Mucosal Healing in IBD

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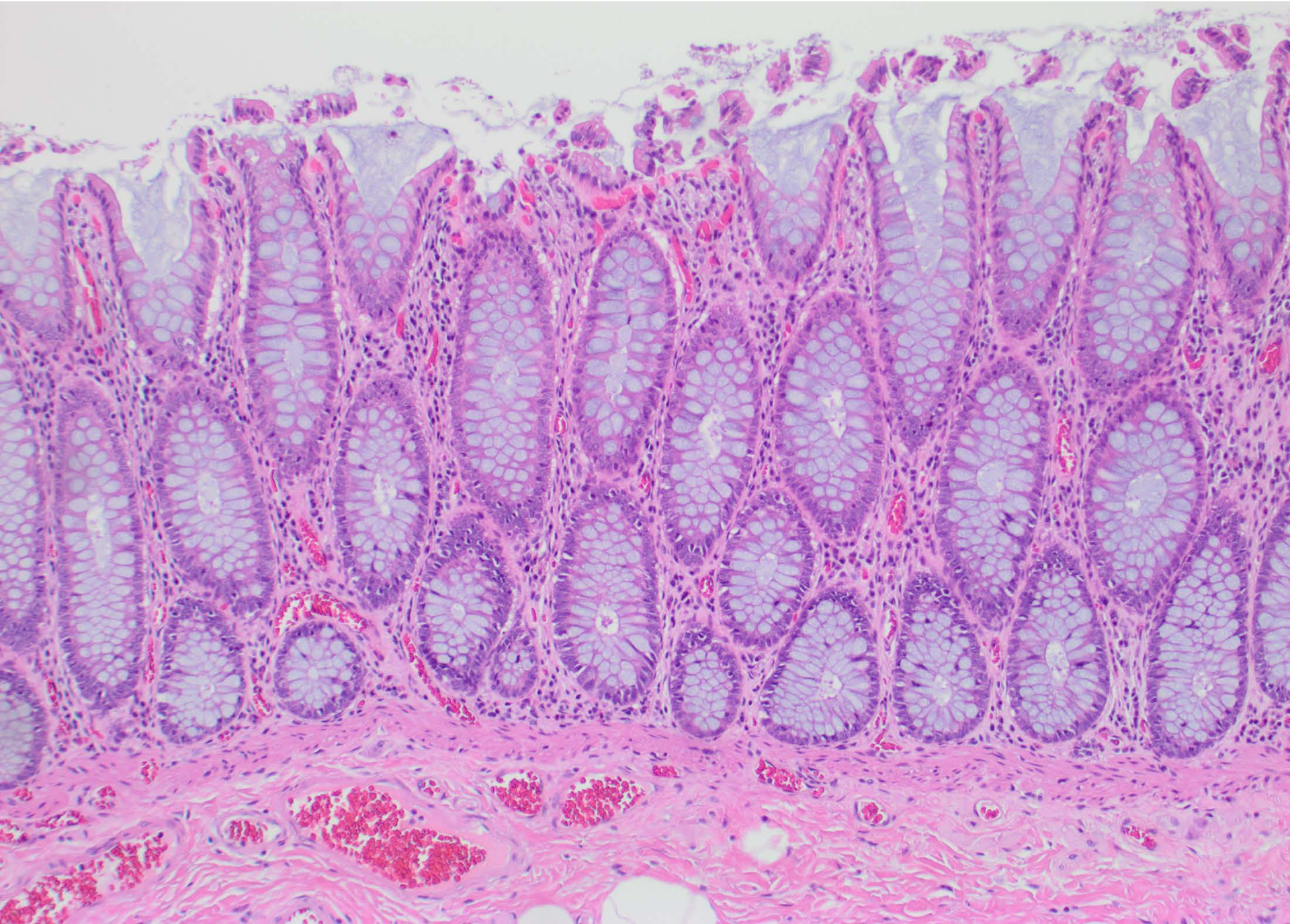


Outline

- Natural history of IBD
- Evolving definition of mucosal healing
- Histological Indices
- Histological Prognostic Factors
- Conclusions

Natural History of IBD

- Thought to be progressive, complications increase over time
  - Up to 50% have surgery within 10 years of diagnosis
  - 70-80% have surgery within 20 years of diagnosis
- Post-surgical CD patients demonstrate the following
  - Inflammation in 1-2 weeks
  - Aphthous ulcers in 3 months
  - Clinical symptoms in 2-3 years
  - 30% will require additional surgery within 10 years
- Therefore, mucosal damage seems to precede clinical symptoms and complications

Olaison G et al. Gut. 1992;33:331–335; Munkholm P et al. Scand J Gastroenterol. 1995;30:699–706; D'Haens GR et al. Gastroenterology. 1998;114: 262–267; Rutgeerts P et al. Gastroenterology. 1990;99:956–963.

Goals of Treatment in IBD

- Improvement in quality of life
- Prevention of complications
- Reduction of hospitalization and surgery rates
- Induction and maintenance of remission

Osterman, MT. Journal of Clinical Gastroenterology. 47(3):212–221, MAR 2013.

Mucosal Healing in IBD

- What is the definition of mucosal healing in IBD?

Problems:

-1. The classical definition of mucosal healing has been based on the endoscopic appearance.

-2. There is no universally accepted histological definition of remission.

-3. There is no consensus on the optimal way to assess disease activity.

Mosli MH et al. Inflamm Bowel Dis. 2014;20:564-575.
Feagan BG et al. Inflamm Bowel Dis. 2012;18:152–160.

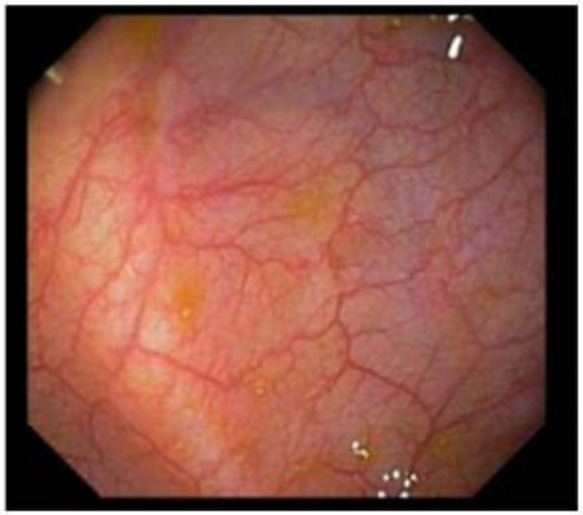
Measures of Disease Activity in IBD

- How do we assess disease activity?
  - Clinical – CDAI, SCCAI, HBI, Montreal, etc.
  - Endoscopic
    - Ulcerative colitis - Mayo, Baron, UCEIS, etc.
    - Crohn's disease – SES-CD, CDEIS, Rutgeerts', etc.
  - Histologic – ~30 indices for UC, several for CD
- How do we define remission?
  - No rectal bleeding/clinical symptoms
  - Mayo 0-1 to Mayo 0 (normal mucosa, inactive ulcerative colitis), CDEIS less than 6 to less than 3, SES-CD 0-2
  - Histologic – ?

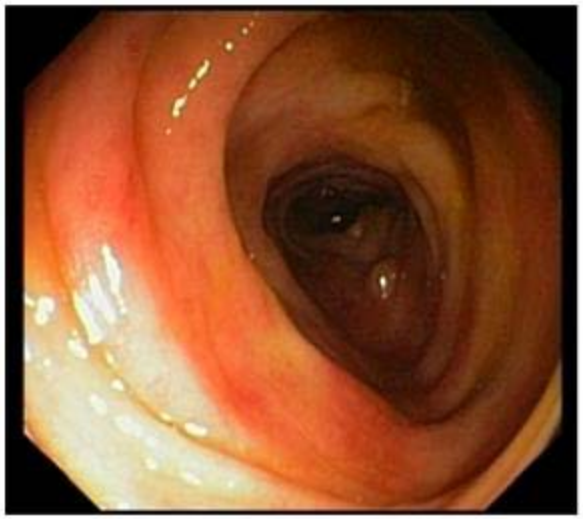
Mayo 0

no friability, granularity, and intact vascular pattern

Normal mucosa



Mild inflammation



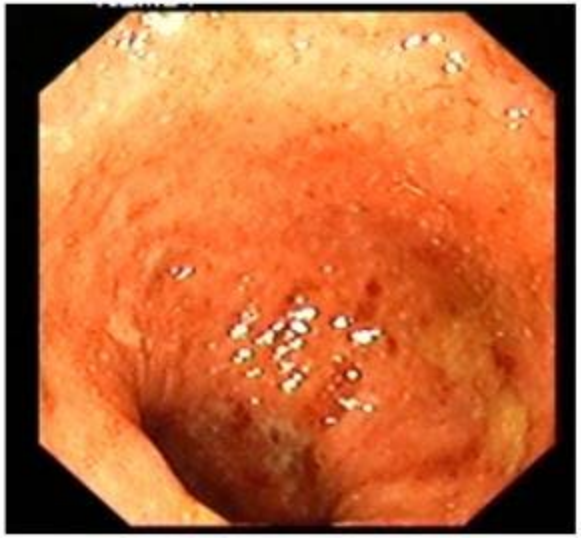
Mayo 1

mild erythema or decreased vascular pattern

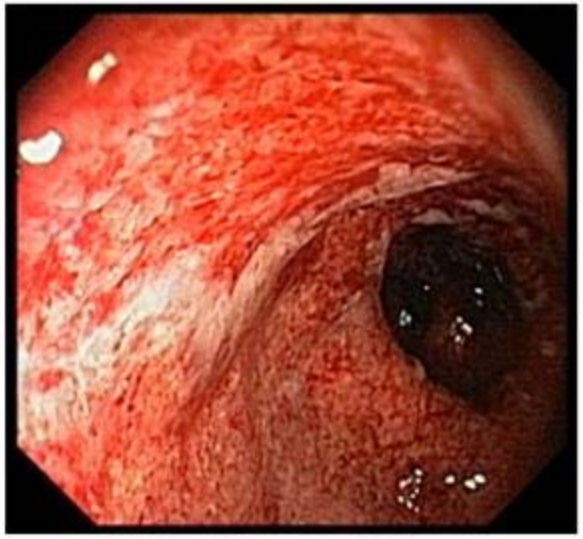
Mayo 2

redness, no vascular pattern, friability, erosions

Moderate inflammation



Severe inflammation



Mayo 3

Spontaneous bleeding, ulcerations

BMC Gastroenterology 4(1):9 . June 2004

Mucosal Healing in IBD

TABLE 1. Endoscopic Activity Indices for UC

Index	Mucosal Features Assessed	Score Range	Remission Score
Truelove and Witts Sigmoidoscopic Assessment[42]	Hyperemia, granularity, change in overall appearance	ND	ND
Baron Score[43]	Vascularity, friability, bleeding	0-3	ND
Powell-Tuck Sigmoidoscopic Assessment[44]	Friability, bleeding	0-2	ND
Mayo Score Flexible Proctosigmoidoscopy Assessment[45]	Erythema, vascularity, friability, bleeding, ulceration	0-3	≤1
Sutherland Mucosal Appearance Assessment (UC-DAI)[46]	Edema, vascularity, granularity, friability, bleeding, ulceration	0-3	ND
Rachmilewitz Endoscopic Index[47]	Granularity, vascularity, mucosal vulnerability, mucus, fibrin, exudate, erosion, ulceration	0-12	≤4
Sigmoidoscopic Index[48]	Erythema, friability, granularity, ulceration, mucopus, vascularity	0-16	≤4
Sigmoidoscopic Inflammation Grade Score[49]	Edema, vascularity, granularity, friability, bleeding, ulceration	0-4	ND
Modified Baron Score[50]	Granularity, vascularity, friability, hyperemia, bleeding, ulceration	0-4	0
Ulcerative Colitis Endoscopic Index of Severity[51]	Vascularity, bleeding, erosions, ulceration	3-11	ND

ND indicates not defined; UC, ulcerative colitis; UC-DAI, UC Disease Activity Index.

Osterman, MT. Journal of Clinical Gastroenterology. 47(3):212–221, MAR 2013.

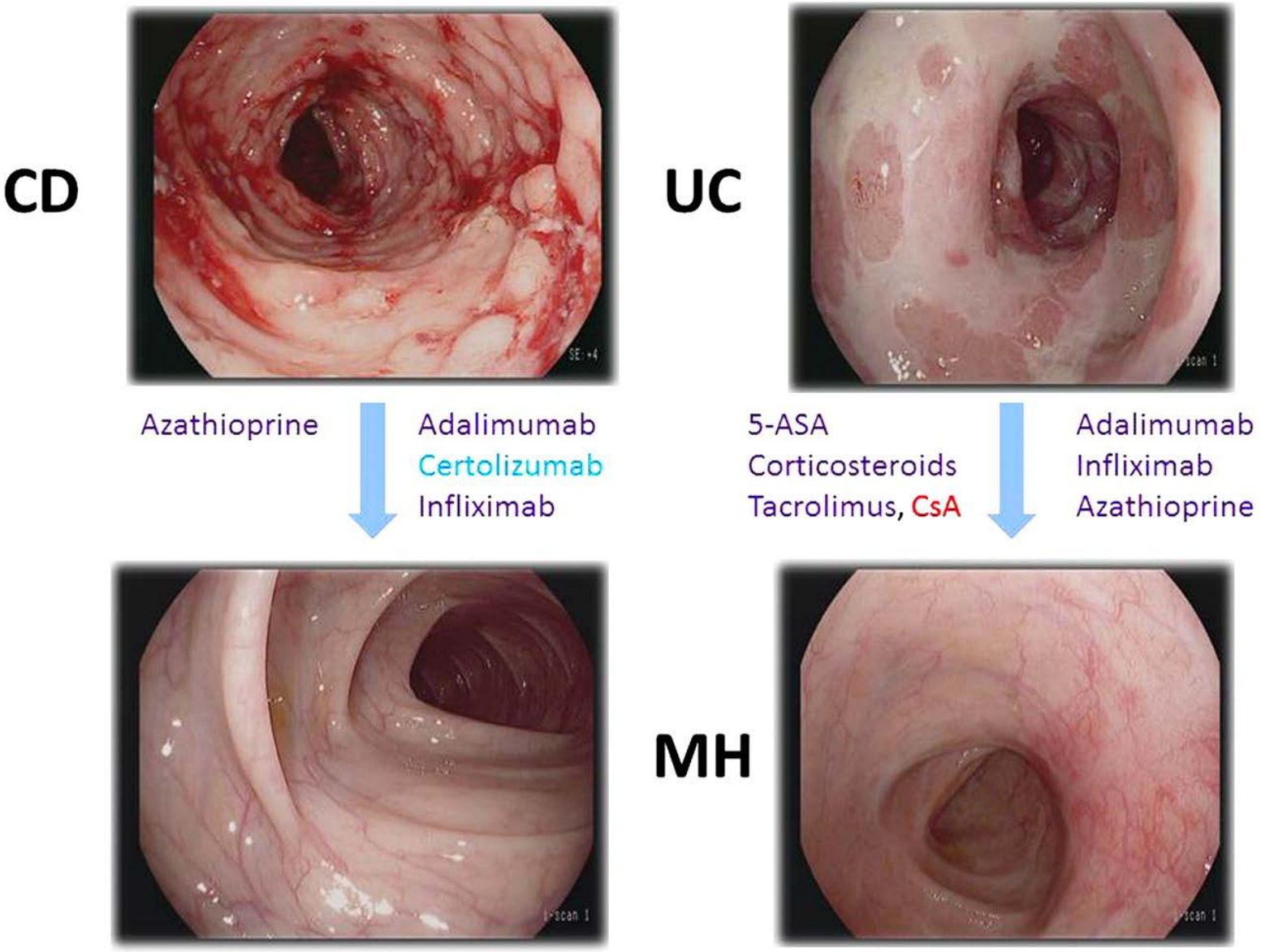
Simple endoscopic score (SES-CD)

SES Score

Variable	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter > 2)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD = sum of all variables for the 5 bowel segments.
Values are given to each variable for every examined bowel segment

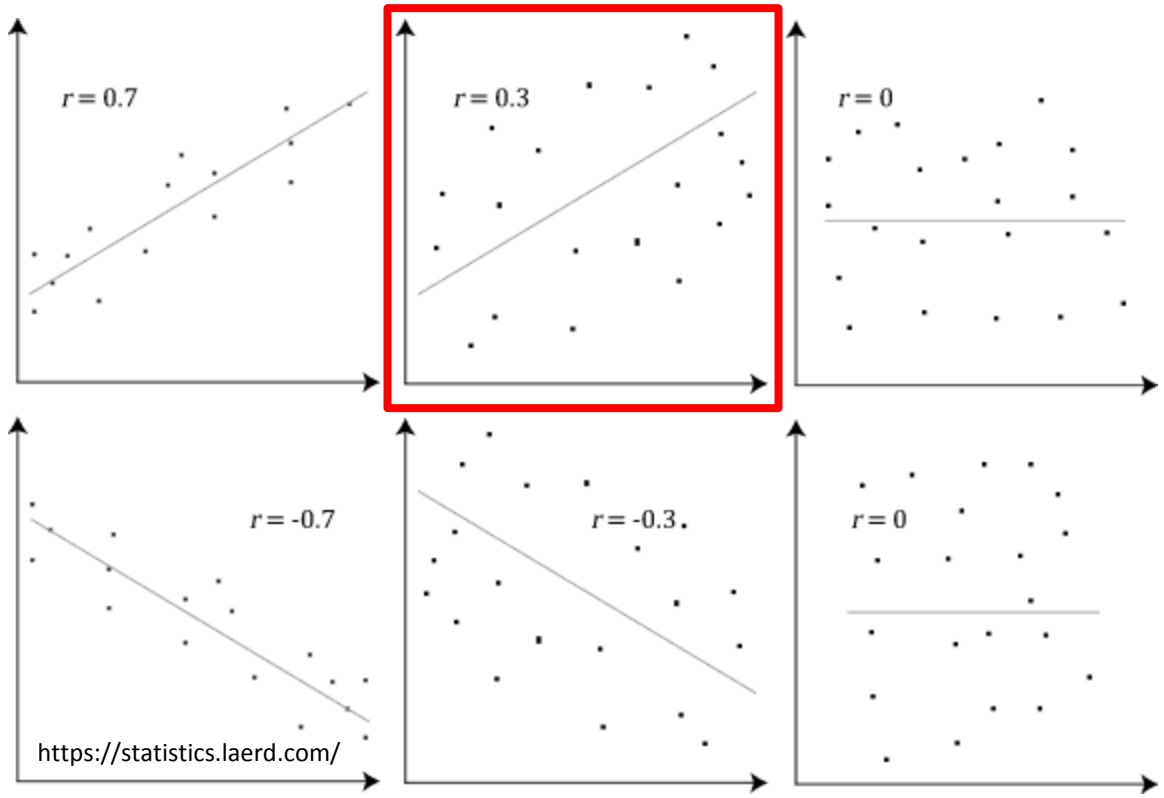
Daperno M, et al.Gastrointest Endosc. 2004 Oct;60(4):505-12.



Neurath MF1, Travis SP. Gut. 2012 Nov;61(11):1619-35.

Mucosal Healing in IBD

- Low observed correlation between clinical and endoscopic activity scores (r=0.13 to 0.39)



Modigliani R et al. Gastroenterology.1990;98:811–818; Cellier C et al. Gut. 1994;35:231–235; Daperno M et al. Gastrointest Endosc. 2004;60:505–512.

Low Correlation Clinic v. Endo

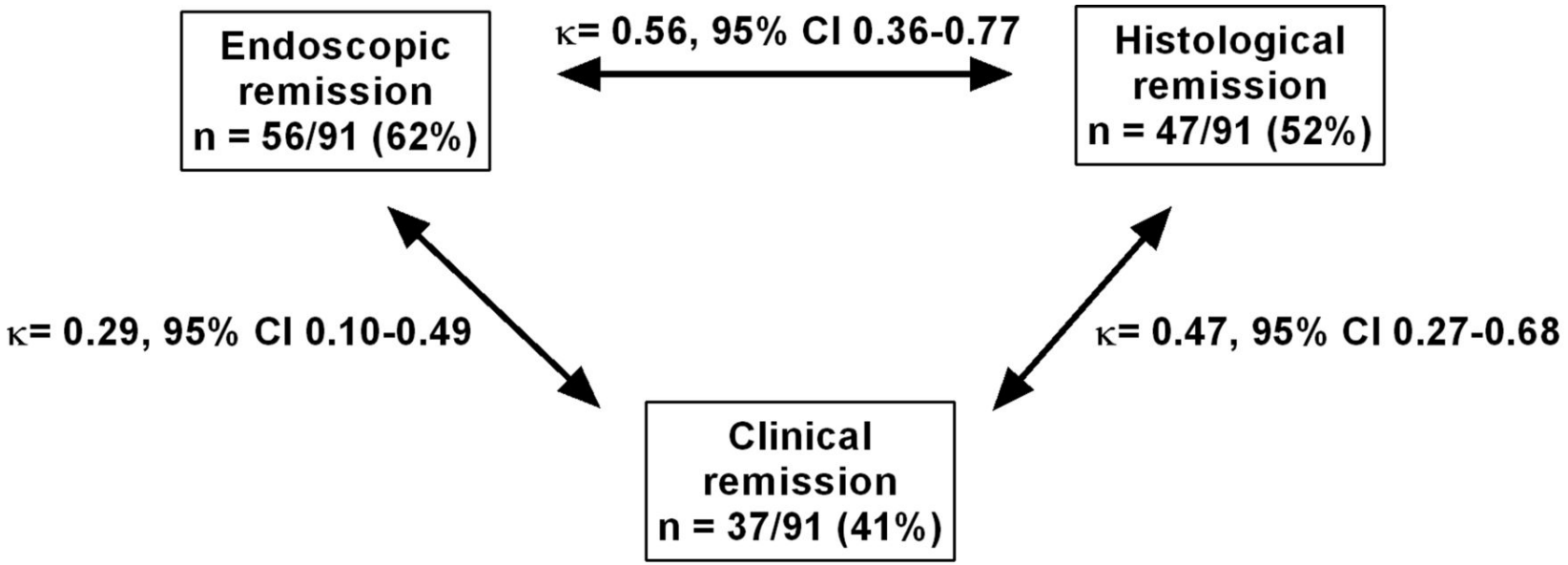
- Infection
- Irritable bowel syndrome
- Bacterial overgrowth
- Bile salt diarrhea
- Steatorrhea
- Depression
- Opioids, antibiotics, other drugs

Variable Correlation Endo v. Histo

- Disease activity in 131 UC patients
- Overall kappa=0.48
- Relatively high concordance in extreme cases (no endoscopic activity or severe disease)
- Diversity of results in endoscopically mild cases (Mayo 1)
  - 37% grade 0
  - 21% grade 1
  - 28% grade 2
  - 14% grade 4

Lemmens B, et al. Inflamm Bowel Dis. 2013 May;19(6):1194-201.

Clinic v. Endo v. Histo



Measure of remission	Concordance with other measures of remission		
	Clinical	Endoscopic	Histological
Clinical (n=37)	100% (n=37)	81% (n=30)	81% (n=30)
Endoscopic (n=56)	54% (n=30)	100% (n=56)	75% (n=42)
Histological (n=47)	64% (n=30)	89% (n=42)	100% (n=47)

Bryant RV, et al. Gut. 2016 Mar;65(3):408-14.

Mucosal Healing – UC v. CD

- May be more meaningful as UC is predominately a mucosal disease
- Rectum involved in most cases of UC facilitating surveillance
- CD may require an advanced cross-sectional imaging component to help fully describe disease activity
  - mucosal disease may still be a good surrogate marker as ulcers correlate with rate of colectomy
  - 62% v. 18% @ 8 years in one study (Allez et al. Am J Gastroenterol. 2002; 97:947-53)

Emergence of Histological Indices

- Truelove and Richards Index (1956)
  - Simple system that categorized patients as having, 1) no inflammation, 2) mild-to-moderate, or 3) severe inflammation
  - >50% of patients in clinical remission had endoscopic or histologic evidence of disease activity
  - 37% of patients without endoscopic findings had histologic disease activity
  - There was fair agreement b/t clin & endo (k=0.27) and moderate agreement b/t clin & histo (k=0.58)

Truelove SC, Richards WC. Br Med J. 1956;1:1315–1318

~30 Histological Indices for UC

- Truelove and Richards (1956)
- Matts Score (1961)
- Watts Score (1966)
- Keren Score (1984)
- The Friedman Index (1985)
- Gomes Score (1986)
- Saverymuttu Index (1986)
- Floren Index (1987)
- Initial Riley Score (1988)
- Riley Score (1991)
- Hanauer Index (1993)
- Odze Index (1993)
- Sandborn Index (1993)
- Geboes Score (2000)
- Scheppach/D'Argenio Score (2001)
- Harpaz Index (2003)
- Modified Riley score (2005)
- Chicago/Rubin score (2007)
- Gramlich (2007)
- Baars (2012)
- Nishiyama (2014)
- Iacucci (2015)
- Wiernicka (2015)
- Theede (2015)
- Jauregui-Amezaga (2016)
- Marchal-Bressenot/Nancy (2017)
- Mosli/RHI (2017)
- etc…

Histological Indices for UC

- 11 of these 30 indices have been partially validated
- Arguably none have been fully validated
- Full validation requires…
  - Content validity – index is sufficient to measure UC (expert & literature support)
  - Criterion validity – index is adequate against a gold standard (no gold standard, usually a lab value)
  - Construct validity – index consistent with other measures of disease activity (clinical & endoscopy)
- *An optimal histological index may not exist*

Mosli MH et al. Cochrane Database of Systematic Reviews 2017, Issue 5.

Mucosal Healing in IBD

- What is the definition of mucosal healing in IBD?

"Restoration of normal mucosal appearance by endoscopy of a previously inflamed region and the complete absence of ulceration and macroscopic and histological signs of inflammation."

Histologic mucosal healing definition (IOIBD proposed):

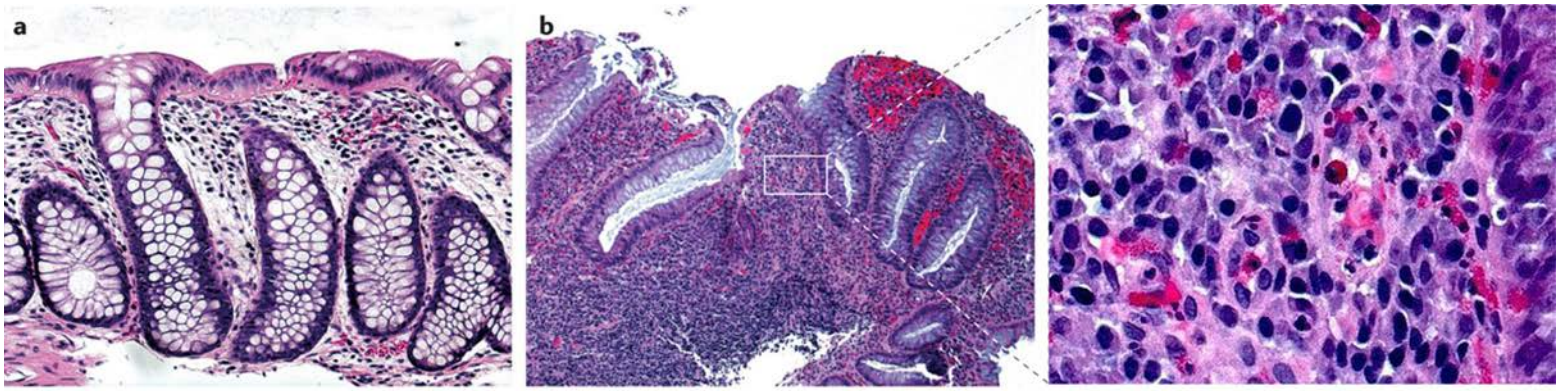
- Induce absence of neutrophils (both in the crypts and lamina propria)
- Induce the absence of basal plasma cells and ideally reduce lamina propria plasma cells to normal; and
- Reduce lamina propria eosinophils to normal.

Feagan BG et al. Inflamm Bowel Dis. 2012;18:152–160.
Bryant RV, et al. Journal of Crohn's and Colitis (2014) 8, 1582–1597

Clinical Predictors of Colectomy and Relapse in UC

- Mayo score > or = 10
- Mayo score > or = 2 after induction therapy
- Elevated CRP
- Prior anti-TNF treatment
- Other factors influence colectomy or relapse
  - Steroid dependency
  - Mayo >2 at baseline
  - No response, late response, or high CRP after induction
  - Others

- “...endoscopic remission is not always correlated with a histologically quiescent disease”

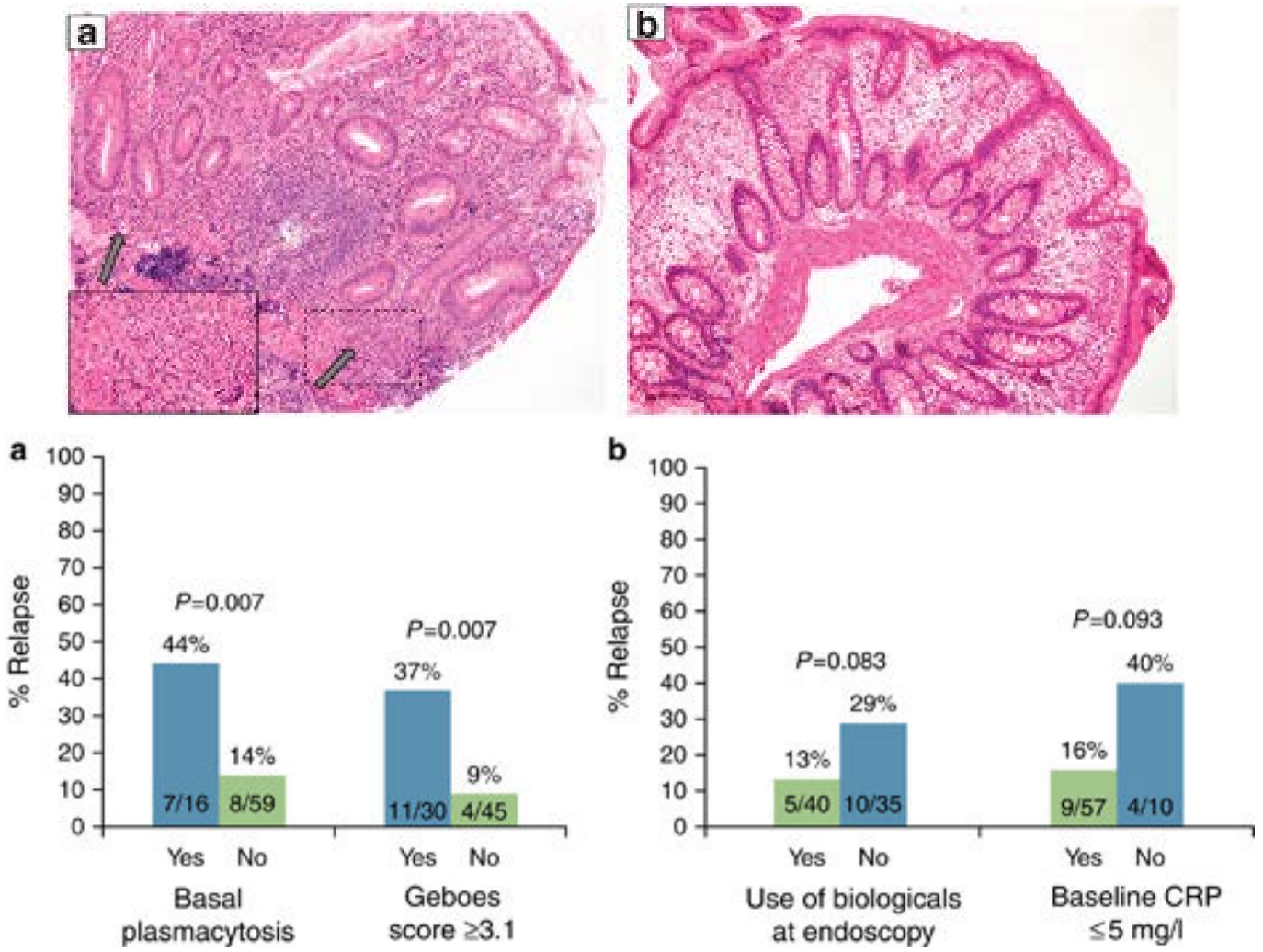


Nature Reviews | Gastroenterology & Hepatology

- Endoscopically quiescent, which will relapse first?

Riddell, R. H. (2016) Mucosal healing in ulcerative colitis: what constitutes remission?
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2016.194

Histological Predictors of Relapse



Bessissow T, et al.Am J Gastroenterol. 2012 Nov;107(11):1684-92.

Histological Predictors of Relapse

- Basal plasmacytosis and neutrophilic activity predicted relapse (37-50% had relapse)
- Patients without basal plasmacytosis had only 14% relapse, while without activity had only a 9% relapse
- Unclear if basal plasmacytosis is an independent predictor of relapse

Bessissow T, et al.Am J Gastroenterol. 2012 Nov;107(11):1684-92.

Histological Predictors of Relapse

- 74 patients with endoscopically inactive UC were evaluated at baseline
- 27 of 74 patients relapsed in 12 mos (36%)
- Independent Predictors of Relapse
  - Younger age
  - Prior relapses in women
  - Basal plasmacytosis (hazard ratio 4.5)

Bitton A, et al. Gastroenterology. 2001 Jan;120(1):13-20.

Histological Predictors of Relapse

	Relapsers[a] (SD)	Nonrelapsers (SD) Baseline	6 mo	Hazard ratios (95% CI)[b]	*P* value[b]
Histology[d] (% of patients with the finding)					
Basal plasmacytosis	29	7	2	4.35 (1.7–11.0)	0.002
Crypt atrophy	56	28	29	2.4 (1.1–5.3)	0.03
Crypt distortion	56	44	44	1.4	NS
Paneth cell metaplasia	16	16	13	1.0	NS
Basal lymphoid aggregates	16	9	7	1.7	NS
PMNs[e]	24	13	4	1.8	NS
Cryptitis	24	13	6	1.7	NS
Crypt abscesses	8	2	0	3.2	NS

[a]Mean calculated using the value measured closest before a relapse. [b]Hazard ratios and *P* values for univariate time-dependent Cox regression analysis. [c]No significant differences in white blood cell, hemoglobin, and albumin levels. [d]No erosions, ulcers, or granulomas detected; no significant difference in types and numbers of mononuclear cells in the upper two thirds of the lamina propria. [e]Polymorphonuclear leukocytes in the lamina propria.

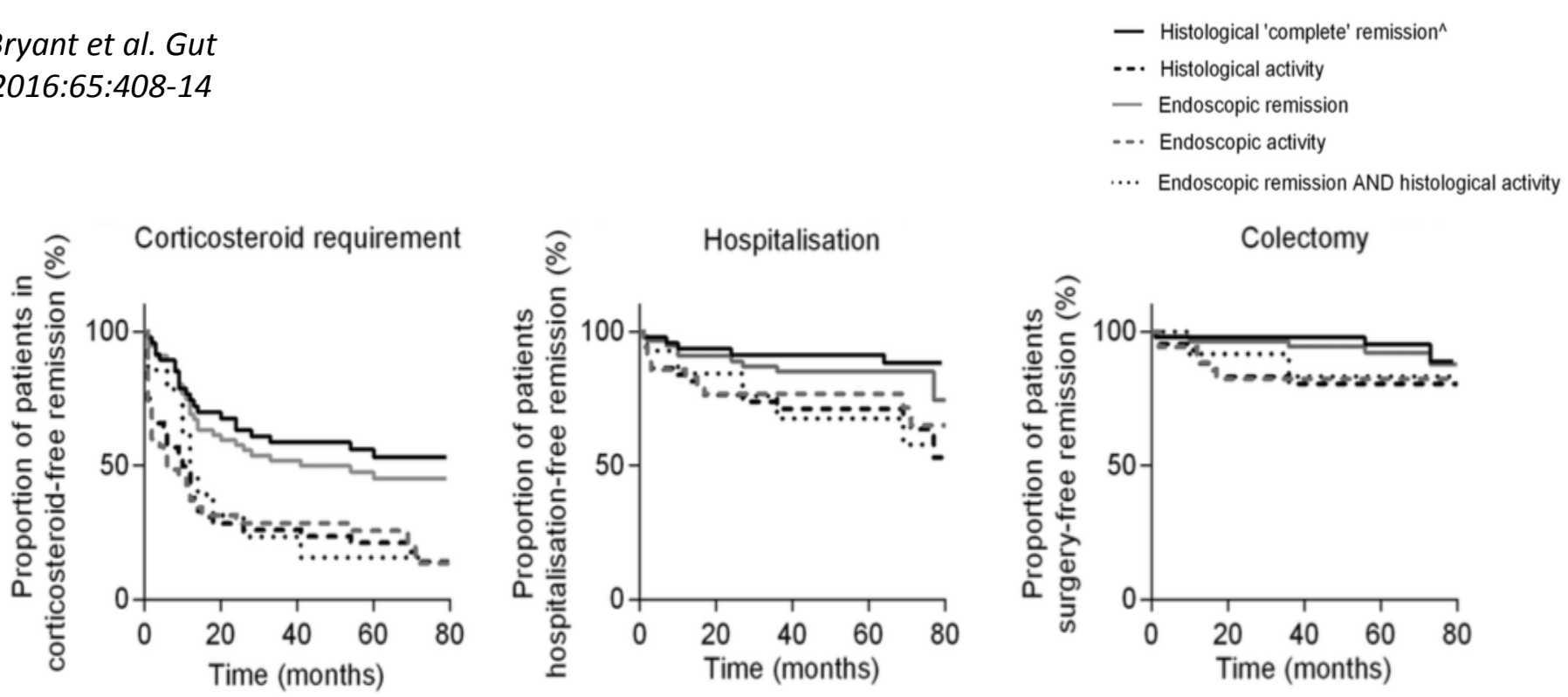
Bitton A, et al. Gastroenterology. 2001 Jan;120(1):13-20.

Histological Predictors of Relapse

- 179 patients with endoscopically inactive UC were evaluated at baseline
- Patients with neutrophilic activity (Geboes 3.1 or greater) had an increased risk of relapse (RR 3.5)
- Remission defined as Geboes 0 or 1 (structural changes and/or chronic inflammation, no neuts)
- Patients in clinical, endoscopic, and histological remission at baseline only had a 7% rate of relapse within the next 12 months

Zenlea T, et al. Am J Gastroenterol. 2016 May;111(5):685-90.

Bryant et al. Gut 2016:65:408-14



Variable	Corticosteroid requirement	Hospitalization for severe colitis	Colectomy
Disease extent	n.s.	3.21, p=0.02	**4.06, p=0.02**
Histologic remission	**0.42, p=0.02**	**0.21, p=0.02**	0.36, p=0.22
Endoscopic remission	0.86, p=0.65	0.83, p=0.74	0.71, p=0.64
Histo and Endo Remission	**0.38, p=0.02**	**0.24, p=0.04**	0.46, p=0.39

Normalization is better than just quiescence

Patients were categorized as…

(1) *Histologic normalization:* completely normal mucosa with no features of chronicity present
(2) *Histologic quiescence:* features of chronicity including crypt atrophy or branching but no active inflammation, such as erosions, crypt abscesses, or focal neutrophil infiltration
(3) *Histologic activity:* presence of any epithelial infiltration by neutrophils, crypt abscesses, erosions or ulceration

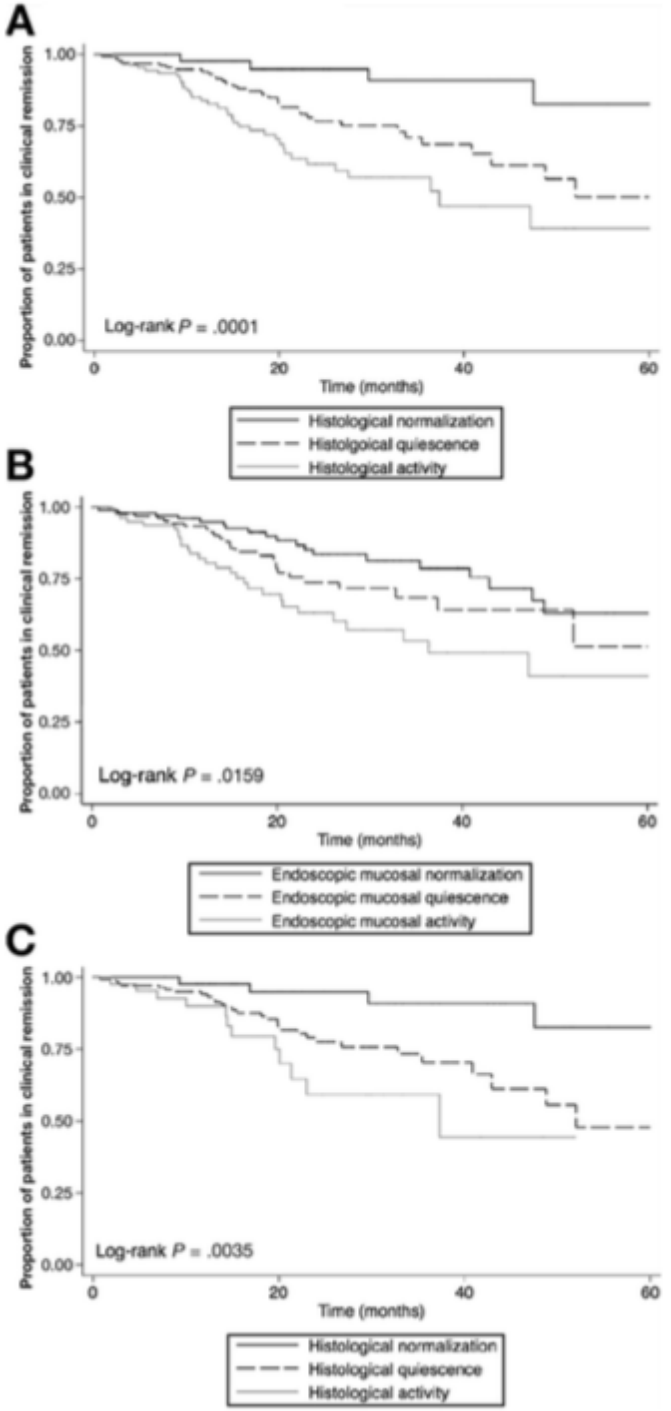


Figure 1. Kaplan-Meier analysis of effect of endoscopic mucosal and histologic activity on clinical relapse-free survival. (*A*) Clinical relapse-free survival versus histologic healing. (*B*) Clinical relapse-free survival versus endoscopic mucosal healing. (*C*) Clinical relapse-free survival versus histologic healing in patients with endoscopic mucosal healing.

Christensen B, et al. Histologic Normalization Occurs in Ulcerative Colitis and Is Associated With Improved Clinical Outcomes. Clin Gastroenterol Hepatol. 2017 Oct;15(10):1557-1564

Mucosal Healing in IBD

Will the post-“mucosal healing”/post- biological agent era allow us to change the natural history of IBD?

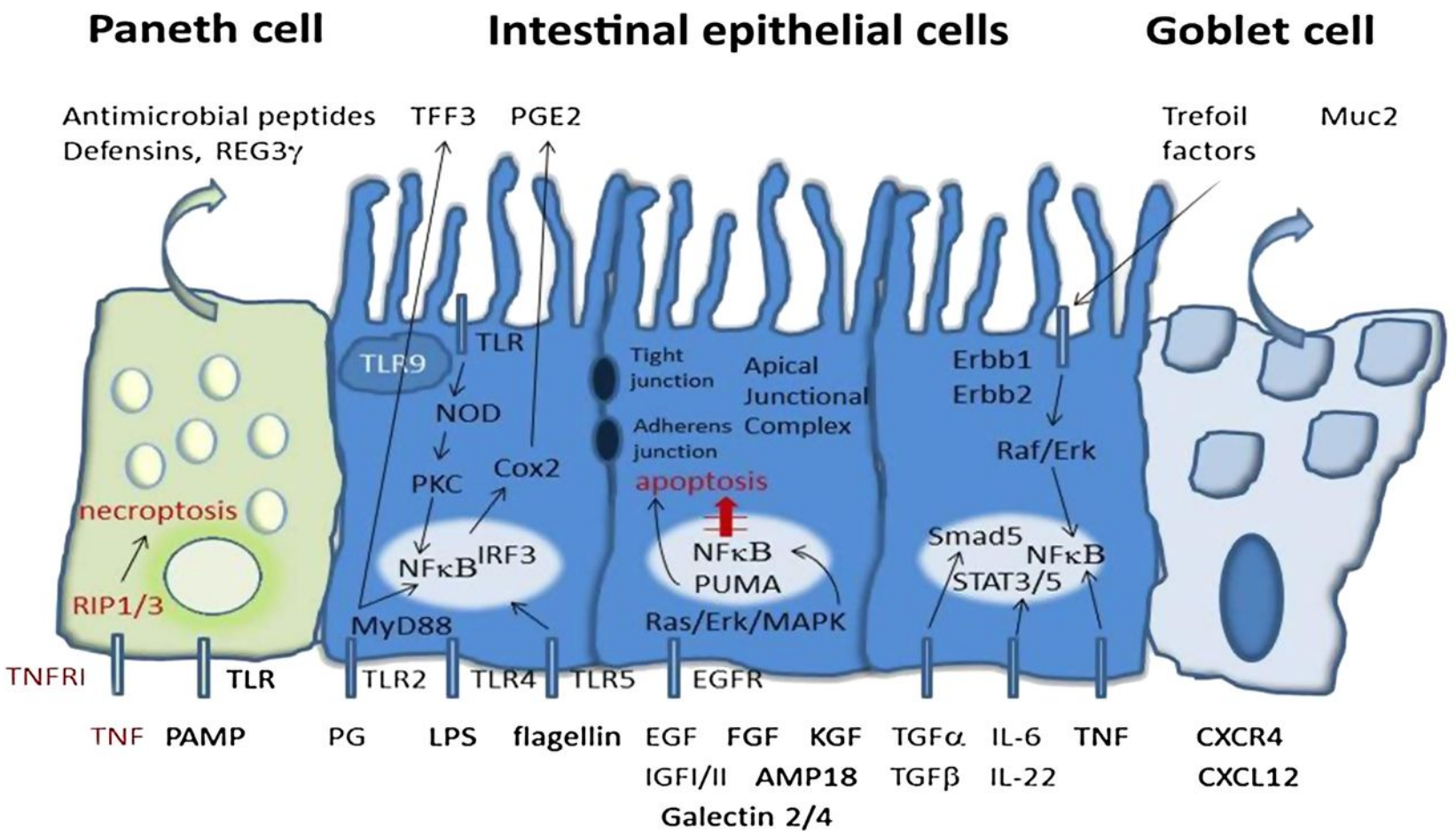
Documentation of Activity in IBD

- Recent studies support the traditional common sense understanding…
  - Active (acute, neutrophilic) inflammation is evidence of disease activity
  - Basal lymphoplasmactyosis (or plasmacytosis) is evidence of residual ongoing disease
  - Crypt architectural distortion and fibrosis are a form of ‘scarring’ of the mucosa (i.e. evidence of prior injury) and may persist without ongoing injury

Documentation of Activity in IBD

- Simple Clinical Diagnostic Approach
  - Colonic mucosa (CM) with crypt architectural distortion (CAD) = “quiescent” colitis
  - CM c CAD + basal plasmacytosis (BP) = chronic colitis
  - CM c CAD + BP + neutrophils = active chronic colitis (min, mild, moderate, severe)
- *May no longer be sufficient*, translation to various index scores may be necessary

Molecular signalling pathways involved in mucosal healing



Neurath and Travis. Gut 2012;61:1619-1635.

GUT

Conclusions and Future Directions

- Mucosal healing is best categorized as a lack of disease activity based on combined endoscopic and histological assessment, sometimes called “complete remission”
- A precise definition of histological remission has not been well established
  - more prospective studies are needed
  - common sense understanding may prevail
- Systematization of clinical treatment and surveillance algorithms will require systematization of pathologic evaluation
  - expect non-neoplastic synoptic “index” reporting for salient IBD activity features
- Incorporation of appropriate biomarkers/ancillary studies (protein, nucleic acid, etc.)
- Is histological mucosal healing a reasonable clinical goal for all patients?