

Beyond Anti-TNFs: positioning of other biologics for Crohn's disease

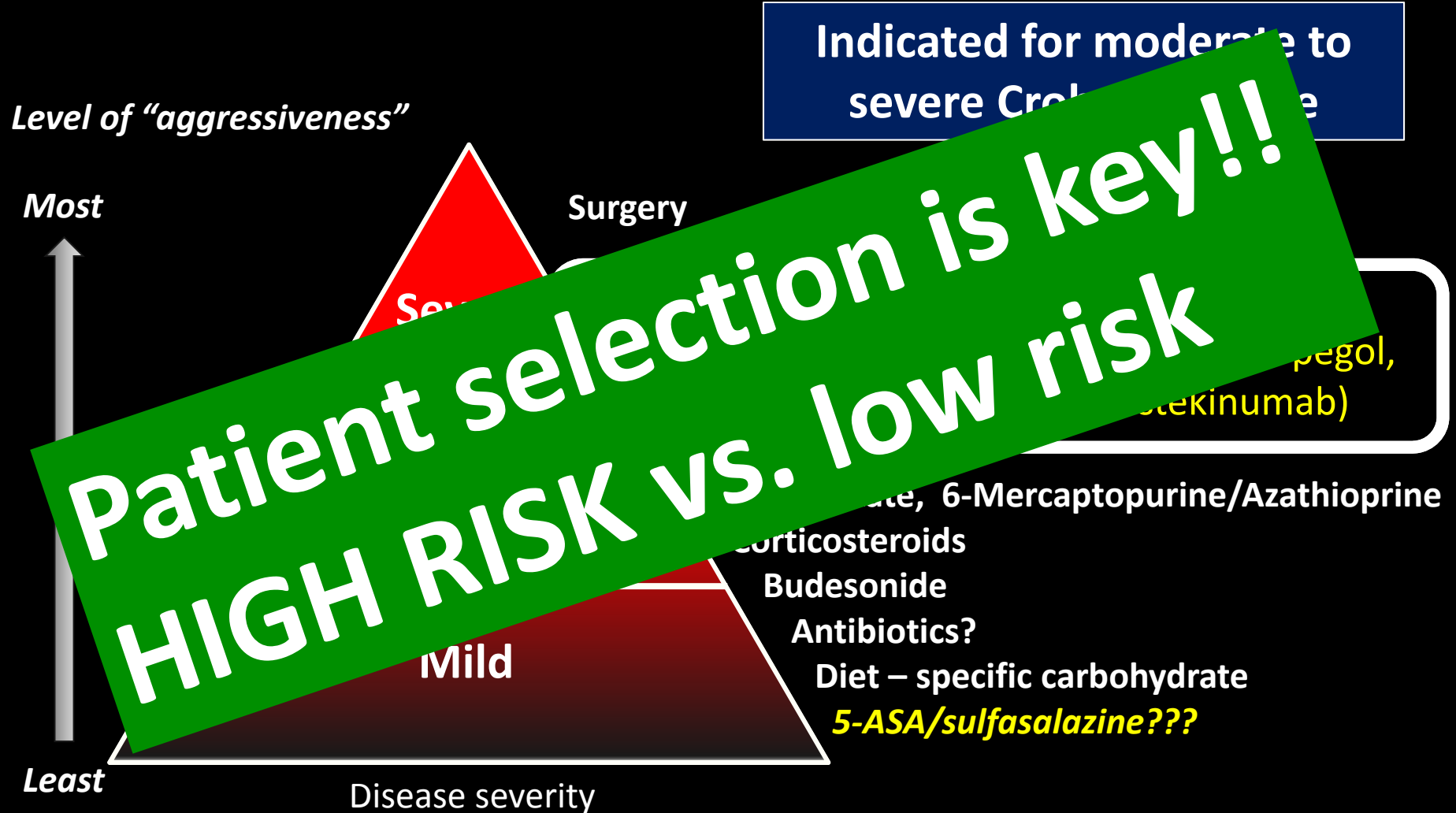
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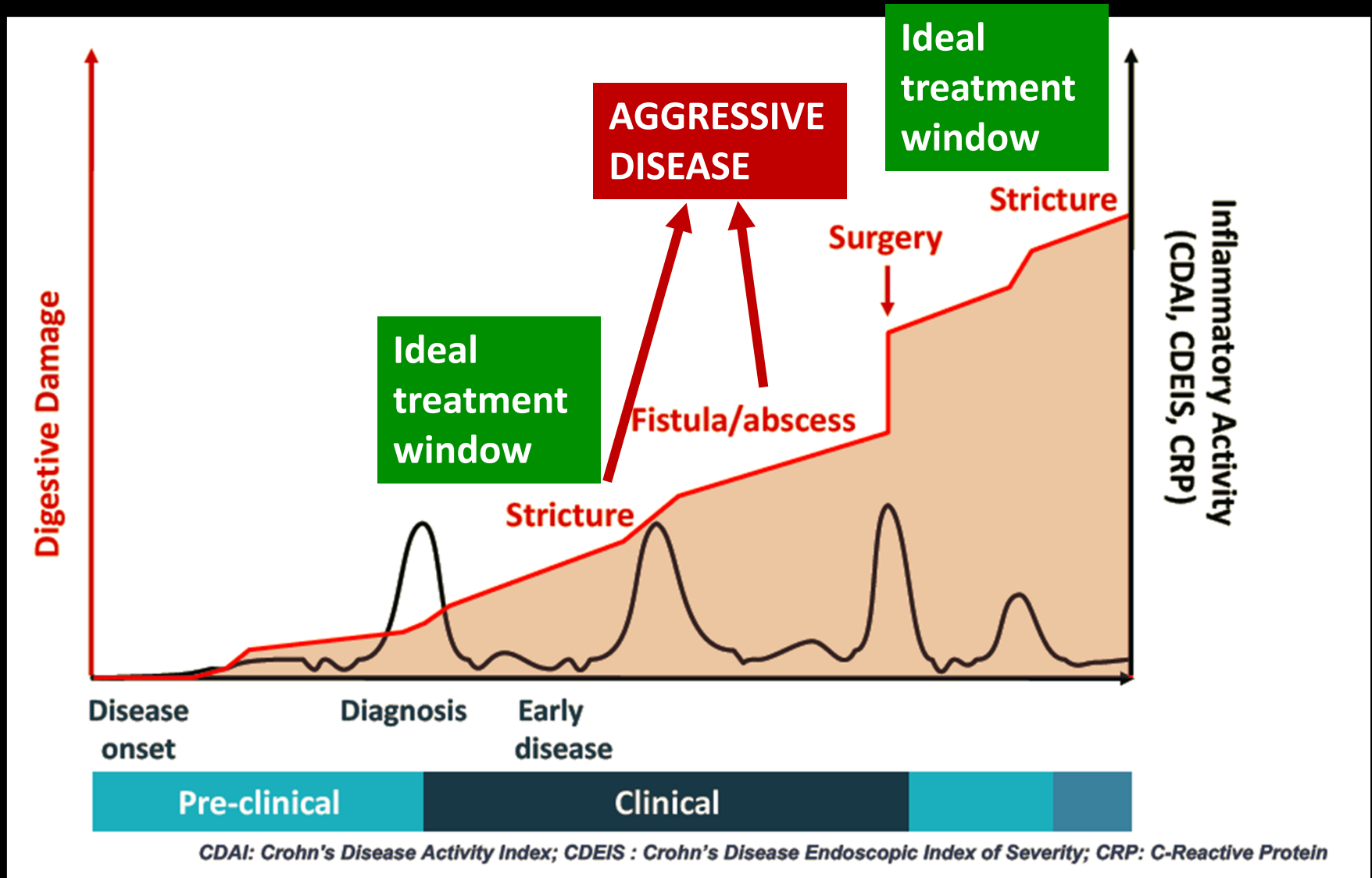
Objectives:

- To define high and low-risk patient and disease features in Crohn's disease
- To classify Crohn's disease activity clinically and endoscopically
- To provide guidance for positioning FDA-approved agents for Crohn's disease

Crohn's disease treatment options



Progression of Digestive Disease Damage and Inflammatory Activity



Step 1: Determine age, location and behavior of Crohn's disease

Age at diagnosis

A1: <16yo

A2: 16-40 yrs

A3: > 40 yrs

Upper GI and small bowel location more common among patients diagnosed

< 20 years of age

- **AGGRESSIVE DISEASE**
- Proximal disease may be clinically silent

Colonic disease location more typical for **older-onset IBD**

- Consider comorbidities
- Adverse effects of therapy

Step 1: Determine age, location and behavior of Crohn's disease

Location

L1: ileal

L2: colonic

L3: ileocolonic

L4: upper GI

L1 = isolated ileal *AND* ileocecal disease

- L4 → esophageal, gastroduodenal and jejunal locations – greater morbidity with untreated disease
- L4 modifier used if upper GI disease is present in addition to L1-L3

Step 1: Determine age, location and behavior of Crohn's disease

Responds best to medical management

Inflammatory stricture

Fibrostenotic stricture

- High likelihood of needing surgery
- Steroids not helpful to treat chronic stricture

“aggressive” disease behavior

- Steroids make penetrating disease worse
- Surgery often necessary followed by medical therapy

Behavior

B1: inflammatory

B2: stricturing

B3: penetrating

p: perianal

Step 1: Determine age, location and behavior of Crohn's disease

Considered an “aggressive” disease behavior

- Steroids make perianal disease worse
- First control pelvic sepsis, then treat with combo therapy + antibiotics
- MRI pelvis = imaging study of choice

Behavior

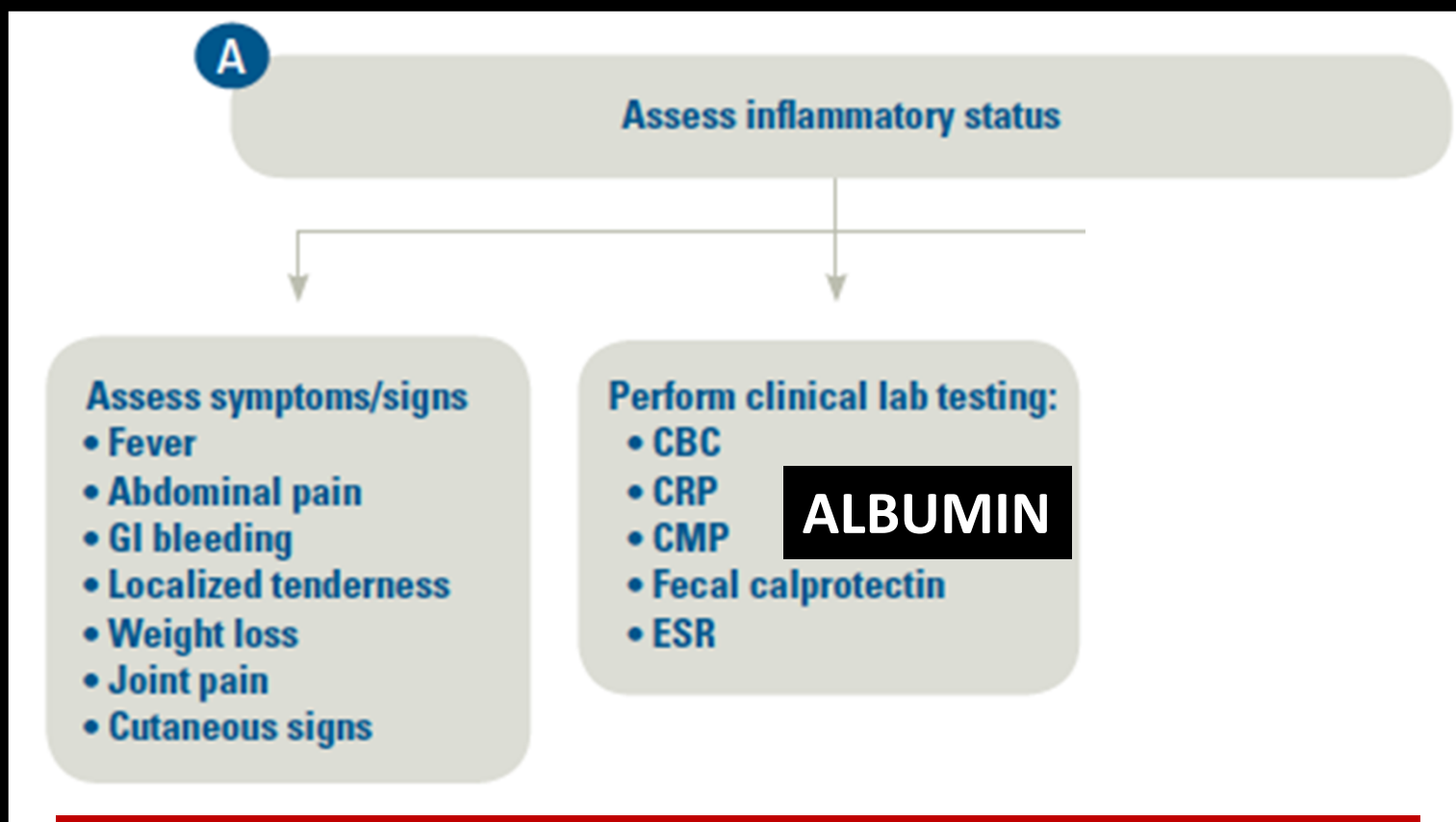
B1: inflammatory

B2: stricturing

B3: penetrating

p: perianal

Step 2: Clinical activity assessment



Are systemic signs of inflammation present?
Are extra-intestinal manifestations present?

Harvey-Bradshaw Index

General well-being (previous day)

0 = Very Well	3 = Very poor
1 = Slightly below average	4 = Terrible
2 = Poor	

Abdominal pain (previous day)

0 = None	2 = Moderate
1 = Mild	3 = Severe

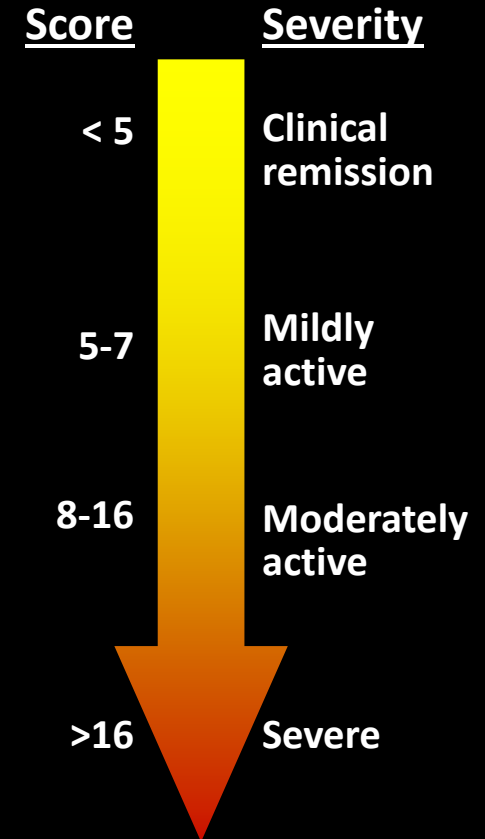
Abdominal mass

0 = None	3 = Definite
1 = Dubious	4 = Definite and tender

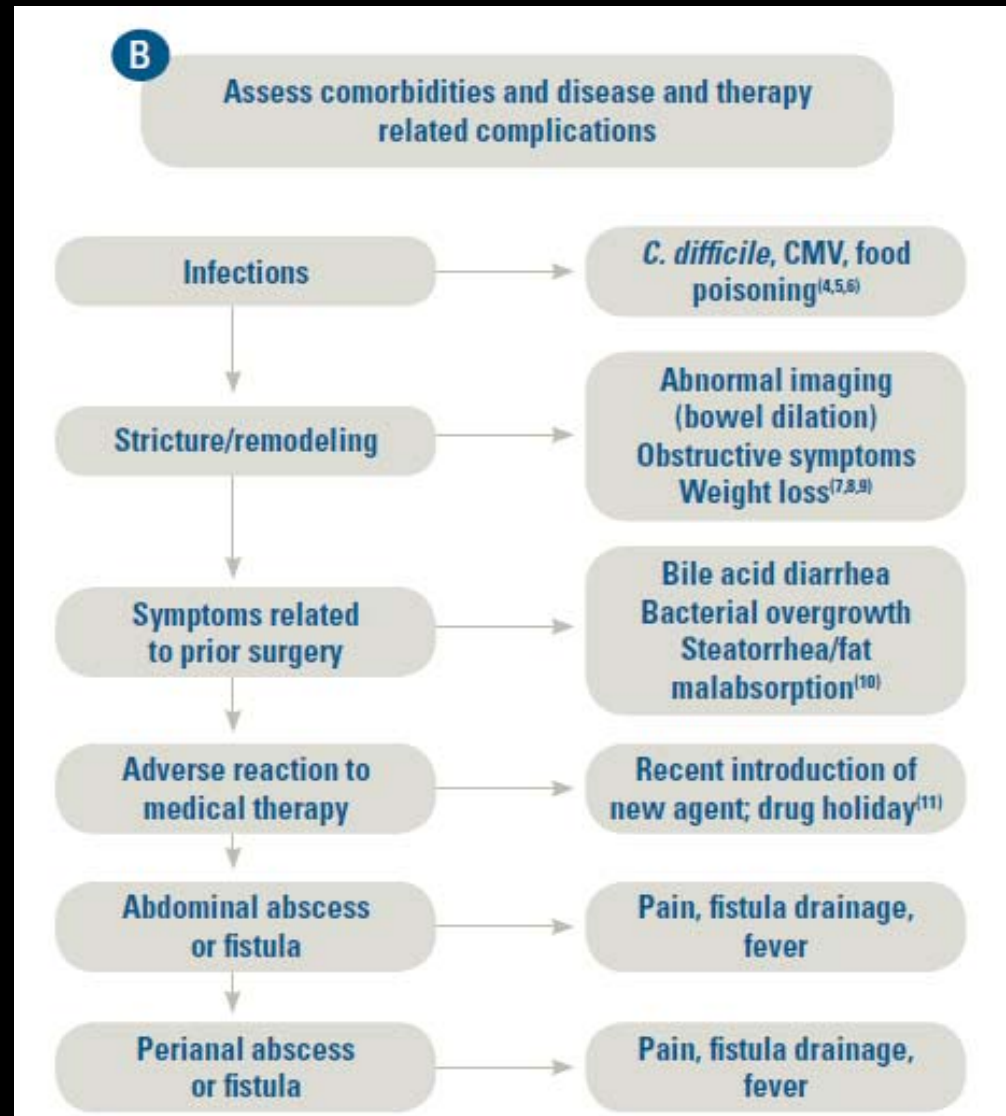
Number of liquid stools per day

Complications (1 point each)

Arthralgias	Pyoderma gangrenosum
Uveitis	Anal fissure
Erythema nodosum	New fistula
Aphthous ulcers	



Clinical activity assessment



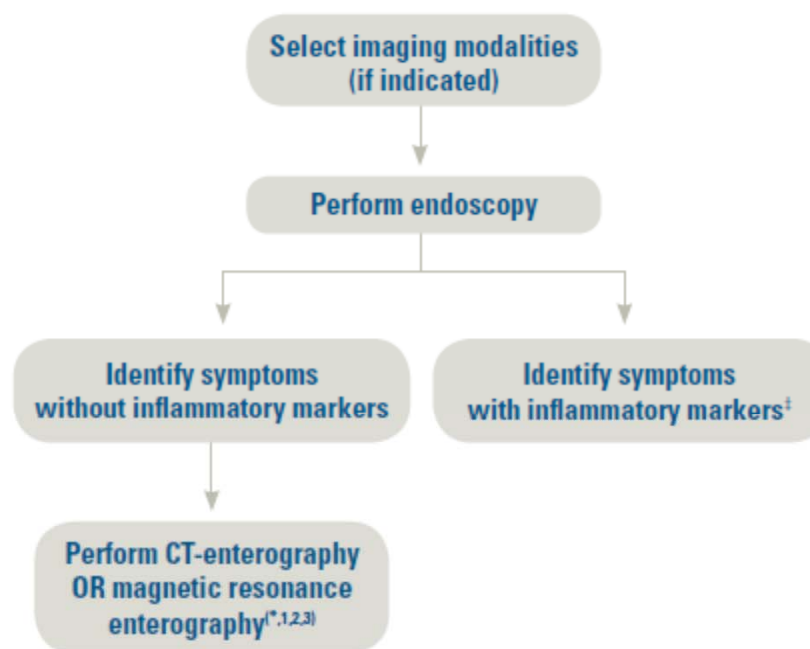
Are features of stricturing/penetrating disease present?
Are there other explanations for symptoms?

Step 3: Diagnostic evaluation

Is endoscopy always the first choice in the evaluation or should imaging be the first choice?

* Selection depends on local expertise and experience with imaging modalities. Magnetic resonance enterography is preferred due to the reduction in ionizing radiation, particularly for younger patients. If patient is less than 50 years of age, we suggest using magnetic resonance enterography.

‡ Consideration could be given as to whether to make treatment decisions based on inflammatory markers versus confirming with colonoscopy. This may depend on whether there was historically good correlation between the biomarker selected and colonoscopy in the specific patient.



If suspect small bowel etiology → obstructive or fistulizing symptoms, then imaging first
If suspect colonic etiology or inflammatory ileal etiology, then colonoscopy first

Step 4: Identify low or high-risk features

C

Assess current and prior disease burden

Identify patient as low risk⁽¹²⁾

- Age at initial diagnosis > 30 years
- Limited anatomic involvement
- No perianal and/or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No stricturing and/or penetrating behavior

Identify patient as moderate/high risk⁽¹²⁾

- Age at initial diagnosis < 30 years
- Extensive anatomic involvement
- Perianal and/or severe rectal disease
- Deep ulcers
- Prior surgical resection
- Stricturing and/or penetrating behavior

Should you recommend combination or monotherapy?

Proactive therapeutic drug monitoring?

**** Assess for response to therapy within 6 months after starting treatment ****

Step 5: IBD Pre-treatment evaluation

Baseline laboratory assessments:	<ul style="list-style-type: none">• Complete blood counts• Comprehensive metabolic profile• Fecal calprotectin• Inflammatory markers – CRP, sedimentation rate
Disease activity assessments:	<ul style="list-style-type: none">• Clinical assessments• Cross-sectional imaging• Endoscopic evaluation• Perianal disease
Medication activity:	<ul style="list-style-type: none">• Thiopurine methyltransferase activity (TPMT): enzyme activity or genetics
Infectious workup:	<ul style="list-style-type: none">• Clostridium difficile• Cytomegalovirus infection
Exposure workup:	<ul style="list-style-type: none">• Hepatitis B testing• TB testing: Quantiferon IGRA or PPD
Vaccinations:	<ul style="list-style-type: none">• MMR, Varicella exposure/vaccination status• Influenza/Pneumonia (Prevnar-13 and PPSV-23)
Prior IBD medication history:	<ul style="list-style-type: none">• Responder/non-responder?• Adherence?• Adverse effects of therapy?

Step 6: Look for factors that Influence the pharmacokinetics of biologics

	Impact on TNF antagonist PK
Presence of ADAs	Decreases drug concentration Increases clearance Worse clinical outcomes
Concomitant use of immunosuppressives	Reduces ADA formation Increases drug concentration Decreases drug clearance Better clinical outcomes
Low serum albumin concentration	Increases drug clearance Worse clinical outcome
High baseline CRP concentration	Increase drug clearance
High baseline TNF concentration	May decrease drug concentration by increasing clearance
High body size	May increase drug clearance
Sex	Males have higher clearance

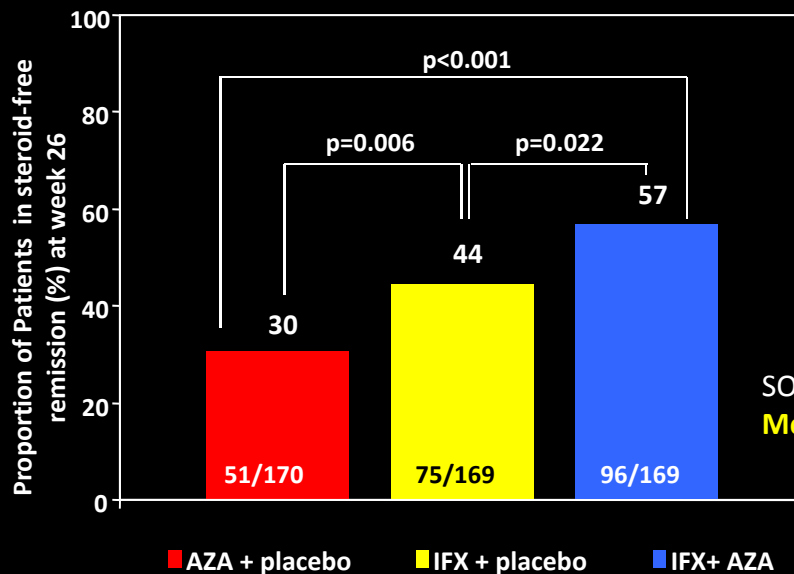
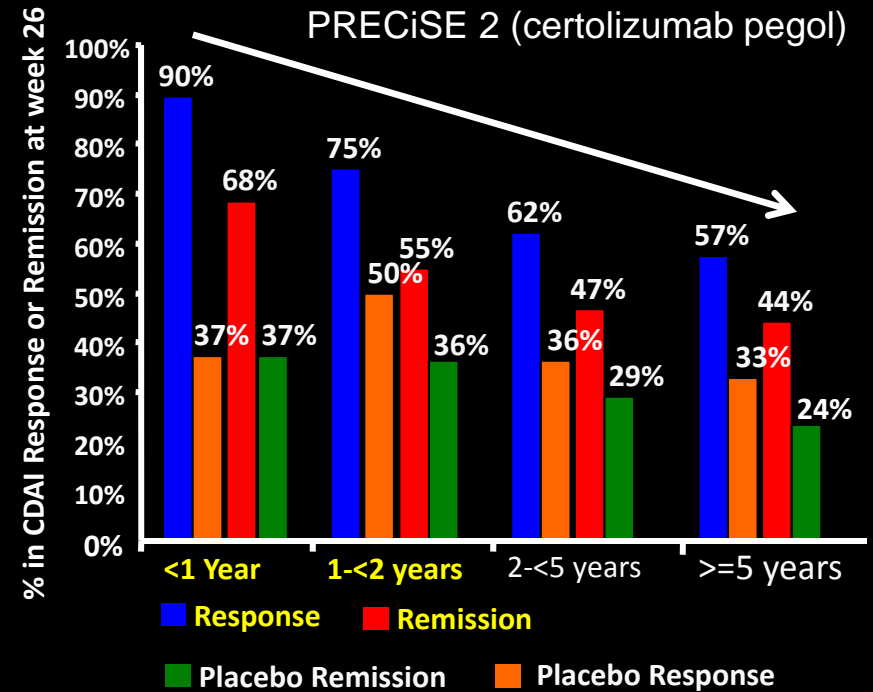
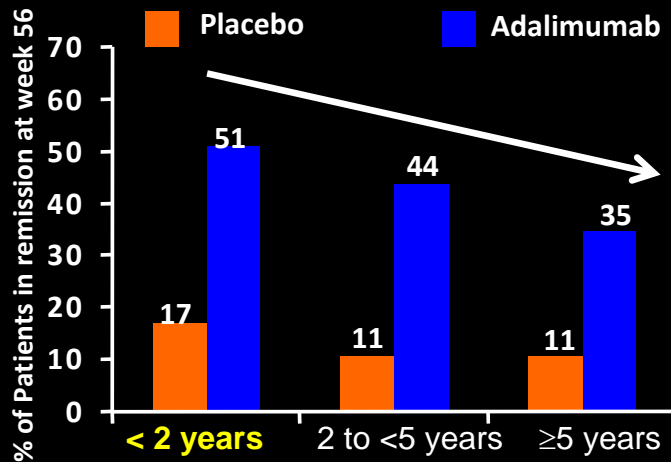
Deep ulcerations on endoscopy

Step 7: Identify treatment options - anti-TNF agents for higher-risk patients



- Right dose
- Right interval
- Right timing
- Right indication
- Evaluate for response to treatment
 - Clinical response
 - Laboratory response
 - Endoscopic/histologic response

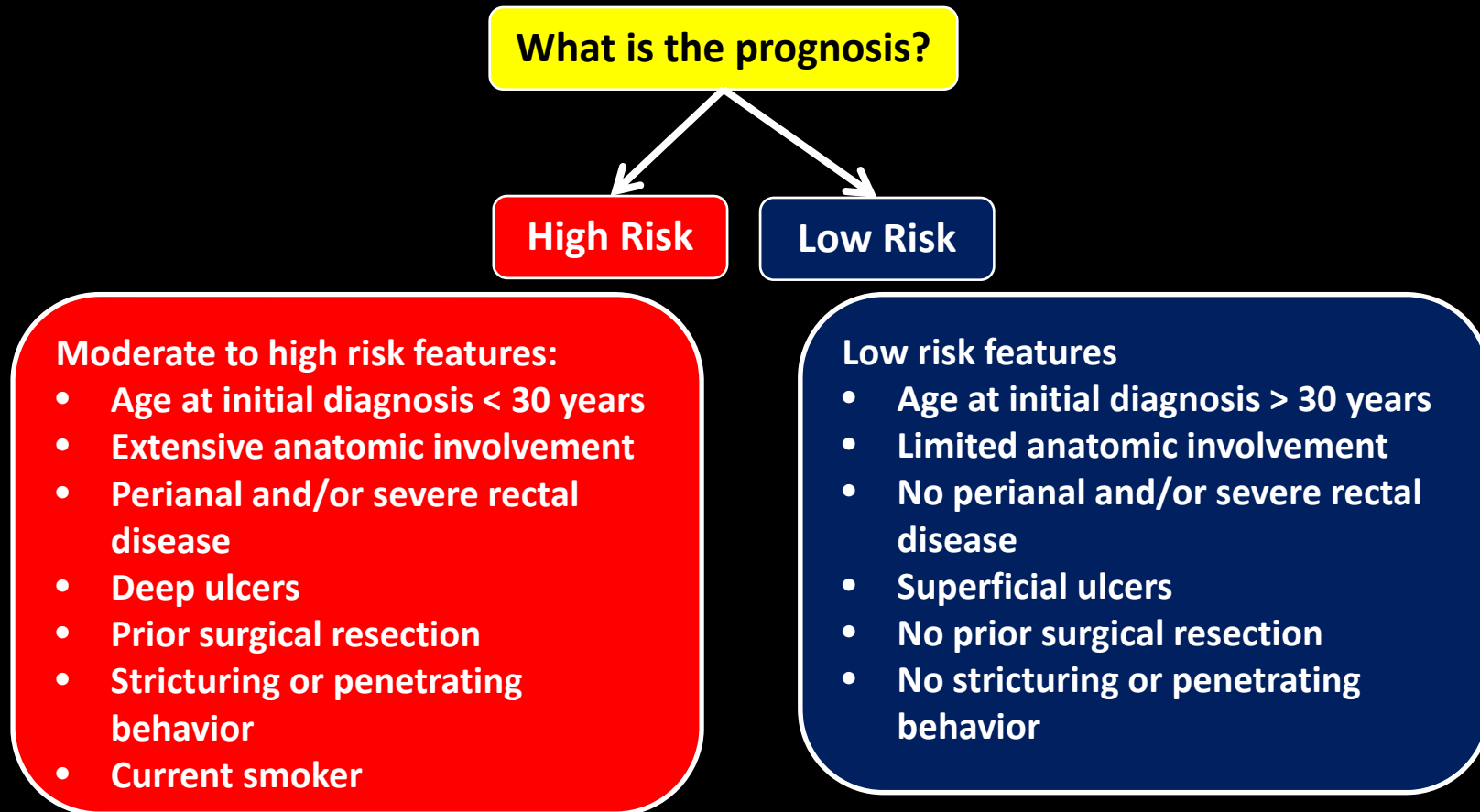
Start the most appropriate regimen early: Earlier-initiation of anti-TNF therapy is associated with an increased likelihood of remission for patients with INFLAMMATORY Crohn's disease



SONIC trial: anti-TNF and IMM naïve patients
Median duration of disease: 2 years

Schreiber S et al. *Gastroenterology*. 2007;132(Suppl 1):A-147.
 Colombel et al. *NEJM*. 2010;362:1383-95.
 Sandborn WJ, et al. *Am J Gastroenterol*. 2006;101:S454-455.
 Schreiber S, et al. *N Engl J Med*. 2007;357(3):239-250.

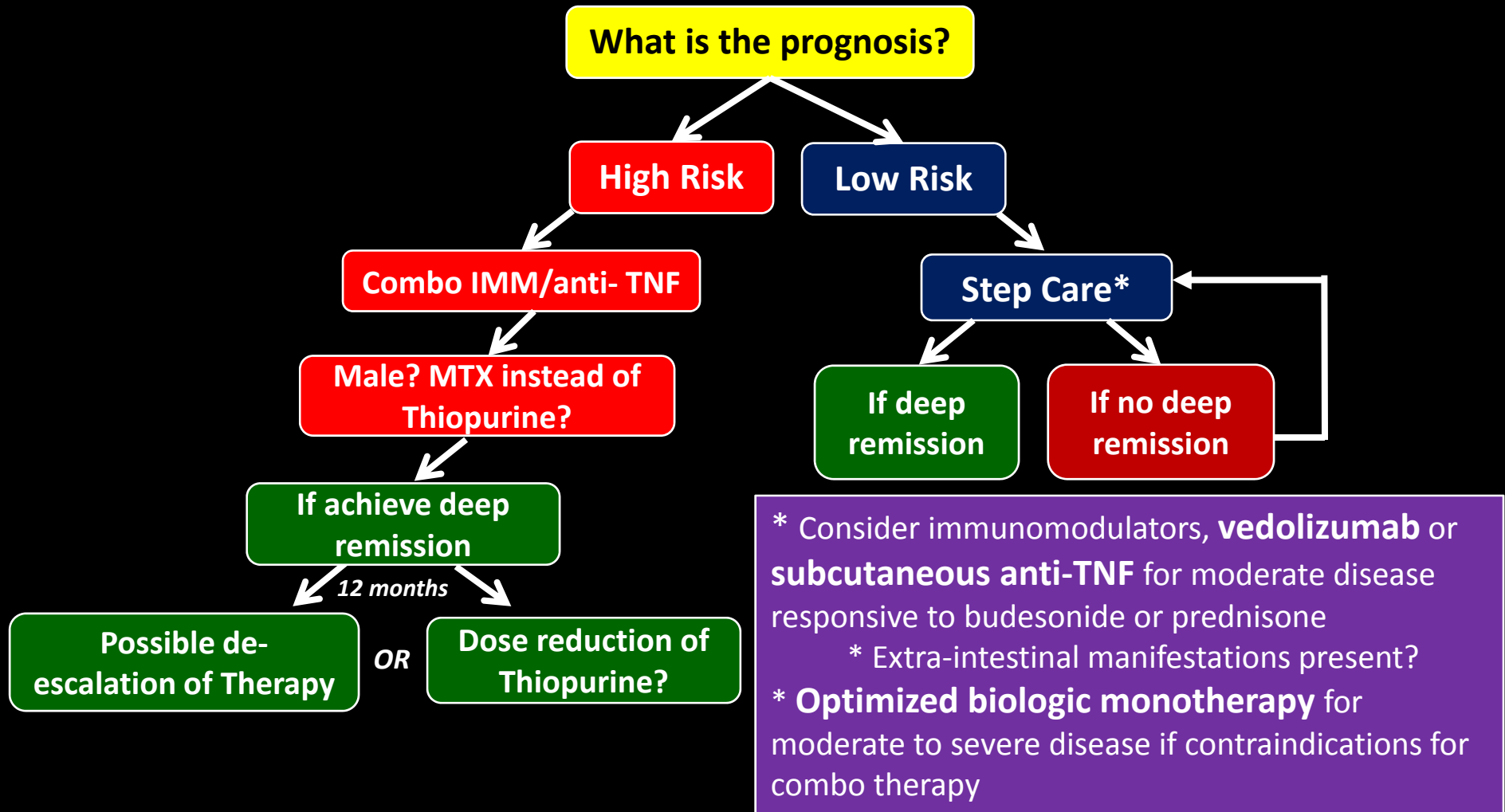
Proposed Approach to Mono or Combo Therapy in IBD



*** Are risk factors for ADA (anti-drug antibody) formation present? ***

LOW ALBUMIN

Proposed Approach to Mono or Combo Therapy in IBD



Proposed Approach to Mono or Combo Therapy in IBD

Anti-TNF therapy

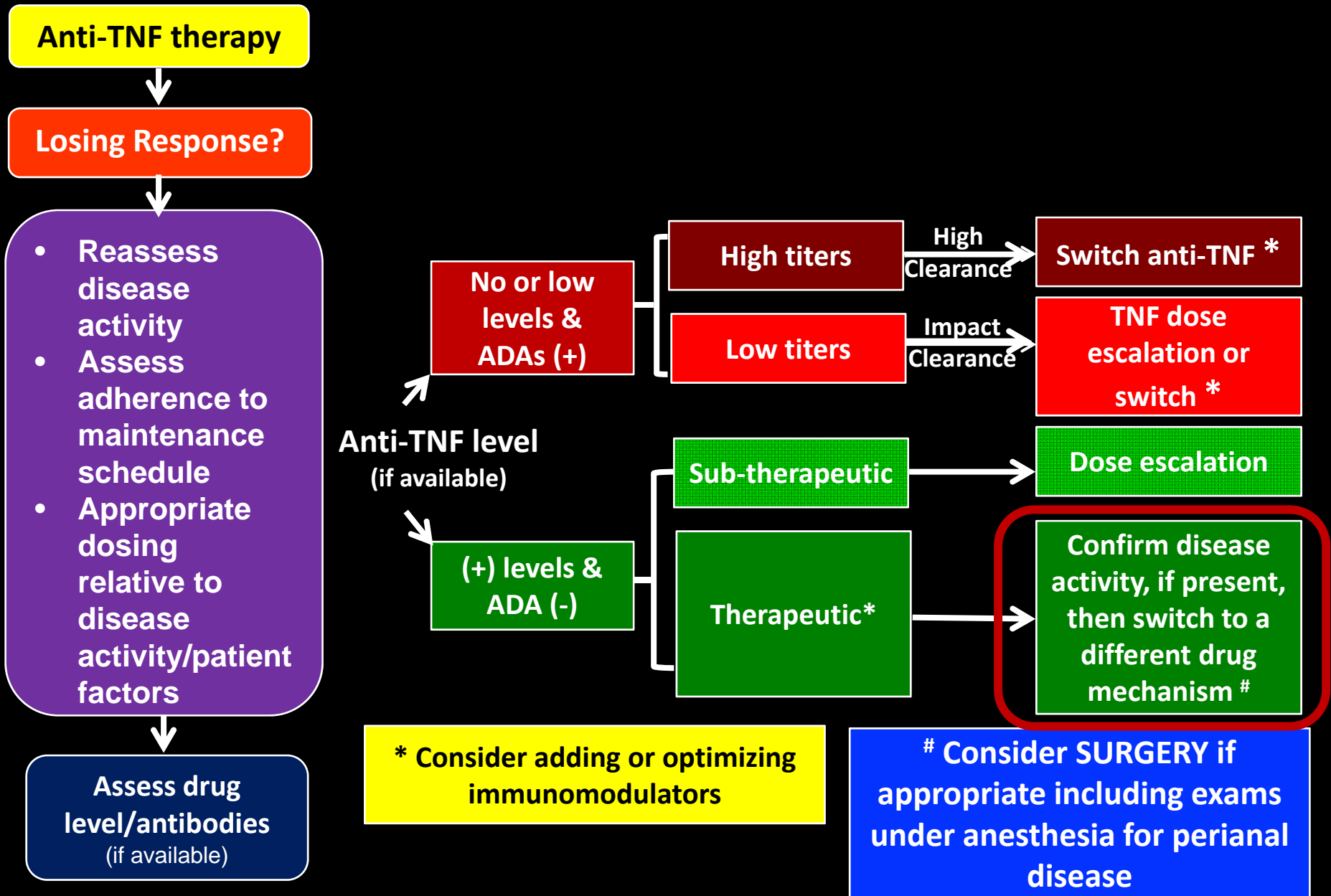


Proactive monitoring:

- Perianal Crohn's
- Upper GI tract/proximal small bowel Crohn's
- Smoking history
- Surgical resections with rapid endoscopic recurrence

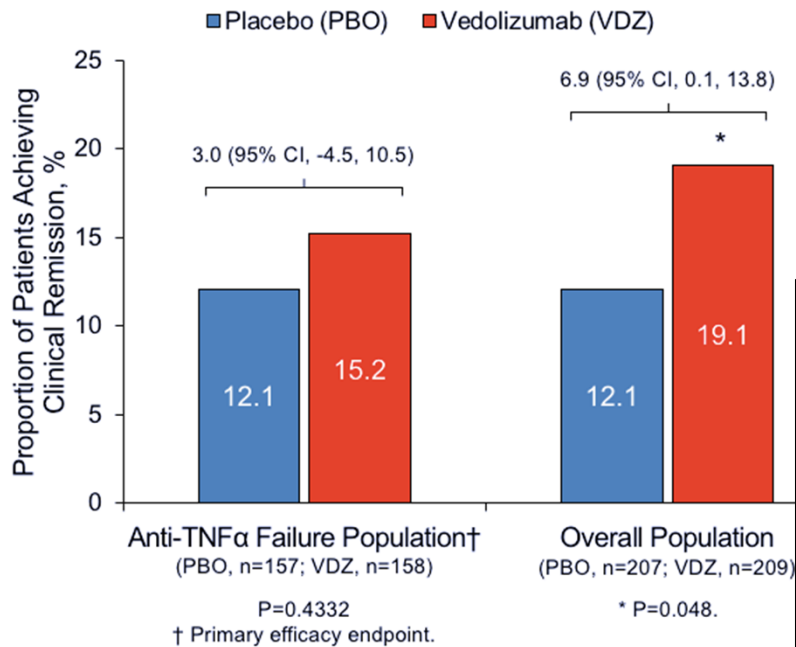
- Aim for higher levels
- If therapeutic levels but persistent activity → consider ustekinumab or vedolizumab with proactive monitoring
 - Ustekinumab if extra-intestinal manifestations
 - Vedolizumab may take longer to work
- Smoking cessation
- Efficacy of combination therapy to be determined, but immunogenicity still possible

Proposed Approach to Mono or Combo Therapy in IBD



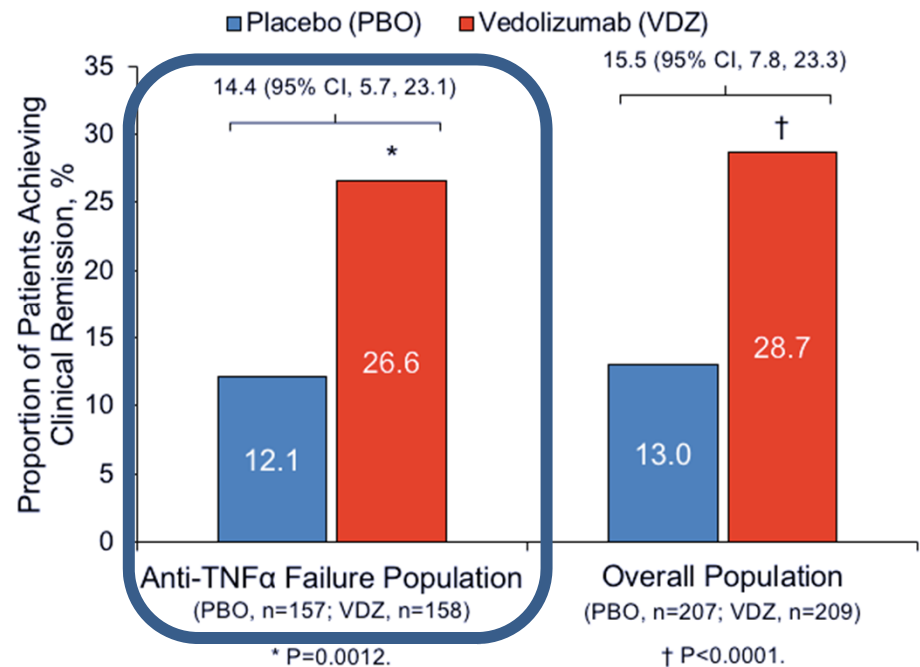
Step 7: Identify treatment options: vedolizumab (anti-TNF failures)

Clinical Remission (CDAI ≤150) at Week 6



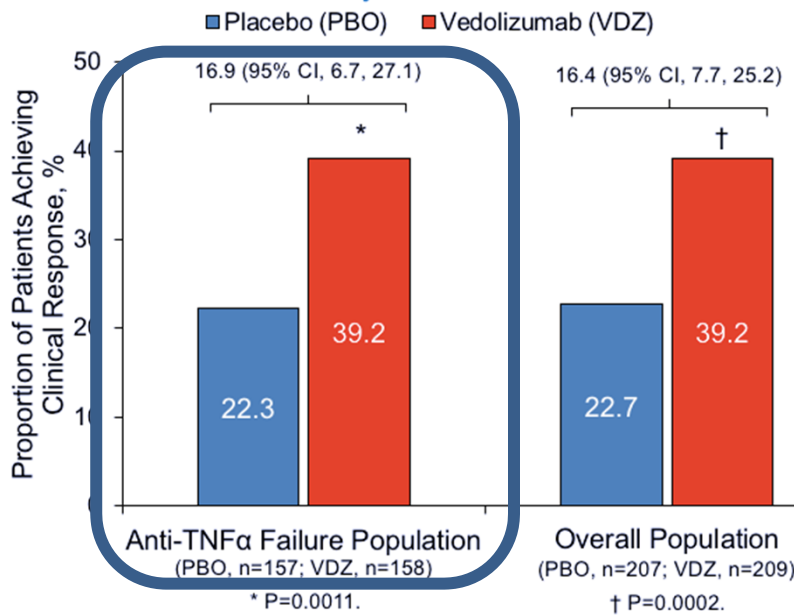
Inclusion criteria – required objective evidence of disease activity and CDAI between 220-400

Clinical Remission (CDAI ≤150) at Week 10

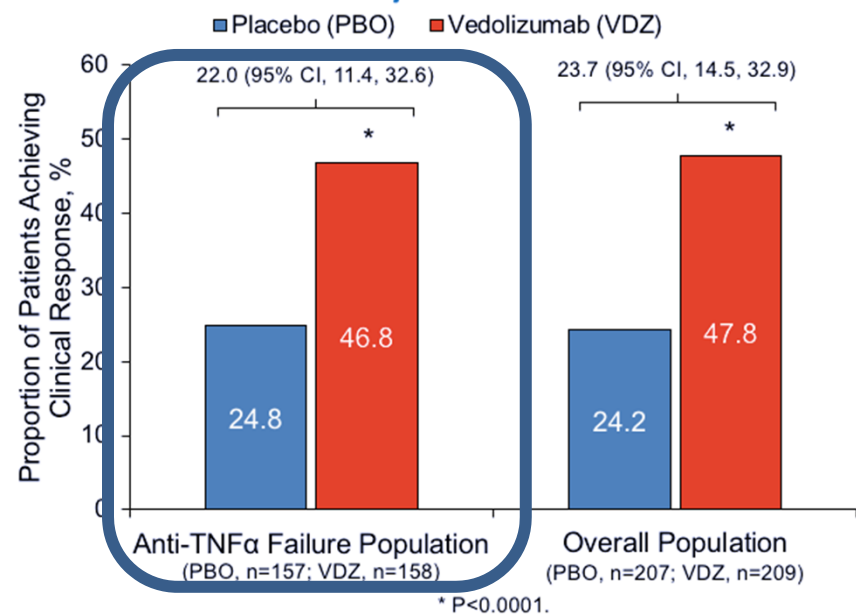


Step 7: Identify treatment options: vedolizumab (anti-TNF failures)

CDAI 100 Response (≥ 100 -Point Reduction in CDAI Score From Baseline to Week 6)



CDAI 100 Response (≥ 100 -Point Reduction in CDAI Score From Baseline to Week 10)



Step 7: Identify treatment options: vedolizumab

Treatment-Emergent Adverse Events: Safety Population

	Anti-TNF α -Failure Population (N=315)		Overall Population (N=416)	
	Placebo n=157	VDZ n=158	Placebo n=207	VDZ n=209
Any adverse event (AE), %	102 (65)	94 (59)	124 (60)	117 (56)
Serious AEs, %	14 (9)	8 (5)	16 (8)	13 (6)
Discontinued due to AE	2 (1)	6 (4)	4 (2)	8 (4)

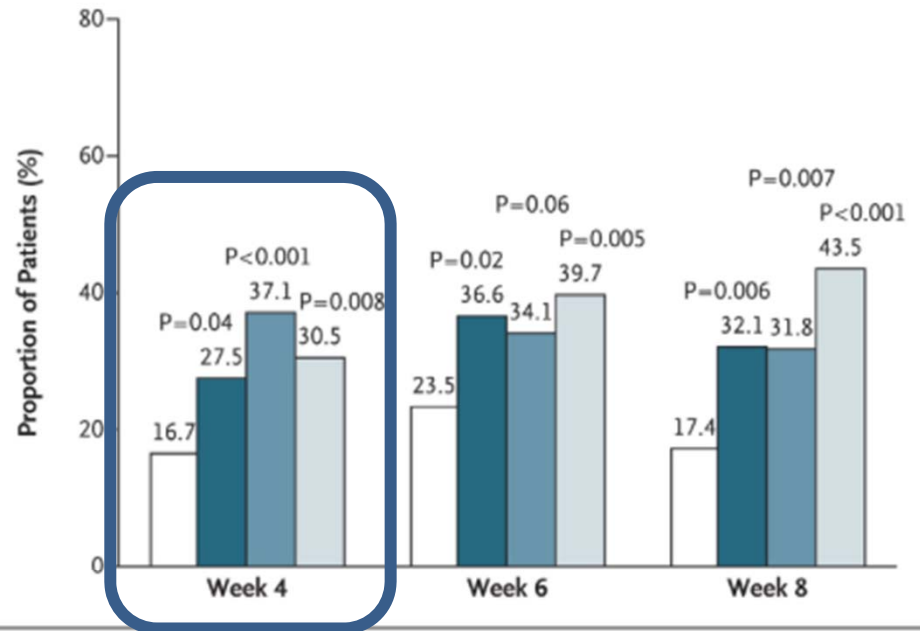
Step 7: Identify treatment options: ustekinumab (all anti-TNF exposed)

Inclusion criteria based on CDAI only

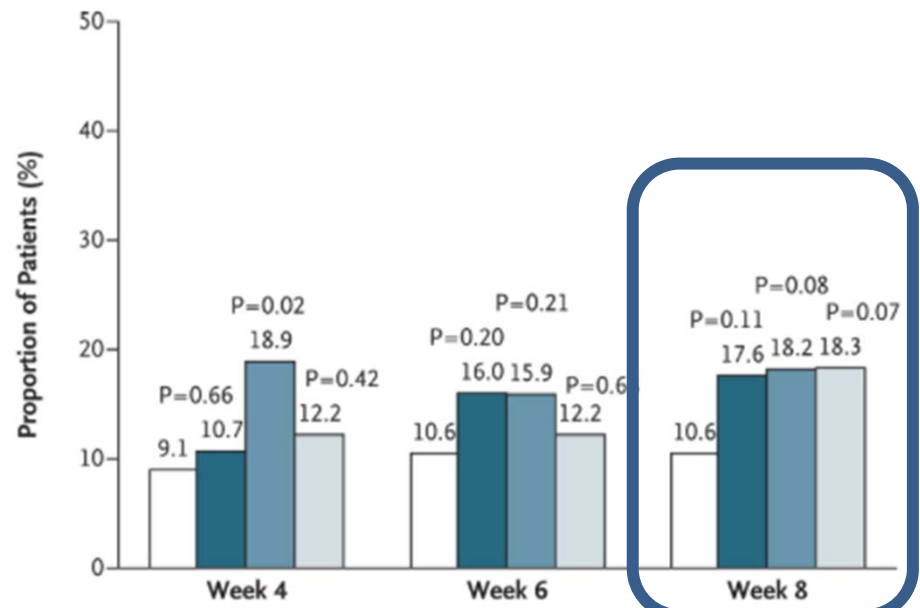
Sandborn et al. NEJM 2012

□ Placebo (N=132) ■ Ustekinumab, 1 mg/kg (N=131) ■ Ustekinumab, 3 mg/kg (N=132) ■ Ustekinumab, 6 mg/kg (N=131)

A Clinical Response



B Clinical Remission



Step 7: Identify treatment options: ustekinumab

Table 2. Adverse Events during the Induction Phase (Week 0 to Week 8).

Adverse Event	Placebo (N=132)	Ustekinumab			
		1 mg/kg (N=130)	3 mg/kg (N=133)	6 mg/kg (N=131)	Combined (N=394)
<i>number of patients (percent)</i>					
Any adverse event	94 (71.2)	89 (68.5)	88 (66.2)	80 (61.1)	257 (65.2)

Step 8: Look for factors that Influence the safety of prescribing biologics

Abscess on imaging	Drain first if accessible via IR Consider surgical resection if appropriate with post-op treatment
Recurrent obstructions	Consider surgical resection first with appropriate post-op treatment
(+) TB testing	Consider vedolizumab Treatment delay by 1-2 months prior to anti-TNF or ustekinumab
Melanoma history	Consider vedolizumab Avoid anti-TNFs, ustekinumab
Current or recent malignancy	Hold treatment if current chemotherapy Consider vedolizumab
Drug-induced lupus	Vedolizumab or ustekinumab
TNF-associated psoriasis	Vedolizumab or ustekinumab
Older age	Moderate disease – vedolizumab Severe disease or higher risk features – ustekinumab Surgery if limited stricturing disease

Summary

- Risk stratification based on disease and patient factors is key for positioning biologics
- Severe disease – infusion based-anti-TNF as combo therapy, optimized infusion-based anti-TNF monotherapy, ustekinumab
- Moderate disease – subcu or IV anti-TNF (IV if obese), vedolizumab (if no EIM)
- Older patients – moderate: vedolizumab, severe: ustekinumab
- Malignancy history – vedolizumab (including melanoma)
- Surgery first for appropriate indications