SHOULD DEEP REMISSION BE A TREATMENT GOAL?

YES!

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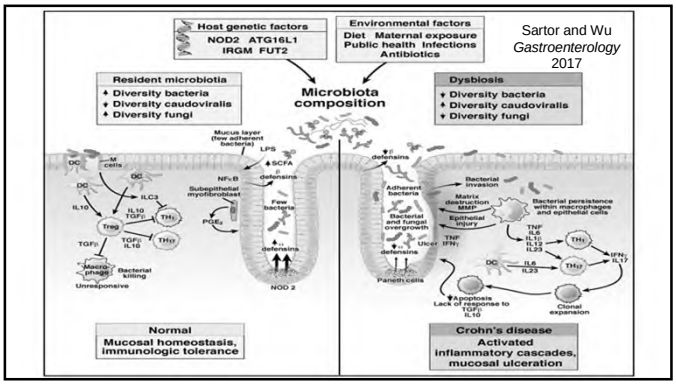
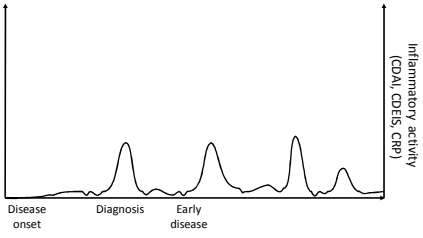
Crohn's disease- a progressive, immune- mediated inflammatory process culminating in symptoms of diarrhea, abdominal pain and weight loss

Bacterial Invasion
↓
Effector immune activation → Tissue injury → Mucosal ulceration → Symptoms
(TH_1, TH_{17}, macrophage)
↓
Fistula, Abscess, Fibrosis



Sartor and Wu
Gastroenterology
2017

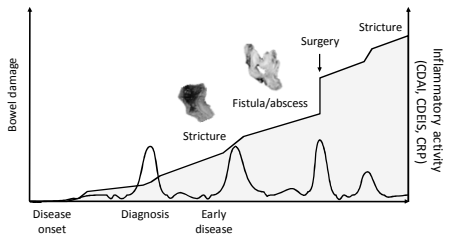
Crohn's disease and UC are intermittent, relapsing diseases



Pariente B, et al. Inflamm Bowel Dis 2011

Crohn's disease is a progressive disease

Progression of tissue damage and inflammatory activity leads to progressive, irreversible fibrosis, complications and surgery



Pariente B, et al. Inflamm Bowel Dis 2011 (modified by JF Colombel)

Crohn's disease- a progressive, immune- mediated inflammatory process that culminates in clinical symptoms

Therapeutic goal should be to induce a deep remission with mucosal healing that *prevents further progression of disease* and additional irreversible tissue damage and complications

Bacterial Invasion

↓

Effector immune activation → Tissue injury → Mucosal ulceration → Symptoms

(TH_1, TH_{17}, macrophage)

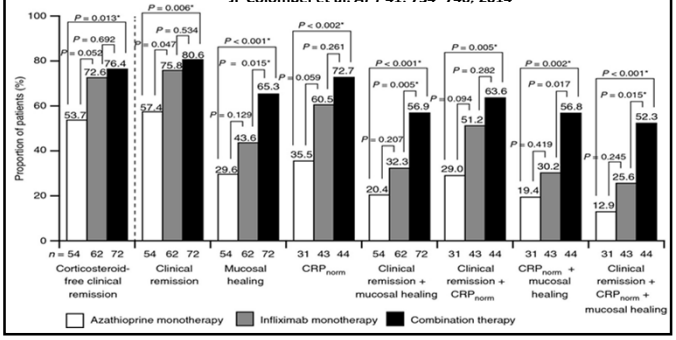
↓

Fistula, Abscess, Fibrosis

Therapeutic targets in IBD

SONIC trial: Results based on different outcome measurements

JF Colombel et al. *APT* 41: 734- 746, 2014

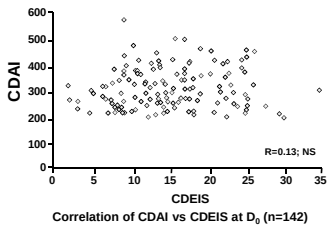


Clinical symptoms (CDAI) are **not** a reliable marker of disease remission defined by mucosal ulceration and CRP

L. Peyrin- Biroulet, *Gut* 2014

- SONIC trial- 72/136 pts (53%) who achieved CDAI ≤ 150 by week 26 exhibited mucosal healing
- 38/90 (42%) achieved both mucosal healing and normal CRP (<0.8 mg/dL)

Crohn's Disease: Clinical Symptoms (CDAI) vs Endoscopic Findings (CDEIS)

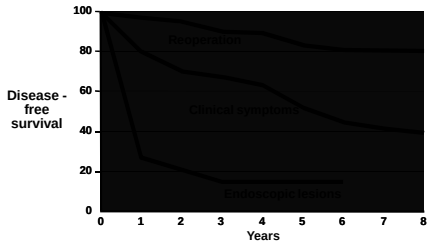


Correlation of CDAI vs CDEIS at D_0 (n=142)

Modigliani R et al. *Gastroenterology*. 1990;98:811.

Crohn's Disease - Post-Operative Recurrence

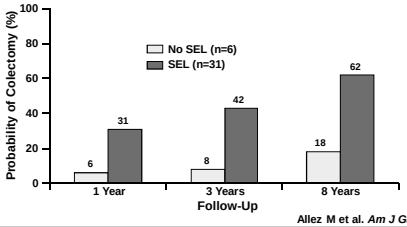
Endoscopic recurrence is clinically silent, but the aggressiveness of mucosal ulcers 6 months post-op predicts clinical recurrence



Rutgeerts P, et al., Gastroenterology 1990; 99:956

Severe Endoscopic Ulcerations Are Associated With Risk of Colectomy in CD

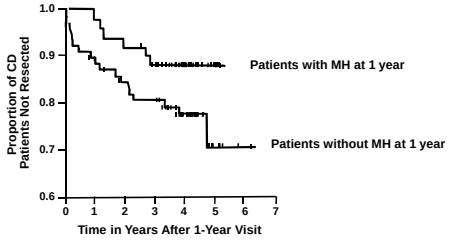
- N=102
- Severe endoscopic lesions (SELs) defined as deep ulcerations involving >10% of mucosal area with at least one colonic segment



Allez M et al. *Am J Gastroenterol*. 2002;97:947

Mucosal Healing After Treatment Predicts Subsequent Disease Course in CD

Community- based incident cohort 740 CD and UC patients followed prospectively 1990-1994, before use of biologic therapies

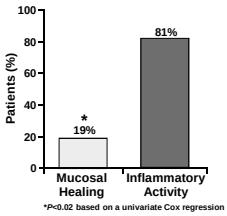


MH, mucosal healing

Frøslie KF et al. *Gastroenterology*. 2007;133:412.

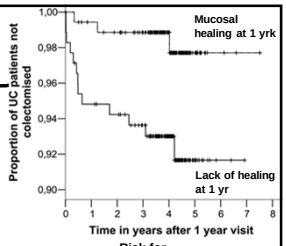
Mucosal Healing at 1 Year Is Associated With Lower Rate of Colectomy in UC patients

Colectomy After 1-year Visit (n=16)



*P<0.02 based on a univariate Cox regression

CI, confidence interval

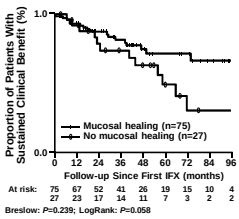


	Risk for Colectomy After 1-year Visit	95% CI
Mucosal healing after 1 year of treatment	0.22	0.06–0.79

Frøslie KF et al. *Gastroenterology*. 2007;133:412.

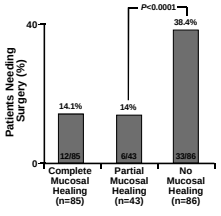
Mucosal Healing Predicts Long-Term Outcome of Maintenance Therapy With Infliximab (IFX) in CD

Sustained Clinical Benefit Long-Term with Respect to Mucosal Healing During IFX Treatment



Breslow: *P*=0.239; LogRank: *P*=0.058

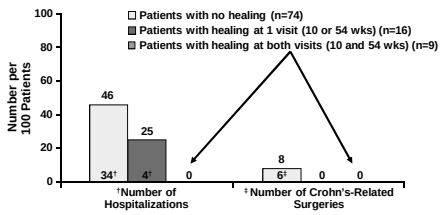
Need for Major Abdominal Surgeries by Degree of Mucosal Healing (Median 22.3 Months Follow-up)



Schnitzler F et al. *Inflamm Bowel Dis*. 2009;15:1295

ACCENT 1: Infliximab

*Hospitalization and Surgery Rate by Mucosal Healing Status**

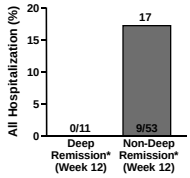


*Endoscopic assessment at weeks 0, 10, and 54; mucosal healing was defined as the absence of mucosal ulceration

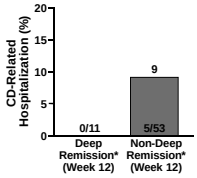
Rutgeerts P et al. *Gastroenterology*. 2002;123:43

EXTEND: Patients Who Achieved Deep Remission* With Adalimumab at Week 12 had fewer Hospitalizations

All-cause Hospitalization through Week 52



CD-related Hospitalization Through Week 52



*Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing

Colombel JF et al. *Clin Gastroenterol Hepatol*. 2014;12:414.

Mucosal healing is associated with improved long-term outcomes in Crohn's disease

Shah S , et al. Aliment Pharmacol Ther 2016

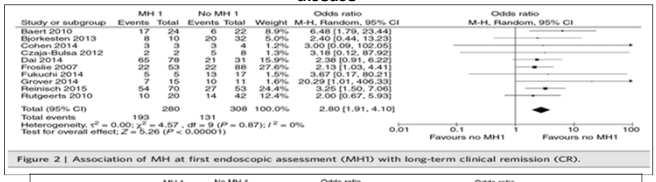


Figure 2 | Association of MH at first endoscopic assessment (MH1) with long-term clinical remission (CR).

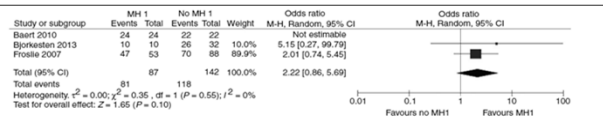


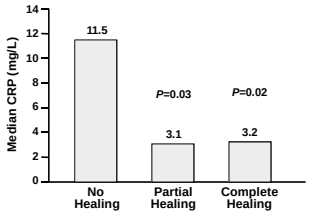
Figure 3 | Association of MH1 with CD-related surgery-free rate.

Noninvasive objective biomarkers of endoscopically- determined mucosal healing

- Serum CRP
- ***Fecal calprotectin (or lactoferrin, lipocalin 2)***

Levels of CRP Are Associated With Mucosal Healing

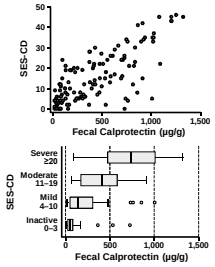
Retrospective analysis of clinical and endoscopic outcomes from serial CRP measurements in 718 CD patients receiving infliximab



Jurgens M et al. *Clin Gas and Hepatol.* 2011;9:421.

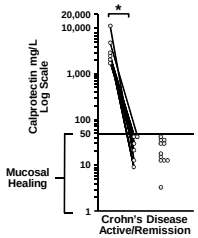
Fecal Calprotectin Is Accurate in Distinguishing Inactive From Mild Crohn's Disease

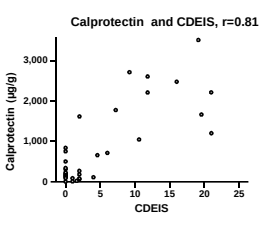
- **122 patients with CD compared to 43 controls**
- **Fecal calprotectin, blood leukocytes, CRP, CDAI measured**
- **Fecal calprotectin correlation with Simple Endoscopic Score for Crohn's Disease (SES-CD) = 0.75**
- **Calprotectin was the only marker able to discriminate inactive from mildly active endoscopic disease**



Schoepfer AM et al. *Am J Gastroenterol.* 2010;105:162.

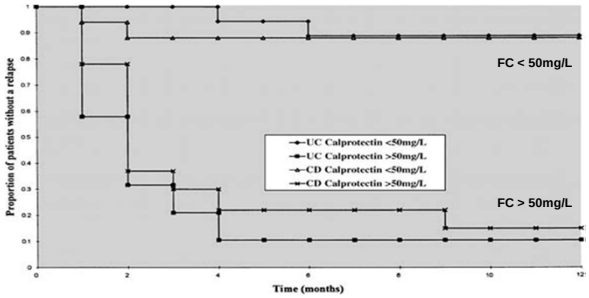
Fecal Calprotectin is an Excellent Predictor of Mucosal Healing





Roseth A et al. *Scand J Gastroenterol.* 2004;39:1017.
Ortega TL et al. at ECCO Congress 2012; Barcelona, Feb. 2012. Poster 180.

Fecal calprotectin predicts relapse in CD and UC patients who have been in clinical remission for 1-4 months

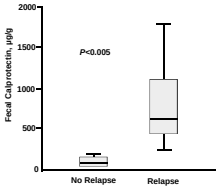


JA Tibble *et al, Gastroenterology* 2000, 119, 15-22

Fecal Calprotectin Can Predict Relapse in CD Patients on Maintenance Adalimumab

- Predicting relapse in CD patients with non-invasive biomarkers could permit early changes of treatment
- **4-month prospective study of 30 CD patients with clinical remission > 6 months on ADA**
- Fecal calprotectin at inclusion was significantly higher in patients who relapsed vs those who maintained remission (803 ± 514 µg/g vs 95 ± 104 µg/g, *P*<0.005)
- Optimal cut-off of fecal calprotectin to predict remission was 204 µg/g
  - Associated with sensitivity 100%, specificity 85.7%, PPV 74.1% and NPV 100%

Mean Fecal Calprotectin Concentrations In Patients with Remission and Relapse (HBI>4)



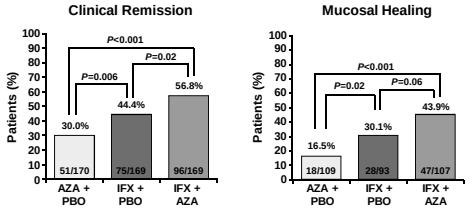
Fecal calprotectin predicts relapse with a high accuracy
Low fecal calprotectin (<204µg/g) excludes relapse within at least the following 4 months
Ferreiro F, et al. DDW. May 4, 2014. Abstract 257

Summary: Surrogate Biomarkers for Mucosal Healing

- **Most data available for MRI, fecal calprotectin, and CRP as surrogate markers for mucosal healing in Crohn's disease**
- **More accurate in distinguishing severely active disease (from less active or remission)**
- **Fecal calprotectin may be more accurate to distinguish mildly active from "healed" mucosa**
- **Likely a combination of objective markers (index) will yield the highest accuracy**

Comparative Effectiveness Study in CD (SONIC)

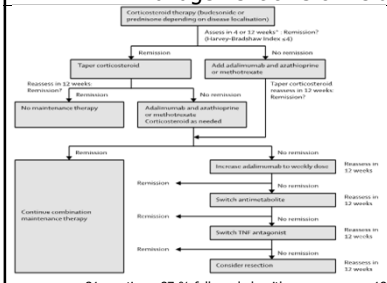
Mucosal Healing as a Secondary End Point



PBO, placebo

Colombel JF et al. *N Engl J Med*. 2010;362:1383.

Early Combined Immunosuppression for the Management of Crohn's disease (REACT)



Practitioners assigned to conventional management were unaware of the early combined immunosuppression-algorithm details and managed patients according to usual practice. Telephone interviews and clinic visits were conducted in the same way as for the ECI group.

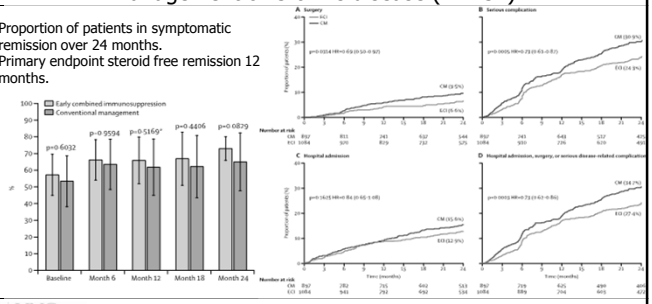
21 practices: 87 % followed algorithm

18 practices: 8 % followed algorithm

Khanna et al. *Lancet* 2015

Early Combined Immunosuppression for the Management of Crohn's disease (REACT)

Proportion of patients in symptomatic remission over 24 months.
Primary endpoint steroid free remission 12 months.



Khanna et al. *Lancet* 2015

CALM study: Comparison between Clinical and Tight Management

Clinical Management

Clinical Management + Calprotectin + CRP

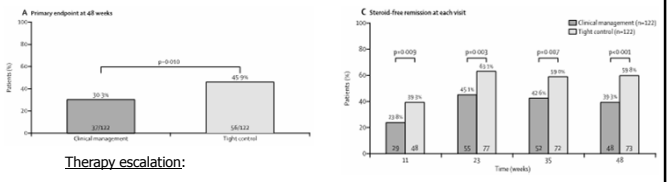
Criteria for therapy escalation

Clinical Management	Tight Management
1. CDAI ≥ 200 points	1. CDAI ≥ 150 points
2. Prednisone use	2. Prednisone use 3. CRP ≥5 mg/L 4. Fecal calprotectin ≥250 µg/g

Colombel et al, *Lancet* 2017

CALM-Study: Tight Control acting upon CRP and Calprotectin Biomarkers Versus Clinical Management

Clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions.



Therapy escalation:

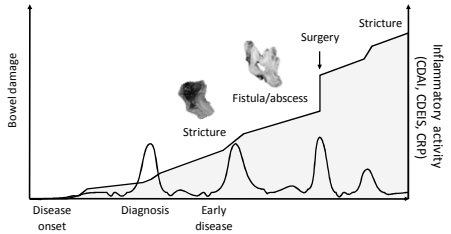
26 % of patients in Tight control group still on adalimumab 40 mg q 2 weeks.

59% of patients in Clinical management still on adalimumab 40 mg q 2 weeks.

Colombel et al. 2017

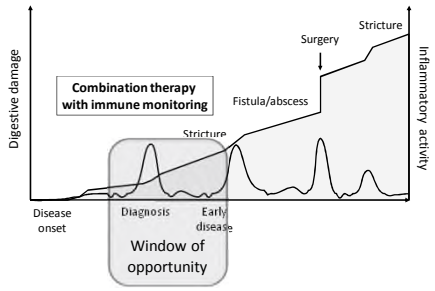
Crohn's disease as a progressive disease

Progression of tissue damage and inflammatory activity leads to progressive, irreversible fibrosis, complications and surgery



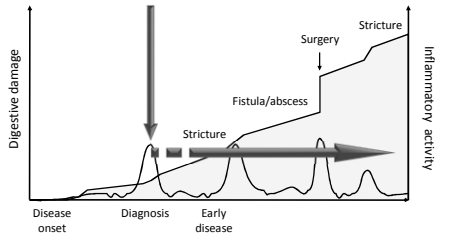
Pariente B, et al. Inflamm Bowel Dis 2011 (modified by JF Colombel)

Early intervention to establish control of CD



Adapted from Pariente B, et al. Inflamm Bowel Dis 2011;17:1415–22

Therapeutic goal - Induce a deep remission that *prevents further progression of disease* and further irreversible tissue damage and complications



Adapted from Pariente B, et al. Inflamm Bowel Dis 2011

SHOULD DEEP REMISSION BE A TREATMENT GOAL? Absolutely!

Benefits of achieving mucosal healing
- Sustain clinical remission
- Decrease steroid use
- Decrease hospitalizations
- Minimize complications
- Reduce surgical resections

Practical Issues
- Current therapies have relatively low rates of mucosal healing
- However, benefits of deep remission are worth optimizing medications, watching carefully for toxicity

This approach makes pathophysiologic sense! **Bacterial Invasion**

↓

Effector immune activation → Tissue injury → Mucosal ulceration → Symptoms
(TH_1, TH_{17}, macrophage)

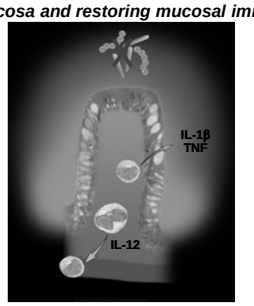
↓

Fistula, Abscess, Fibrosis

More effective, safer approach to treating IBD: *Induce a deep remission with combination therapy, then sustain remission by correcting dysbiosis, healing mucosa and restoring mucosal immune homeostasis*

Eliminate antigenic drive
Antibiotics, probiotics *prebiotics, diet, fecal transplant,* block bacterial binding, enhance bacterial killing (stimulate defensins)

Paralyze TH_1, TH_{17}, innate immune responses
Combination biologics and immunosuppressives (Transient use for induction)



Restore mucosal barrier function
SCFAs, probiotics fiber/ prebiotics

Promote regulatory cell activity (TR_1, Treg, B cells, DC)

Omega 3 FAs, retinoic acid, vit D *Bacteroides fragilis PSA. Clostridium subsets, F. prausnitzii,* Lachnospiraceae

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