

Inflammatory Bowel Disease: An Overview

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- Clinical focus: IBD and Women's Health
- Research focus: IBD, Women's Health, Psychosocial Factors affecting IBD and Pediatric to Adult Transition

DISCLOSURES

Research Support: AbbVie, Janssen, Takeda
Consultant: AbbVie



OBJECTIVES

- Identify symptoms of IBD and learn how to diagnose Crohn's disease and ulcerative colitis
- Understand differences between Crohn's disease and ulcerative colitis
- Review medical management of inflammatory bowel disease



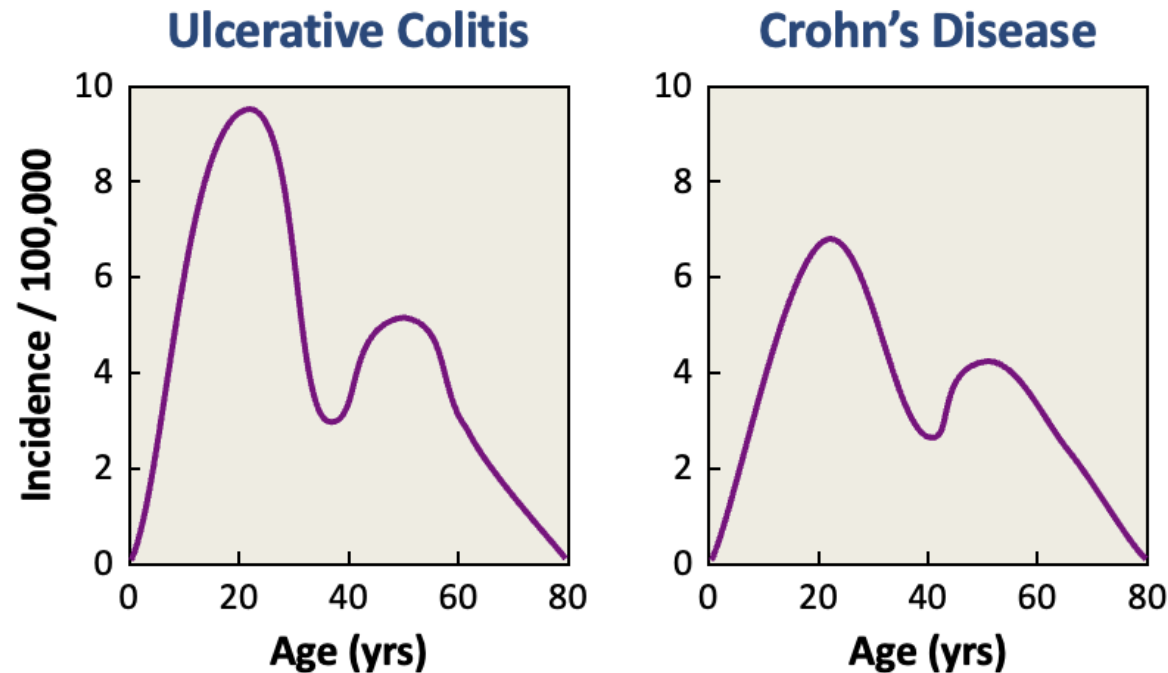
What is IBD?

- Chronic inflammatory condition of the gastrointestinal tract
- Consists of 2 diseases:
 - Crohn's disease
 - Ulcerative colitis
 - (Indeterminate colitis)
- Approximately 2.4 million patients in the US have Crohn's disease or ulcerative colitis
- The incidence and prevalence of IBD are increasing worldwide, particularly in low-prevalence areas



Age-Specific Incidence of IBD*

- Age of onset usually young (15-35) though can also occur later in life

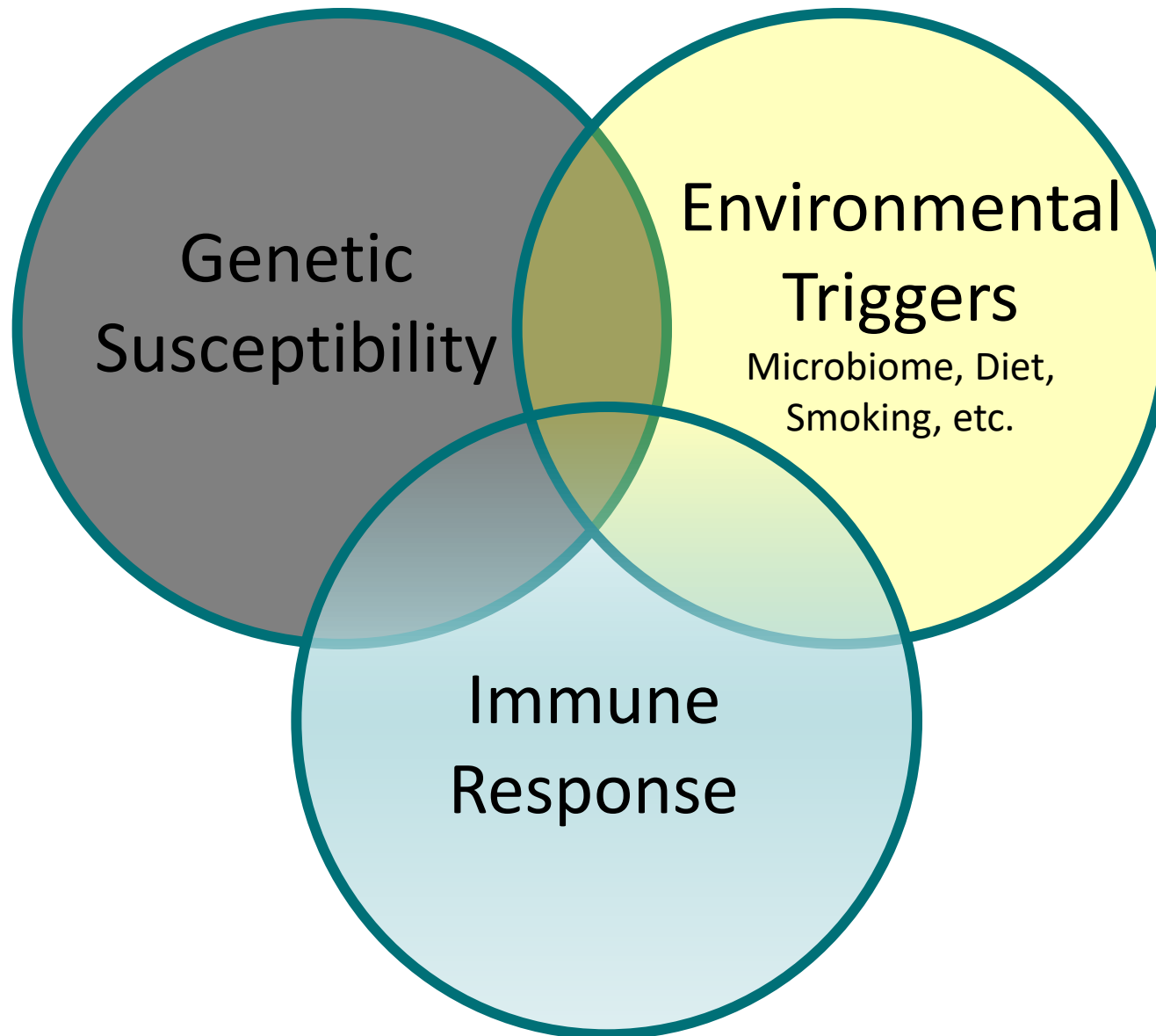


*Per 100,000 population

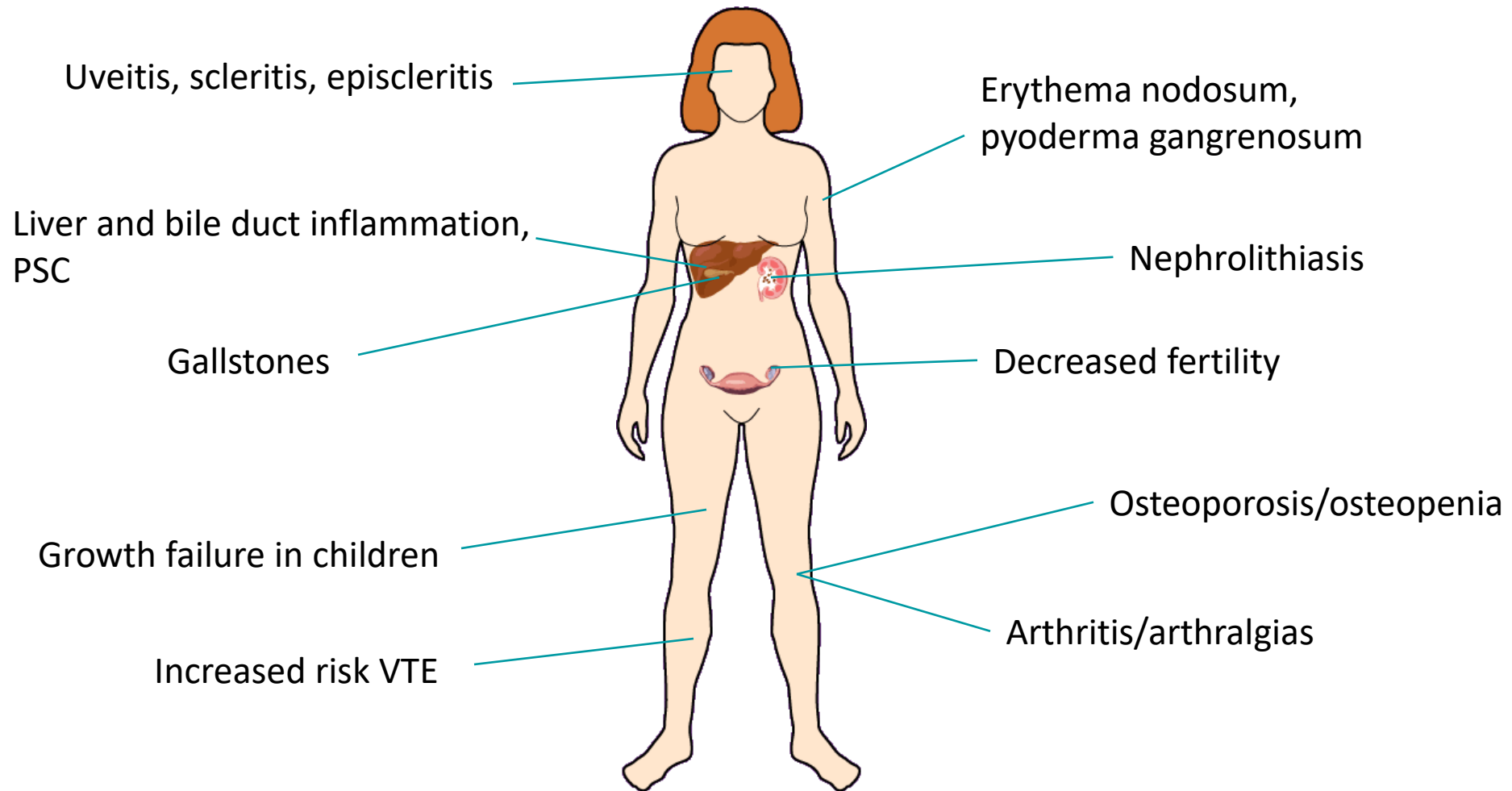
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Epidemiology of IBD



Systemic Complications of IBD



Ulcerative Colitis



Clinical Features of Ulcerative Colitis

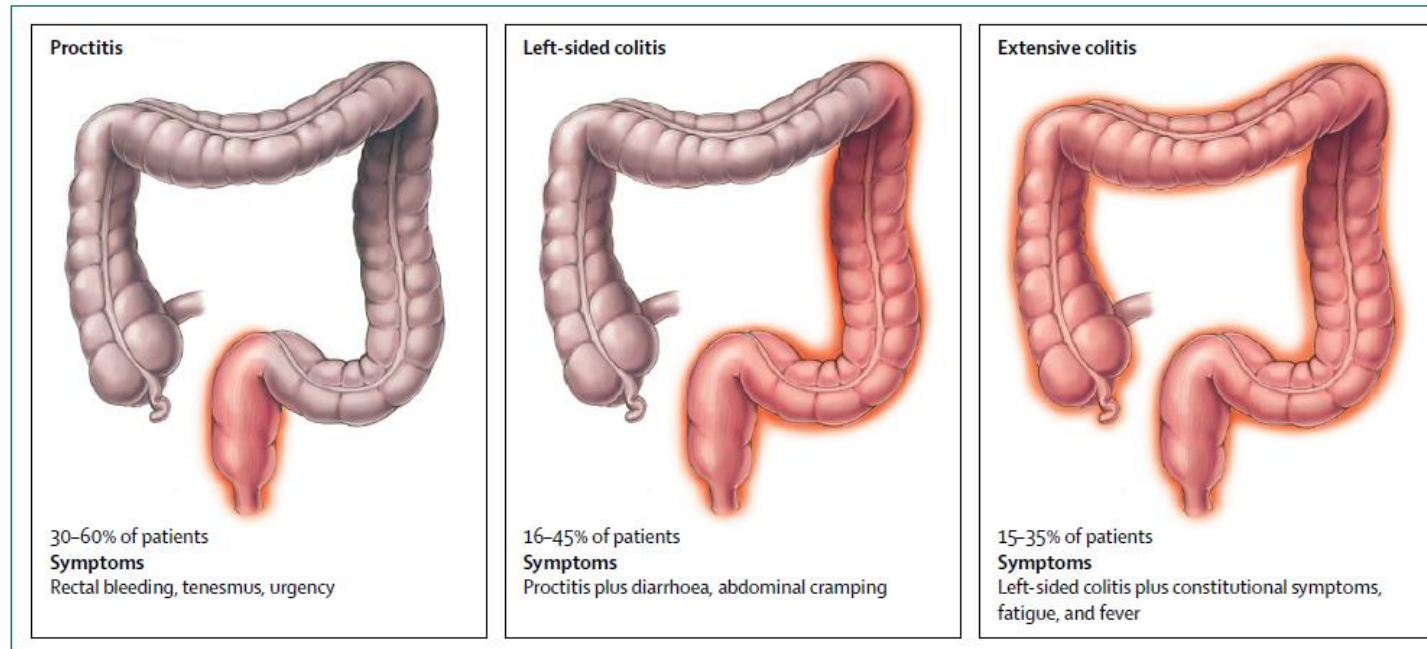
- Ulcerative colitis was first described in 1859
- Starts in the rectum and moves proximally to affect part or all of the colon
- Symptoms (depend on extent and severity of inflammation):
 - Bloody diarrhea with or without mucus is the hallmark finding of ulcerative colitis
 - Increased frequency
 - Urgency, tenesmus
 - Nocturnal diarrhea
 - Some patients may demonstrate paradoxical constipation
 - More severe presentations may lead to abdominal pain, fever, weight loss, and malaise



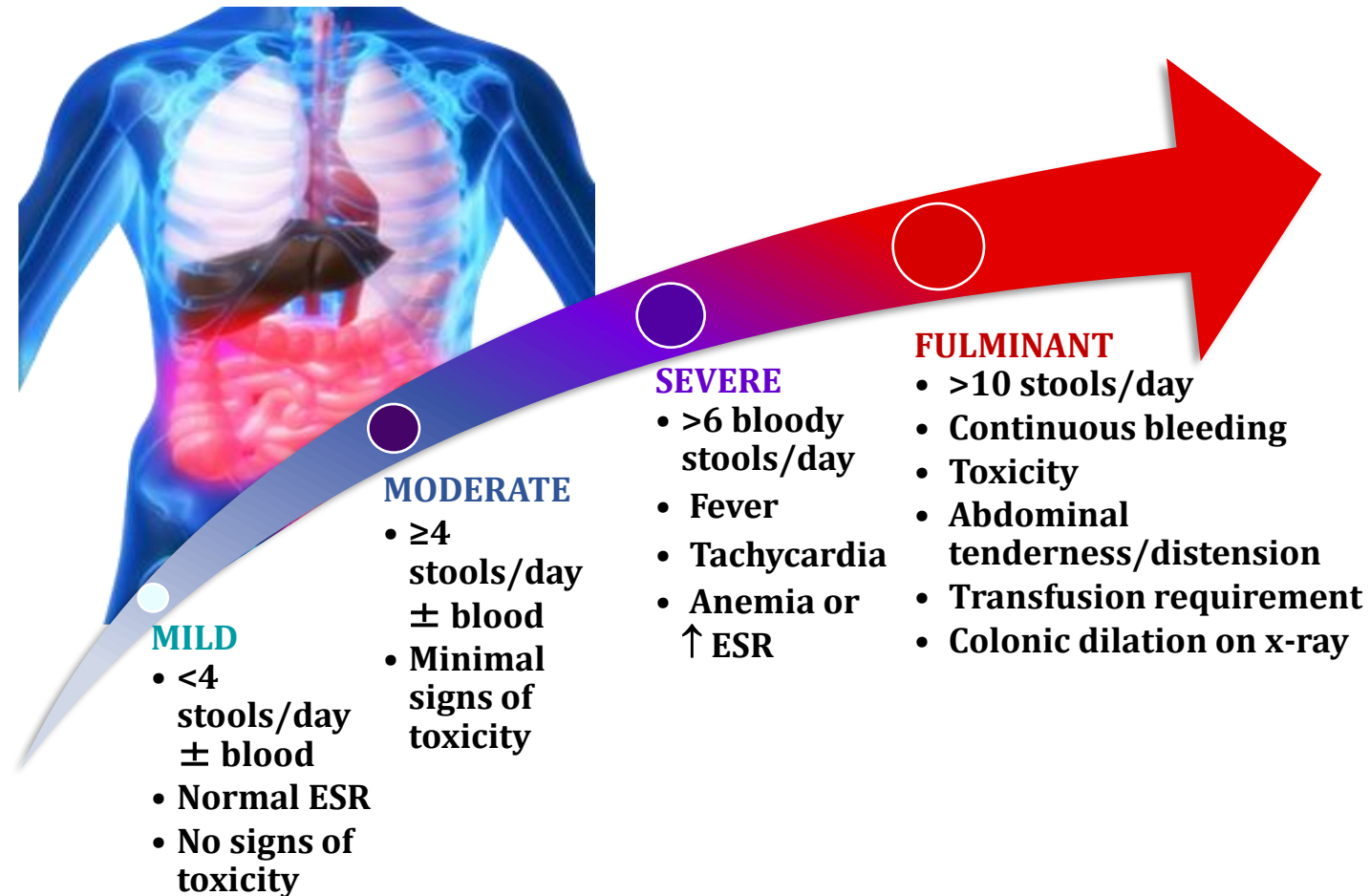
Classification of Disease: Montreal Classification

Table 2 Montreal classification of extent of ulcerative colitis (UC)

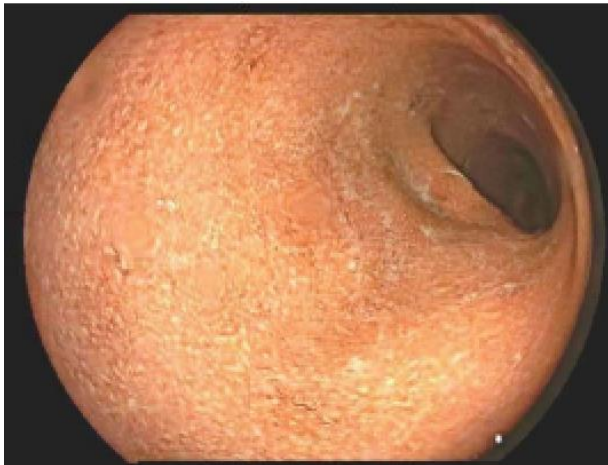
Extent	Anatomy
E1	Ulcerative proctitis Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC) Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis) Involvement extends proximal to the splenic flexure



Classification of UC Severity



Ulcerative colitis - endoscopically

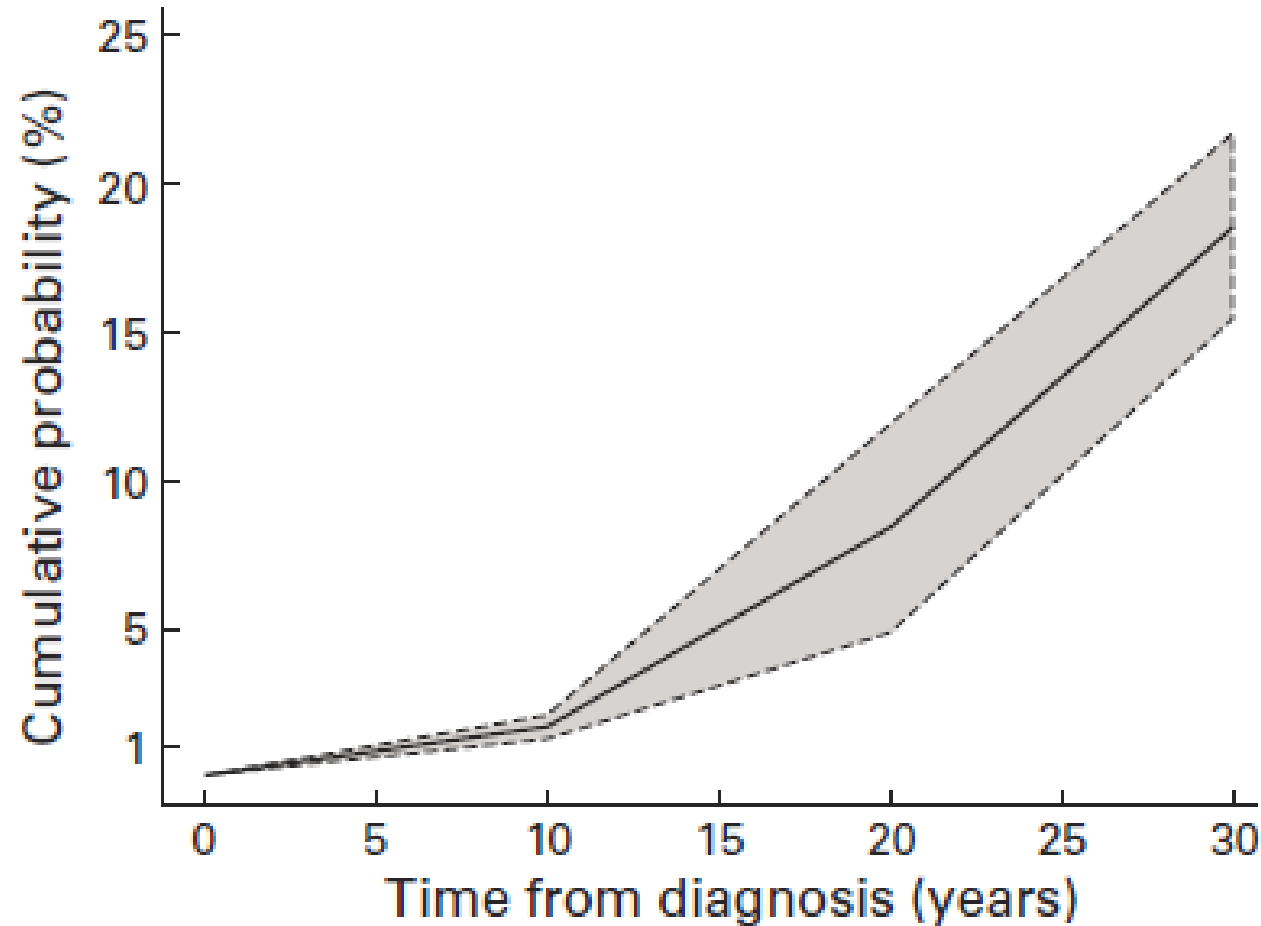


Disease Extent is Dynamic and Important

- Among patients initially diagnosed with proctitis or left sided disease, 27-54% will go on to develop extensive colitis
- Patients initially diagnosed with extensive colitis are more likely to:
 - have frequent complications
 - have extraintestinal manifestations
 - develop colon cancer
 - require colectomy



Ulcerative Colitis and Colorectal Cancer



Current recommendation is to start dysplasia/colon cancer screening with a colonoscopy every 2 years starting 8-10 years after diagnosis

Crohn's Disease



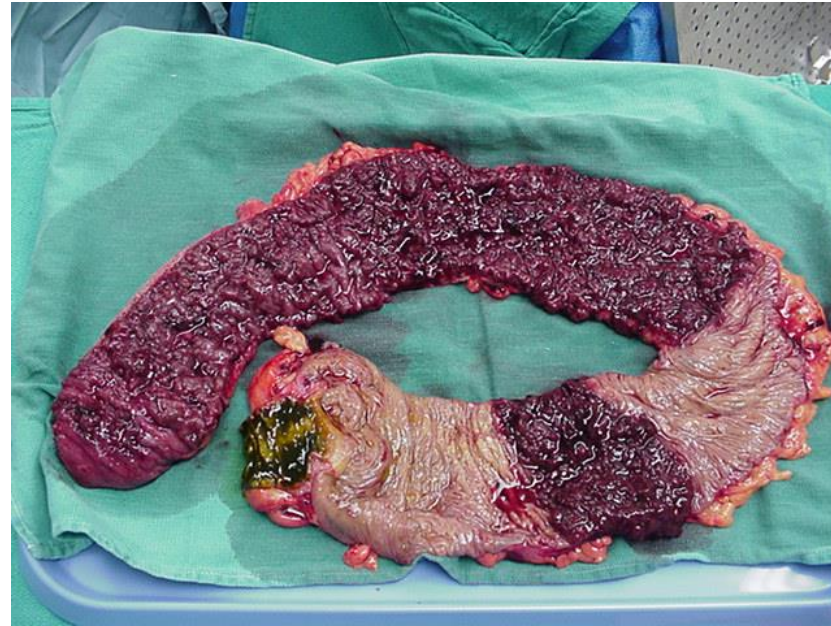
Clinical Features of Crohn's Disease

- The clinical presentation of Crohn's disease is dependent on the location and behavior of the disease
 - Location: small bowel (usually ileum), large bowel (colon) or both, though can affect any part/all of the GI tract
 - Patchy in distribution; “skip lesions”
 - Behavior: inflammatory, stricturing, fistulizing/penetrating
- Common presenting symptoms include:
 - Abdominal pain
 - Weight loss
 - Diarrhea
 - Fatigue
 - Fever
 - Malnourishment
 - Growth retardation among children
 - Rectal bleeding
- Up to 1/3 of patients will present with perianal involvement at the time of diagnosis



Diagnosis of Crohn's Disease

- Colonoscopy +/- Upper Endoscopy with biopsies
- Cross-sectional imaging:
 - CT Enterography
 - MR Enterography (consider radiation burden of CT)
 - Intestinal ultrasound
- Video Capsule Endoscopy



Images courtesy of Kim Isaacs, MD, PhD/Ed Barnes, MD, MPH

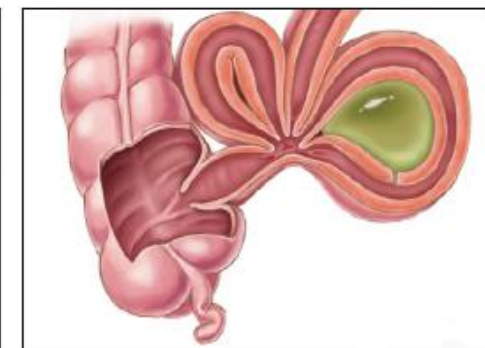
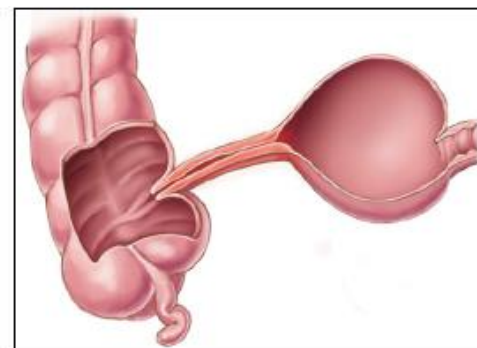
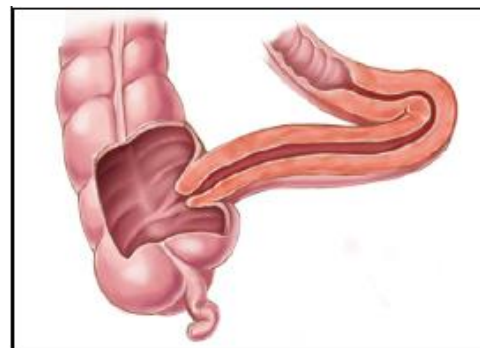
Montreal Classification of Crohn's Disease

Montreal

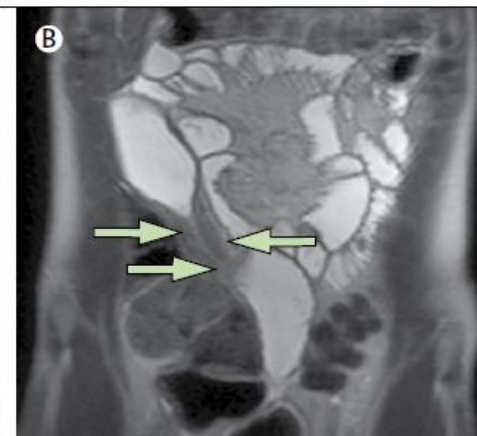
A1 below 16 y
A2 between 17 and 40 y
A3 above 40 y

L1 ileal
L2 colonic
L3 ileocolonic
L4 isolated upper disease*

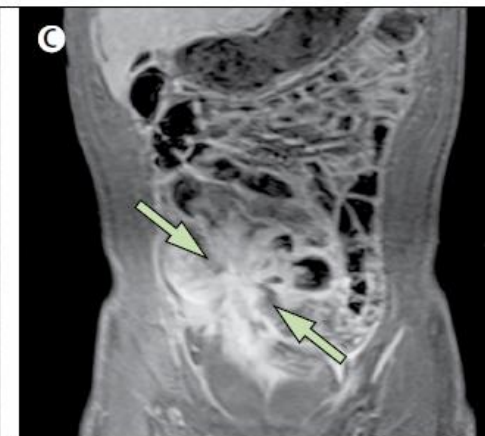
B1 non-stricturing, non-penetrating
B2 stricturing
B3 penetrating
p perianal disease modifier†



B1: Inflammatory

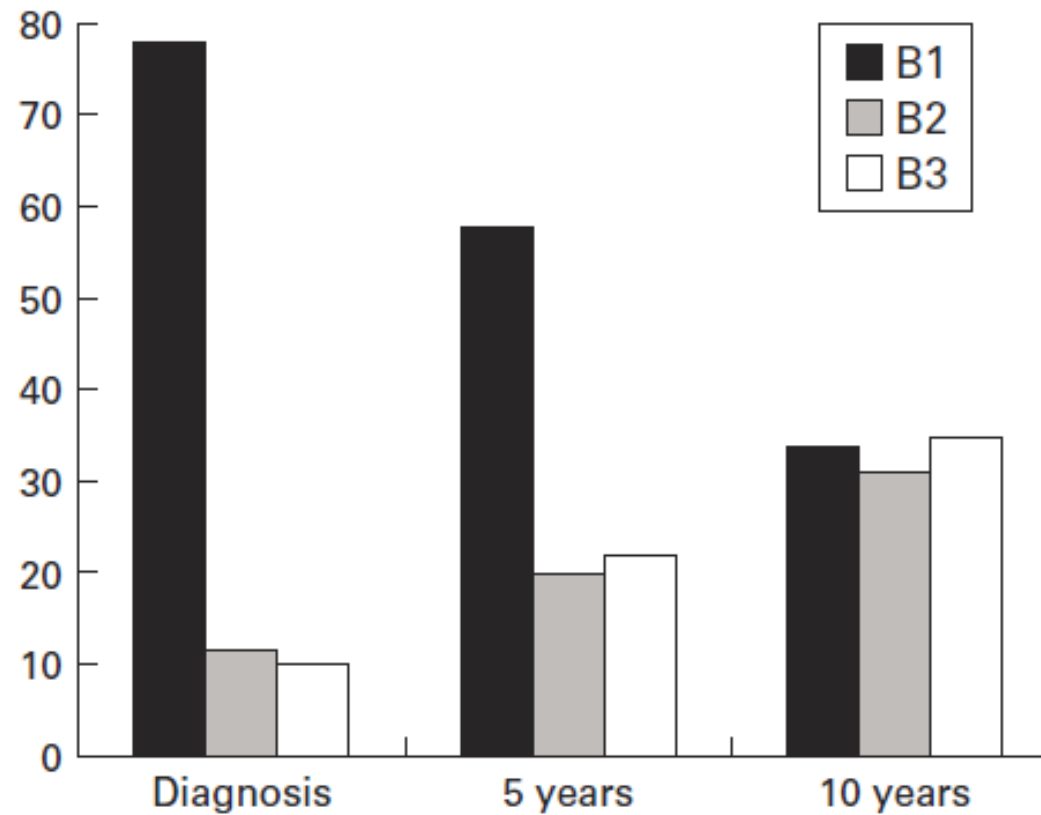


B2: Stricturing



B3: Penetrating

Changes in Disease Behavior over Time



Differentiating Crohn's Disease from Ulcerative Colitis

Crohn's Disease

- Can affect the entire GI tract (mouth to anus)
- Rectal sparing
- Patchy, non-continuous presentation
- Transmural inflammation
- Complications include fistulas and strictures
- Granulomas on biopsy

Ulcerative Colitis

- Only affects the colon
- Starts in the rectum and progresses in an ascending manner
- Mucosal involvement only

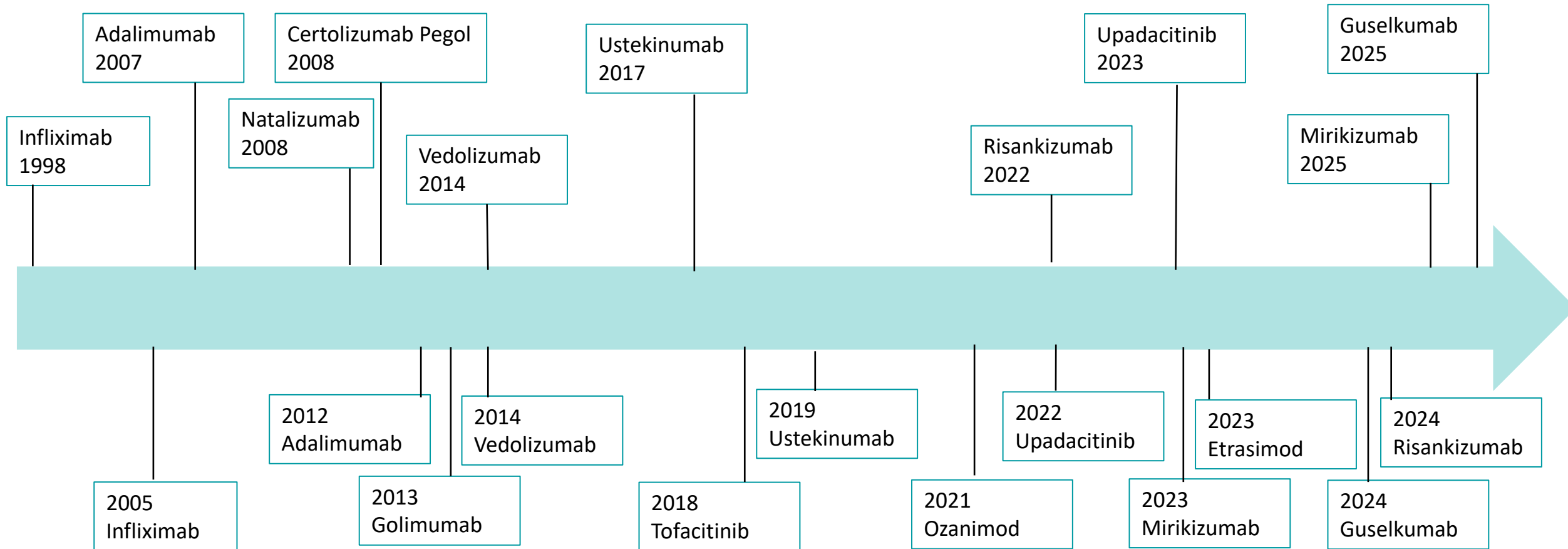


Medical Therapy for IBD



Timeline of therapies

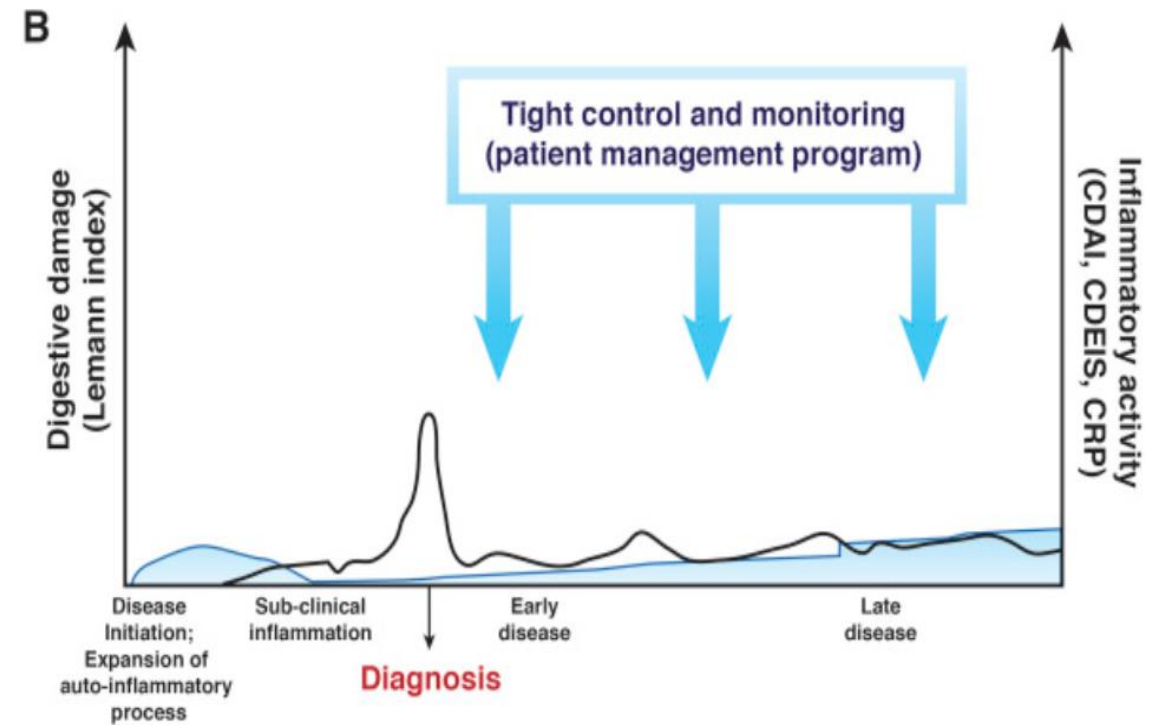
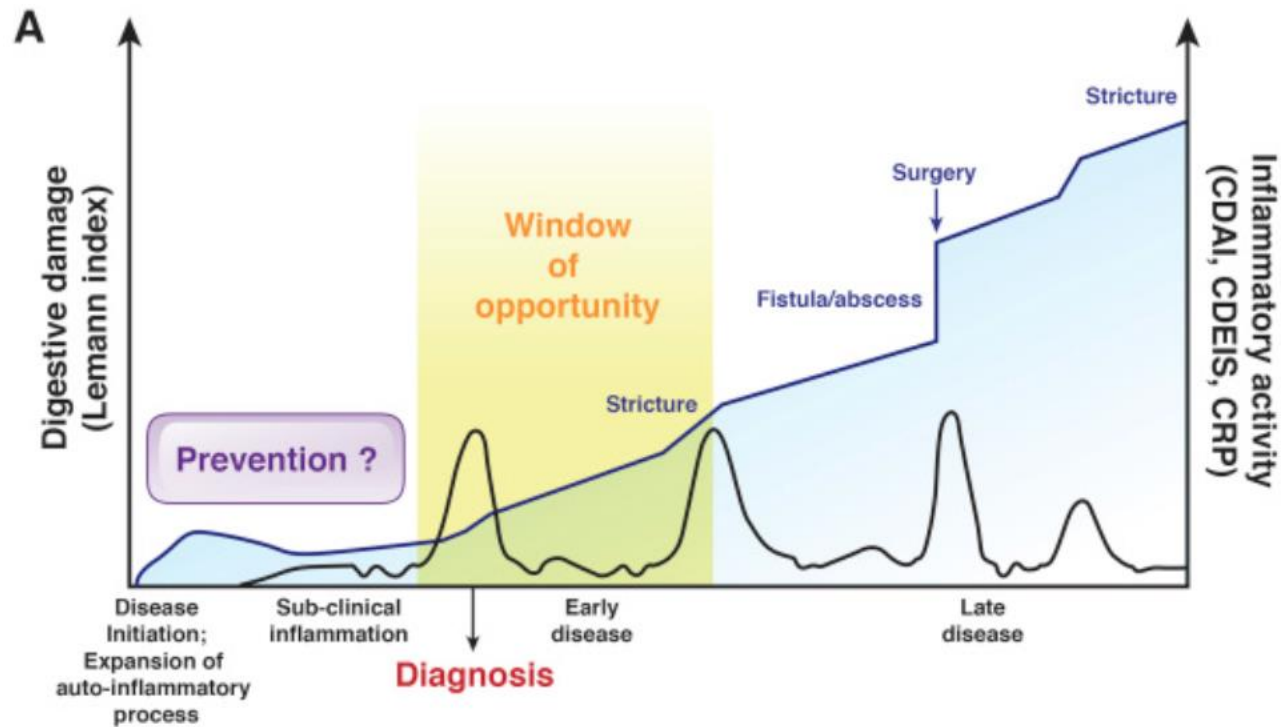
Crohn's Disease



Ulcerative Colitis



Importance of Early and Effective Therapy



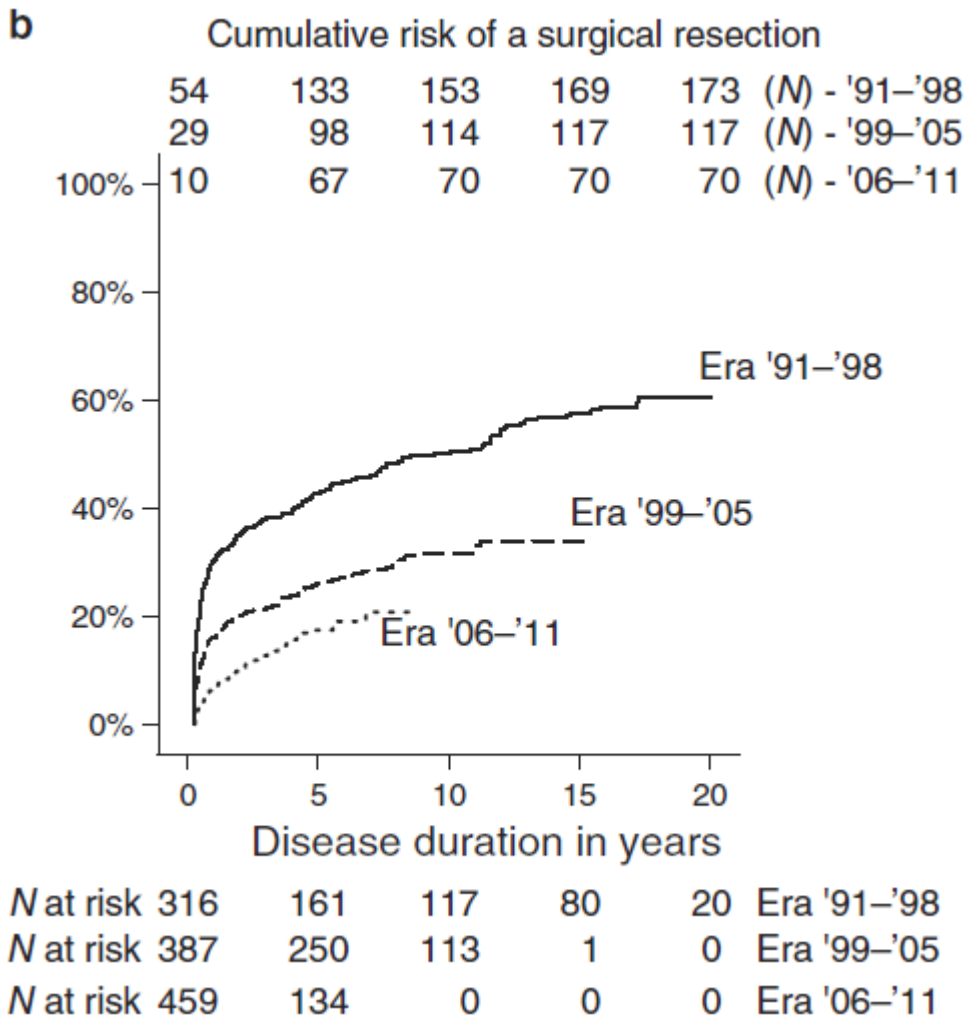
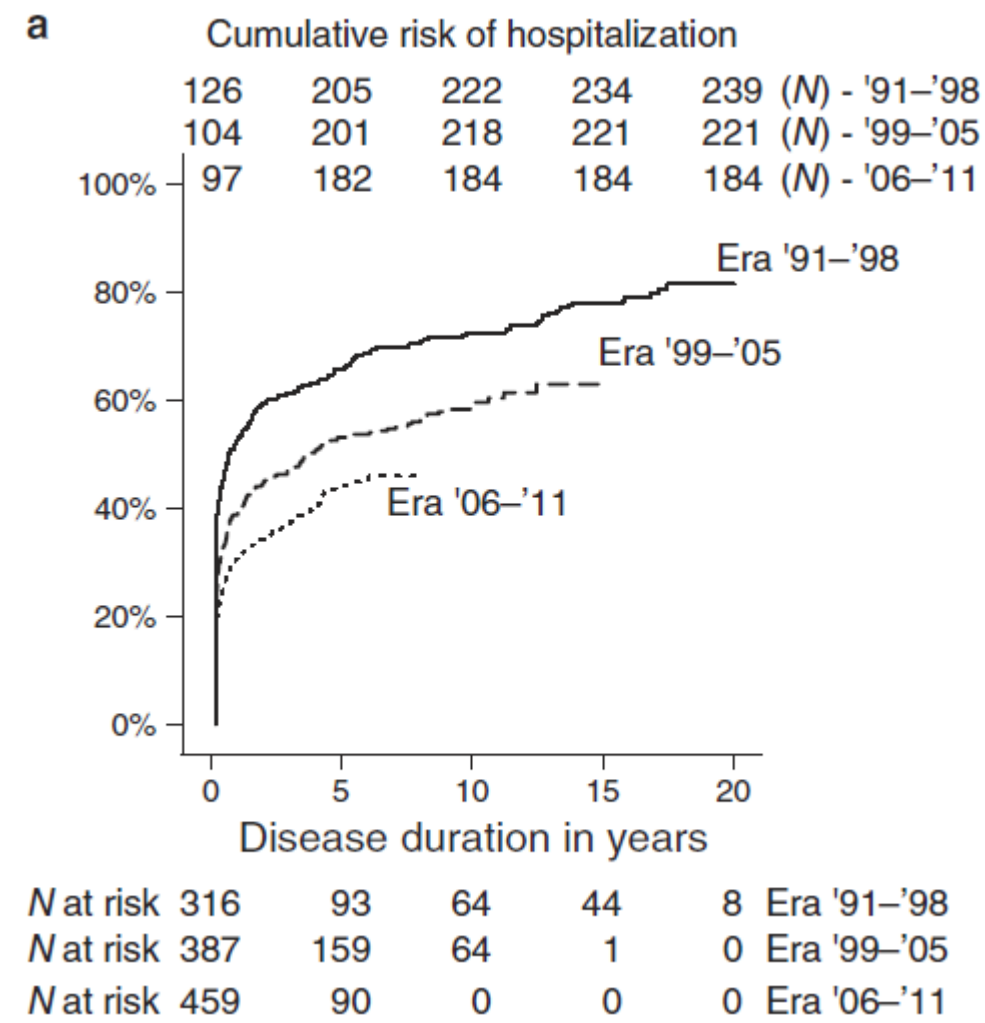
UC Assessment of Disease and Risk of Surgery

Prior classification of mild, moderate or severe colitis is no longer sufficient in selection of therapy
Must also assess risk of colectomy, and assess both activity and severity

	Low Risk	High Risk
Disease Extent	Limited colonic involvement	Extensive Colitis
Disease Severity	Mild endoscopic disease	Deep ulcers/more severe inflammation
Age	Age >40	Age <40
Hospitalization History	No prior hospitalization	History of hospitalization
Infection		History of C. difficile or CMV
Steroids		Steroid dependent
Labs		High inflammatory markers (ESR, CPR) Low albumin



How well do therapies work?

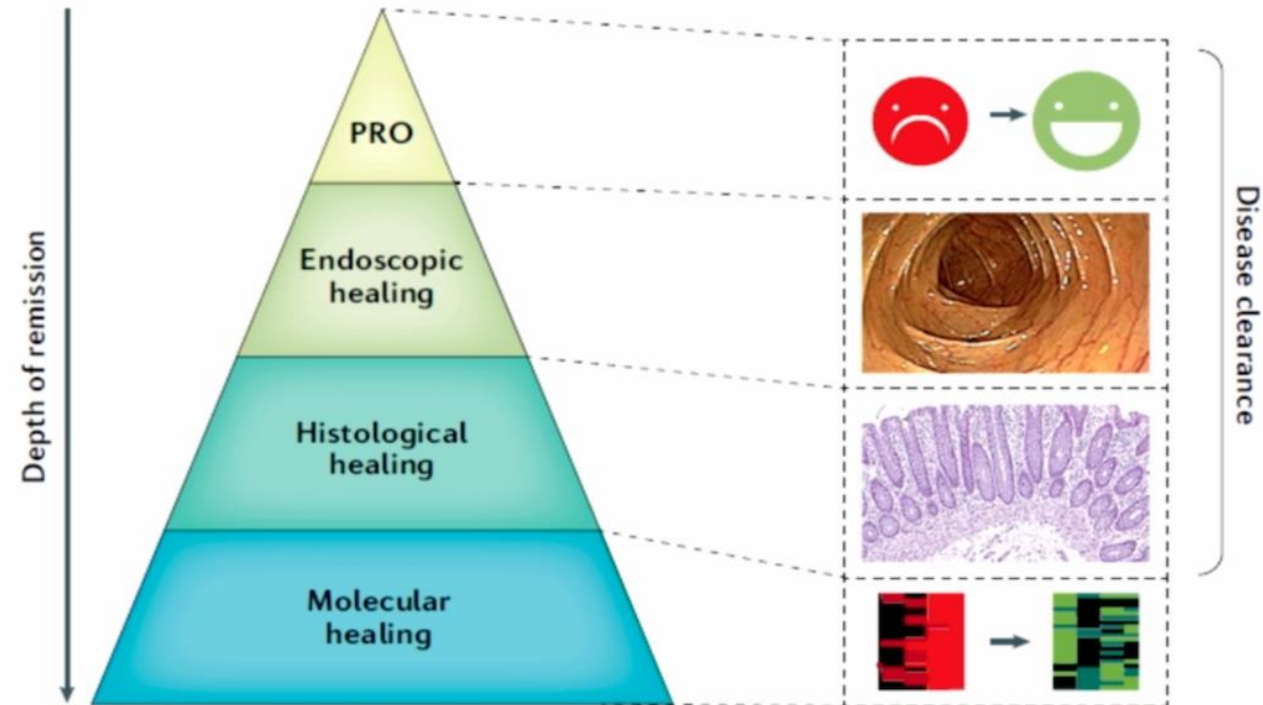


How do we Choose Medications?

Factors:

- Medication availability
- Insurance coverage/cost
- What medications has a patient tried?
 - Why did they fail prior medications?
- Patient preference
 - Infusion, injection, oral
- Comorbidities
- Should we combine medications?
 - Traditional combination therapy
 - Combination of 2 biologics
- Can we predict which medication an individual will respond to?

What are our targets?



Available medications

Aminosalicylates

- Mesalamine (oral and rectal)
- Sulfasalazine
- Balsalazide

Immunomodulators

- Methotrexate
- Azathioprine
- Mercaptopurine\

Sphingosine-1-Phosphate Receptor agonist

- Ozanimod (UC)
- Etrasimod (UC)

Anti-Tumor Necrosis Factor Alpha

- Infliximab
- Adalimumab
- Certolizumab pegol (CD)
- Golimumab (UC)

Anti-Integrin Therapy

- Vedolizumab

JAK Inhibitor

- Tofacitinib (UC)
- Upadacitinib

IL12/23 Inhibitor

- Ustekinumab

IL23 inhibitor

- Risankizumab
- Guselkumab
- Mirikizumab

Glucocorticoids (IV,
oral, rectal)



Aminosalicylates in IBD

ULCERATIVE COLITIS

- In patients with extensive mild-moderate UC, the AGA recommends using:
 - Standard-dose mesalamine (2-3 g/day) or
 - Diazo-bonded 5-ASA
- Patients already on sulfasalazine in remission or patients with prominent arthritic symptoms may reasonably choose sulfasalazine 2-4 g/day
- In patients with extensive or left-sided mild-moderate UC, add rectal mesalamine to oral 5-ASA

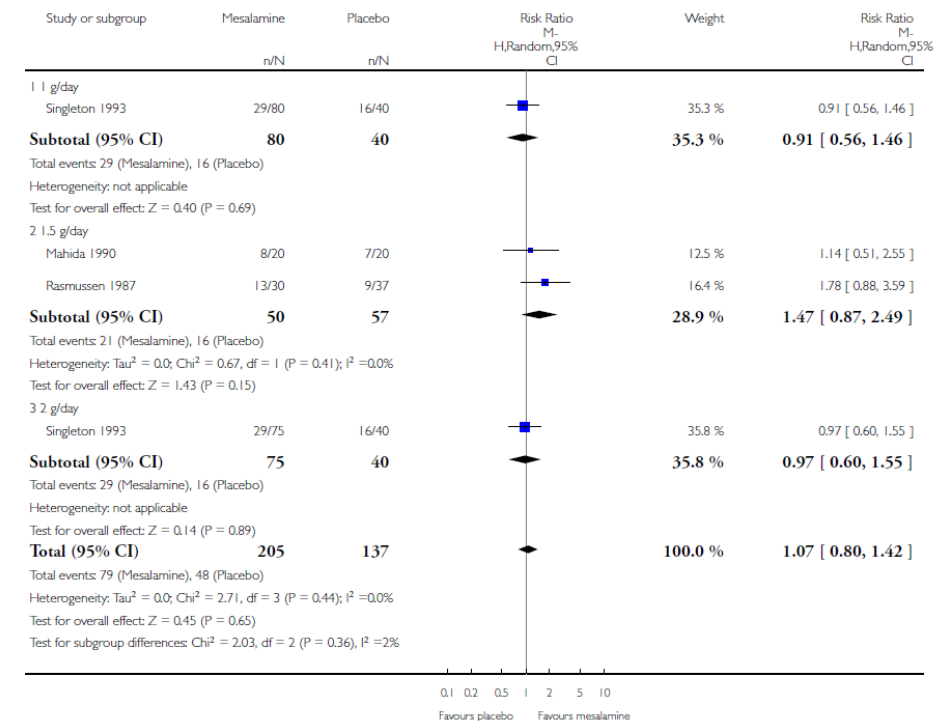
CROHN'S DISEASE: RARELY USED

Analysis 4.1. Comparison 4 Controlled-release mesalamine (1 - 2 g/day) versus placebo, Outcome 1 Decrease in CDAI ≥ 50 , HBI ≥ 2 or improvement/remission (as defined by Tvede et al).

Review: Aminosalicylates for induction of remission or response in Crohn's disease

Comparison: 4 Controlled-release mesalamine (1 - 2 g/day) versus placebo

Outcome: 1 Decrease in CDAI ≥ 50 , HBI ≥ 2 or improvement/remission (as defined by Tvede et al)



Management Concepts for Moderate to Severe IBD

- Treat early in disease
- Treat aggressively with “top down” biologics
- Check drug levels (anti-TNF medications)
- Dual therapy (immunomodulator + biologic)
- Aim for deep remission (histologic and endoscopic remission)



Indications for Early Biologic Therapy in IBD



Indications in Crohn's Disease (CD):

- Complex fistula
- Deep ulceration on endoscopy
- Young age (Age <30)
- Steroid dependence/resistance
- High risk anatomy
- Severe disease activity (weight loss, low albumin and/or hemoglobin)



Indications in Ulcerative Colitis (UC):

- Moderate to Severe UC
- Steroid-dependent, refractory UC
- Refractory Pouchitis

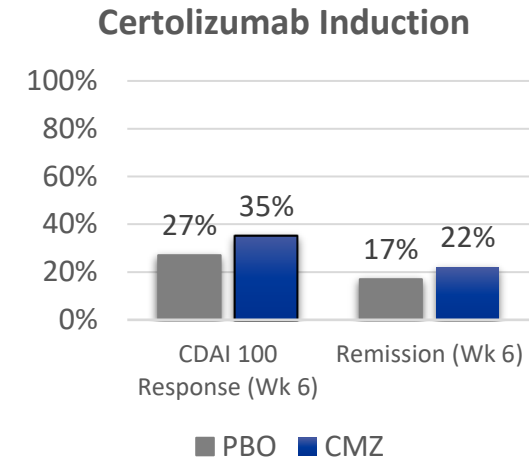
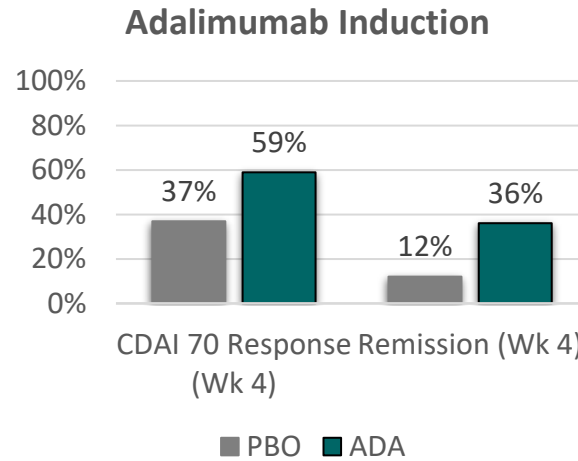
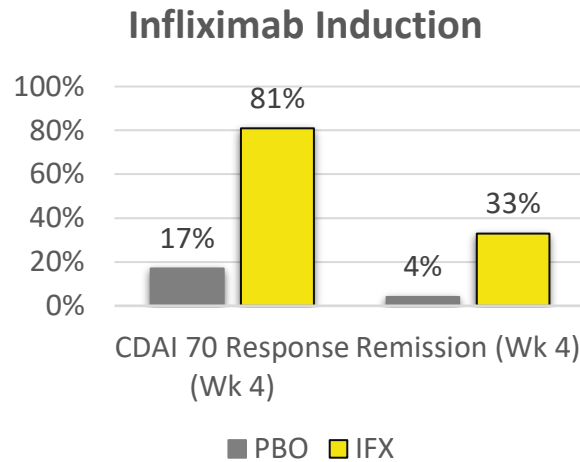
INDICATIONS for anti-TNF use

- Moderate to severe Crohn's disease and ulcerative colitis
 - Stricturing and fistulizing Crohn's disease
 - Acute severe ulcerative colitis (hospitalized patient)
- Can treat more than one condition
 - Concomitant rheumatologic, ophthalmologic and/or dermatologic indications
 - Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, uveitis

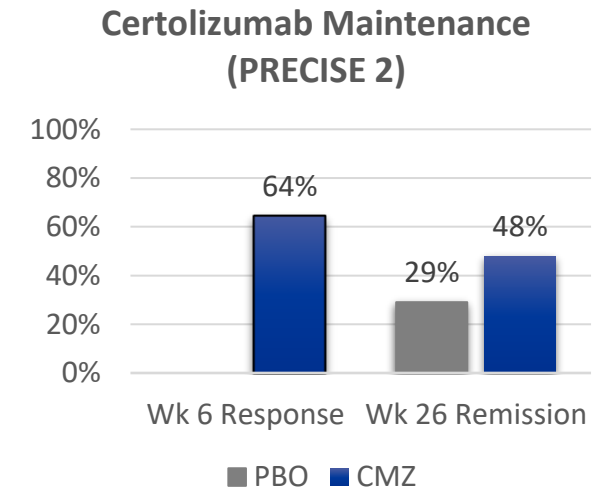
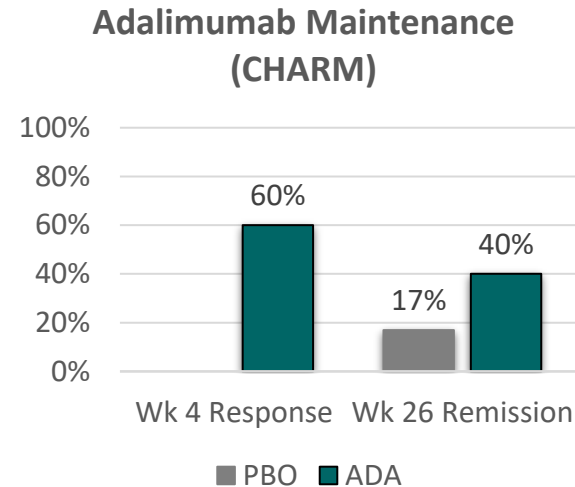
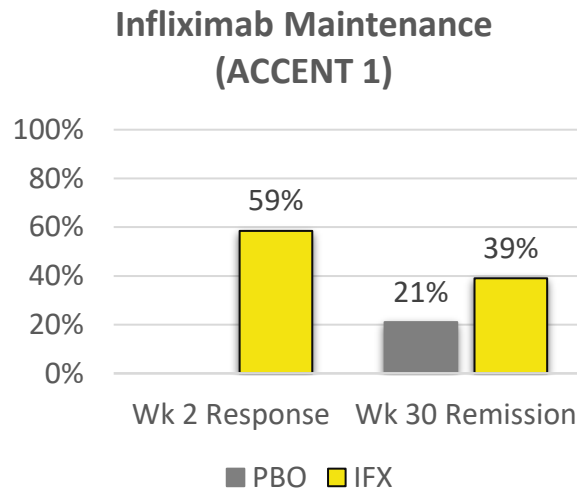


Anti-TNF: Crohn's Disease

Induction



Maintenance

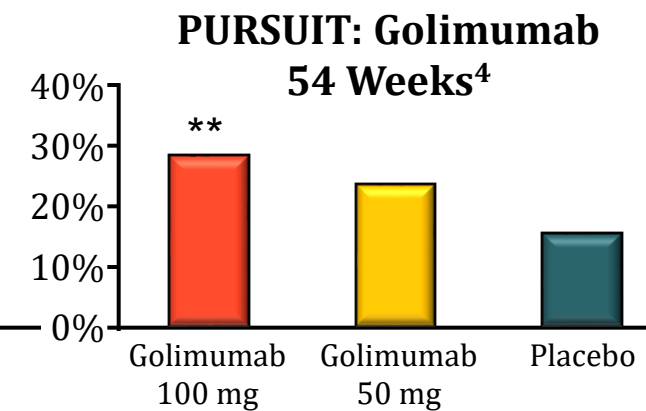
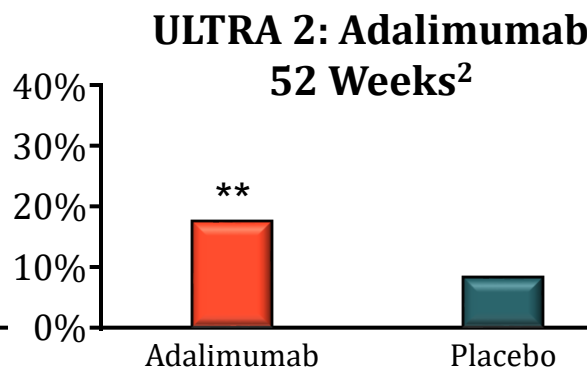
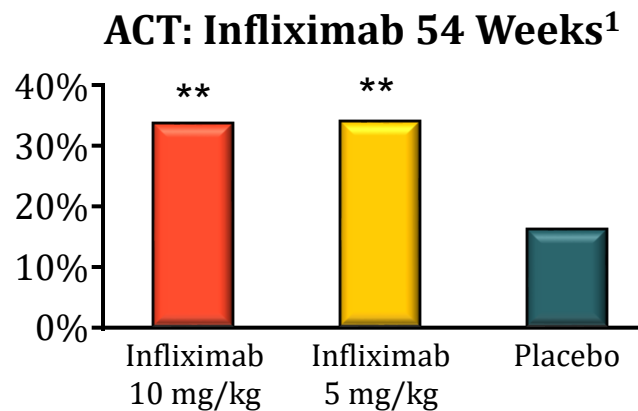
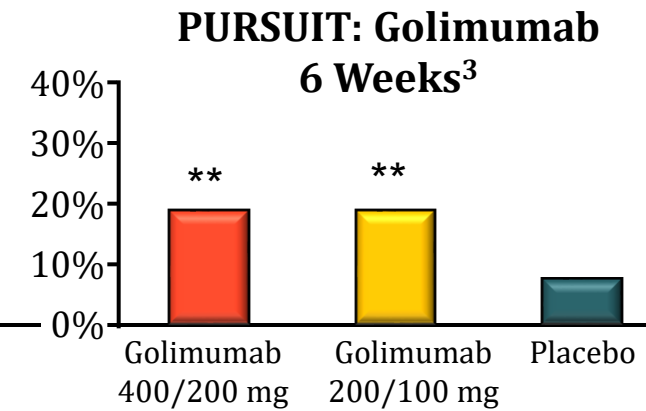
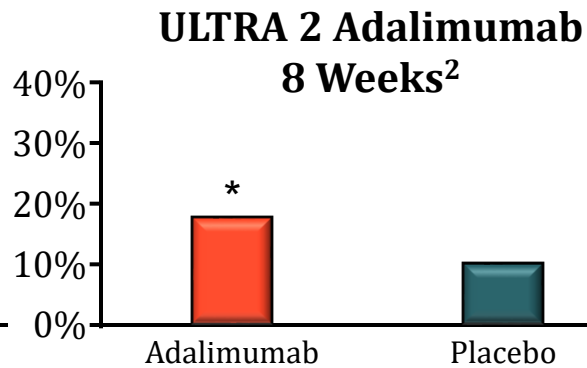
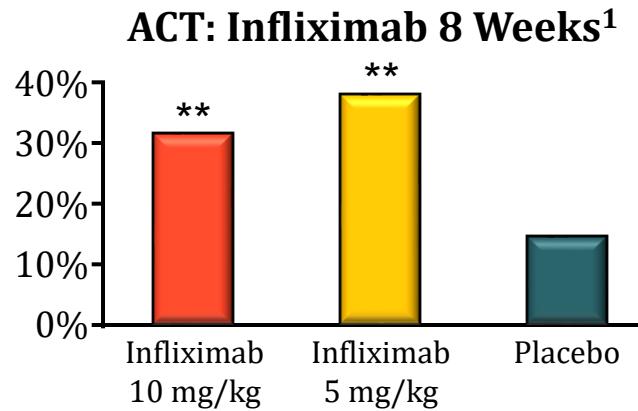


1. Targan SR, et al. NEJM 1997; 337(15): 1029-1035.
2. Hanauer SB, et al. Lancet 2002; 359(9317): 1541-1549.
3. Sands BE, et al. NEJM 2004; 350: 876-865

1. Hanauer SB, et al. Gastro 2006; 130(2): 323-332.
2. Colombel JF, et al. Gastro 2007; 132(1): 52-65.

1. Sandborn WJ, et al. NEJM 2007; 357(3): 228-238.
2. Schreiber S, et al. NEJM 2007; 357(3): 239-250.

Anti-TNF: Ulcerative Colitis



¹Rutgeerts P, et al. *N Engl J Med*. 2005;353(23):2462-76; ²Sandborn WJ, et al. *Gastroenterology*. 2012;142(2):257-65; ³Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):85-95; ⁴Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):96-109.

* $P < .05$ vs. placebo;
** $P < .01$ vs. placebo

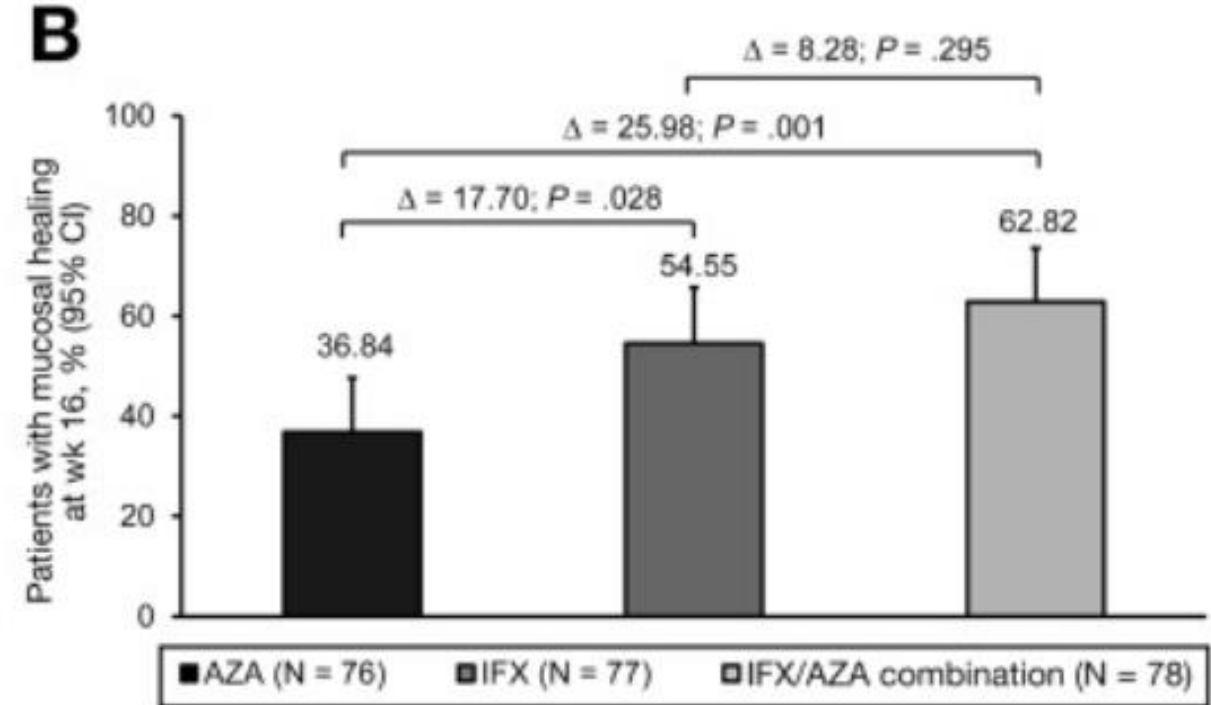
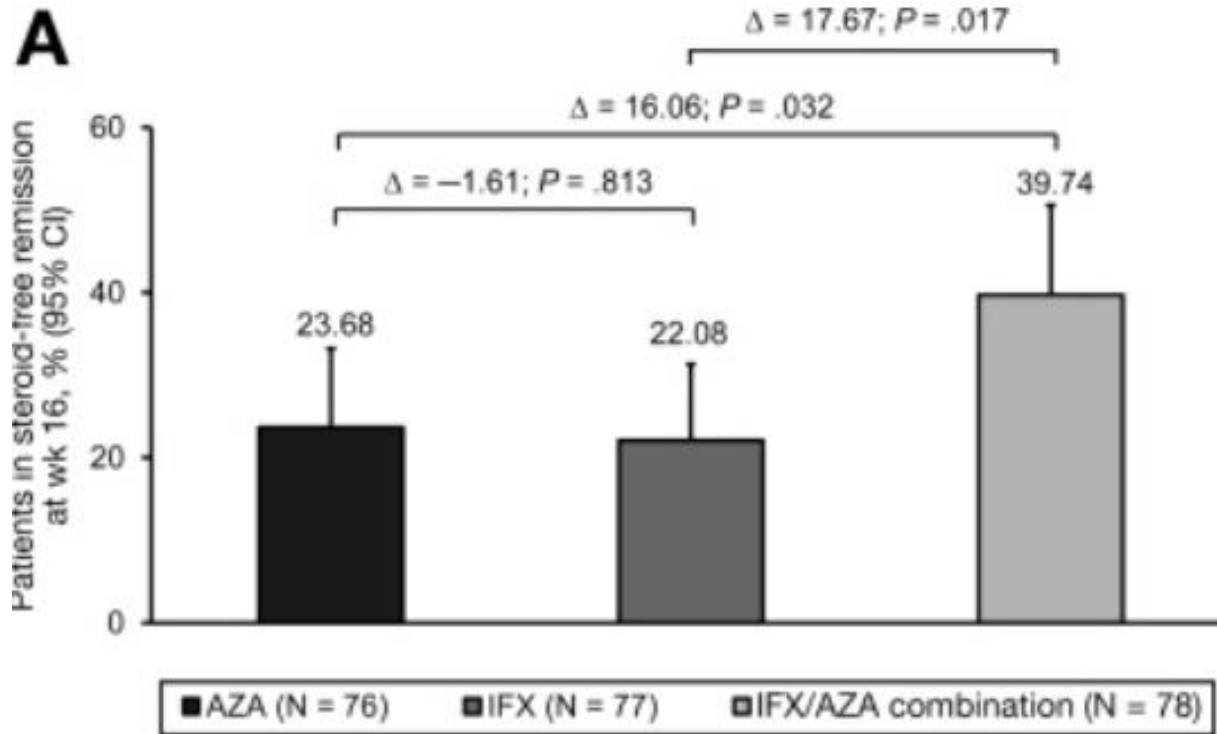


Risks of Anti-TNF Therapies

Infection	Malignancy (rare)	Immunogenicity	Infusion/Injection Reaction	Miscellaneous (rare)
<ul style="list-style-type: none">• Bacterial• Fungal• Viral• Granulomatous (TB)• Hepatitis B reactivation	<ul style="list-style-type: none">• Low absolute risk• Small skin cancer risk (melanoma)• Small lymphoma risk (1/4,000 patients per year)			<ul style="list-style-type: none">• Serum sickness• Paradoxical psoriasis• Hepatotoxicity• Drug-induced lupus• White matter disease (can mimic multiple sclerosis)• Exacerbation of heart failure• Exacerbation of dermatomyositis

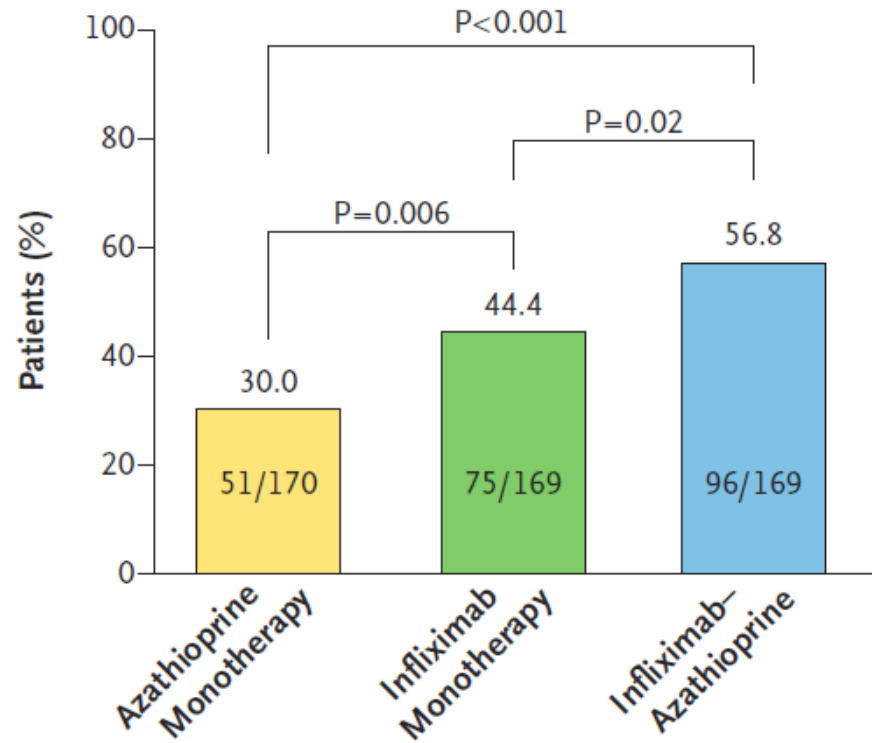


Combination Therapy for Ulcerative Colitis: UC-SUCCESS

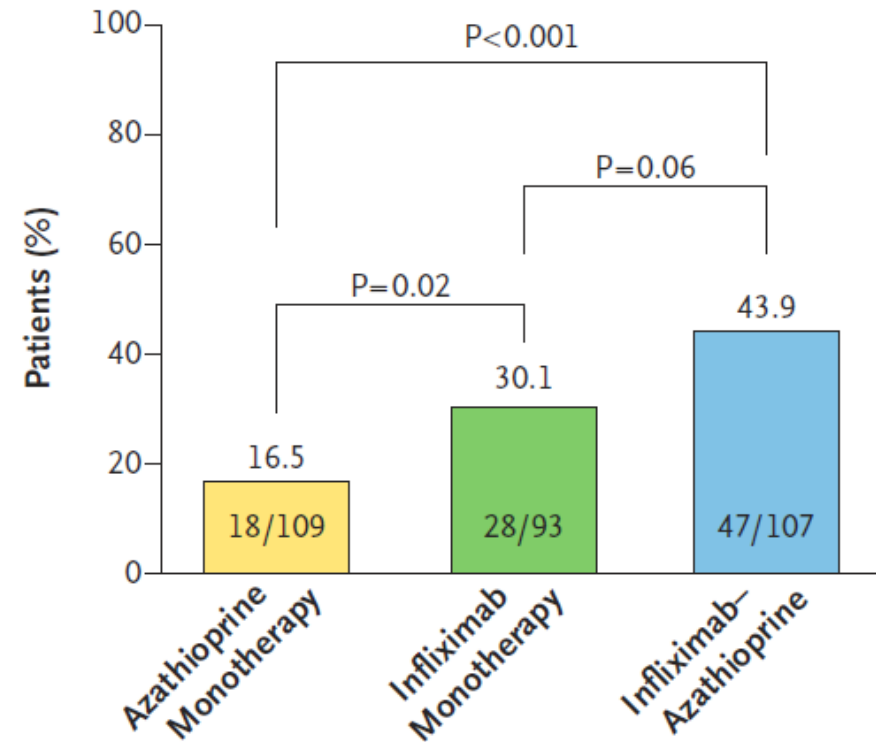


Combination Therapy for Crohn's Disease: SONIC

A Corticosteroid-free Clinical Remission at Wk 26

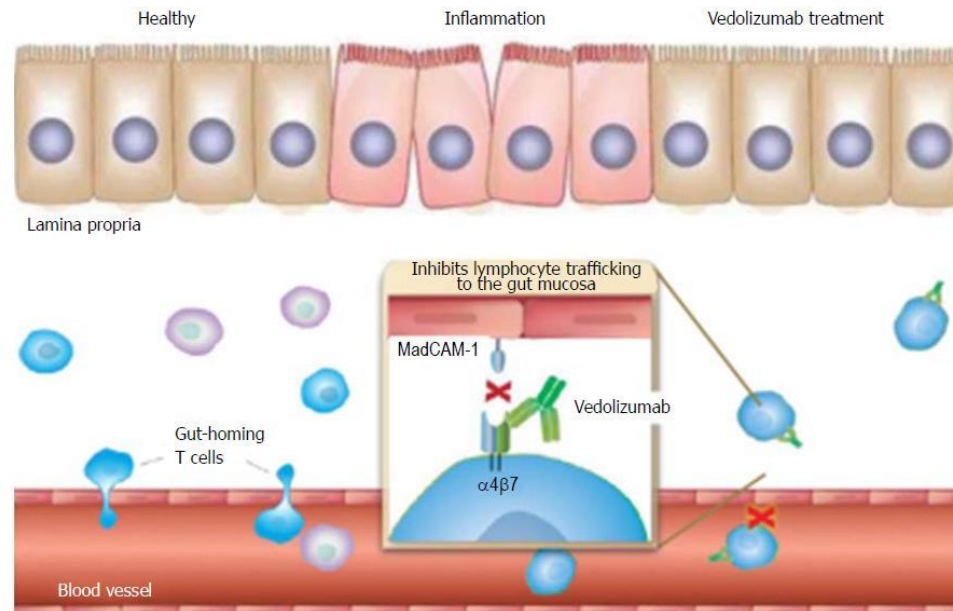


B Mucosal Healing at Wk 26



Vedolizumab

- Vedolizumab is a humanized monoclonal antibody directed against the $\alpha 4\beta 7$ integrin
- Selectively blocks gut lymphocyte trafficking without interfering with trafficking to the central nervous system
- Favorable safety profile; not immunosuppressive
- Patient considerations: elderly, immunocompromised, medical co-morbidities



Where do we position vedolizumab?

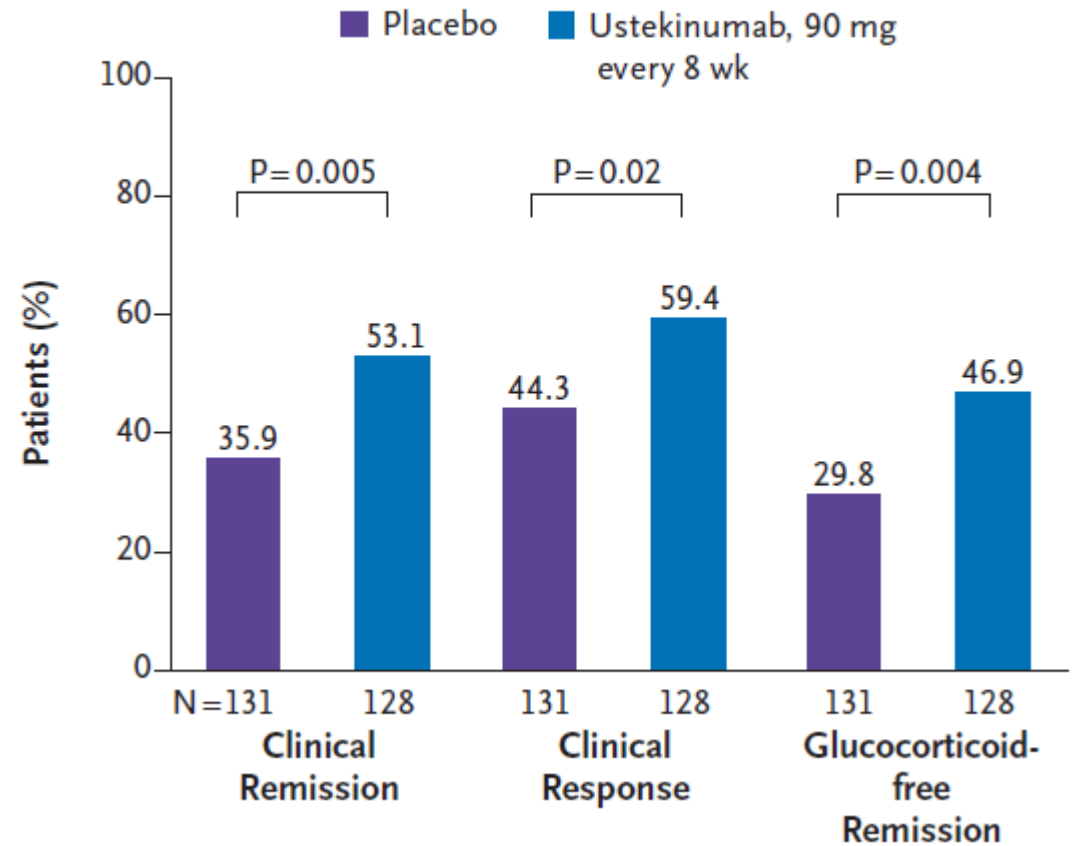
- First line therapy
- In patients unresponsive or intolerant to conventional therapies and anti-TNF agents
- In patients with unusual or other immune conditions such that additional systemic immune modification may be relatively contraindicated
 - Organ transplant patients
 - Hereditary or acquired immune deficiencies
 - Elderly patients
 - Cancer patients (skin cancers)
- Probably not best for patients with certain extraintestinal manifestations given gut selectivity



Anti-IL 12/23 and Anti-IL 23

- IL-12/23: Ustekinumab
- IL-23: Risankizumab, Guselkumab, Mirikizumab
- Benefits
 - Safety/side effect profile
 - Psoriasis/psoriatic arthritis efficacy
 - Rare to develop antibodies
 - Option for fistulizing disease

A Primary and Major Secondary End Points in IM-UNITI



Where should we position IL12/23 and IL-23 Medications?

- Possibly 1st line therapy in CD
- After failures of anti-integrins or anti-TNFs?
- In patients with concomitant psoriasis?



Approved Small Molecules For IBD

Ulcerative colitis:

- Tofacitinib (JAK inhibitor)
- Upadacitinib (JAK inhibitor)
- Ozanimod (S1P1 receptor modulator)
- Etrasimod (S1P1 receptor modulator)

Crohn's disease:

- Upadacitinib (JAK inhibitor)



Small Molecules For IBD

Advantages:

- Low-molecular weight
- Oral administration
- Resist gastric degradation
- Rapidly enter the systemic circulation
- Short half-life
- Lack immunogenicity
- Easier to manufacture than biologics, which may improve cost effectiveness
- Bind to specific intracellular targets

Risks/Side Effects:

JAK inhibitors:

- Infection including Herpes zoster-vaccinate for shingles
- VTE (PE, DVT)
- Contraindicated in pregnancy
- Increase in lipids

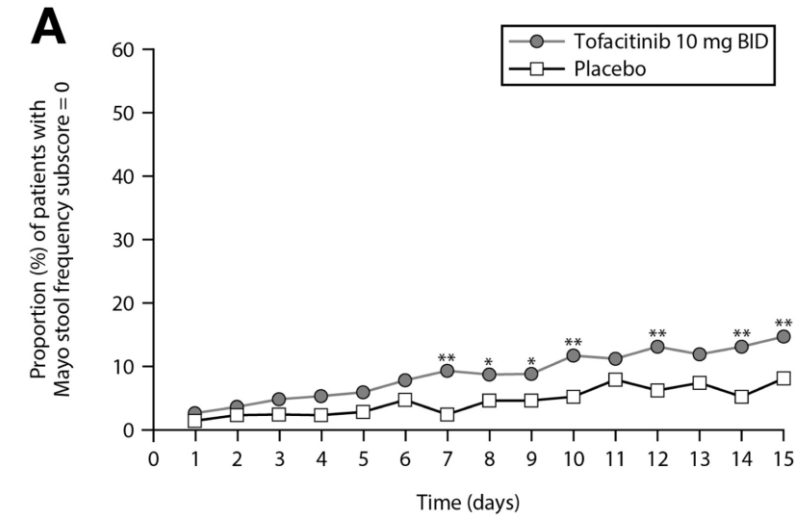
S1P-r modulators:

- Infection
- Bradycardia (baseline EKG required)
- Macular edema
- Elevated liver tests
- Contraindicated in pregnancy



JAK inhibitors: Onset of Action

Mayo Stool
Frequency
Subscore =0



Mayo Rectal
Bleeding
Subscore =0

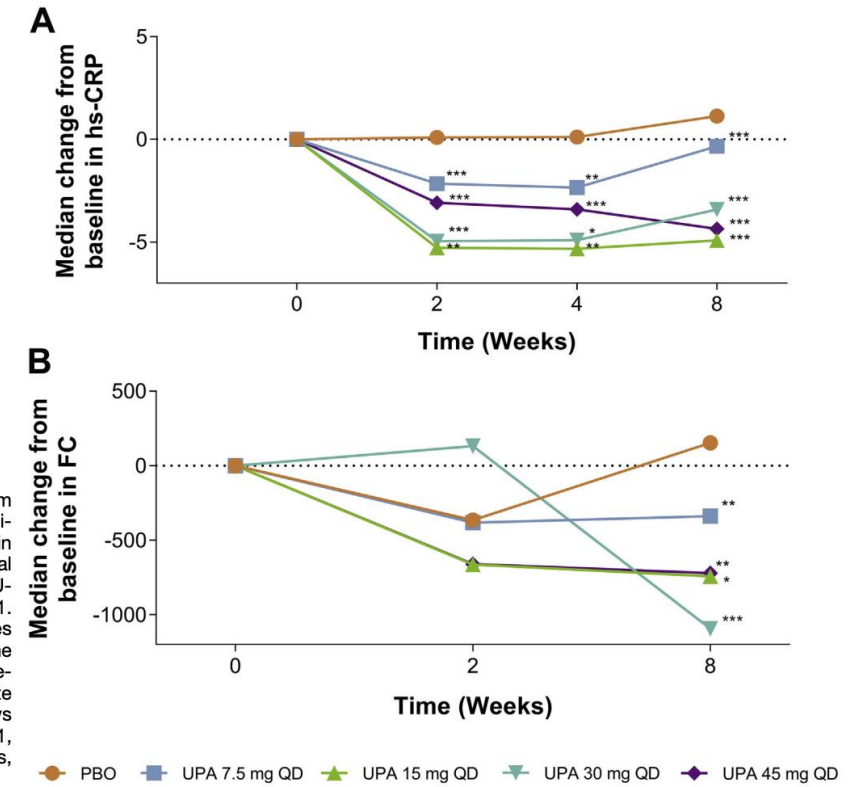
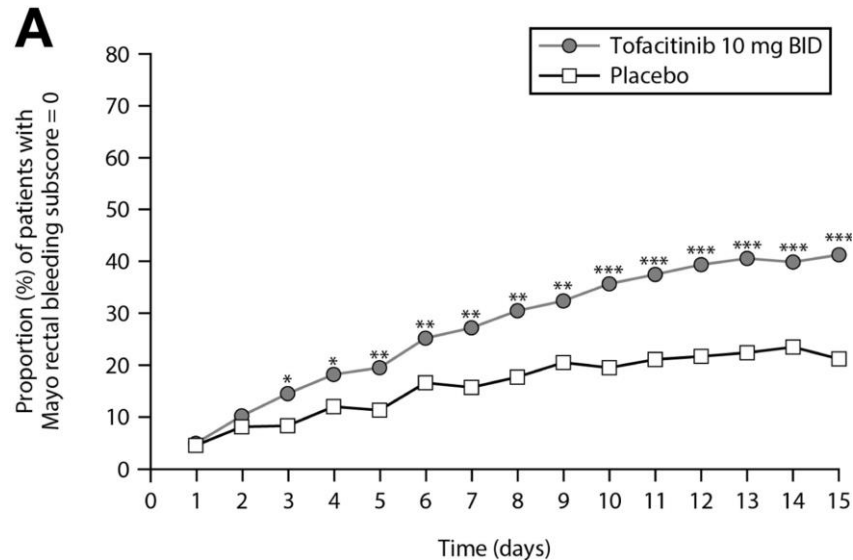
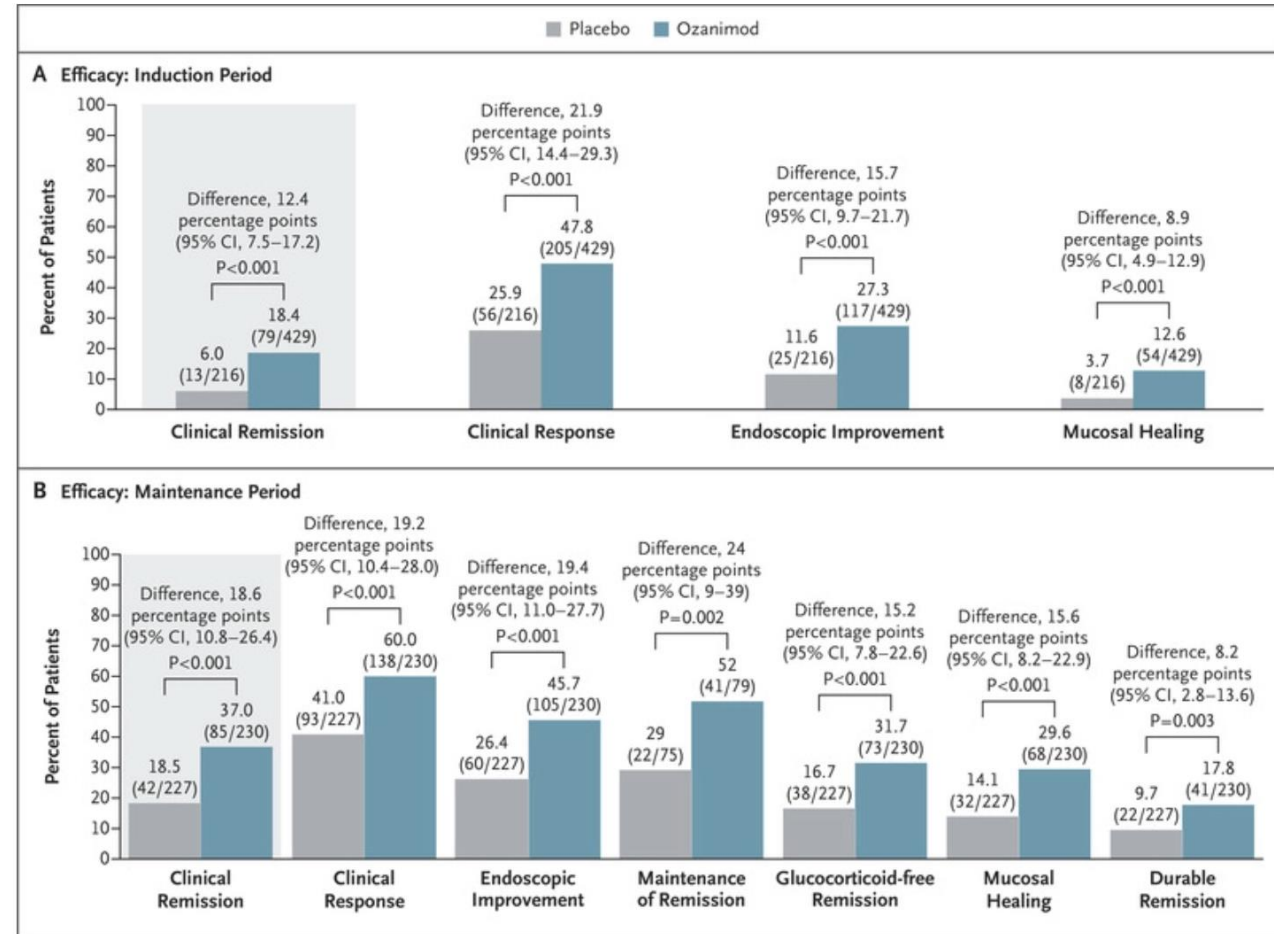


Figure 3. Change from baseline in (A) high sensitivity C-reactive protein (hs-CRP) and (B) fecal calprotectin (FC) in the U-ACHIEVE study 1 part 1. QD: once daily. *P* values are for comparing the mean change from baseline. Asterisks indicate statistical significance vs placebo at the *.05, **.01, and ***.001 levels, respectively.

Ozanimod

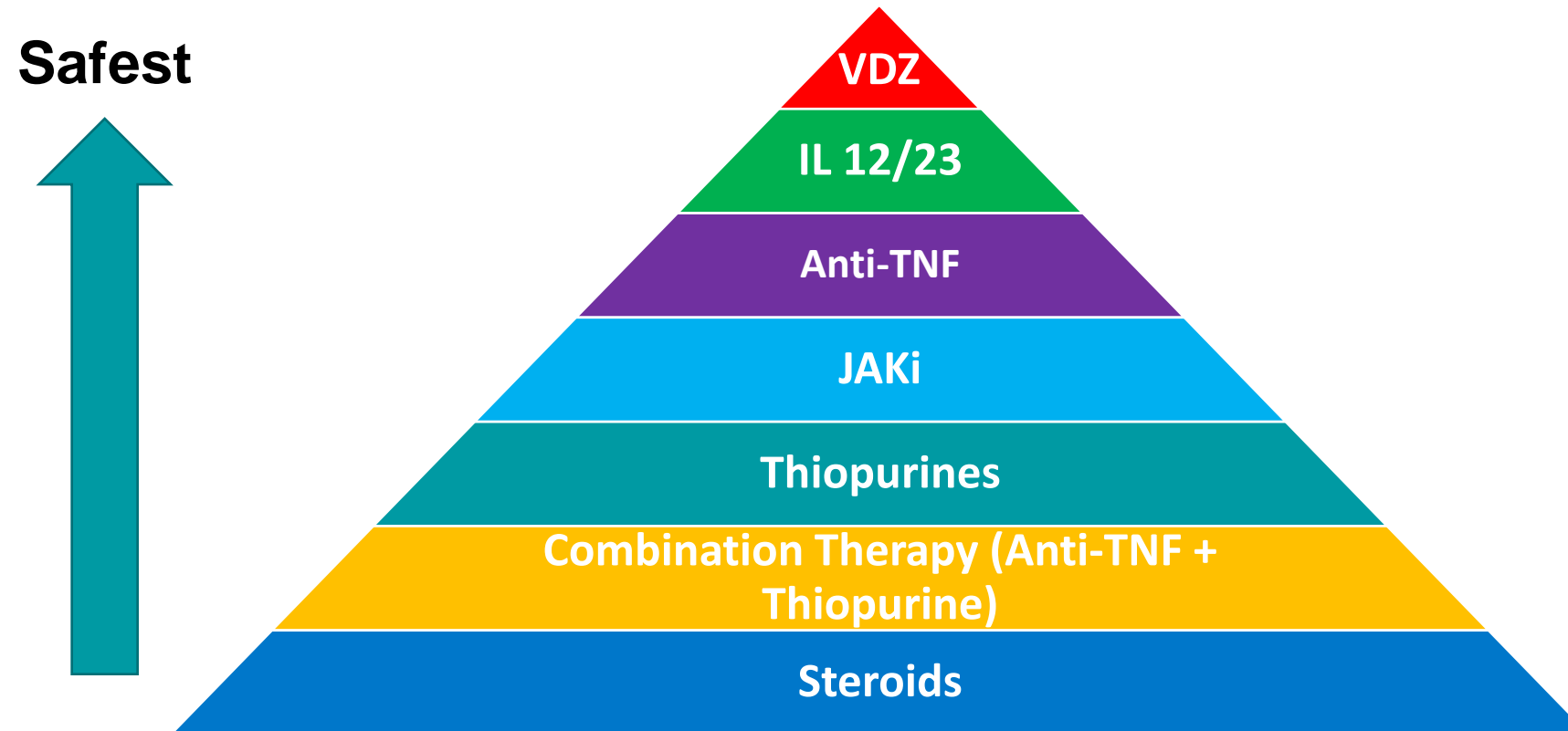
- Selective sphingosine-1-phosphate receptor modulator
- Indication: Mild-moderate ulcerative colitis
- Oral administration
- Short onset of action
 - Decreased rectal bleeding and stool frequency at 2 weeks



Additional Therapy Considerations



Safety Pyramid for IBD medications



Assessing Response to Medication

- **Primary non-response:** A patient does not respond to a loading dose of a biological agent when he/she receives it for the first time.
 - This patient may be a non-responder to all drugs targeting the same pathway
- **Secondary non-response:** A patient has responded to biological therapy at onset but loses response or becomes intolerant to the molecule.
 - This patient may respond to dose adjustment or is likely to benefit from other agents targeting the same pathway, especially if they have developed antibodies to the initial drug.



Therapeutic Drug Monitoring (TDM)

- Proactive versus Reactive
- Which drugs should be monitored
 - Anti-TNF vs non-Anti-TNF
- Timing of TDM
 - After Induction +/- Maintenance
- Target levels
 - IFX ≥ 5
 - ADA ≥ 8

A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease

Adam S. Cheifetz, MD¹, Maria T. Abreu, MD², Waqqas Afif, MD³, Raymond K. Cross, MD, MS⁴, Marla C. Dubinsky, MD⁵, Edward V. Loftus Jr, MD⁶, Mark T. Osterman, MD, MS⁷, Ariana Saroufim, BS¹, Corey A. Siegel, MD, MS⁸, Andres J. Yarur, MD⁹, Gil Y. Melmed, MD¹⁰ and Konstantinos Papamichael, MD, PhD¹



Combination biologics

- Observational data
- Meta-analysis of 30 studies reporting 288 trials of dual biologic or small molecule therapy in 279 patients (76% CD)
- Pooled rates of:
 - AE/SAE: 31% (95% CI, 13%-54%)/6.5% (95% CI, 2.1%-13.1%)
 - Clinical remission: 59% (95% CI, 42%-74%)
 - Endoscopic remission: 34% (95% CI, 23%-46%)



Table 2. Dual Biologic or Small Molecule Therapies

Characteristic	Data	Reported patients or combinations
Duration of treatment, wk	24 (13–32)	231
Previous biologics, wk	2 (2–4)	160
Corticosteroids at baseline	43%	88/204
Immunomodulator at baseline	44%	75/172
Previous exposure to therapy	61%	62/101
Indication for therapy		
Medically refractory intestinal disease	81%	225/279
EIM	12%	34/279
Both	5%	14/279
Other	2%	6/279
Dual therapy		
Anti-TNF and anti-integrin	48%	138/288
Anti-TNF and ustekinumab	7%	20/288
Anti-TNF and tofacitinib	3%	10/288
Vedolizumab and ustekinumab	19%	54/288
Vedolizumab and tofacitinib	11%	32/288
Ustekinumab and tofacitinib	6%	16/288
Anti-TNF and other	3%	8/288
Vedolizumab and other	3%	8/288
Ustekinumab and other	1%	2/288

NOTE. Values are mean \pm SD, median (interquartile range), or %. EIM, extraintestinal manifestation; TNF, tumor necrosis factor.

Dietary Therapy

Common Diets in IBD:

- Specific Carbohydrate Diet
- Gluten free
- Mediterranean
- Dairy free
- Sugar free
- EEN/PEN
- IBD Anti-inflammatory Diet (IBD AID)
- Crohn's Disease Exclusion Diet (CDED)

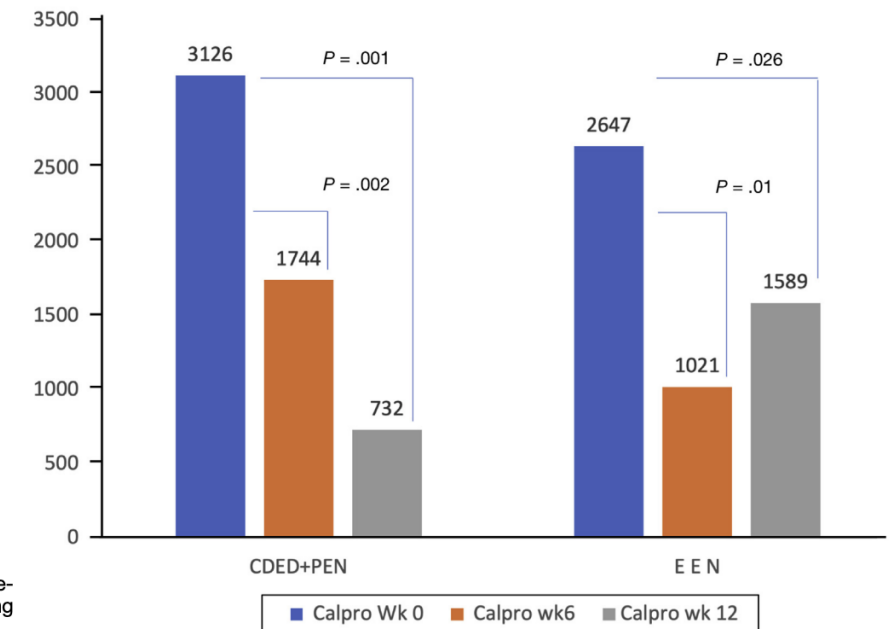
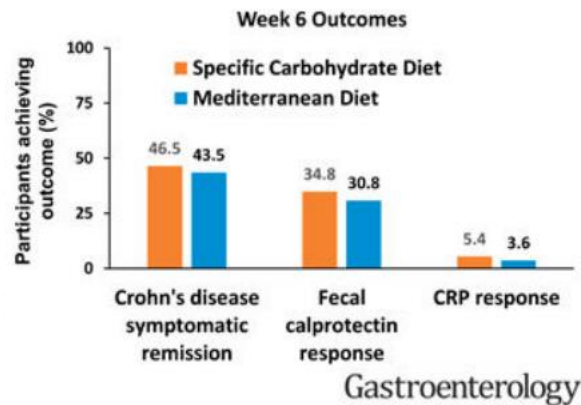
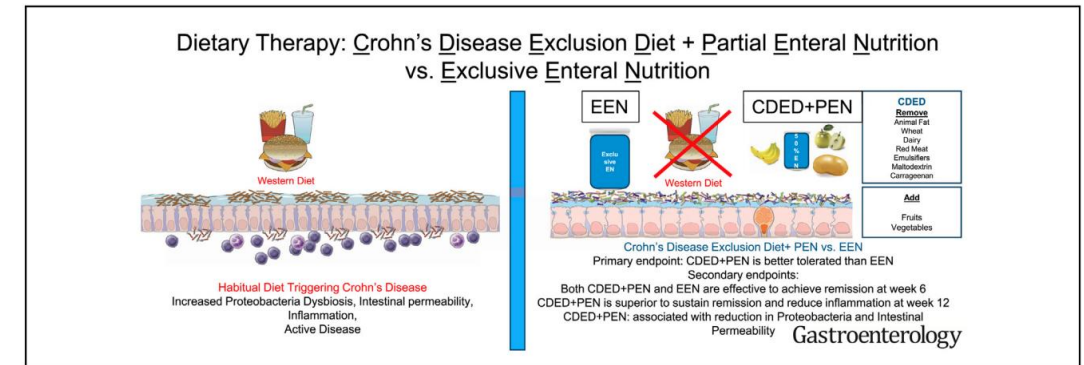


Figure 4. Change in median calprotectin during CDED study.

Identifying Psychosocial Issues

- Rates of anxiety and depression are increased among patients with IBD and are now considered extraintestinal manifestations of IBD
- Anxiety and depression have been associated with higher rates of re-hospitalization and healthcare utilization
- Important to screen for anxiety and depression as they may contribute to medication adherence

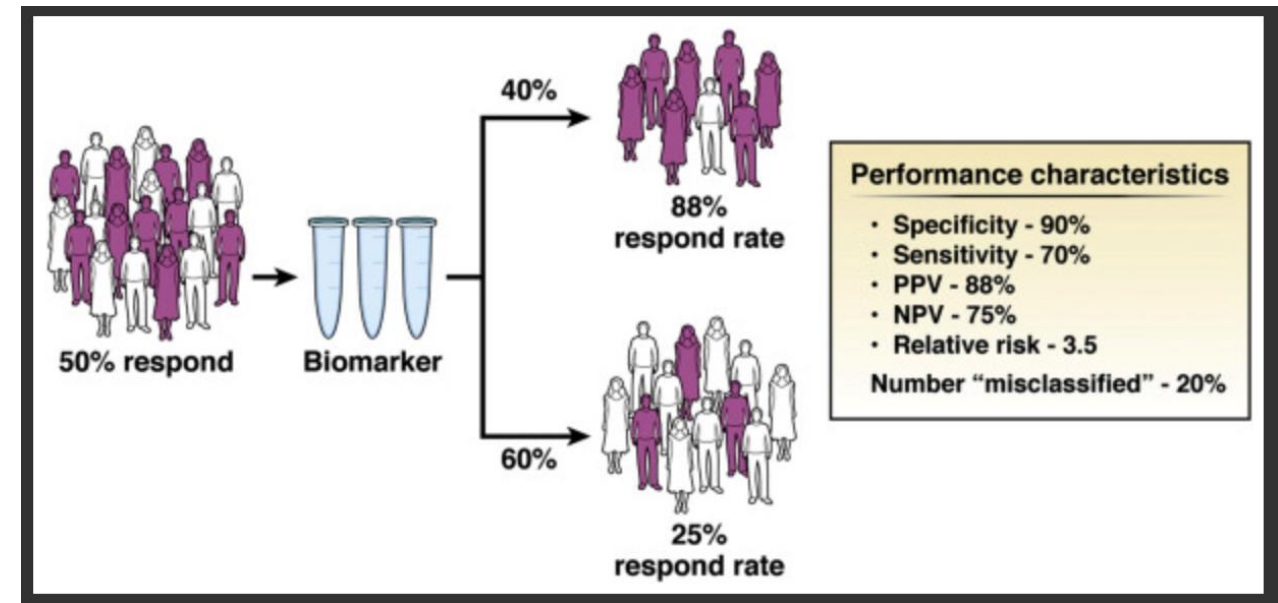
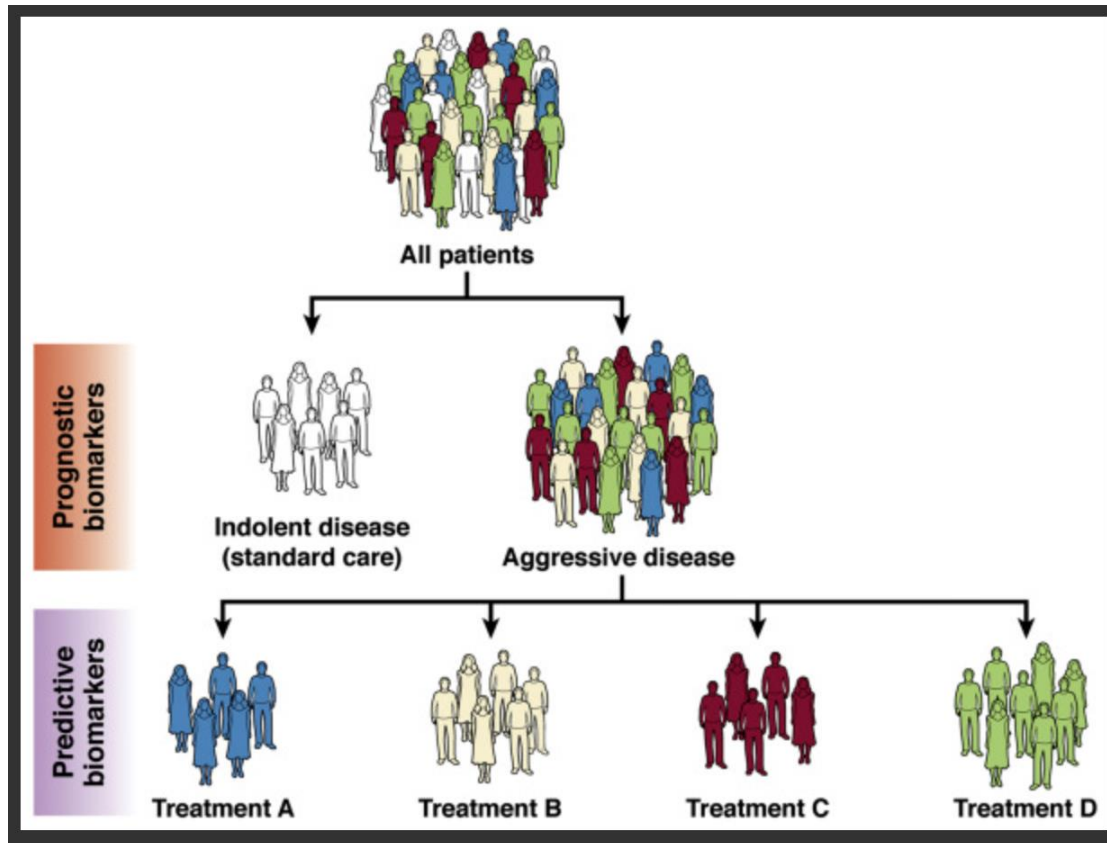


Health maintenance

- **Malignancy:**
 - Skin cancer
 - Colon cancer
 - Cervical cancer
- **Bone health:**
 - Osteopenia/osteoporosis
- **Nutritional deficiencies**
 - Vitamin D
 - Vitamin B12
 - Iron studies
- **Mental health**
 - Anxiety
 - Depression
- **Infection**
 - Screening prior to medications
 - Latent TB
 - Hepatitis B
 - Vaccines
 - Influenza
 - Pneumococcus
 - Zoster



Looking towards the Future: Personalization



MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

- IBD includes Crohn's disease and ulcerative colitis
- Treat early and treat moderate to severe IBD aggressively
- Medication selection should be based on many factors including disease severity, activity and prognosis as well as patient profile and preference and also medical history
- Aim for endoscopic and histologic remission
- Identify extraintestinal manifestations of IBD including psychosocial issues
- Future therapy will hopefully have a more personalized approach to drug selection





Thank You



Brigham and Women's Hospital
Founding Member, Mass General Brigham



HARVARD
MEDICAL SCHOOL

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Question 1

A 56-year-old female with a medical history of inflammatory ileocolonic Crohn's Disease, currently on infliximab at 5mg/kg every 8 weeks, presents with worsening abdominal pain, increased frequency to 10 bowel movements/day and loose stools. Infectious stool studies are negative. Fecal calprotectin is 714. Serum CRP is 32 mg/dL. Infliximab trough level is 14µg/mL (adequate therapeutic level is >5µg/mL); no antibody level detected.

What is the next best therapeutic option in managing her disease?

- A. Increase the infliximab dose to 10mg/kg every 8 weeks
- B. Decrease interval between infliximab infusions to every 4 weeks
- C. Discontinue infliximab and start adalimumab
- D. Discontinue infliximab and start risankizumab
- E. Start prednisone to treat the flare and continue infliximab dosing as is



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- D. **Discontinue infliximab and start risankizumab**
- E. Start prednisone to treat the flare and continue infliximab dosing as is

****The infliximab level is therapeutic with no antibodies, so she is not responding to anti-TNF therapy. Recommendation is to switch to another class of medication.**



Question 2

A 30-year-old male with acute severe pan ulcerative colitis is hospitalized after failing oral prednisone as an outpatient. He had been in clinical and endoscopic remission on mesalamine and has never been on a biologic or small molecule. Infectious stool studies are negative. Flexible sigmoidoscopy on admission shows Mayo 3 UC to the descending colon. He is started on IV steroids. After 3 days on IV solumedrol 20mg every 8 hours, he is not improving. What is the next step?

- A. Start vedolizumab 300 mg IV
- B. Increase the solumedrol dose
- C. Start infliximab 10 mg/kg IV
- D. Start upadacitinib 45 mg PO
- E. Start antibiotics



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