22062358]
58. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johannis J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2013 Jun. [Epub ahead of print].
59. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel J-F, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013 Aug; 369(8):699–710. [PubMed: 23964932] Landmark trial for effectiveness of vedolizumab in Ulcerative colitis
60. Lahiff C, Safaie P, Awais A, Akbari M, Gashin L, Sheth S, et al. The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 2013 Apr; 37(8):786–794. [PubMed: 23432394]
61. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2012 Aug; 107(10):1474–1482. [PubMed: 22929759]
62. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijis I, van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis*. 2009 Sep; 15(9):1295–1301. [PubMed: 19340881]
63. Baert F, Moortgat L, van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology*. 2010 Feb; 138(2):463–468. [PubMed: 19818785]
64. Allez M, Lemann M, Bonnet J, Cattani P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. *Am J Gastroenterol*. 2002 Apr; 97(4):947–953. [PubMed: 12003431]
65. af Björkesten C-G, Nieminen U, Sipponen T, Turunen U, Arkkila P, Färkkilä M. Mucosal healing at 3 months predicts long-term endoscopic remission in anti- TNF-treated luminal Crohn's disease. *Scand J Gastroenterol*. 2013 May; 48(5):543–551. [PubMed: 23477356]
66. Frøslie KF, Jahnsen J, Moum BA, Vatn MH. Mucosal Healing in Inflammatory Bowel Disease: Results From a Norwegian Population-Based Cohort. *Gastroenterology*. 2007 Aug; 133(2):412–422. [PubMed: 17681162]
67. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early Mucosal Healing With Infliximab Is Associated With Improved Long- term Clinical Outcomes in Ulcerative Colitis. *Gastroenterology*. 2011 Oct; 141(4):1194–1201. [PubMed: 21723220]
68. Laharie D, Filippi J, Roblin X, Nancey S, Chevaux JB, Hébuterne X, et al. Impact of mucosal healing on long-term outcomes in ulcerative colitis treated with infliximab: a multicenter experience. *Aliment Pharmacol Ther*. 2013 Mar; 37(10):998–1004. [PubMed: 23521659]
69. Travis SP, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, et al. Predicting outcome in severe ulcerative colitis. *Gut*. 1996 Jun; 38(6):905–910. [PubMed: 8984031]
70. Cacheux W, Seksik P, Lemann M, Marteau P, Nion-Larmurier I, Afchain P, et al. Predictive Factors of Response to Cyclosporine in Steroid-Refractory Ulcerative Colitis. *Am J Gastroenterol*. 2008 Mar; 103(3):637–642. [PubMed: 18047542]
71. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology*. 2004 Feb; 126(2):451–459. [PubMed: 14762782]
72. Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, et al. Histologic Inflammation Is a Risk Factor for Progression to Colorectal Neoplasia in Ulcerative Colitis: A Cohort Study. *Gastroenterology*. 2007 Oct; 133(4):1099–1105. [PubMed: 17919486]
73. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, et al. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut*. 2004 Dec; 53(12):1813–1816. [PubMed: 15542520]

74. Terdiman JP, Steinbuch M, Blumentals WA, Ullman TA, Rubin DT. 5- Aminosalicyclic Acid Therapy and the Risk of Colorectal Cancer Among Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2007 Apr; 13(4):367–371. [PubMed: 17206695]
75. Rubin DT, Huo D, Kinnucan JA, Sedrak MS, McCullom NE, Bunnag AP, et al. Inflammation Is an Independent Risk Factor for Colonic Neoplasia in Patients With Ulcerative Colitis: A Case-Control Study. *Clin Gastroenterol Hepatol*. 2013 Jul; 11(12):1601–1608. [PubMed: 23872237]

Opinion Statement

Mucosal healing is a promising therapeutic endpoint in the treatment of inflammatory bowel disease. Currently, the treatment of IBD focuses predominantly on clinical remission, without requiring a demonstration of mucosal healing. However, recent studies suggest that achieving mucosal healing engenders better outcomes. In this review, we will examine the concept of mucosal healing, including its definitions and assessment techniques, and will evaluate the data regarding the potential benefits of achieving mucosal healing in the treatment of IBD. Furthermore, we will discuss how often mucosal healing can be expected with each of the therapies for IBD. While achieving mucosal healing is an ideal outcome, it may not be practical or feasible in any given patient. Although we suggest that mucosal healing be discussed with all patients, the practicing physician should realize that this goal may not be possible and should manage the patient accordingly.

Table 1

Rates of mucosal healing with various drug therapies in Crohn's disease

Therapy	Definition of mucosal healing	Rate of mucosal healing (%)	Time Endpoint
Steroids	Endoscopists' assessment	29%	3–7 weeks [13]
Azathioprine	CDEIS	36–58	12–42 months [30,31]
Methotrexate	Disappearance of mucosal ulceration	11	24 months (median) [35]
Infliximab	Disappearance of mucosal ulcerations	45–50	6.7–12.5 months [36,37]
Infliximab+azathioprine	Disappearance of mucosal ulcerations, SES-CD	44–73	6–24 months [32,38]
Adalimumab	CDEIS	24	12 months [39]
Certolizumab pegol	Disappearance of mucosal ulceration	8	12.5 months [40]
Natalizumab	Decrease in SES-CD >70%	42	14.1 months (mean) [41]

Table 2

Rates of mucosal healing with various classes of medications in Ulcerative Colitis

Therapy	Definition of mucosal healing	Rate of mucosal healing (%)	Time Endpoint
Steroids	Baron score 0/1	12 – 38%	2–12 weeks[51–53]
5-ASA	Mayo Endoscopy subscore 0/1, Modified UC-DAI	19–88	6–12 weeks[43–49,54]
Azathioprine	Baron Index of 0/1	53	6 months[54]
Infliximab	Mayo Endoscopy subscore 0/1	46–62	2–12.5 months[20]
Adalimumab	Mayo Endoscopy subscore 0/1	25–47	2–12 months[55,57]
Golimumab	Mayo Endoscopy subscore 0/1	42–45	1.5–12.5 months[56,58]
Vedolizumab	Mayo Endoscopic subscore 0/1	52–56	12 months[59]