



# Biologic Therapy in IBD: Old, New and What Clinicians Should Know

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DIMEC

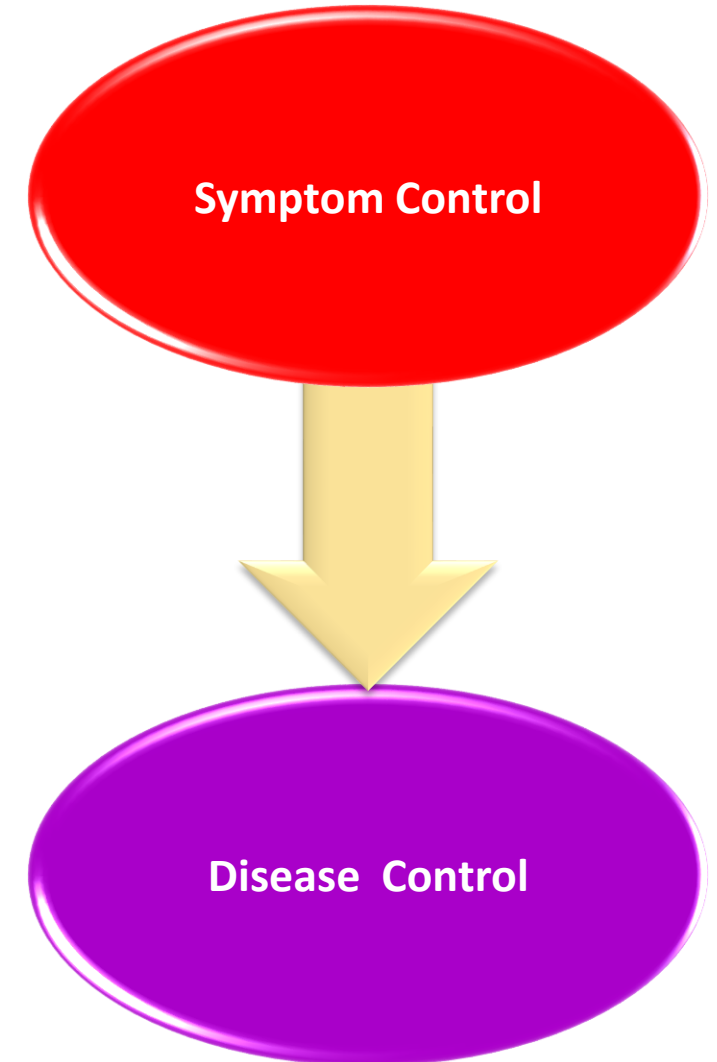
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# The goals of therapy in IBD have changed

## Strive for comprehensive control of disease

- Induction of response / remission
- Maintenance of response / remission
- Elimination of steroids
- Healing of fistulae
- Reduction of hospitalization and surgeries
- Normalization of QOL/Improve Social function
- Mucosal healing
- Structural normality
- Histological remission



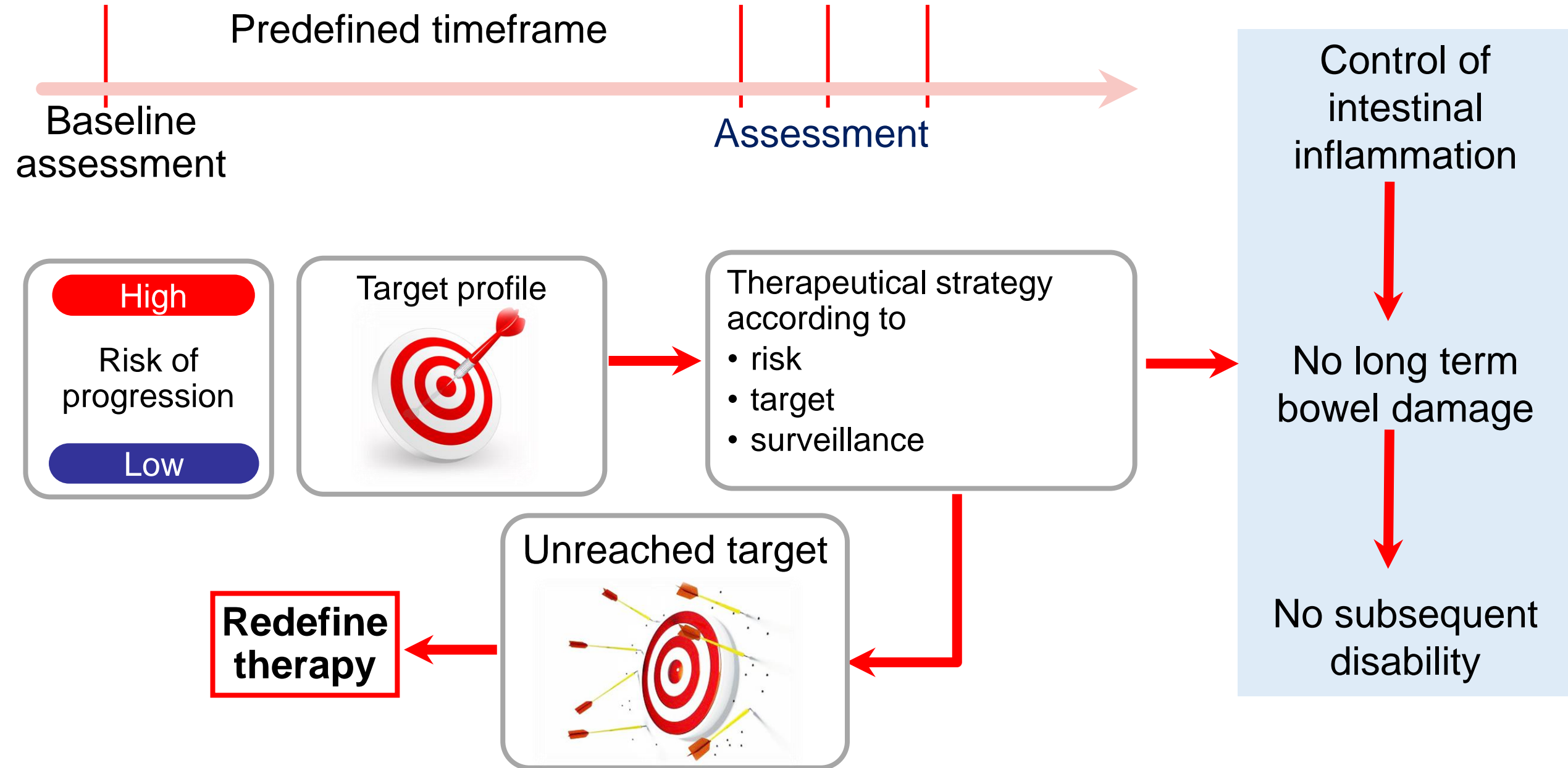
# Treatment Strategy in IBD have changed



## A top-down approach

- A significant number of patients would be over-treated if a top-down approach would be recommended for all patients
- The cost raised by a top-down approach for every patient would be significant and no health care system could cover such a strategy making it unrealistic at the end

# Treat to Target Approach



# STRIDE: treat-to-target recommendations in IBD



**Clinical / PRO remission**

**AND**

**Endoscopic remission**

**UC: Defined as resolution of rectal bleeding and normalisation of bowel habit**

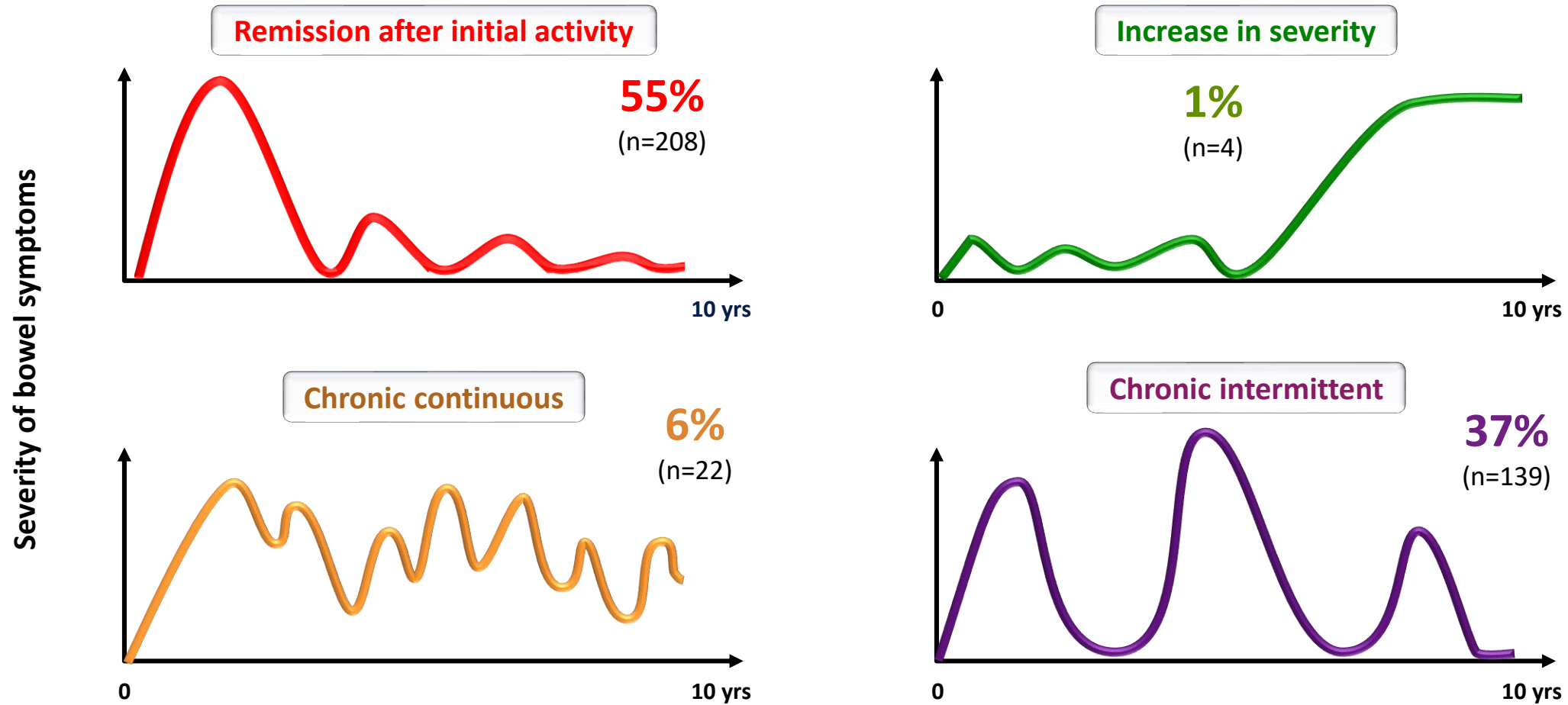
**CD: defined as resolution of abdominal pain and diarrhoea/altered bowel habit**

**UC: Defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy (Mayo 0–1)**

**CD: defined as resolution of ulceration at ileocolonoscopy**

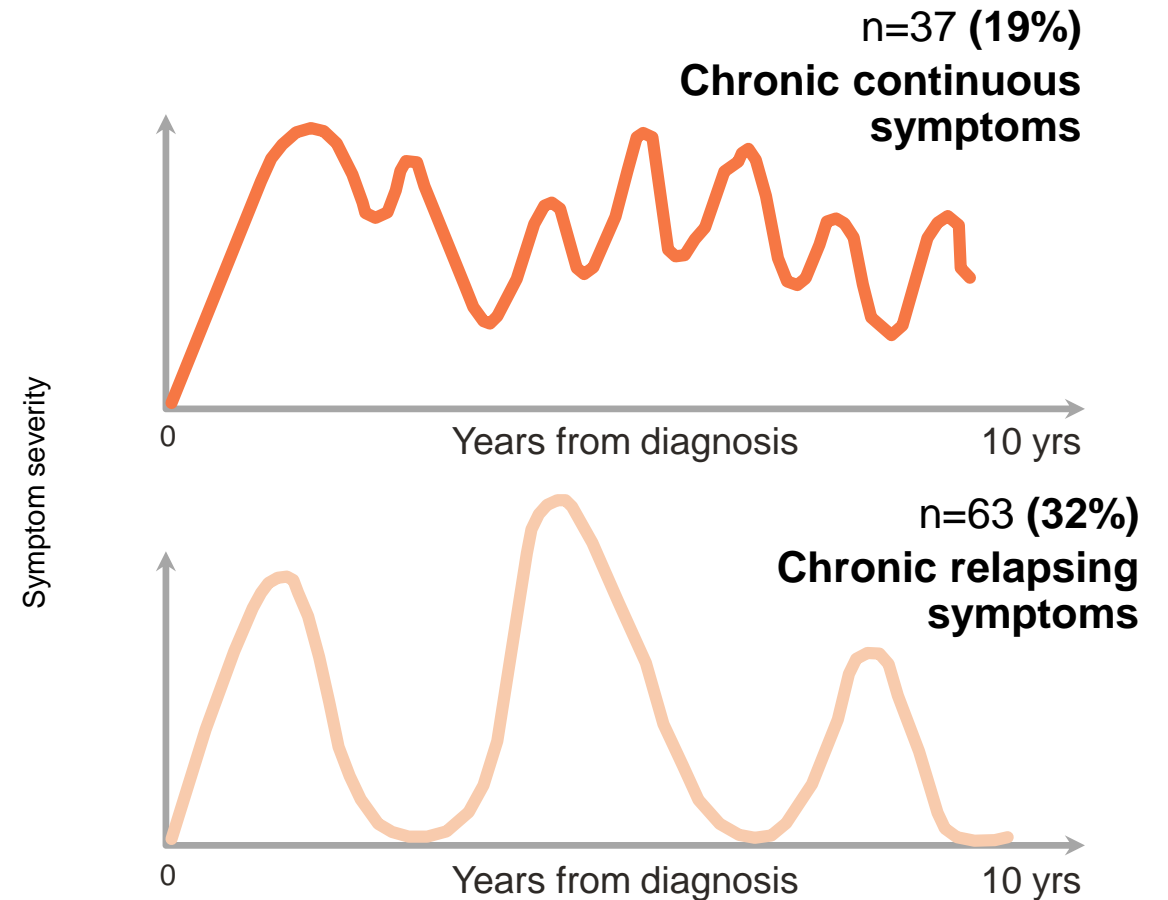
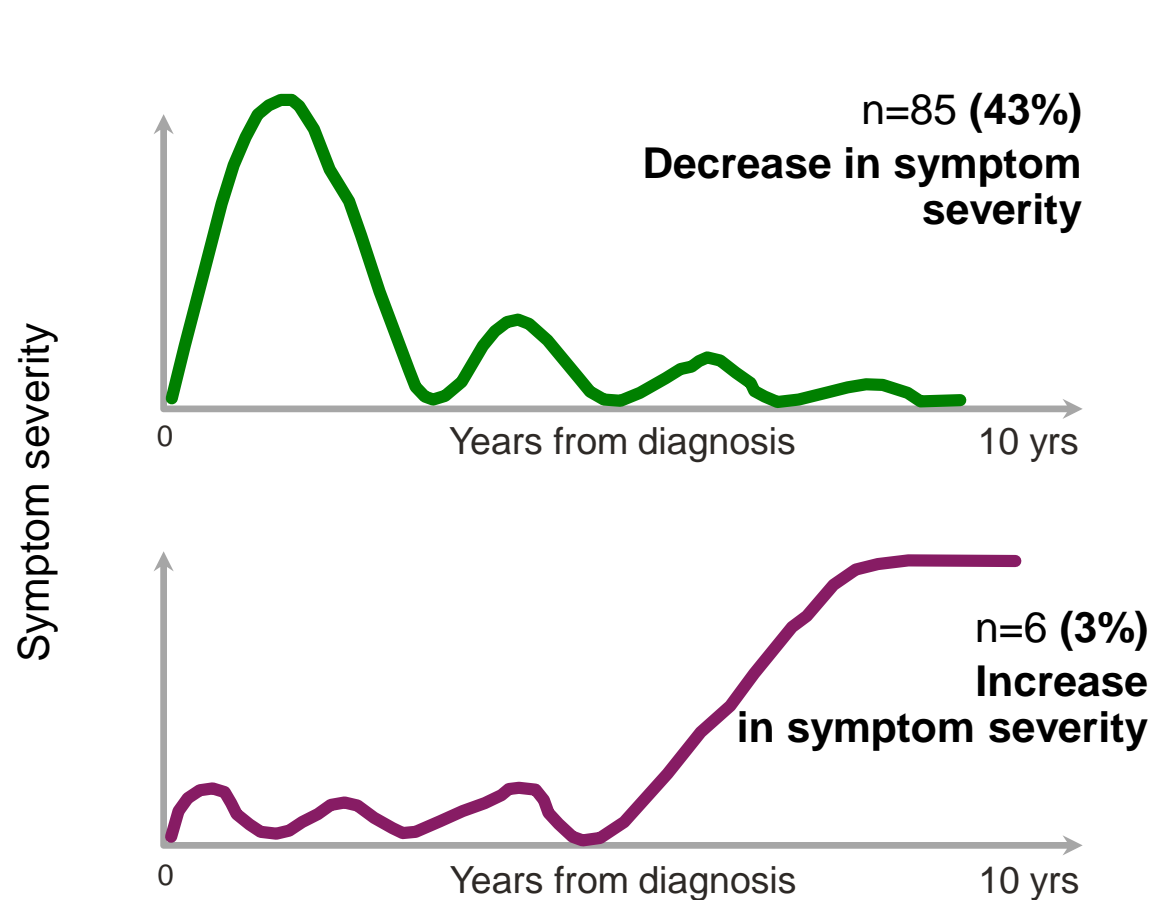
# Potential UC disease course over first 10 years

Norwegian IBSEN cohort study (N=379\*)



# Potential CD disease course over first 10 years

## Norwegian IBSEN cohort study (n=197)



Missing data: n=6 (3%)

Solberg IC, et al. *Clin Gastroenterol Hepatol* 2007;5:1430–8



Or Treatment Strategy in IBD should be changed?



# An individualised approach for the care of IBD



**Understand who is your patient**

Select the most adapted  
individualised therapeutic  
approach

# Tailored management in IBD

## **Establish management goals, in conjunction with the patient**

- With understanding of the patient's unmet needs

## **Categorise patients effectively**

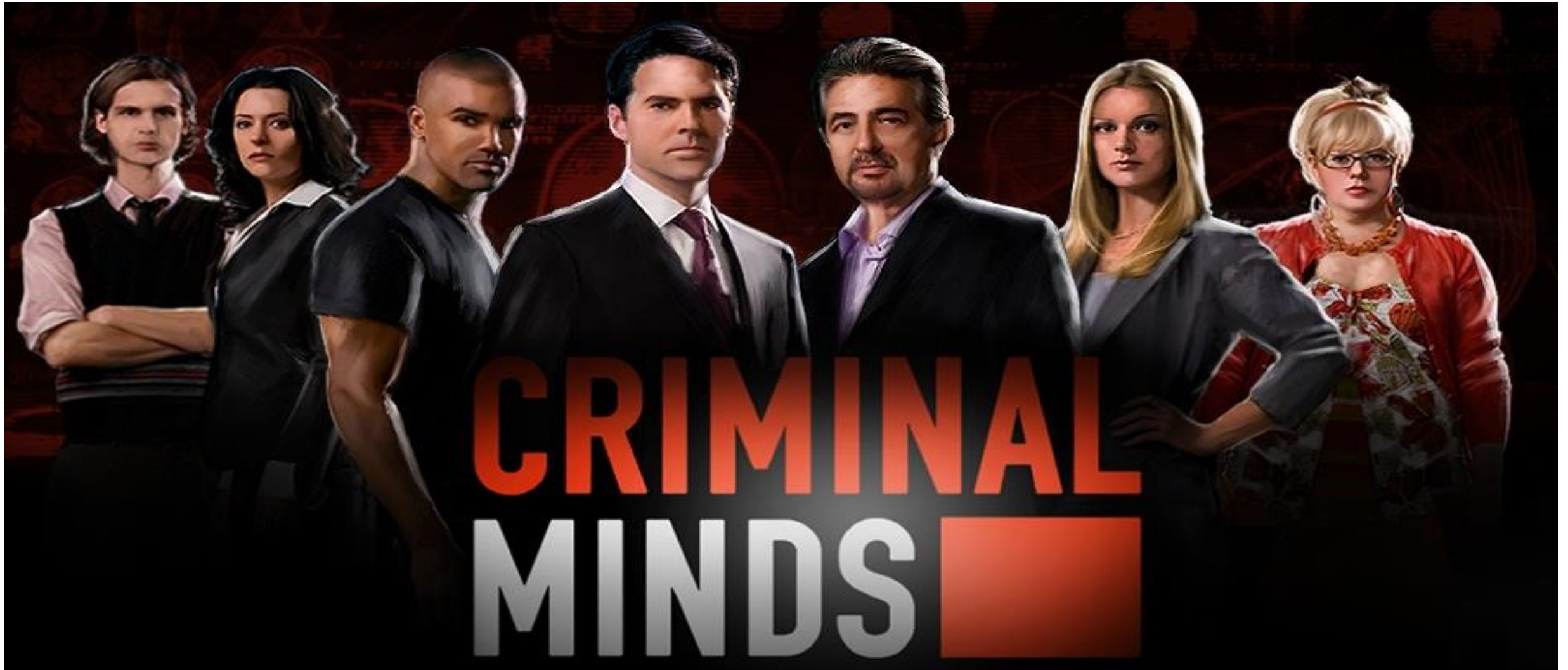
- With understanding of the patient's clinical characteristics and prognosis

## **Establish the management plan**

- With selection of appropriate initial therapy
- With monitoring and adaptation of therapy moving forwards



Patient's profiling in order to take the best  
therapeutic decision



## Biologics: how to use

- Deep Evaluation of the patient to be treated
- Know the contra-indications!
- Treat only active inflammatory disease
- Early treatment
- Define endpoint you want to achieve: steroid weaning, fistula healing...
- Carefully monitor the patient
- Choose the right moment to stop
- Choose the most appropriate biologic

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# Deep evaluation

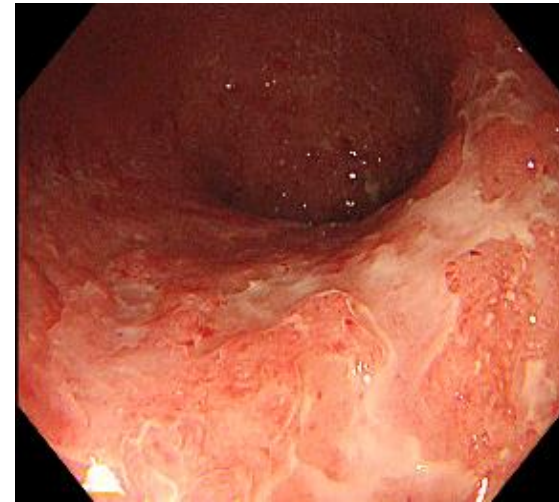
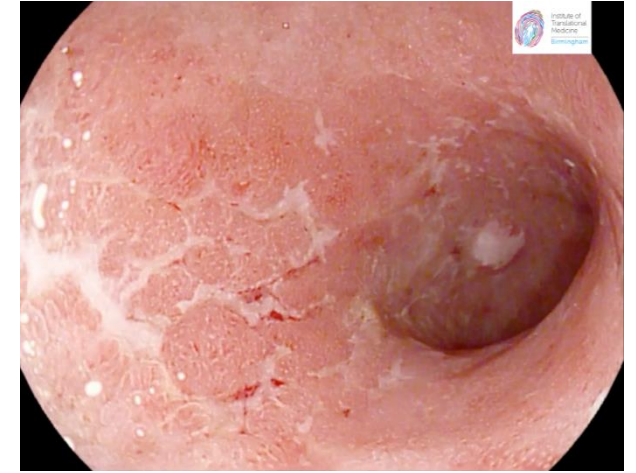
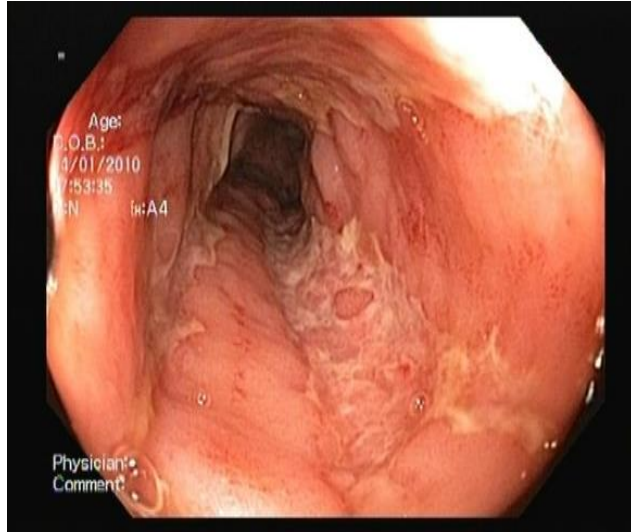
- Disease localization/extension
- Previous effectiveness / refractariety / intolerance to treatments
- Initial presentation or relapses
- Frequency and severity of relapses
- Presence of extraintestinal manifestations
- Steroid dependency
- Steroid refractariety
- Risks of therapy
- Relapse while on immunomodulators or biologics
- Presence of bad prognostic factors

Patients should be encouraged to participate in the decision-making process.

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- Carefully plan rescue strategies for each agent
- Choose the right moment to stop
- Choose the most appropriate biologics





## Biologics: how to use

Should we use early treatment with biologics in all patients?

# Early or Late Disease



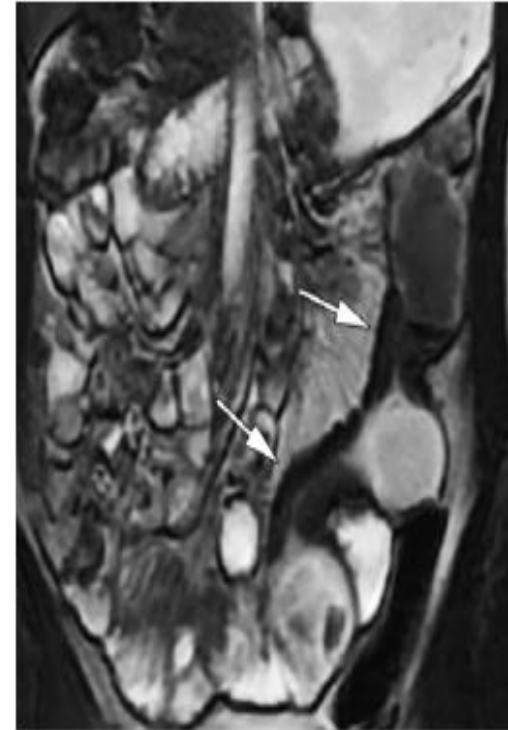
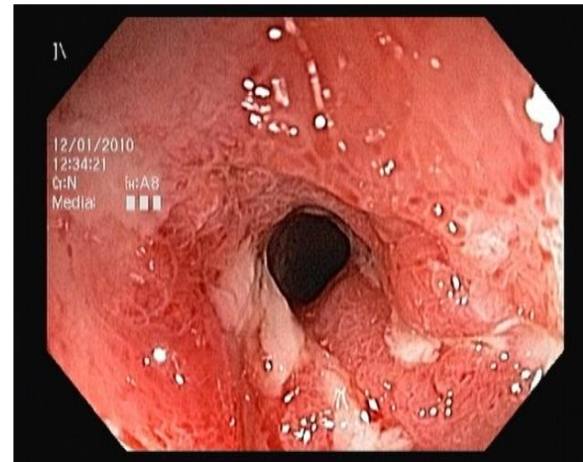
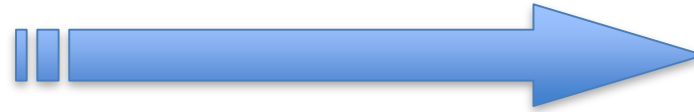
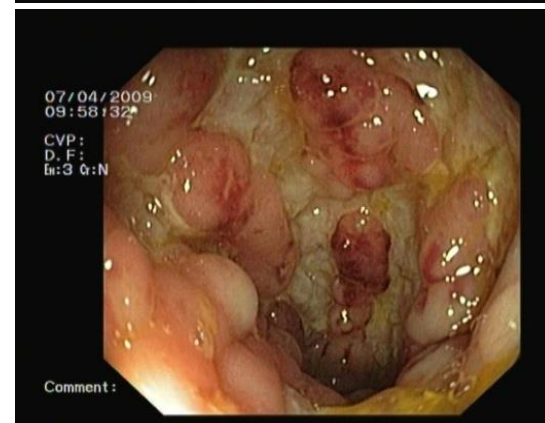
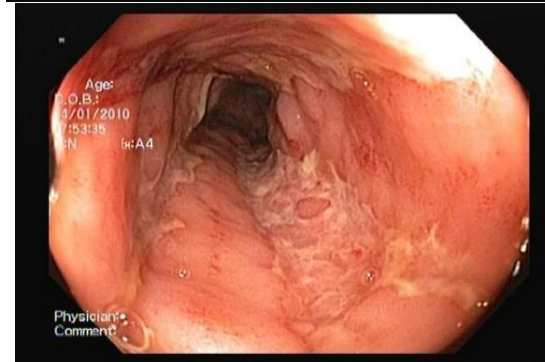


# Early or Late Disease



- Disease duration may alter treatment goals
  - Late disease has inflammatory and non-inflammatory symptoms
- Aim of treatment should be **different for different patient types**
  - e.g. *absence* of symptoms and complete MH in early disease, and *improvement* in symptoms and partial MH in late disease

# Good therapy starts with good timing!



# Response to Biologic Therapy in Crohn's Disease Is Improved with Early Treatment: An Analysis of Health Claims Data

'Real-World' data (3750 patients)

3 groups:

- Early TNF
- IS-to-TNF
- Step-Up



Associated with Lower Risk of:

- Concomitant corticosteroid use
- Anti-TNF dose escalation
- Discontinuation/switch of anti-TNF
- CD-related surgery

# 2013 – History of 2 pts

## Patient -1

- 19 year old boy with weight loss and diarrhea
- Diagnosis – Crohn's disease of ileum and colon with diffuse ulceration
- Treated with steroids + immune modifiers

## Patient -2

- 21 year old boy with weight loss and diarrhea
- Diagnosis – Crohn's disease of ileum and colon with diffuse ulceration
- Treated with steroids + immune modifiers

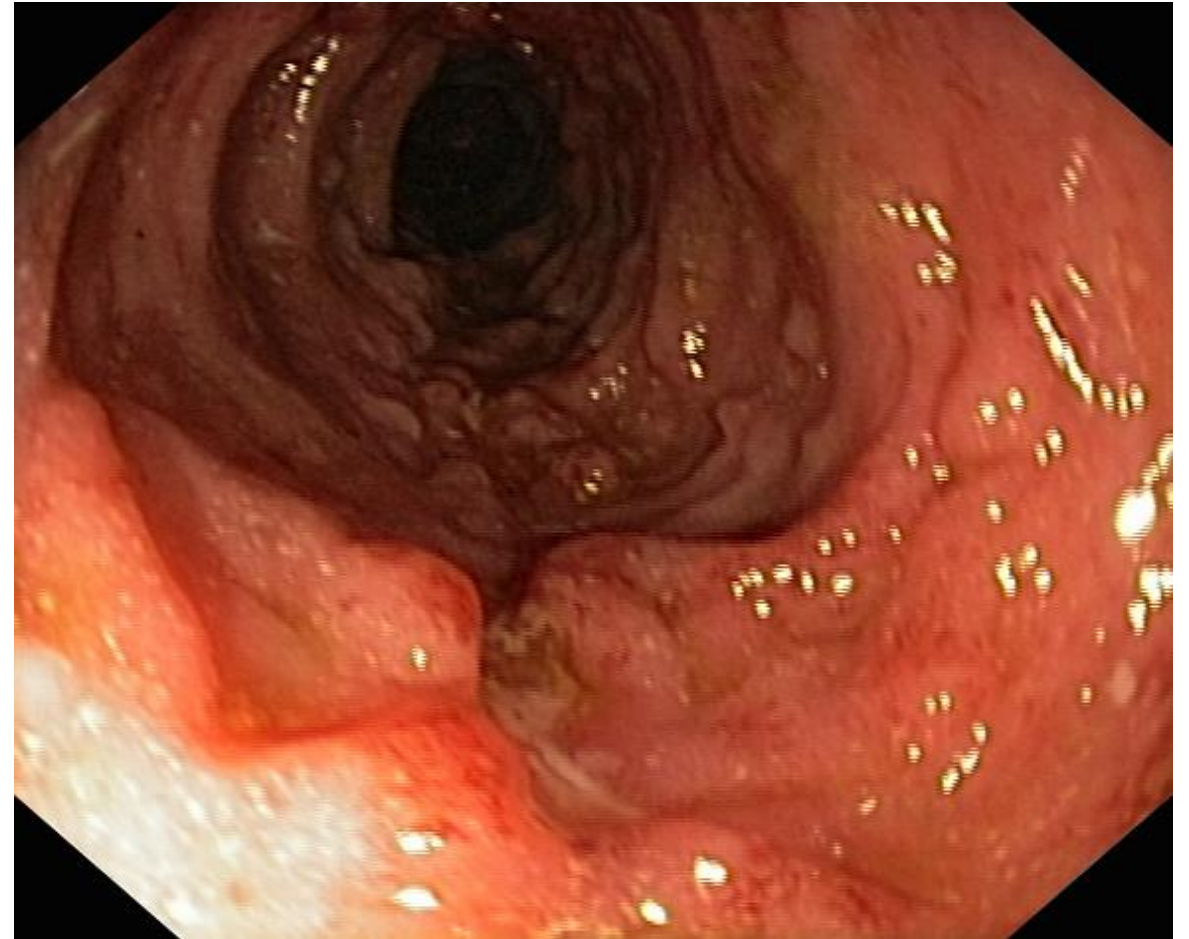


# 2017 - History of 2 pts

Patient -1



Patient -2



reconnected in future



# Long-term Outcome of Early Combined Immunosuppression Versus Conventional Management in Newly Diagnosed Crohn's Disease

Hoekman DR et al *Journal of Crohn's and Colitis*, 2018, 517–524

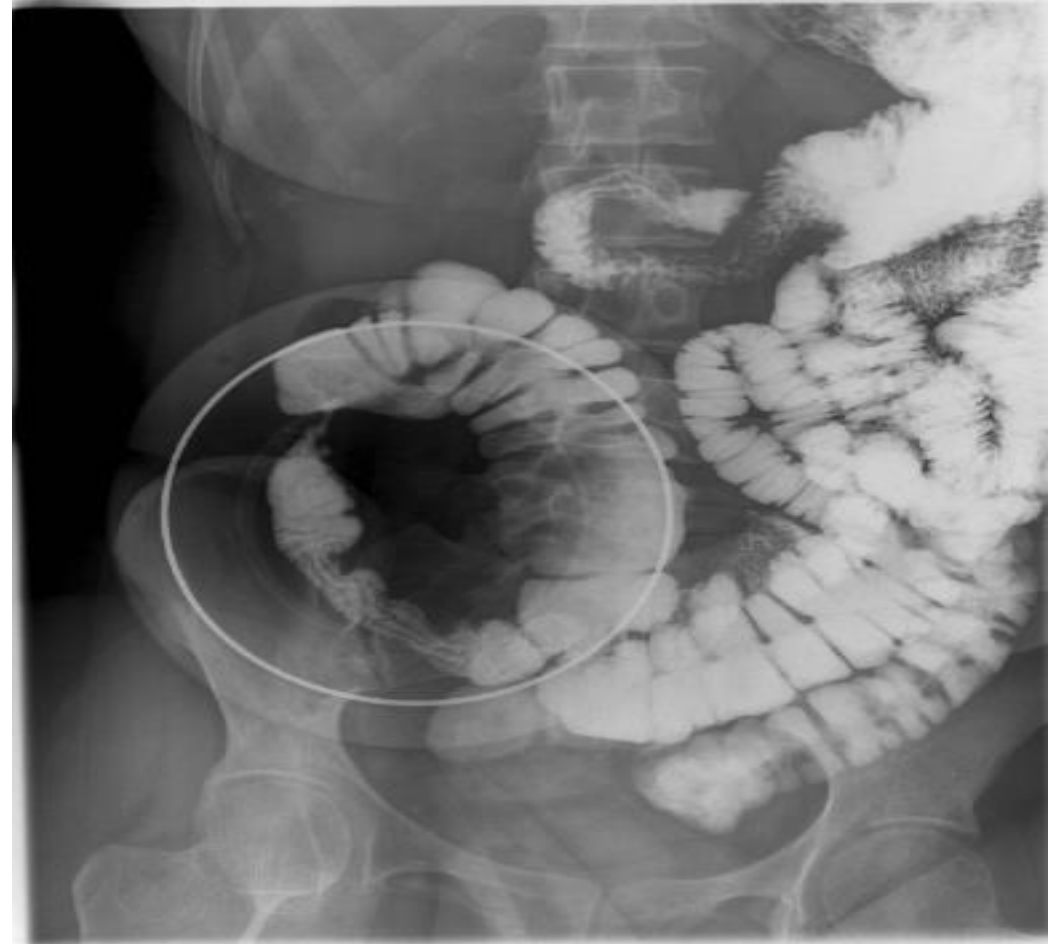
**Results:** Data were available from 119/133 patients [step-up  $n = 60$ ]. During a median follow-up of 8 years, clinical remission rates were similar (70% vs 73% [ $p = 0.85$ ] in step-up and top-down patients, respectively). A shorter time to flare was observed in step-up patients [median five vs nine semesters,  $p = 0.01$ ]. Cumulatively, 62% of step-up patients used corticosteroids compared to 41% of top-down patients [ $p = 0.02$ ]. Anti-tumour necrosis factor [anti-TNF] use was higher in the step-up group [73% vs 54%,  $p = 0.04$ ]. No differences were found in time to CD hospitalization [respectively 13 vs 14 semesters,  $p = 0.30$ ], new fistula [14 vs 15 semesters,  $p = 0.20$ ] or CD surgery [14 vs 15 semesters,  $p = 0.25$ ]. Mucosal healing 2 years after treatment was associated with a reduced anti-TNF use, but not with differences in other long-term outcomes. Endoscopic remission occurred at similar rates between groups.

**Conclusions: Top-down treatment did not result in increased clinical remission during long-term follow-up, compared to step-up**

**treatment.** However, lower relapse rates and a reduced use of anti-TNF agents and corticosteroids were observed. **No difference was found in rates of endoscopic remission, hospitalization, surgery or new fistulas.**

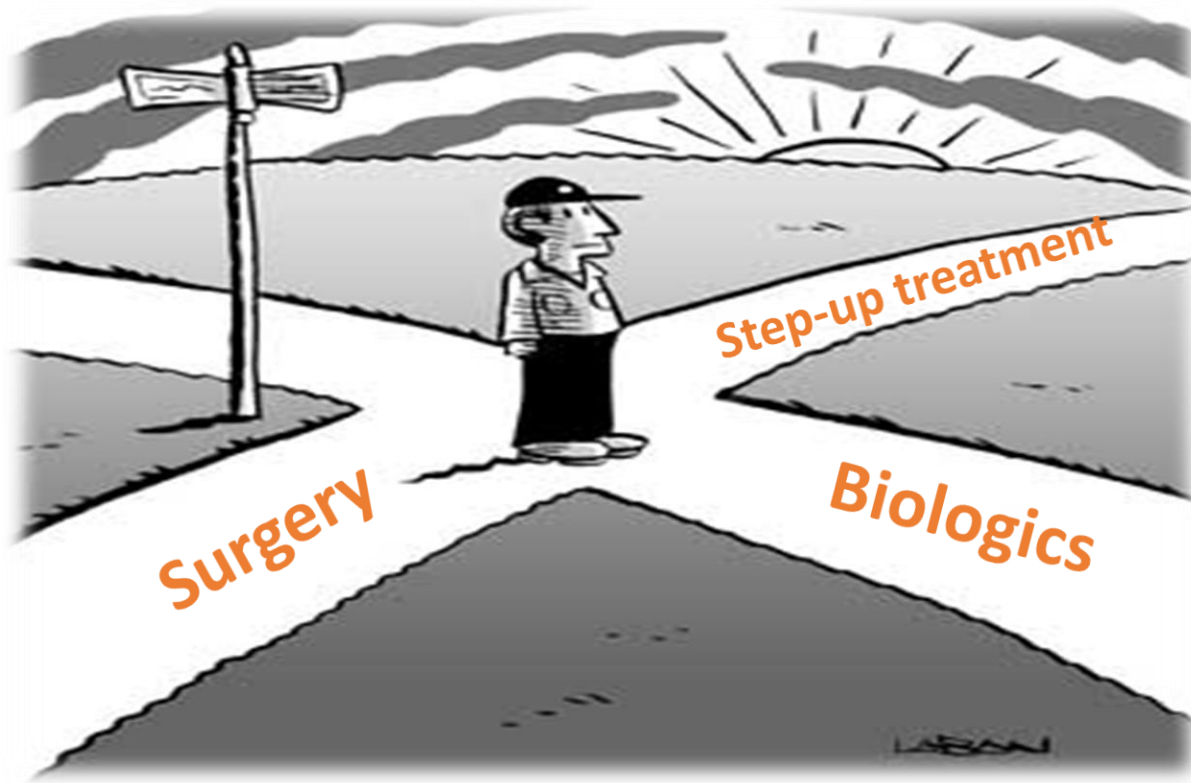
## Case 31 years female

- 2014 CD terminal ileitis
- Started IFX treatment
- Jan 2016: postprandial abdominal cramps 3 weeks – no diarrhea
- Normal CRP



# Terminal Ileitis

Surgery or medical therapy?



# Biological Therapy in terminal Ileitis



Mucosal Healing

but ....

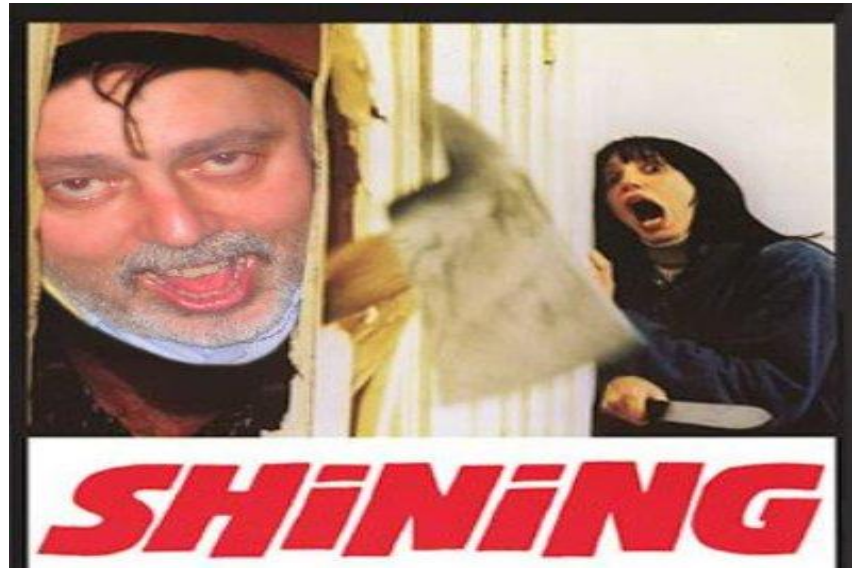
Increased or almost  
unchanged fibrosis and  
thickness of small bowel wall

Reduction in possibility to  
perform conservative surgery

# Failure of Medical treatment

Goal of pharmacological treatment should be not to avoid surgery at any cost but rather to improve QoL

When the latter cannot be achieved then surgery should be considered as the next treatment step





# Timing of surgery in Crohn's disease

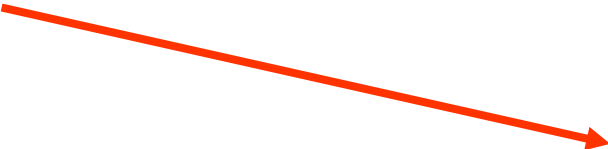
## Timing of ileocolonic resection for symptomatic Crohn's disease – the patient's view



Scott NA GUT 1994

Questionnaire sent to 70 pts undergone elective ileocolic resection

Would have preferred resection to have been done:

<b>Earlier:</b>	<b>74 %</b>	 Almost 100 % due to severity of their symptoms
<b>Same time</b>	<b>26 %</b>	
<b>Later</b>	<b>None</b>	

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# Key question to address when starting a treatment

**What is the aim / endpoint of therapy in my patient?**

Important for choice of therapy, duration of treatment,  
timepoints for re-assessing patient, which examinations to use, stopping or not and when, changing biologics.....



# Which patients could benefit from receiving biologicals?

## Steroid/Azathioprine “incomplete control” patients

- Steroid-dependent / resistant patients
- Azathioprine resistant patients (patients with frequent need of additional treatments - with continuous biological activity - without steroid-sparing effect)
- Patients who suffer from steroid or azathioprine side effects

## Patients with high risk of disabling disease

# Perianal Disease



# Complex Perianal Fistula

## **ECCO Statement 9G**

Seton placement after surgical treatment of sepsis is recommended for complex fistulae [EL2]. The timing of removal depends on subsequent therapy.

## **ECCO Statement 9H**

Active luminal Crohn's disease should be treated if present, in conjunction with appropriate surgical management of fistulae [EL5]

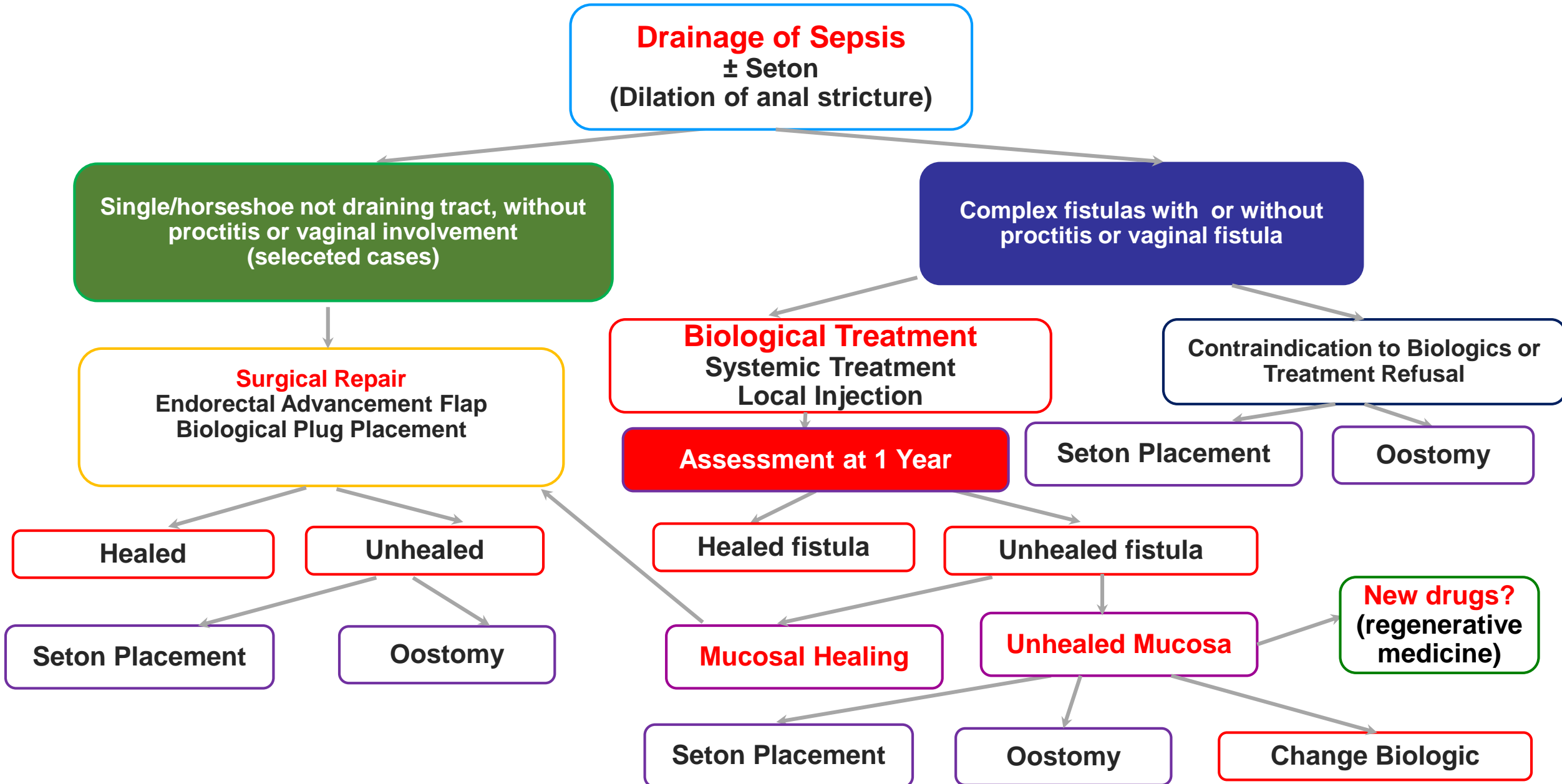
## **ECCO statement 9I**

**In complex perianal fistulizing disease Influximab (EL1) or Adalimumab (EL 2) can be used as first line therapy following adequate surgical drainage if indicated.** A combination of ciprofloxacin and anti-TNF improves short term outcome (EL1) To enhance the effect of anti-TNF in complex fistulising disease combination of anti-TNF treatment with thiopurines may be considered (EL 5)

## **ECCO Statement 9J**

Imaging before surgical drainage is recommended. EUA for surgical drainage of sepsis is mandatory for complex fistulas. [EL 4]. In complex fistulas, abscess drainage and loose seton placement should be performed. [EL4].

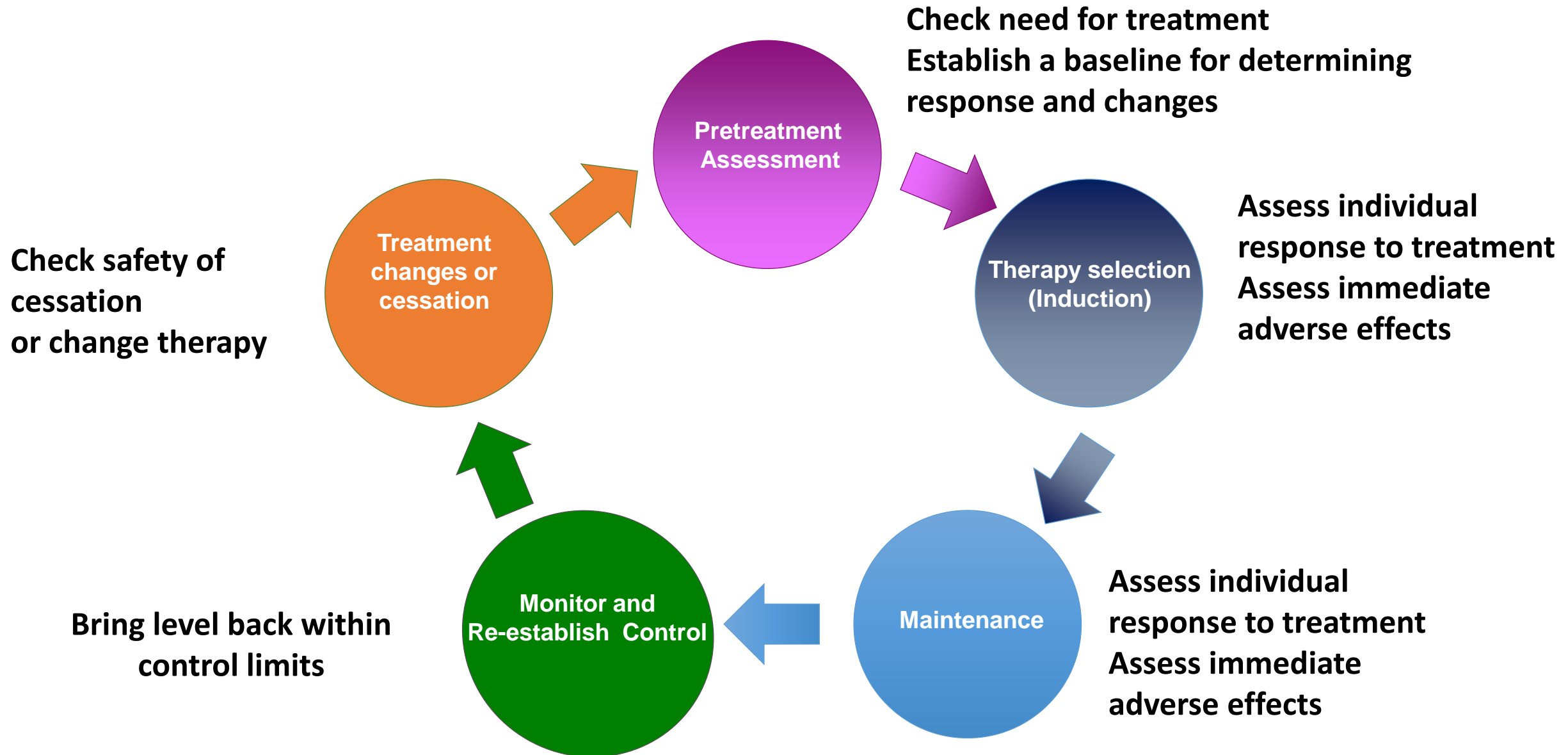
# Suggested Algorithm for treatment of perianal fistulas



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# The Five Phases of Chronic Disease Management



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Should we stop biological therapy? When?





# When to Stop Biological Therapy

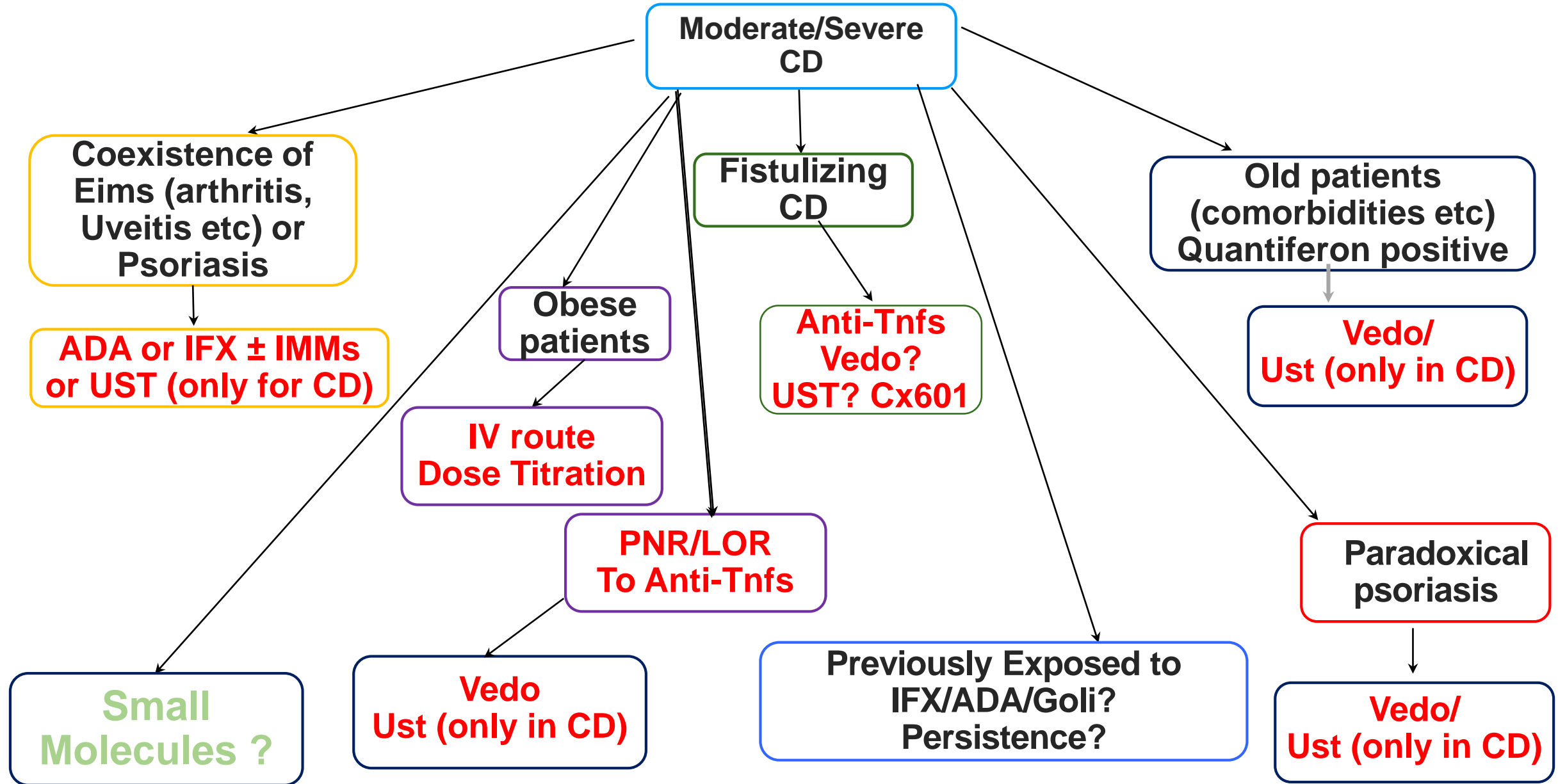
## Deep Evaluation of the patient:

- Steroid-dependency duration
- Tolerance/Intolerance to Thiopurines
- Presence/Absence of a stable Deep Remission, defined as Clinical, laboratory and Endoscopic stable Remission (for at least 6 months)
- Previous relapsing course (need for steroids or dose-intensification)
- Extensive disease
- Previous multiple surgeries (CD)
- Presence/absence of complex perianal disease (CD)

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# Which Biologic ?



*“Primo non nuocere”*

**Henry Marsh**

# Systematic approach to better control the disease

## #HASHTAG

- **H**ave a long-term strategy!
- **A**llow you to completely map the disease and its complications
- **S**tratify patients according to prognosis
- **H**ear the needs of the patient
- **T**ailor therapy to individual patients
- **A**ppropriately monitor patients to maintain 'tight control'
- **G**uess response to therapy and enables changes in strategy before symptoms or damage occurs

“Chi più in alto sale più lontano vede, chi più lontano vede più a lungo sogna” (W. Bonatti)

