Value of Fecal Calprotectin and CRP in monitoring IBD

Dr Wisdom F. Mudombi

Inanda IBD Meeting

25/03/2017

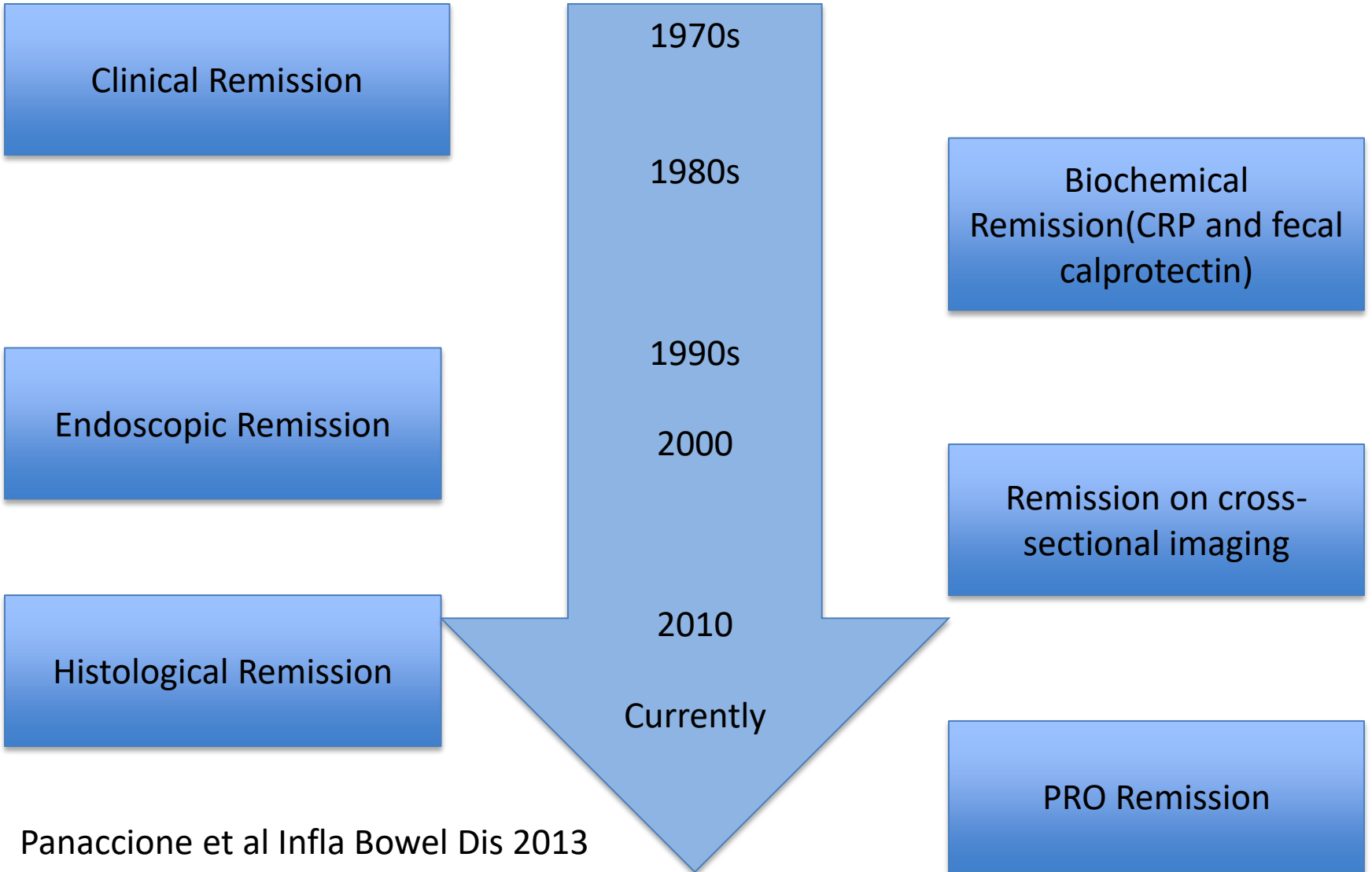
Disclosures

- Nil

Key Cornerstones

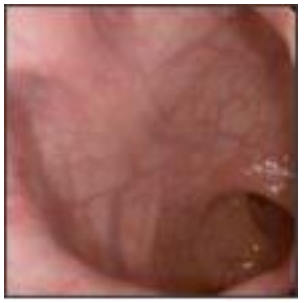
- Initial evaluation and risk stratification
- Setting the treatment goals
- Evidence-based use of available treatment options
- Objective re-evaluation: treatment target reached
- Optimizing treatment (**biomarkers**,TDM)

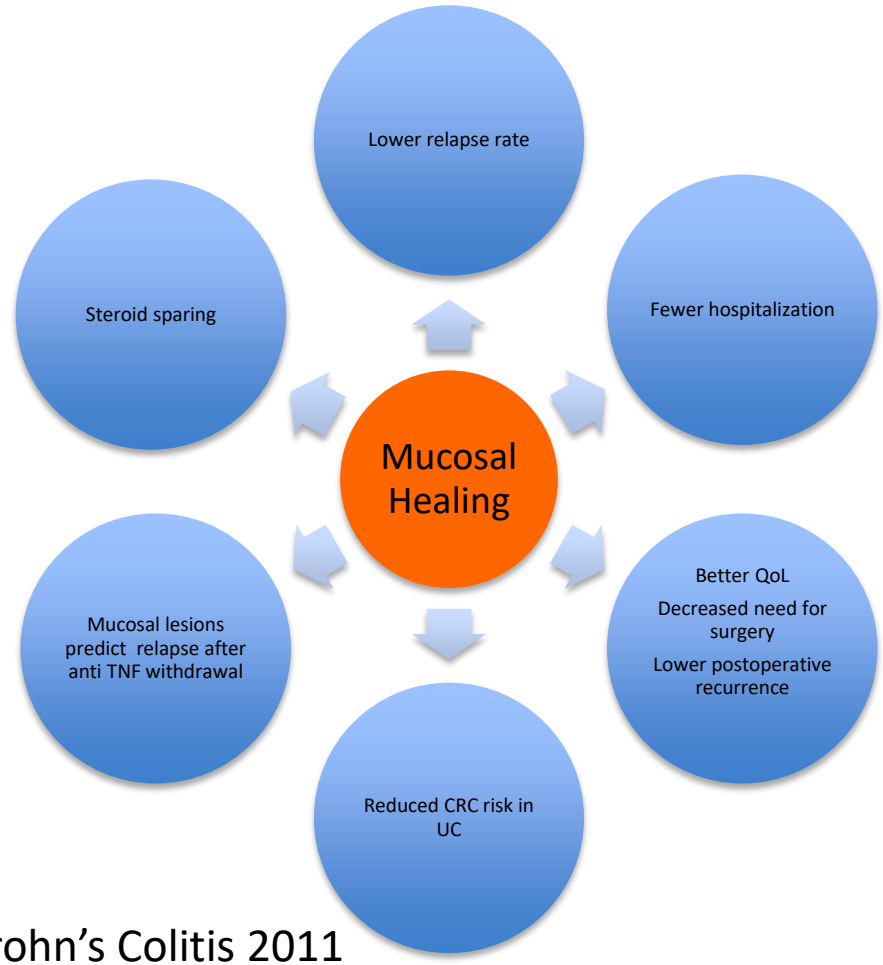
Evolution of treatment goals



Panaccione et al Infla Bowel Dis 2013

Why Mucosal healing?





Peyrin Biroulet L *et al* J Crohn's Colitis 2011
Rutgeerts P *et al* Gastroenterology 1990
Neurath M *et al* Gut 2012, Bougeun G *et al* Clin Gastroenterol Hepatology 2014

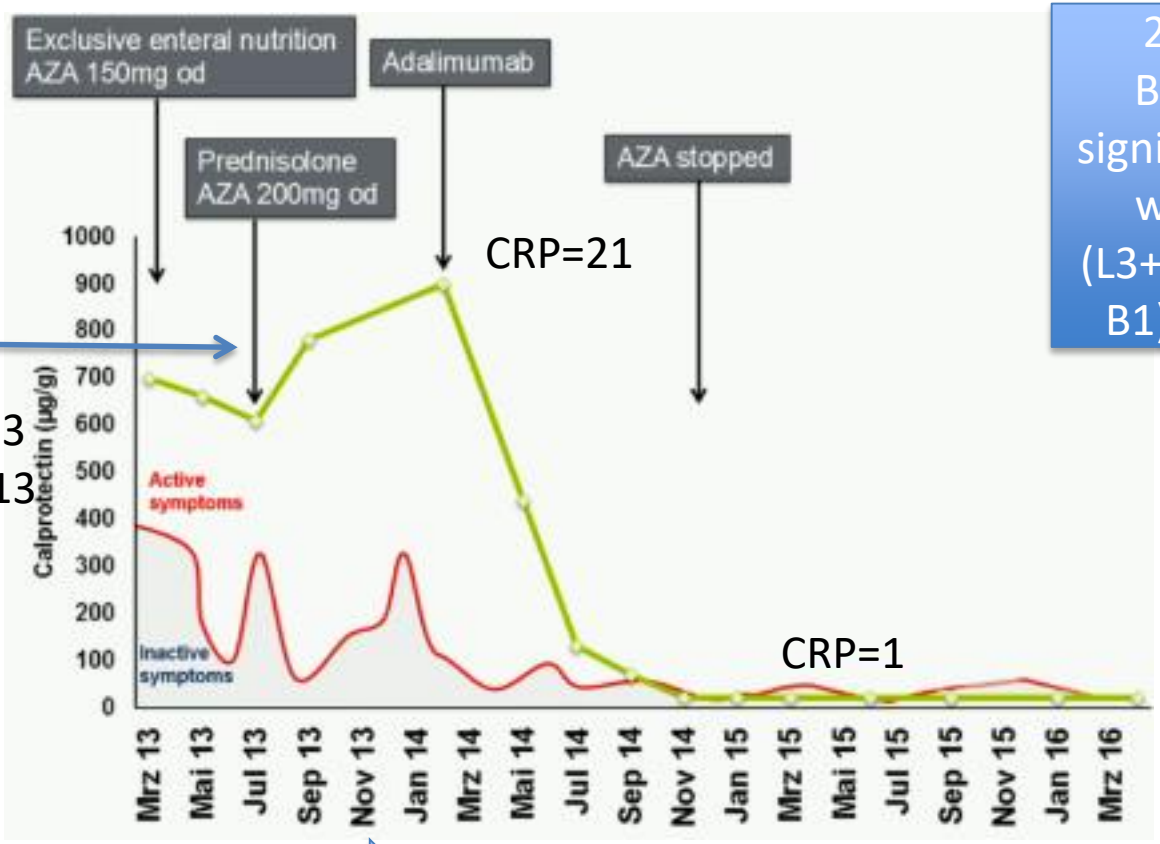
Patient expectations

- Symptom free
- Normal QoL
- Uninterrupted school/work
- Normal social/sex life
- No unsightly scars/stoma

Gastroenterologist goals

- **Deep remission**
- **Avoid hospitalization and surgery**
- **Prevent complications**
- **Minimize “bowel damage”**
- **No drug toxicity**

Monitoring : Knowing When to Say When

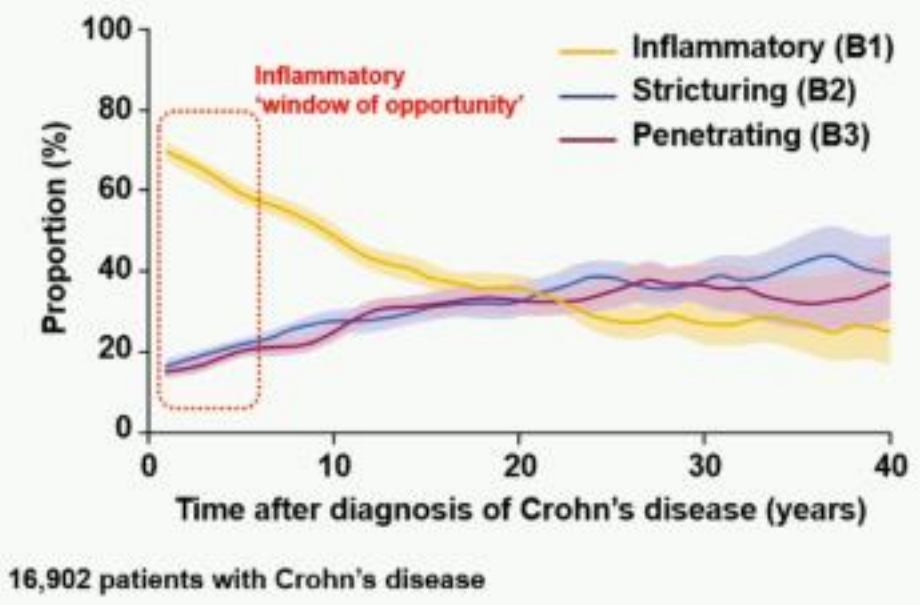


27 yo male(A2), Brother CD, with significant weight loss, with pan-enteric (L3+L4),inflammatory(B1) Crohn's Disease

Registrar
CRP <1 in May 2013
Then 21 in July 2013

1 year to induce deep remission?

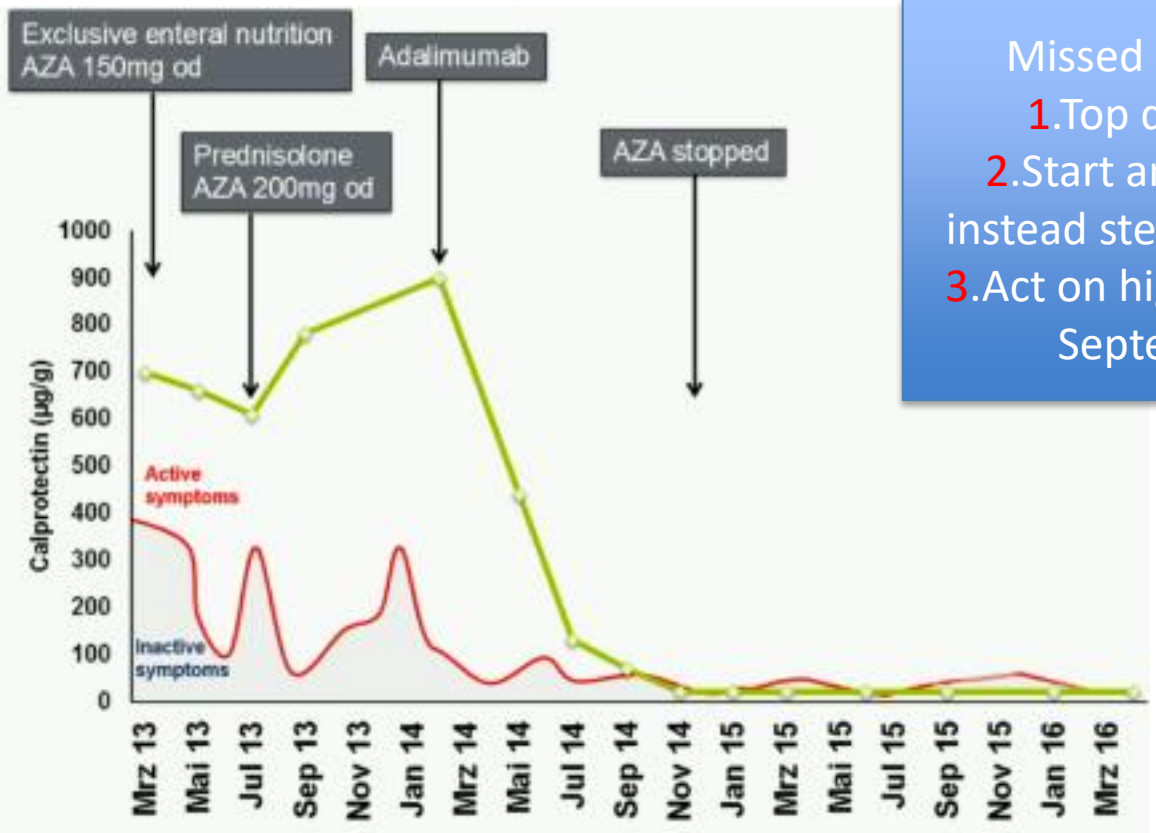
Monitoring and “Window of Opportunity”



Cleynen I *et al* Lancet 2016;387:156-67

IBD Genetics

Monitoring avoids “missed opportunity”



Missed opportunities:
1.Top down therapy
2.Start anti-TNF therapy instead steroids in July 2013
3.Act on high calprotectin in September 2013

Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target

L. Peyrin-Biroulet, MD, PhD[1], W. Sandborn, MD[2], B.E. Sands, MD, MS[3], W. Reinisch, MD[4,5], W. Bemelman, MD, PhD[6], R.V. Bryant, MD[7], G. D'Haens, MD, PhD[8], I. Dotan, MD[9], M. Dubinsky, MD[10], B. Feagan, MD[11], G. Fiorino, MD, PhD[12], R. Gearry, MBChB, PhD[13], S. Krishnareddy, MD[14], P.L. Lakatos, MD[15], E.V. Loftus Jr, MD[16], P. Marteau, MD, PhD[17], P. Munkholm, MD[18], T.B. Murdoch, MD, MSc, FRCPC[19], I. Ordás, MD, PhD[20], R. Panaccione, MD, FRCPC[21], R.H. Riddell, MD[22], J. Ruel, MD, FRCPC[23], D.T. Rubin, MD[24], M. Samaan, MBBS[8], C.A. Siegel, MD[25], M.S. Silverberg, MD, PhD[26], J. Stoker, MD, PhD[27], S. Schreiber, MD, PhD[28], S. Travis, DPhil, FRCP[29], G. Van Assche, MD, PhD[30,31], S. Danese, MD, PhD[12], J. Panes, MD, PhD[20], G. Bouguen, MD[32], S. O'Donnell, MD[26], B. Pariente, MD, PhD[33], S. Winer, MD, PhD[34], S. Hanauer, MD[35] and J.-F. Colombel, MD[3]

Peyrin-Biroulet L *et al* American Journal of Gastroenterology,2015;110:1324-1338

STRIDE Consensus: Treatment goals in CD & UC

- Target is a combination of
  - **Clinical/PRO remission**-resolution of abdominal pain & normalization of bowel habits
  - **Endoscopic remission** resolution of findings of inflammation on cross-sectional imaging

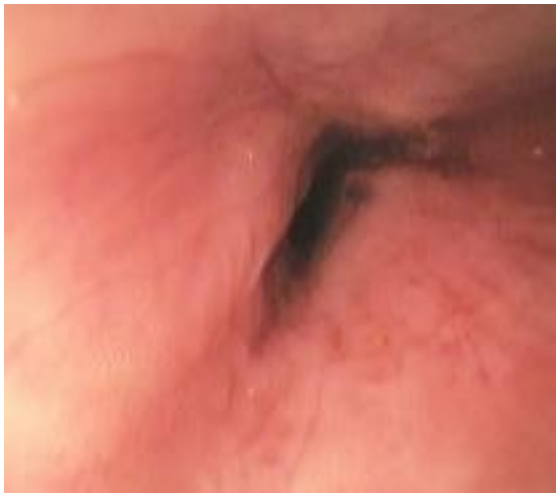
Peyrin-Biroulet L *et al* American Journal of Gastroenterology,2015;110:1324-1338

STRIDE Consensus: Treatment goals in CD

- Adjunctive measures of disease activity but are not a target include:
  - **CRP**
  - **Fecal calprotectin**
- Measures of disease activity that are not a target:
  - **Histology**
  - **Cross-sectional imaging**

Peyrin-Biroulet L *et al* American Journal of Gastroenterology,2015;110:1324-1338

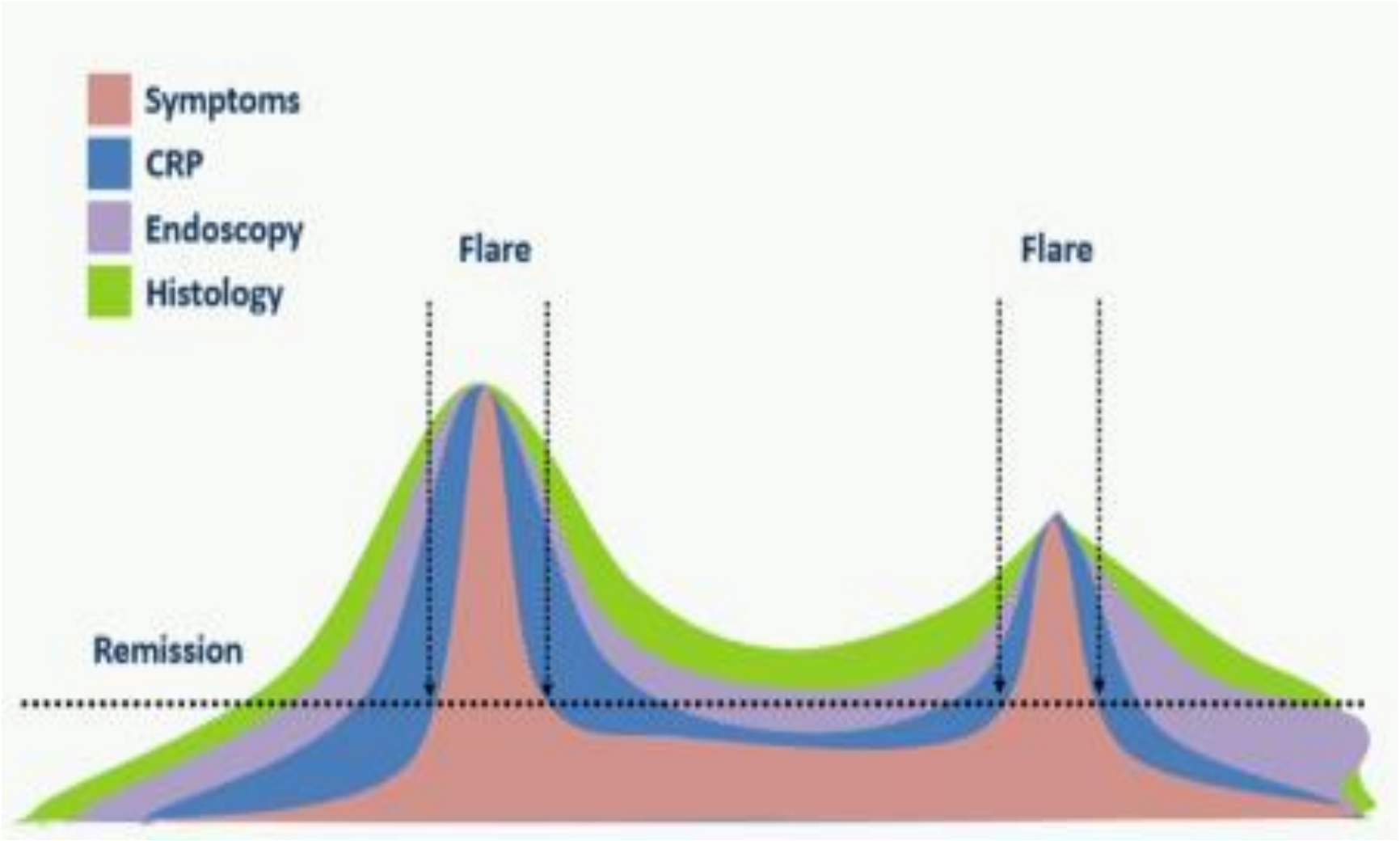
Disease monitoring



- **Symptoms ≠ Active inflammation**
  - NB: stenosis , IBS, Bile acid diarrhea
  - 20% of CD and UC patients have symptoms in absence of inflammation
- **NO symptoms ≠ Absence of mucosal lesions**
  - NB: CDAI do not correlate well with endoscopic activity
- **Normal mucosa ≠ No disease activity**
  - NB: transmural and extramural complication

Peyrin-Biroulet L *et al* Gut 2014;63:88-95
Rutgeerts P et al N Eng J Med 2005

Monitoring disease severity



Objective re-evaluation

Endoscopy/imaging

Colonoscopy/ileoscopy/Enteroscopy/CE

MR enterography/CT enterography

Transabdominal Doppler/contrast enhanced ultrasonography

Biomakers

CRP

Fecal calprotectin

Desirable attributes of “IDEAL” biomaker in IBD

- Non-invasive
- Convenient
- Rapid
- Reproducible
- Inexpensive
- Responsive
- Well defined threshold

- Differentiate organic from functional
- Grades severity of inflammation
- Predicts and measures response to therapy
- Monitors and predicts relapse
- Monitors for post-operative recurrence

Sands B, Gastroenterology , 2015;149:1275-1285

Serum CRP in CD

- Acute phase protein produced by the liver (and mesenteric adipocytes in CD) in response to inflammation stimulated by cytokines such as IL-6, TNF-α and IL-1β
- Single nucleotide polymorphisms (SNPs) reported within various regions of the CRP gene (as well as regulating cytokine genes), which may affect baseline or stimulated CRP production
- 25% of patients with demonstrable activity of CD on endoscopy do not express CRP above the normal threshold.

Peyrin-Biroulet L *et al* Gut 2012
Vermeire S *et al* Inflamm Bowel Dis 2004

Clinically active Crohn's disease in the presence of a low C-reactive protein

- Patients were prospectively recruited over 12 years in Brisbane IBD.
- Subjects in the low CRP group was < 10 mg/l.
- Active disease was defined as CDAI > 200.

Florin TH *et al* Scand J Gastroenterol 2006; 41:306-11

Clinically active Crohn's disease in the presence of a low C-reactive protein

	Group 1(CRP < 10mg/L)	Group 2	P values
Number	22	201	
Pure ileal disease	95%	53%	0.01
Lack of pure colonic disease	0%	24%	0.01
BMI(significantly lower)	20.3	25.0	0.006

Conclusions:
Patients with CD and a persistently low CRP in the face of active disease were characterized by an almost pure ileal disease distribution and
a low BMI, compared to those with a raised CRP.
Despite the abnormally low BMI,
fat wrapping was noted in the majority of low CRP patients undergoing ileal resection.

Florin TH *et al* Scand J Gastroenterol 2006; 41:306-11

Baseline CRP predicts response to anti-TNF in CD-ACCENT 1

- 45% of patients with baseline CRP ≥ 7mg/L vs. 22% with CRP< 7mg/L maintained remission (p=0.012).
- Patients with an elevated baseline CRP level that did not normalize by week 14 were less likely to maintain remission through the remaining 40 –week study period compared with patients whose CRP level had normalized at week 14

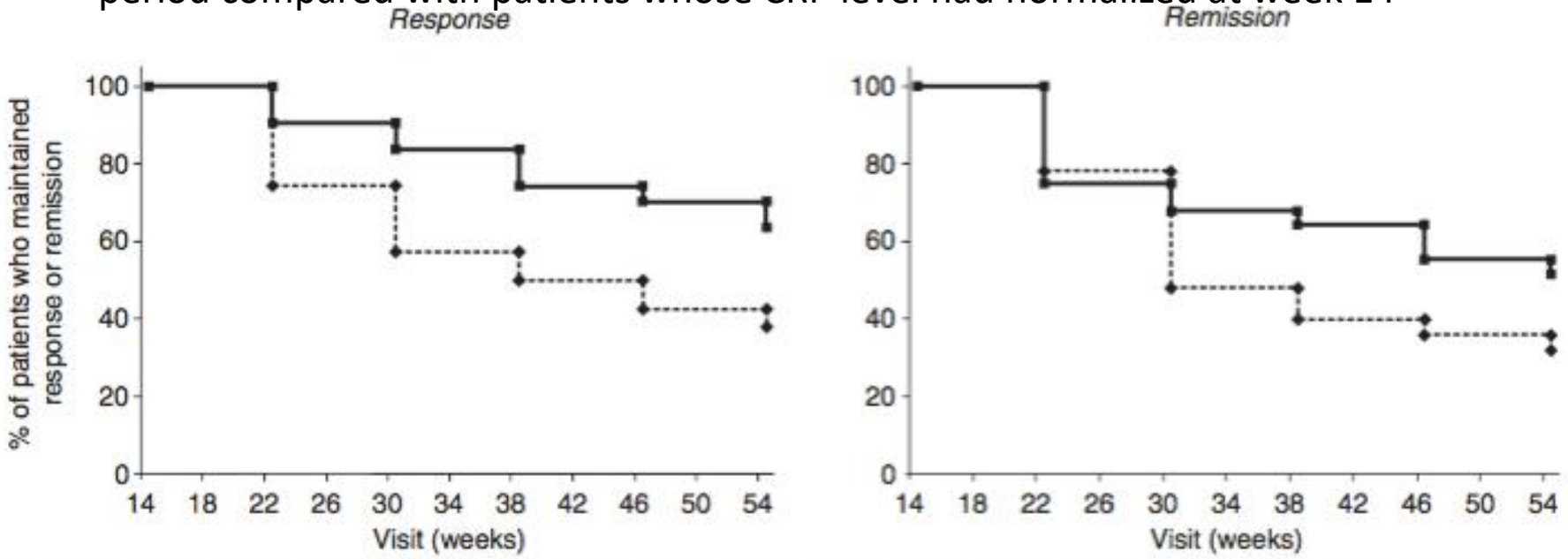
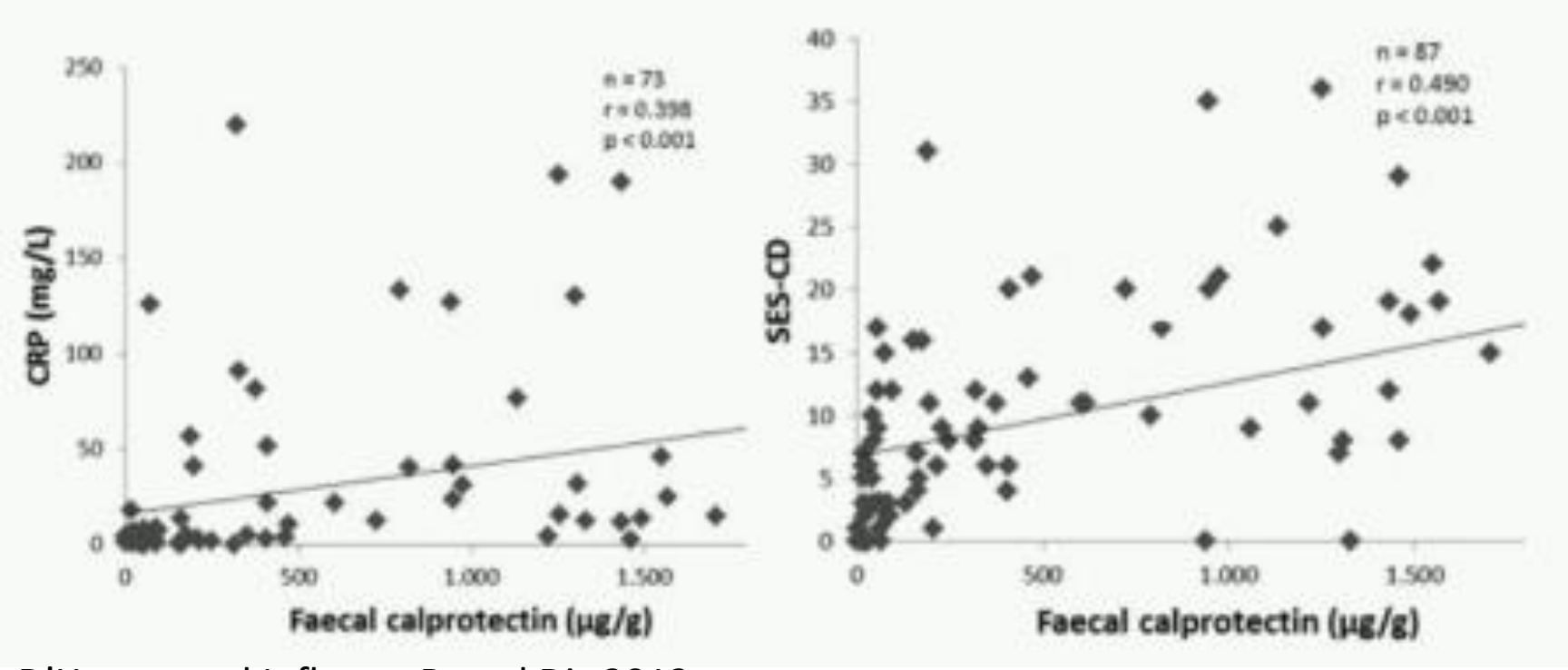


Figure 3 | Kaplan–Meier analysis of the proportion of patients treated with infliximab who maintained response or remission between week 14 and week 54 according to whether their elevated CRP at baseline had dropped by week 14 to < 0.5 mg/dL (fixed line) or remained elevated (> 0.5 mg/dL, dotted line) [analysis restricted to patients with CRP > 0.5 mg/dL at baseline who were in response (n = 158) or remission (n = 107) at week 14].

Reinisch W *et al* Aliment Pharmacol Ther 2012; 35: 568–576

Fecal calprotectin in CD

- 60% cytosolic protein mostly contained in neutrophil granulocytes
- High specificity and sensitivity (93-100%)
- Quantitative, non-invasive , stable
- Marker of biochemical and mucosal activity in CD



D'Haens et al Inflamm Bowel Dis 2012

Disease activity and biomakers in CD

	IL-6	Calprotectin	Lf	CDAI	SES-CD
hsCRP	**0.65**	**0.47**	**0.52**	0.16	**0.46**
IL-6		**0.45**	**0.55**	0.15	**0.43**
Calprotectin			**0.76**	**0.23**	**0.45**
Lactoferrin				**0.19**	**0.48**
CDAI					0.15

NOTE. Coefficients in bold are significant at the 0.05 level.

Jones J *et al* Clin Gastroenterol Hepatol 2008;6:1218-1224

Evidence from the STORI ?

- STORI(infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with immunosuppressors)

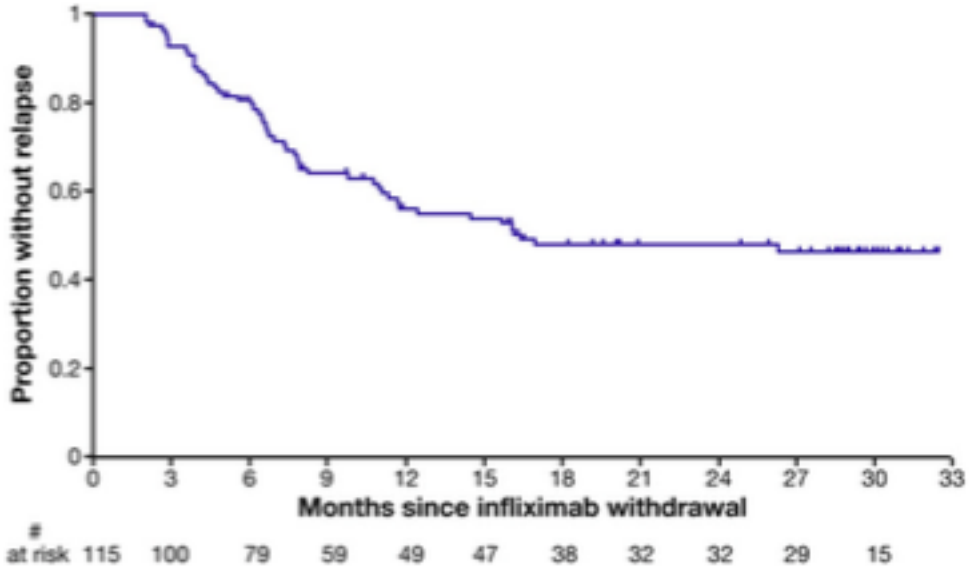
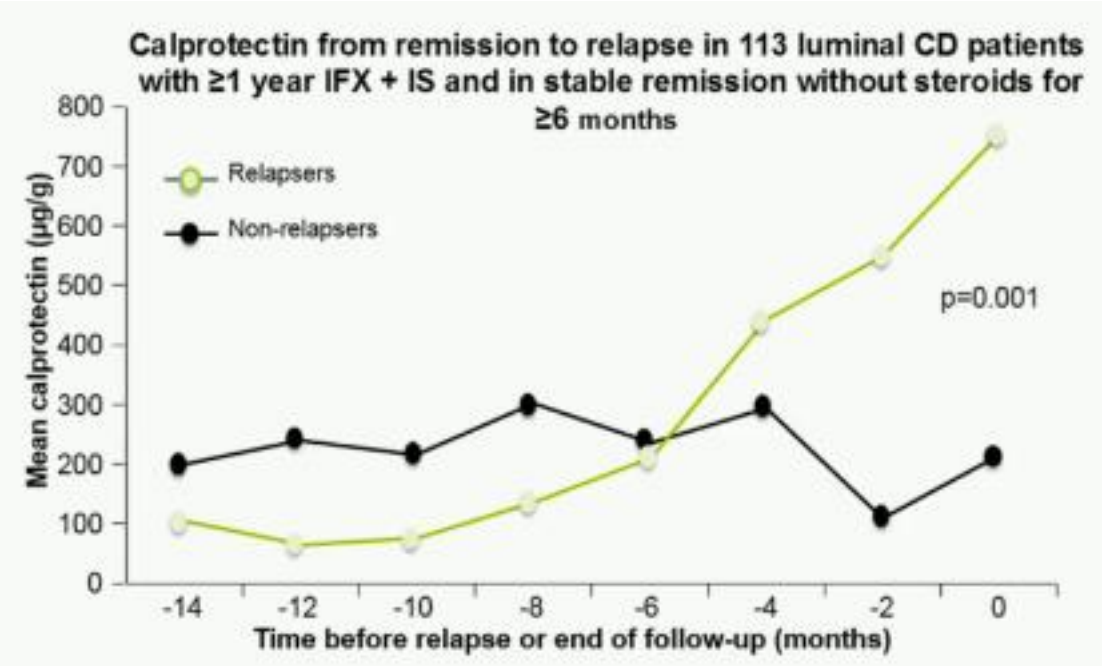


Figure 2. Kaplan–Meier time-to-relapse curve of the 115 included patients. The median ± SE follow-up time was 28 ± 2 months. There were 52 patients with confirmed relapse. The median time to relapse was 16.4 months.

- Factors independently associated with time to relapse:
  - **hsCRP level≥5 mg/L**
  - **Fecal calprotectin ≥ 300µg/g**
  - Leukocyte count ≥$6x10^9$/L & Hb ≤ 145 g/L
  - Male sex
  - No previous surgical resection

Calprotectin predicts relapse in CD



Louis E *et al* Gastroenterology 2012;142:63-70

The STORI with CRP and fecal calprotectin

- CRP ≤5mg/L can predict mucosal healing with a sensitivity of (70%), low specificity of (40%).
- Fecal calprotectin 250mg/g more effective than CRP at predicting mucosal healing sensitivity (80%), specificity(50%).
- The combination of these 2 markers may further improve accuracy

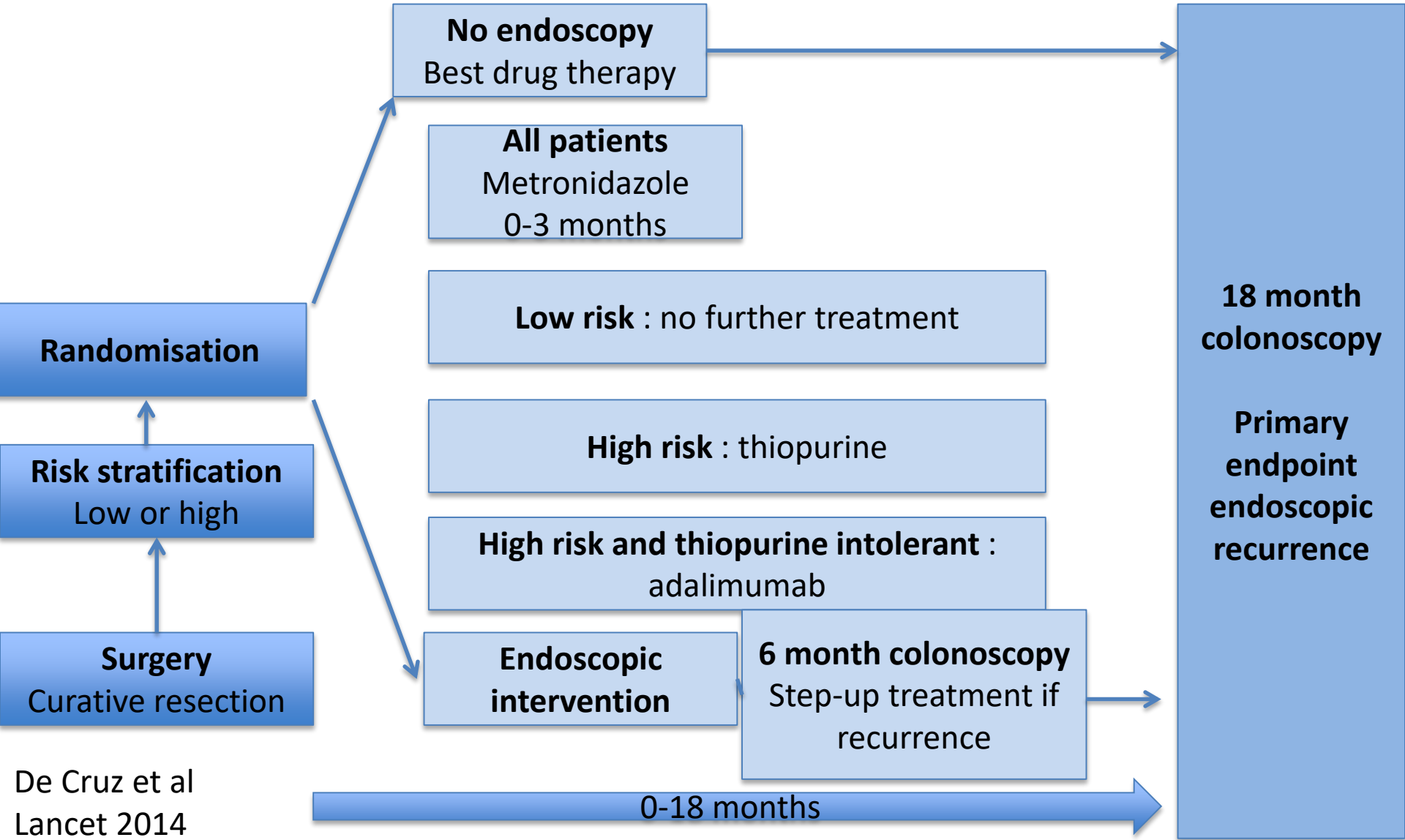
Louis E *et al* Gastroenterology 2012;142:63-70

How about Monitoring in postoperative CD

- Half of CD patients require surgery with 10 years after diagnosis
- Endoscopic recurrence within 1 year after surgery is 35%-85%
- Endoscopic recurrence preceeds clinical recurrence with approx. 1 year
- ECCO recommends endoscopic monitoring 6-12 months after surgery

Solberg IC *et al* Clin Gastro Hepatol 2007
Rutgeerts P *et al* Gastroenterology 1990
Annese V *et al* J Crohn's Colitis 2013

POCER the trial?

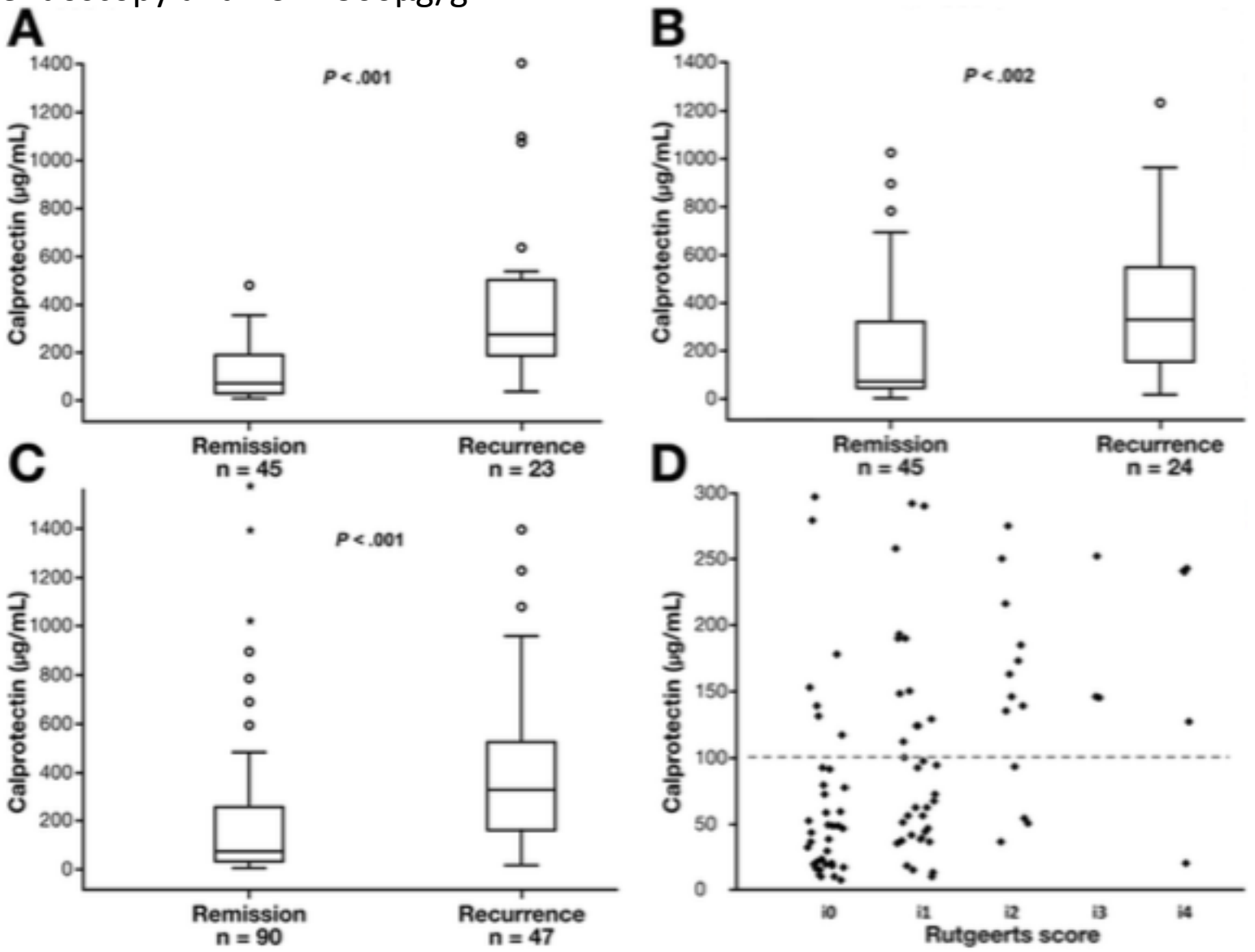


De Cruz et al
Lancet 2014

POCER trial sub-analysis

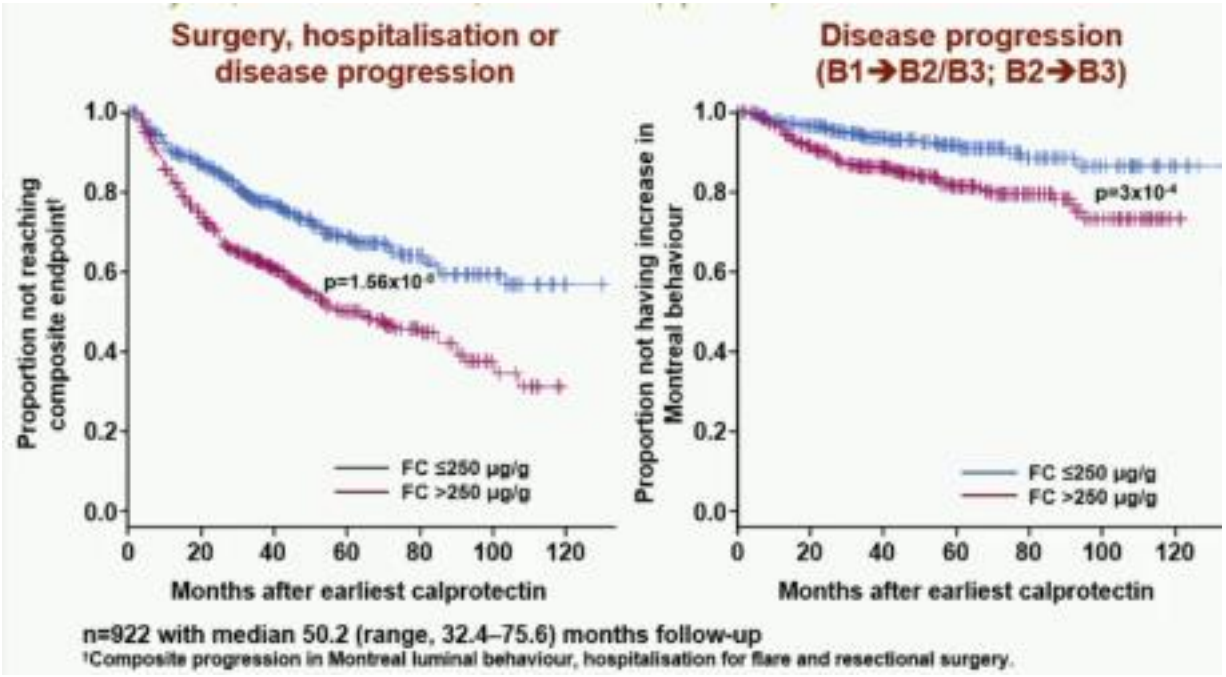
Endoscopic remission vs recurrence at 6 & 18 months

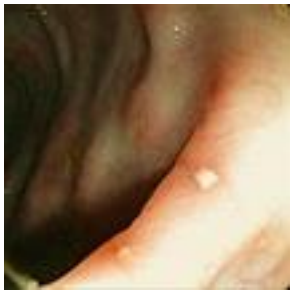
Matched endoscopy and FCP <300µg/g

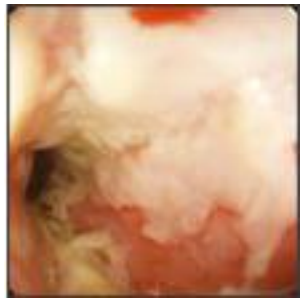


Wright EK et al Gastroenterology 2015;148:938-947

Calprotectin and disease progression





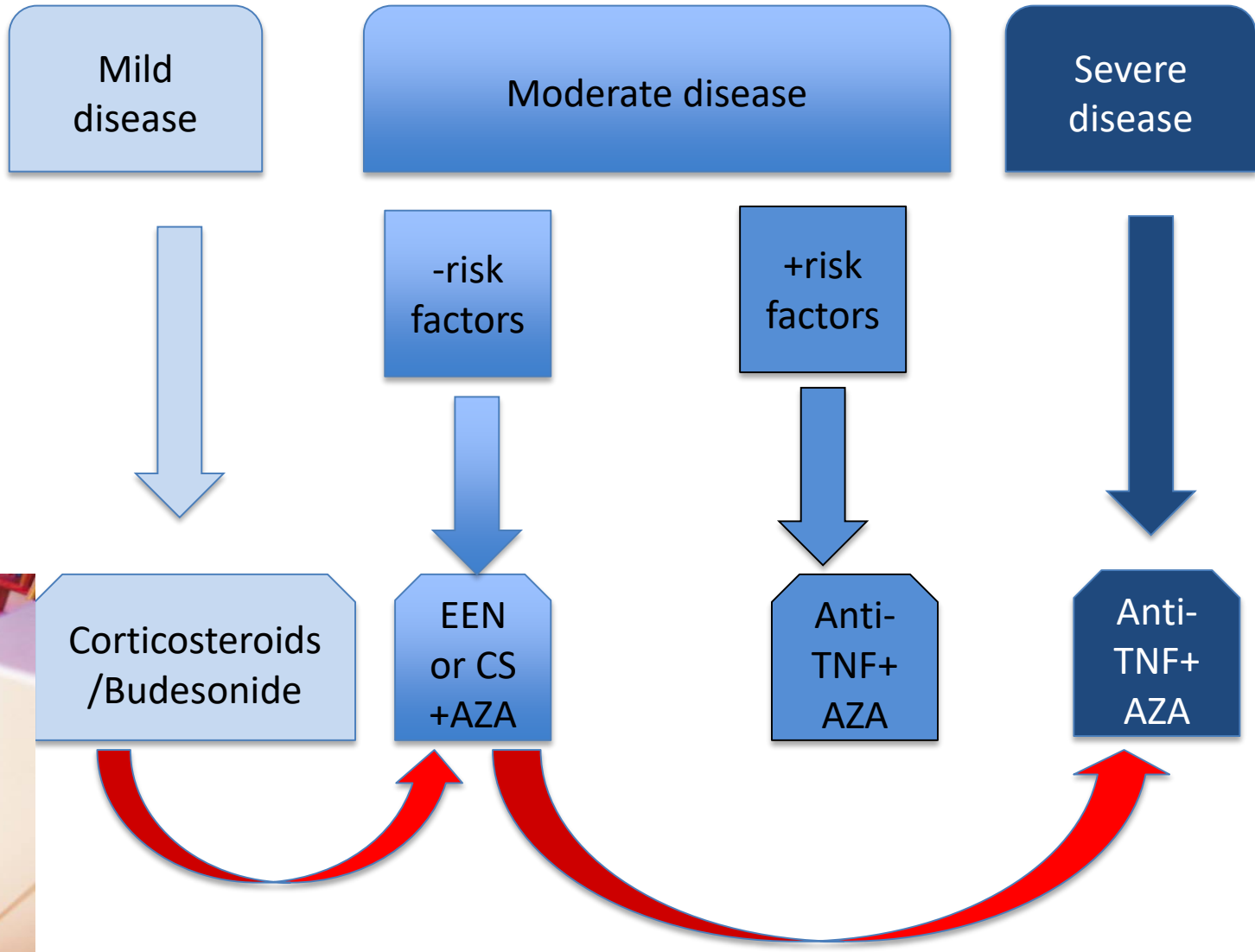


NB: Measuring the calprotectin helps decide on magnitude of inflammatory burden given the disconnect with symptoms

*****FC monitoring gives enough to help you decide the next step in therapy

Kennedy NA *et al* ECCO 2012 Poster P250

Tight monitoring



Biomakers in UC

- CRP
  - Reduction in CRP corresponds with response to treatment
  - CRP (and albumin) is predictive of colectomy
  - Correlation of CRP levels with mucosal healing is modest
  - ASUC on day 3, CRP > 45mg/L to decide for IFX/CSP
- Fecal calprotectin
  - Correlates with response to induction therapy
  - Is predictive of LOR to maintenance treatment
  - Correlates well with mucosal healing

Henriksen M et al Gut 2008
Cacheux W et al Am J Gastroenterology 2008

Take Home Messages

- Biomakers reflect residual intestinal inflammation.
- Biomakers **facilitate** the monitoring of a patient rather than being a target for treatment *per se*.
- Failure of CRP & FC normalization should prompt further endoscopic evaluation, irrespective of symptoms.

Take Home Messages

- Be aware of potential missed opportunities
- Remember 25% in CD do not express CRP above the normal threshold.
- There is **value** to monitor using both CRP and FCP
- Close monitoring……and act on the results of monitoring

Thank You