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REVIEW ARTICLE

Systematic review: Histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative

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Abstract

Background and aims: Advances in the medical management of inflammatory bowel disease (IBD) have altered treatment targets. Endoscopic mucosal healing is associated with better outcomes in IBD, though less is known about the significance of achieving histological remission. Our aim was to perform a systematic review to investigate whether histological or 'complete' remission constitutes a further therapeutic target in IBD.
Methods: A bibliographic search was performed on the 1st of October 2013 and subsequently on the 1st of March 2014 of online databases (OVID SP MEDLINE, OVID EMBASE, National Pubmed Central Medline, Cochrane Library, ISI, conference abstracts), using MeSH terms and key words: ("inflammatory bowel diseases" OR "crohn disease" OR "ulcerative colitis" OR "colitis") AND ("mucosal healing" OR "histological healing" OR "pathological healing" OR "histological scoring" OR "pathological scoring").
Results: The search returned 2951 articles. 120 articles were cited in the final analysis. There is no validated definition of histological remission in IBD. There are 22 different histological scoring systems for IBD, none of which are fully validated. Microscopic inflammation persists in 16–100% of cases of endoscopically quiescent disease. There is evidence that histological remission may predict risk of complications in ulcerative colitis beyond endoscopic mucosal healing, though data are scarce in Crohn's disease.
Conclusions: Histological remission in IBD represents a target distinct from endoscopic mucosal healing, not yet routinely sought in clinical trials or practice. There remains a need for a standardized and validated histological scoring system and to confirm the prognostic value of histological remission as a treatment target in IBD.

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1. Introduction

Therapeutic advances in medical management have altered treatment targets for inflammatory bowel disease (IBD).[1,2] Consensus recommendations for clinical practice and trial endpoints support striving not only for resolution of symptoms, but also for endoscopic mucosal healing.[2–9] This has been defined as resolution of visible inflammation and ulceration at endoscopy, variably Mayo 0 or 1.[2] This endoscopic endpoint is associated with prolonged clinical remission, lower rates of hospitalization and lower rates of colectomy.[10–16] The question is whether biopsies, taken at the time of endoscopy for evaluation of microscopic mucosal healing, add sufficient therapeutic value to constitute a further target: 'complete' mucosal healing, or 'complete remission'.

Endoscopic mucosal healing does not necessarily reflect quiescent microscopic disease.[17–19] Persistent microscopic inflammation, both acute and chronic, in patients with ulcerative colitis (UC) has been associated with increased relapse rates, hospitalization, colectomy and risk of colorectal neoplasia.[18,20–27] Despite the intuitive importance of microscopic activity as the harbinger of visible disease and clinical relapse, histological remission has yet to be recommended as a therapeutic endpoint for clinical trials or practice in IBD.[1,2,28] Yet it is worth reflecting that 50 years ago, Sidney Truelove described clinical, endoscopic and histological endpoints in trials of UC,[29] and that it was histopathology that identified the difference in efficacy between sulfapyridine and 5-aminosalicylic acid to define the active moiety of sulfasalazine.[30] A histological endpoint is likely to be more relevant in UC than Crohn's disease (CD), because the diffuse mucosal inflammation in UC is less subject to biopsy bias than the patchy transmural inflammation of CD, although the transmural component is invariable in areas with severe mucosal disease.

This systematic review was conducted as part of an initiative by the International Organisation of Inflammatory Bowel Disease (IOIBD) to analyze the available evidence for treatment targets in IBD, including histopathology.

2. Methods

A bibliographic search was performed on the 1st of October 2013 of the online databases: OVID SP MEDLINE (1946 to present), OVID EMBASE (1980 to present), National Library of Medicine's Pubmed Central Medline (1950 to present), the Cochrane Library, the ISI Web of Science and conference abstracts (Digestive Diseases Week and European Crohn's Colitis Organisation Congress) (2005 to present). An updated search was performed on the 1st of March 2014. Each database was searched for Medical Library Subject heading (MeSH) terms and key words: ("inflammatory bowel diseases" OR "crohn disease" OR "ulcerative colitis" OR "colitis") AND ("mucosal healing" OR "histological healing" OR "pathological healing" OR "histological scoring" OR "pathological scoring"). Randomized studies, case–control studies, cohort studies and

review articles were included. Case reports, non-English articles, and studies pertaining to non-human subjects were excluded. Citations, abstracts and retrieved full-text publications of all eligible articles were reviewed and screened for relevance by two authors (RVB and SW).

3. Results

A total of 2951 articles were returned using the initial search, and after application of exclusion criteria, 1265 articles were screened for relevance and a recursive search of articles referenced in the bibliographies of retrieved articles was performed. 120 articles were included in the final analysis; 22 review articles, 3 Cochrane review articles, 92 original research papers, and 3 conference abstracts. Histological scoring systems were extracted for analysis; a total of 18 different scoring systems were identified. Two authors independently judged study eligibility with full agreement.

4. What is histological healing in IBD?

4.1. Histopathology in IBD and mechanisms of mucosal healing

Histological changes in UC are characterized by evidence of prior crypt destruction (crypt architectural distortion, atrophy in which crypts may not reach the muscularis mucosae, and Paneth cell metaplasia) and a mucosal inflammatory infiltrate that is typically diffuse. Inflammatory changes are characteristically continuous (being maximal distally), though patchy inflammation can occur, especially after treatment. Active disease is reflected by neutrophils within the crypt epithelium and crypt lumen (cryptitis and crypt abscesses), and ultimately by erosions and ulcers. Quiescent disease is characterized by the lack of mucosal neutrophils, although degrees of chronic inflammation may remain.

Severe chronic inflammation in the lamina propria invariably includes basal plasmacytosis. This means a plasma cell infiltrate in the lower third of the lamina propria immediately above the muscularis mucosae and between crypt bases.[31–33] Basal plasmacytosis can be seen in all forms of longstanding colitis, so has a high predictive value for a diagnosis of IBD, particularly in differentiating it from infective colitis.[34,35] Care has to be taken in adults not to include biopsies from the region of the ileocaecal valve because, like ileal biopsies, plasma cells can normally be seen in a basal location.

In resected specimens, CD is characterized by focal, often discontinuous, chronic active mucosal inflammation that includes transmural lymphoid hyperplasia in the most severe areas of mucosal inflammation. Architectural distortion may be similar to UC, but when present, granulomas unrelated to crypt injury are then virtually pathognomonic of CD. Granulomatous inflammation may be associated with a higher rate of clinical relapse and surgery in patients with CD.[32,33,36]

Recurrent epithelial damage with consequent disruption of intestinal barrier function is a key feature of IBD.[16,37] Mucosal healing, contingent on epithelial restitution and repair, is associated with suppression of inflammation and enhanced barrier function.[16] This is a complex process controlled by regulatory growth factors, peptides and cytokines, dependent on the balance of proliferation, migration and functional differentiation of intestinal epithelial cells at the injured edge.[16] Pivotal molecules include growth factors (TGF α/β, epidermal growth factor, cytokines IL-6 and Il-22, and bacterial lipopolysaccharide through Toll-like receptors) all of which induce intracellular signaling cascades to activate NF-kB and STAT-3 pathways in epithelial cells.[16,37,38]

4.2. Defining histological remission in IBD

No standard definition of histological remission exists, either for UC or CD.[2,39–44] Unfortunately, the terms histological 'healing' and 'remission' appear interchangeable, although they are not necessarily synonymous.[17,40,45,46] The term 'mucosal healing' is unclear with regard to cells that are, or are no longer, present or change their number or proportion, and needs to be separated from endoscopic healing. Furthermore, the emerging concept of 'deep remission' in CD, defined as 'clinical remission' (a CDAI $<$ 150 merits the inverted commas) and endoscopic healing without ulceration, does not include histopathology,[47,48] which sheds light on all other cellular elements short of overt ulceration.

As a consequence of multiple histological scoring systems for UC, definitions of pathological remission range from residual inflammation with persistent architectural distortion, to normalization of the colonic mucosa,[18,22,49–56] although all generally accept it to mean at least a lack of active mucosal inflammation (neutrophils). The 'Global Histologic Disease Activity Score' offers a tool for measurable histological improvement in CD, but is not validated.[57] In an expert position statement on endpoints for clinical trials in CD in 2009, there was no consideration of histological endpoints or remission, neither was there a pathologist on the study.[1]

5. Appraisal

Despite 60 years of clinical trials in IBD, no definition of histological remission has been validated. It has been stated that validation of any definition will require a process of regression analysis of specific histological features, alongside assessment of interobserver and intraobserver reliability using multiple, credible central readers.[44] However, central reading means that the system is not robust enough to be generalizable and is therefore not usable by practicing pathologists. While central reading may be a good tool to validate a system initially, ultimately the system needs to be usable by all interested practicing pathologists. Thereafter, histological remission may be incorporated as an endpoint in clinical trials to assess its role in predicting disease-related complications and outcomes, and ultimately into general clinical practice.

We propose that the histological treatment target for UC or CD is to:

a) induce absence of neutrophils (both in the crypts and lamina propria);
b) induce the absence of basal plasma cells and ideally reduce lamina propria plasma cells to normal; and
c) reduce lamina propria eosinophils to normal.

The target will be easier to detect (and conceivably easier to achieve) in UC rather than CD, but the histopathological

principle is the same. Incorporation of histopathological examination of biopsies in establishing remission in IBD goes beyond 'deep remission' and may be better termed 'complete remission', implying concordance between clinical, endoscopic and histological remission.

6. How to measure histological remission?

6.1. Practical aspects

The accuracy of diagnosing colitis not surprisingly increases from 66% to 92% when segmental biopsies throughout the colon are taken, rather than two biopsies.[58] Multiple sections from each sample stained for hematoxylin and eosin increase the yield.[32] The same seems likely for assessing disease activity in IBD, and correlation of pre- and post-treatment disease activity stratified to location (e.g. rectum, sigmoid colon, etc.) will be critical for accurate comparison. Rectal biopsies are also invaluable as UC sparing the rectum may not exist, although in patients with primary sclerosing cholangitis, colitis may be predominantly right-sided.[59] In clinical trials, the operating characteristics of histopathological scores will vary depending on the number, quality, and distribution of the samples taken.[44]

For any scoring system that requires evaluation of basal plasma cells, the basal part of the mucosa needs to be identified. This can only occur in biopsies that have sections cut to allow the surface and the deep part of the biopsy to be identified in perpendicular sections. This in turn requires large biopsy forceps (e.g. radial jaw 4 or equivalent), taken through standard endoscopy biopsy channels, and laboratory technicians skilled in embedding, cutting and staining these biopsies.

6.2. Histological scoring systems

Many indices to assess disease activity in UC have been described since the 1950s, though none are fully validated (Table 1).[18,26,27,49–52,54–56,60–67] This systematic review and that of Mosli et al., has identified 22 histological scoring systems for UC.[44] The first described was that by Truelove and Richards in 1956 in a study of 111 serial biopsy specimens from 42 patients with UC.[56]

The most widely used histological indices of disease activity in UC are the Riley Index (1991)[18] and the Geboes Index (2000).[50] The Riley Index evaluates six features (acute inflammatory infiltrate, crypt abscesses, mucin depletion, epithelial integrity, chronic inflammatory infiltrate, and crypt architectural abnormalities), each of which is graded subjectively on a 4 point scale, and given equal weight.[18] The Geboes Index includes five features (architectural change, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction, and erosion or ulceration). This is the best validated (interobserver variability κ 0.59–0.70, indicating moderate to good agreement between 3 specialist pathologists).[50] It also predicts relapse in patients with clinically and endoscopically quiescent UC over 12 months.[20,24] However, there is no grading for basal plasmacytosis in any system and this appears to be a deficiency.

Scoring systems for CD are limited by discontinuous disease so they require targeted biopsies, while transmural inflammation can only be evaluated in resections, so it is not amenable to a biopsy driven scoring system. Validation remains challenging.[57,68,69] The Colonic and Ileal Global Histologic Disease Activity Score (CGHAS or IGHAS)[57,70,71] incorporates epithelial damage, architectural changes, mononuclear or polymorphonuclear cells in the lamina propria and epithelium, presence of erosions/ulcers and granulomata, as well as the number of segmental biopsy specimens affected.[57] It is not validated so its role remains undefined.

6.2.1. Appraisal

Standardization and optimization of the collection and processing of biopsy specimens in IBD is imperative for accurate assessment of histopathological activity or remission.

Histological scoring systems in IBD vary in histological features, terminology and classification of severity. None of the scoring systems are fully validated, though several UC indices are partially validated.

As described, the Riley Index is difficult to reproduce, because criteria for separating grades are not provided, the best being illustrations of mean grades of acute inflammation and mucin depletion. Any subsequent use of this index therefore requires specific modifications. Although statistical validation is unlikely to give equal weight to six measures, the score did predict the likelihood of relapse in the following year. The Geboes Index is also subjective for chronic inflammation (grade 1), and eosinophils and neutrophils in the lamina propria (grade 2), but acute inflammation in the crypts through ulceration is well defined. The Geboes Index has all of the prerequisites to grade all aspects of inflammation, as well as architecture and we believe that it should be the basis for an agreed scoring system to define histological remission and disease activity. Nevertheless, modification of the existing Geboes Index to include of basal plasmacytosis, shown independently to predict clinical relapse in UC (see below), appears appropriate.

A scoring system is essential to measure improvement in an individual, or to relate histopathology to clinical outcomes for patients. Assessment will require further regression analysis of specific histological features, as well as the relationship with an endoscopic scoring system such as the Mayo Clinic index or ulcerative colitis endoscopic index of severity (UCEIS).[72]

7. Current trials and evidence for histological remission as an endpoint

7.1. Histological healing versus endoscopic mucosal healing

Histological healing is distinct from endoscopic mucosal healing in UC. Studies have demonstrated that microscopic inflammation persists in 16–100% of cases of endoscopically quiescent disease (Table 2).[18,19,21,24,49,51,55,56,63,65,66,73–76] Histopathology is more likely to reflect residual inflammation than endoscopy, particularly in the presence of 'minimal' or 'mild' disease identified endoscopically.[19,76] Better concordance between endoscopy and histopathology is evident during the presence of inactive or severely active disease, but between these extremes there was a full range of histological grades, and therefore a poor correlation between the two.[76] Persistent histological inflammation also occurs in 25–37% of patients with clinical and endoscopically quiescent CD,[48,77] although inflammation beyond the reaches of the endoscope and patchy inflammation make interpretation more difficult.

Table 1 Histological Scoring Systems in Inflammatory Bowel Disease.

IBD	Author, year	Key features of score	Comments
Ulcerative colitis	Truelove & Richards, (1956)[56]	3 grade scale: 1) no inflammation 2) mild to moderate inflammation 3) severe inflammation	Partially validated. Extensive use in clinical trials and RCT's.
	Matts et al. (1961)[63]	5 grade scale: 1) normal to 5) ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all of its layers	No validated. Extensive use in clinical trials and RCT's.
	Watts et al. (1966)[65]	4 grade scale: 0) normal to 3) severe inflammatory change	Not validated
	Korelitz et al. (1976)[54]	Mucosal cell counting in addition to histologic features	Not validated Cell counting labor intensive
	Powell-Tuck et al. (1982)[55]	3 grade scale: 1) no inflammation 2) mild inflammation 3) moderate/severe inflammation	Not validated
	Keren et al. (1984)[62]	Dichotomized: active versus inactive inflammation	Not validated
	Friedman et al. (1986)[61]	4 grade scale: 0) normal 1) lamina propria inflammation 2) crypt injury 3) ulceration	Not validated. Subsequent use in clinical trials.
	Gomes et al. (1986)[51]	5 grade scale 0) normal, to 4) severe inflammation and active ulceration	Not validated Subsequent use in clinical trials
	Saverymutti et al. (1986)[60]	4 histological features: 1) enterocyte damage 2) crypt abnormalities 3) lamina propria involvement 4) acute inflammatory infiltrate in the lamina propria. Each graded from 0) normal to 3) severe.	Not validated Extensive clinical trials and RCT's.
	Floren et al. (1987)[49]	5 grade scale: 0) normal, to 5) severe inflammation and ulceration	Not validated. Extensive clinical trials and RCT's.
	Riley et al. (1991)[18]	6 histological features assessed; each graded on a 4 point scale	Partially validated. Prognosticates time to relapse. Extensive clinical trials and RCTs.
	Hanauer et al. (1993)[52]	4 grade scale: 0) normal colonic mucosa to 3) high grade active inflammatory bowel disease (combines histologic and endoscopic appearances)	Not validated. Central reference pathologist
	Sandborn et al. (1993)[64]	4 grade scale: 0) inactive chronic colitis to 3) severely active chronic colitis	Not validated.
	Geboes et al. (2000)[50]	7 histological features graded Scoring from 0 to 5.4	Partially validated. Subsequent clinical studies.
	Harpaz Score Fiel et al. (2003)[67]	Harpaz Score: 4 grade scale: 0) no cryptitis, 1) cryptitis <50% crypts, 2) cryptitis >50% crypts 4) ulcerations or erosions.	Partially validated. Subsequent clinical studies.
	Rutter et al. (2004)[27]	5 grade scale: 0) normal to 4) severe active inflammation	Not validated.
	Rubin et al. (2007)[26]	6 grade scale: 0) normal to 5) crypt abscesses in >50% of crypts or erosion/ulceration	Not validated. Case control prospective grading by two pathologists to validate internally
	Baars et al. (2012)[66]	4 grade scale: 0) no active disease to 4) severe inflammation (numerous crypt abscesses)	Not validated.
Crohn's Disease	D'Haens et al. (1998)[57]	16 point grading system 8 histological and distribution features	Subsequently called the CGHAS and IGHAS in clinical trials^
	Nicholls et al. (1994)[69]	4 grades: 1) worse 2) no change, 3) improvement, 4) resolution of inflammation	Subjective. Not validated.
	Breese et al. (1995)[68]	5 histological features (ulceration, acute and chronic inflammation, crypt distortion, goblet cell depletion and villous atrophy). 4 grades: 0) normal to 3) severely inflamed.	Not validated.
	Baars et al. (2012)[66]	4 grade scale: 0) no active disease to 4) severe inflammation (numerous crypt abscesses)	Not validated.

Key: RCT, randomized controlled trial; CGHAS, Colonic Global Histologic Disease Activity Score; IGHAS, Ileal Global Histologic Disease Activity Score.

Table 2 Endoscopic mucosal assessment versus histological assessment of disease activity.

IBD	Author, year	Patient number (n)	Endoscopic versus Histologic Findings
Ulcerative colitis	Truelove &Richards (1956)[56]	111	Normal sigmoidoscopy: 6/16 (38%) mild/mod inflammation
	Dick and Grayson (1961)[73]	48	Normal sigmoidoscopy: 6/19 (32%) acute or chronic inflammatory infiltrate
	Watts et al. (1966)[65]	105	Normal sigmoidoscopy: 31/60 (52%) mild or severe inflammation
	Powell-Tuck (1982)[55]	72	Normal sigmoidoscopy: 3/11 (27%) mild or mod-severe inflammation
	Gomes (1986)[51]	28	Sigmoidoscopic score well correlated with histological score: (R 0.61 $p < 0.001$)
	Floren et al. (1987)[49]	33	In 57 endoscopically normal colonic segments assessed: 100% 'slight' inflammation, 16% intermediate/severe inflammation
	Riley et al. (1991)[18]	82	Normal mucosa endoscopic appearance or erythema: 100% chronic inflammatory infiltrate, 58% crypt irregularities, 28% acute inflammatory infiltrate.
	Bitton et al. (2001)[21]	74	Normal endoscopic appearance: basal plasmacytosis predictive of relapse (HR 4.5 CI 1.7–11.9 $p = 0.003$)
	Thomas et al. (2009)[74]	91	Endoscopic remission as per Baron score[121]: agreement between histologic and endoscopic assessment in 58%
	Bessissow et al. (2012)[24]	75	Normal endoscopic appearance: Geboes score ≥ 3.1 in 40%, basal plasmacytosis in 21%
	Baars et al. (2012)[66]	98	Endoscopic remission as per Mayo score: 31% at least mild histological inflammation
	Lemmens et al. (2013)[76]	131	Significant correlation between Mayo endoscopic subscore and histology (Kendall's T = 0.482 $p < 0.001$), highest for inactive or severely active disease
	Rosenberg et al. (2013)[19]	103	Colonic segment with Mayo endoscopy subscore 0: 6% histological inflammation
	Molander et al. (2013)[48]	62	Patients in 'deep remission' (Physician global assessment and Mayo Clinic endoscopic subscore): 7% histological inflammation
Crohn's disease	Korelitz et al. (1984)[77]	38	37% histological inflammation in presence of endoscopic disease quiescence
	Molander et al. (2013)[48]	183	Patients in 'deep remission' (according to Physician global assessment and Simple Endoscopic Score for Crohn's Disease): 25% histological inflammation
	Baars et al. (2012)[66]	46	Endoscopic remission as per Mayo score: 40% histologic inflammation

Nevertheless endoscopic assessment so far has no role in predicting relapse in CD.

7.2. Prognostic value of histology in IBD

Early studies in UC by Wright and Truelove proposed that persistent histologic inflammation may be a better predictor of future clinical relapse than endoscopic appearances alone.[23] This has been borne out in subsequent studies for predicting relapse in patients with UC that is evaluated as clinically and endoscopically quiescent (Table 3).

Riley et al. showed that active histological inflammation predicted clinical relapse during 12 months of follow-up, whereas endoscopic features (normal mucosa or erythema at study entry) did not.[18] Relapse rates were higher in the presence of an acute inflammatory infiltrate (52% vs 25% $p = 0.02$), crypts abscesses (78% vs 27% $p < 0.0005$), mucin depletion (56% vs 26% $p < 0.02$), and any breach in surface epithelium (75% vs 31% $p = 0.01$). Bitton et al. showed that basal plasmacytosis was the principal histological predictor of relapse, independent of maintenance therapy, among 74 patients with clinically and endoscopically quiescent UC.[21] Azad et al. found that increased numbers of lamina propria neutrophils and eosinophils are associated with a higher risk of relapse over 12 months in patients with quiescent UC,[20] while Bessissow et al. found that a Geboes score of ≥ 3.1 (any crypt abscesses – but in addition an increase in lamina propria neutrophils (2B-1) or eosinophils (2A-1)) predicts clinical relapse (Mayo Clinic score changing from 0 to ≥ 3).[24] This latter study also confirmed that basal plasmacytosis (not part of the Geboes Index) was associated with a higher risk of relapse ($p = 0.007$).[24]

Resolution of histological inflammation in UC has also been associated with a higher likelihood of remaining symptom-free at 12 months after a course of corticosteroids[78] and a reduction in hospitalization or colectomy rates,[25,26,79,80] in one case over the course of 2.5 years.[80] Consistent with this observation, a higher mean inflammation score during a colonoscopic screening program for UC was a significant predictor for colectomy.[25] Furthermore, histological remission has been shown to correlate with a reduction in colorectal cancer risk in UC.[22,27]

The prognostic value of histology has only been assessed in a single study in CD, which found that mucosal inflammation was not associated with more frequent clinical relapse, stricture formation, or surgery,[66] although patchiness of inflammation makes this difficult to interpret.

7.3. Therapeutic trials and histological remission

Few therapeutic trials have incorporated histological assessment of activity in IBD, most being concerned with histology for diagnostic purposes, and even fewer report histological remission (Table 4).[29,45,46,48,53,81–93]

Table 3 Prognostic value of histopathology in IBD.

IBD type	Author, date	Patient number/ follow-up period	Scoring system	Disease-related outcome and histological predictor
Ulcerative colitis	Wright and Truelove (1966)[23]	n = 77 12 months	Truelove and Richards Score (see Table 1)	*Clinical relapse rate* Predicted by histological disease activity.
	Riley et al. (1991)[18]	n = 82 12 months	Riley Score (see Table 1)	*Clinical relapse rate* 33% clinical relapse. Predicted by acute inflammation 52 vs. 25% (p 0.02); Crypt abscesses: 78 vs. 27% ($p < 0.005$); Mucin depletion: 56 vs. 26% ($p < 0.02$); Surface epithelium breach: 75 vs. 31% (p = 0.1).
	Bitton et al. (2001)[21]	n = 74 12 months	Normal or abnormal. If abnormal: active colitis, chronic colitis, Paneth cell metaplasia, basal lymphoid aggregates and plasmacytosis.	*Clinical and endoscopic relapse rate* 36.5% relapse rate. Predicted by basal plasmacytosis (HR 4.3 1.7–11.0, p = 0.003).
	Azad et al. (2011)[20]	n = 26 12 months	Geboes Score (see Table 1)	*Clinical relapse rate* 57.7% clinical relapse. Predicted by eosinophils & neutrophils in lamina propria (p = 0.01).
	Hefti et al. (2009)[25]	n = 561 21.4 years	Harpaz Index (see Table 1)	*Colectomy rate* 17.3% colectomy rate; 26% of these for dysplasia. Mean mucosal inflammation predictive of colectomy overall ($p < 0.001$).
	Rubin et al. (2007)[26]	n = 106	Rubin et al. Score (see Table 1)	*Colectomy and hospitalization rates* Correlated with increased histological inflammation (HR 1.9, 95% CI 1.02–3.51, p 0.042; HR 1.52 95% CI 0.9–2.61, p 0.123 respectively; relative to a 1 point increase in inflammation).
	Burger et al. (2011)[80]	n = 91 29 months	Truelove and Richards Score (see Table 1)	*Colectomy and hospitalization rates* Predicted by histologic activity.
	Bessissow et al. (2012)[24]	n = 75 12 months	Geboes Score (see Table 1) Basal plasmacytosis	*Clinical relapse rate* 20% relapse rate. Predicted by basal plasmacytosis (p = 0.007), and Geboes Score ≥ 3.1 (p = 0.007)
	Gupta et al. (2007)[22]	n = 418 2168 patients years	Harpaz Score (see Table 1)	*Colorectal dysplasia and neoplasia* 3.6% advanced neoplasia. Inflammation over follow-up period (IS-mean) correlated with risk of neoplasia (HR 3.0, 95% CI 1.4–6.3)
	Rutter et al. (2004)[27]	n = 68 (136 controls with colorectal neoplasia)	Rutter et al. score (see Table 1)	*Colorectal neoplasia* 68 UC patients with colorectal neoplasia matched to controls. Histologic inflammation correlates with risk of colorectal neoplasia (OR 5.1 $p < 0.001$)
	Baars et al. (2012)[66]	n = 98 6.8 years	Baars Score (See Table 1)	*Relapse, surgery, mortality* No evidence of increased relapse rates, surgery, or mortality in patients with histological inflammation and normal endoscopic appearances ($p > 0.05$)
Crohn's disease	Baars et al. (2012)[66]	n = 46 6.8 years	Baars Score (see Table 1)	*Relapse, surgery, mortality* No evidence of increased relapse rates, surgery, or mortality in patients with histological inflammation and normal endoscopic appearances ($p > 0.05$)

Histological response to therapy has been reported in multiple trials in UC, the first of which was in the 1950s in patients treated with steroids (Table 4).[29,45,53,83,85,90–92] Histological improvement has been reported after oral budesonide therapy (47% of patients with UC in a review including three randomized controlled trials)[92] and also after aminosalicylates, occasionally achieving histological remission.[46,82,84,86,88,89] In a Cochrane review, rectal 5-ASA was superior to placebo for inducing histologic improvement (OR 7.69 $p < 0.0001$) and remission (OR 6.28 $p < 0.0001$) in the 6/38 trials using histopathology as a secondary or post-hoc endpoint.[46] In a comparison between single and divided doses of oral 5-ASA (3 g daily) in 380 patients with active UC, histological remission was achieved in 35% and 41% respectively.[84] Remarkably few studies have assessed histological response to immunomodulator or biological therapy.[48,81,87] In one study of 62 patients treated with infliximab for UC, clinical and endoscopic remission was achieved in 62%, of whom 93% also demonstrated histological healing.[48] As a twist in the tail for clinical studies of UC, independent evidence of histological activity at trial entry was a pre-specified requirement for the analysis in two recent trials of mild-moderate UC, to ensure that the population studied had objective evidence of disease activity at the time of recruitment: up to 20% with apparent endoscopic activity did not meet this simple criterion.[94,95]

Even fewer studies have assessed the histological response to therapy in CD, but most have involved biological therapy.[11,48,71,96–100] In a study of 30 steroid-refractory patients with CD, D'Haens et al. showed that infliximab induced improvement in the mucosal inflammatory infiltrate, although cytoarchitectural changes persisted after 4 weeks of therapy.[70] This result therefore mimics findings in ulcerative colitis; in neither disease are architectural changes expected to regress with resolution of the acute inflammation. Histologic improvement after 10 weeks of therapy with infliximab was also a feature of the pivotal ACCENT1 Trial.[71,101] Some studies have also demonstrated histological improvement after enteral feeding in patients with CD.[102–104]

7.3.1. Appraisal

Collectively this literature implies that histological remission offers the potential for predicting the risk of disease-related complications in UC beyond endoscopic mucosal healing, though data are scarce in CD. Despite the variable reporting of histopathology in therapeutic trials, there is evidence to suggest that histological remission may be achieved, and may be associated with better patient-related outcomes after treatment for UC. Both Riley and Geboes indices have been shown to predict clinical relapse, though neither scoring system incorporates basal plasmacytosis, which has shown to be an independent predictor of relapse in UC. The data are less strong in CD, although this may be attributable to the fact that histology has been less frequently incorporated into trial design as a treatment endpoint. Yet, endoscopic mucosal healing in CD, analogous to UC, has been shown to be associated with a reduced likelihood of requiring surgery or hospitalization in an endoscopic sub-study of maintenance infliximab.[13] Biopsies were not taken to allow histological evaluation in this study, despite the fact that a previous study had shown that histological healing occurs following therapy.[70]

Ideally remission should include clinical, endoscopic and histological components. Concordance between these three components might be termed 'complete remission'. This will require a paradigm shift in clinical trials and practice, but pathologists are rarely consulted in the design of trials. However, since the FDA are moving toward documentation of both active histological disease at trial inclusion, as well as tissue evidence of remission, especially for trials of biological therapy, this may change.

8. Limitations of histological assessment in IBD

Assessment of histological healing in IBD has several limitations. The relative lack of validation or standardization of histological reporting, scoring, and definition of remission are current notable limitations for using histological healing as a therapeutic endpoint,[40] even though in well orientated biopsies, it is actually fairly easy to determine whether neutrophils or deep plasma cells are present. Furthermore, mucosal biopsy necessitates invasive endoscopic investigation, which risks complications and increases costs and time for patients, clinicians and pathologists alike. However, this is a "Catch-22" situation, because unless these issues are either confirmed or refuted, the questions will remain unanswered. In this case we will continue to titrate treatment of patients against symptoms or endoscopic appearance. The demonstration of mucosal healing by endoscopy, itself an indication of healing, requires some form of endoscopy, which although "invasive", is minimal compared to many other procedures. It is logical to argue that if an endoscopic endpoint is adopted, then this should include biopsies for histopathology.

While it is possible that acute inflammatory mediators or biomarkers may be detectable in stools, these are at best an aid. It is currently difficult to extend this to stool tests that might reasonably substitute for biopsy to estimate the quantity or depth of mucosal chronic inflammation, or eosinophils. Discontinuous inflammation, characteristic of CD, introduces sampling error for histological assessment. In UC, disease duration and treatment may alter the distribution and nature of microscopic changes.[40,41,105–110] Transmural inflammation in CD may also mean that histologic mucosal healing does not represent quiescent disease, since deeper inflammation, although invariably in the form of lymphoid hyperplasia, and therefore reflecting chronic inflammation rather than acute inflammation, may persist.[28,41] Myenteric plexitis, for example, which is relatively uncommon but also a variant of chronic inflammation, predicts post-operative relapse in CD, and obviously is also not amenable to biopsy.[111] In both UC and CD, it is pertinent to take multiple, quality, segmental biopsies, targeting areas of visible endoscopic inflammation, in order to reduce sampling error for histological assessment. Correct cutting and orientation of biopsies by pathologists is extremely important for assessing the depth of inflammation or basal plasmacytosis.

9. Summary and future directions

The concept of histological healing as a therapeutic endpoint is based on the premise that persistent inflammation in IBD leads to earlier relapse, progressive damage and cumulative

Table 4 Histologic remission and therapy in IBD.

IBD type	Therapy	Author, date	Patient number	Key features	Outcomes
Ulcerative colitis	Corticosteroids	Truelove et al. (1958)[29]	n = 40 Distal UC	Rectal hydrocortisone 1 week therapy Truelove and Richards score	55% shift to a mild grading. No histological 'normalization'.
		Sommers et al. (1975)	n = 215	Prednisolone (+/−mercaptopurine) for 2 weeks	Mucosal cell counts: decreased neutrophils and plasma cells.
		Ruddell et al. (1980)[90]	n = 30 Distal UC	Hydrocortisone enema vs. foam 2 weeks therapy	Significant improvement in active inflammation in enema group.
		Lee et al. (1996)[85]	n = 295 Distal UC	Randomized trial Prednisolone foam enema vs. mesalazine foam enema assessed at 4 weeks	Histologic remission in 27% mesalazine vs 21% steroid group.
		Hanauer et al. (1998)[53]	n = 233 Distal UC	Budesonide enema (dose finding) vs. placebo. Modified Truelove and Richards score	Overall histologic improvement in budesonide groups (2 mg/100 mL and 8 mg/100 mL).
		Gross et al. (2006)[83]	n = 449 Distal UC	Budesonide foam vs. enema Riley scoring[18]	Histological improvement in 51% foam enema and 57% liquid enema.
		Sherlock et al. (2010)[92]	3 studies	Cochrane review: oral budesonide therapy	46.9% histological remission
		Hartmann et al. (2010)[45]	n = 237 Left-sided UC	Mesalazine enema vs. budesonide enema assessed at 4 weeks	Non-significantly higher histologic remission with mesalazine (48.6%) vs budesonide (43%) (p = 0.145)
	Salicylates	Rao et al. (1989)[89]	n = 37 Distal UC	Olsalazine (2 g/day) vs. sulfasalazine (3 g/day) assessed at 4 weeks	Histologic improvement in both groups similar (44% and 46% respectively, p = NS)
		Green et al. (2002)[82]	n = 57 Active UC, variable distribution	Balsalazide (6.75 g/day) vs. sulfasalazine (3 g/day) (+steroids if needed) assessed at 12 weeks	Similar histological improvement in both groups
		Mansfield et al. (2002)[86]	n = 50 Active UC variable distribution	Balsalazide (6.75 g/day) vs. sulfasalazine (3 g/day) assessed at 12 weeks	Histological improvement overall. 34% no histological inflammation overall.
		Prantera et al. (2005)[88]	n = 79 Active Left-sided UC	Slow release mesalazine vs. topical 5ASA Floren score[49]	Histological remission in 15% of oral and 8% of enema treated groups.
		Kruis et al. (2009)[84]	n = 380 Active UC Variable distribution	Mesalazine granules 3 g/day in single or thrice daily dosing	Histological remission in 35% of single dosing and 41% of thrice daily dosing groups
		Marshall et al. (2010)[46]	Cochrane Review 6 trials (of 38 included)	Rectal 5ASA for induction of remission in UC	Superior to placebo in inducing histologic remission (OR 6.28, p < 0.0001)
	Immunomodulator	Paoluzi et al. (2002)[87]	n = 32 Active refractory UC	Azathioprine or methotrexate for 6 months Truelove and Richards score[56]	78% histological remission at 6 months
	Biological agents	Chey et al. (2007)[81]	n = 16 Active refractory UC	Infliximab Single infusion (5 mg/kg), 6/16 patients had a 2nd infusion at 5 months	Significant improvement from baseline in histologic score (p < 0.001)

Table 4 (*continued*)

IBD type	Therapy	Author, date	Patient number	Key features	Outcomes
		Molander et al. (2013)[48]	n = 62	TNF-alpha antagonists (infliximab and adalimumab) for >11 months	UC patients in 'deep remission' (clinical and endoscopic), 93% histologically inactive disease
Crohn's disease	Corticosteroids	Mantzanis et al. (2009)[100]	n = 77 Steroid dependent inflammatory colonic or ileocolonic CD	Budesonide vs azathioprine 1 year therapy D'Haens Score[57]	No significant improvement in histology on budesonide
		Baars et al. (2010)[96]	n = 30 CD colonic distribution	Oral prednisolone 20 mg for 2 weeks Geboes Score[50]	Decrease in histological activity compare with placebo, no significant differences in severity of inflammation
	Immunomodulator	D'Haens et al. (1997)[97]	n = 19 Recurrent neoterminal ileal disease	Azathioprine for 6 months	Microscopic inflammatory infiltrate resolved only in those with macroscopic healing at endoscopy (70%).
		D'Haens et al. (1999)[98]	n = 20 Ileocolonic distribution	Azathioprine for 9 months D'Haens Score[57]	Colonic endoscopic healing: decreased histological score. Ileal endoscopic healing, decreased histological score.
		Mantzaris et al. (2009)[100]	n = 77 Steroid dependent inflammatory colonic or ileocolonic CD	Budesonide vs azathioprine, 1 year of therapy D'Haens Score[57]	Endoscopic mucosal healing in 83% of patients, significant reduction in histologic scores (mainly inflammatory) but not remission
		Kozarek et al. (1989)[99]	n = 14 Refractory disease	Methotrexate 25 mg IM weekly 12 weeks	28.5% patients 'normal' histology at 12 weeks
	Biological agents	D'Haens et al. (1999)[70]	n = 30 Steroid refractory ileocolonic	Infliximab Single infusion of 5–20 mg/kg vs. placebo assessed at 4 weeks	Improvement in histological inflammatory infiltrate but persistent cytoarchitectural changes
		Baert et al. (1999)[93]	n = 13 Steroid refractory ileocolonic	Infliximab Single infusion 5–20 mg/kg vs. placebo assessed at 4 weeks	Reduced histological activity
		Geboes et al. (2005)[71]	n = 48	Infliximab 5–10 mg/kg (ACCENT1 Study follow-up)[101] D'Haens Scoring[57]	Improved colonic histological disease activity at week 10.
		Molander et al. (2013)[48]	n = 183	Tumor necrosis factor-alpha antagonists (infliximab and adalimumab) >11 months	43% endoscopic remission, 75% of these patients in histological remission.

disability. This confers an increased risk of hospitalization, colectomy, and colorectal cancer.[112,113] It is conceived that suppression of inflammation early in the course of disease may prevent disease-related complications and prolong remission, akin to other chronic inflammatory conditions such as rheumatoid arthritis.[114,115]

Histological remission in either UC or CD is currently not considered a clinical target; indeed, even endoscopic remission may not be sought. However, histological remission is a potential target quite distinct from endoscopic mucosal healing, and, data suggest that it is likely to be of greater value for improving patient outcomes and reducing disease-related complications. There is a need for a standardized histological scoring system for IBD, which must be validated, reliable and reproducible. Modification of the existing Geboes Index to incorporate basal plasmacytosis would be rational and achievable

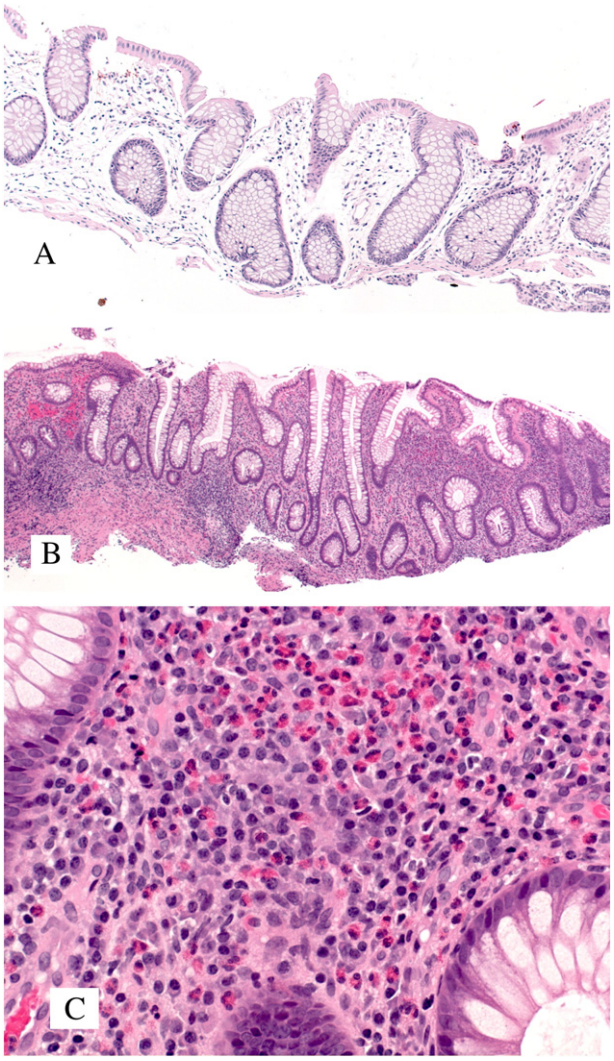

Figure 1 Biopsies taken from two patients in clinical and endoscopic remission (Mayo score of 0 or 1) following therapy for ulcerative colitis. A There is residual architectural distortion but a dearth of inflammatory cells in the lamina propria. Residual cells are all mononuclear with no neutrophils or eosinophils and scant plasma cells. B,C. Biopsy from a second patient following therapy in which there is architectural distortion but a dense lamina propria infiltrate. C. Detail of B in which, while there are no neutrophils, and therefore no "activity", but there are numerous eosinophils and plasma cells in the lamina propria.

in the process of further work on validation. It remains necessary to confirm the prognostic value of histologic remission beyond, or independent of, that associated with endoscopic mucosal healing alone, through clinical trials. While histological healing occurs in CD, the benefits of achieving histological remission in CD remain unclear. Incorporation of histological remission into routine clinical practice is a transition that will require a paradigm shift in thinking among clinicians.

Initially histological healing may seem too difficult a treatment target, however, the implied changes in the management algorithm require common sense and not extreme measures (such as putting patients on biologicals to get rid of the last crypt abscess). Rather, in patients in clinical remission, assessment of histology can assist with the clinical question being asked: is it reasonable to reduce therapy? Compare the two biopsies shown in Fig. 1, both from patients in clinical and endoscopic remission (Mayo Clinic score of 0 or 1) following therapy. Which is the most likely to relapse first? Incorporation of histology into clinical decision-making is likely to be far more applicable to patients either in remission or with mild activity, in whom 5-aminosalicylic agents, or possibly non-systemic steroids (budesonide) are being used. This is because such patients are the easiest to maintain in that state without reducing the dose. On the other hand, the appearances of endoscopic remission in these patients may be falsely reassuring and lead to a potentially inappropriate reduction in treatment. Histopathology would provide additional information that predicts an increased rate of relapse (mucosal neutrophils, basal plamacytosis), providing a reason not to reduce therapy further, until these changes have also regressed. This simply reflects common sense and may not be so far from specialist practice today. Conversely this policy may be less easy to implement in patients on immunosuppressives, including biologicals, in whom the immediate objective may be simple symptom reduction to the point that hospitalization is not required. This is because histopathological activity would imply dose escalation in (potentially) asymptomatic patients, which would raise greater concerns about risk versus benefit. These differing clinical scenarios need to be kept separate from each other when examining treatment to targets.

Clinical trials will be required to determine whether patients should be "titrated" against lack of histological features that predict risk of relapse, as well as established clinical and endoscopic features, in order to maintain remission. One arm would inevitably need to explore whether reappearance of these histological features should, by themselves, result in some form of increase in therapy.

Future histological assessment in IBD must validate the role of histopathology in the standard management of patients, both in clinical trials and practice, especially those in apparent clinical remission. Looking beyond conventional staining, mucosal whole-genome analysis suggests that there may be a transcriptional signature in patients with quiescent UC, possibly associated with defective healing and failure to restore mucosa-associated microbiota.[116,117] Since mucosal gene signatures, their translation, epigenetic modification, post translational modification and their proteomic expression may predict response to biological therapy in UC.[118] The latter are often detectable by immunohistochemistry, and are therefore one future direction for predicting disease outcomes, or response to therapy. Histological assessment in IBD may also involve new technology. Confocal laser endomicroscopy, especially for UC, has the potential to provide real-time microscopic assessment ('endopathology'), that may represent a new way of evaluating histologic healing that may predict relapse.[16,119,120]

That histological remission as a target for therapy in IBD is currently far removed from traditional thinking and the standard management mindset of academic gastroenterologists, despite supporting evidence, is reflected in current trial design. This can, and we argue, should, change. Surprisingly, it may be the FDA, who increasingly requires independent evidence of activity for recruitment to clinical trials, or histopathological remission as part of the endpoint of clinical trials, who

will be the catalyst for changing the mindset of clinicians. This is likely to be in the long-term interests of changing the course of IBD, toward 'complete' remission as a target for treatment.

Conflict of interest

There is no financial conflict of interest to declare for any of the authors.

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