Dr. Ayaz Chowdhury

MBBS; FRACP

Dip. Clinical Epidemiology & Biostatistics

- **Dr. Ayaz Chowdhury** is a Senior Consultant Gastroenterologist at Sydney west Area Health Service. He was the first Bangladeshi Fellow of the Royal Australasian College of Physician awarded in 1994.
- Dr. Chowdhury is the current & Founder President of the Federation of Bangladesh Medical Societies of Australia representing over 1000 Bangladeshi Doctors. He has taught and provided Clinical Observership over 100 Bangladeshi Doctors in Australia over the last 33 years.
- He is the President of Bangladesh Forum for Community Engagement (BFCA) and had raised over 200 thousand dollars for both Cancer Council Australia and Dhaka Ahsania Mission Cancer and General Hospital.
- He is also the Goodwill Ambassador of Dhaka Ahsania Mission in Australia.

New Trends in the Management of IBD And Improving Patient Outcome

Dr. Ayaz Chowdhury

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Senior Consultant Gastroenterologist
Sydney West Area Health Service

Founder President
Federation of Bangladesh Medical Societies of Australia

Goodwill Ambassador Australia, Dhaka Ahsania Mission

IBD – CROHNS AND UC

- ‘Autoimmune’ disease
- Relapsing/remitting
- Dysregulation of inflammatory response by mucosal immune system to the microbiota that reside within intestinal lumen
  - Both due to excessive immune reactivity and inadequate immune response to intestinal microbiota.

Genetic Susceptibility

- 200 distinct susceptibility loci for IBD identified
- 70% genes shared between CD & UC
- Concordance rate for monozygotic twins markedly higher in CD than UC (50% vs 19%)
- First gene identified NOD2 (Crohns)
- 15% of IBD, 1st degree relative (CD > UC)
- Sibling with CD increase the risk of developing CD by 30 times compared to general population.
- Positive FH of IBD – strongest risk factor for developing IBD

Infection & Immune Response

- Implicated in the pathogenesis of IBD
- Association between acute gastroenteritis & IBD
- Salmonella & Campylobacter
- Possible role of mycrobactaria, viruses, fungi

IBD – CROHNS AND UC - PATHOPHYSIOLOGY

- Dysregulation of pro-inflammatory response to normal gut flora
- Infection + Failure of regulation + genetic susceptibility = clinical disease
- Damaged/defective barrier leads to increased permeability and uptake of antigens
- Pro-inflammatory response to normal flora leads to release of cytokines (IL-6, IL-1, IL-8, TNF-a), stimulating T-cell infiltration which amplifies the response
- Large numbers of T-cells and antibodies result in formation of lesions
- Variations in flora may be linked to disease severity and phenotype

IBD – CROHNS PATHOPHYSIOLOGY

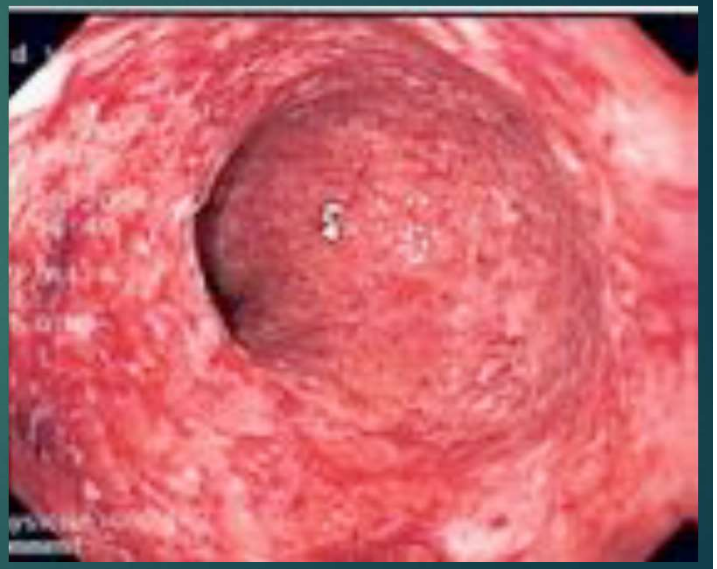
- Serosa – Dull grey. 'Fat wrapping'
- Mesentery – thickend, oedematous, fibrotic
- Intestinal wall – thickend (oedema, inflammations, fibrosis, hypertrophy of muscularis propria) = small lumen, strictures
- CD = sharp demarcation of affected bowel to healthy bowel (Skip lesions)

UC vs Crohns

	Ulcerative Coli's	Crohn's disease
Macroscopic		
Distribution	Rectum and Colon	GI tract
Rectum	Usually involved	Spared
Perianal disease	Rare	50%
Intestinal fistula	Rare	Common
Stricture	Rare	Common
Cobble stoning	No	Yes
Microscopic		
Bowel wall involvement	Mucosa and sub-mucosa	Full thickness
Granulomas	No	Yes
Fissures	No	Yes
Crypt abscesses	Common	Rare

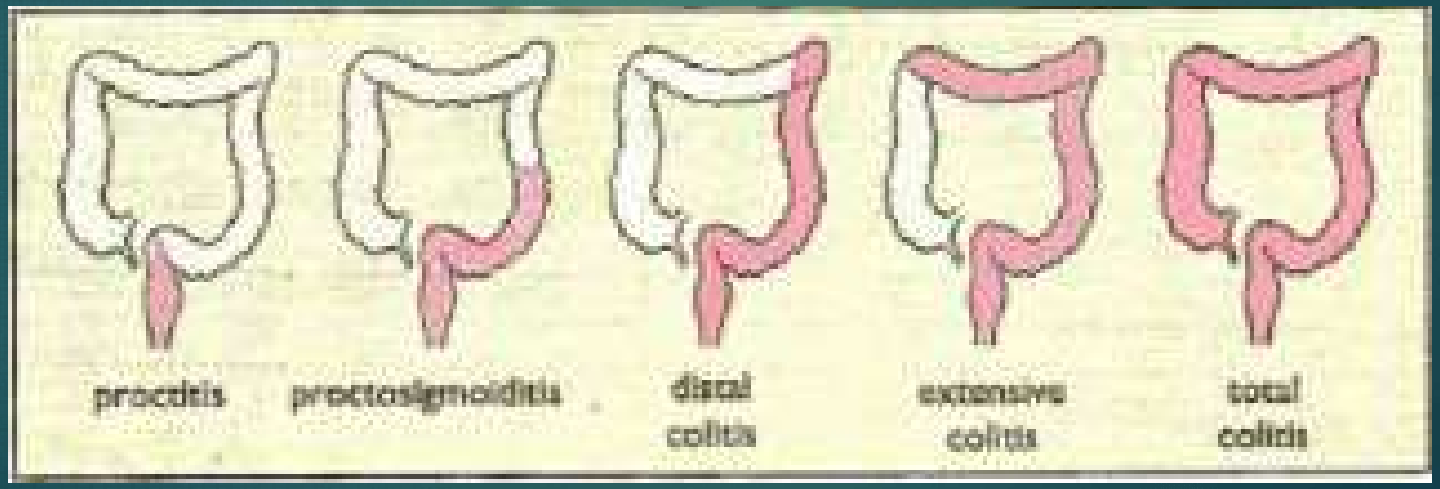
Ulcerative Colitis

- Disease of mucosal inflammation confined to the large intestine
- Patients usually diagnosed between 20 to 40 years of age.
- Equal prevalence in males & females
- Affects 160 per 100,000
- Usually controlled medically but 20 percent with pancolitis will come to surgery
- 10 percent of patents will present as an emergency



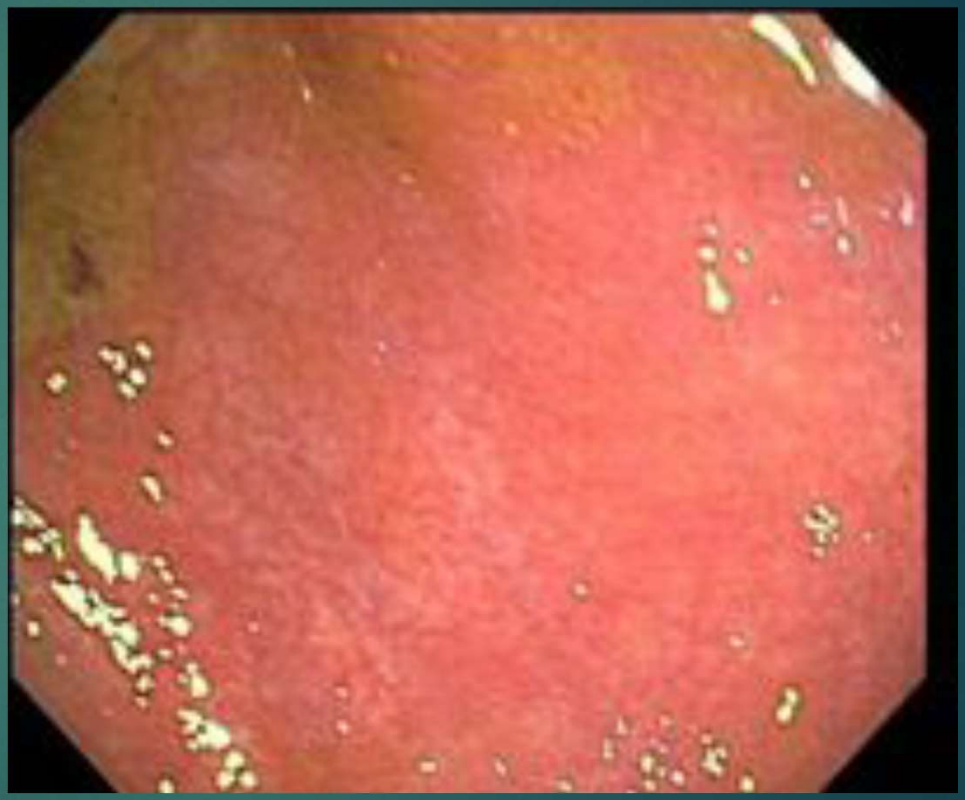
UC Presentation

- Rectum almost always involved
- 50 percent have disease confined to the rectum and sigmoid
- 30 percent will have extension into the left colon
- 20 percent will have total colitis



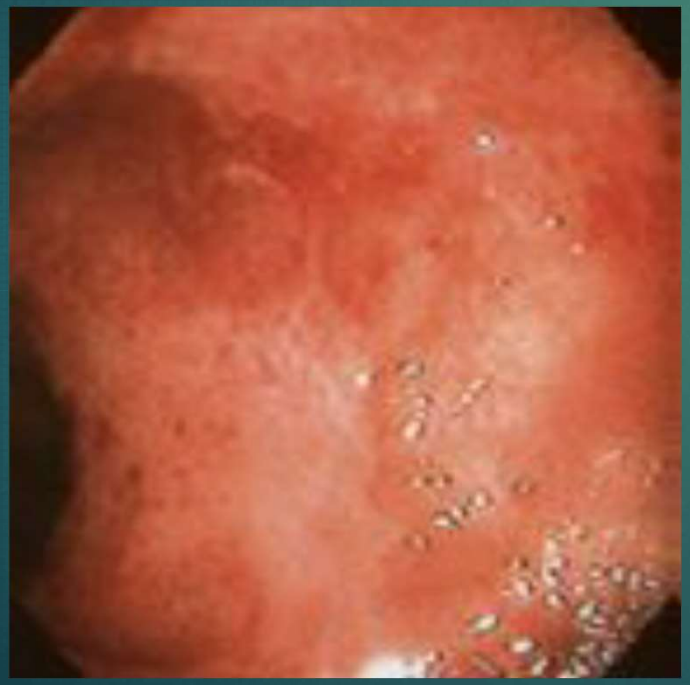
Grading: Mild Colitis

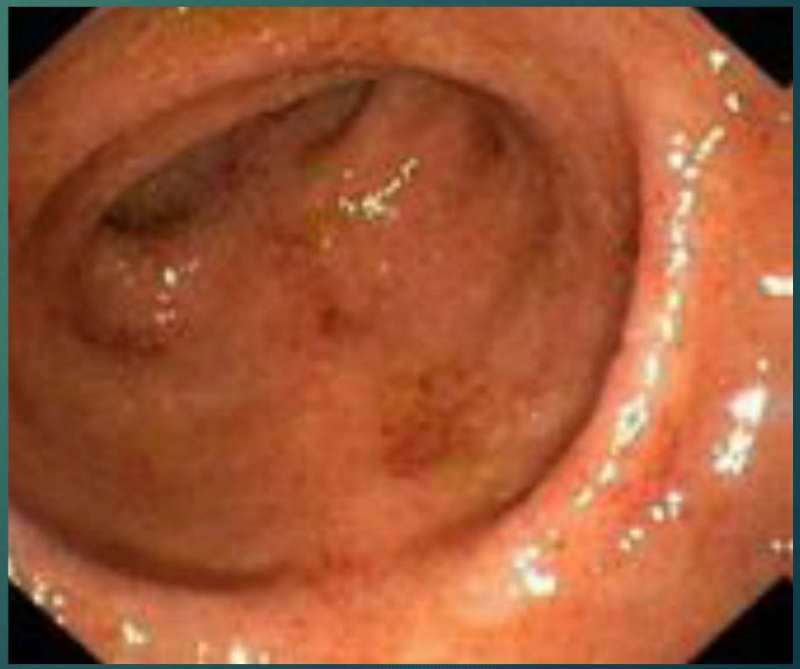
- Oedema, erythema, granularity, decreased vascular pattern
- No bleeding



Grading: Moderate Colitis

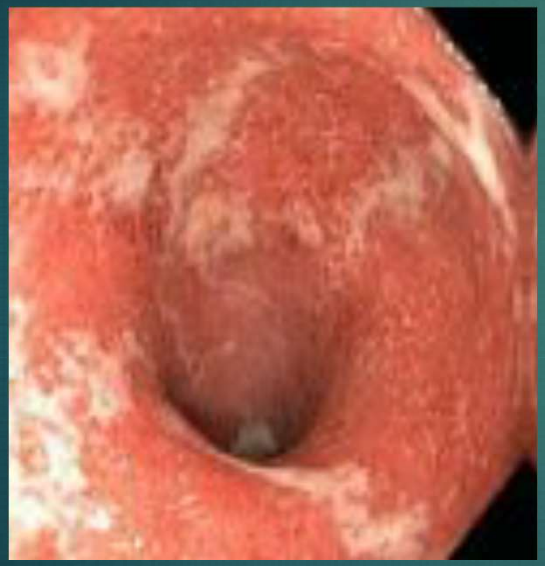
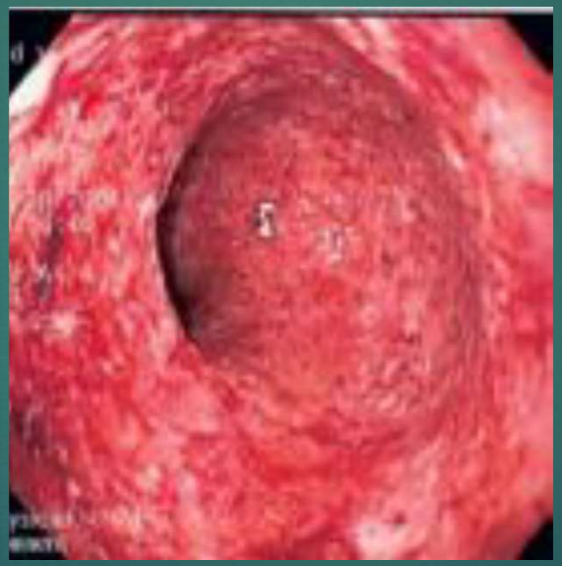
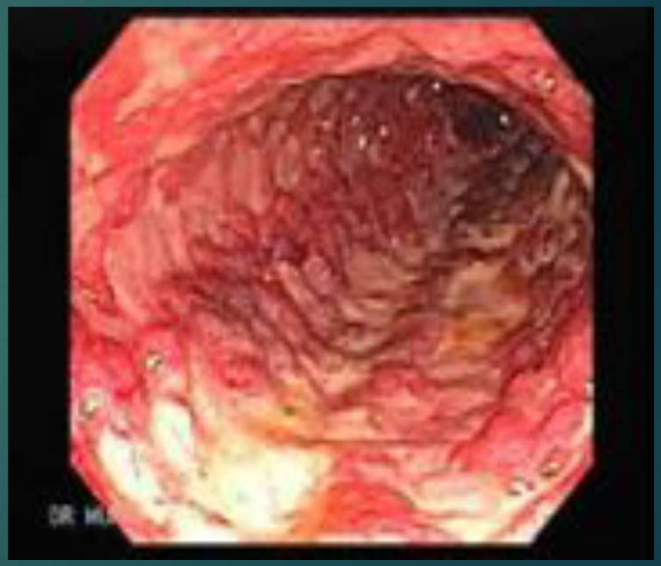
- Loss of vascular pattern, marked erythema,
- friability, contact bleeding and erosions (< 5mm)





Grading: Severe Colitis

- Spontaneous bleeding, marked exudate, ulceration (>5mm), deep or superficial.

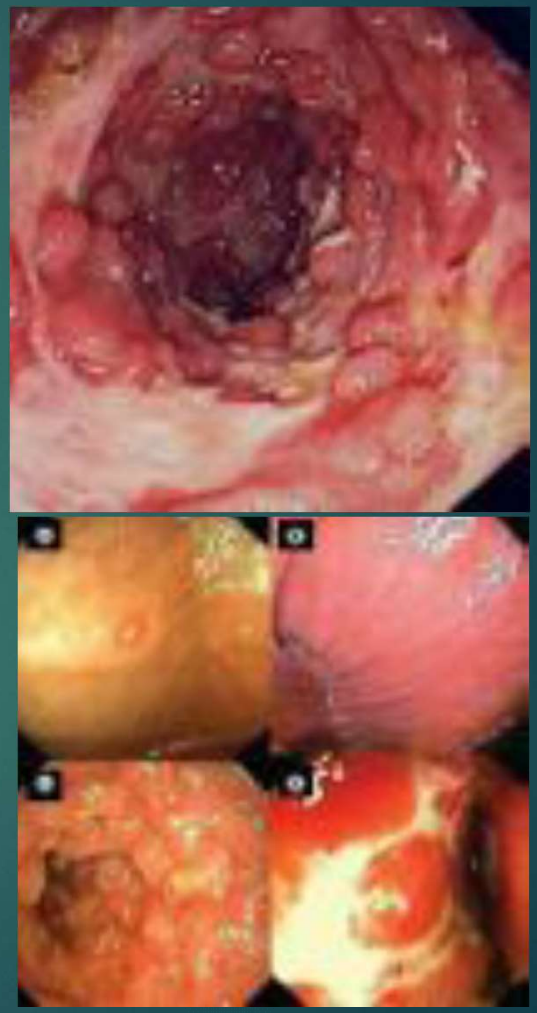




Risk Factors for Progressive disease (CD)

- Inflammatory CD was 50% at 20 years after diagnosis
- Ileal involvement associated with shorter time interval to onset of complications
- Age <40 years
- Tobacco use
- Perianal or rectal involvement
- Steroid requiring disease

Staging of Crohn's Disease

- As for UC
- Deep/extensive ulceration, cobblestoning
- Percentage of colon involved (e.g. 20%)
- <40 yo do a gastroscopy
- Describe Ileitis –
  - < 5 aphthous ulcers
  - > 5 aphthous ulcers, normal intervening mucosa
  - Diffuse inflammation and aphthous ulcers
  - Diffuse inflammation, large ulcers/nodules and/or stenosis



Diagnosis

- History
  - Depends on the site of involvement
    - Small bowel
      - Pain, weight loss & diarrhoea
    - Large bowel
      - Diarrhoea & bleeding

*No clinical difference in presentation between ulcerative colitis & Crohns Colitis except Crohns Colitis may have abdominal pain

Diagnosis

- Radiological
  - Chest X-Ray
  - CT or MR Enterography
  - Pelvic MRI/ Endoanal US
  - Trans abdominal US
- Endoscopy & Histology
  - Gastroscopy & Colonoscopy
  - Enteroscopy
  - Capsule Endoscopy (Must be preceded by CTE or MRE)

Laboratory Studies

- **Blood tests**
  - FBC, UEC, LFT, CRP, Iron Studies, B12, Vit D, TSH, Glucose
  - ANCA, ASCA, Coeliac
  - Quantiferon Gold assay for TB
  - Serology for chronic hepatitis B & C, pneumococcus, varicella zoster, Mumps, measles, Diphtheria, EBV & CMV
- **Stool Examination**
  - Testing for enteric pathogen including C.Dificille infection
  - WBC, RBC
  - Fecal Calprotecting

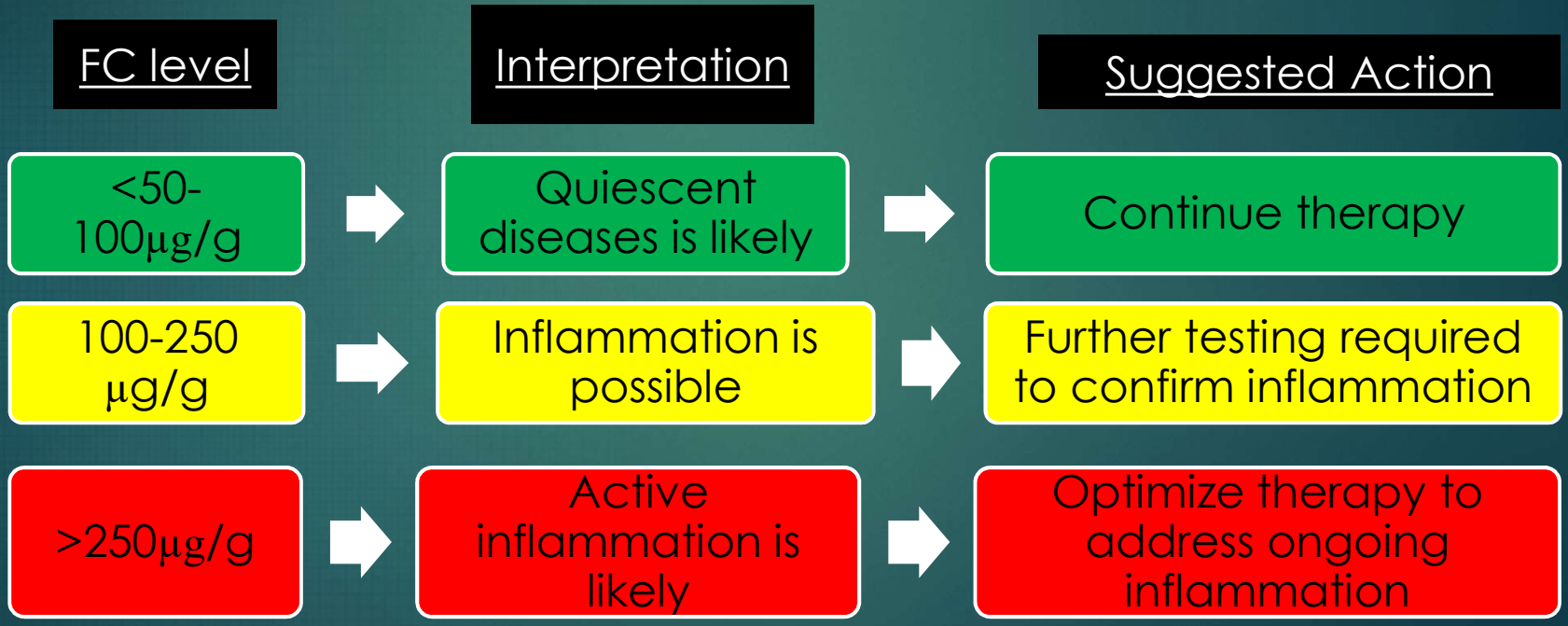
Clinician's Guide to Fecal Calprotectin

- 60% of neutrophil cytosol protein

  Secreted extracellulerly by stimulated neutrophils and monocytes

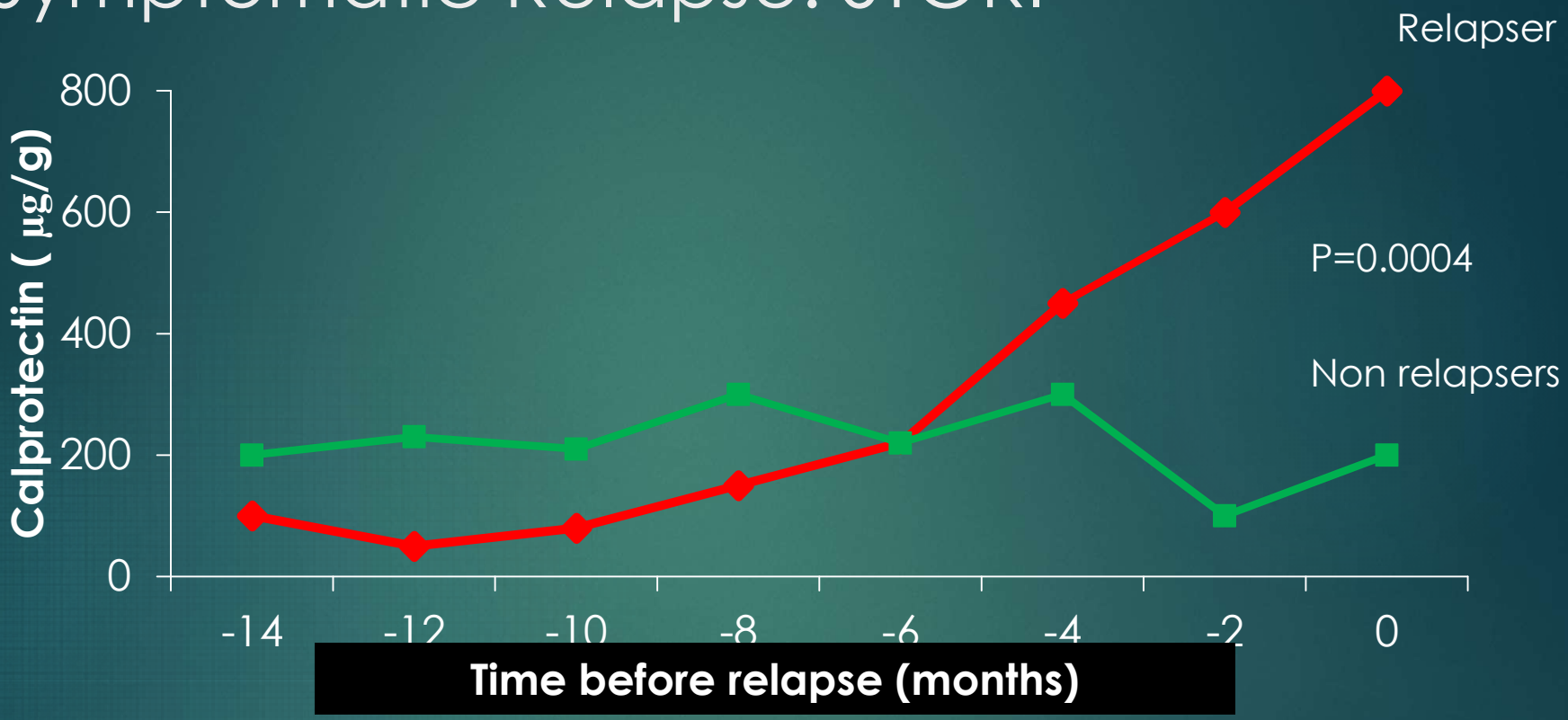
  Fecal concentration correlates with inflammation

- Stable for up to one week at room temperature



Bressler B .Can J Gastroenterol Hepatol 2015;29:36

Rising Fecal Calprotectin Predicts Symptomatic Relapse: STORI

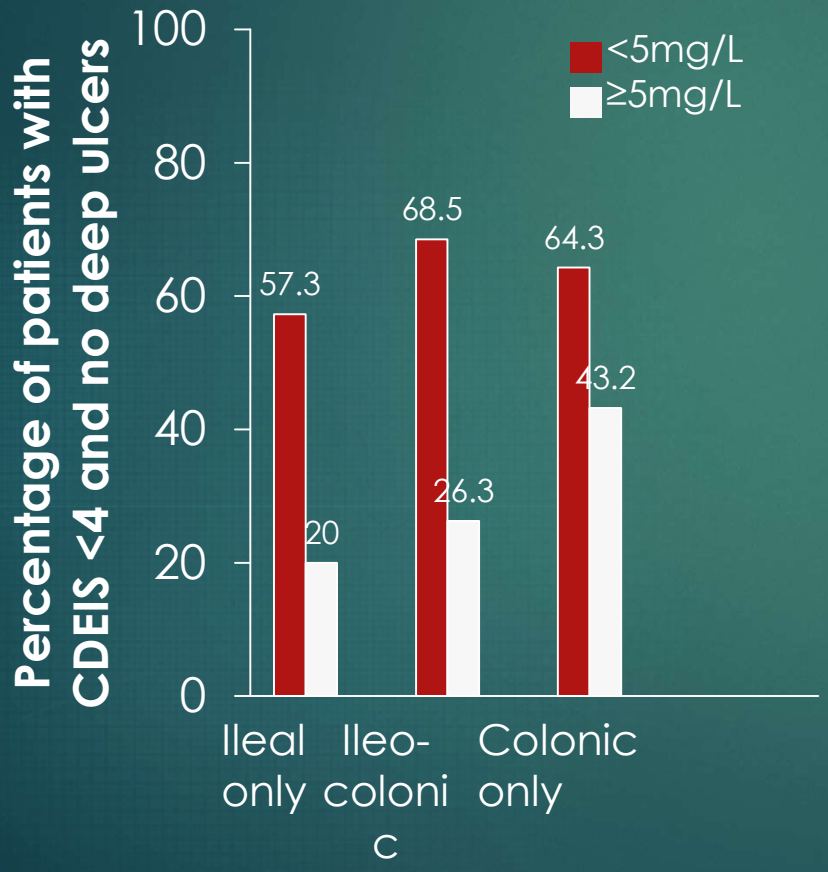


- Prospective study of 113 CD patients treated with scheduled IFX+ IS for at least one year.
- IFX stopped in patients in symptom free remission for ≥ 6 months
- Single FC >300 mg/kg : sensitivity 58.3% and specificity 93.3%fpr flare
- Two FC >300mg/kg: sensitivity 61.5% and specificity 100% for flare

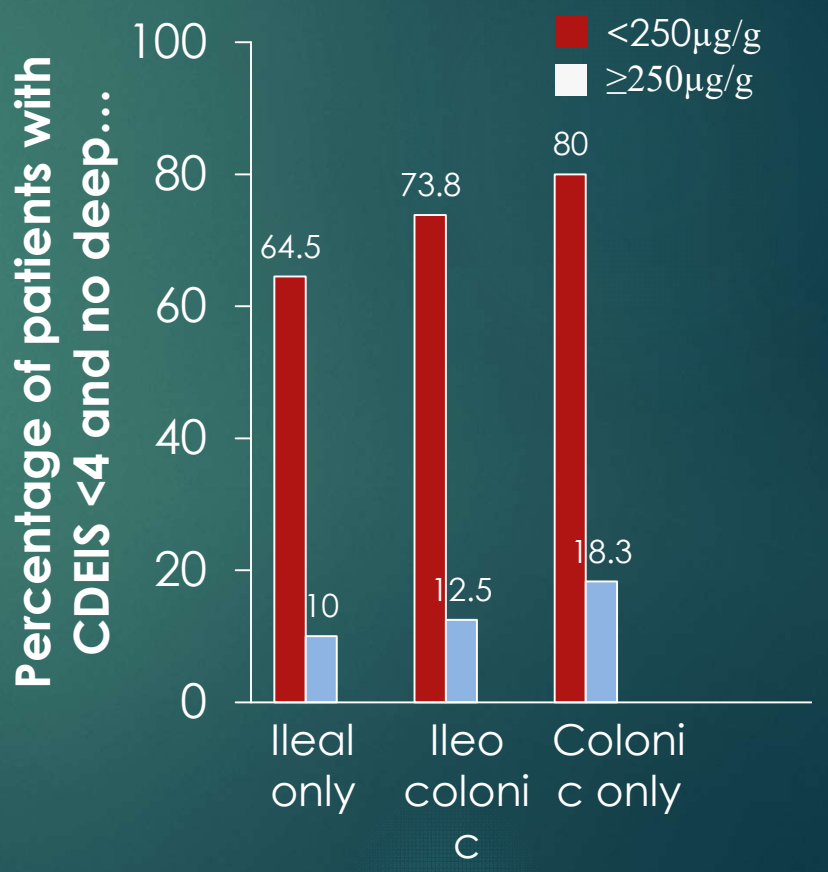
De Vos M Inflamm Bowel Dis 2013

Proportion of patients with CDEIS <4 and no deep ulcer by biomarker cut offs at 48 weeks and by disease location at baseline

C reactive protein

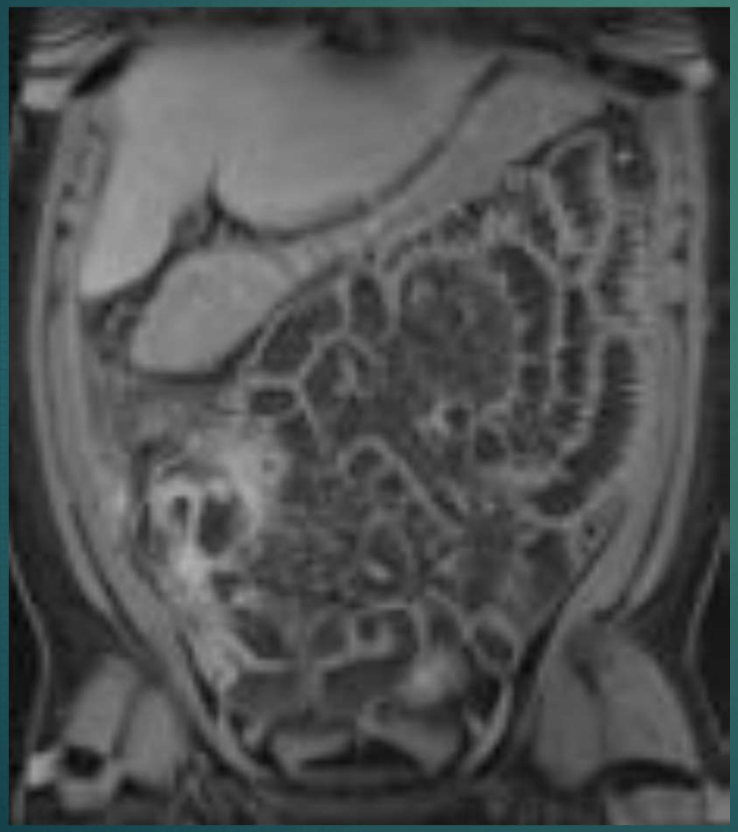


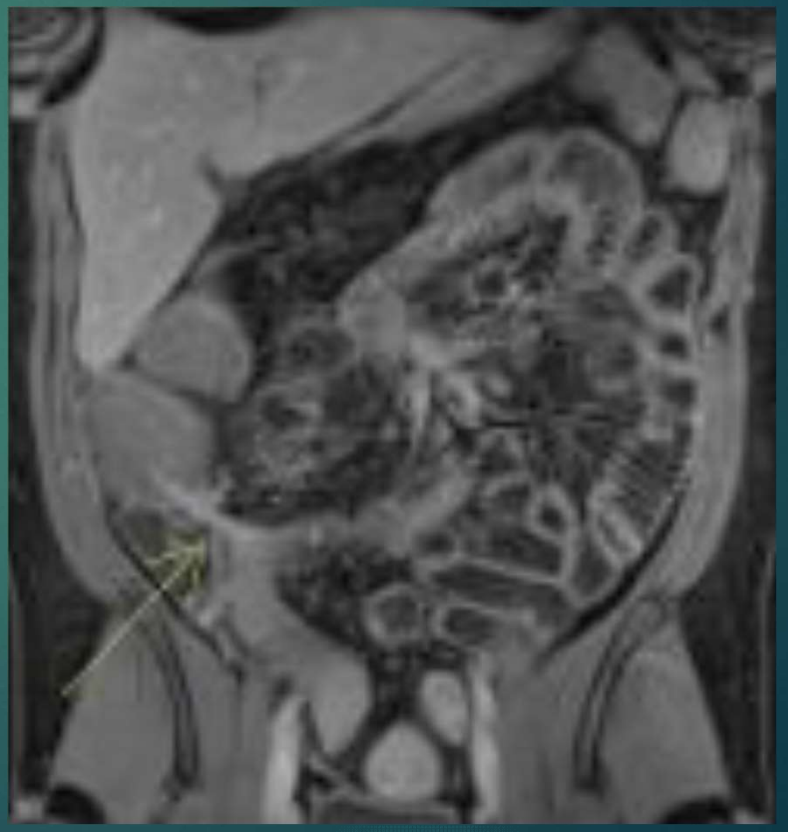
Faecal calprotectin



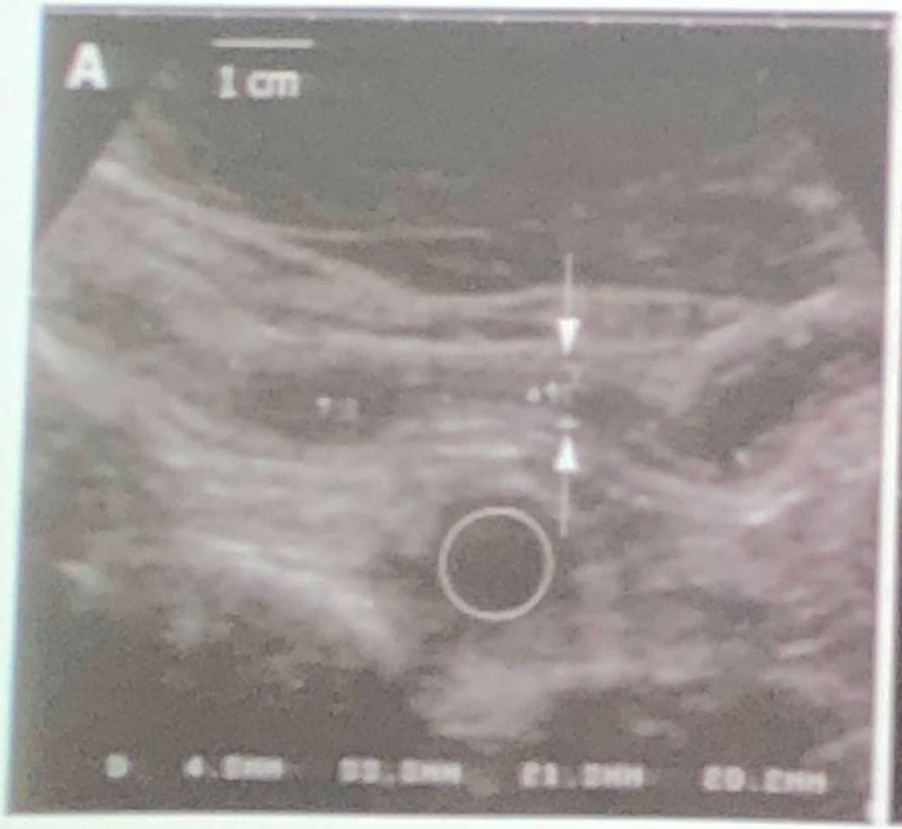
MR Enterography

MRE demonstrated ileocolic fistula between TI and mid sigmoid, enhancement and thickening involving approximately 5cm of terminal ileum, in keeping with terminal ileitis



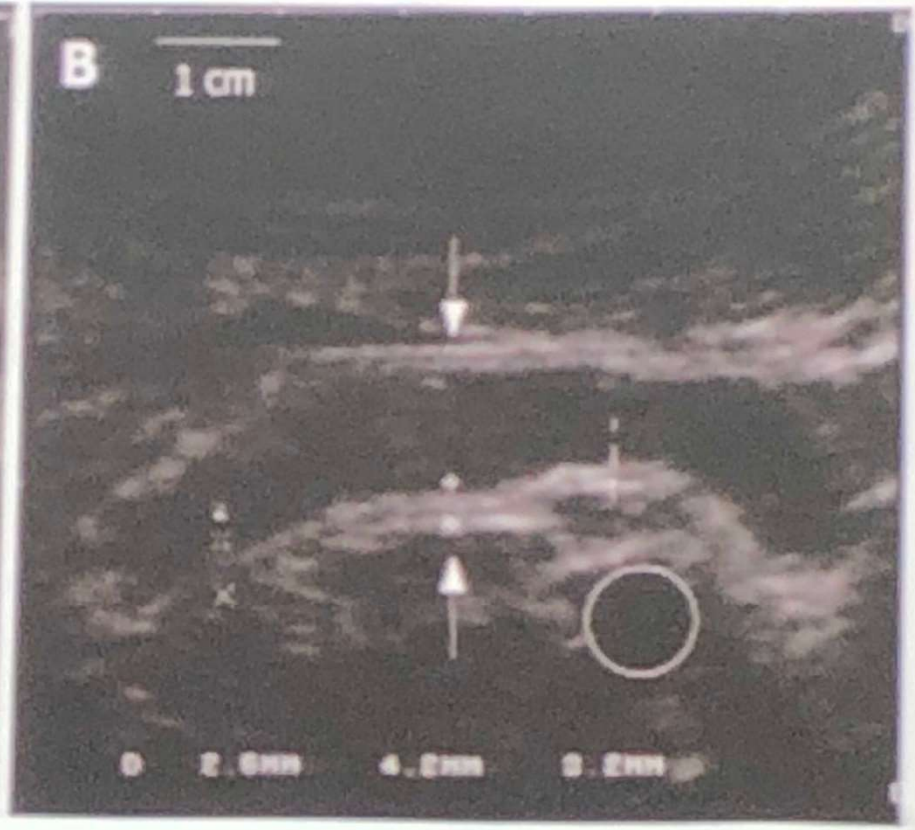


Before adalimumab



Narrowed lumen with thickened intestinal wall

After adalimumab at Week 12



Widely patent lumen with significant reduction of intestinal wall thickening

Medical management - UC

Goals:

- Clinical remission, endoscopic and histological remission
- Clinical and endoscopic remission after 6/52 of acute treatment are less likely to relapse than if clinical remission alone

Proctitis

- Mesalazine sup (1-1.5g/day nocte or divided)

Mild-mod distal colitis (30-40cm)

- Mesalazine enema (4g nocte) is preferred (60% remission)
- If no response in 2-4/52, add mesalazine or hydrocortisone enema
- Oral mesalazine can be used if declines enema
- IV/PO steroids only if refractory to steroid enama or 5-ASA compounds

Mild-mod extensive colitis

- Oral mesalazine (3 – 4.5g/day) +/- mesalazine enema
- If not responding to oral mesalazine, PO pred which is tapered once remission
- Thiopurines (6-mercaptopurine, AZ) if steroids not tolerated or cannot come off steroids
  - Slow onset and prolonged Rx (3-6mths) needed
- Failing this, biologic agents

Azathioprine & 6-MP in IBD (1) (Immunodulator)

- AZA-Prodrug converted to 6-MP
- TPMT genotype & TPMT enzyme activity
- AZA initiated at 50mg and increased over 12 weeks (max 2.5mg /kg daily)
- 6-MP initial dose 50mg increased over 12 weeks (max 1.5mg /kg daily)
- FBC (Lymphocyte), LFT and amylase q 2 weeks
- Therapeutic response observed after 3 months

Azathioprine & 6-MP in IBD (2)

- Side affects
  - Dose Dependent
    - Bone marrow suppression
    - Hepatotoxicity
  - Dose Independent
    - Nausea & vomiting
    - Pancreatitis
  - Increased Risk of Infection
  - 6-TG & 6-MMP levels to predict toxicity with history of Lymphopenia or elevated LFT
  - 6-TG (230 – 400 preferred); 6-MMP >5000 predicts liver toxicity

Azathioprine & 6-MP in IBD (3)

- Malignancy
  - Lymphoma
  - Hepatosplenic – T cell lymphoma
  - Skin Cancer (non-melanotic)
- Fertility
  - Relatively safe

Advanced Therapies for IBD

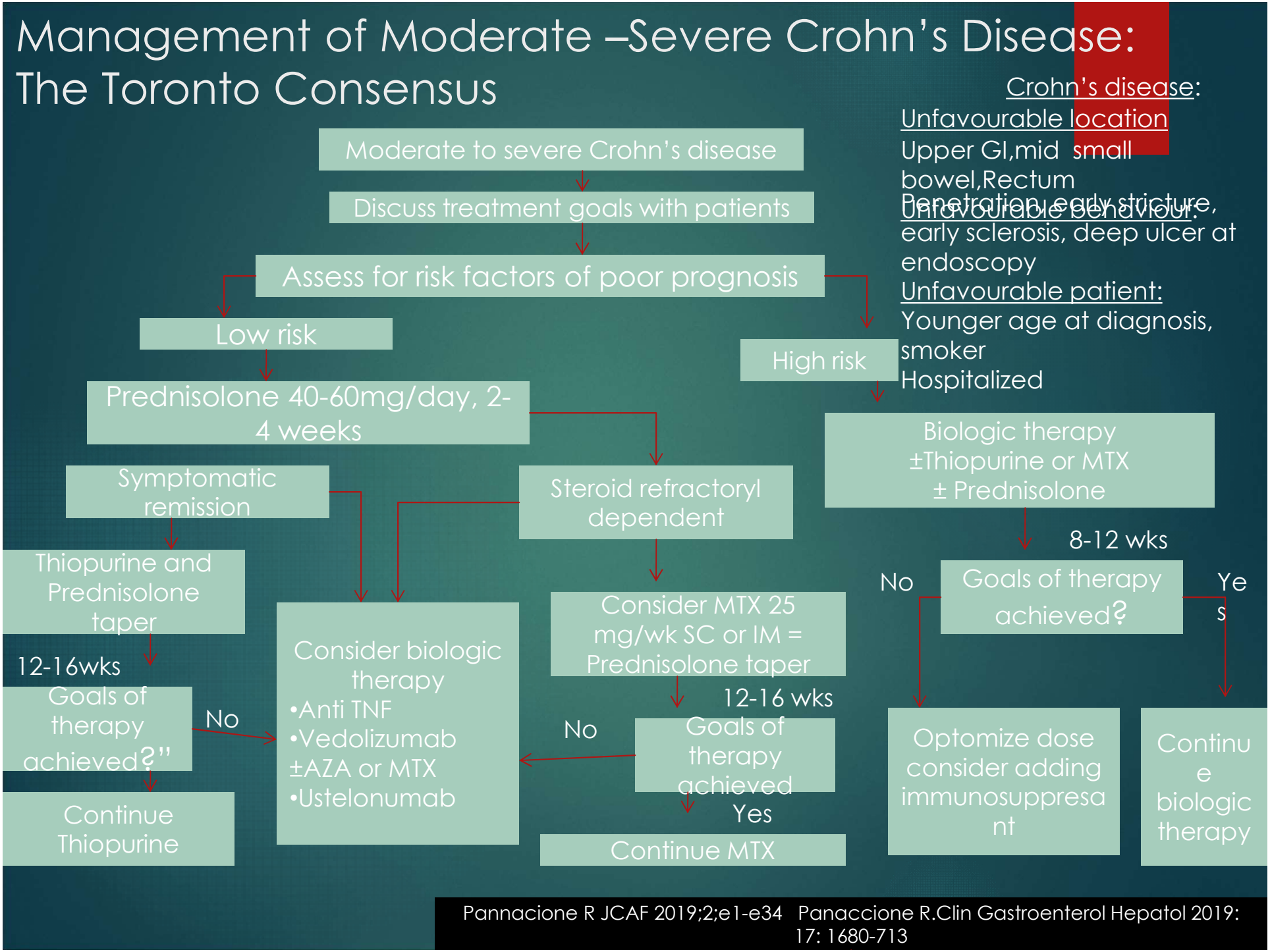
Class	Agent	Indication		Route of Administration	Standard Dose Regimen
		Crohn's disease	Ulcerative colitis		
Anti TNF alpha	Adalimumab	Yes	Yes	Subcutaneous	160/80 mg wks0/2 Then 40mg q2 wks
	Certilizumab	(yes)*		Subcutaneous	400mg wks0/2/4 then 400mg q4 wks
	Golimumab		Yes	Subcutaneous	200mg then 100mg Then 100mg q 4 wks
	Infliximab	Yes	Yes	Intravenous	5mg/kg wks0/2/6 Then 5mg/kg q 8 wks
Anti - Integrin	Vedolizumab	Yes	Yes	Intravenus	300mg wks 0/2/6 Then 300mg q 8 wks
	Natalizumab	(Yes)*		Intravenus	300mg wks 0/4/8 Then 300mg q 4 wks
Anti IL 12/23	Ustekinumab	Yes		Intravenous then Subcutaneous	~6mg/kg then 90mg q8 wks
JAK Inhibitor	Tofacitinib		Yes	Oral	10mg BID for 8 wks Then 5mg BID

*not approved in Canada/Australia

Induction Therapy

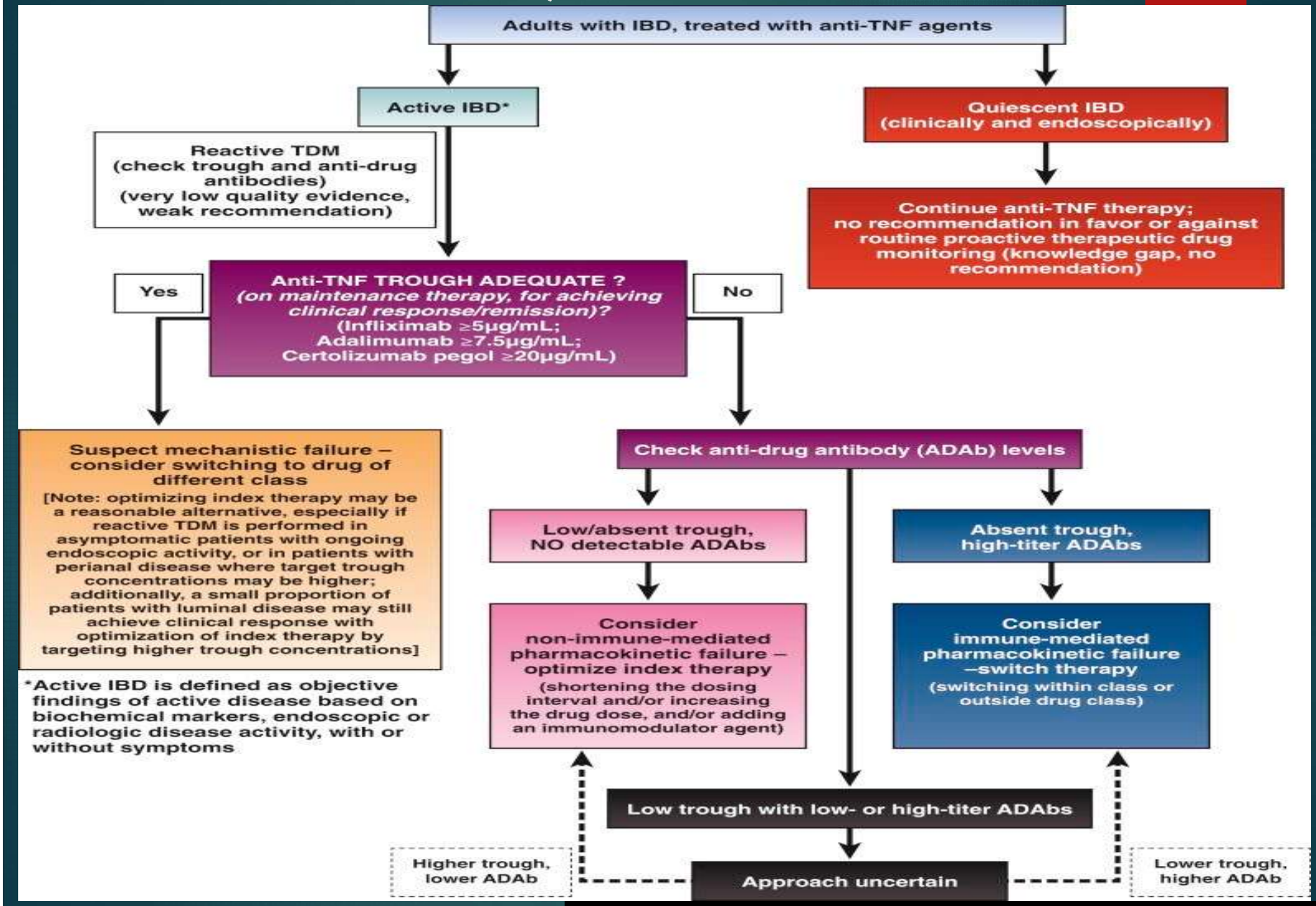
- Combination Therapy
  - Top down approach using biologic agents in combination with an Immunodulator
- Two different mechanism of action and synergistic affect of the combination of drugs
- To reduce immunogenicity against biologic therapy which is highest when the biologic agent is first started
- To improve the pharmacokinetics of biologic therapy
- TNF Monotherapy as Induction Therapy
  - Patients over 60
  - Young Male (Biologic + MTx)
  - Increased risk of Infectious complication or malignancy

Management of Moderate –Severe Crohn's Disease: The Toronto Consensus



Pannacione R JCAF 2019;2;e1-e34 Panaccione R.Clin Gastroenterol Hepatol 2019: 17: 1680-713

Adult with IBD, treated with anti-TNF



Gastroenterology 2017;153/(3)853-859 dci:10 1053/j gastro 2017.07.039

Consensus on TDM for Anti-TNF Therapy in IBD

IBD Sydney Organization and Australian IBD Consensus Working Group

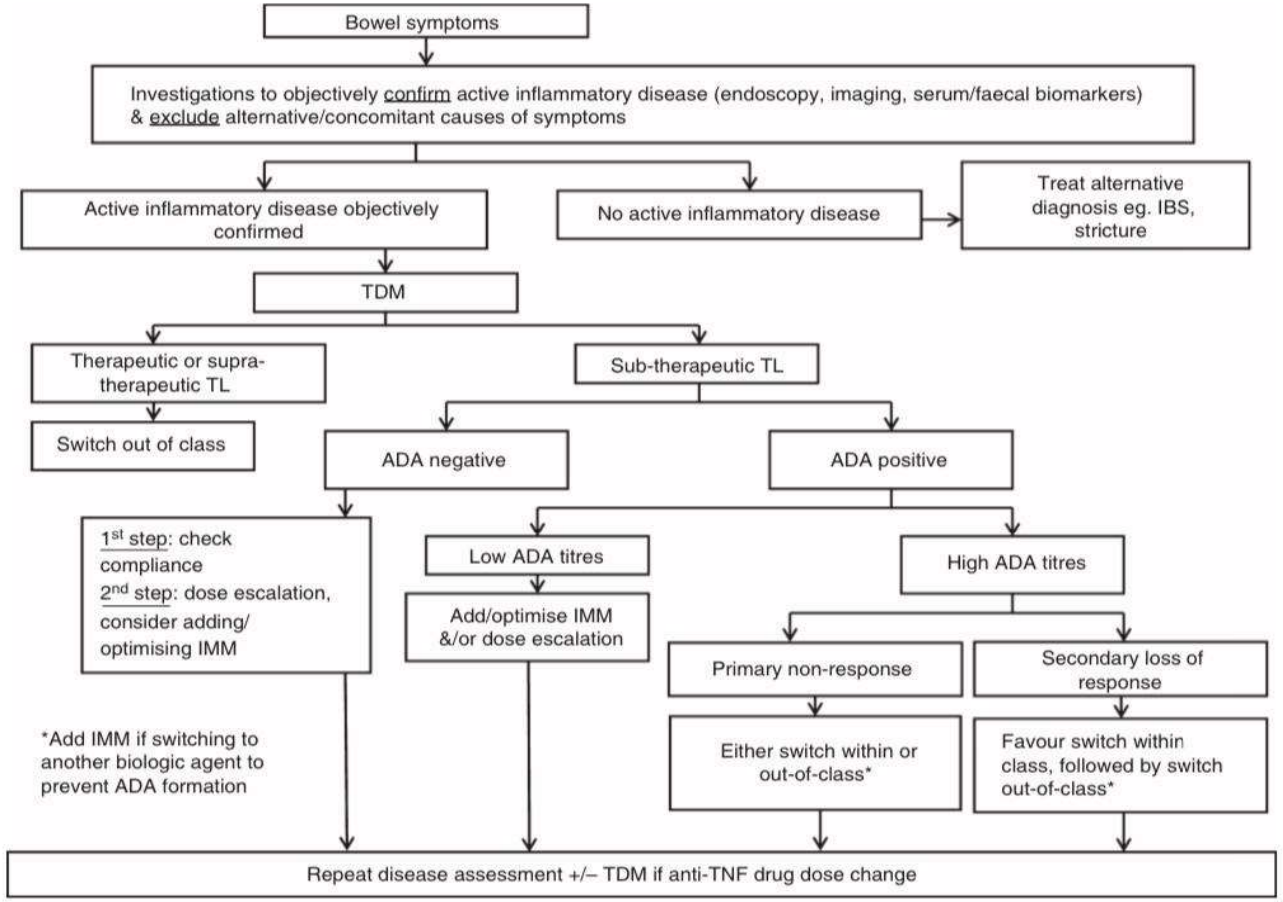


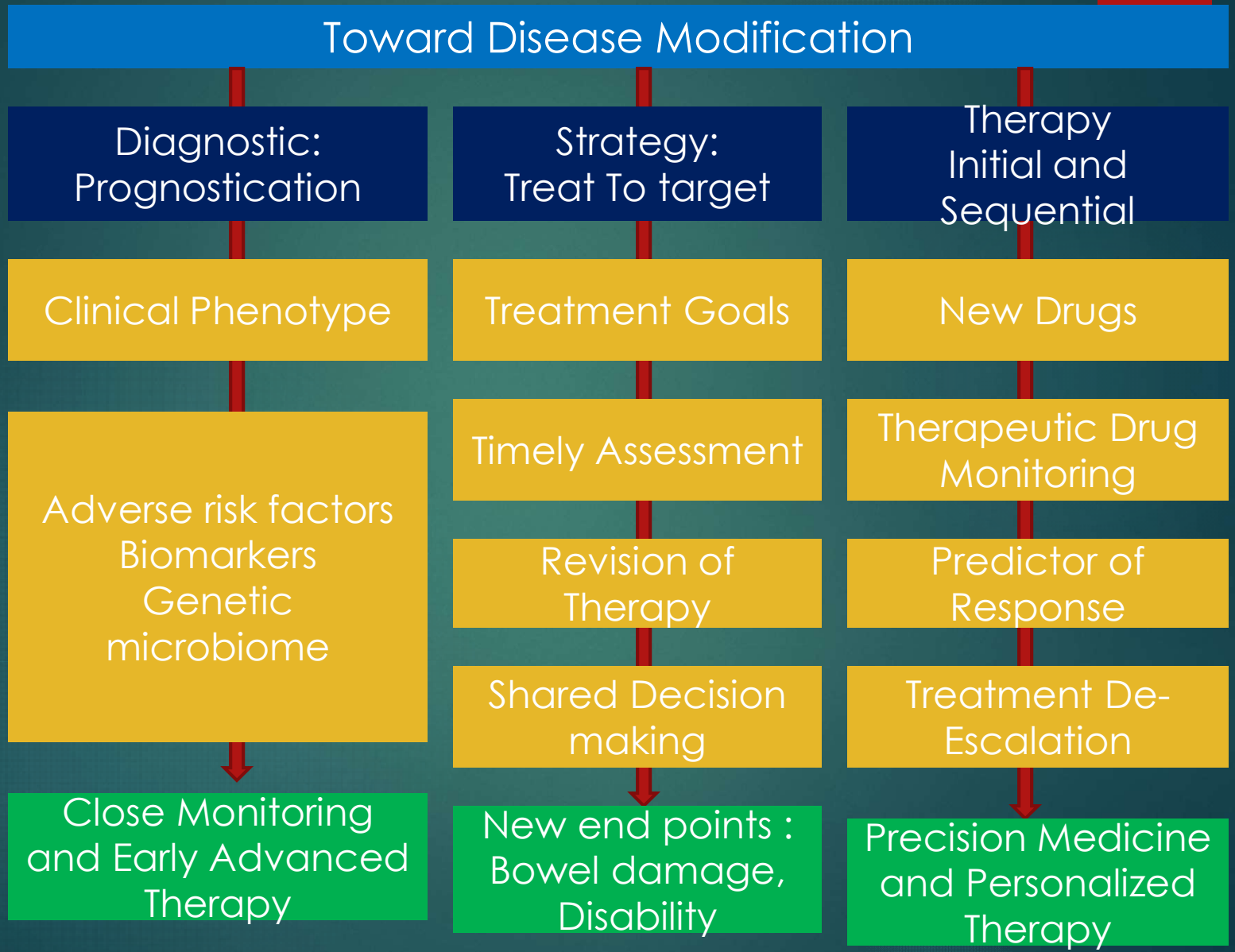
FIGURE 1 Interpreting TDM results in patients with bowel symptoms while on anti-TNF therapy. Evidence for this algorithm is mainly in secondary loss-of-response; however, it may also be used to elicit mechanisms of failure and guide treatment decisions in primary nonresponders. ADA, anti-drug antibodies; TDM, therapeutic drug monitoring; IMM, immunomodulator; IBS, irritable bowel syndrome; TL, trough level

Trough Target IFX 3-8 mcg/ml

ADA=5-12 mcg/ml

Mitrev N. Aliment Pharmacol Ther 2017;46:1037-53

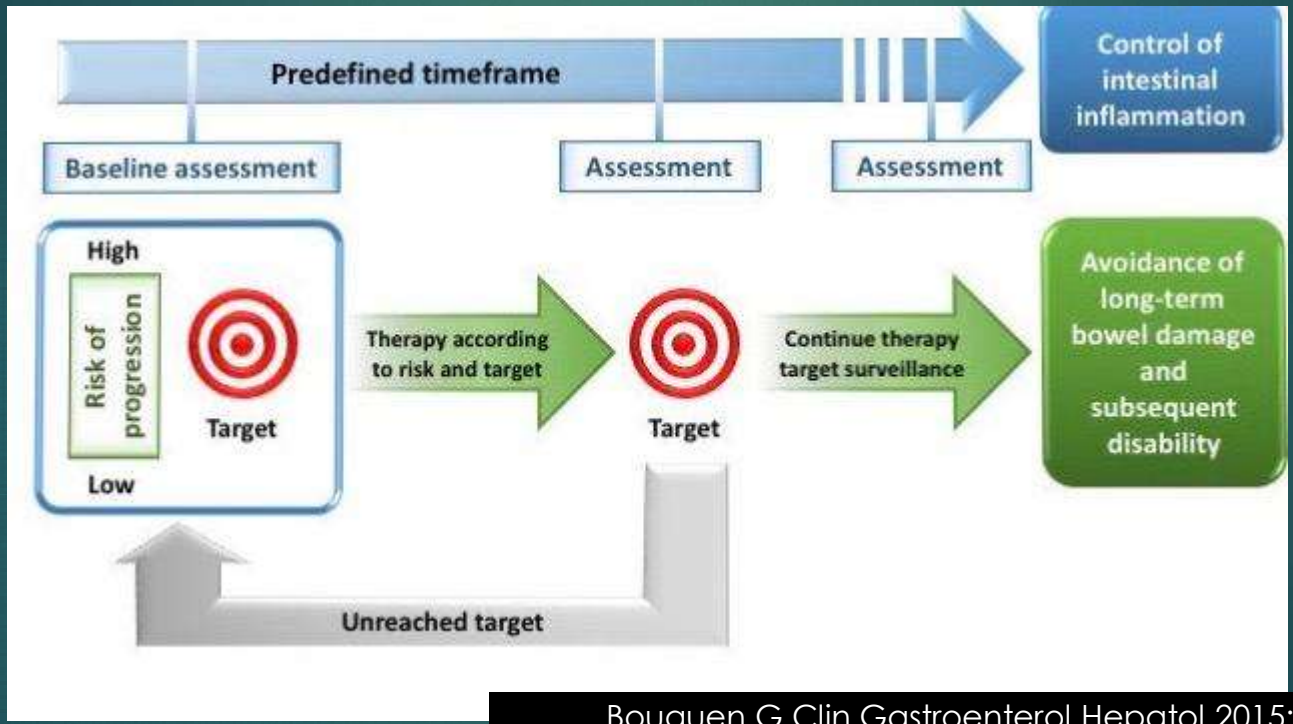
New Trends In IBD



Palema C.GE Port J Gastroenterol 2015;11:10


Normal Quality of Life
Normal Life expectancy
Freedom from Disability
Improved symptoms
Mucosal Healing
Clinical Remission
No Steroid

Treat-to-Target Concept in IBD



Bouguen G Clin Gastroenterol Hepatol 2015;13z;1042-5C

Treating to Target in IBD: STRIDE Working group

Both Clinical and Endoscopic Remission are

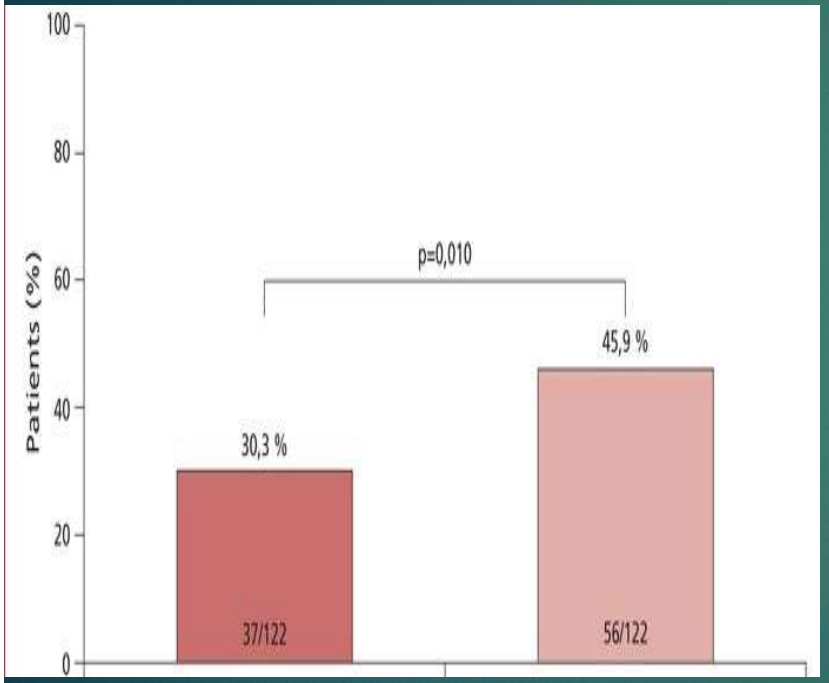
Crohn's Disease
Clinical (pro) remission
Resolution of abdominal pain AND Normalization of bowel habit (Assess at minimum of 3 months)
Endoscopic Remission:
Absence of ulceration (Assessed after 6-9 months of therapy) (Cross-sectional imaging as alternative)
Biomarkers (CRP and fecal calprotectin are adjunctive measures Histologic remission is not a target

Ulcerative Colitis
Clinical (pro) Remission
Resolution of rectal bleeding AND Normalization of bowel habit (Assess at minimum of 3 months)
Endoscopic Remission:
Mayo Endoscopic sub score 0-1 (Intervals of 3-6 months in active phase And 12-24 months if asymptomatic)
Biomarkers (CRP and fecal calprotectin) and histologic activity adjunctive measures Cross-sectional imaging is not a target

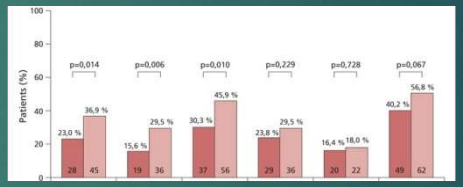
Peyrin-Biroulet L.Am J Gastroenterol 2015;110:1324-

CALM : Conventional Management vs. "Treat to Target" in Crohn's Disease

Open Label Multicenter Study comparing Tight Control (monitoring symptoms and biomarkers) to symptom-driven management



Clinical management
Tight control (n=122)



Clinical management

Tight control

Deep remission

Biological remission

CDEIS <4

CDEIS<4 plus CDEIS<4 in all segments

Complete Endoscopic remission

Endoscopic response

Colombel JF.Lancet 2018;390:2779-89

Anti-TNF Agents: AGA Institute Guidance on Therapeutic Drug Monitoring

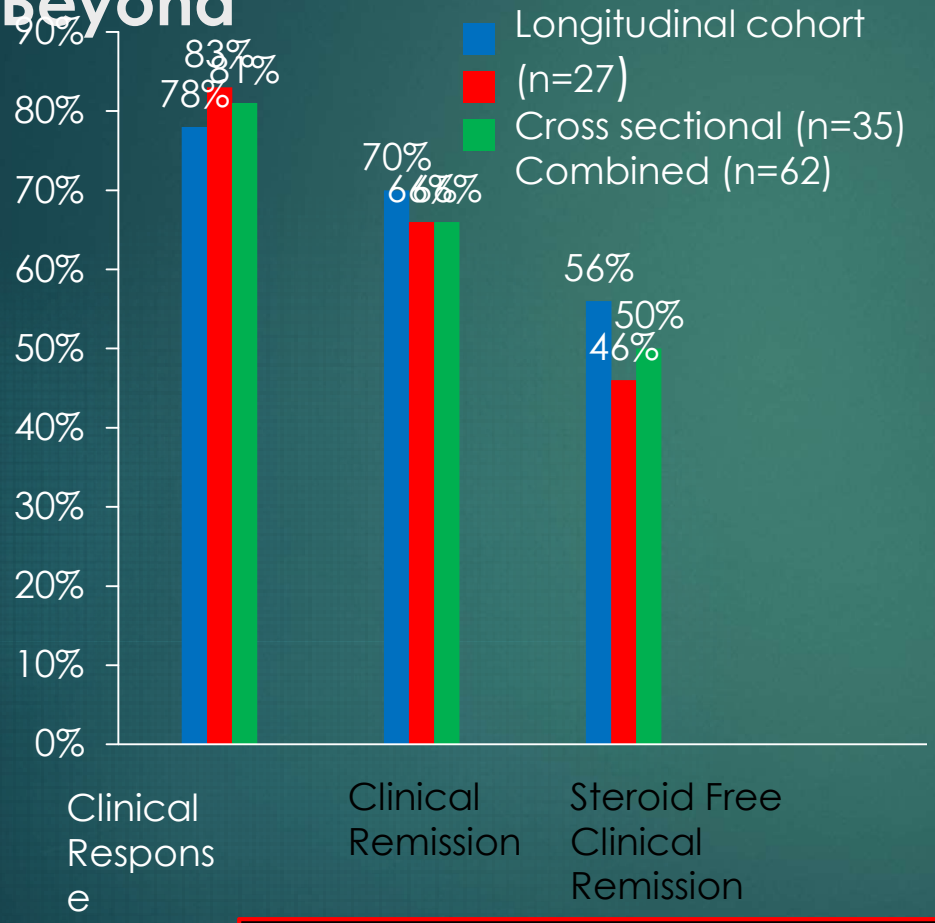
- In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes
- Target trough levels:

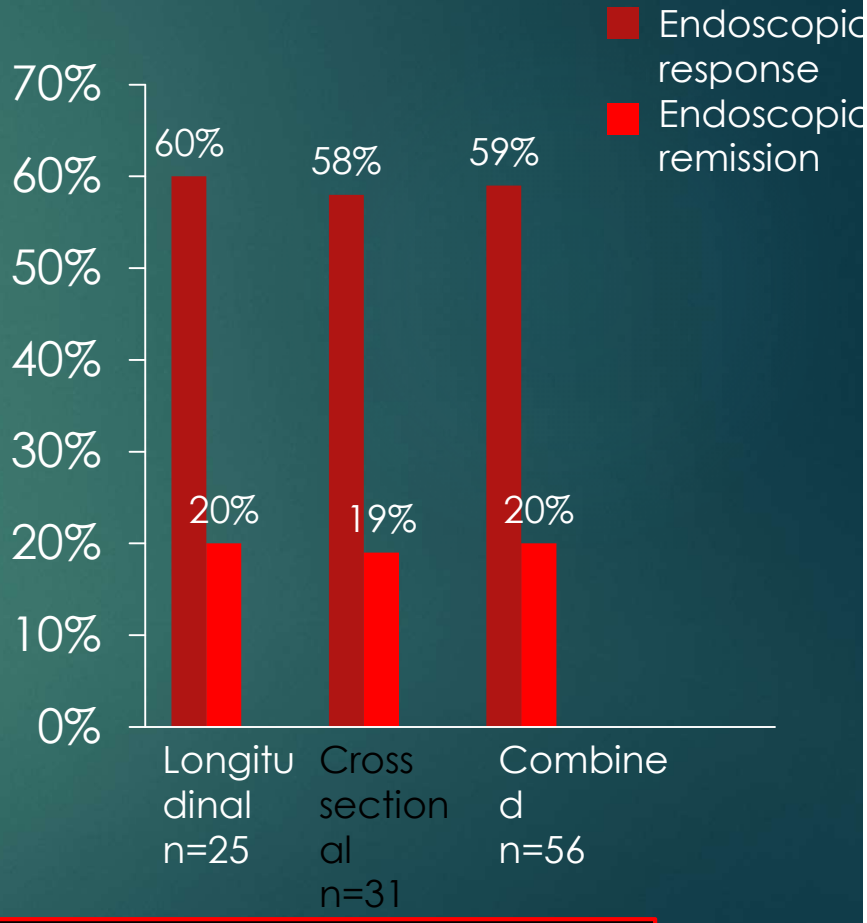
Infliximab	5.0 mcg/ml
Adalimumab	7.5mcg/ml
Certolizumab	20mcg/ml
Golimumab	Unknown

- Subgroups (e.g. fistulizing and severe endoscopic disease) may respond to higher target concentrations

Ustekinumab Therapy for Crohn's Disease Refractory or Intolerant to TNF Inhibitors

Clinical and Endoscopic outcomes at week 26 or Beyond

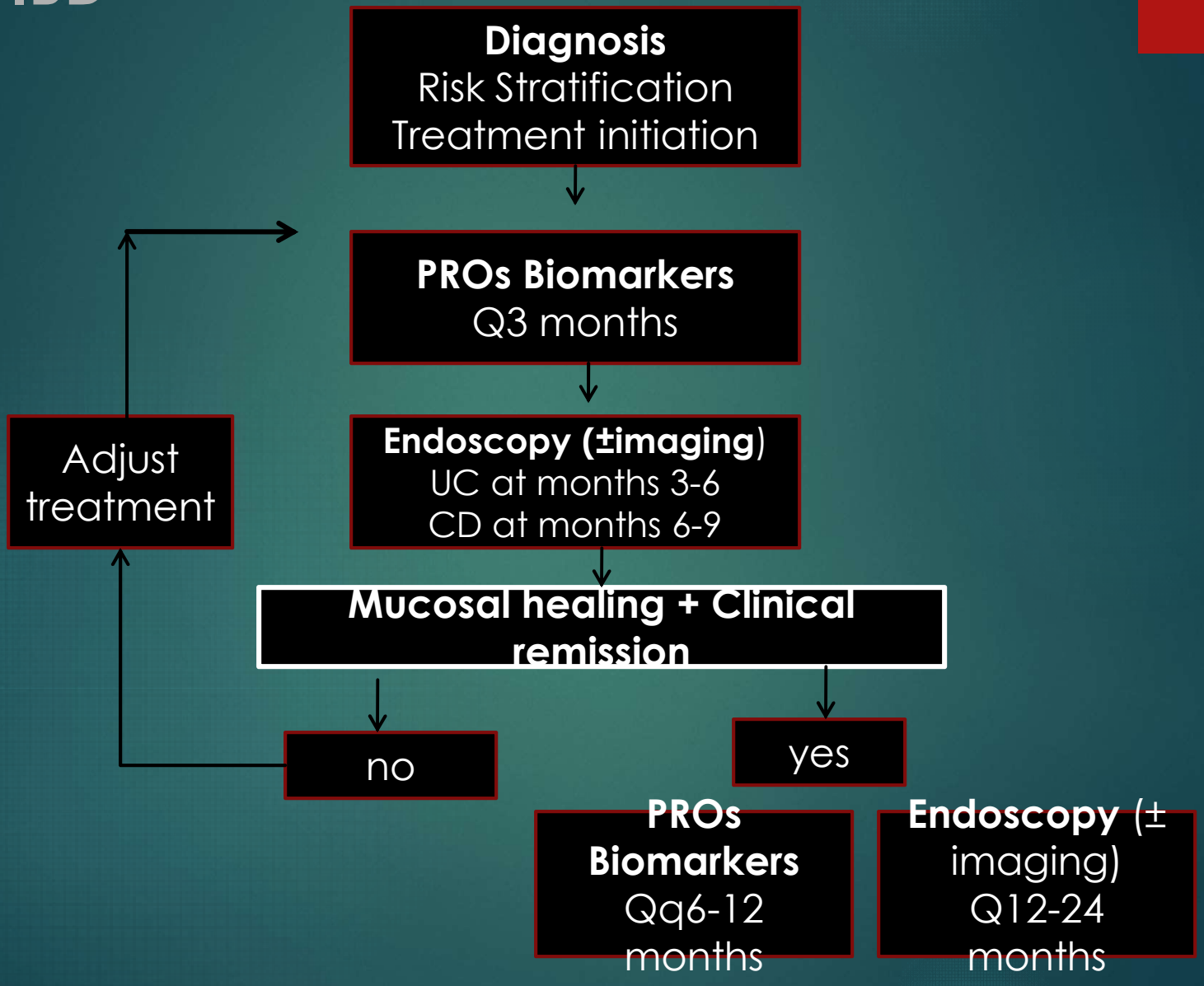




No anti Ustekinumab antibodies detected (drug tolerant assay)

Battat R. Clin Gastroenterol HEPATOL 2017;15:1427-34

Algorithm for Implementing a TTT Strategy in IBD



Vega S inflamm Bowel Dis 2018;24:1670-5

Dose Optimization to Maintain Remission or Recapture Response

2016 ECCO guidelines recommend dose optimization of anti-TNF therapy and staying within the anti-TNF class

Early in the course of the disease	To maintain remission	As long term treatment
Early Anti-TNF therapy should be initiated in patient with high disease activity and features indicating a poor prognosis -from Ecco statement SG	If remission has been achieved with the combination of anti-TNF therapy and Thiopurines , maintenance with the same regimen is recommended - From Ecco statement 6F	Prolong use of anti TNF agents may be considered if needed. - From Ecco statement 6G

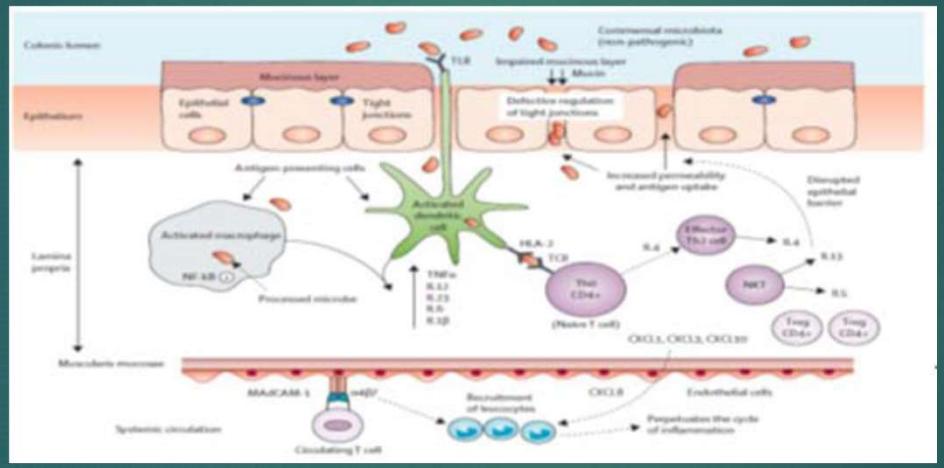
Summary

- Plan scheduled and objective monitoring of IBD
- STRIDE guidelines define treatment targets for IBD
- But be flexible when judging individual success and failure
  - how far have you come
  - what alternatives do you have?
  - What does the patient value and prefer?
- Our IBD armamentarium is robust
- Engage the patient in deciding both treatment and target
- The future of IBD therapy is bright

IBD – CROHNS- HISTOLOGY

- Mucosal inflammation -> Chronic Mucosal Damage -> Mucosal metaplasia -> Ulceration (superficial to deep) -> transmural inflammation -> non-casceating granulomas -> fibrosis 3

IBD – CROHNSAND UC - PATHOPHYSIOLOGY

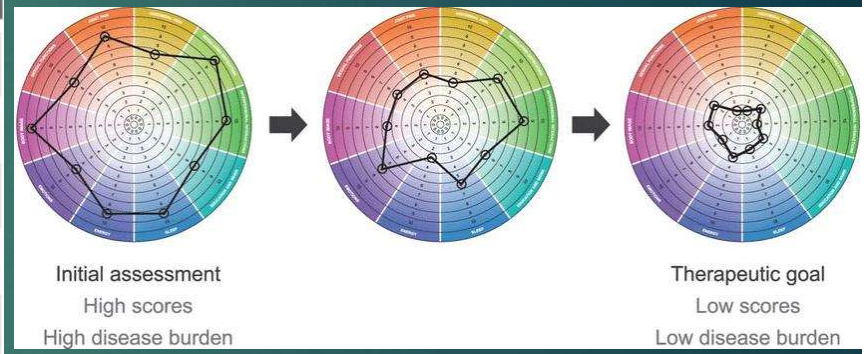


IBD Disk:
Visual Tour for Assessment of

For each of the ten statements below, score your level of agreement on a scale of 0 to 10. Circle your scores on the coloured disc.

Absolutely disagree				Neither agree or disagree						Absolutely agree
0	1	2	3	4	5	6	7	8	9	10

In the last week, because of my Crohn's disease or ulcerative colitis...	
Abdominal pain	...I have had aches or pains in my stomach or abdomen
Regulating defecation	...I have had difficulty coordinating and managing defecation, including choosing and getting to an appropriate place for defecation and cleaning myself afterwards
Interpersonal interactions	...I have had difficulty with personal relationships and/or difficulty participating in the community
Education and work	...I have had difficulty with school or studying activities, and/or difficulty with work or household activities
Sleep	...I have had difficulty sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning
Energy	...I have not felt rested and refreshed during the day, and have felt tired and without energy
Emotions	...I have felt sad, low or depressed, and/or worried or anxious
Body image	...I have not liked the way my body or body parts look
Sexual functions	...I have had difficulty with the mental and/or physical aspects of sex
Joint pain	...I have had pains in the joints of my body



Initial assessment
High scores
High disease burden

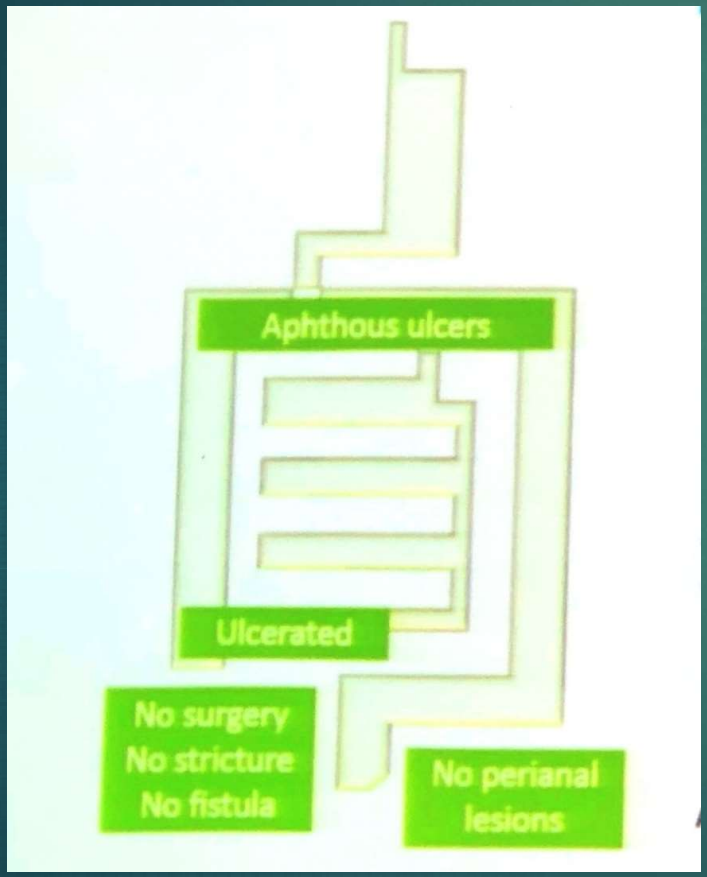
Therapeutic goal
Low scores
Low disease burden

Ghosh S.Inflamm Bowel Dis 2017;23:333-40

Immune Dysregulation & IBD

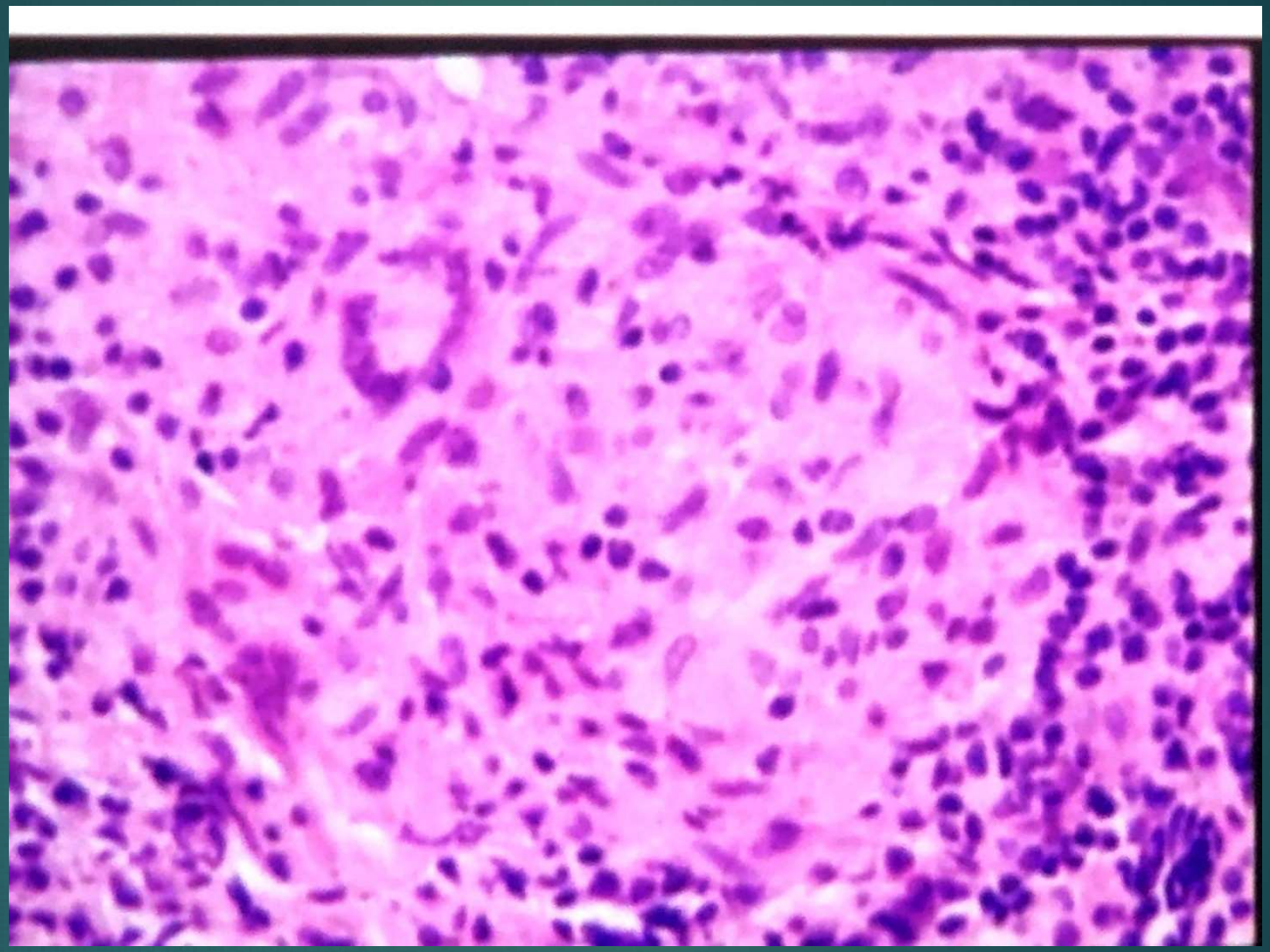
- Dysregulation at the epithelial barrier
- Dysregulation in immune cells
- Dysregulation in secretory mediators
- Alteration in both the composition & function of intestinal microbiota

Assessment of digestive damage



Organ	Segment
Upper digestive tract	esophagus
	Stomach
	Duodenum
Small bowel	In segment of 20cm (up to 20)
Colon and Rectum	Cecum
	Ascending colon
	Transverse colon
	Descending colon

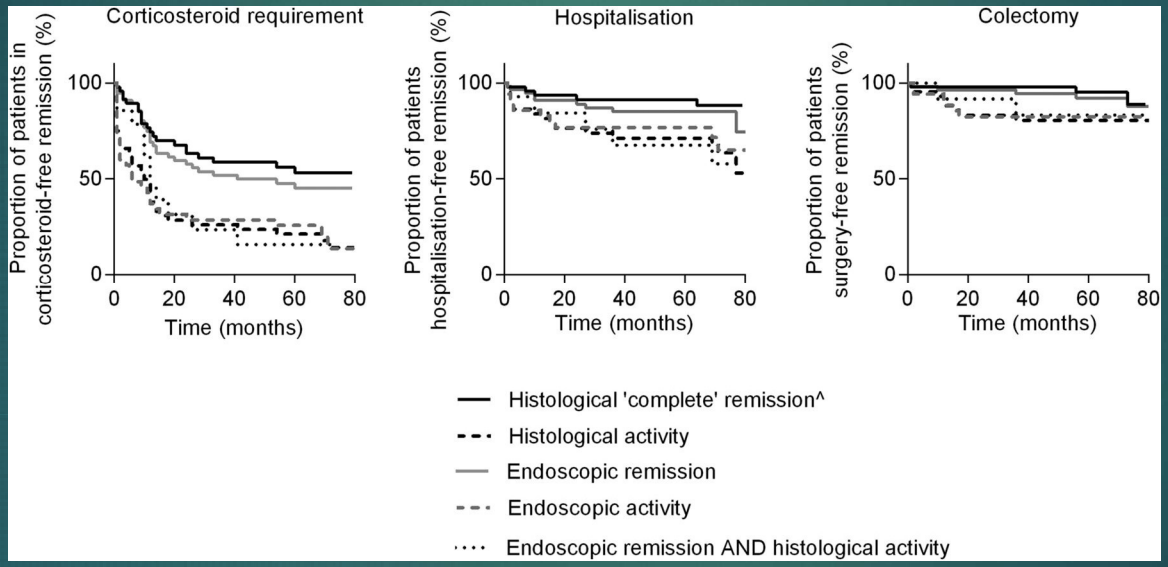
1 Pariente B, et al. inflamm Bowel Dis. 2011: 17 1415-



Adverse Risk Factors

- Lifestyle Factors
  - Smoking (Crohns), protective (UC)
  - Physical activity (Crohns)
  - Dietary factors
    - Fiber (reduced risks in Crohns)
    - Fats (CD & UC increased risk)
    - Vitamin D
  - Sleep Deprivation

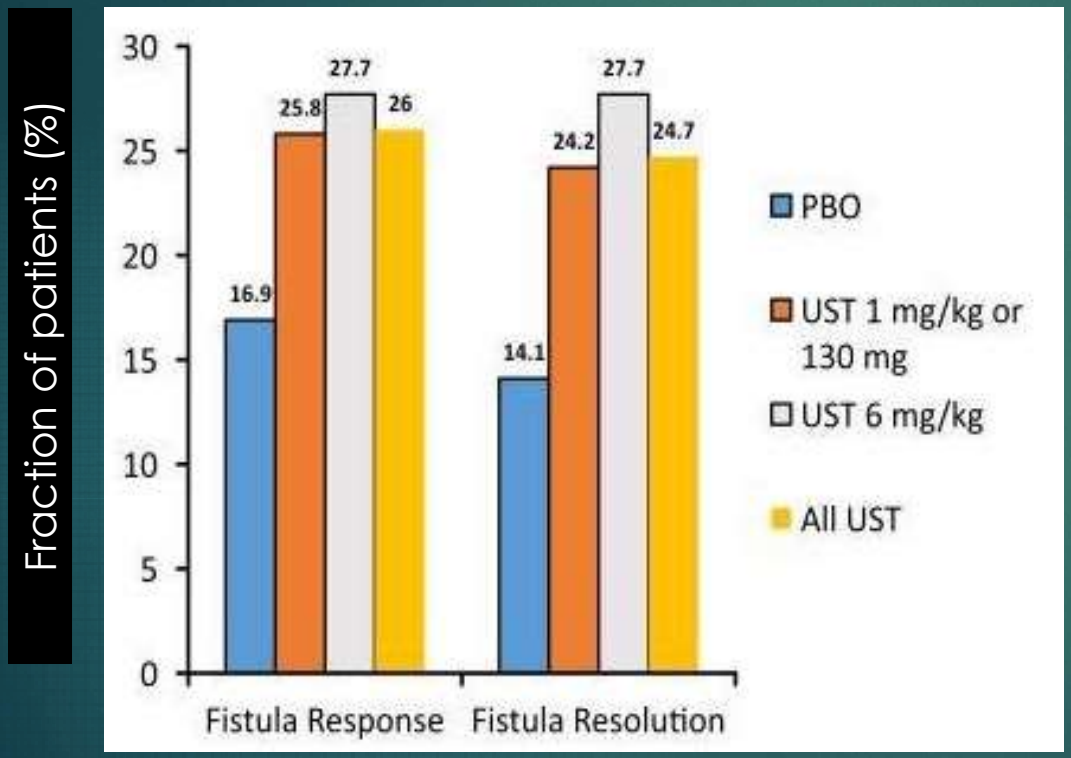
Predict Value of Histology vs. Endoscopy in Ulcerative Colitis



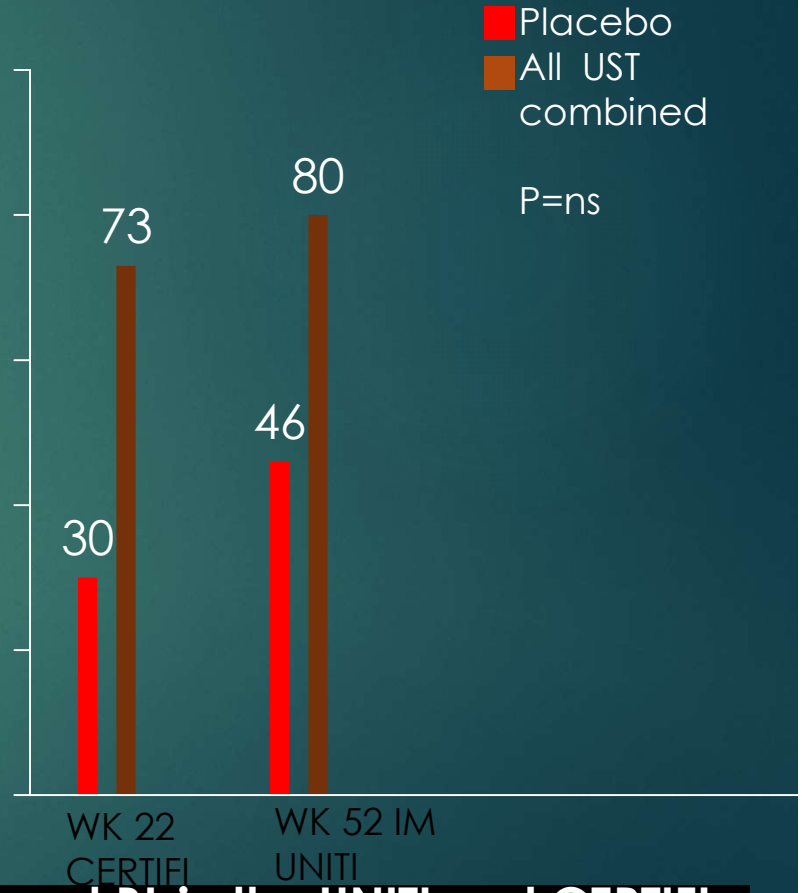
Bryant RV.Gut 2016;65:408-14

Ustekinumab in Fistulizing CD: UNITI and CERTIFI Sub-Analyses

Pooled Data on Fistula Response and Fistula resolution at week 8



FIstula Response in UST Responders



12.3%(161/1306) of pts had active fistulas at BL in the UNITI and CERTIFI studies

Sands BE DOW

IBD – CROHNS AND UC - STATS

- Common in Australia (One of highest in world)
- 29.2 per 100 000 people aged 5-49
- 75 000 Australians
- Hospital Costs $100 000 000 (100 million)
- Lost Productivity $380 000 000 (380 million)
- Peak 10-20 years. Second peak at 50

Assessment of damage severity: small bowel

Severity assessment for each 20 cm segment

Grade	Stricturing lesions (0-3)	Penetrating lesions (0-3)	History of surgery or other interventional procedure(0-3)
Null	Normal	Normal	No procedure
Mild	Wall thickening <3mm without pre-stenotic dilatation	-------	Endoscopic dilatation
Moderate	Wall thickening ≥3mmwithout prestenotic dilatation	Transmural fissure with increased density in perienteric fat	By-pass diversion stricturoplasty
Severe	Stricture with pre-stenotic dilatation	Abscss or fistula	Resection

1 Pariente 5 ; et al. inflamm Bowel Dis 2011;17 1415-1422

Most Common EIMs Associated with IBD: Estimates of frequency

System/Organ	Extra-intestinal manifestation	Estimated frequency in IBD
Musculoskeletal	Peripheral arthralgia/ arthritis	UC: 5-10%; CD: 10-20%
	Axial arthritis	3-5%
	Sacroiliitis	Upto 25%
Skin	Erythema nodosum	UC:up to 10% ; CD: up to 15%
	Pyoderma gangrenosum	0.4-2.0%
	Sweets's syndrome	Rare (case reports)
	Oral lesions	Up to 10%
Ocular	Episcleritis Uveitis Iritis	Ocular combined: UC1.6-4.6% CD 3.5-6.3%
Hepatobiliary	Primary sclerosing cholangitis,small duct PSC ,fatty liver disease, granulomatous hepatitis,autimmune liver and pancreatic disease cholestasis,gallstone formation, liver injury	Overall hepatobiliary : Up to 50% PSC: 2.4-7.5% in UC
Pulmonary	Various, including bronchiectasis, Bronchiolitis, pulmonary function abnormalities	Rare: exact frequency unknown

E/M= Extra intestinal manifestation; PSC= Primary sclerosing cholangitis

Vavricka SR et al Inflamm Bowel Dis 2015;21 1982 -1992 Schleiermacher D, et el J Crohn's Colitis 2007;1:61-69

Selecting a First-Line Advanced Therapy for IBD

Infliximab

Adalimumab

Golimumab

Certolizumab

Ustekinumab

Vedolizumab

Tofacitinib

- **IBD phenotypes/ severity/risk**
- **Co-morbidity and overlap**
- **Extra-intestinal manifestations**
- **Pregnancy plans**
- **Need for combination therapy**
- **Strength of evidence for efficacy**
- **Safety**
- **Reimbursement support**
- **Route of administration**
- **Dose frequency**
- **Experience**
- **Patient Preference**

  short term

  long term