A Practical Approach to Endoscopic Scoring

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Role of Endoscopic Healing in UC

- Forms a critical component of the outcome measures used for regulatory approval
- Useful clinically as well
- Prognostic value (surgery, cancer)?
- Facilitates histopathology

UC: Mayo Disease Activity Index

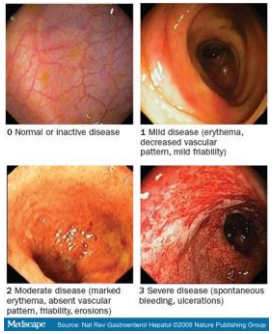
Grade	Bowel frequency	Rectal bleeding	Physician's global assessment	Endoscopy/sigmoidoscopy finding
0	Normal number of stools per day	No blood seen	Normal	Normal or inactive disease
1	1 or 2 more stools than normal	Streaks of blood with stool less than half the time	Mild disease	Mild disease (erythema, decreased vascular pattern
2	3 or 4 more stools than normal	Obvious blood with stool most of the time	Moderate disease	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	5 or more stools than normal	Blood alone passed	Severe disease	Severe disease (spontaneous bleeding, ulceration)

Response: reduction in the Mayo Clinic score of at least 3 points and 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.

Remission: Total Mayo Clinic score of 2 or lower and no subscore higher than 1 (including mucosal healing, defined as an endoscopic subscore of 0 or 1).

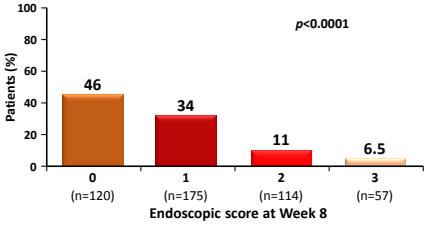
Schroeder KW, et al. *N Engl J Med* 1987;317:1625–1629, Feagan BG et al. *N Engl J Med* 2013;369:699-710
Panaccione R et al. *Gastroenterology* 2014;146:392–400

The Mayo Clinic Score



Endoscopic Healing and Remission in UC

Steroid-free remission at Week 30 with infliximab

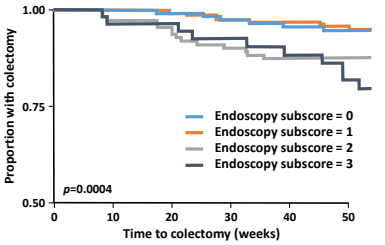


Remission was defined as a total Mayo score ≤2, with no individual subscore >1
ACT 1/2 subanalysis; primary endpoint was clinical response at Week 8 ($p<0.001$); patients randomised to placebo or infliximab induction and maintenance therapy at Week 0

Colombel JF et al. Gastroenterology 2011;141:1194–201.

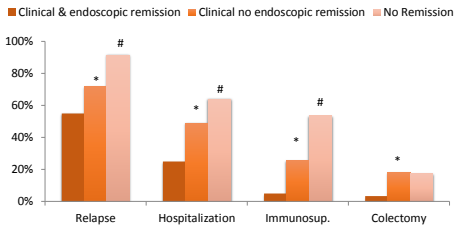
Mucosal healing and colectomy in UC

ACT 1/2: risk of colectomy in infliximab-treated patients who were colectomy-free at Week 8 (n=466)



Colombel JF et al. Gastroenterology 2011;141:1194–201.

UC: Outcomes at 5-Year Follow-up According to Early Response to Steroids



*p<0.05 vs. Clinical and endoacopic remission
# p<0.05 vs. Clinical remission (+/- endoscopic remission)

Ardizzone S, et al. *Clin Gastroenterol Hepatol*. 2011;9:483-9

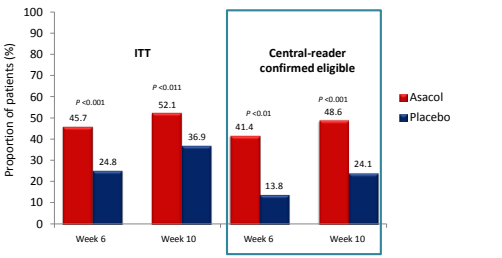
Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis

Variable	Controls (n=136)	Cases (n=68)	Odds ratio (95% confidence interval)	P value
Colonoscopy inflammation score[1]	1.89 (0.52)	2.22 (0.78)	2.54 (1.45–4.44)	0.001
Histological inflammation score[2]	2.05 (0.41)	2.38 (0.56)	5.13 (2.36–11.14)	<0.001
Family history of CRC (%)	18 (14)	7 (12)	1.09 (0.40–2.94)	0.17
PSC (%)	2 (2)	4 (6)	4.00 (0.73–21.84)	0.11
Mesalamine use (%)	122 (90)	65 (96)	2.38 (0.67–8.54)	0.32
Azathioprine use (%)	37 (28)	12 (18)	0.73 (0.30–1.78)	0.22
Folate supplement (%)	5 (4)	1 (1)	0.40 (0.05–3.42)	0.40
Current smoker (%)	9 (7)	2 (4)	0.43 (0.08–2.23)	0.37

Segmental colonoscopic and histological inflammation was recorded by using a simple score (0, normal; 1, quiescent/chronic inflammation; and 2, 3, and 4, mild, moderate, and severe active inflammation, respectively).

Rutter M et al. *Gastroenterology*. 2004;126:451-9

The Origin of Central Reading



*a sole central reader without knowledge of treatment assignment

Feagan BG et al. *Gastroenterology* 2013;145:149–157

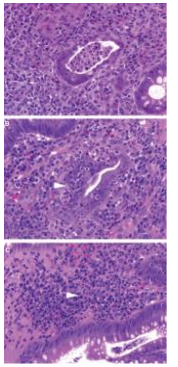
Estimates of Intrarater and Interrater Agreement Based on Data from 50 Random Videos Evaluated 3 Times by 7 Blinded Central Readers, Including the Trial Central Reader

	Instrument			
	UCDAI Sigmoidoscopy Score	Modified Baron Score	Ulcerative Colitis Endoscopic Index of Severity	Visual Analogue Scale
Intraobserver Agreement				
All 7 Central Readers	0.89 (0.85-0.92)	0.88 (0.84-0.92)	0.89 (0.85-0.93)	0.91 (0.88 – 0.94)

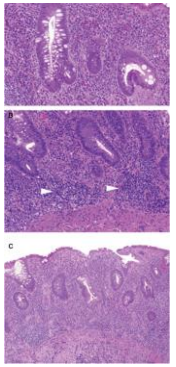
Feagan BG. et al. Gastroenterology 2013;145:149-157

Placebo Rates in Central Read UC Trials

- Etrolizumab Phase 2 trial of anti beta 7 antibody– 0%
- Phase 2 RCT of RPC1063 (sphingosine receptor 1 and 5 modulator) - 6.2%
- Phase 2 anti-MadCam antibody – 5%



Mosli MH, et al. Inflammatory Bowel Disease. 2014;20(3):564-575



Mosli MH, et al. Inflammatory Bowel Disease. 2014;20(3):564-575

Predictors of Relapse in UC

	Hazard ratio (95% CI)	P value
Age	0.4[a] (0.2–0.7)	0.003
Basal plasmacytosis	4.5 (1.7–11.9)	0.003
No. of prior relapses (women)	1.6[b] (1.2–1.9)	<0.001
No. of prior relapses (men)	0.93 (0.7–1.3)	0.64

[a]Per decade.
[b]No significant differences in WBC, Hb, and albumin.

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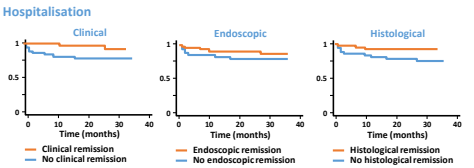
Bitton A, et al. *Gastroenterology* 2001;120:13–20

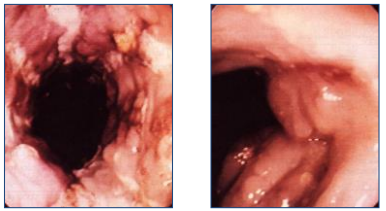
Histological Remission Predicts Lower Hospitalisation Rates



	Clinical remission	Endoscopic remission	Histological remission
Hazard Ratio (95% CI)	0.24 (0.05– 1.10)	0.53 (0.18–1.56)	0.27 (0.07–0.95)
P value	0.07	0.25	0.048

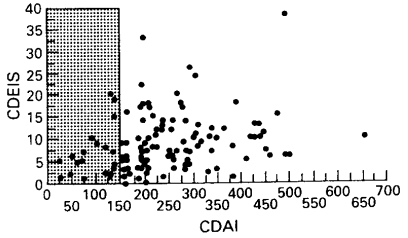
Burger D, et al. *J Crohn's Colitis* 2011;5:S4

What About Endoscopy in CD?



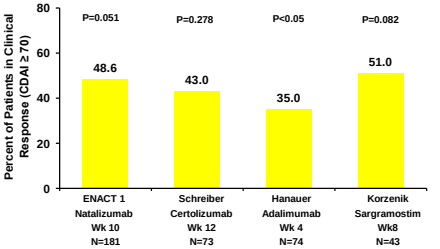
van Dulleman H et al. Gastroenterology1995 Jul;109(1):129-35

Lack of Correlation between Symptoms and Endoscopy

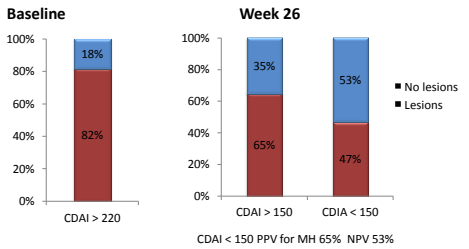


Cellier C. et al. Gut. 1994;35:231-235.

High Placebo Response in CD Trials



CD: CDAI & endoscopic lesions* SONIC study



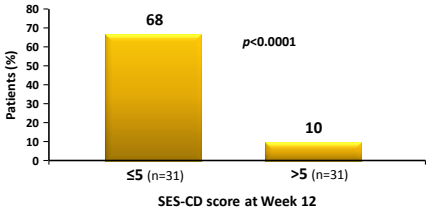
CDAI < 150 PPV for MH 65% NPV 53%

*Lesions: presence of ulcers

Peyrin-Biroulet L et al. *Gut* 2014;63:88–95.

Endoscopic Healing and Long-term Remission in CD

EXTEND: clinical remission at Week 52 with adalimumab



Clinical remission defined as a CDAI score <150
EXTEND subanalysis; primary endpoint was complete mucosal healing at Week 12 (p=0.056); all patients received adalimumab induction therapy from Week 0, before being randomised to placebo or adalimumab maintenance therapy at Week 4

Rutgeerts P et al. Gastroenterology. 2012 May;142(5):1102-1111

Prognosis and Severe Endoscopic Lesions

- Retrospective cohort
- 102 patients with active CD
- Severe endoscopic lesions defined as deep ulcerations >10% of mucosal area with at least one colonic segment
- Risk of colectomy associated with SELs, high CDAI, absence of immunosuppression

Kaser et al. Am J Gastro 2002;97(4):947-53

Endoscopic Scoring Systems

CDEIS

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	TOTAL
Deep ulceration If present, score 12 If absent, score 0						
Superficial ulceration If present, score 6 If absent, score 0						
Surface involved by the disease (measured in cm²)						
Ulcerated surface (measured in cm²)						

TOTAL A

Number (n) of segments totally or partially explored (1-5) n

Total A divided by n B

Ulcerated Stenosis If present anywhere, score 3 If absent, score 0 C

Non-Ulcerated Stenosis If present anywhere, score 3 If absent, score 0 D

TOTAL A+C+D

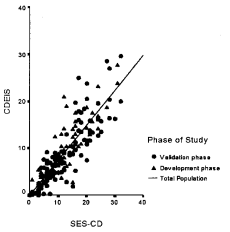
* For partially explored segments and for the ileum, the 10 cm linear scale represents the surface effectively explored.

SES-CD

	SES-CD values			
Variable	0	1	2	3
Ulcers	None	Aphthous ulcers (Diameter 0.1-0.5 cm)	Large ulcers (Diameter 0.5-2 cm)	Very large ulcers (Diameter >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

A Simple Endoscopic Score for Crohn's Disease

- **SES-CD developed to overcome the scoring difficulties inherent to the CDEIS**
- **Developed and validated in independent studies**
- **Good inter-observer reliability**
- **Highly correlate with CDEIS**



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

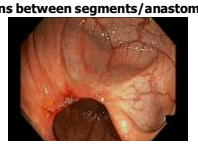
Rater Agreement

	ICCs (95% CI)	
	Intra-rater	Inter-rater
CDEIS	0.89 (0.86 to 0.93)	0.71 (0.61 to 0.79)
SES-CD	0.91 (0.87 to 0.94)	0.83 (0.75 to 0.89)

Khanna R et al Gut 2015

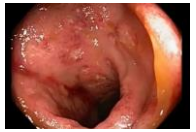
Sources of Disagreement

Lesions between segments/anastomosis

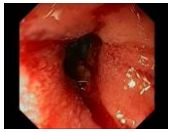


Anal lesions

Superficial ulcers



Stenosis



Role of Endoscopic Healing in Clinical Practice Who, When, How, and Why?

- WHO? – high risk patients
- WHEN ?- UC 12-16 weeks CD :24 weeks plus
- HOW ?- flex sig adequate for UC
- WHY ? – capability to optimize therapy has increased - change the natural history of the disease

Role of Endoscopic Healing in Clinical Practice

- Mayo Score is easily implementable – highly reliable – will ultimately become part of drug labels as a treatment target (Mayo 0)
- UC endoscopy correlates with relevant clinical outcomes , facilitates histopathology
- No easily used score available for CD but evidence supports prognostic value
- Existing scores are highy reliable when read by experts bt impracticable for clinical use
- Absence of ulceration is a practicable treatment target