MODULE IV
GASTROENTEROLOGY:
THE CROSSROADS OF HEALTH

# Inflammatory Bowel Disease

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# Disclosures

- Disclosure of Financial Relationships:
  - Pfizer (consulting and research grant)

- Off-Label Usage:
  - None

# Learning Objectives

Part I

1. What are the Inflammatory Bowel Diseases (IBD)?
2. What causes IBD?
3. How does IBD affect other organ systems?

Part II

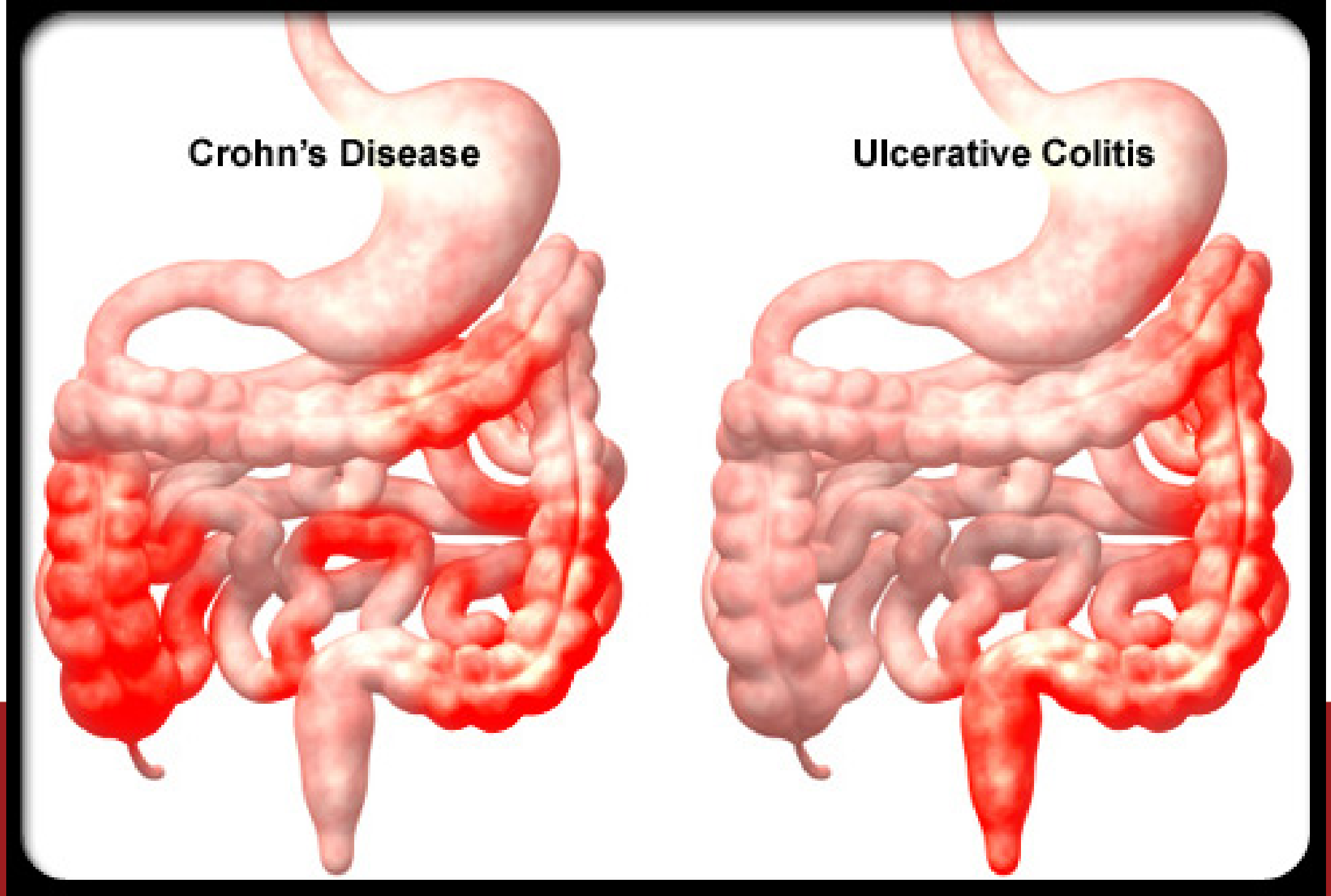
1. What are the current medical therapies for IBD?
2. What is the role for complementary and nutritional therapies in IBD?

Part III

1. Patient Stories and Questions

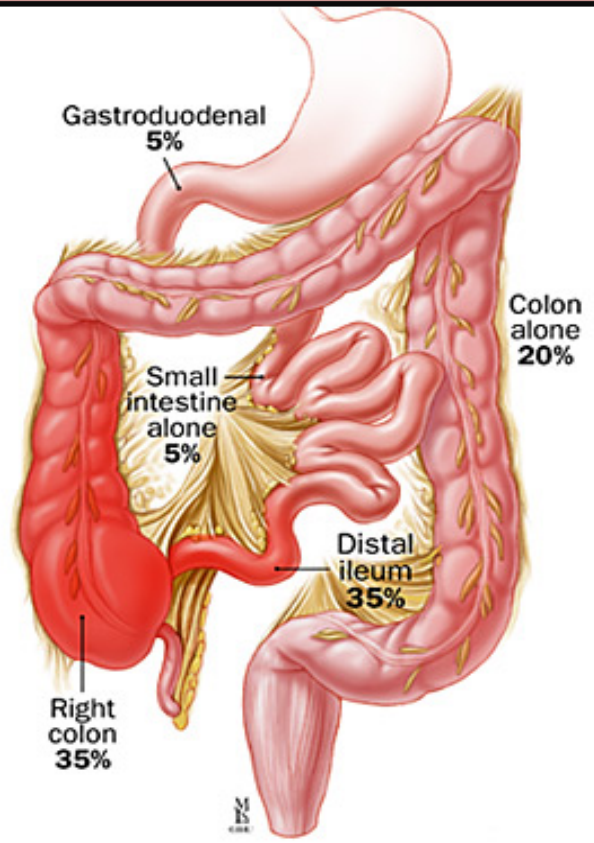
# Objectives: Part I

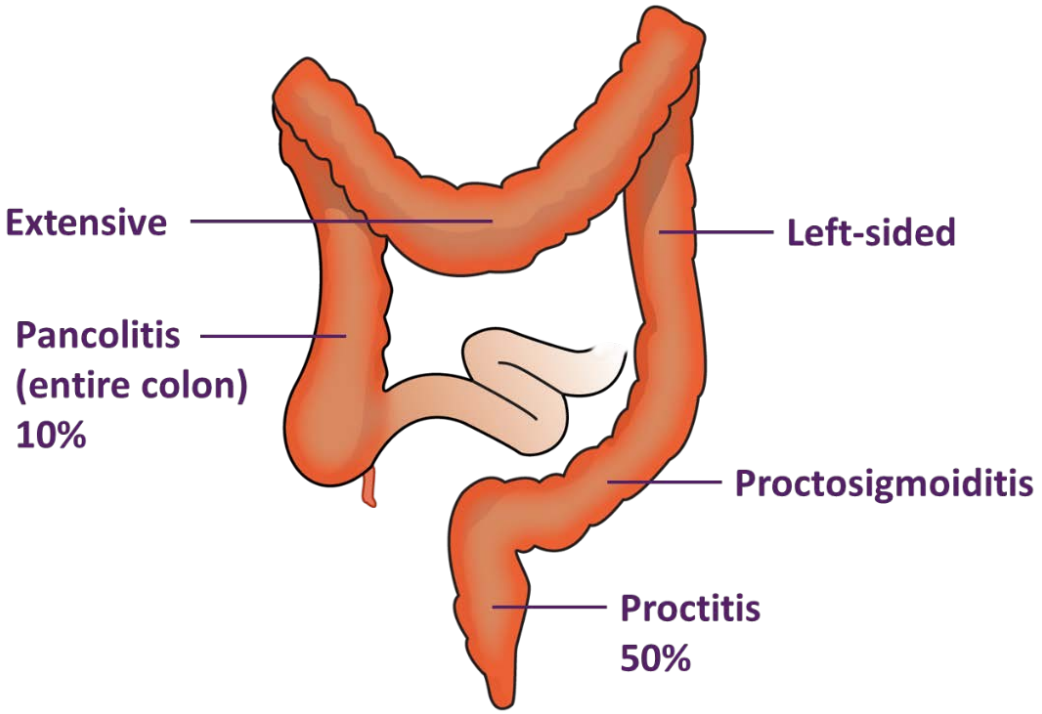
- Background on Inflammatory Bowel Diseases
  - Differentiating Crohn's and Ulcerative Colitis
- Clinical Presentation
- Epidemiology and Natural History
- Pathophysiology

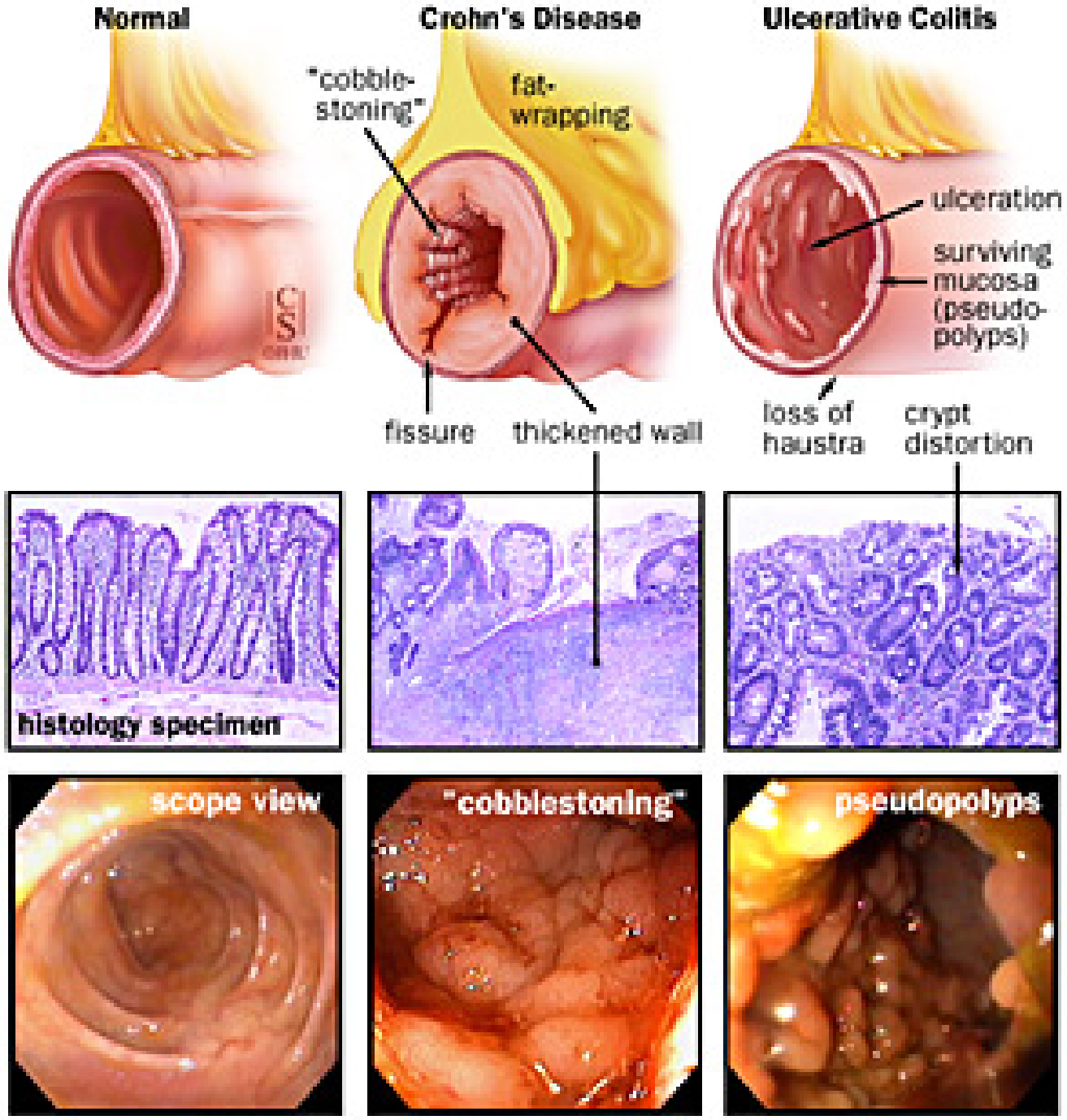

Crohn's Disease
Ulcerative Colitis

# Disease Location

| Crohn's Disease | Ulcerative Colitis |
| --- | --- |
| Mouth to Anus | Rectum to Cecum |
| Skip Lesions | Continuous |
| Perianal Fistula | Limited to Mucosa |



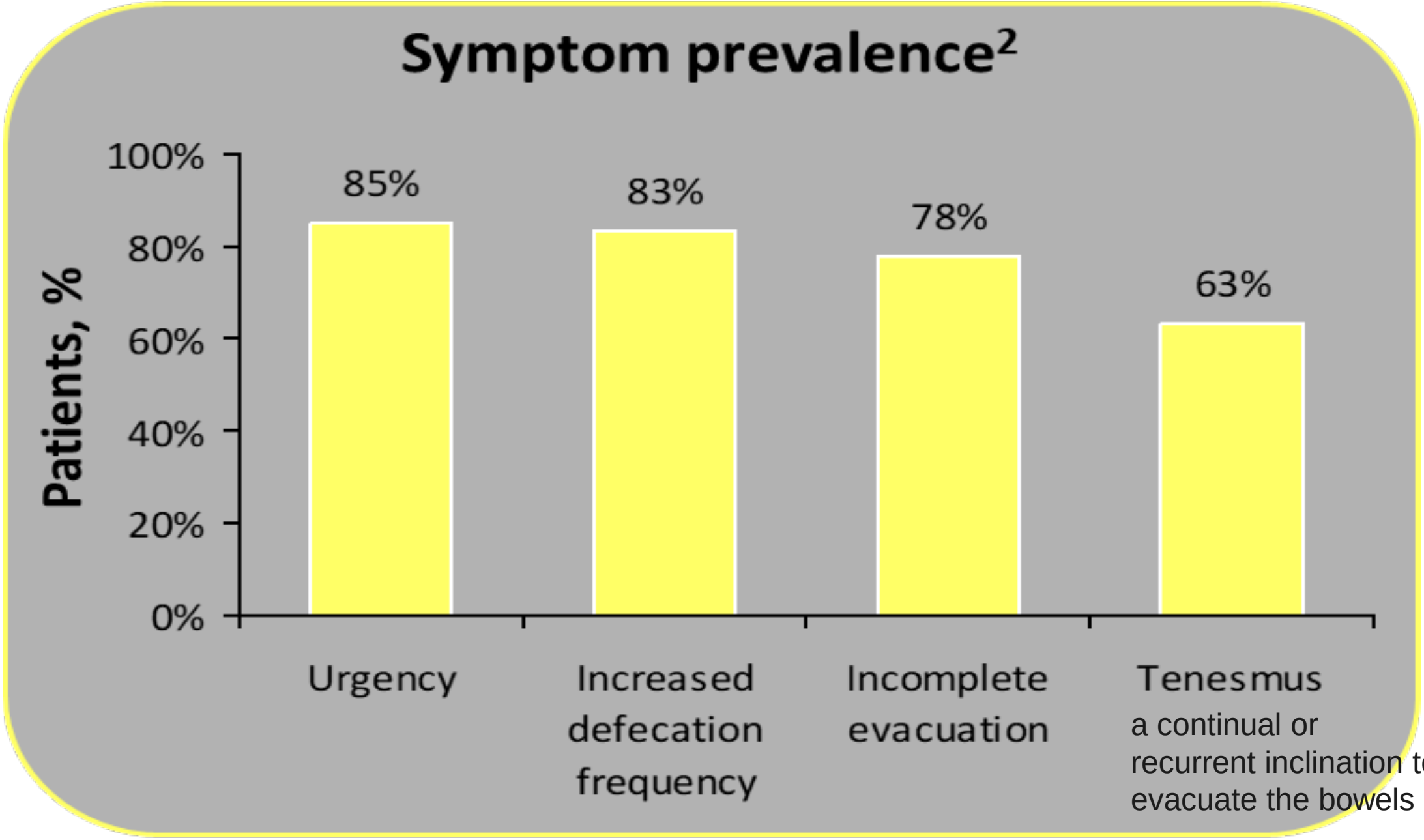




Normal
Crohn's Disease
Ulcerative Colitis
"cobble-stoning"
fat-wrapping
ulceration
surviving mucosa (pseudo-polyps)
fissure
thickened wall
loss of haustra
crypt distortion
histology specimen
scope view
"cobblestoning"
pseudopolyps

# Clinical Presentation

| Similarities in Presentation. | Ulcerative Colitis | Crohn's Disease |
|---|---|---|
| Age of onset | Any age: Peak 10-35 | Any age: Peak 10-35 |
| Diarrhea | Common: 80-95% | Common: 70-90% |
| Abdominal pain | 15-60% (mild) | 70-80% (moderate-severe) |
| Fever | Less frequent | Frequent |
| Anorexia, weight loss | 20-60% (mild) | 45-70% (weight loss may be severe) |

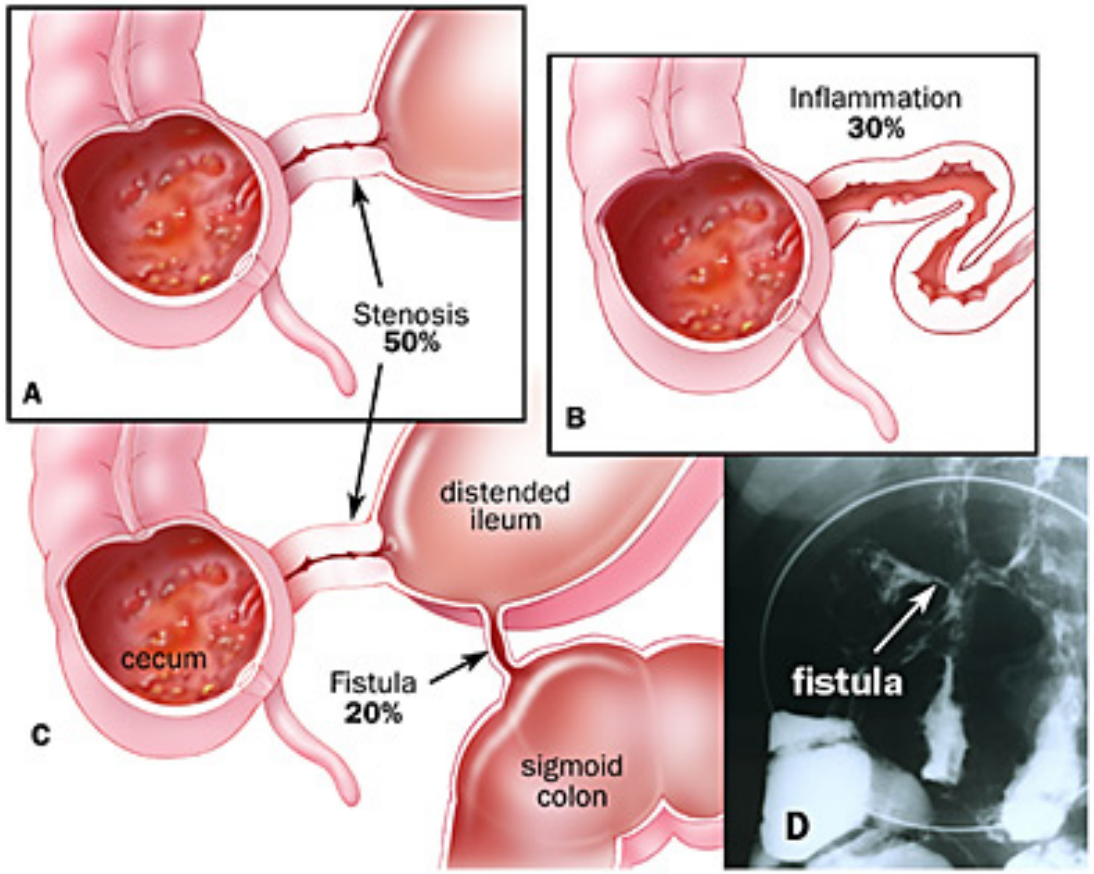
| Differences in Presentation. | Ulcerative Colitis | Crohn's Disease |
|---|---|---|
| Rectal bleeding | Common: 70-100% | Occasional: 10-20% |
| Rectal involvement | More than 95% | Less than 50% |
| Anal lesions (fissures, fistulae) | Unusual | Common |
| Abdominal mass | Rare | Common |

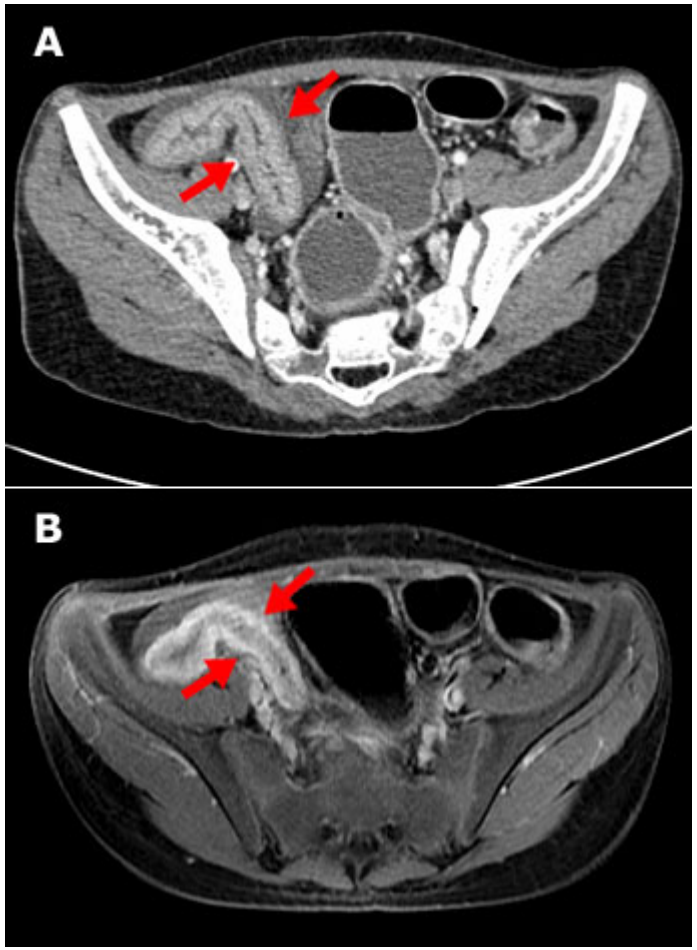


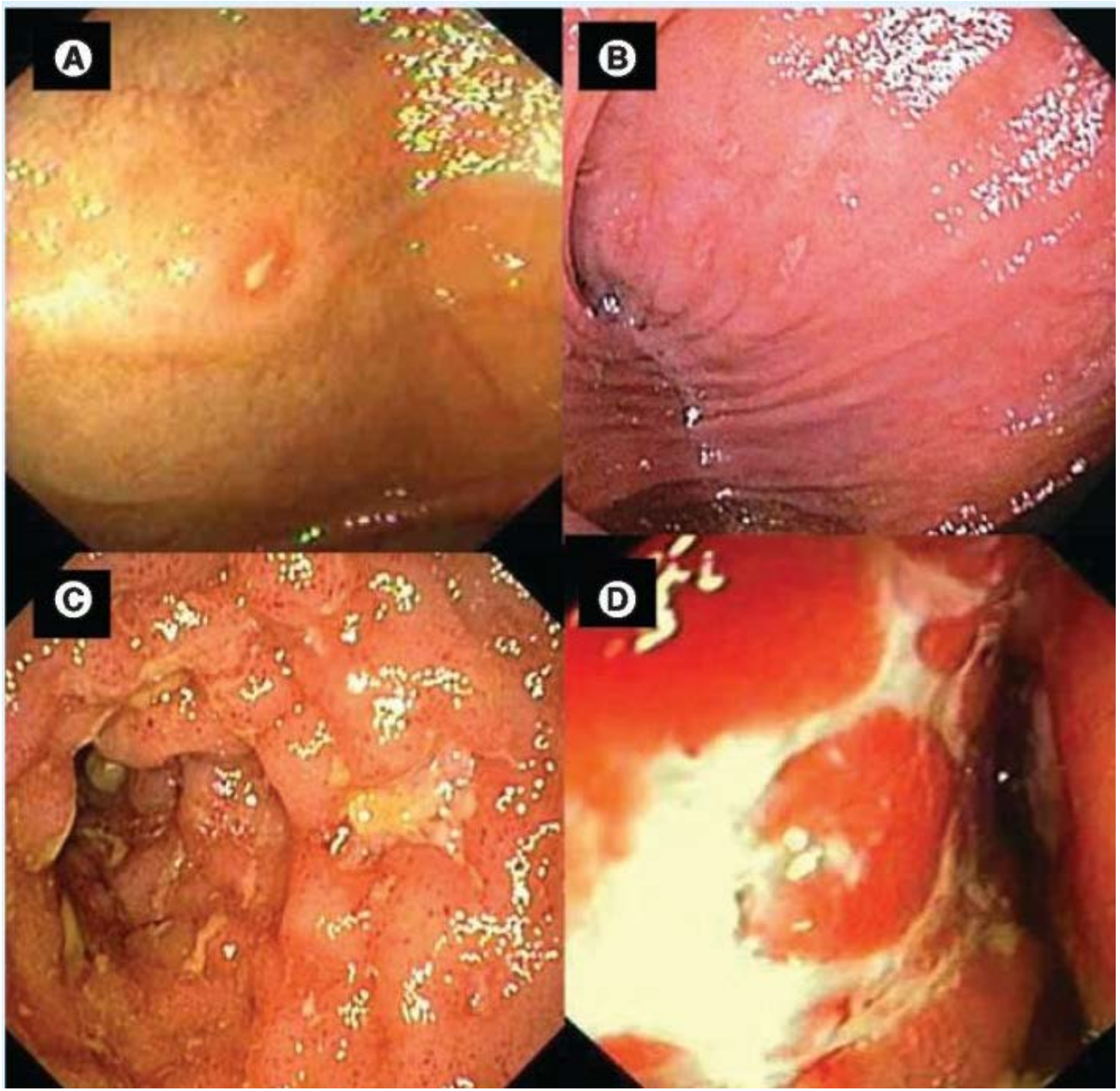



1. Kornbluth A, Sachar D. *Am J Gastroenterol*. 2004;99:1371-1385. 2. Rao SS, et al. *Gut*. 1988;29:342-345.

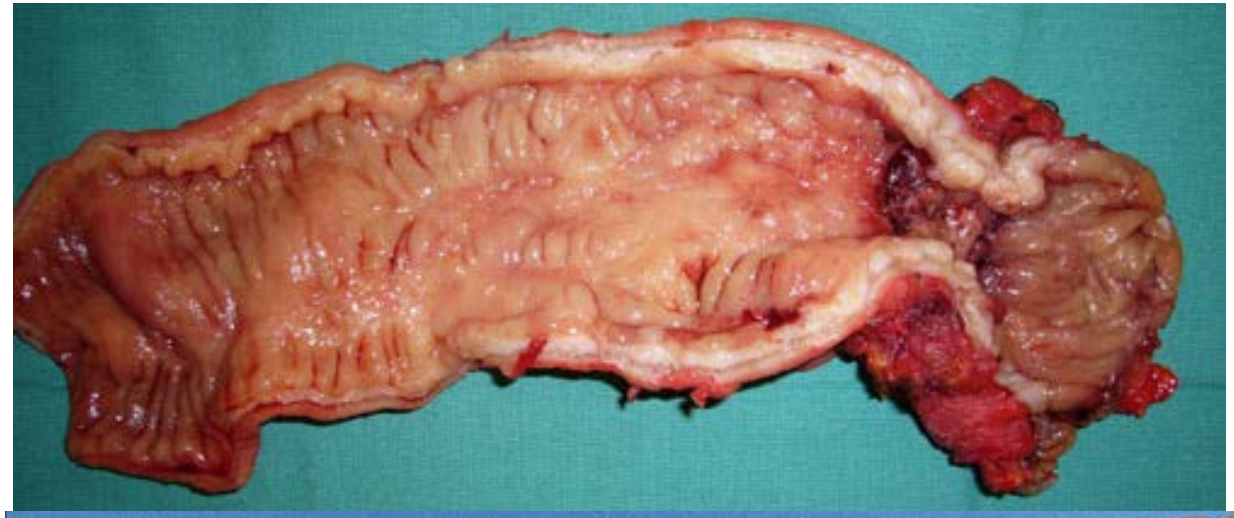
# Crohn's Disease

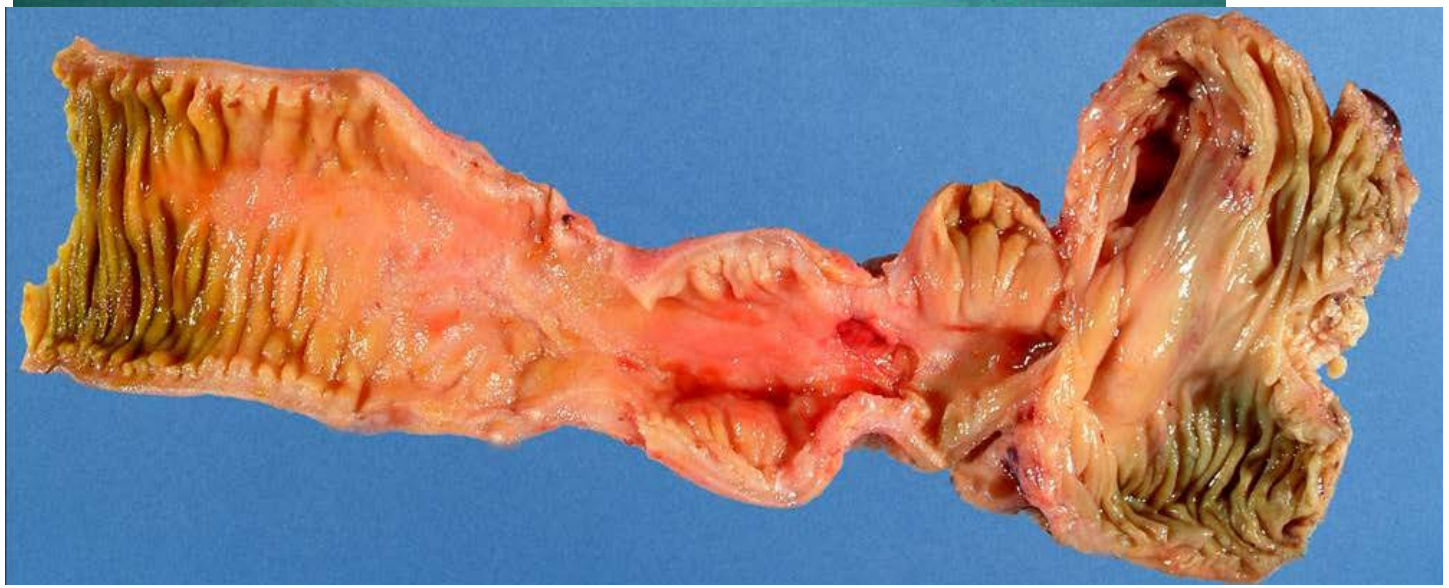


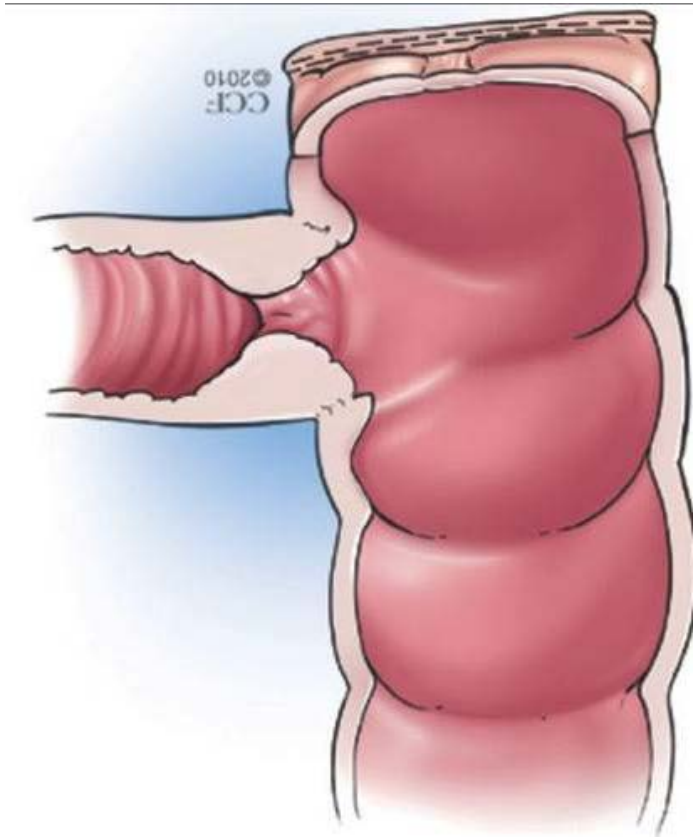




A
B
C
D

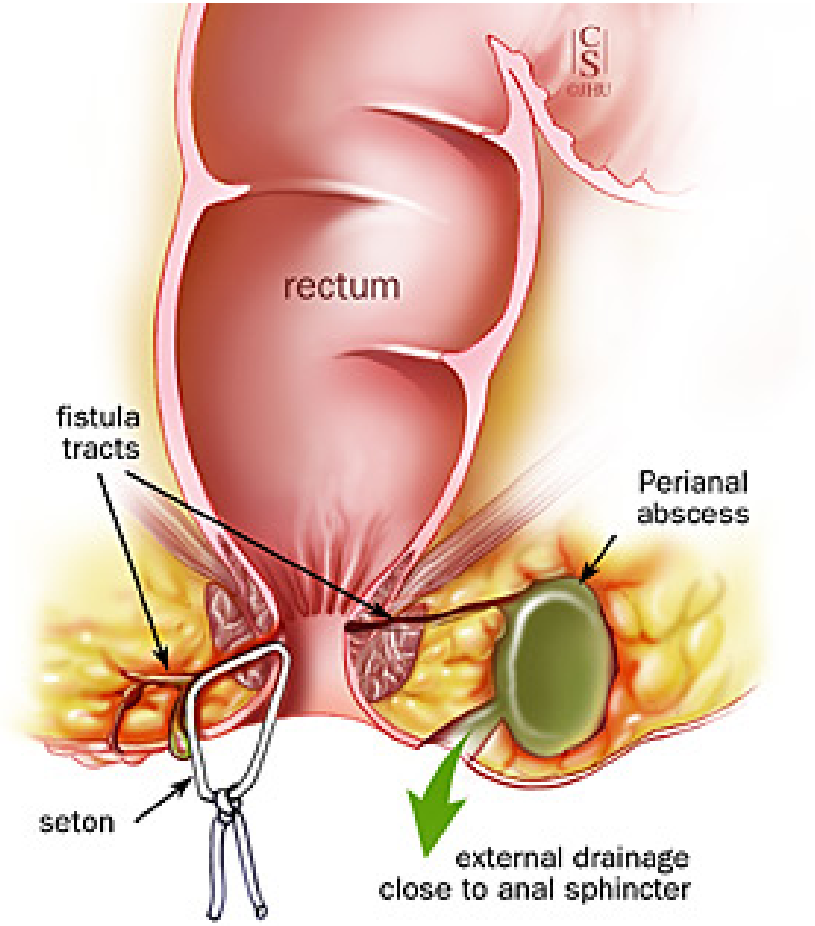
# Ileal Stricture in Crohn's

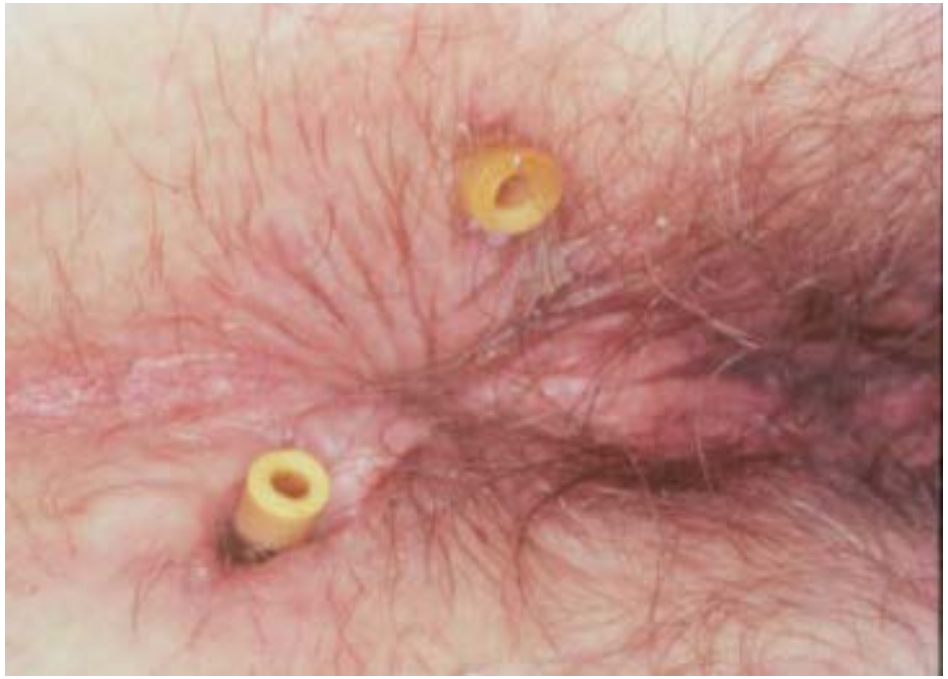


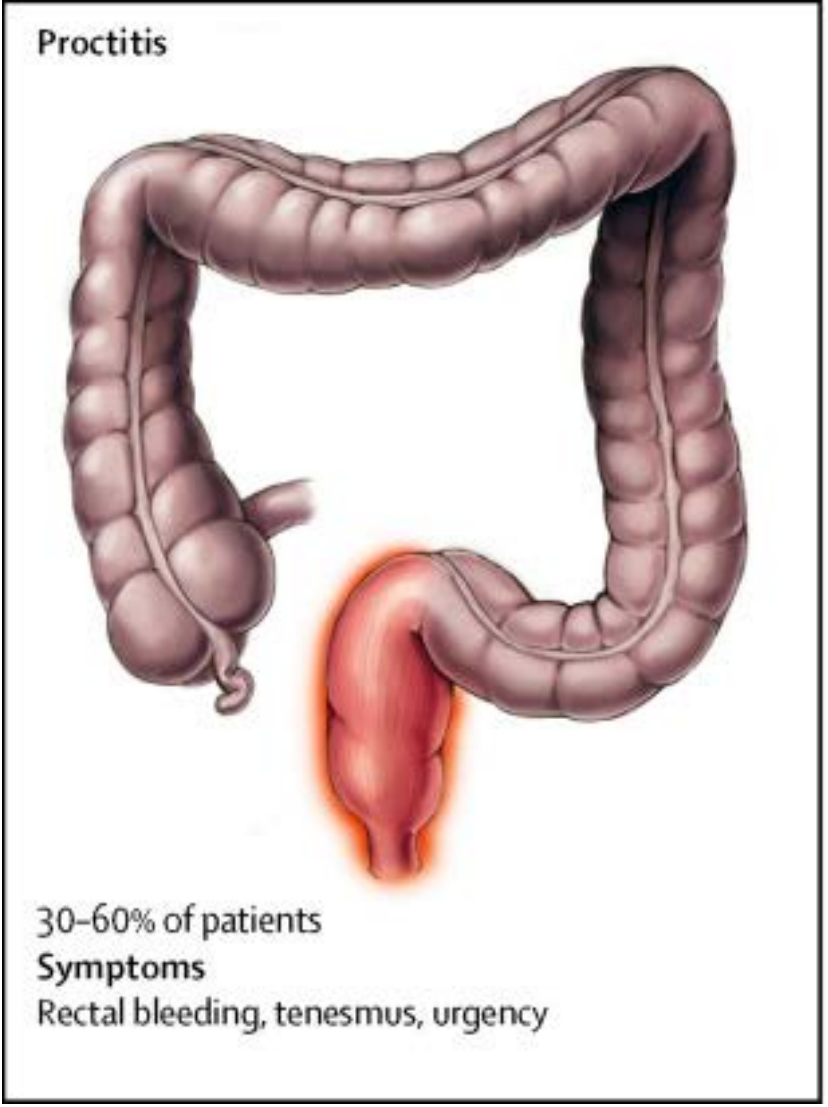


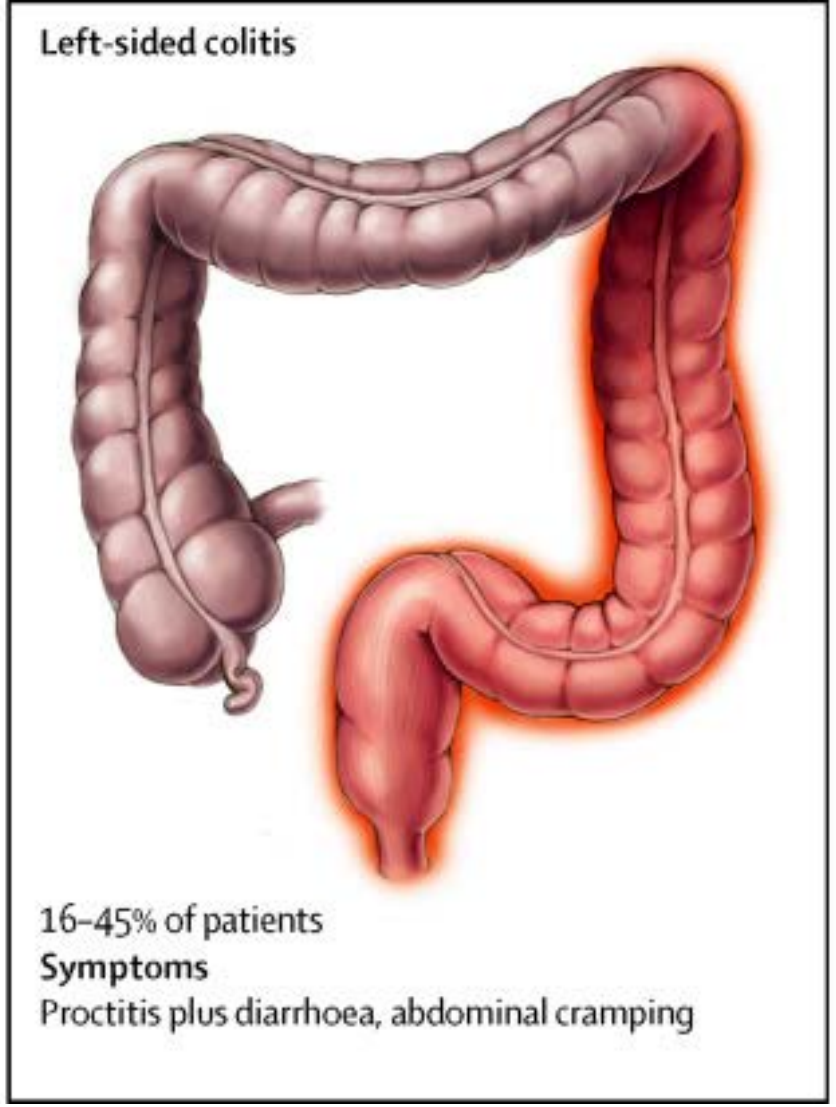


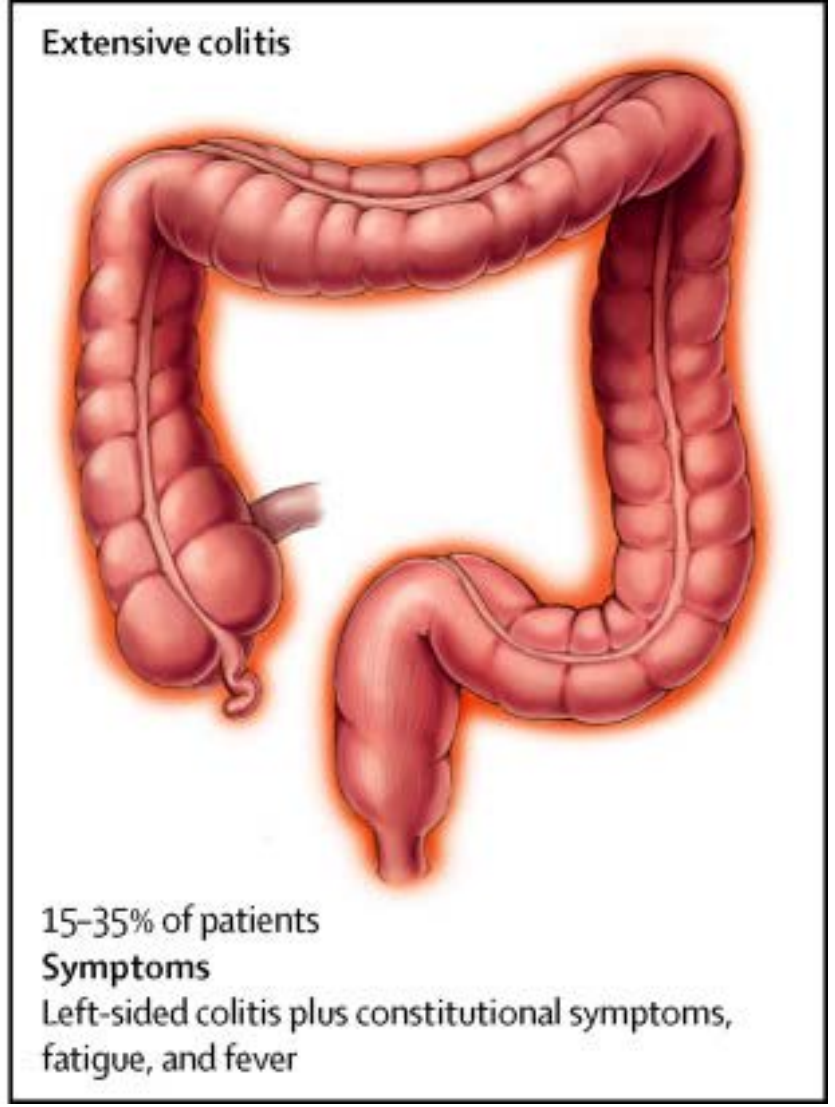
# Perianal Fistula in Crohn's



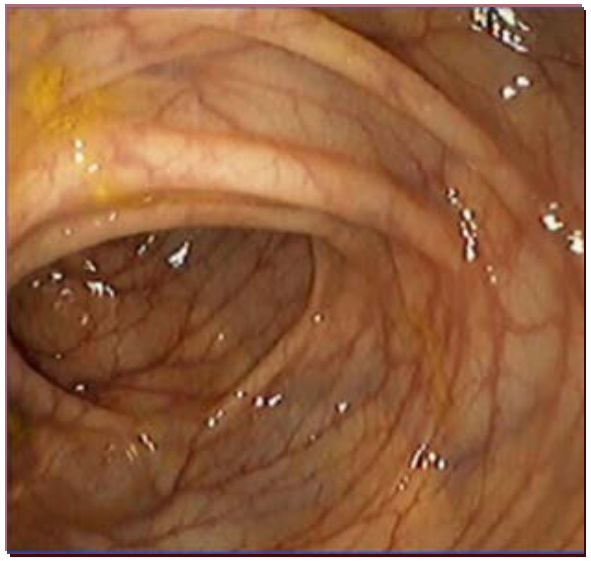

Proctitis
30–60% of patients
**Symptoms**
Rectal bleeding, tenesmus, urgency

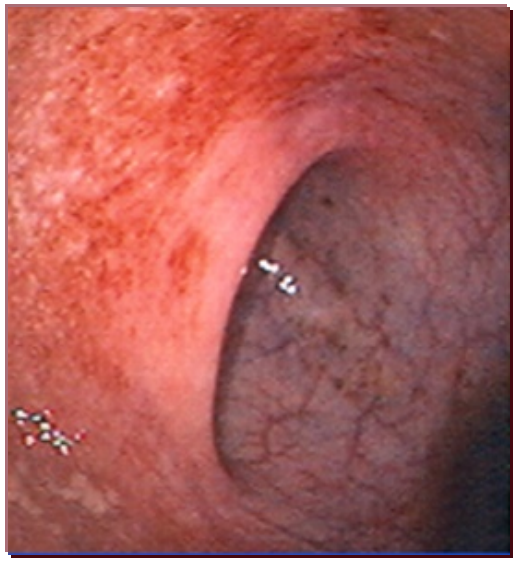

Left-sided colitis
16–45% of patients
**Symptoms**
Proctitis plus diarrhoea, abdominal cramping


Extensive colitis
15–35% of patients
**Symptoms**
Left-sided colitis plus constitutional symptoms, fatigue, and fever

# Ulcerative Colitis – Spectrum of Disease

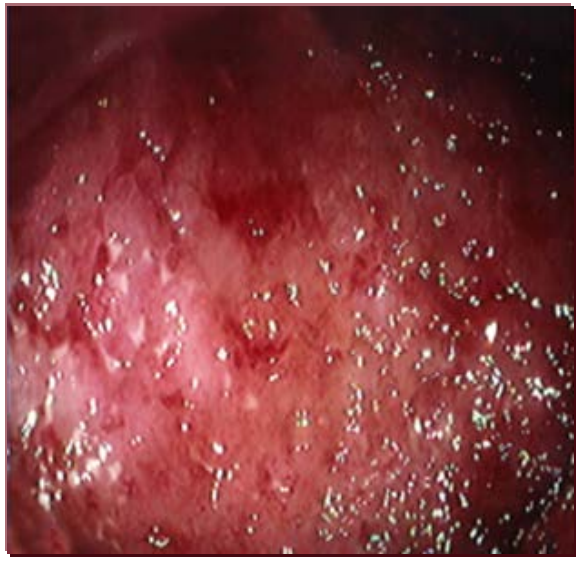
**Normal**
Healthy
Colon

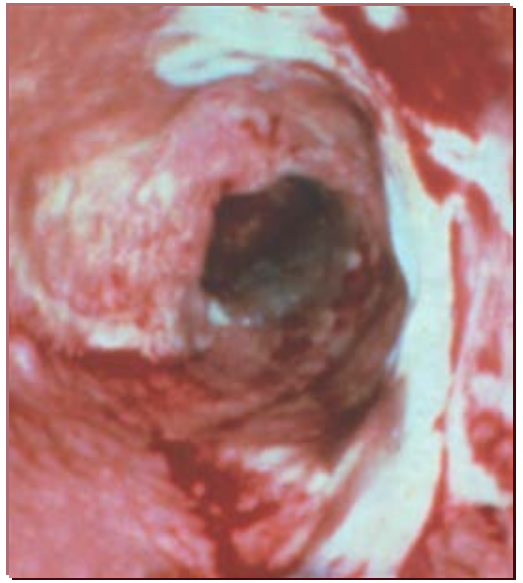




**Mild-**
Erythema,
Mild Friability

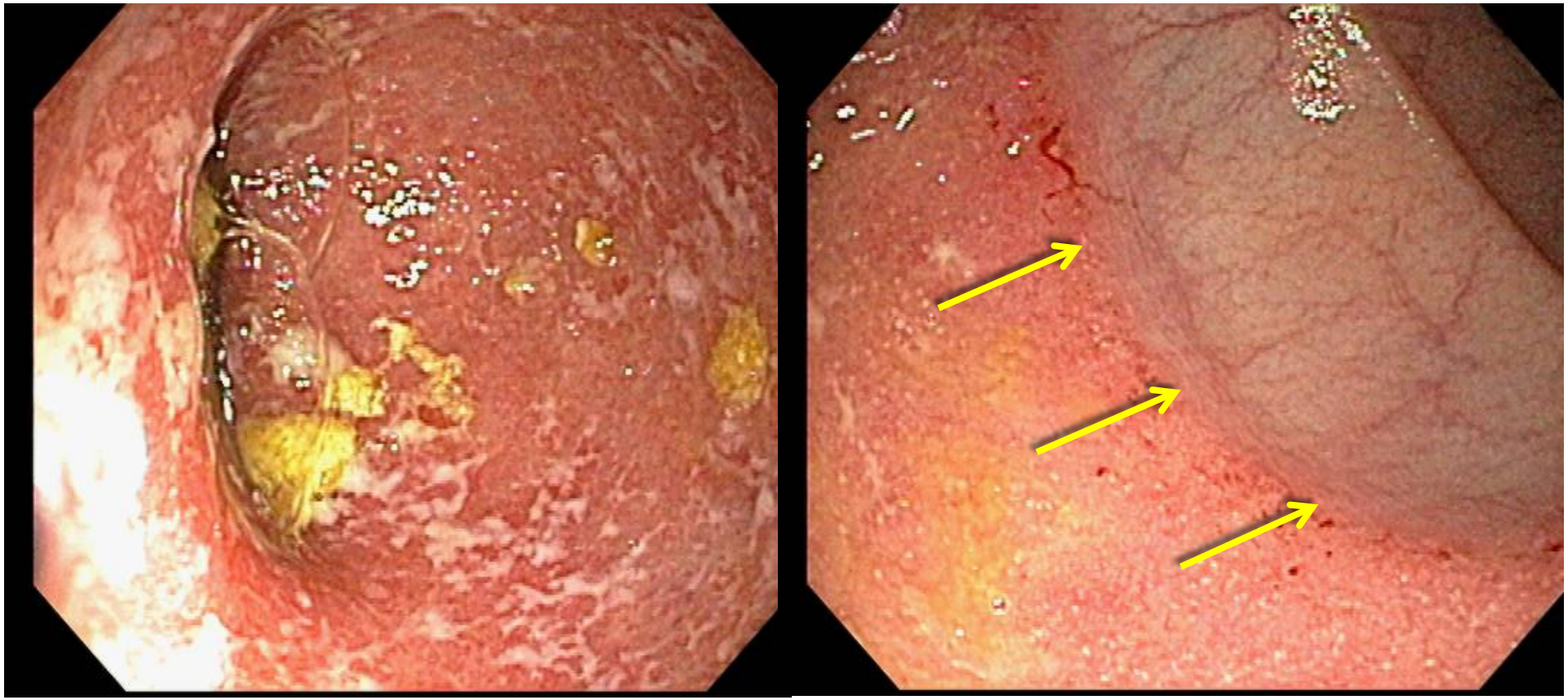
**Moderate**
Marked
Erythema,
Friability,
Erosions





**Severe**
Spontaneous
Bleeding,
Ulcers

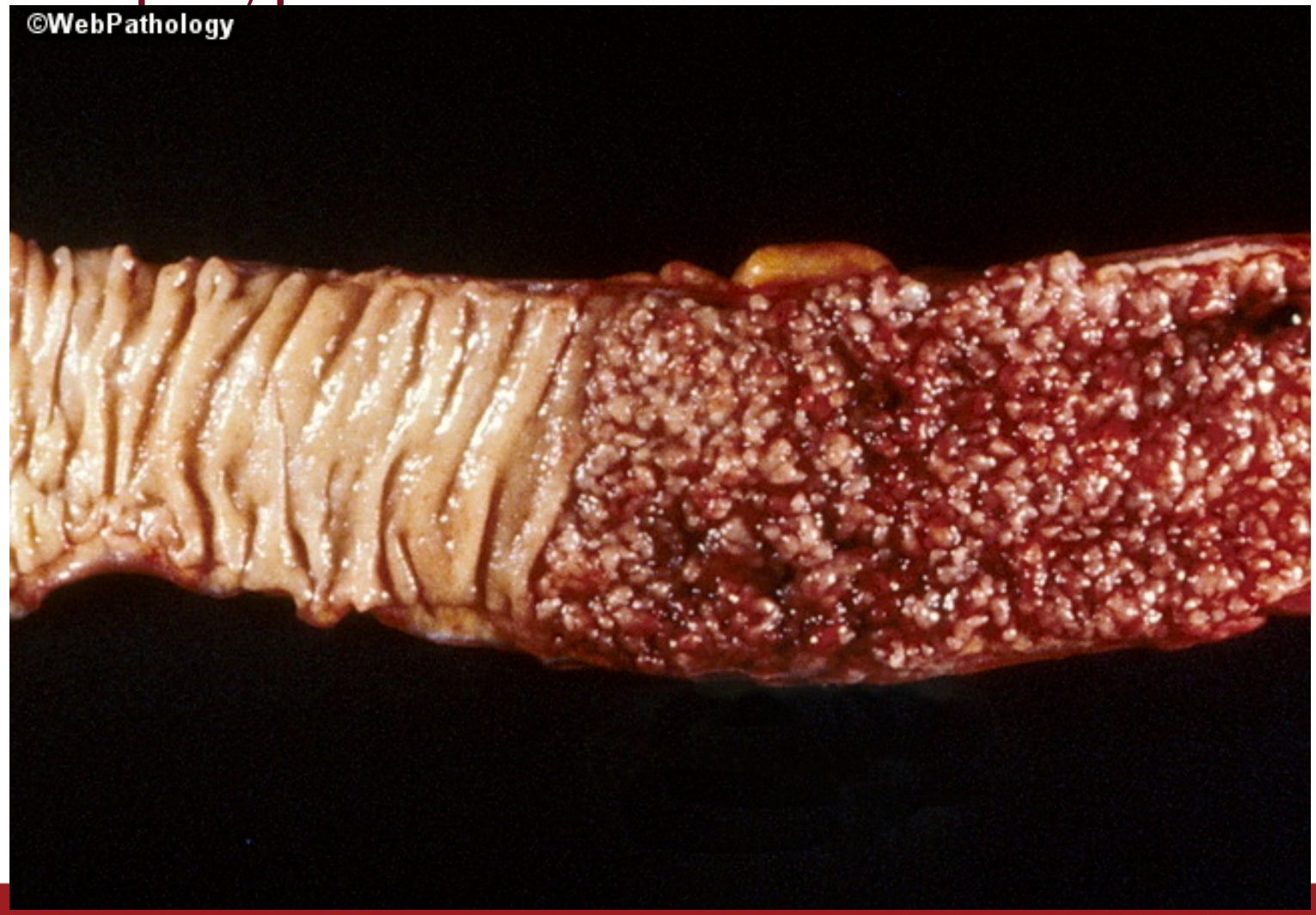
# Endoscopic Images in a Patient With Left-sided Ulcerative Colitis



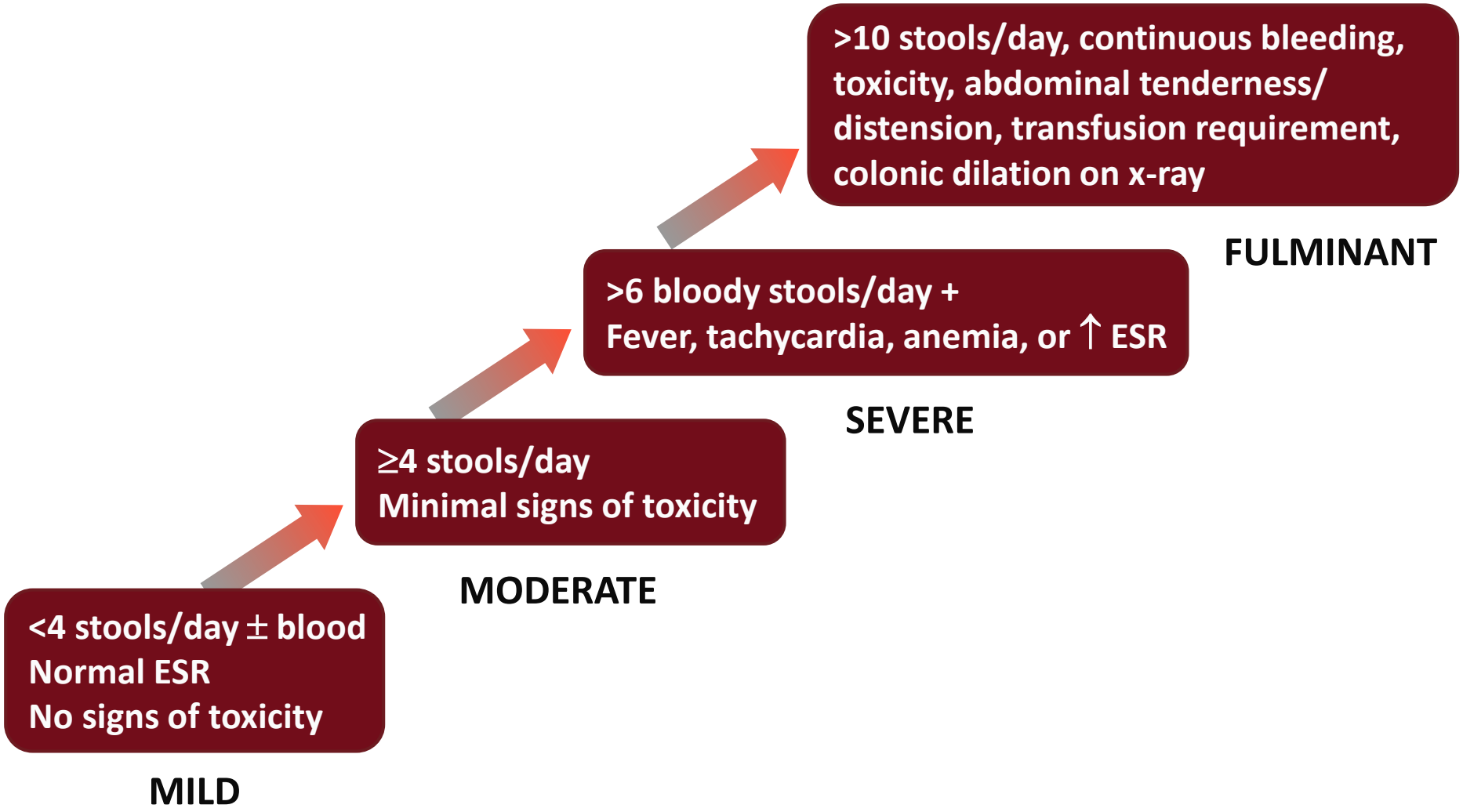
Arrows indicate margin of demarcation in sigmoid colon

Images courtesy of David T. Rubin, MD.

# UC with Pseudopolyps



# Definitions of Clinical Severity of Disease[a]

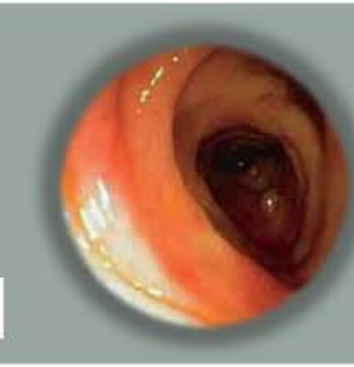
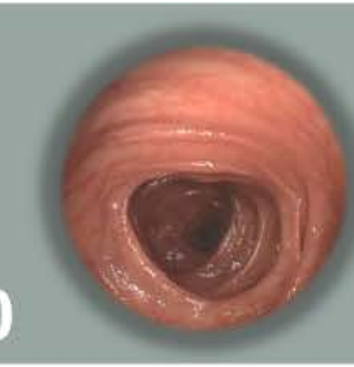



ESR= Erythrocyte sedimentation rate.

[a]Does not include endoscopic findings. Kornbluth A, Sachar D. *Am J Gastroenterol*. 2004;99:1371-1385.

Adapted from Truelove SC, Witts LJ. *Br Med J*. 1955;2:1041-1048.

# Mayo Ulcerative Colitis Scoring Index

| Example endoscopic images | | | | |
|---|---|---|---|---|
| **Endoscopic subscore** | 3  | 2  | 1  | 0  |
| Definition | **Severe disease**<br>Spontaneous bleeding, ulceration | **Moderate disease**<br>Marked erythema, absent vascular pattern, erosions | **Mild disease**<br>Erythema, decreased vascular pattern, mild friability | **Normal or inactive disease** |

# Mayo Ulcerative Colitis Scoring Index

| Variable | 0 Points | 1 Points | 2 Points | 3 Points |
|---|---|---|---|---|
| **Bowel movement (BM) frequency** | Normal | 1-2 BM > normal | 3-4 BM > normal | >5 BM > normal |
| **Rectal bleeding** | None | Streaks on stool < 50% BM's | Obvious fresh blood with most BM's | BM's with fresh blood |
| **Endoscopy** | Normal | Mild Erythema, ↓ vascularity, Mild friability | Marked erythema, Lack vascular pattern, Friability, Erosions | Severe spontaneous bleeding, Ulceration |
| **Physician Global Assessment (PGA)** | Normal | Mild | Moderate | Severe |

| Scores (Points) | Disease severity |
|---|---|
| ≤ 2 and no subscore >1 | Clinical remission |
| 3-5 | Mild activity |
| 6-10 | Moderate activity |
| 11-12 | Severe activity |

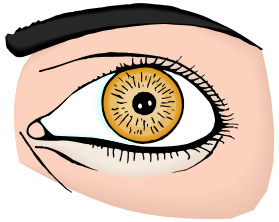
[a]The global medical evaluation takes into account the daily complaint of the patient with regard to abdominal discomfort, pain, a feeling of well-being (normal, above or below the average), physical examination findings and the patient's performance of daily activities.

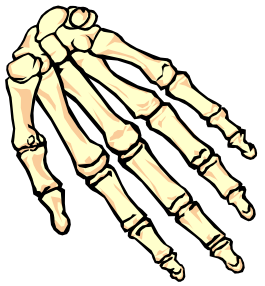
# Differential Diagnosis

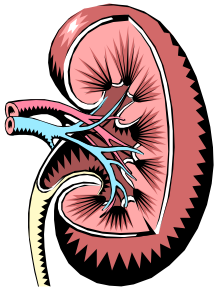
- Infectious colitis: bacterial, viral, fungal (histoplasmosis), mycobacterial, and *Clostridium difficile*
- Ischemic colitis
- Segmental colitis associated with diverticulitis
- Radiation-induced colitis or proctitis
- Medication-induced colitis (in particular non-steroidal anti-inflammatory drugs)
- Crohn's disease
- Sexually transmitted diseases (particularly in patients with proctitis who have engaged in anal intercourse): *Chlamydia trachomatis*, Neisseria gonorrhoeae, herpes, and syphilis
- If predominant symptom is diarrhea and not bleeding: coeliac disease, microscopic colitis, lactose or other food intolerances, and irritable bowel syndrome

# Extraintestinal Manifestations

- Skin (e.g., psoriasis, erythema nodosum)
- Eye (e.g., iritis, uveitis)
- Bones/Joints (e.g., arthritis, osteoporosis)
- Liver/Gall Bladder (e.g., primary sclerosing cholangitis)
- Kidney (e.g., kidney stones)
- Hematologic (e.g., anemia)



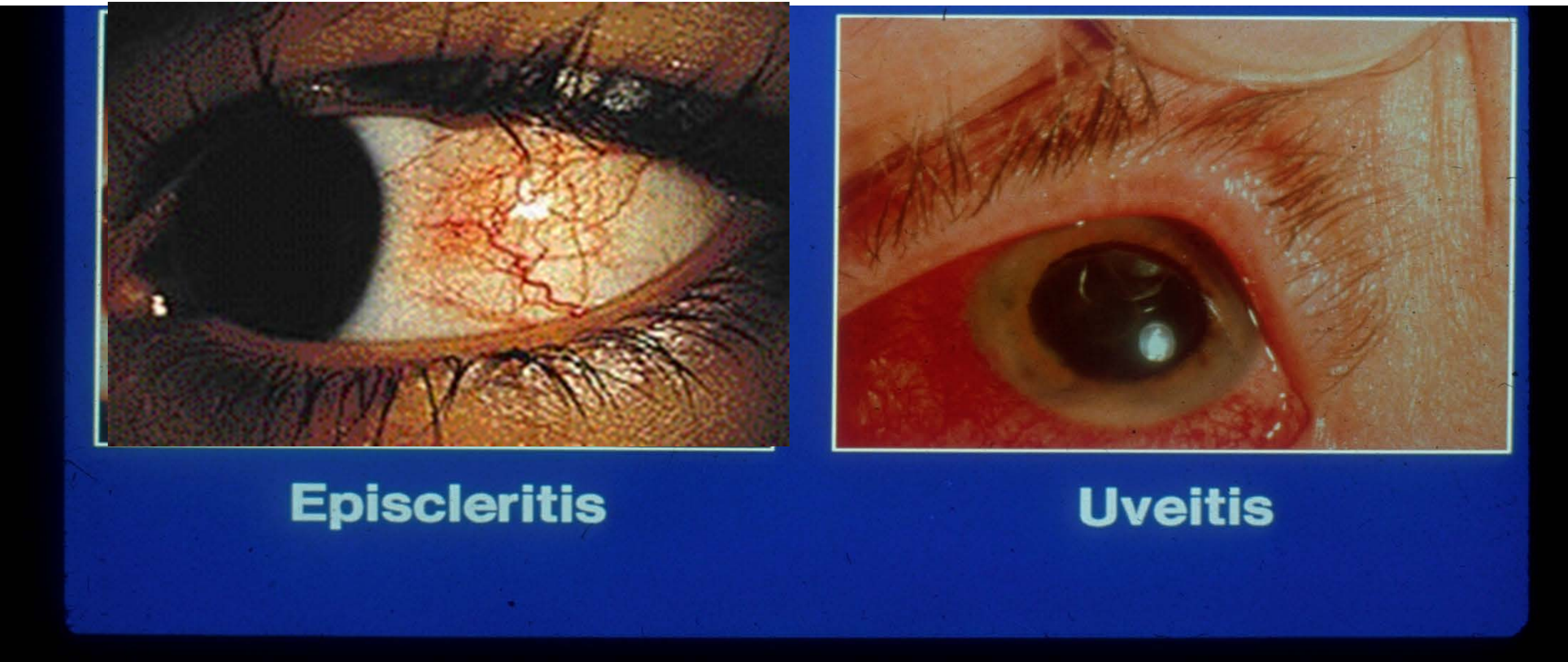




# Extra-Intestinal manifestations of UC

| | Parallel bowel disease activity | Independent from bowel disease activity |
|---|---|---|
| **Joints** | Peripheral arthritis | Axial arthritis (sacroiliitis, ankylosing spondylitis) |
| **Skin** | Erythema nodosum | Pyoderma gangrenosum |
| **Ocular** | Episcleritis, scleritis | Uveitis |
| **Hepatobiliary** | | PSC (primary sclerosing cholangitis) |

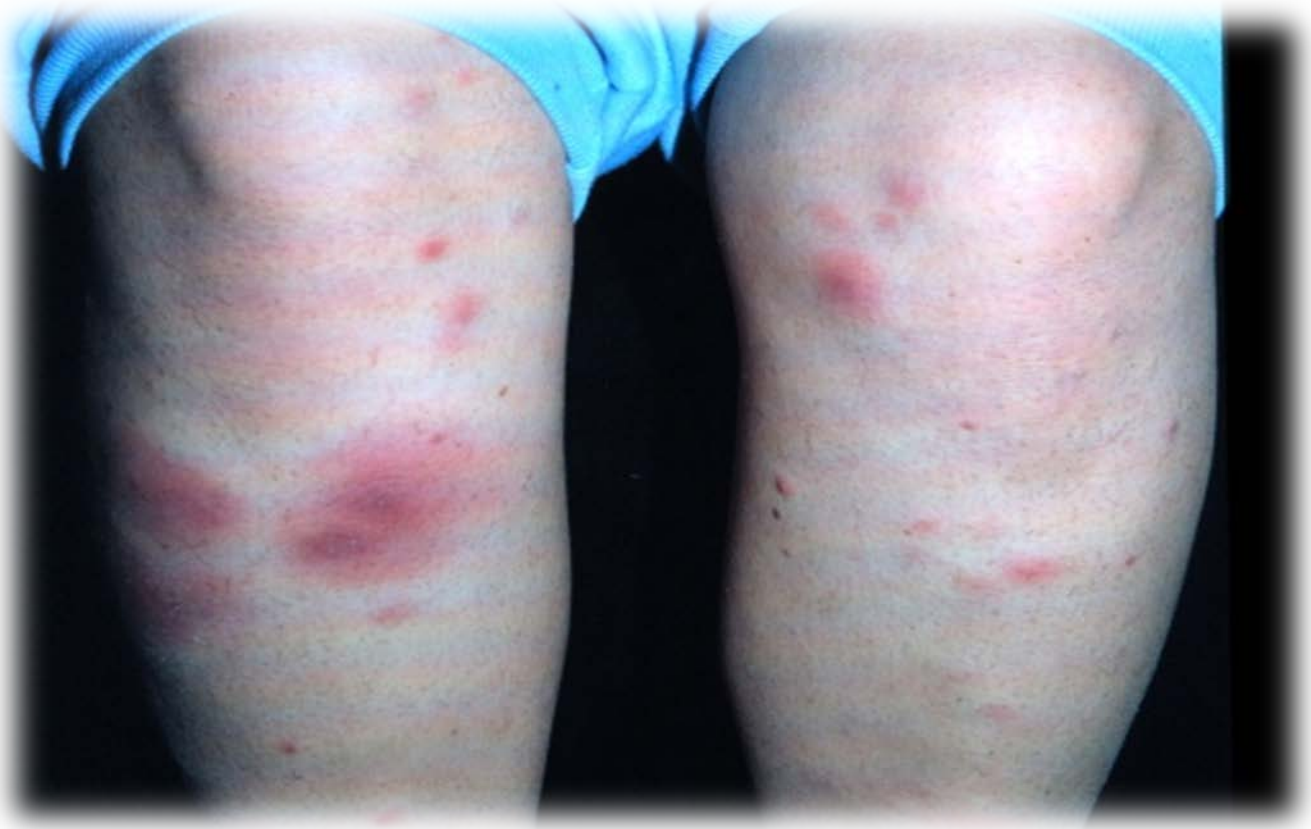
# UC Complications of the Eye

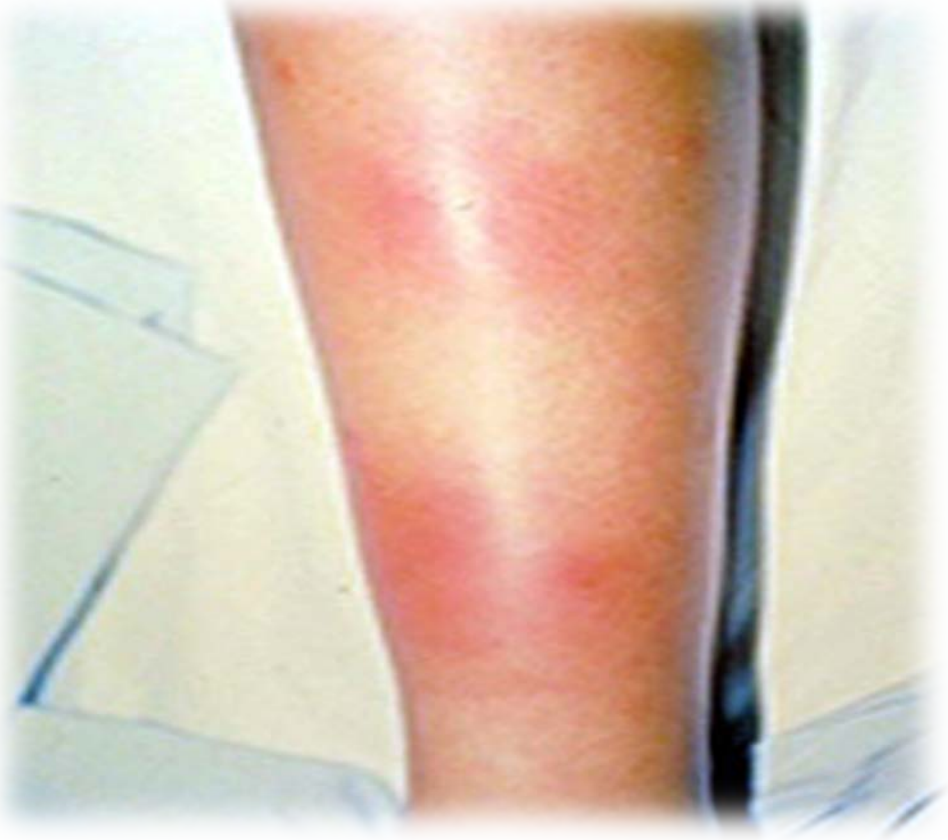


# Erythema Nodosum

- More common in CD (15%), less in UC (5%)
- Young women at most risk
- Painful tender erythematous nodules: pretibial, or areas of trauma
- Correlates with IBD activity
- Treat underlying IBD
  - Bedrest, steroids, dapsone, cyclo

# Erythema Nodosum

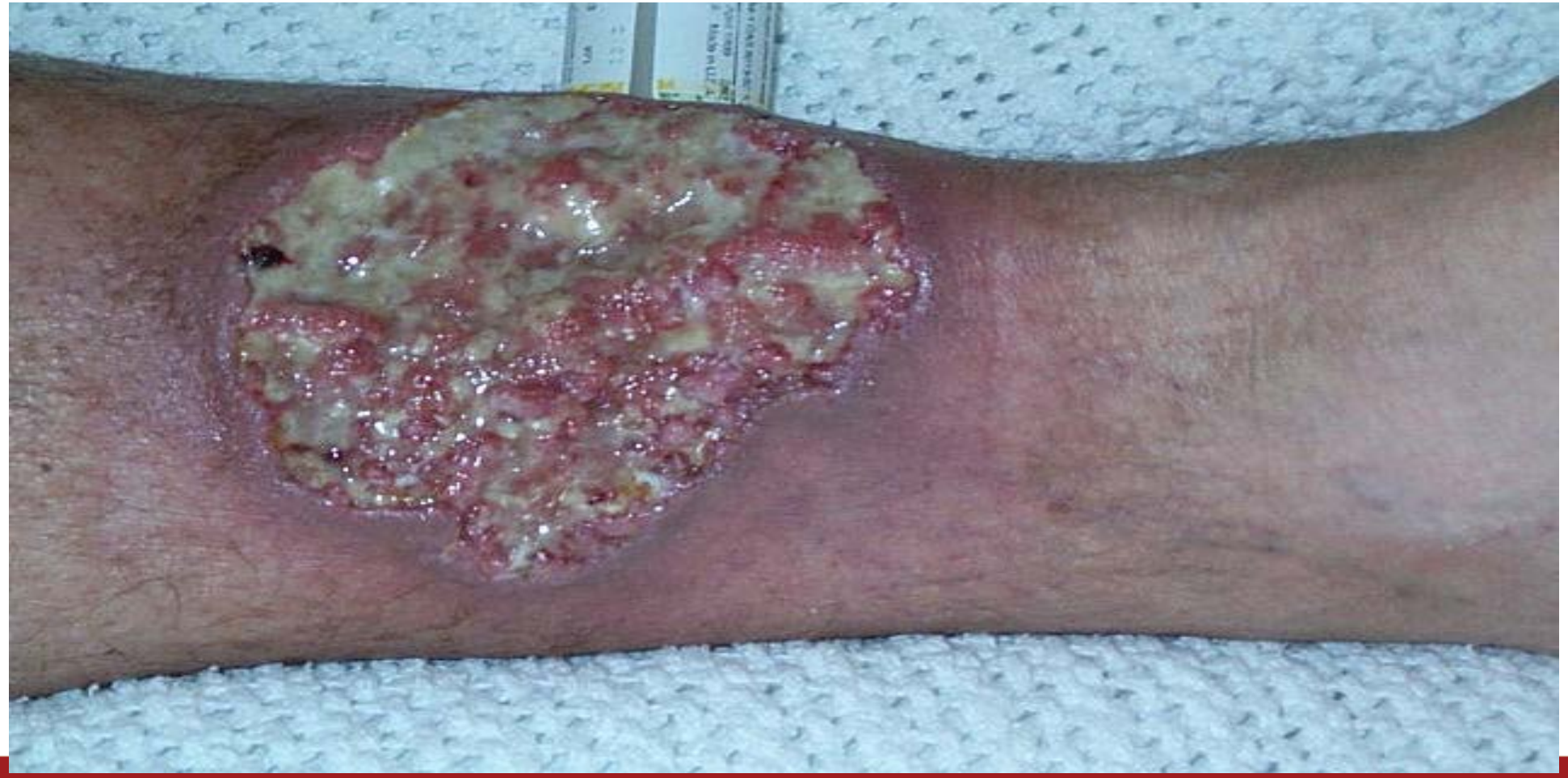




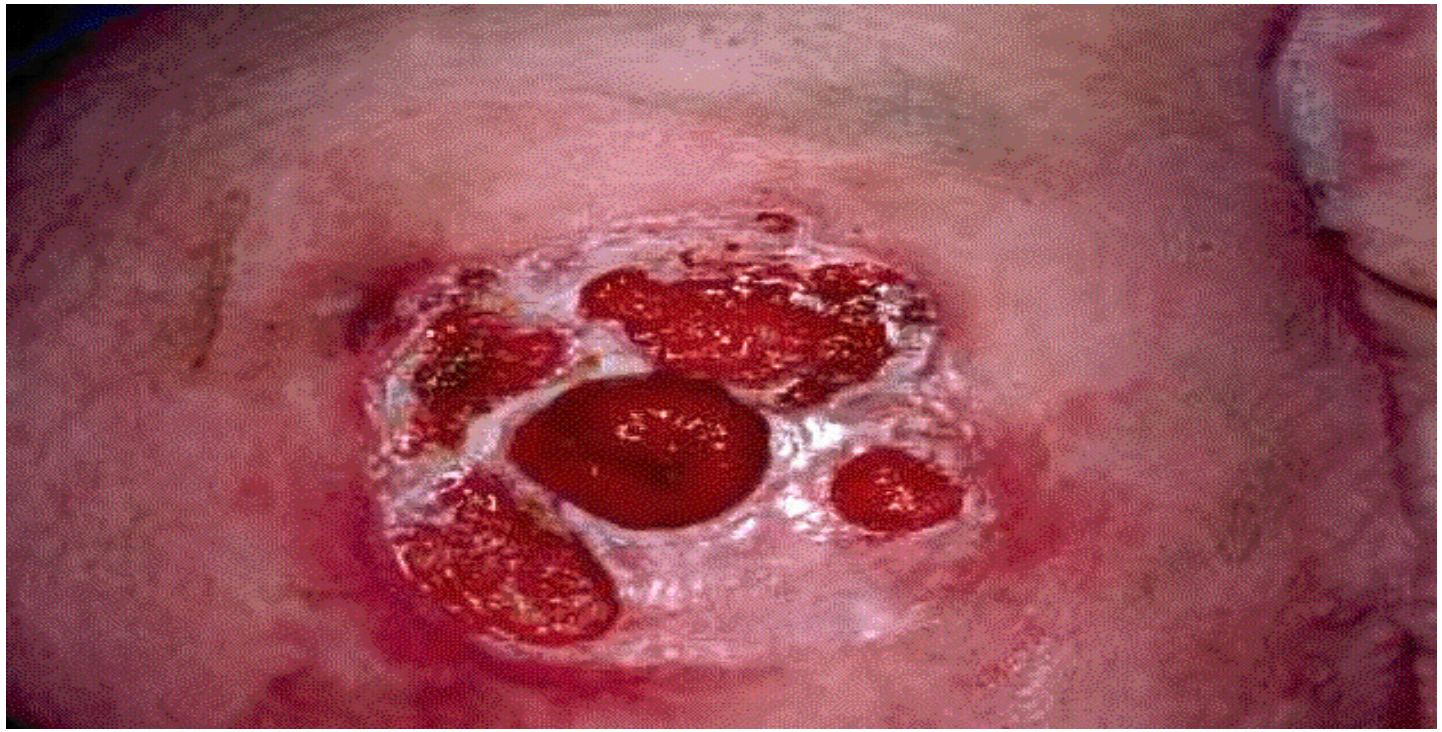
# Pyoderma Gangrenosum

- Pustular lesion
- Evolves to an ulcer with undermining violaceous borders
- “Pathergy”: worsens with trauma
- Clinical course often independent of IBD

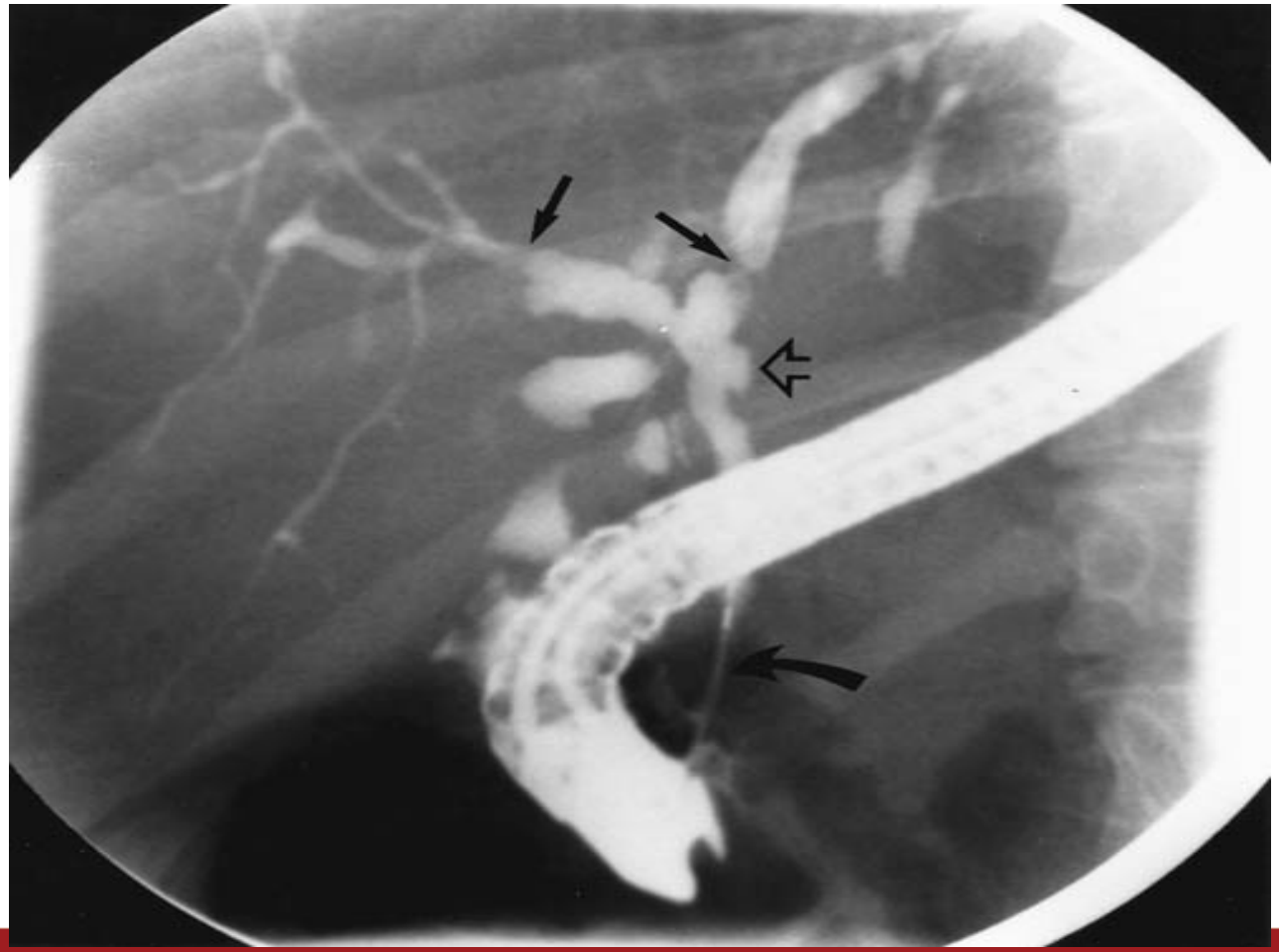
# Pyoderma Gangrenosum



# Peristomal Pyoderma



# Sclerosing Cholangitis

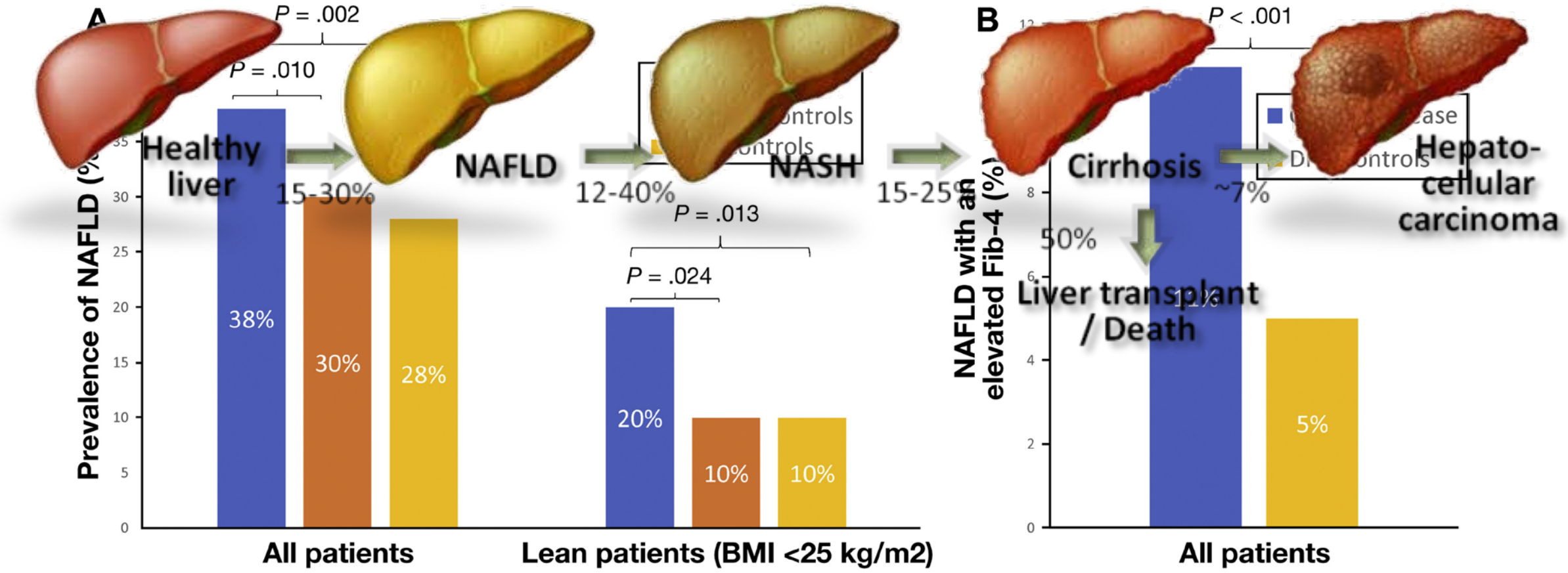


# PSC

- Cholestatic disease
- Bile ducts with “string of pearls”
- Progress to cirrhosis
- Increase risk of cholangiocarcinoma
- Treatment: supportive until liver transplant
- Colorectal cancer risk in pts with PSC is 33% at 20 years after UC diagnosis


Inflammatory Bowel Dis. 2008;14(4):622-625.

# Crohn's increases the risk of Non-Alcoholic Fatty Liver Disease

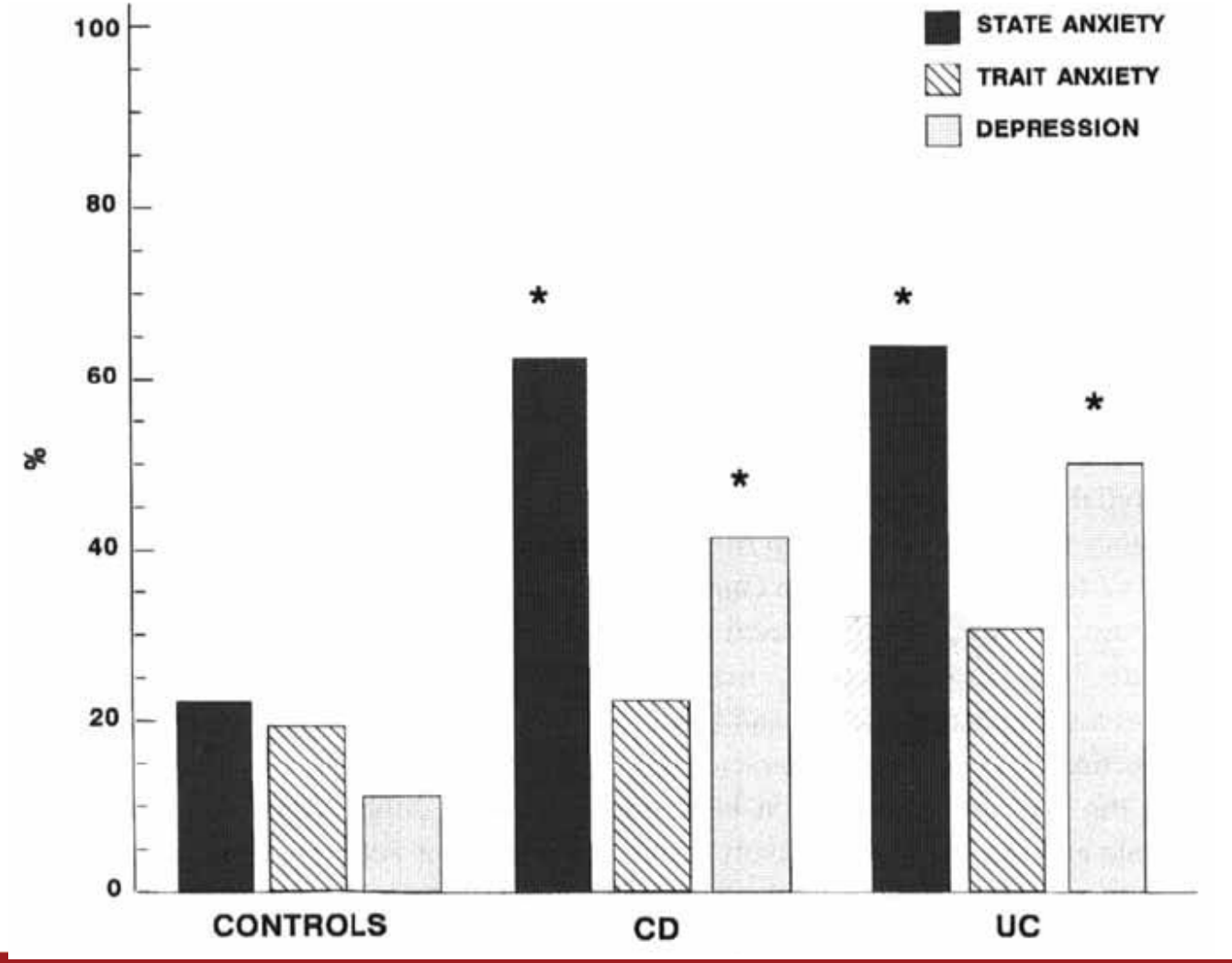


# NAFLD is a Major Risk for IBD Mortality

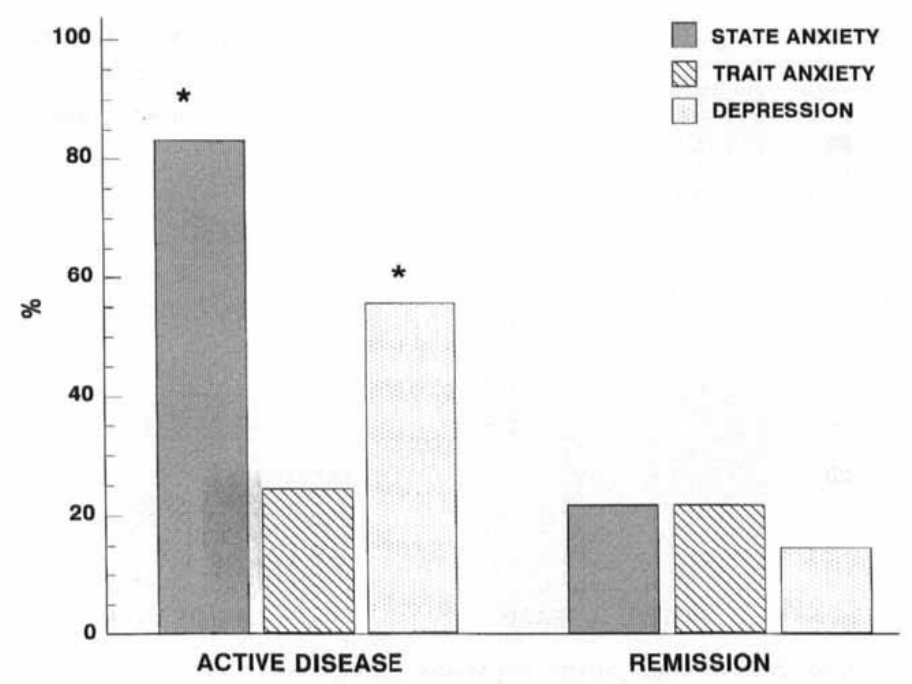
| | Summary SMR | L95% | U95% | $I^2$ | Het P | No. of Studies |
|---|---|---|---|---|---|---|
| Overall: UC | 1.16 | 1.04 | 1.29 | 84% | 0.00 | 25 |
| Overall: CD | 1.46 | 1.30 | 1.63 | 71% | 0.00 | 19 |
| CRC: UC | 2.82 | 1.68 | 4.74 | 80% | 0.00 | 7 |
| CRC: CD | 3.12 | 0.97 | 10.10 | 73% | 0.00 | 6 |
| Cardiovascular disease: UC | 0.90 | 0.80 | 1.02 | 39% | 0.09 | 11 |
| Cardiovascular disease: CD | 1.00 | 0.88 | 1.13 | 0.0% | 0.73 | 9 |
| Pulmonary disease: UC | 1.41 | 1.12 | 1.77 | 39% | 0.10 | 10 |
| Pulmonary disease: CD | 1.60 | 1.24 | 2.05 | 0.0% | 0.43 | 8 |
| Nonalcoholic liver disease: UC | 2.26 | 1.14 | 4.49 | 55% | 0.06 | 5 |
| Nonalcoholic liver disease: CD | 2.82 | 1.52 | 5.21 | 0.0% | 0.63 | 3 |

2013 Mar;19(3):599-613.

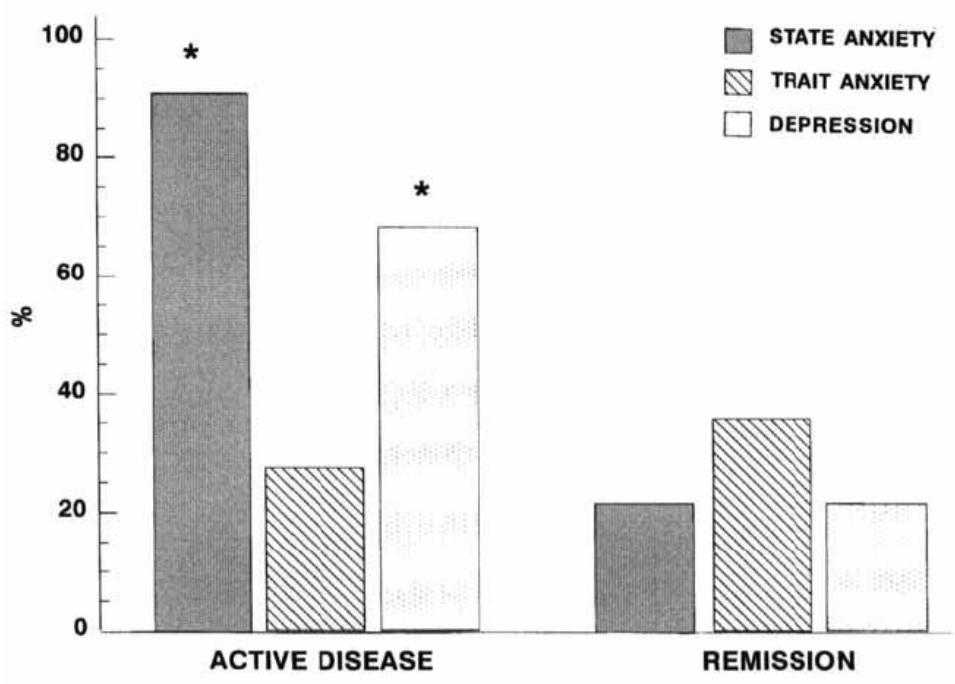
# Anxiety State and Depression associate with IBD Diagnosis



# Anxiety State and Depression associate with IBD Activity



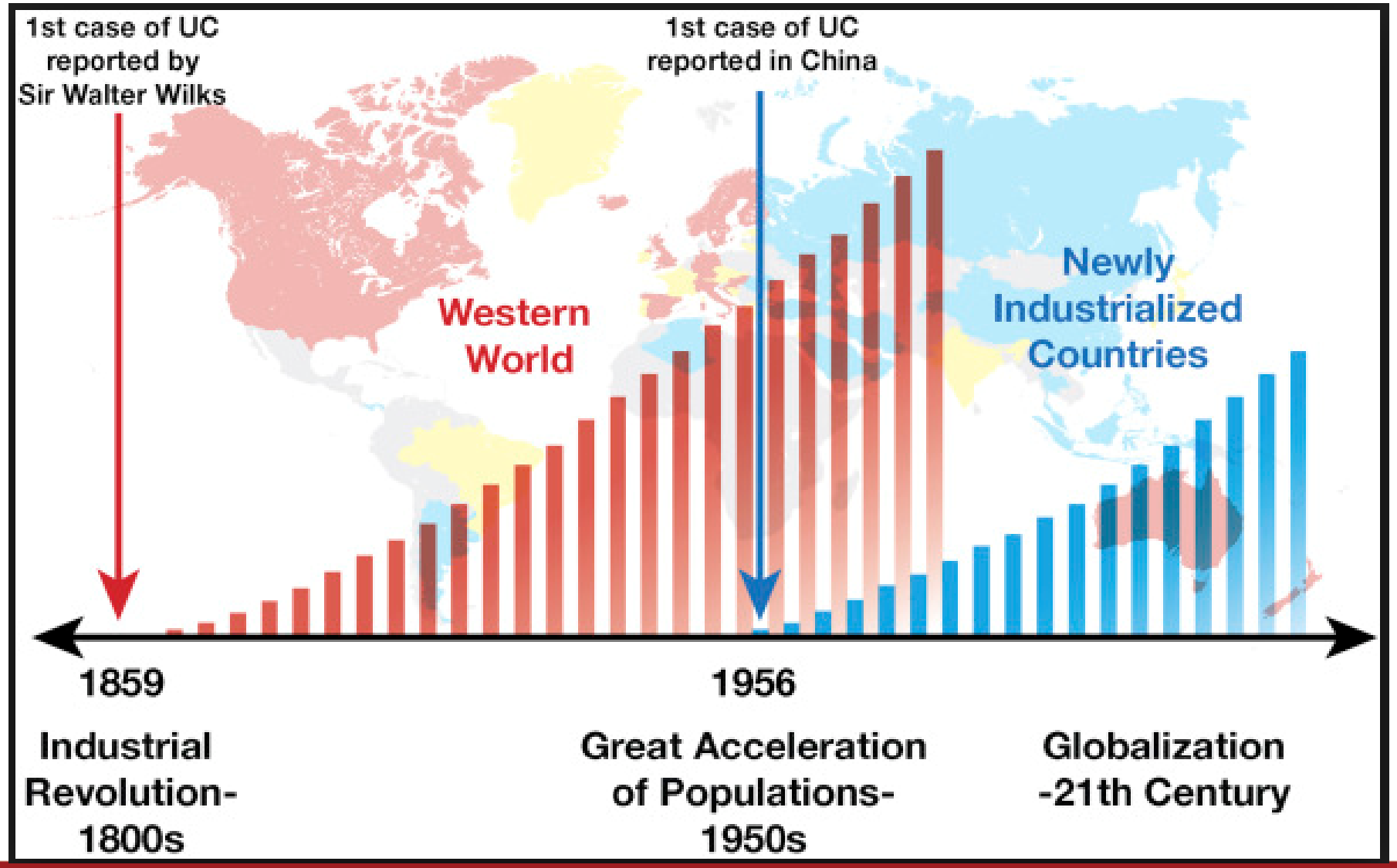

Crohn's




Ulcerative Colitis

# Natural History and Epidemiology of IBD

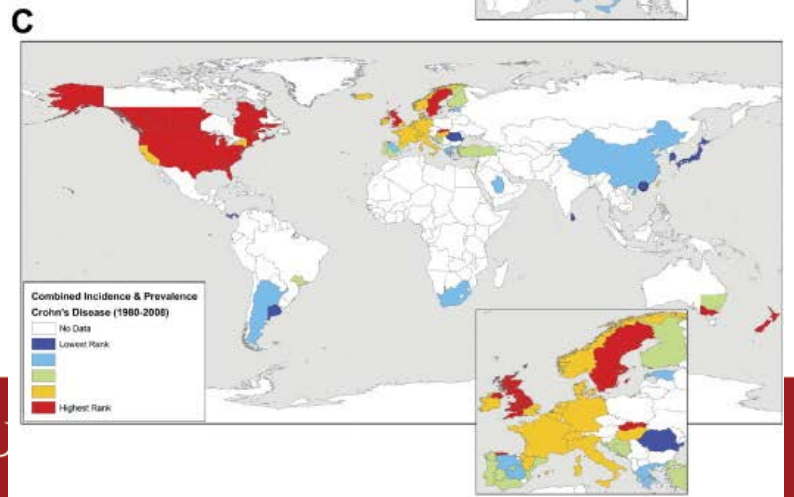
# Increasing Prevalence of IBD



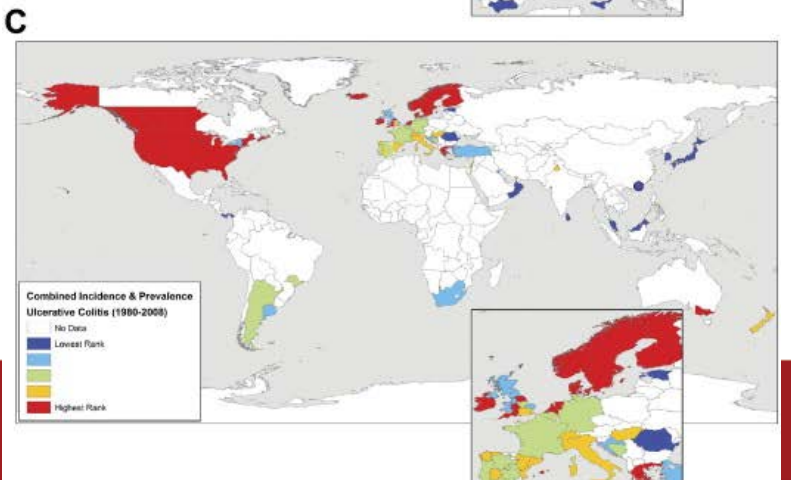

Kaplan G, et al. Gastroenterology 2017;152:313–321


<1960


~3 million in US today have IBD



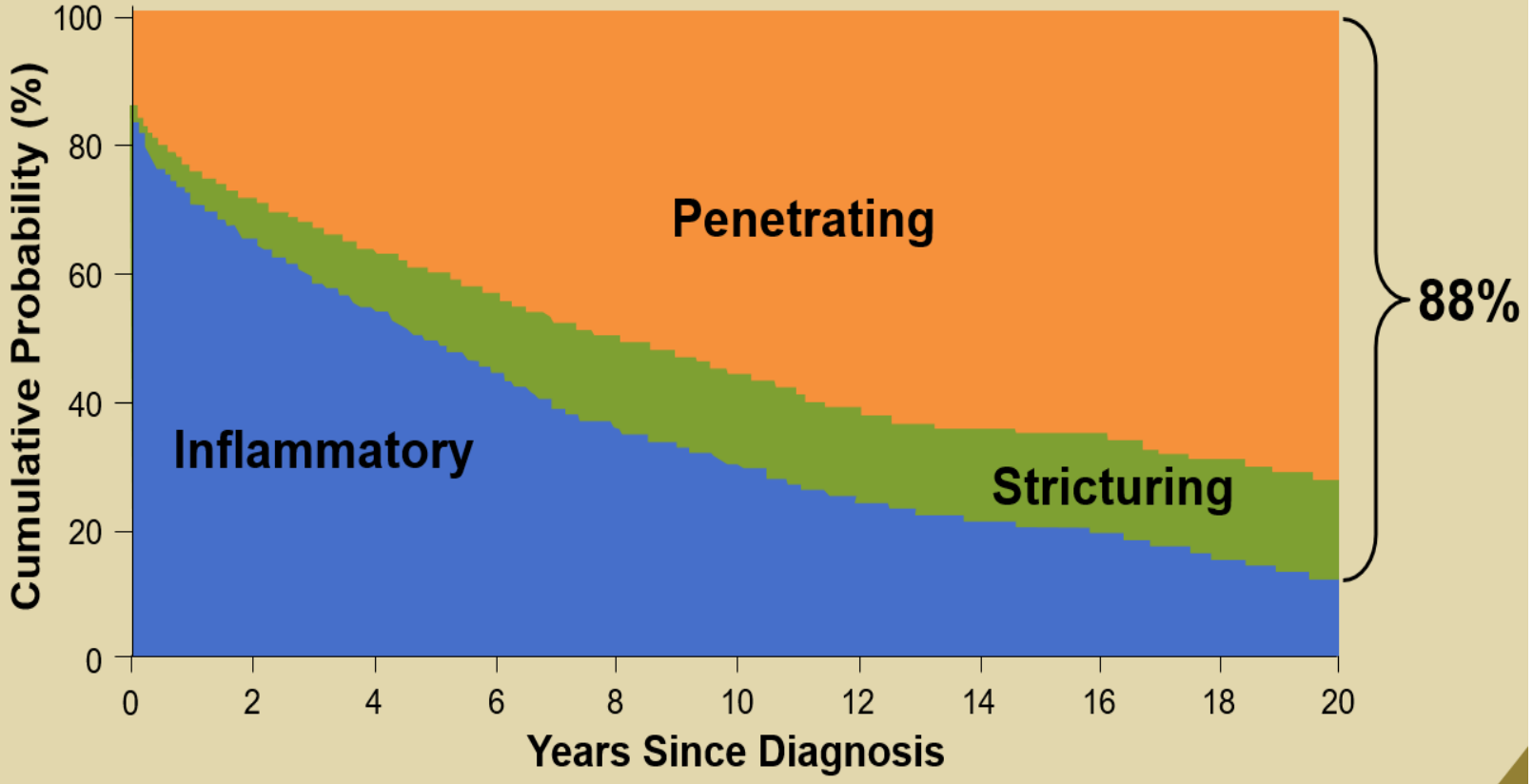

1980-2008



# Crohn's

## Risk of Disease Progression Over Time

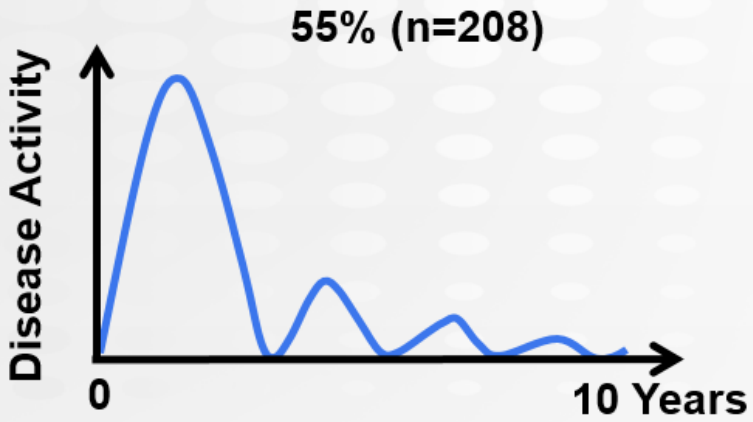
### 88% of Patients May Develop Stricturing or Penetrating Disease Over Time[1]



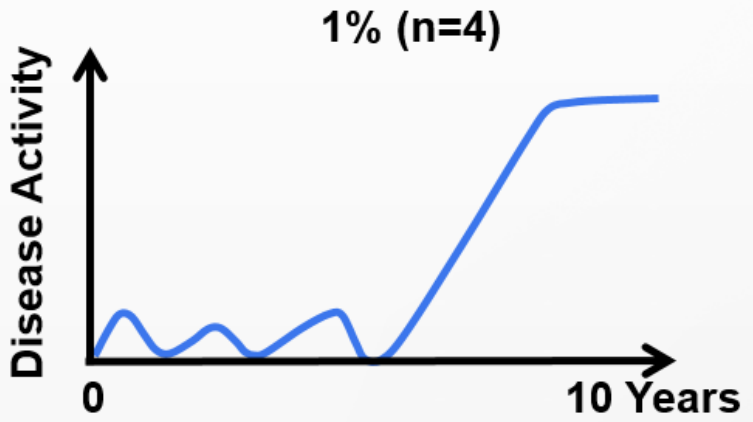

N=2002 patients with CD since diagnosis of the disease. These data precede biologic therapy for CD.

1. Cosnes J, et al. *Inflamm Bowel Dis*. 2002;8:244-250.

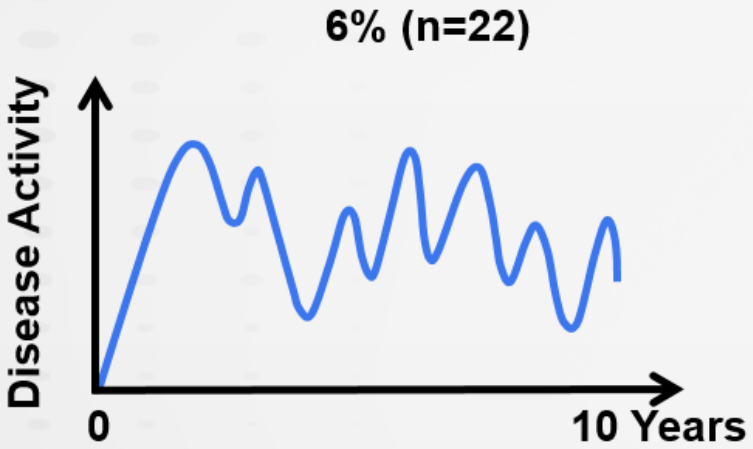
# UC Clinical Course is Complex and Unpredictable



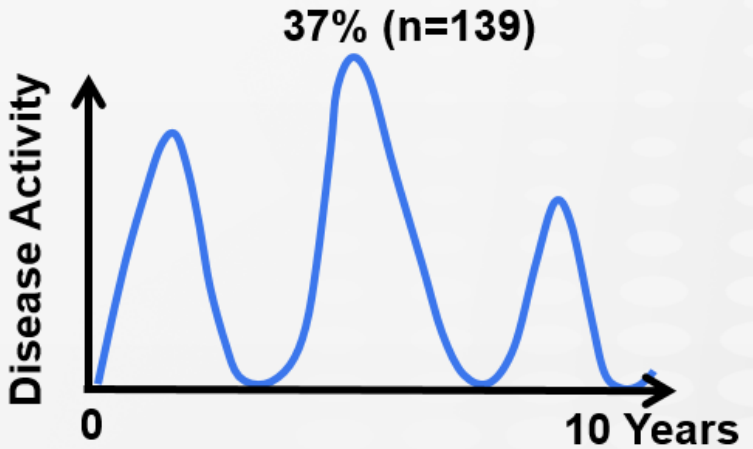

**Curve 1:** Remission or mild severity of intestinal symptoms after initial high activity




**Curve 2:** Increase in the severity of intestinal symptoms after initial low activity

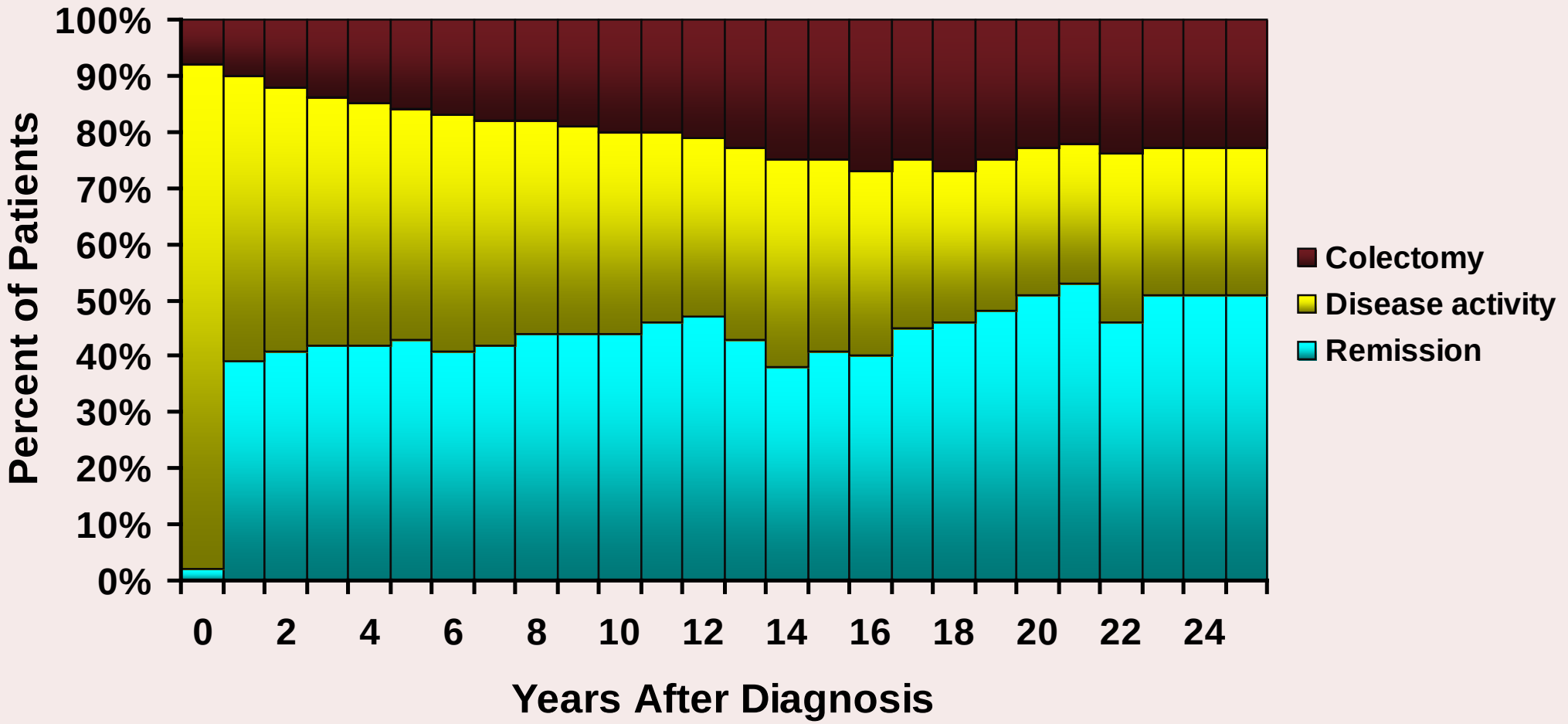



**Curve 3:** Chronic continuous symptoms



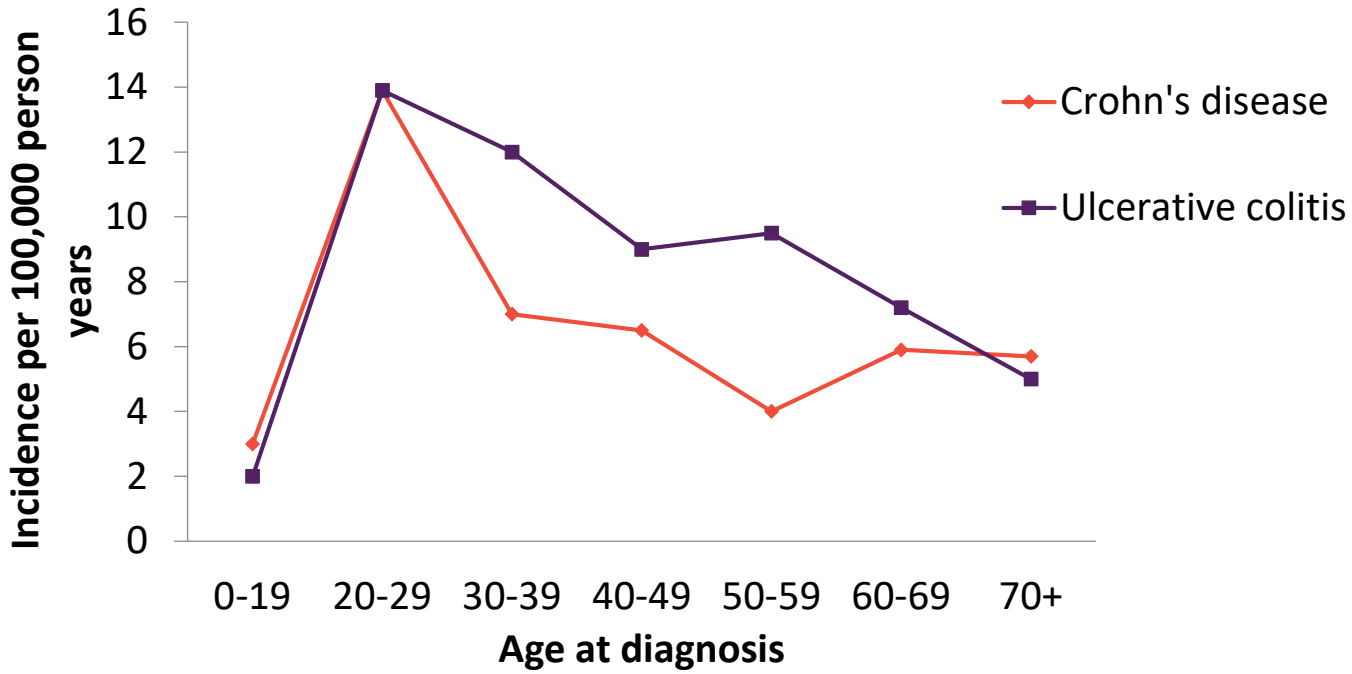

**Curve 4:** Chronic intermittent symptoms

# The Natural History of UC




Langholz E, et al. *Gastroenterology*. 1994;107:3-11.

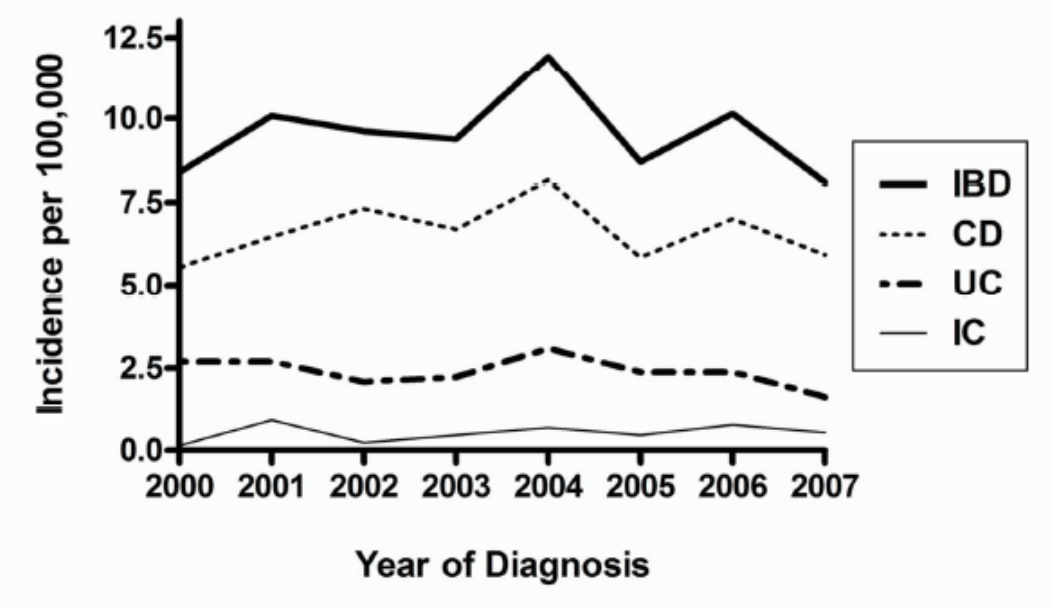
# IBD Incidence

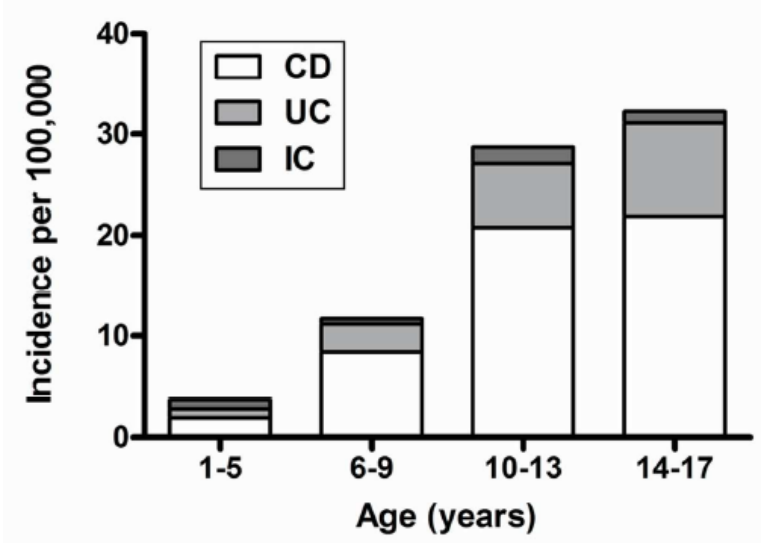



- Overall incidence = 6-14 per 100K
- Peak age of onset: 2nd to 4th decades
- In U.S., 60,000 new cases each year

Herrinton, Am J Gastroenterol, 2008; Loftus, Inflamm Bowel Dis, 2007; Bernstein, Am J Epidemiol 1999; Shivananda, Gut, 1996

# Incidence: Pediatric IBD is seeing earlier onset




Overall incidence of pediatric IBD: 9.5 per 100,000

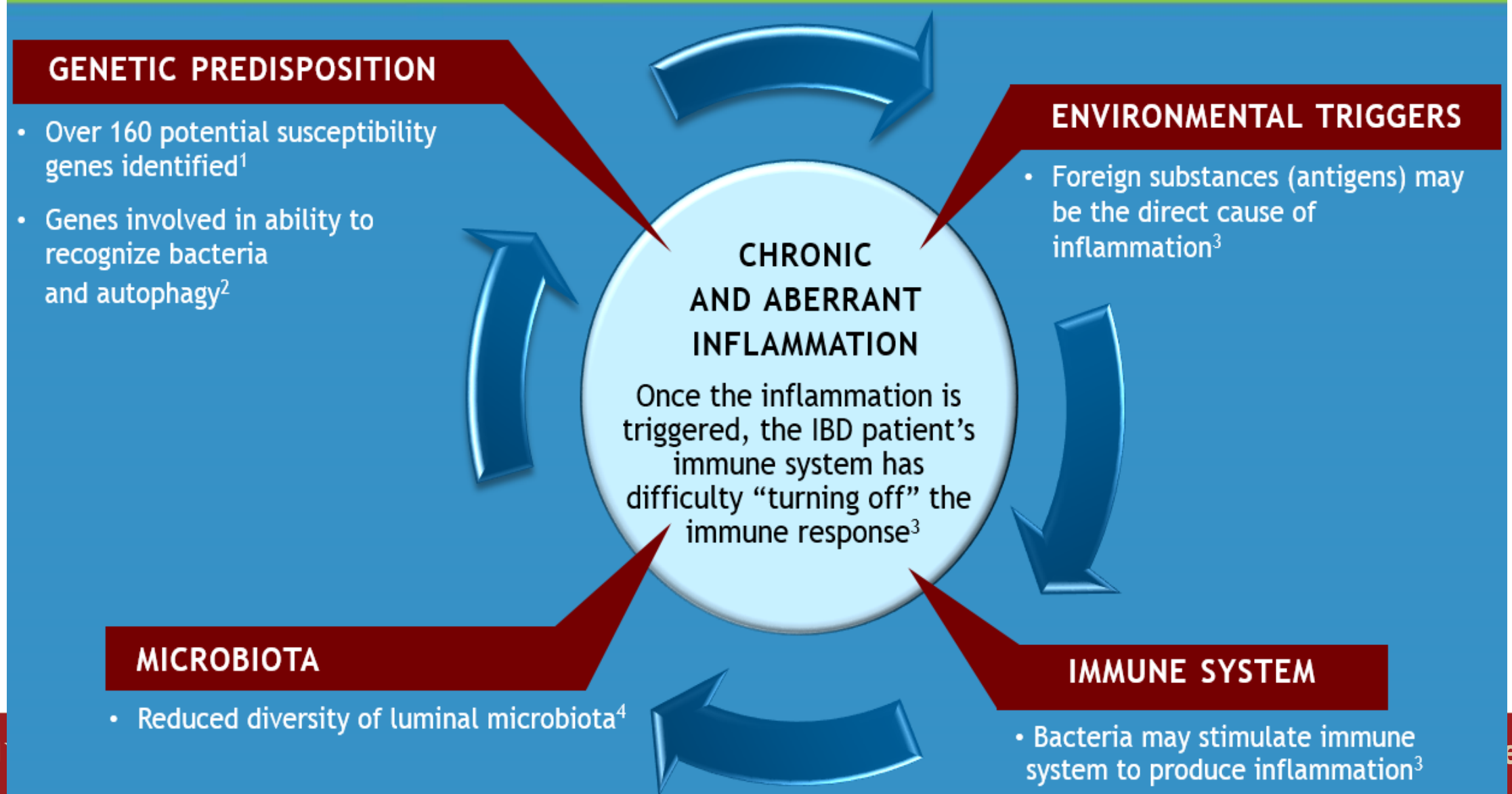
CD twice as common as UC in childhood

Overall incidence stable over last 8 years, but increasing incidence among very young children (VEO-IBD)

Adamiak, et al. Inflamm Bowel Dis. 2013 May;19(6):1218-23.
Benchimol EI, Gut. 2009 Nov;58(11):1490-7.

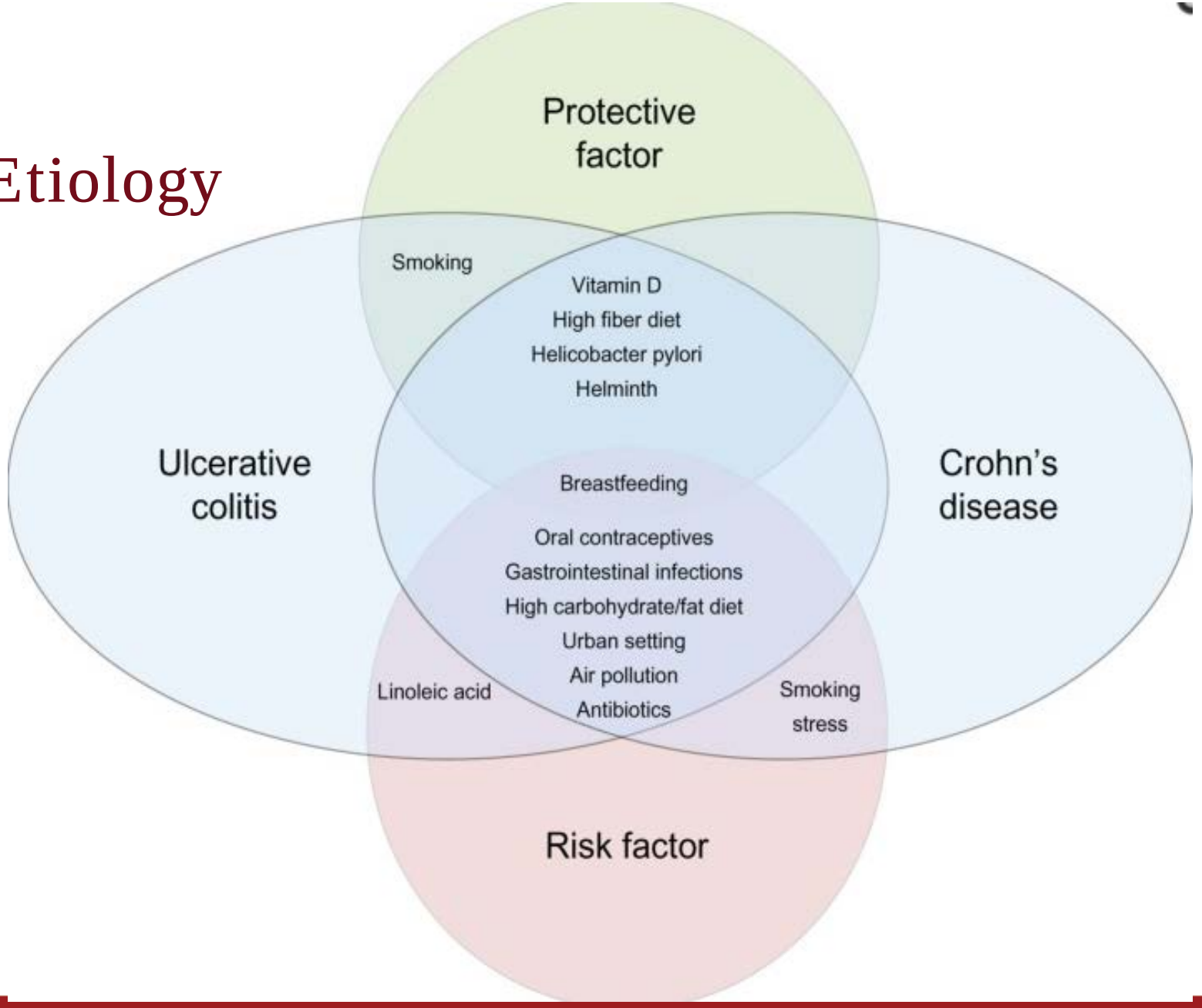
# IBD Pathophysiology and Etiology

# Complex Interactions Contribute to Inflammation in IBD



# Pathophysiology and Etiology

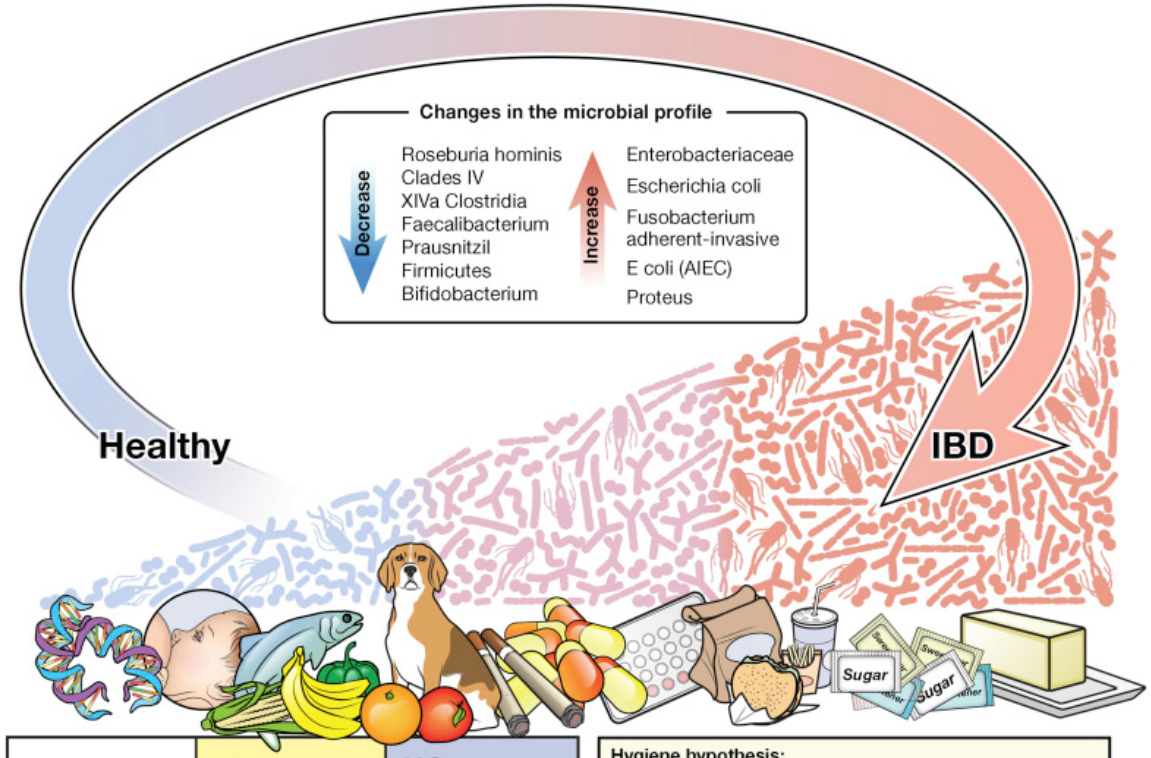
- The case for environmental factors
- Selected examples
  - Antibiotics: CD > UC
  - NSAID: UC > CD
  - Dietary factors Fiber
  - Microbiota
- Future of IBD epidemiology




Ponder A, Long MD. Clin Epidemiol. 2013; 5: 237-247.

# How does the environment contribute?

- We know something is out there, but we don't know what it is
- Inconsistent findings
  - Exception is tobacco
- Small effect sizes
- IBD epidemiology is challenging!




| | CD | UC |
|---|---|---|
| Smoking | Risk in Caucasians and Middle Eastern migrants | Protective in Caucasians and Asians |
| Antibiotic use in childhood | Risk in Caucasians, protective in Asians/ Middle Eastern migrants | Risk in Caucasians, protective in Asians/ Middle Eastern migrants |
| Breastfeeding | Protective in Asians and most studies in Caucasians | Protective in Asians and most studies in Caucasians |
| Oral contraceptives | Risk in Caucasians | Inconclusive |
| Appendectomy | Risk in Caucasians | Protective in Caucasians |
| Low levels of vitamin D | Risk in Caucasians | Risk in Caucasians |
| Tea or coffee consumption | Protective in Asians | Protective in Asians |

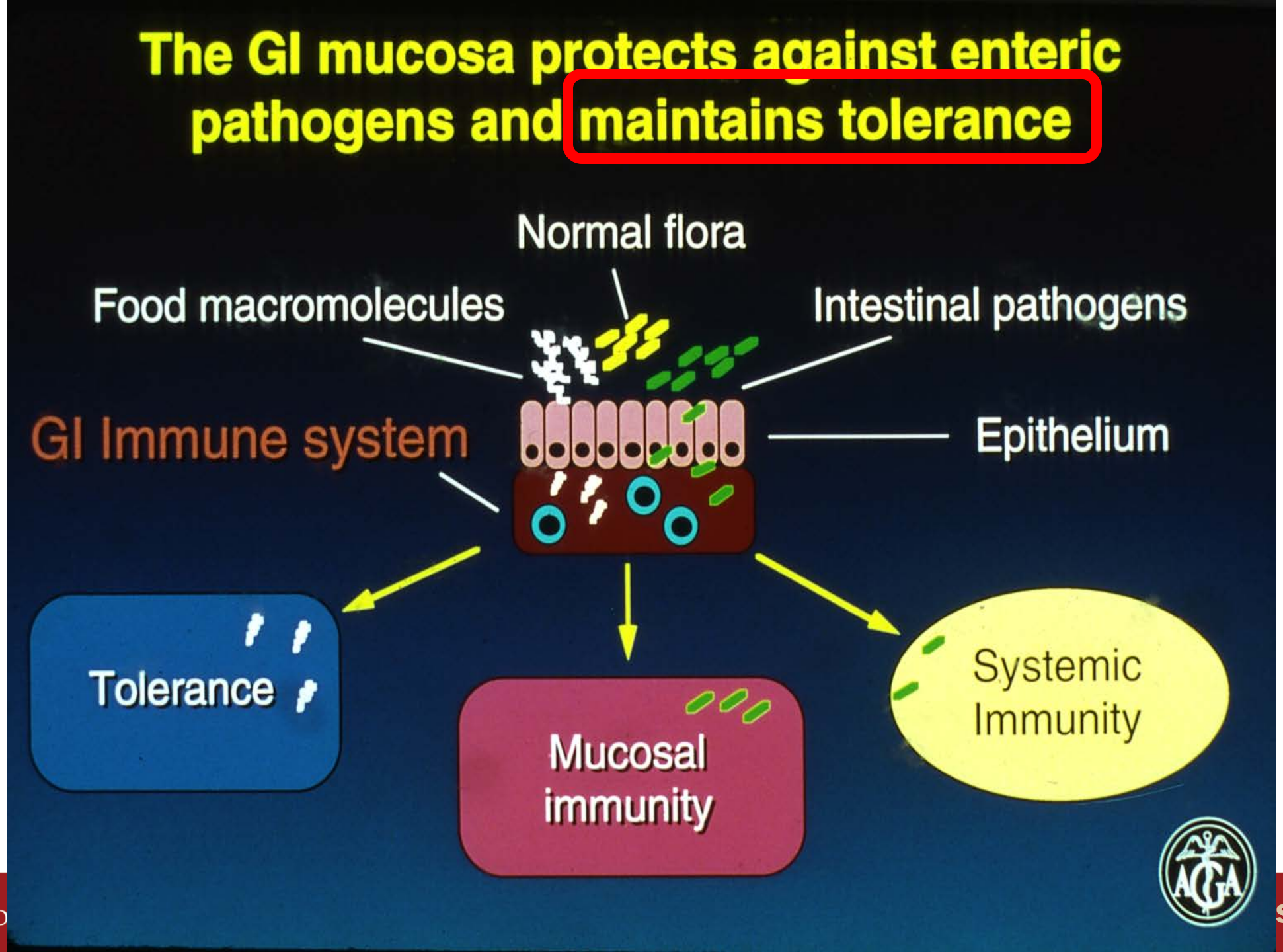
**Hygiene hypothesis:**
Having pets in childhood, living on a farm, larger family size, and drinking unpasteurized milk were inversely associated with the risk of CD and UC

**Changing diet:**
Introduction of packaged food, fast food chains, increased use of antibiotics, increased fat (monounsaturated and polyunsaturated fatty acids) consumption and sugar intake, less dietary fibers is associated with risk of IBD

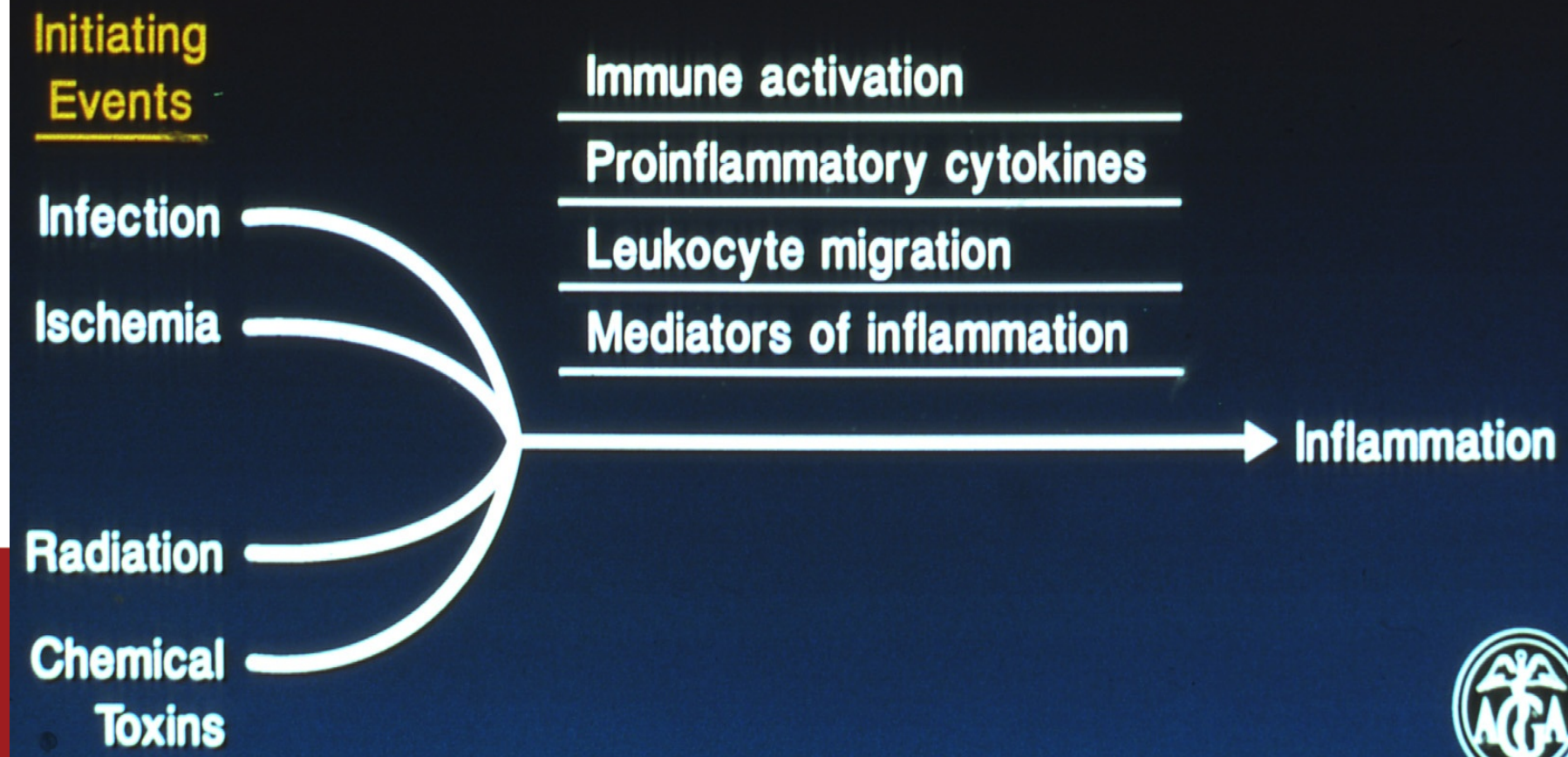
**Dietary chemicals:**
Food additives – saccharin, sucralose, carboxymethycellulose and polysorbate-80, common emulsifiers (including polysorbates, sorbate esters, lecithin), might increase risk of IBD (data are derived from animal models)

**Over 200 IBD risk loci (37 specific for Crohn's disease and 32 for ulcerative colitis) have been discovered. However, modest fraction of predicted heritability can be explained by known genes or loci.**

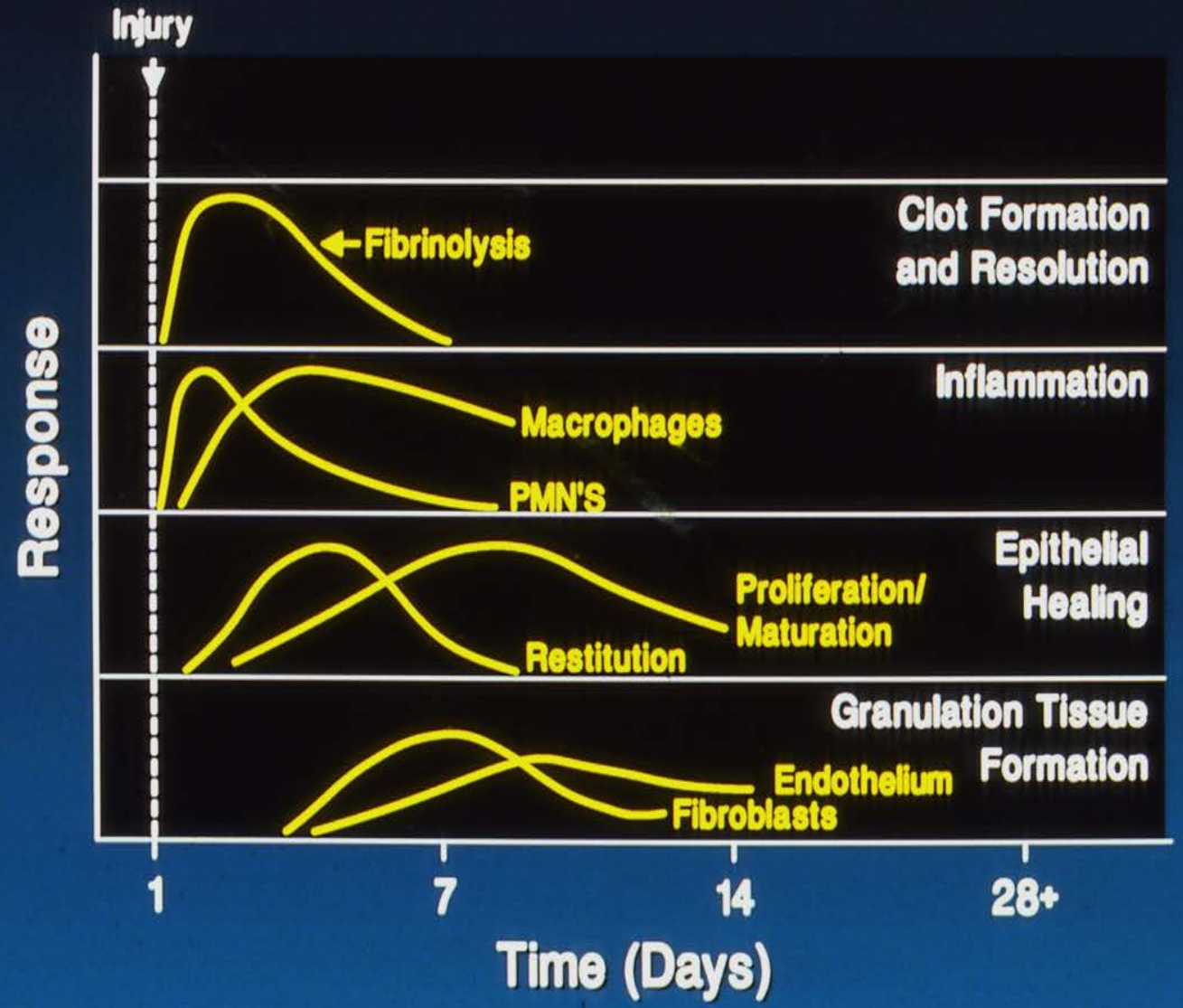
Kaplan G, et al. Gastroenterology 2017;152:313–321


The GI mucosa protects against enteric pathogens and maintains tolerance
Normal flora
Food macromolecules
Intestinal pathogens
GI Immune system
Epithelium
Tolerance
Mucosal immunity
Systemic Immunity

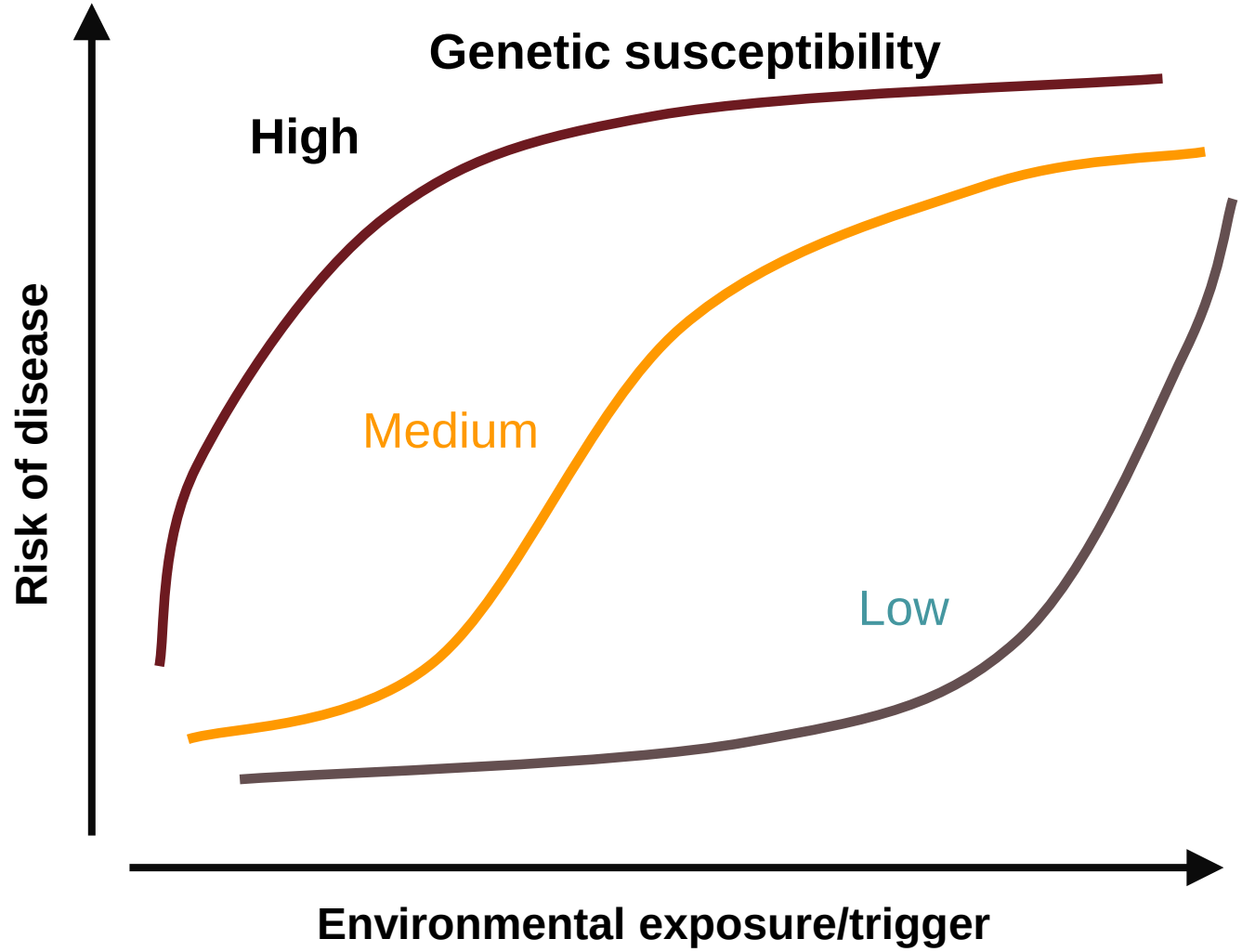
# Intestine has a stereotyped inflammatory response to injury

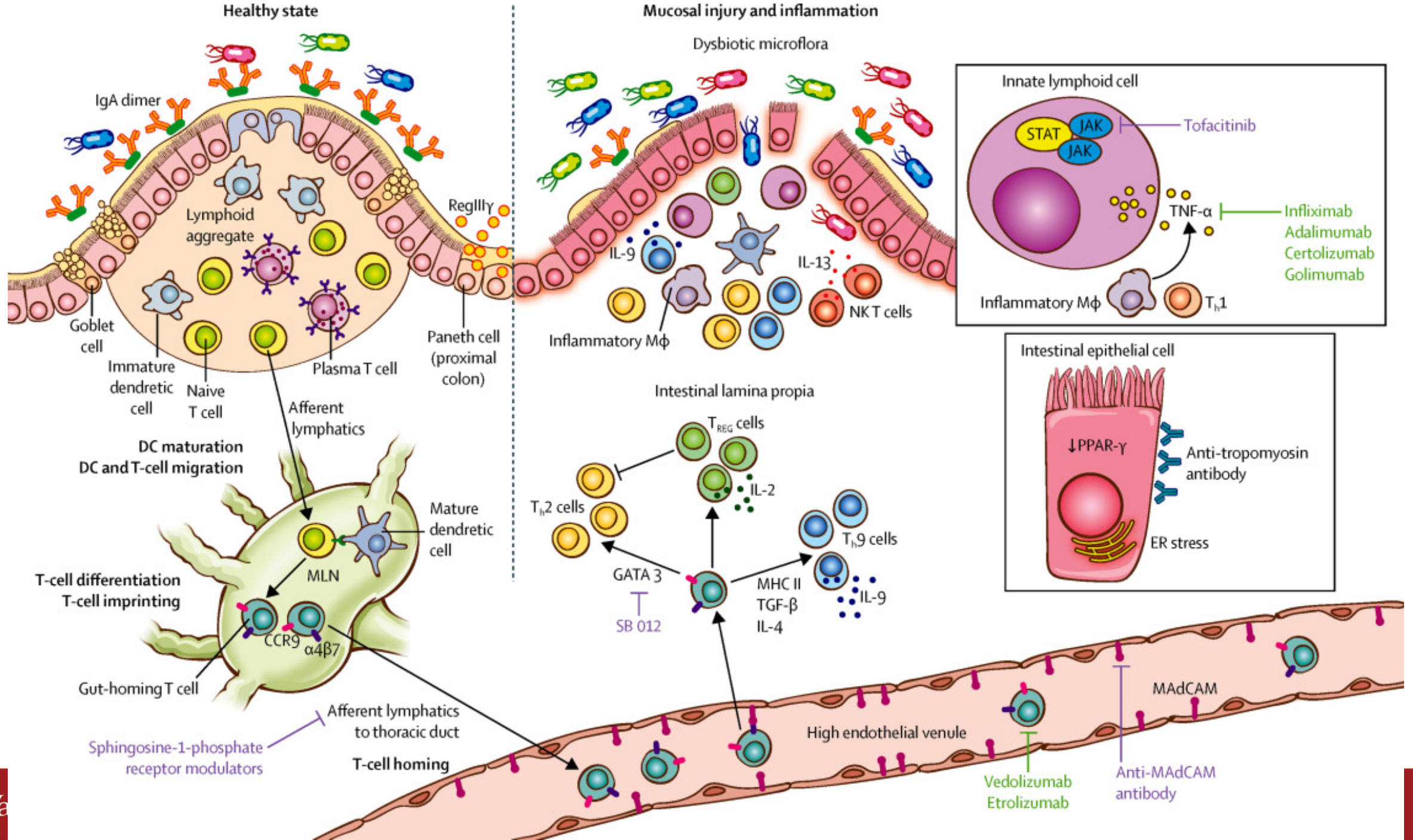


# Inflammation is a component of the continuing process of wound healing

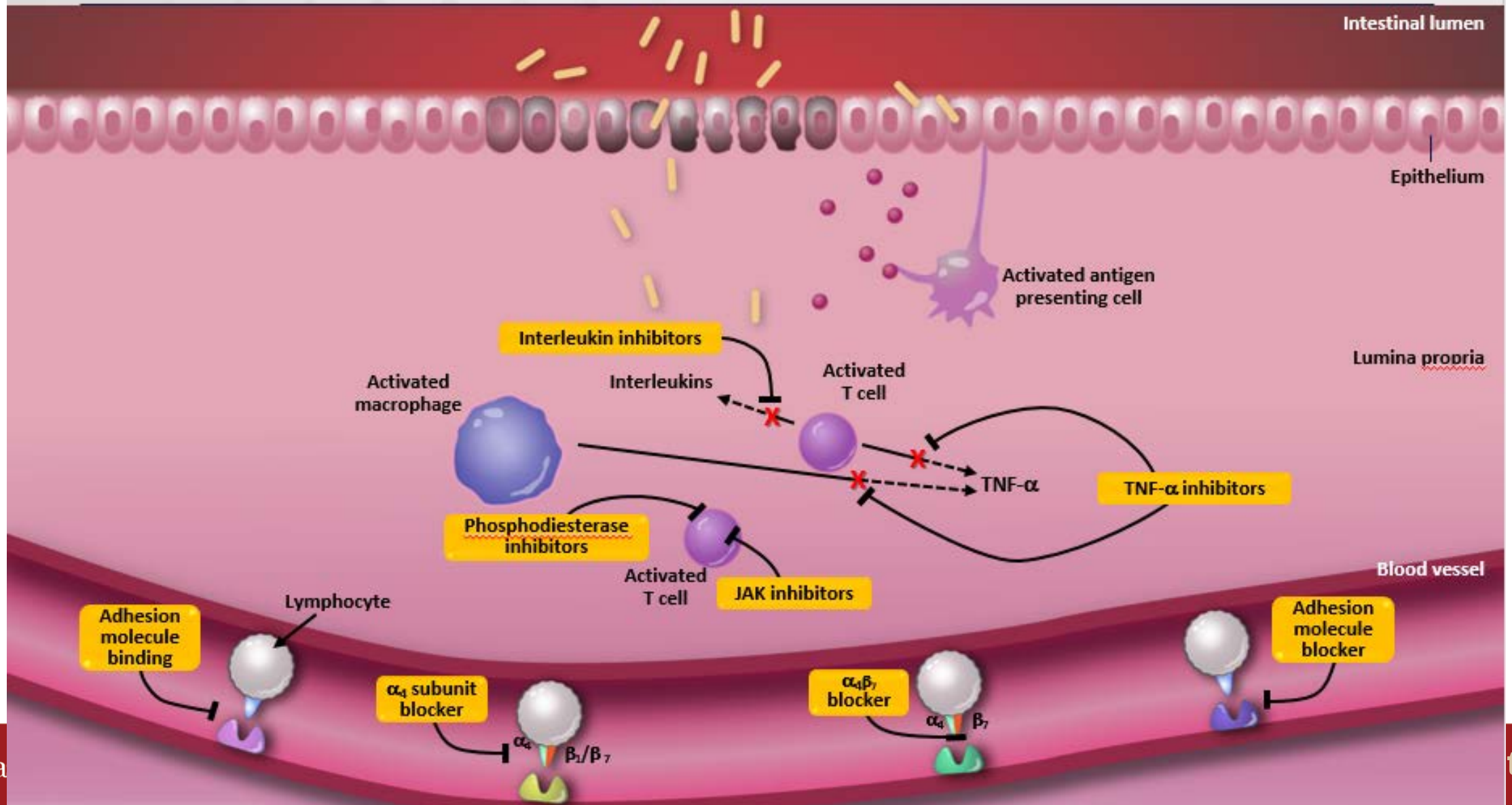


# Gene-environment interaction




Healthy state
Mucosal injury and inflammation
IgA dimer
Lymphoid aggregate
RegIIIγ
Goblet cell
Immature dendretic cell
Naive T cell
Plasma T cell
Paneth cell (proximal colon)
Afferent lymphatics
DC maturation
DC and T-cell migration
Mature dendretic cell
MLN
T-cell differentiation
T-cell imprinting
CCR9
α4β7
Gut-homing T cell
Afferent lymphatics to thoracic duct
Sphingosine-1-phosphate receptor modulators
T-cell homing
Dysbiotic microflora
IL-9
IL-13
NK T cells
Inflammatory Mϕ
Intestinal lamina propia
T_REG cells
IL-2
T_h2 cells
GATA 3
SB 012
MHC II
TGF-β
IL-4
T_h9 cells
IL-9
High endothelial venule
MAdCAM
Vedolizumab
Etrolizumab
Anti-MAdCAM antibody
Innate lymphoid cell
STAT
JAK
JAK
Tofacitinib
TNF-α
Infliximab
Adalimumab
Certolizumab
Golimumab
Inflammatory Mϕ
T_h1
Intestinal epithelial cell
↓PPAR-γ
Anti-tropomyosin antibody
ER stress

# Selective Targeting of Immune Regulators That Mediate Inflammation[1,2]



# Environmental Triggers For Precipitating or Flaring Ulcerative Colitis and Crohn's Disease

- Antibiotics
- Enteric Infections
- NSAIDs
- Smoking cessation (UC)

# Genetics: Familial Patterns of Inheritance

- 10% patients with positive family history.
- 5% risk of first-degree relative affected.
- For monozygotic twins 60% concordance for Crohn's disease.
- For monozygotic twins 6% concordance for ulcerative colitis.

# Learning Objectives

Part I

1. What are the Inflammatory Bowel Diseases (IBD)?
2. What causes IBD?
3. How does IBD affect other organ systems?

Part II

1. What are the current medical therapies for IBD?
2. What is the role for complementary and nutritional therapies in IBD?

Part III

1. Patient Stories and Questions

# Current IBD Drug Therapies

## Supportive Agents
- Antidiarrheals
- Bile sequestrants
- Bulk formers
- Antidepressants
- Pain management
- Antispasmodics

## Aminosalicylates
- Sulfasalazine
- Mesalamine
- Olsalazine
- Balsalazide

## Immunomodulators
- 6MP/Azathioprine
- Methotrexate
- Cyclosporine/Tacrolimus
- JAK inhibitors (July 2018)

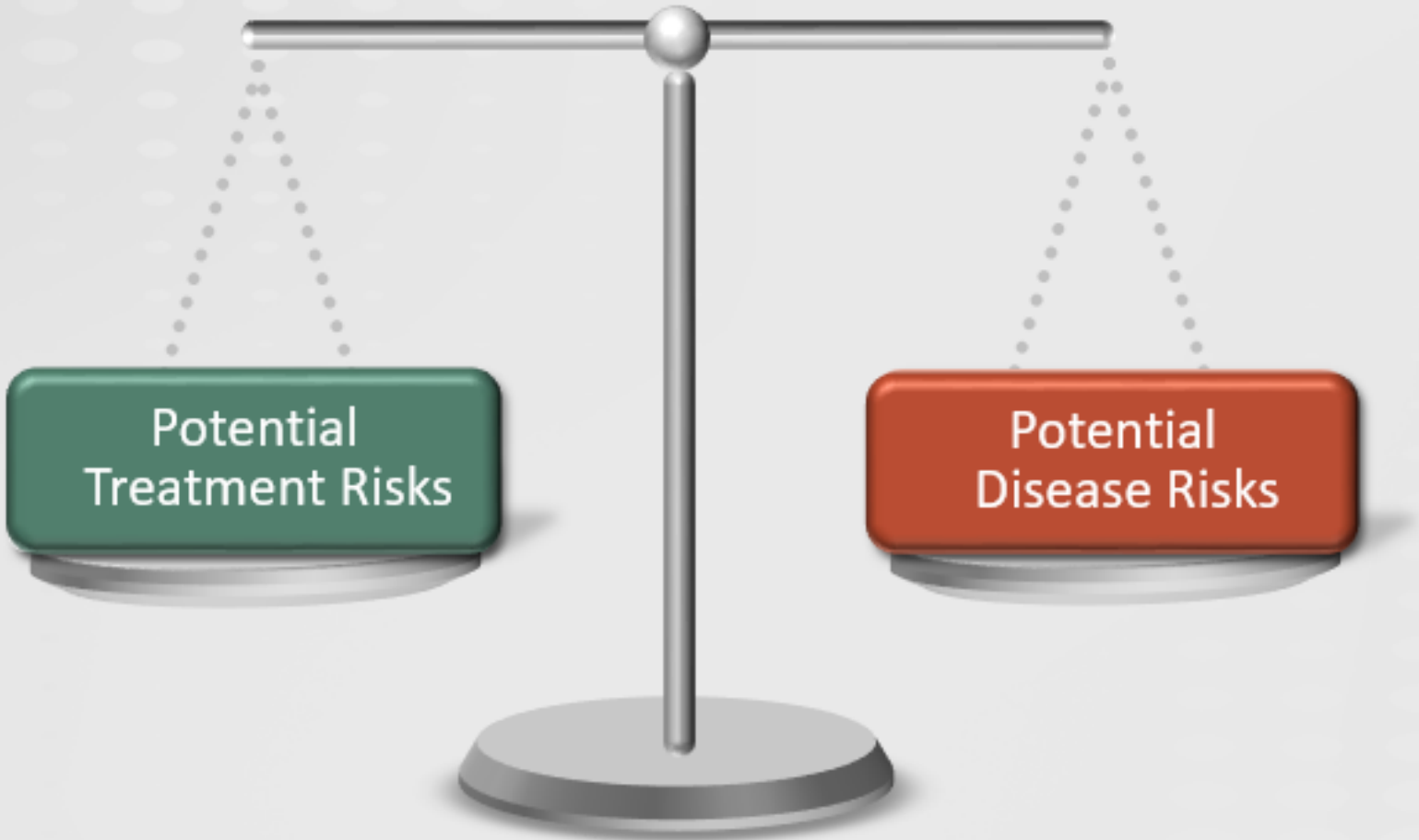
## Biologics
- Anti-TNF
- Selective adhesion molecule – Anti-integrin
- IL12/23

## Antibiotics
- Metronidazole
- Quinolones
- Other

## Corticosteroids
- Prednisone/Prednisolone
- Budesonide
- ACTH?

# Risks of Treatment, Risks of Disease

- Risks of medication are not the only risks patients face[1]
- Undertreated disease may lead to serious consequences[1]



# Predictors of Serious Infection and Death in CD

**6273 patients in the TREAT registry; Mean follow-up: 5.2 years**

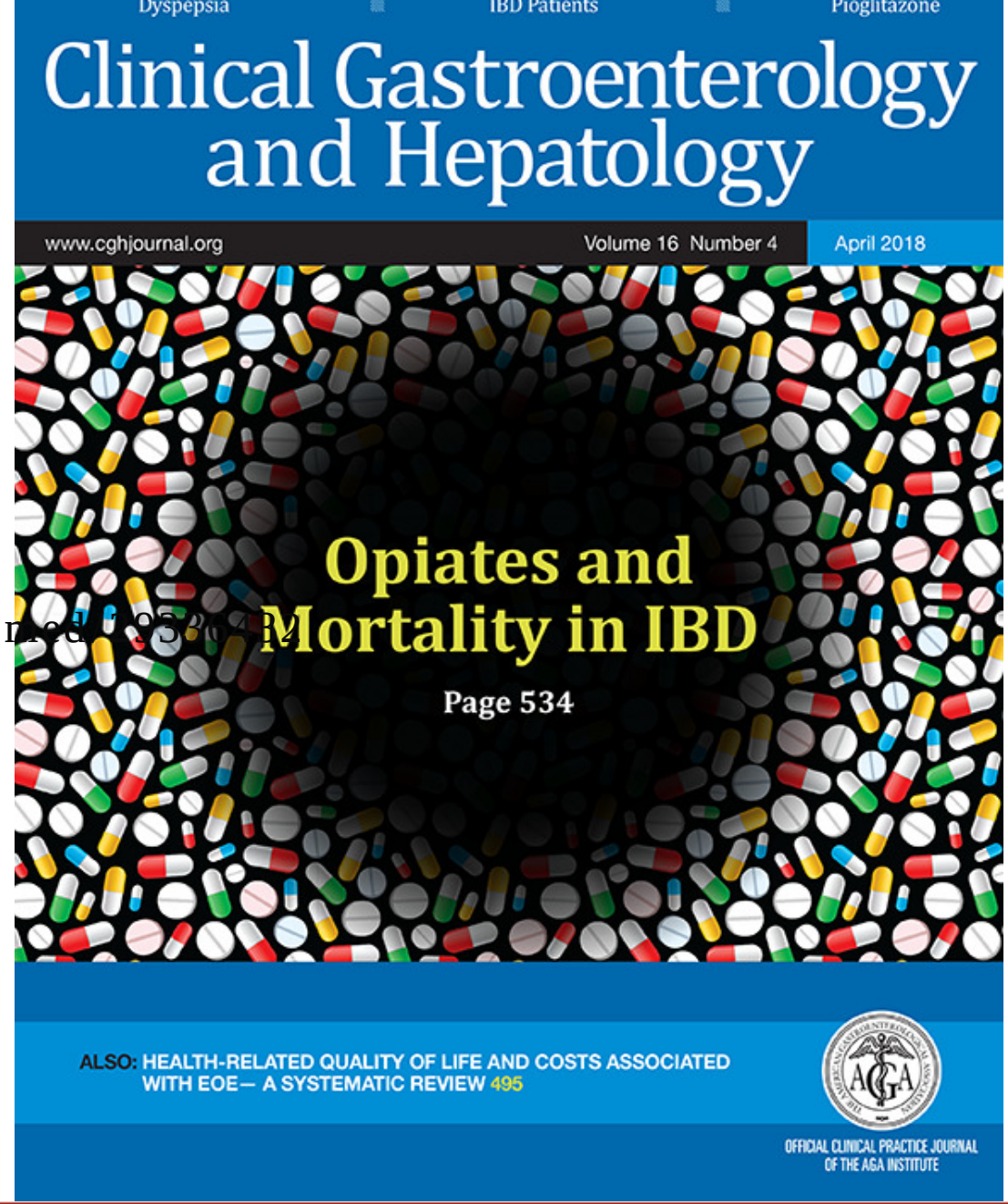
| Serious Infection | HR |
|---|---|
| Moderate to severe CD | 2.24 |
| **Use of narcotic pain relievers** | 1.98 |
| **Use of prednisone** | **1.57** |
| Use of IFX | 1.43 |

| Death | HR |
|---|---|
| **Use of prednisone** | **2.14** |
| **Use of narcotic pain relievers** | **1.79** |

**Abbreviations: IFX, infliximab; HR, hazard ratio. P < .05 for all.**

**Lichtenstein GR, et al. *Am J Gastroenterol* 2012;107(9):1409-1422.**

https://www.ncbi.nlm.nih.gov/pubmed/29304541



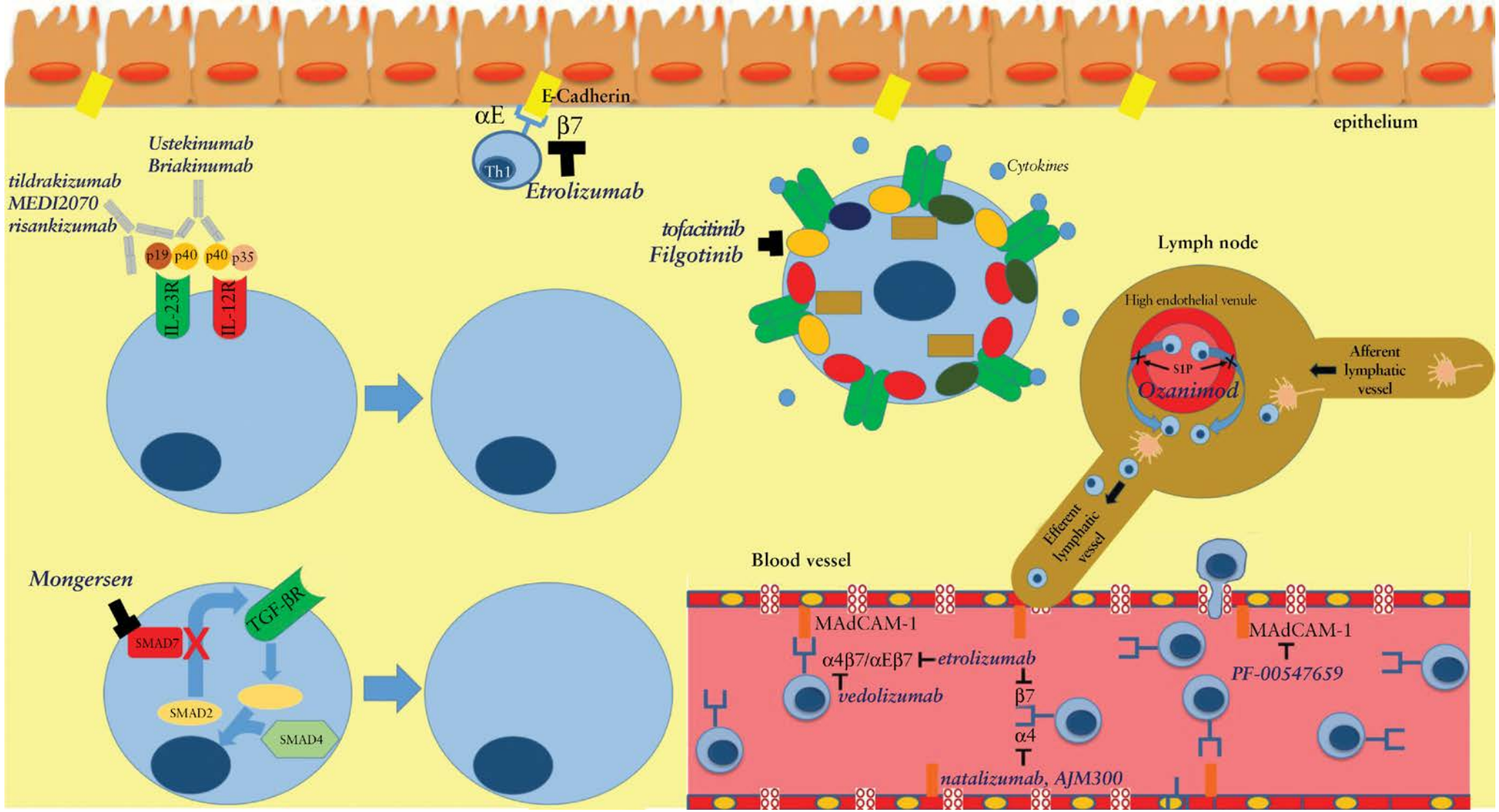

Clinical Gastroenterology and Hepatology 2018;16:534–541

# Heavy use of strong opiates among patients with IBD associates with increased all-cause premature mortality

| | Crohn's disease | Ulcerative colitis |
|---|---|---|
| | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
| Any opiate medication | | |
| None/infrequent use (<1 prescription per year) | 1 | 1 |
| Moderate use (1–3 prescriptions per year) | 0.94 (0.64–1.39) | 0.83 (0.56–1.21) |
| Heavy use (>3 prescriptions per calendar year) | 1.15 (0.85–1.55) | 1.67 (1.25–2.23) |
| Coc | | |
| Nor | | |
| Moc | | |
| Hea | | |
| Trar | | |
| Nor | | |
| Moc | | |
| Hea | | |
| Strong opiates | | |
| None/infrequent use (<1 prescription per year) | 1 | 1 |
| Moderate use (1–3 prescriptions per year) | 1.34 (0.67–2.70) | 2.44 (1.16–5.15) |
| Heavy use (>3 prescriptions per calendar year) | 2.18 (1.20–3.95) | 3.30 (1.77–6.18) |
| Strong opiates versus weak opiates | | |
| None/infrequent use (<1 prescription per year) | 1 | 1 |
| Moderate use (1–3 prescriptions per year) | 1.36 (0.69–2.69) | 1.81 (0.91–3.62) |
| Heavy use (>3 prescriptions per calendar year) | 2.04 (1.14–3.65) | 2.47 (1.41–4.33) |

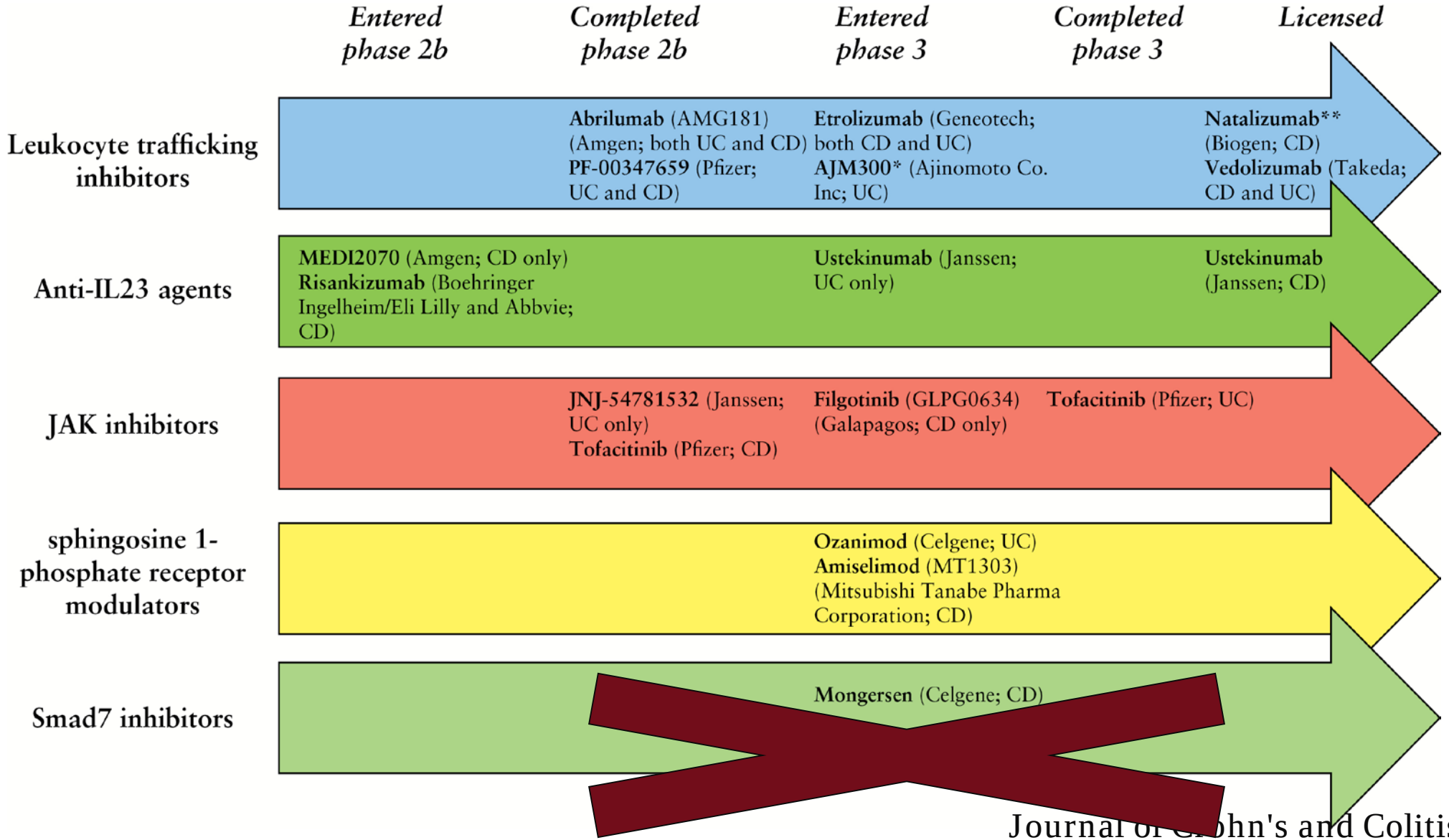
**IBD Specialist *Almost* Never Rx Opiates**

# Therapeutic targets of new and late pipeline IBD drugs




Journal of Crohn's and Colitis, 2018, 105–119

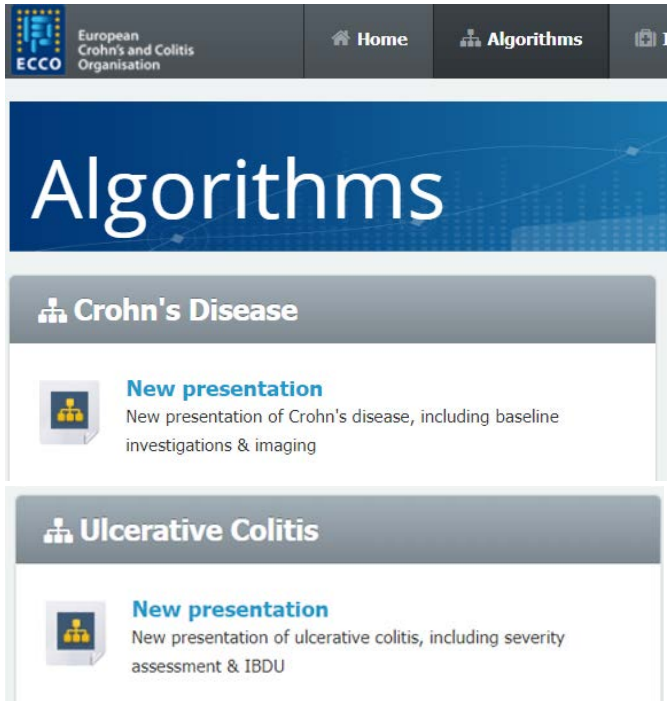
# Recently licensed and late-stage IBD pipeline drugs



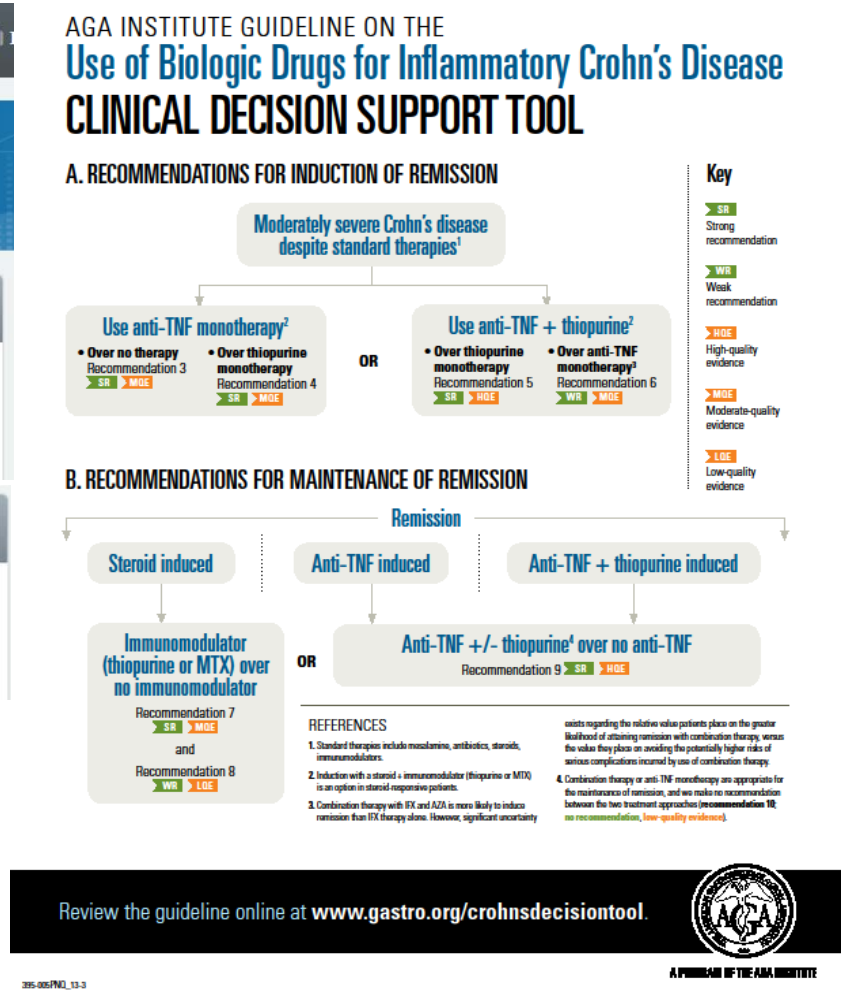

Journal of Crohn's and Colitis, 2018, 105–119

# Algorithms and Guidelines

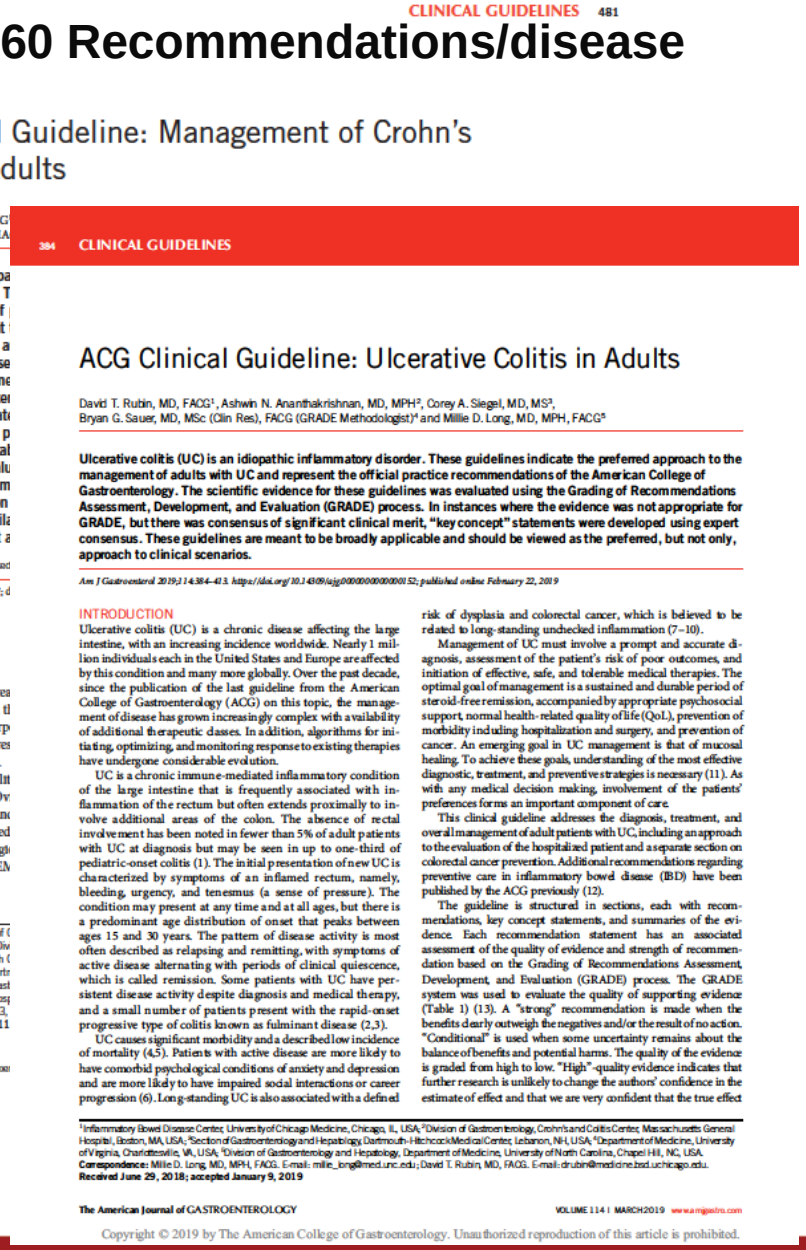
## ECCO: Many Algorithms



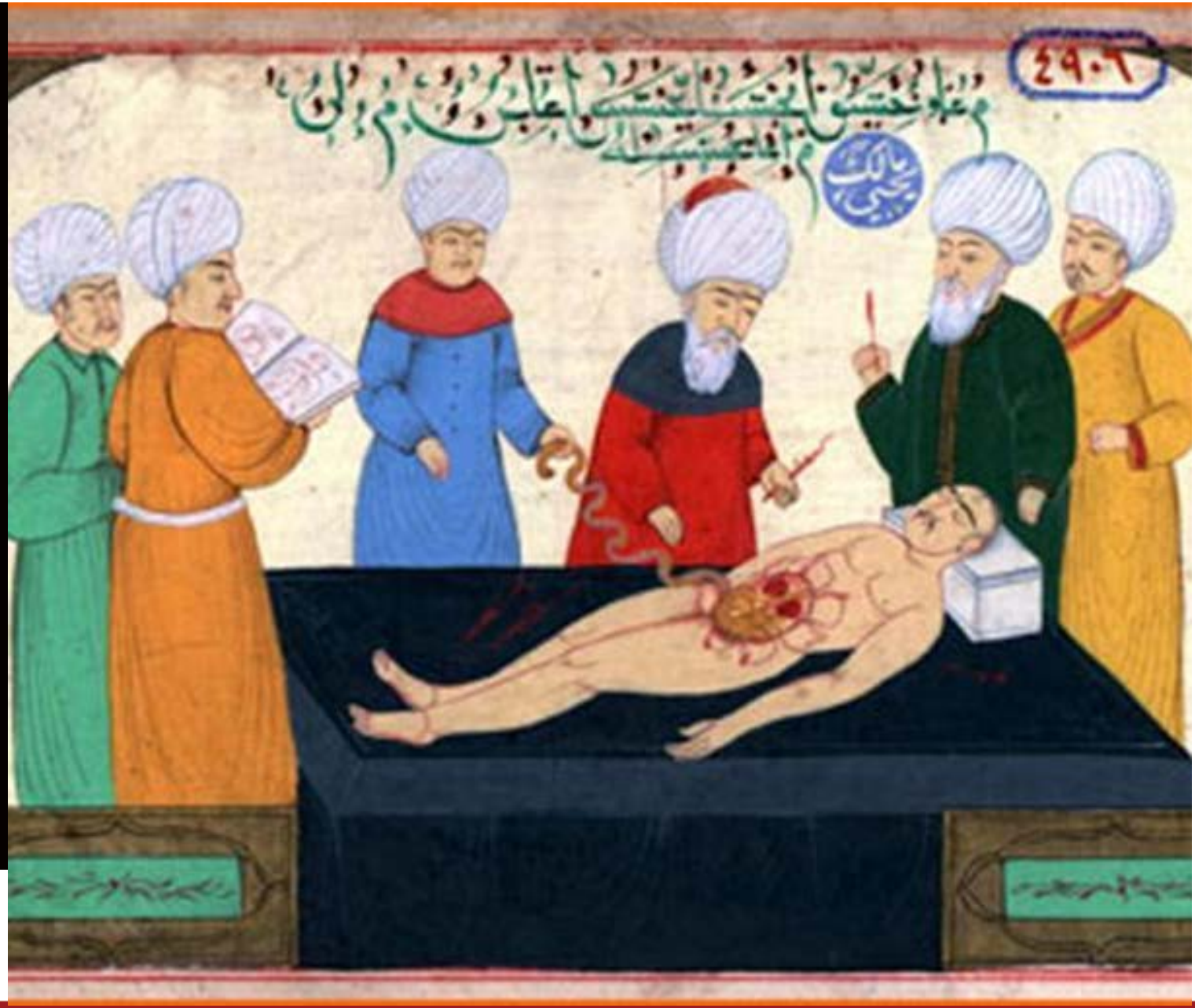

## AGA: Out of Date




## ACG: >60 Recommendations/disease



# Golden Age



# New Opportunities and New Challenges


# Distilling it down to Key Points

1. Treat inflammation and Treat-to-Target
   - Active IBD
   - Ideally before onset of complicated disease behavior

2. Older therapies still have a role, especially in mild disease

3. Moderate to Severe IBD (Activity and Risk)
   - TNFα, Integrins, IL-12/23 and JAK inhibitors are the most effective therapies
     - Differ in MOA, side-effects and other indications
     - Choose therapy based on patient and disease based factors
     - Comparative Effectiveness Trials are coming/here…
     - Proactively manage risks (vaccinations, AE education, etc)

# 1. Treat inflammation, then Treat to Achieve a Target

- Don’t settle for symptoms alone in assessing “severity and risk”
- Pay attention to labs: WBC, CRP, Calprotectin and Lactoferrin
- Plan frequent scheduled follow-up
- Adjustments to Therapy (Treat To Target)
  - Confirm adherence
  - Optimize therapy dosing and therapeutic drug monitoring
  - Adjust based on disease severity, best evidence, comparative effectiveness
- Patient buy-in is very important

# 2. Older therapies still have roles

- 5-ASA's in mild to moderate UC
  - Rectal and oral
- Topical Steroids/budesonide in Crohn's and UC
  - Induction
  - Rectal and oral
- Azathioprine (CD and UC) and Methotrexate (CD) still has a role as
  - Monotherapy if that's what you and the patient are most comfortable with
  - Combination therapy
    - In severe disease
    - In patients with antibodies to first biologic
    - To augment drug levels or enhance response to biologic

# 3. Moderate to Severe IBD (Activity and Risk)

- TNFα, Integrins, IL-12/23 and JAK are the most effective therapies at both inducing and maintaining remission

- How to choose? Know the:
  1. **Drug**
     - Mechanism of Action, Side Effects, Mode of Administration
  2. **Patient**
     - Disease state, Comorbidities, EIMs, Preferences for adherence
  3. **You**
     - Experience, Office support
  4. **System**
     - Insurance, Practice Model

# Dosing of IBD Biologics and New Oral Agents

| Medication | Route of administration (IV, SC, PO) | Approved dose |
|---|---|---|
| Infliximab | IV | Induction: 5-10 mg/kg (weeks 0, 2, and 6)<br>Maintenance: 5-10 mg/kg every 4-8 wk |
| Adalimumab | SC | Induction: 160 mg (week 0), 80 mg (week 2)<br>Maintenance: 40 mg every 7-14 d |
| Golimumab | SC | Induction: 200 mg (week 0), 100 mg (week 2)<br>Maintenance: 100 mg every 4 wk |
| Certolizumab | SC | Induction: 400 mg (weeks 0, 2, and 4)<br>Maintenance: 400 mg every 4 wk |
| Vedolizumab | IV | Induction: 300 mg (weeks 0, 2, and 6)<br>Maintenance: 300 mg every 4-8 wk |
| Ustekinumab | IV then SC | Induction: < 55 kg: 260 mg 55-85 kg: 390 mg > 85 kg: 520 mg Maintenance: 90 mg every 8 wk |
| Tofacitanib | PO | Induction: 10 mg BID<br>Maintenance: 5 mg or 10 mg BID |

World J Gastroenterol. Aug 28, 2018; 24(32): 3567-3582

# Relative efficacy of drug classes for key endpoints

| Drug class | Onset of action | Clinical remission | | Endoscopic healing | | Histological healing | |
|---|---|---|---|---|---|---|---|
| | | UC | CD | UC | CD | UC | CD |
| TNF-antagonists | ≤ 8 weeks | ++ | ++ | + | + | ? | ? |
| | > 8 weeks | ++ | ++ | + | + | ? | ? |
| Anti-adhesion | ≤ 8 weeks | + | +/- | + | ? | + | ? |
| | > 8 weeks | ++ | ++ | ++ | ? | ? | ? |
| Anti-IL23 | ≤ 8 weeks | + | ++ | ? | +/- | + | ? |
| | > 8 weeks | ? | ++ | ? | +/- | ? | ? |
| JAK inhibitors | ≤ 8 weeks | ++ | + | ++ | ? | ? | ? |
| | > 8 weeks | ++ | + | ++ | ? | ? | ? |

Modified from World J Gastroenterol. Aug 28, 2018; 24(32): 3567-3582

# Cross Indications for IBD Biologics and New Oral Agents

| TNFi | Anti-Integrin | IL-12/23 | JAKi |
|---|---|---|---|
| • Gut<br>• Joints<br>• Axial<br>• Skin<br>• Uveitis (Ada) | • Gut | • Gut<br>• Skin<br>• Joints (PsA) | • Gut<br>• Joints (RA/PsA) |

# Anti-TNFα Biologics

- Effective for induction and maintenance of remission in UC and CD
  - No comparative effectiveness trials between TNFi's
  - Biosimilars are here
- Multiple indications and systemic anti-inflammatory
- Toxicity profiles similar, indications and delivery routes differ
- Special situations
  - Hospitalized: If steroid refractory, Infliximab
  - Most Flexible dosing: Infliximab and Adalimumab
  - Fistulizing: Infliximab
  - Fertility/Pregnancy: Certolizumab Ann Rheum Dis. 2018 Feb;77(2):228-233

Black Box Warnings: Serious Infection, Malignancy, HSTCL

# Vedolizumab (Anti-α4β7 Integrin)

- Targets **gut specific** Memory T-cells
  - Best Safety Profile
  - Less good for EIMs
- Indicated for Induction and Maintenance of Remission
  - Crohn's and Ulcerative Colitis
- Special Considerations
  - Slower onset?
    - : Judge Efficacy at Week 12-14 (not at week 6)
    - Steroids or other induction
  - Some benefit to Q4 week dosing if incomplete response (~25% patients)
  - SQ is coming: IV induction x 2 or 3, then SQ

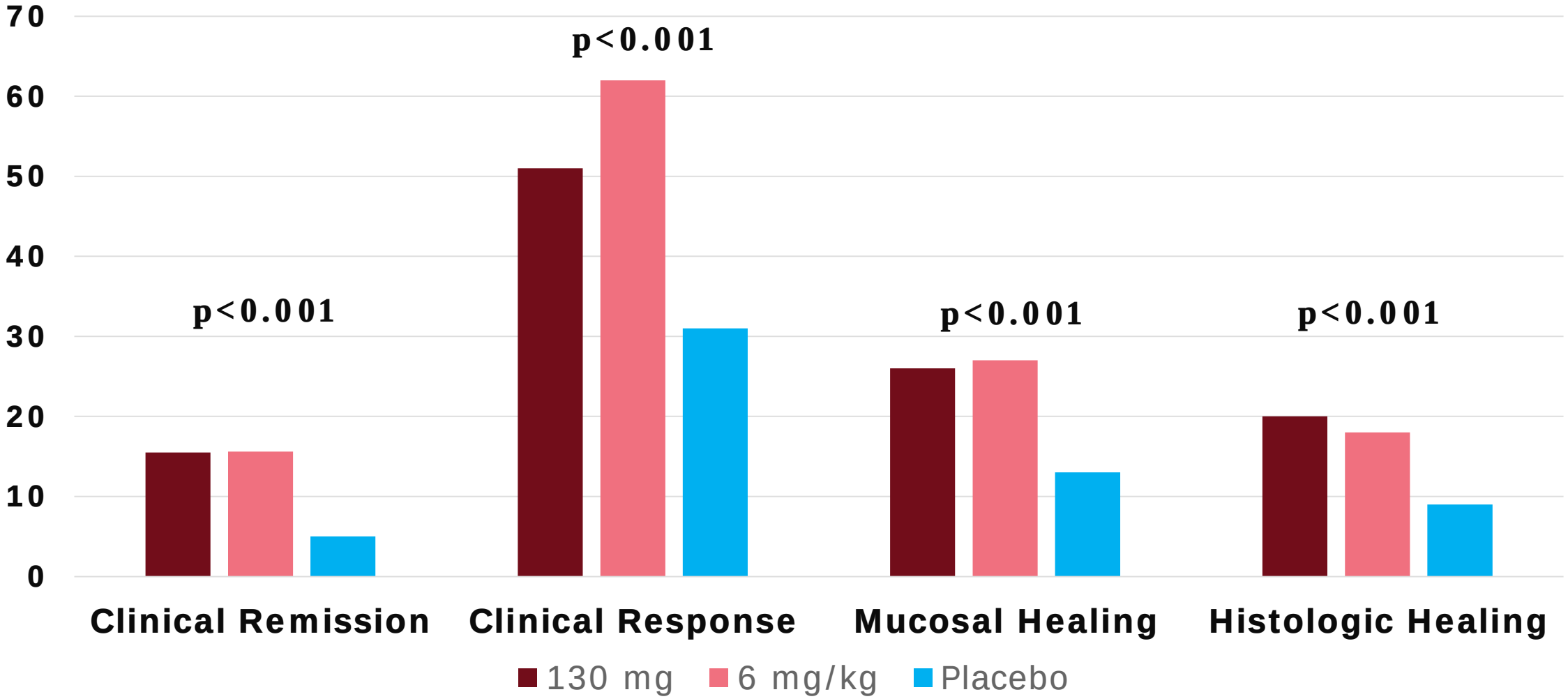
**No Black Box Warning**

# Ustekinumab

- Targets Common P40 subunit of IL-12 and IL-23
- Induction and Maintenance in Mod/Severe CD
  - Infusion: 390 mg or 520 mg (Induction)
  - SQ Injection: 90 mg Q 8 weeks (Maintenance)
- Also Treats Psoriasis and Psoriatic Arthritis
- Good Safety (malignancy/infection) in LTE at psoriasis dosing
- UC data looks good

**No Black Box Warning**

# Ustekinumab in Mod-Severe Ulcerative Colitis: UNIFI Trial



# Tofacitanib

- Small molecule targeting Janus Kinase 1 and 3
  - Reducing STAT signaling and ongoing cytokine production (cellular)
- Ulcerative Colitis
  - Induction: 10 mg BID x 8 weeks
  - Maintenance: 5 mg or 10 mg BID
- Systemic anti-inflammatory and affects many cellular functions
  - Also treats Rheumatoid Arthritis and PsA
  - Lipids: no change in LDL/HDL ratio
  - Vascular Events: at 10 mg dosing in RA pop with ≥ 1 CV Risk Factor
  - Cytopenias: hold if ANC or ALC <500
  - Herpes Zoster (~5% year, but don't need to vaccinate to start)
  - NMSC

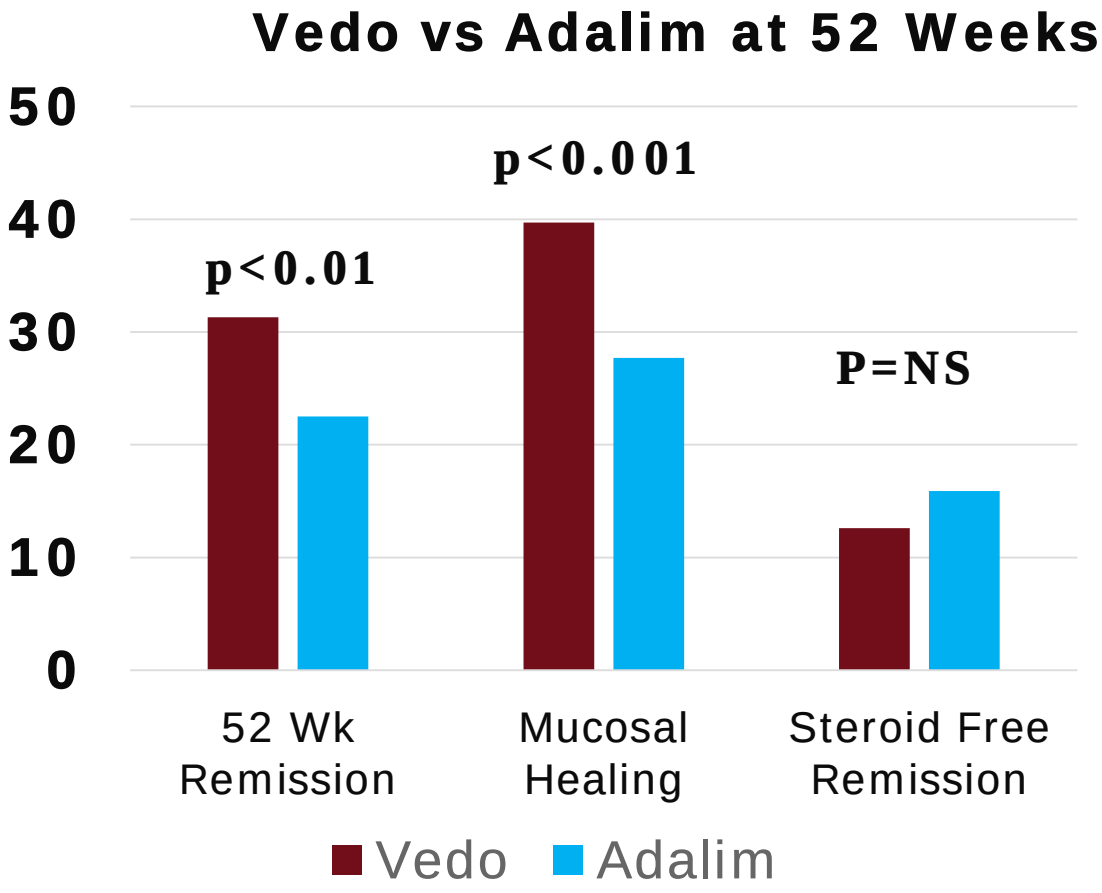
**Serious infections (TB), Malignancy (Lymph), MACE**

# Comparative Effectiveness Trials

- UC: Vedolizumab vs. Adalimumab (VARSITY) at 1 year
  - Sponsored: ECCO 2019

- Crohn's: Ustekinumab vs Adalibumab (SEAVUE) at 1 year
  - Sponsored
  - 52 week clinical and endoscopic remission in 350 patients
  - Completing in 2020

# Comparator Trial in Mod-Severe UC
# Vedolizumab vs Adalimumab at 52 weeks (VARSITY)




- Considerations
  - Standard dosing
  - No Dose escalation
  - Corticosteroid Free Remission non-signif higher in Adalimumab treated group
  - More data coming

**ECCO March 2019; OP34 VARSITY: A double-blind, double-dummy, randomised, controlled trial of vedolizumab versus adalimumab in patients with active ulcerative colitis**

Stefan. Schreiber[1], Laurent. Peyrin-Biroulet[2], Edward. V. LoftusJr.[3], Silvio. Danese[4], Jean-Frederic. Colombel[5], Brihad. Abhyankar[6], Jingjing. Chen[7], Raquel. Rogers[7], Richard. A. Lirio[7], Jeffrey. D. Bornstein[7], Bruce. E. Sands

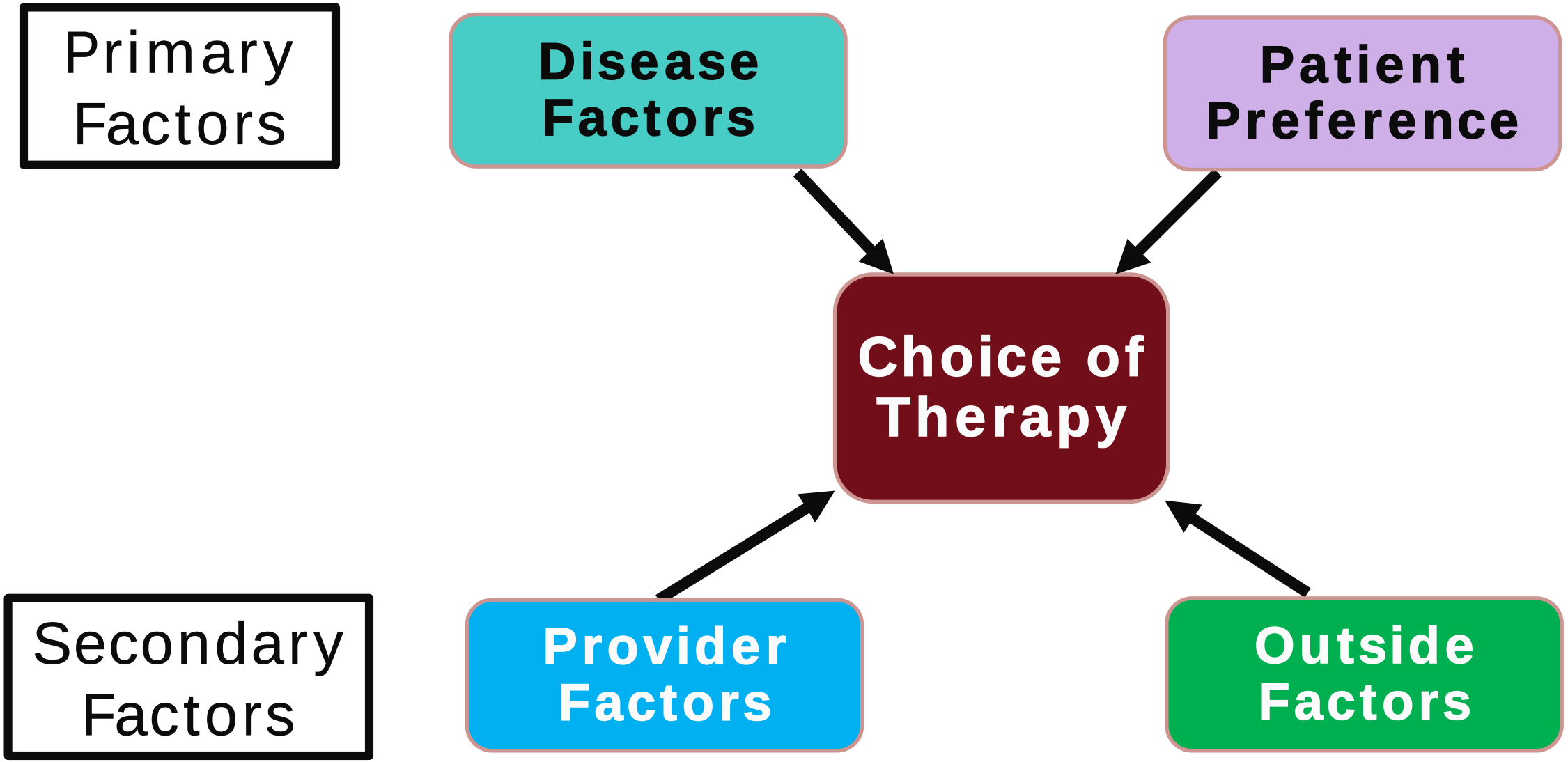
14th Congress of the European Crohn's and Colitis Organisation (ECCO) in Copenhagen, Denmark.

# Distilling it down to Key Points

1. Treat inflammation and Treat-to-Target
   - Active IBD
   - Ideally before onset of complicated disease behavior

2. Older therapies still have a role, especially in mild disease

3. Moderate to Severe IBD (Activity and Risk)
   - TNFα, Integrins, IL-12/23 and JAK inhibitors are the most effective therapies
     - Differ in MOA, side-effects and other indications
     - Choose therapy based on patient and disease based factors
     - Comparative Effectiveness Trials are coming/here…
     - Proactively manage risks (vaccinations, AE education, etc)


Primary Factors
Disease Factors
Patient Preference
Choice of Therapy
Secondary Factors
Provider Factors
Outside Factors

# Complementary and Alternative Therapies to IBD

## Case

Your 23 year old patient with Crohn's wants to know what more "natural" treatments are available for her disease. She has been to a holistic healer who has suggested some therapies but wants your opinion first.

# Why do patients use CAM?

| N = 344 | Values (%) |
|---|---|
| Search for “optimum” therapy | 78.9 |
| **Terminate or avoid steroid medication** | **63.1** |
| Side effects of conventional therapy | 43.7 |
| Wish to take responsibility for treatment | 42.0 |
| Holistic therapeutic approach | 35.2 |
| Fear of side effects of conventional therapy | 27.6 |
| Lack of response to current therapy | 27.6 |


Langhorst J, et al. Inflamm Bowel Dis. 2005 Mar;11(3):287.

# Complimentary and Alternative Medicines (CAMs) in IBD

| CAM's | Concepts |
| --- | --- |
| • Probiotics<br>  • FMT<br>• Cannabis<br>• Curcumin<br>• Fish Oil<br>• Special Diets<br>• TUDCA | • Data is mostly small trials<br>• Symptoms vs Inflammation<br>• Best as<br>  • Adjunctive Therapy<br>  • Mild/Mod Disease<br>• Cost – Benefit Ratio? |

# Probiotics in IBD: Pro's and Cons

| Pro's : Evidence | CON-siderations |
| --- | --- |
| • Pouchitis (VSL#3)<br>  • Prevention and Maintenance<br>• UC (VSL#3, E.coli Nissl)<br>  • Mild to Mod Active or Maintenance<br>• Crohn's<br>  - little evidence of benefit<br>  - > flatulence/bloating | • Mild to Moderate only<br>• Add on therapy<br>• May worsen bloating<br>• Monitor Effect/Benefit<br>• Most trials not in US |

CLINICAL PRACTICE GUIDELINE | VOLUME 159, ISSUE 2, P697-705, AUGUST 01, 2020

# AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders

| Recommendations | Strength of recommendation | Quality of evidence |
|---|---|---|
| In adults and children with Crohn's disease, we recommend the use of probiotics only in the context of a clinical trial. | No recommendation | Knowledge gap |
| In adults and children with ulcerative colitis, we recommend the use of probiotics only in the context of a clinical trial. | No recommendation | Knowledge gap |

# FMT in IBD

| Authors | Diagnosis | Number of patients (P) or studies (S)*# | FMT |
|---|---|---|---|
| Paramsothy et al. (2017b) | UC | *n* = 41 (S) | N.A |
| | CD | *n* = 11 (S) | N.A |
| Moayyedi et al. (2015) | UC | *n* = 70 (P) | Enen |
| Paramsothy et al. (2017a) | | | |
| Rossen et al. (2015) | | | |
| Vaughn et al. (2016) | | | |
| Cui et al. (2015) | | | |
| Suskind et al. (2015) | | | |

Not there yet.
Donor selection (d
Durability?
Safety....
Cdiff, probably

The New York Times

***How Contaminated Stool Stored in a Freezer Left a Fecal Transplant Patient Dead***

remission at
clinical remission

*CD, Crohn's disease; N.A, Not applicable; UC, Ulcerative colitis. *Both total number of patients for clinical trials and number of studies for systematic analysis or meta-analysis were included. #Includes the number of control patients. &Feces may have undergone additional steps for FMT samples preparation. $Initial solution concentration is not available.*

JAMA Network™

**QUESTION** Can a short duration of fecal microbiota transplantation (FMT) using anaerobically prepared pooled stool suspension induce remission in active ulcerative colitis?

**CONCLUSION** In this preliminary study, 1 week of anaerobically prepared donor FMT resulted in a higher likelihood of remission than autologous FMT, but further research is needed to assess efficacy and safety.

## POPULATION

**40** Men
**33** Women

Adults with mild or moderate ulcerative colitis

Mean age: **39** years

## LOCATIONS

**3**
Tertiary referral centers in Australia

## INTERVENTION


**73** Patients randomized

**38**

**Anaerobically prepared pooled donor FMT**
Stool from 3 to 4 donors blended with normal saline (65%) and glycerol (10%) under anaerobic conditions

**35**

**Autologous FMT**
The patient's own stool blended with normal saline (65%) and glycerol (10%) under aerobic conditions

## PRIMARY OUTCOME

Steroid-free remission of ulcerative colitis (Mayo score ≤2; range, 0-12, with 12 being most severe disease)

## FINDINGS

Patients in steroid-free remission at 8 weeks

**Anaerobically prepared pooled donor FMT**
12 of 38 patients


**Autologous FMT**
3 of 35 patients


Between-group difference:

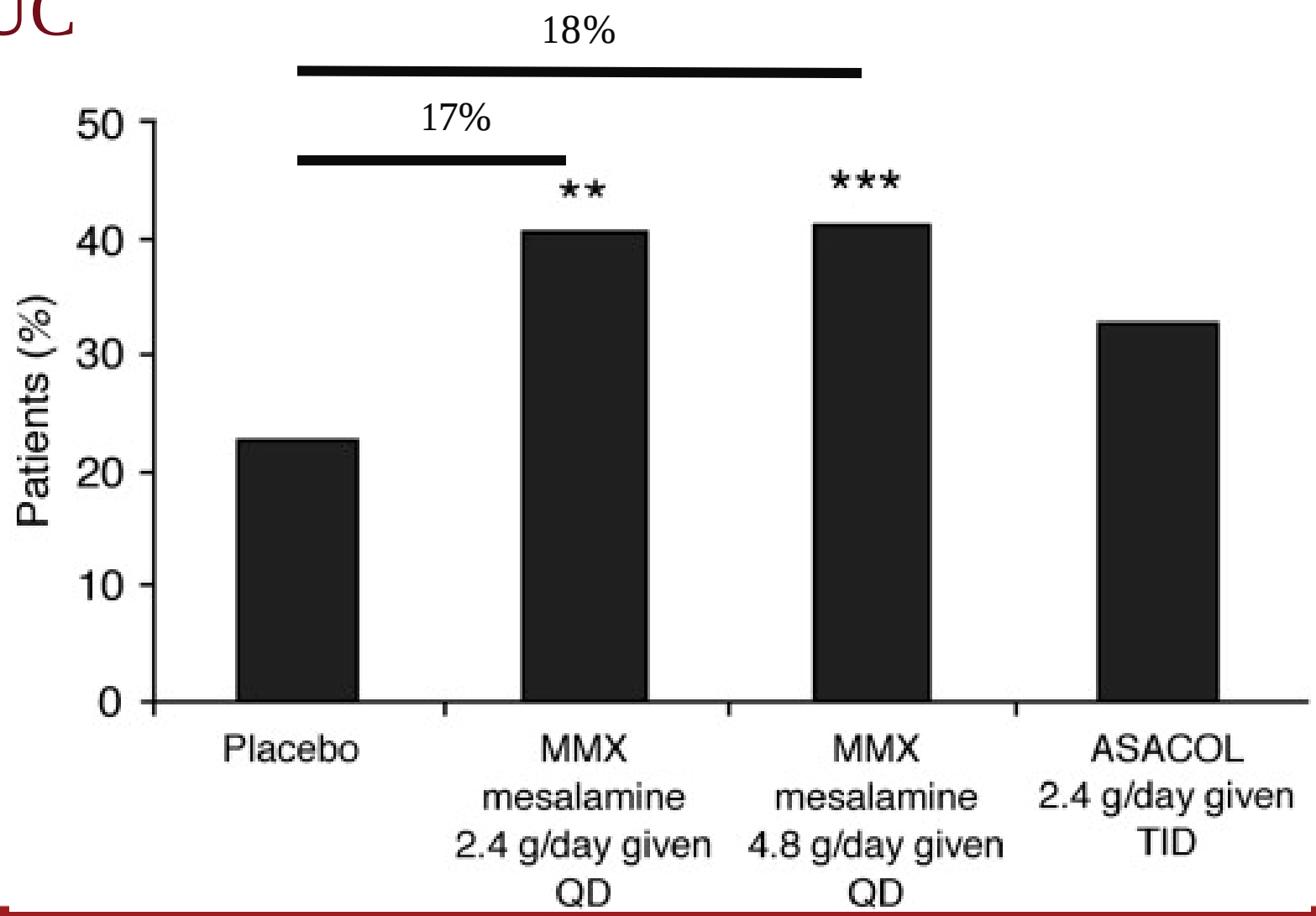
**23%**

(95% CI, 4% to 42%)



Costello SP, Hughes PA, Waters O, et al. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial [published online January 15, 2019]. *JAMA*. doi:10.1001/jama.2018.20046

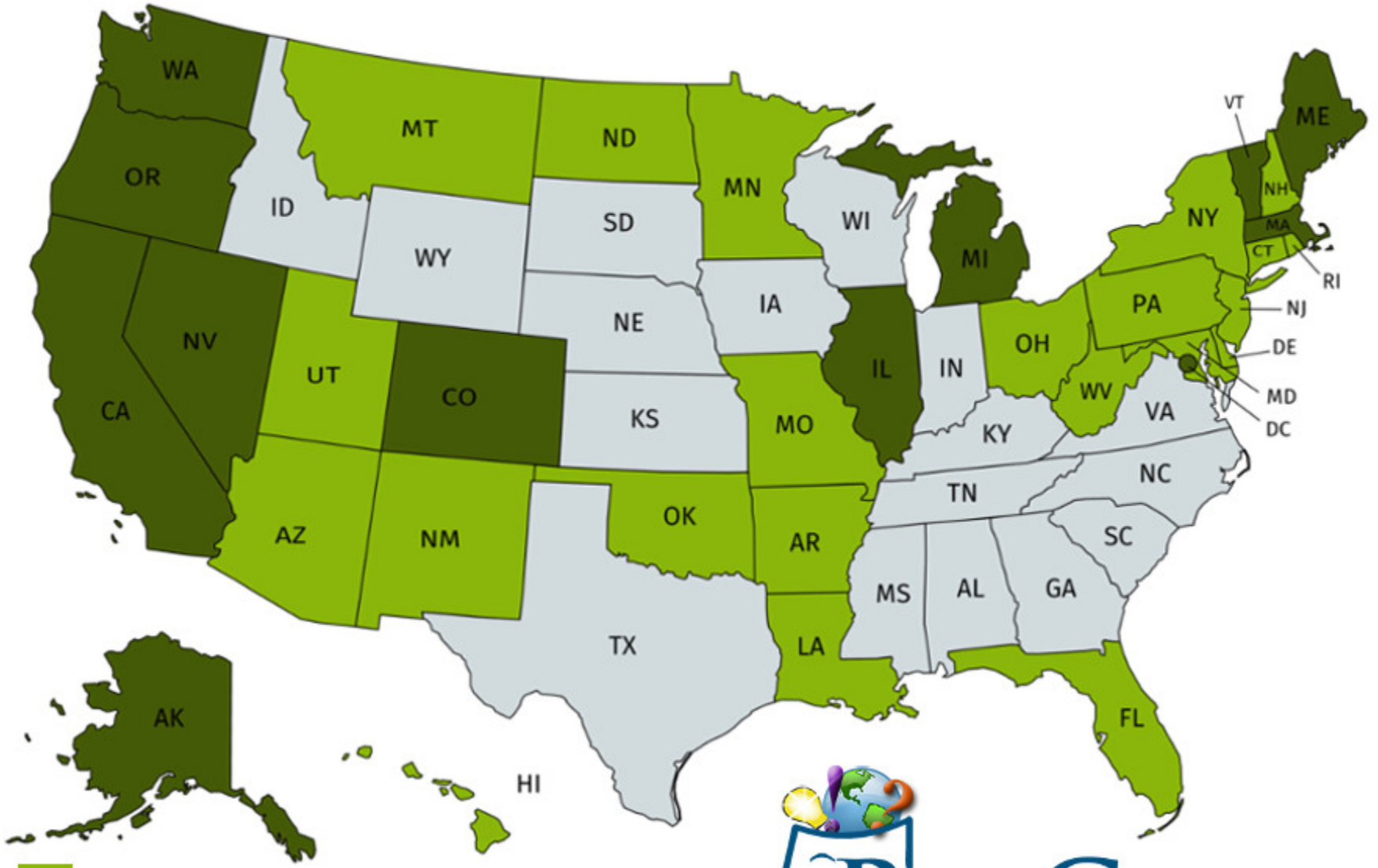
# Steroid Free, Clinical and Endoscopic Remission on 5-ASA in Mild/Mod UC



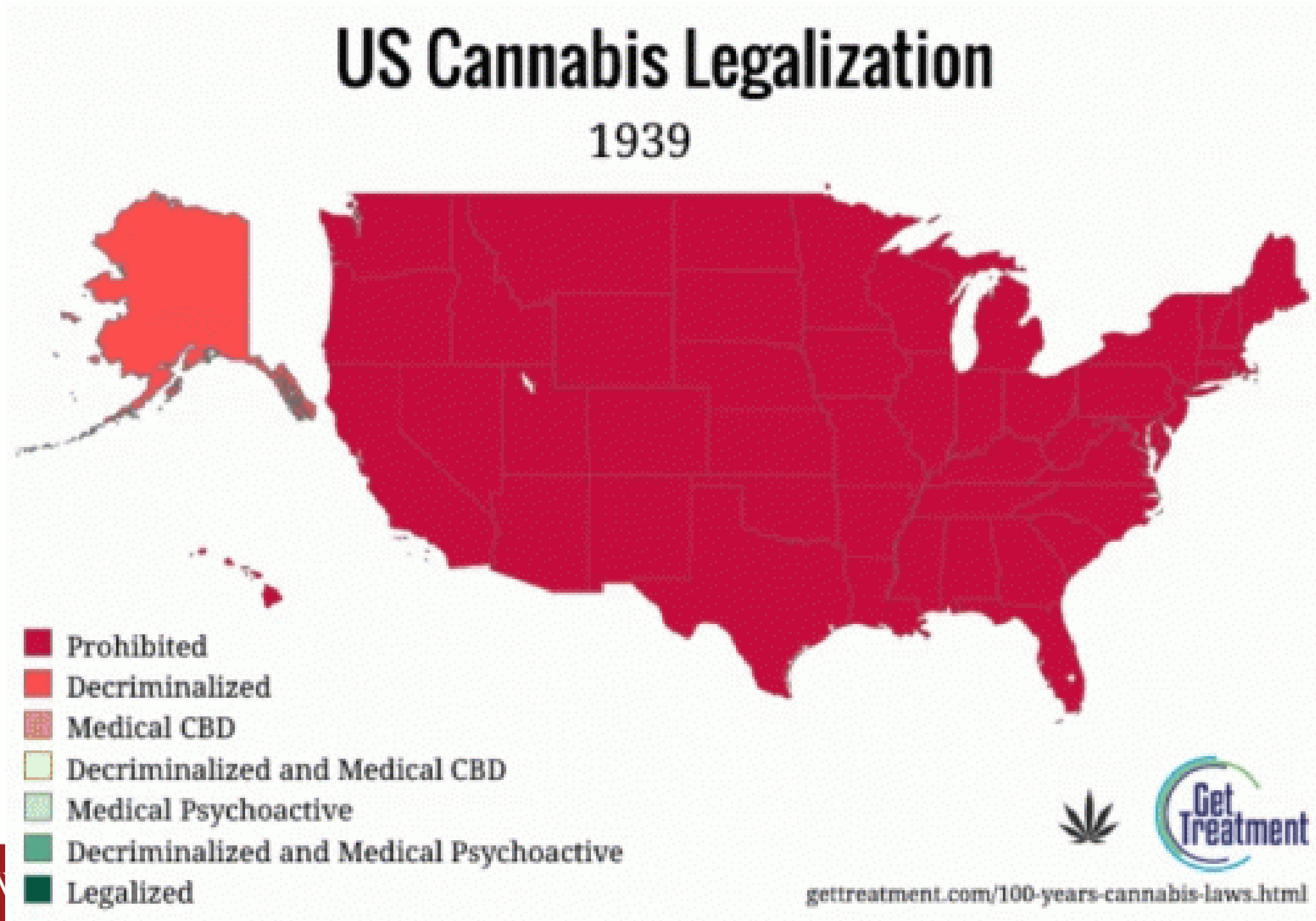



Kamm M et al Gastro Jan 2007

# 33 Legal Medical Marijuana States & DC
# 11 Legal Recreational Marijuana States & DC




ProCon.org


US Cannabis Legalization
1939
Prohibited
Decriminalized
Medical CBD
Decriminalized and Medical CBD
Medical Psychoactive
Decriminalized and Medical Psychoactive
Legalized
Get Treatment
gettreatment.com/100-years-cannabis-laws.html

# The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses. The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.


THC
Tetrahydrocannabinol

CBD
Cannabidiol

CBN
Cannabinol

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

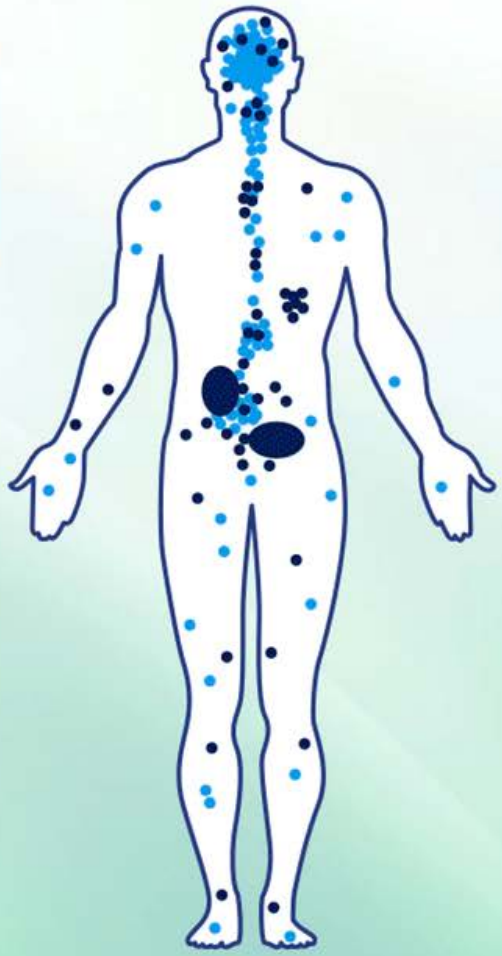
**CB1**

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

**CB2**

CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

## Receptors are found on cell surfaces



# What is the Clinical Data?

**Two Studies:**

1. **Marijuana with THC:**
   - Helps Symptoms, but not inflammation
2. **CBD (Cannabidiol)**
   - No benefit observed


Inflammatory Bowel Diseases Center

# Cannabis with THC induces “Clinical” Response in Crohn’s

## Cannabis Induces a Clinical Response in Patients With Crohn’s Disease: A Prospective Placebo-Controlled Study

TIMNA NAFTALI,* LIHI BAR-LEV SCHLEIDER,‡ IRIS DOTAN,§ EPHRAIM PHILIP LANSKY,‖
FABIANA SKLEROVSKY BENJAMINOV,* and FRED MEIR KONIKOFF*

*Department of Gastroenterology and Hepatology, Meir Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Kfar Saba; ‡Tikun Olam for Promotion of Medical Cannabis, Tel Aviv; §IBD Center, Department of Gastroenterology, Sourasky Medical Center, Tel Aviv; and ‖Laboratory of Applied Metabolomics and Pharmacognosy, Institute of Evolution, University of Haifa, Haifa, Israel

# Figure 1: Crohn's Disease Activity Scores

| Clinical or laboratory variable | Weighting factor |
|---|---|
| Number of liquid or soft stools each day for 7 days | × 2 |
| Abdominal pain (graded from 0 to 3 based on severity) each day for 7 days | × 5 |
| General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days | × 7 |
| Complications* | × 20 |
| Use of diphenoxylate or opiates for diarrhea | × 30 |
| An abdominal mass (0 for none; 2 for questionable; 5 for definite) | × 10 |
| Absolute deviation of hematocrit from 47% in men and 42% in women | × 6 |
| Percentage deviation from standard weight | × 1 |

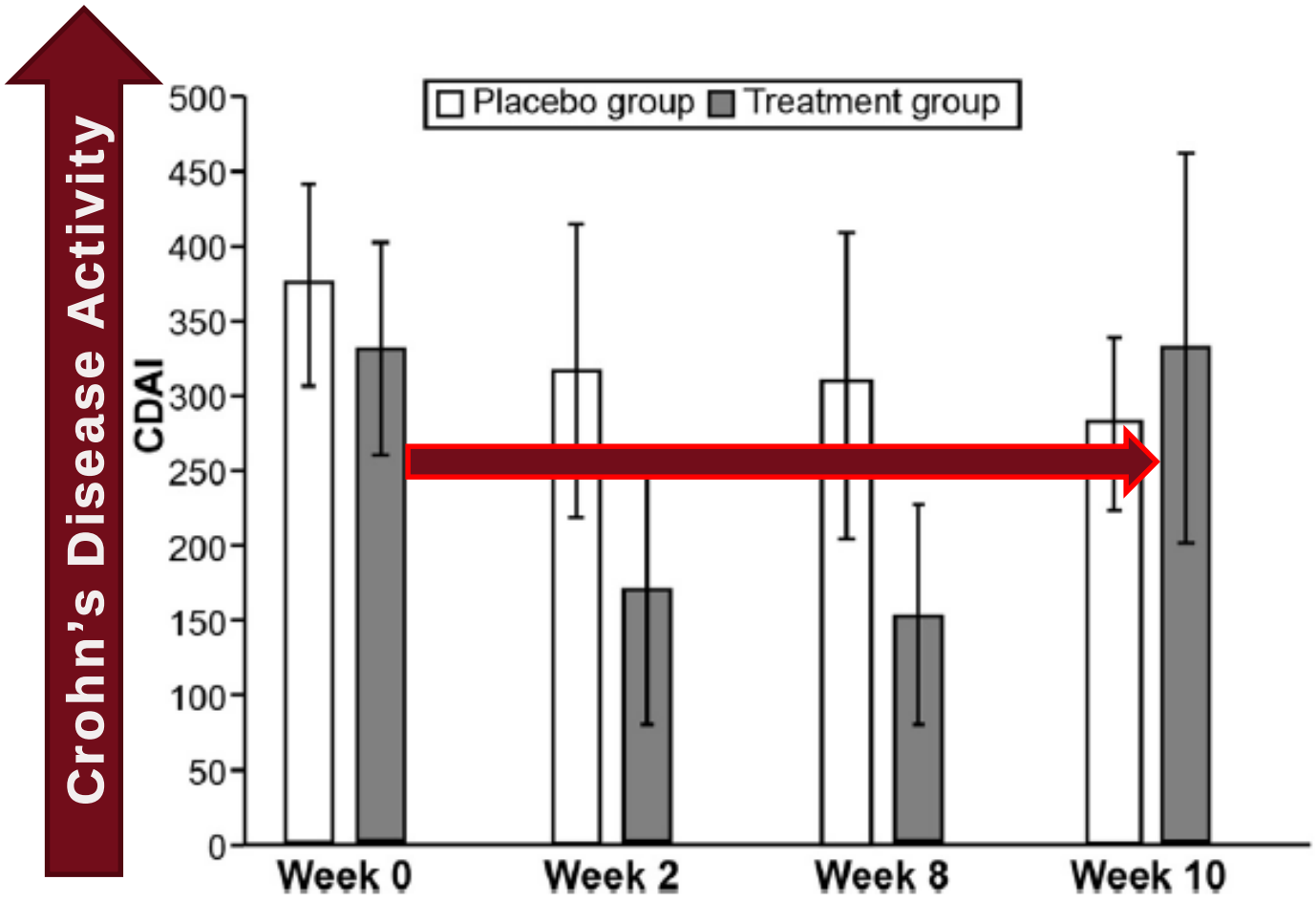


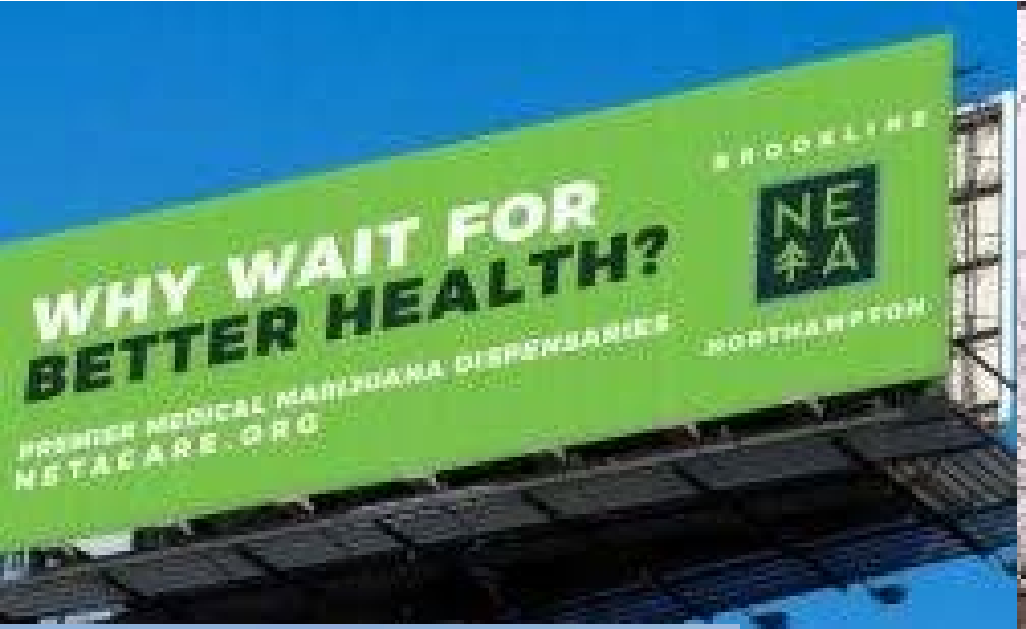

**Figure 1.** CDAI scores in study and placebo groups before and after treatment.

# Table 4:

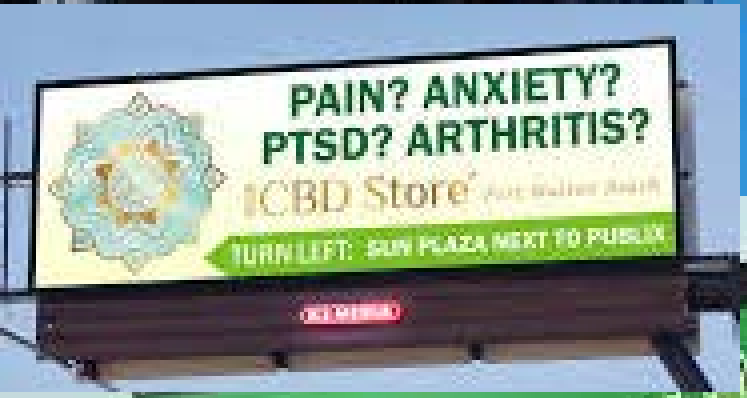
**Table 4.** Side Effects

| | Placebo median (minimum–maximum) | Cannabis median (minimum–maximum) | *P* value |
|---|---|---|---|
| Negative side effects[a] | | | |
| Sleepiness | 4 (3–4) | 3 (1–6) | .5 |
| Nausea | 4 (3–4) | 4 (1–4) | .3 |
| Concentration | 4 (4–5) | 4 (4–7) | .3 |
| Memory loss | 4 (4–4) | 4 (4–6) | .4 |
| Confusion | 2 (2–2) | 2 (1–2) | .4 |
| Dizziness | 2 (1–2) | 2 (1–2) | .9 |
| Positive side effects[b] | | | |
| Pain | 4 (3–4) | 1 (1–2) | .001 |
| Appetite | 4 (4–4) | 2 (1–4) | .008 |
| Satisfaction | 7 (3–7) | 1 (1–4) | .002 |

[a]On a scale from 1 to 7, where 1 = no effect; 7 = very strong effect.
[b]On a scale from 1 to 7, where 1 = very satisfied; 7 = very dissatisfied.











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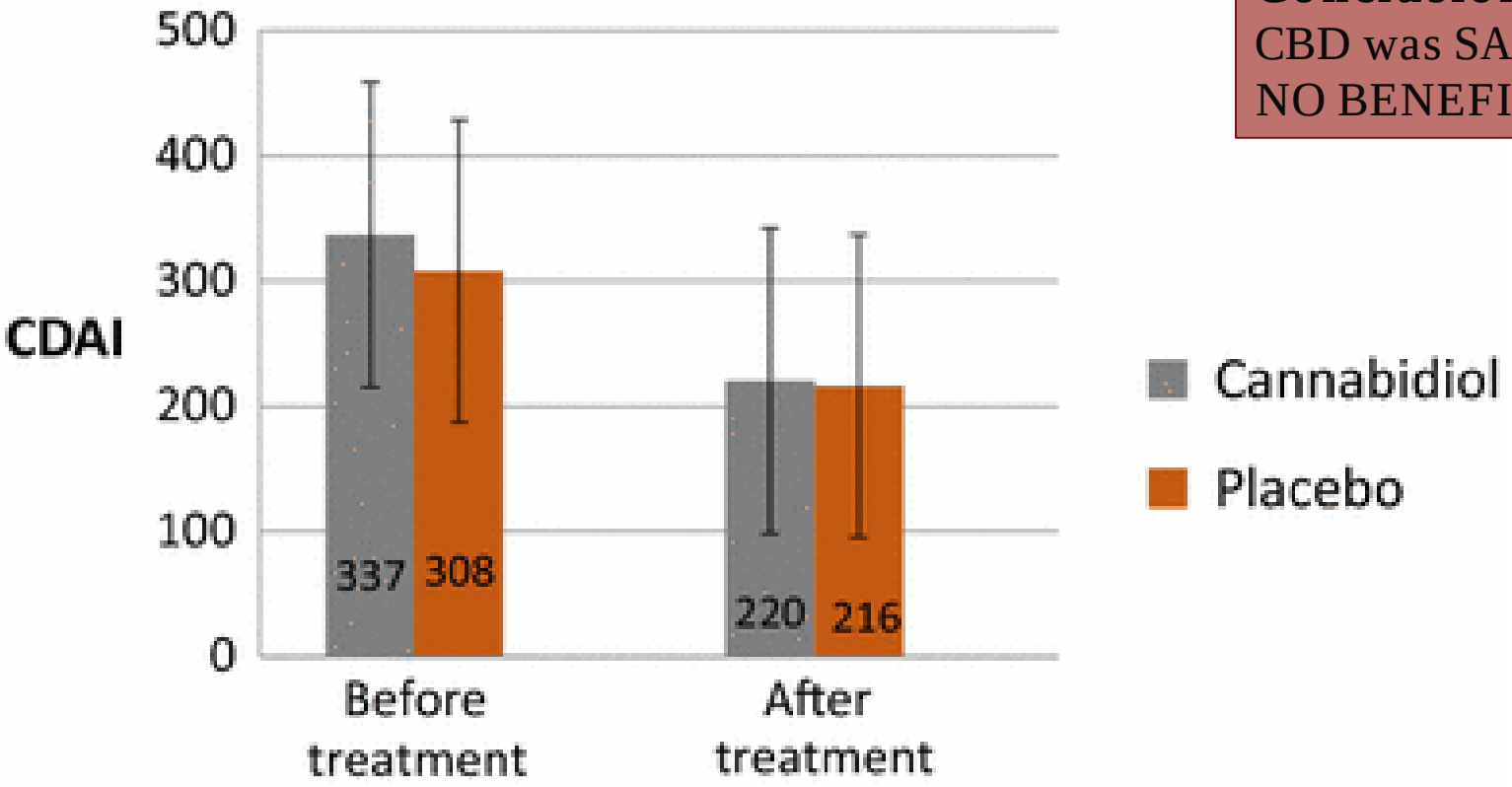
ses Center

Dig Dis Sci (2017) 62:1615–1620
DOI 10.1007/s10620-017-4540-z

ORIGINAL ARTICLE

# Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial

Timna Naftali[1,2] · Refael Mechulam[3,4] · Amir Marii[5] · Gila Gabay[1,2] · Asaf Stein[1,2] · Miriam Bronshtain[1,2] · Ido Laish[1,2] · Fabiana Benjaminov[1,2] ·




**Conclusion**:
CBD was SAFE but had
NO BENEFICIAL EFFECTS.

# SUMMARY of Marijuana and CBD in IBD

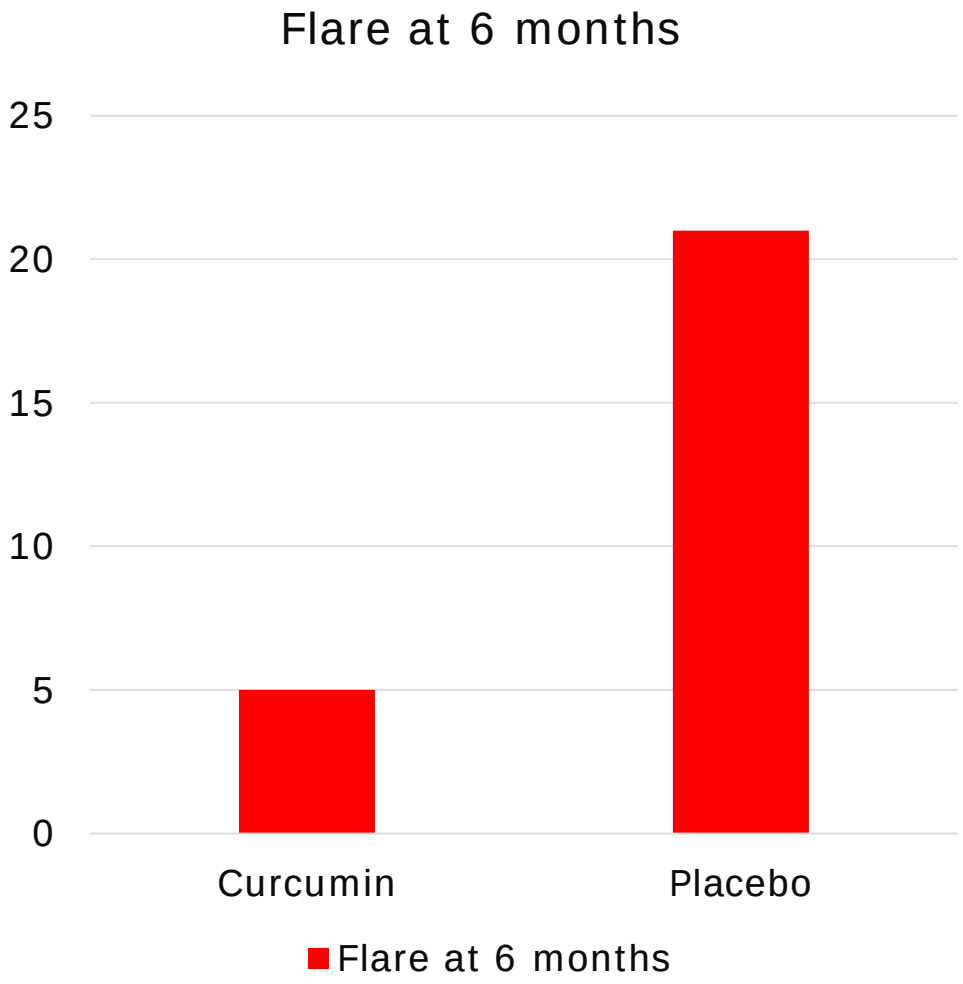
- Learn the facts
  - THC: helps some symptoms
  - CBD: No evidence of Benefit
- Talk to your Doctor
- Monitor your benefits
- Understand the side effects

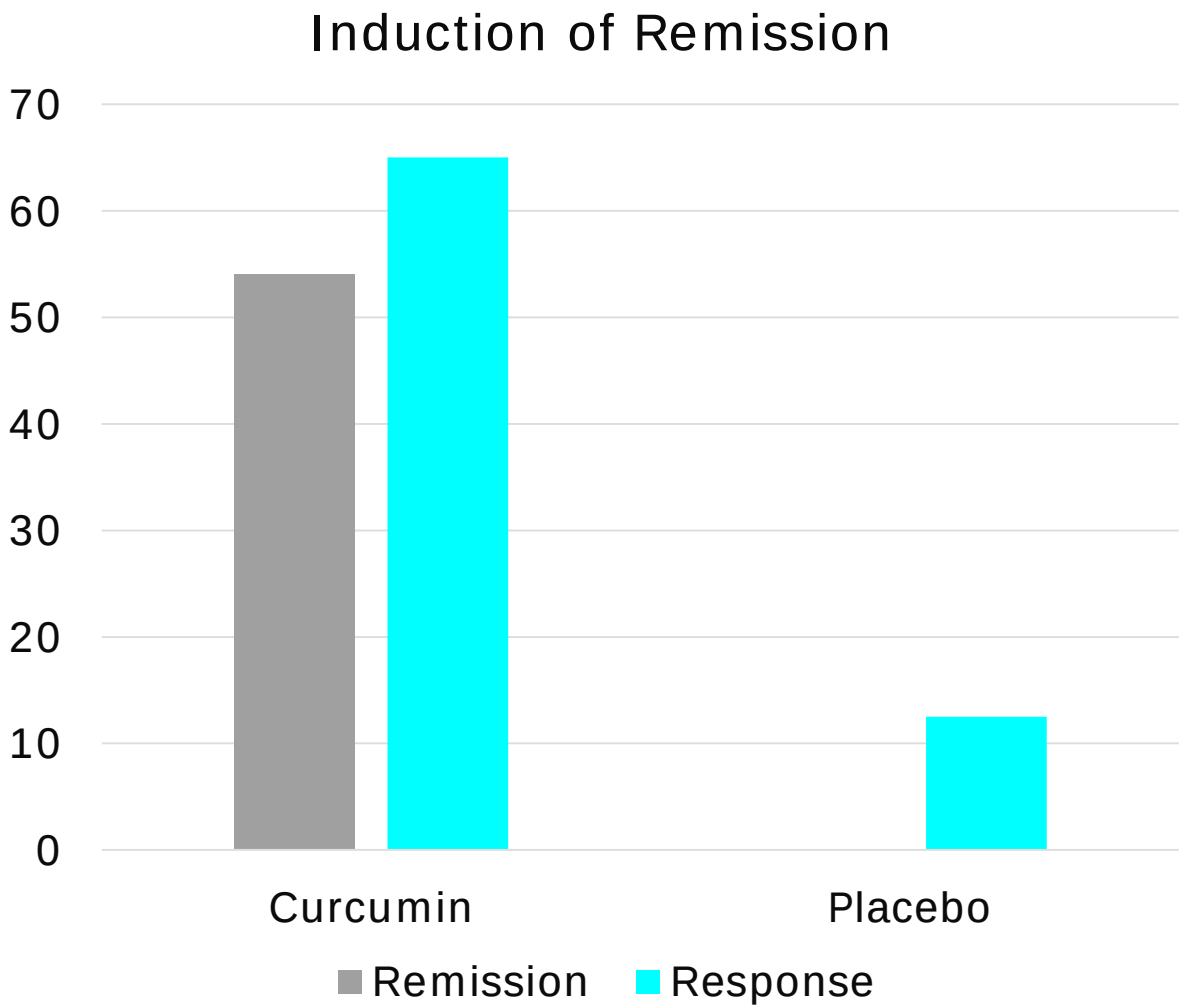
# Curcumin in Ulcerative Colitis

- 2 RCTs (50-81 patients)
  - Maintenance of Remission 6 month
    - 2 grams
  - Induction of Remission at 1 month
    - 3 grams
  - Concurrent 5-ASA in both

Hanai, *et al.* Clin Gastroenterol Hepatol. 2006 Dec;4(12):1502-6.
Lang A. et al. Clin Gastroenterol Hepatol. 2015 Aug;13(8):1444-9.

# Adding Curcumin to 5-ASA in UC




Lang A. et al. Clin Gastroenterol Hepatol. 2015 Aug;13(8):1444-9

# Curcumin Purity Varies
# 5-95% Pure


## Supplement Facts

**Serving Size:** 2 Quick Release Capsules

**Servings Per Container:** 60

| | Amount Per Serving | % Daily Value (DV) |
|---|---|---|
| Vitamin C (as Ascorbic Acid) | 100 mg | 111% |
| Turmeric Curcumin Advanced Complex<br>Turmeric (Curcuma longa) (root), Turmeric Extract (Curcuma longa) (root) (Standardized to contain 95% Curcuminoids), Tart Cherry (Prunus cerasus ) (fruit) (from 4:1 extract), Olive Leaf Extract (Olea europaea) (Standardized to contain 20% oleuropein) | 1,500 mg | * |
| Black Pepper Extract (Piper nigrum) (fruit) (Standardized to contain 95% Piperine) | 6 mg | * |

# Low-Dose Naltrexone in Adult CD

- Efficacy and safety in 12 week placebo controlled study of LDN (4.5 mg/day) (n=34 patients)
  - 30% obtained clinical remission on LDN as compared to 18%
  -
  -
  -
- **E with need for more studies (insufficient evidence)**

Evidence rated as low in COCHRANE systematic review

Parker C. Cochrane Database Syst Rev. 2018 April 1;(4):CD010410.

# Fish Oil in IBD

- For UC:
  - 3 EPA, 1 EPA/DHA, 2 combination agents
    - Double blind, placebo controlled, some with crossover
    - Some improvement in histology and clinical symptoms but **no consistent tre**
- For CD:
  - 3 Ome
    - Ran
    - Earl
      studies did not

**No Clear Efficacy Benefit in Large RCTs**

Turner D. Inflamm Bowel Dis. 2011 Jan;17(1):336-45.

# A Translational Phase I Study of Tauroursodeoxycholic acid (TUDCA) in Ulcerative Colitis

**PI: Matthew A Ciorba MD**

**Co-I's:** Nicholas Davidson MD and Randal Kaufman PhD

Washington University in Saint Louis School of Medicine

Sanford-Burnham-Prebys Medical Discovery Institute

Litwin IBD PIONEERS

CROHN'S & COLITIS FOUNDATION

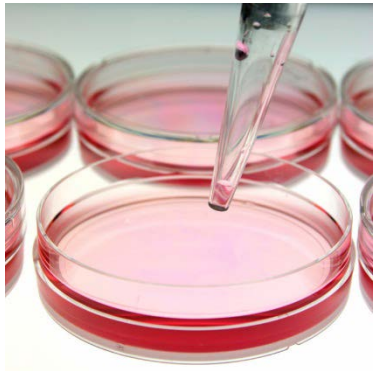
Washington University in St. Louis IBD Center of Excellence

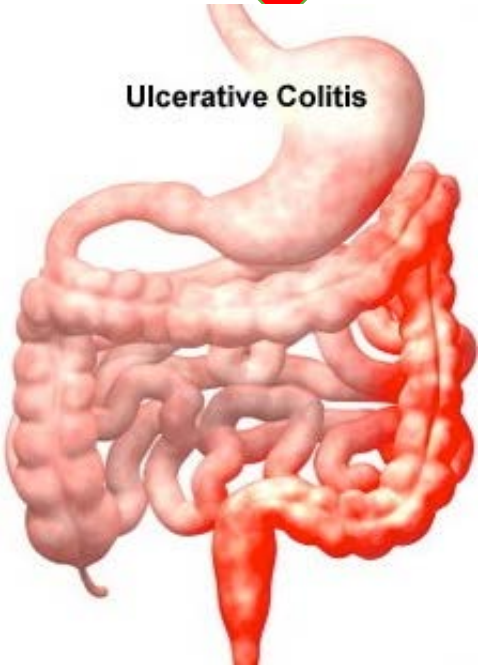
SBP SANFORD BURNHAM PREBYS

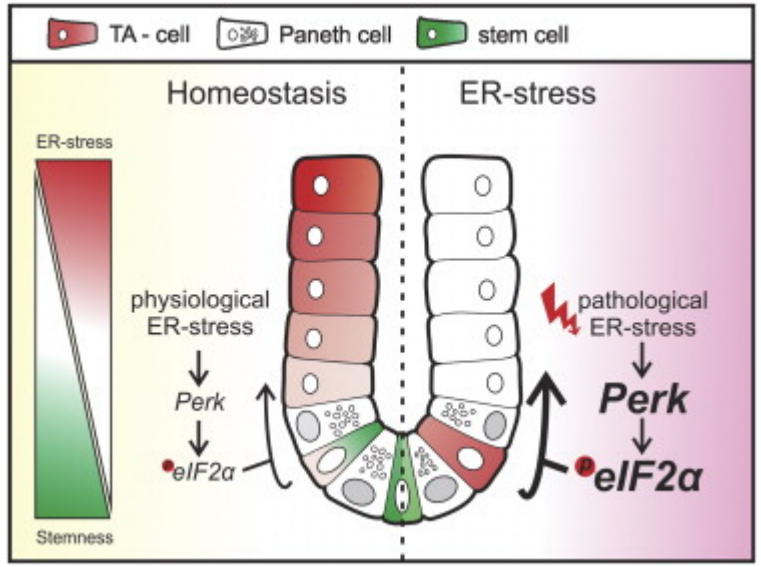
Litwin IBD PIONEERS

CROHN'S & COLITIS FOUNDATION

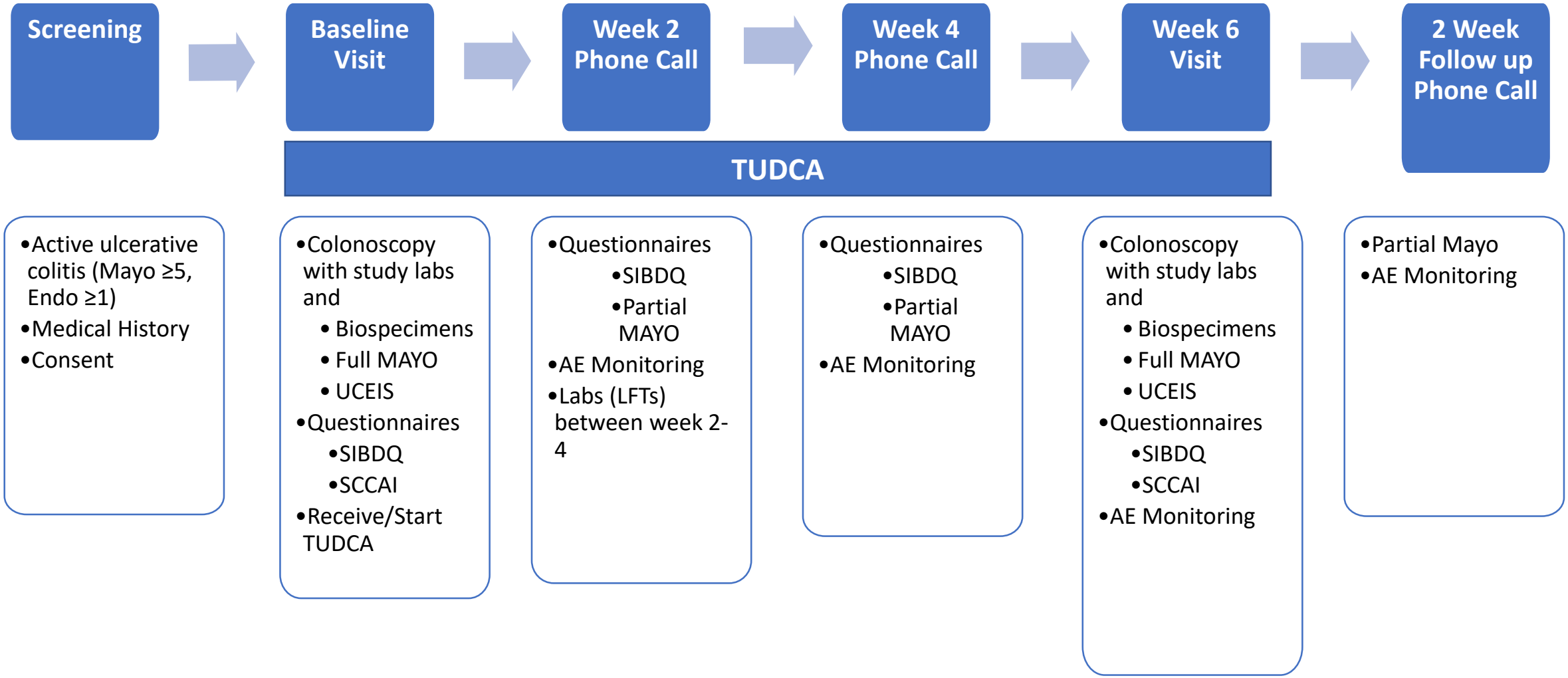
# Efficacy and Safety Study of TUDCA in Ulcerative Colitis Treatment

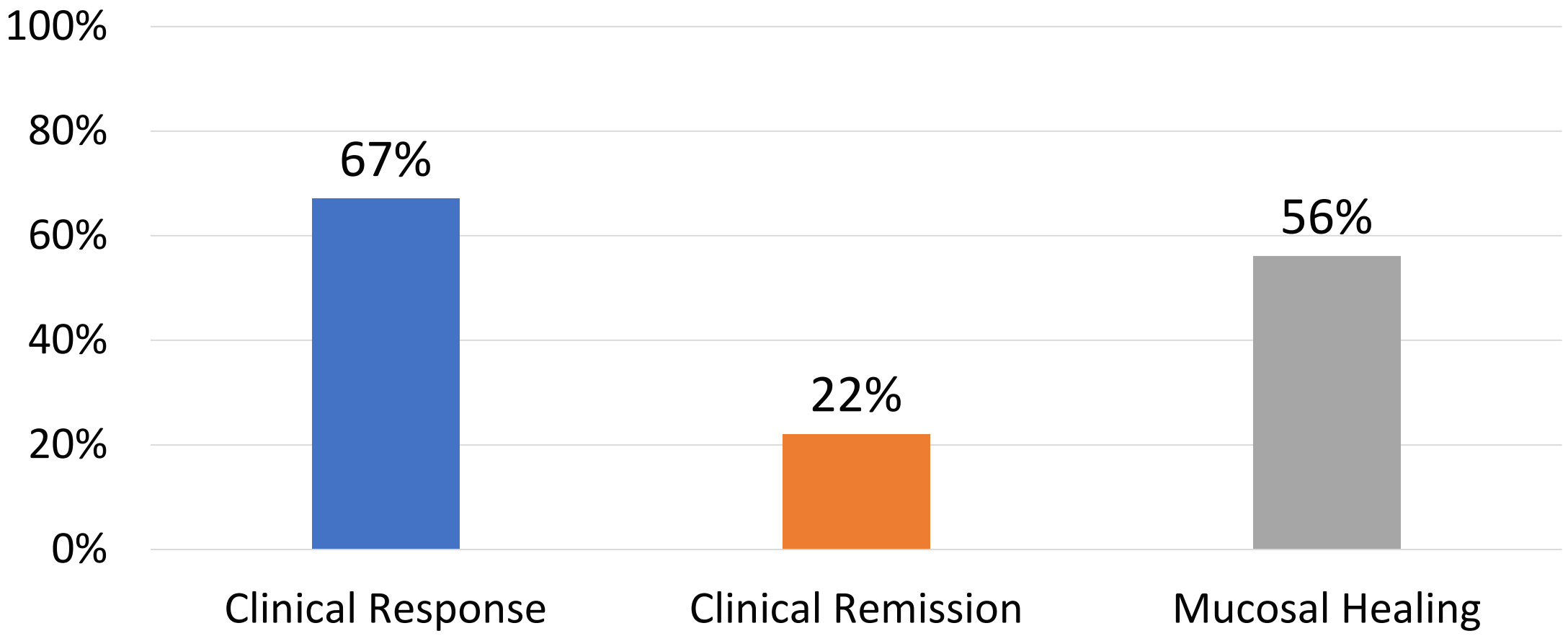


# Trial Schema



# Total Mayo UC Score Outcomes at 6 Weeks



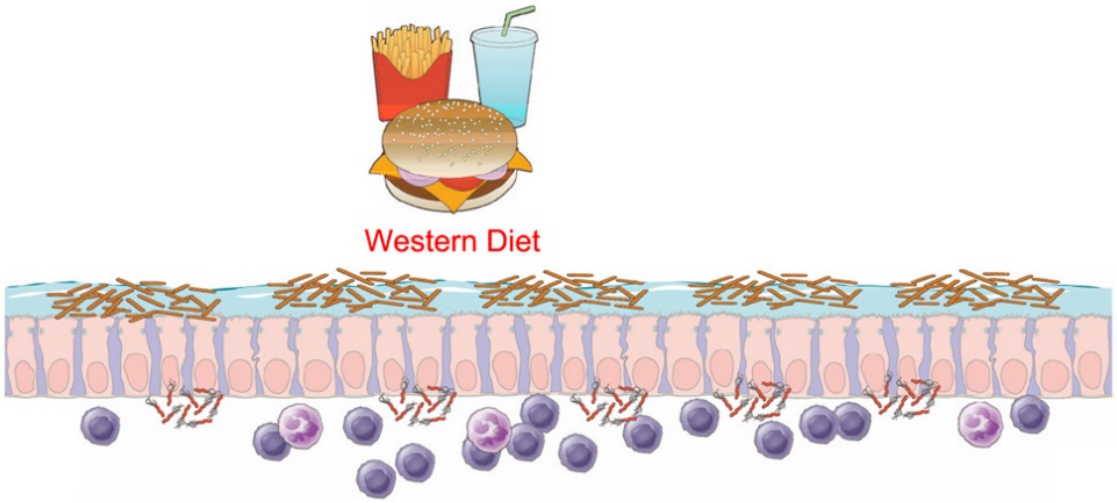

1) **Mucosal Healing:** A decrease of at least 1 point on the Mayo endoscopic subscore with a final score of 0 or 1 will be used as a marker of mucosal healing.
2) **Clinical Response**: A decrease in Mayo Score of ≥ 3 points and a decrease in Mayo Score of ≥ 30% from baseline and a decrease in the rectal bleeding score of ≥ 1 or an absolute rectal bleeding score of 0-1.
   a. **Clinical Remission** will also be recorded if achieved as defined by a total Mayo Score of ≤2 with no subscore >1 and improvement of endoscopic appearance of the mucosa (Mayo 0 or 1).

# Eating with IBD

Kristin Cunningham, MHA, RD
Dietitian/Nutritionist

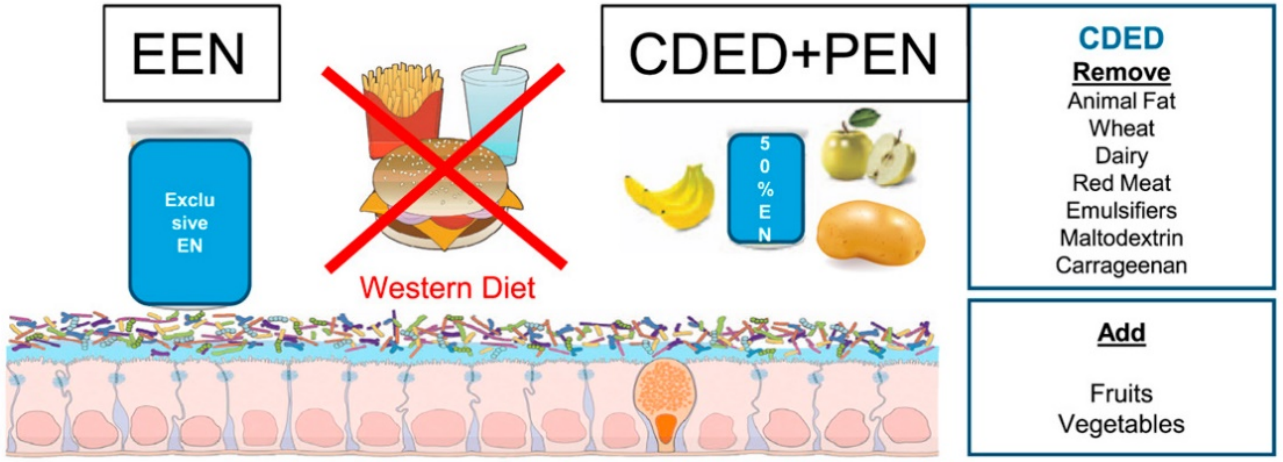
Nothing  being here!

# Dietary Therapy: Crohn's Disease Exclusion Diet + Partial Enteral Nutrition vs. Exclusive Enteral Nutrition




Habitual Diet Triggering Crohn's Disease

Increased Proteobacteria Dysbiosis, Intestinal permeability, Inflammation,
Active Disease




Crohn's Disease Exclusion Diet+ PEN vs. EEN

Primary endpoint: CDED+PEN is better tolerated than EEN

Secondary endpoints:

Both CDED+PEN and EEN are effective to achieve remission at week 6

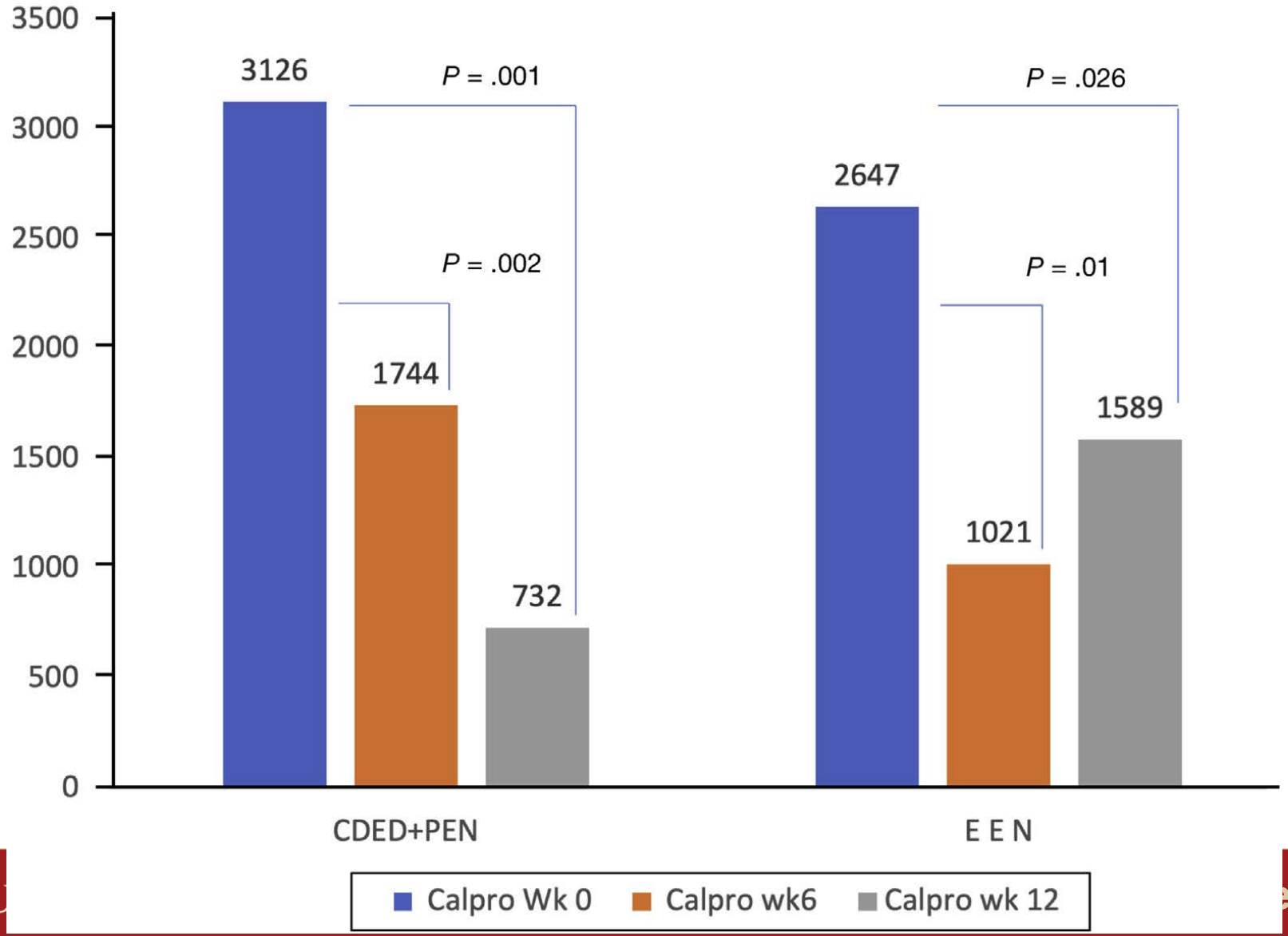
CDED+PEN is superior to sustain remission and reduce inflammation at week 12

CDED+PEN: associated with reduction in Proteobacteria and Intestinal Permeability

Gastroenterology

Gastroenterology 2019;157:440–450

# CRP is lower in CDED+PEN at 12 weeks



# Specific Carbohydrate Diet (SCD)

## Inflammatory Bowel Disease Anti-Inflammatory Diet (IBD-AID)

## Nutrition in Immune Balance (NIMBAL) Therapy

**What is it?**

- SCD: gastroenterologist Sidney Haas (1951); Elaine Gottschall (1986)
- IBD-AID: dietitian Barbara Olendzki (2007)
- NIMBAL: gastroenterologist David Suskind (2016)
- Excludes complex carbohydrates, thought to cause inflammation

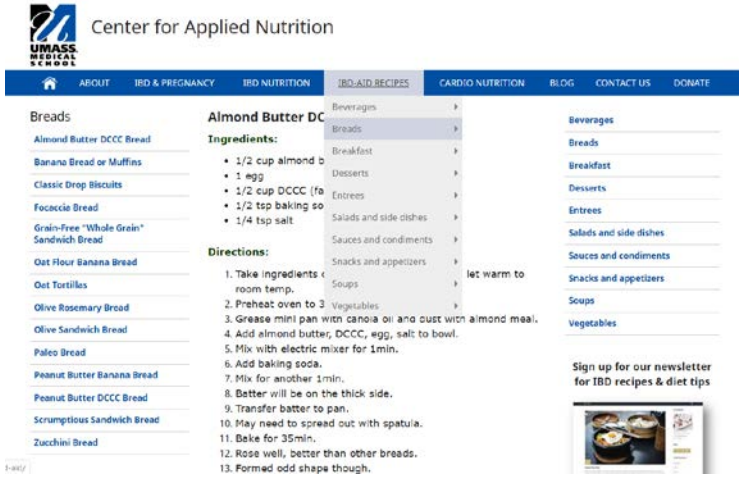



*Image source: umassmed.edu*

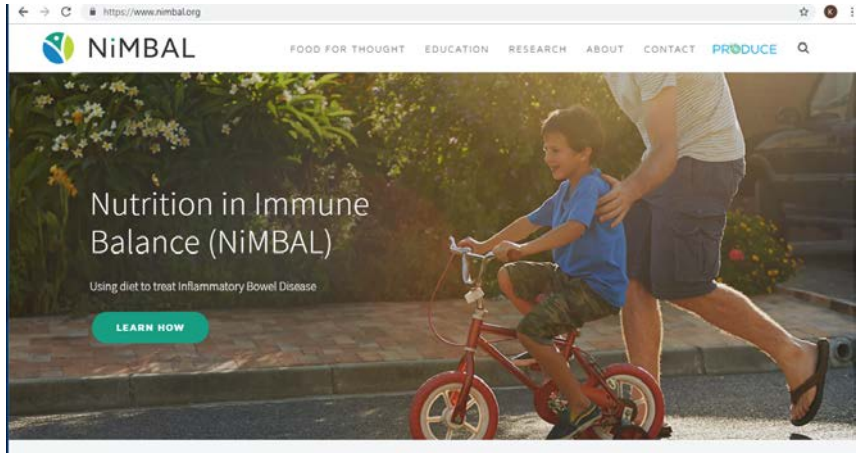



*Image source: amazon.com*

# Evidence for SCD/IBD-AID/ NIMBAL

**12 studies reviewed:**

**10 retrospective**
**2 prospective**
**(6 pediatric only)**

**Weaknesses:**

- Low # of studies/participants
- Study design


**Strengths:**

- Studies generally report improvement in:
  - Labs
  - Clinical disease activity
  - Symptoms
  - Height/weight percentiles (pediatric)
  - Medication dependence
  - Microbial diversity

**Considerations:**

- Compliance must be 100%
- Food preparation
- Cost
- Must be an open-minded eater
- Challenges with eating out/socialization
- Losing sight of the big picture
- Vegetarian/vegan

**Contraindications:**

Not appropriate as sole therapy for:

- Stricturing disease
- Abscess or fistula formation
- Severe perianal disease
- Severe symptoms of abdominal pain and diarrhea
- Pediatric failure to thrive or stunted growth

# Exclusive Enteral Nutrition (EEN)

**What is it?**

- EEN = 100% of calories through formula
- No regular food for 4-12 weeks

*Image source: pixabay.com*




*Image source: amazon.com*

# Evidence for EEN

**Examined 3 journal review articles which pulled from >50 research articles**

**Weaknesses:**

- On medications
- Lack of studies in some populations

**Strengths:**

- Well studied in pediatric Crohn's population
- Efficacy for remission (Crohn's)
  - Pediatric up to 85%
  - Adult up to 80%
- Studies generally report improvement in:
  - Inflammation
  - Mucosal healing
  - Overall nutrition status

**Considerations:**

- Difficult to follow
- No difference in effectiveness with formula type
- Cost/insurance
- Lack of strategy after EEN
- Health provider support/expertise
- Advantages beyond inducing remission

**Contraindications:**

- Ulcerative colitis

# Crohn's Disease Exclusion Diet (CDED)

# +

# Partial Enteral Nutrition (PEN)

## Also known as Modulife Diet

**What is it?**

- A whole food diet combined with partial enteral nutrition (PEN)
- Exclusion of some dietary components with mandatory inclusion of others

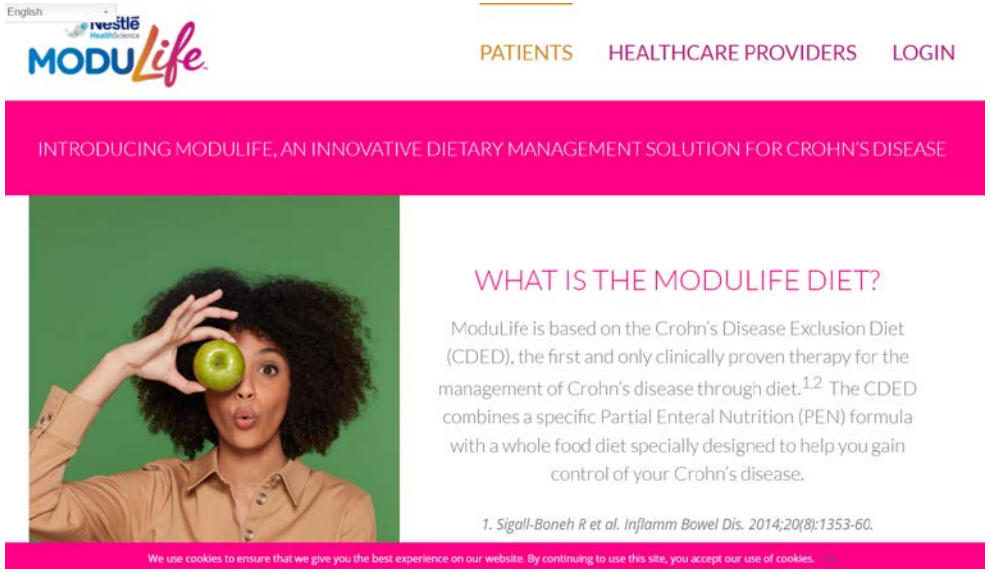




*Image source: mymodulife.com*

# Evidence for CDED + PEN

**3 studies reviewed:**

**2 prospective, uncontrolled &**
**1 prospective RCT**

**Weaknesses:**

- Low # of studies/participants
- Lack of studies in some populations
- No studies track beyond 12 weeks


**Strengths:**

- Efficacy for remission (Crohn's)
  - Pediatric & Adults up to 70%
  - *Pediatric alone up to 80%*
- Studies generally report improvement in:
  - Adherence (compared to EEN)
  - Inflammation
  - Mucosal healing
  - Overall nutrition status

**Considerations:**

- Difficult to follow
- Cost/insurance (for PEN)
- Health provider support/expertise
- Vegetarians/Vegans would need to rely more heavily on formula

**Contraindications:**

- Ulcerative colitis
- Perianal Crohn's disease
- Fistulizing Crohn's disease
- Severe Crohn's colitis

# Low FODMAP Diet

**FODMAP = Fermentable, Oligosaccharides, Disaccharides, Monosaccharides And Polyols**

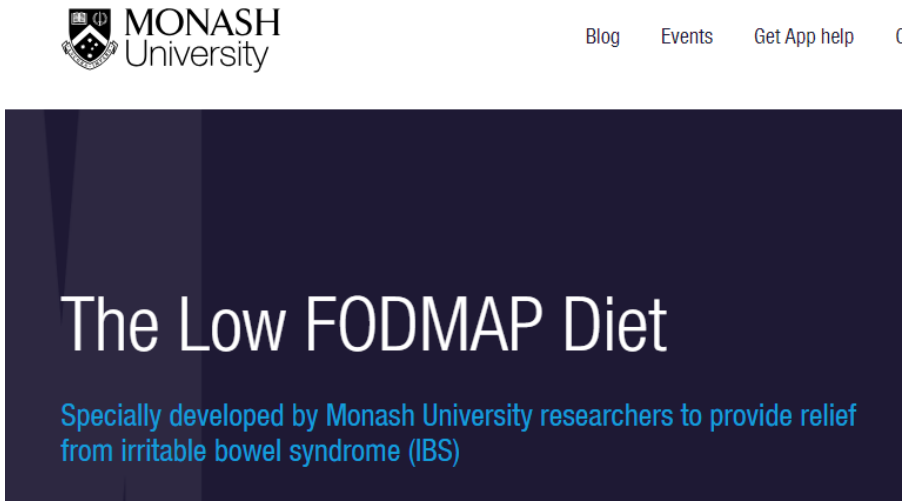



*Image source: monashfodmap.com*

**What is it?**

- Developed in 2008 by researchers to provide relief for patients with Irritable Bowel Syndrome (IBS)
- FODMAPs are short-chain carbohydrates that are rapidly fermented and can be poorly absorbed
- Is a learning process, not a list of foods to eat or not eat

APPROVED FOOD PRODUCT
FODMAP FRIENDLY

MONASH UNIVERSITY LOW FODMAP CERTIFIED™


*Image source: fodyfoods.com*

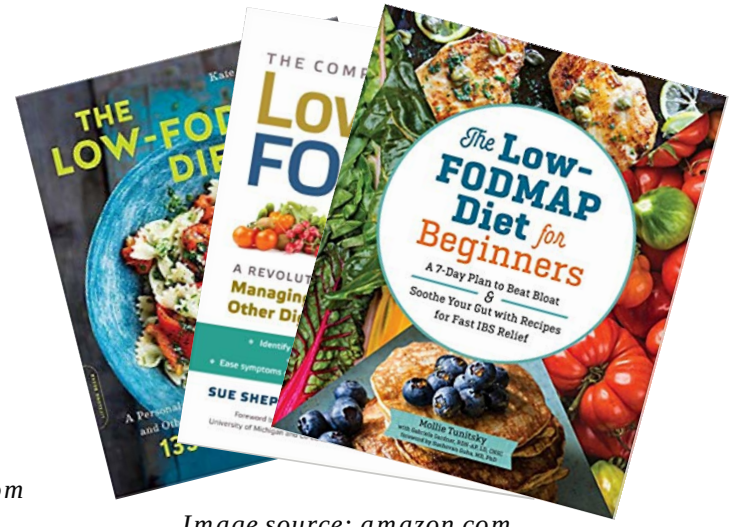



*Image source: amazon.com*


*Image source: rachelpaulsfood.com*

# Evidence for Low FODMAP Diet

**4 studies reviewed:**

**1 RCT-open label**
**1 retrospective**
**1 prospective**
**1 combined retrospective/ prospective**

**Weaknesses:**

- Low # of studies/participants
- No studies have focused on:
  - Microbiome changes in IBD
  - Moderate-severe active IBD
  - Measures of disease activity

**Strengths:**

- Studies generally report improvement in:
  - Symptoms
    - Stool frequency
    - Stool consistency
    - Abdominal pain
    - Bloating
    - Gas

**Considerations:**

- Intended to help functional symptoms
- Likely to result in a low-fiber diet
- May decrease beneficial bacteria
- Fermentation = a normal process
- Phone apps available

**Contraindications:**

- Pouchitis
- Sticturing disease (possibly)
- Avoid starting during a flare

# Key takeaways

- **No diet can be broadly recommended for inducing (getting you into) and/or maintaining (keeping you in) remission**

**So, what is the role of diet in IBD?**

## Now

- Symptom management
  - Basic tips
  - During remission: low FODMAP diet
- Prevent/treat malnutrition
- Overall health
- Enjoyment
- Decrease inflammation
  - Evidence-based: EEN for select Crohn's patients
  - Low evidence/experimental: seek dietitian support to trial

## Future

(Hopefully) food-based diet for the management/co-management of inflammation

*Getting closer, but not quite there yet.*

# What diet recommendations do I make?

EEN

## Eating with Inflammatory Bowel Disease (IBD):
### *During a Flare*

Crohn's Disease and Ulcerative Colitis are both types of IBD. During a flare, some foods and drinks may help to ease your symptoms and will provide you with nutrients, vitamins and minerals to maintain or improve your nutritional health. Other foods and drinks may worsen some symptoms, such as cramping, bloating and diarrhea.

**Foods and drinks to enjoy are:**
- Low in insoluble fiber (or roughage, found in stalks, skins and seeds of fruits and vegetables)
- High in protein
- Low in lactose (a sugar in milk products)
- Lower in sugar
- Lower in fat

**Foods and drinks to limit are:**
- High in insoluble fiber
- High in lactose
- Contain artificial sweeteners*
- High in sugar and/or fat
- Spicy
- Contain caffeine
- Contain alcohol

**See the food/drink list to learn more about artificial sweeteners*

See the next 2 pages for examples of foods and drinks.

**A few more thoughts:**
- The "Limit" list is meant to provide general guidelines, but you may find that you can handle some of these items during a flare, especially in smaller amounts.
- Some people may struggle to stay well hydrated during a flare. Aim for 6-8 glasses of water each day.
- Notice how foods and drinks affect your symptoms to help you learn which choices may worsen symptoms. Some people with IBD keep a food journal to help them with this.
- Eating 4-6 smaller meals each day may make it easier to meet your nutrition needs.
- If you are having trouble getting enough foods and drinks or are losing weight, it could help to drink oral nutrition supplements (such as Boost® or Ensure®). Talk to your healthcare provider or dietitian if you lose weight without trying (and to learn more about these drinks).



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## Eating for Crohn's disease with strictures

A stricture is a narrowing in the small intestines that makes it hard for food to pass through. People with Crohn's disease sometimes get strictures. They can happen from inflammation or from scar tissue buildup.

If you have a stricture in your small intestines, eating less fiber may help prevent a blockage. Fiber is in fruits, vegetables and some grains.

**The goal of a low-fiber diet is to get less than 8 grams of fiber each day.**

**Foods and drinks to enjoy are:**
- Low in fiber - less than 2 grams of dietary fiber per serving
- Small portions
- Cooked until soft

**Foods and drinks to avoid are:**
- High in fiber - more than 2 grams of dietary fiber per serving
- Large portions
- Raw

See the next page for examples of foods and drinks.

**A few more thoughts:**
- It may help to spread your meals out into 6 or more small meals during the day. This way, less food must make it through the stricture at once.
- Be sure to drink plenty of fluids, water is the best choice. Aim for at least 8 cups (64 ounces) of water each day. Sip fluids throughout the day instead of gulping a large amount at once.
- Cut foods up into smaller pieces and chew well.
- If you are having trouble eating enough or are losing weight, it could help to drink low fiber oral nutrition supplements (such as Boost® or Ensure®). Talk to your healthcare provider or dietitian if you lose weight without trying (and to learn more about these drinks).



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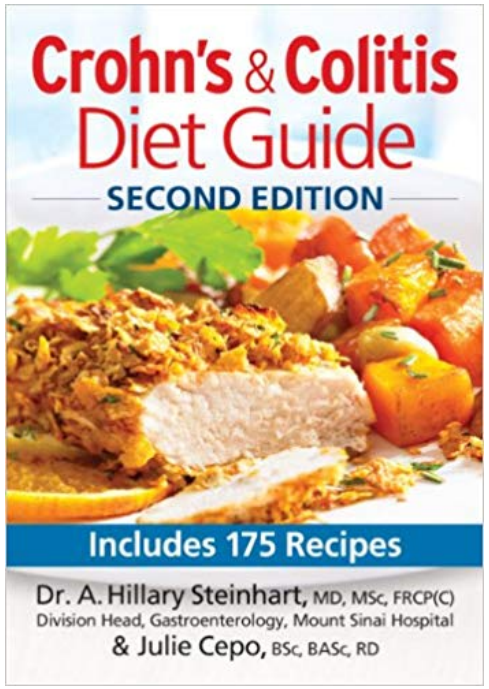
Low FODMAP diet

# Diet-related resources:



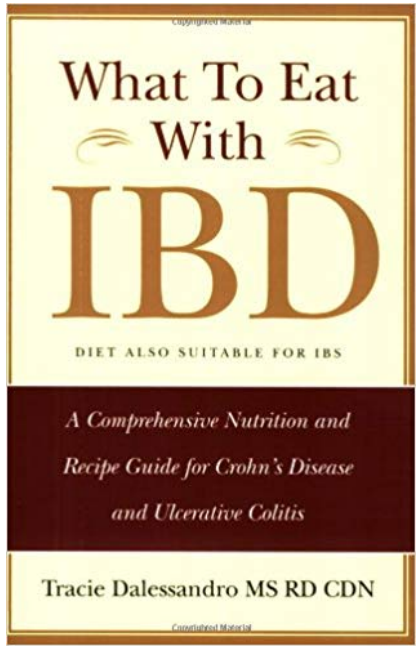




Image source: amazon.com

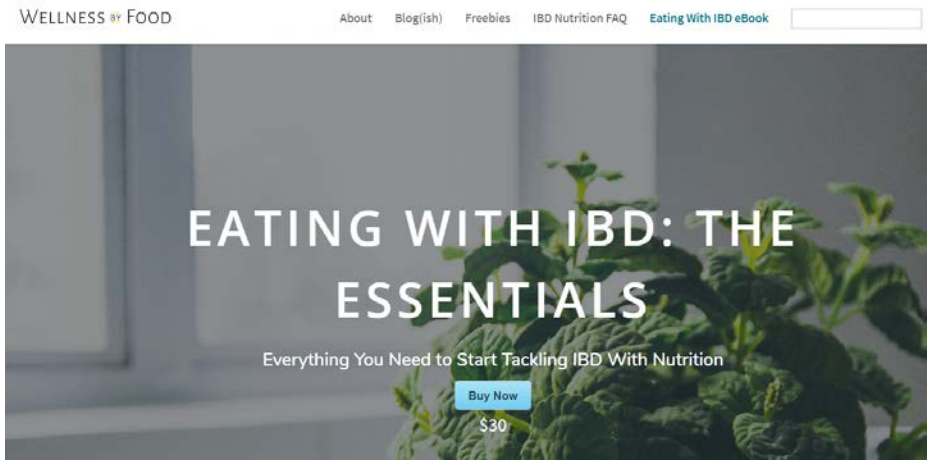



Image source: wellnessbyfood.com

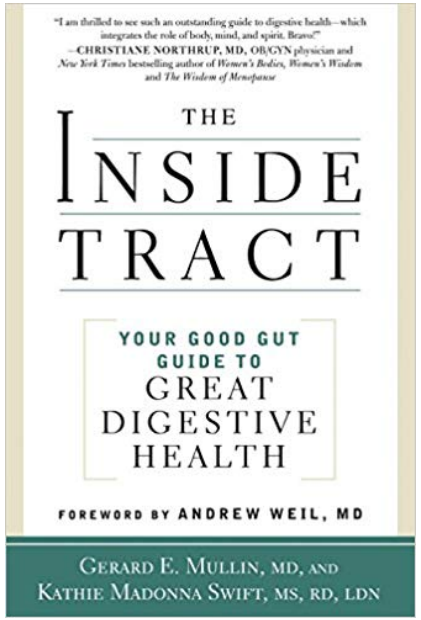



Image source: amazon.com

EPICURED®

Image source: epicured.com

Image source: modifyhealth.com

# Noteworthy IBD Diet Research in Progress


*Image source: dinecd.web.unc.edu*

https://clinicaltrials.gov/ct2/show/NCT03058679

- Randomized controlled study
- Mediterranean Diet versus Specific Carbohydrate Diet
- 194 participants randomly assigned to follow one of the diets for 12 weeks
- 1st 6 weeks: provided all of their food (at no cost)
- 2nd 6 weeks: they can choose to receive all meals (at a cost) OR are provided recipes for buying and preparing the food themselves
- Study started 9/2017; completion date 1/2020

# Noteworthy IBD Diet Research in Progress

UMASS MEDICAL SCHOOL | CENTER FOR MICROBIOME RESEARCH

*Image source: umassmed.edu*

- Cross-sectional study
- Normal diet versus IBD-AID
- 19 participants (13 Crohn's, 6 Ulcerative Colitis, aged 17-69)
- Study is completed with data being analyzed currently; expect dissemination of results summer/fall 2019

https://www.umassmed.edu/microbiome/probiotics/

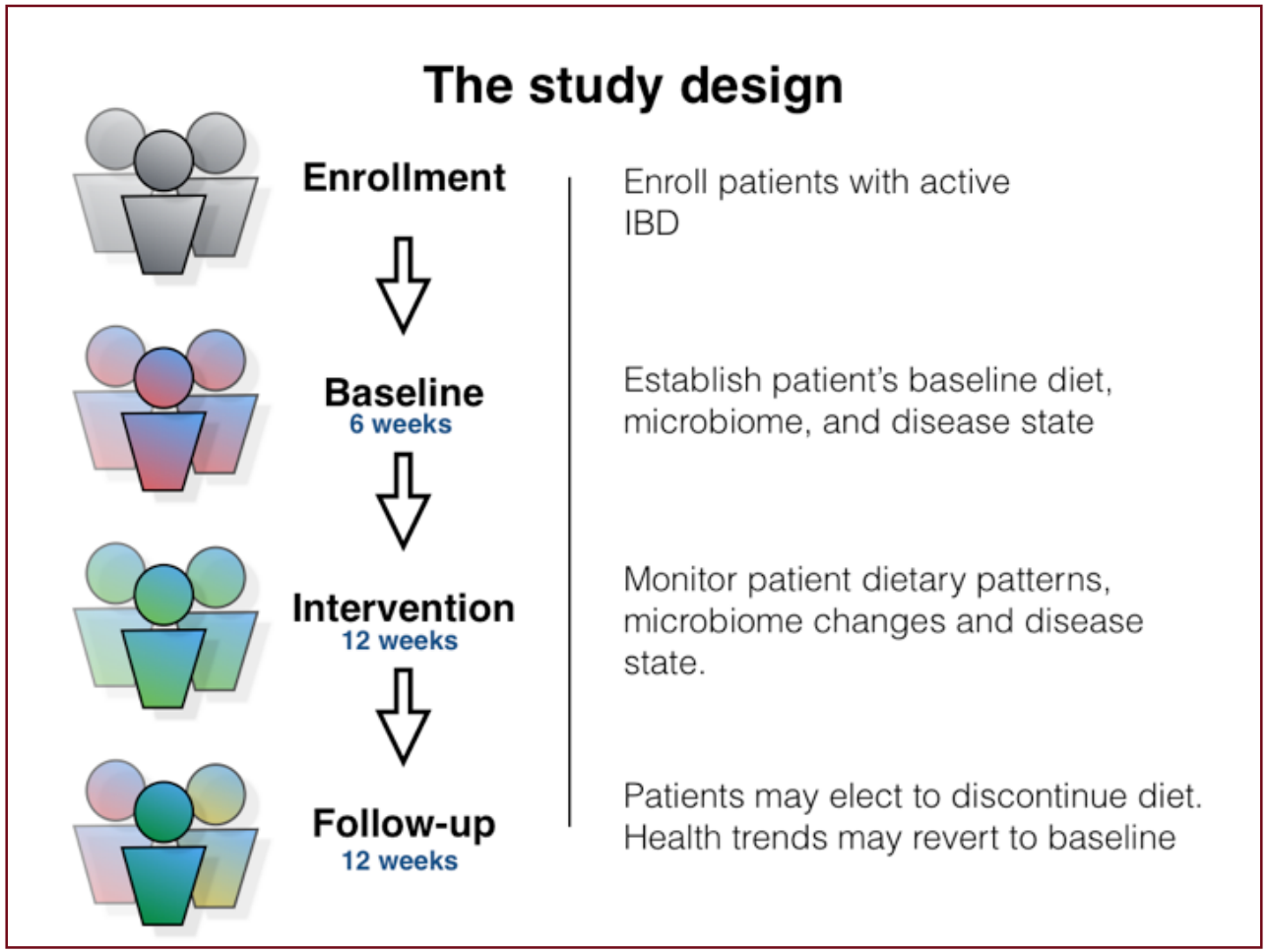



*Image source: Barbara Olendzki, RD, MPH*

# How Should We Approach CAM in IBD?

Be proactive and open: ask about CAM usage/interest and listen without judgment

## Understand the literature

- Adjunct versus primary therapies
- Recognize the potential downsides of CAM (i.e. therapy toxicities)

## Research opportunities

- Larger scale studies
- Delineating mechanisms and treatment efficacy including endoscopic outcomes

# Resources

- AAP Section on Integrative Medicine
  - http://www2.aap.org/sections/chim/
- Arizona Center of Integrative Medicine
  - http://integrativemedicine.arizona.edu/education/peds_imr.html
- CCF
  - http://www.crohnscolitisfoundation.org/resources/complementary-alternative.html
- NIH National Center on Complementary and Alternative Medicine (NCCAM)
  - http://nccam.nih.gov

# Ulcerative Colitis Cases

**Matthew A Ciorba, MD**
**Associate Professor of Medicine**
**Director, IBD Program and IBD Research**

**Internal Medicine**
**Division of Gastroenterology**


Inflammatory Bowel Diseases Center

# Case 1: Delayed Diagnosis and Fulminant Disease


Inflammatory Bowel Diseases Center

# Presentation

- 22 year old female college student
- Presented to the surgery department of a tertiary care hospital having been referred from a private clinic, with a two month history of severe abdominal cramps, persistent bloody and mucoid diarrhea, weight loss and tiredness.

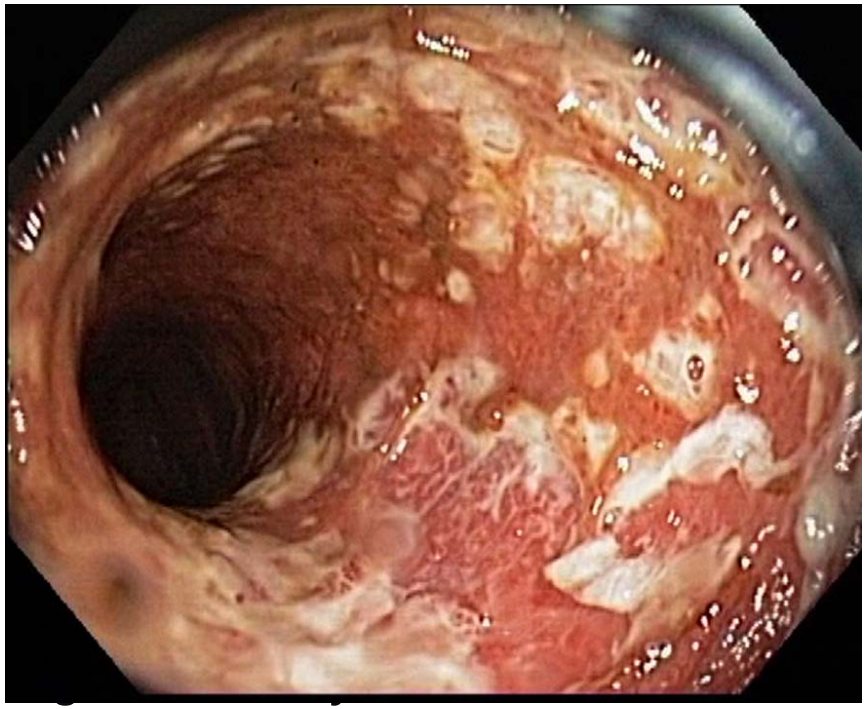
# History

- **2 months ago:** Symptoms began with abdominal cramps and an intense urge to pass stool after every meal. Her symptoms rapidly worsened with passage of stool becoming more frequent. Within two days she was passing persistently watery diarrhea mixed with fresh blood and mucous.
  - She was seen by her general practitioner who treated her for infectious colitis.
  - One week later she collapsed at home and was admitted to hospital for investigations. She was discharged two days later without a diagnosis.
- **1 month ago:** She felt somewhat improved, but moderate symptoms persisted and she experienced diarrhea and vomiting after eating or drinking, which lasted for 10 days. She was admitted to hospital for rehydration and further investigations. No conclusive diagnosis was made.
- **Currently:** Patient is passing 10-20 liquid stools per day. Diarrhea is mucoid and bloody. Occurs day and night. Patient complains of malaise, lethargy and anorexia. She has lost 8 kg in the past 2 months.

- No past surgical history
  No significant medical history

# Clinical Course

- Admitted to hospital
- Anemic with Hemoglobin of 6.2
- Albumin 1.8
- Flex Sig: Severe Inflammation with Ulcers and bleeding
- Treatments:
  - IV Antibiotics
  - IV Steroids x 4 days:
    - Decreased to 10 bowel movements still bloody
  - C.Diff/CMV/Stool cultures negative
  - Infliximab infusion
    - Slight response, then recurrence
  - Surgery (3 stage) vs Cyclosporine
  - Undergoes urgent colectomy with temporary divert



# Case 2: Severe Ulcerative colitis


Inflammatory Bowel Diseases Center

# Presentation

## Patient Information

- 44 year old Male
- Left sided UC diagnosed 6 years ago
- Symptoms worse over 6 months with acute worsening 3 weeks

## Treatment history

- Oral Colazal 2.25 g bid
- 75 mg 6-MP
- 5 days of Prednisone 20 mg

## Lab Tests

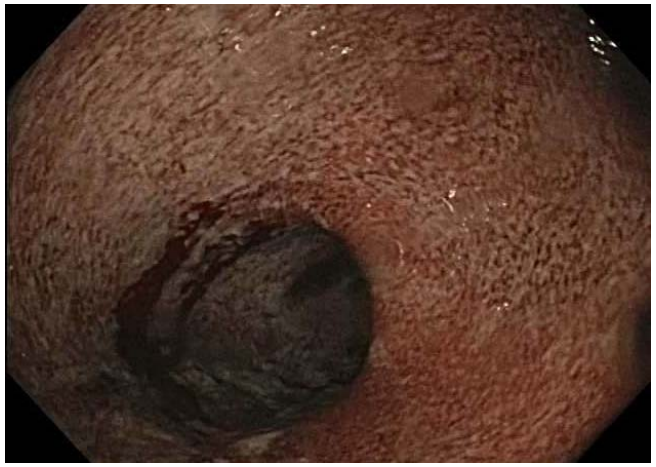
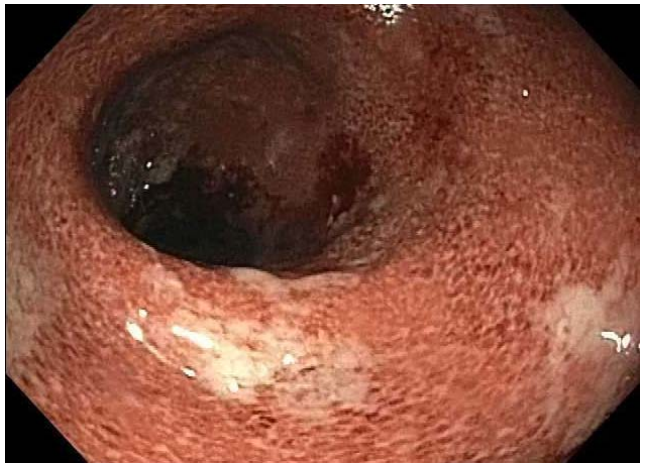
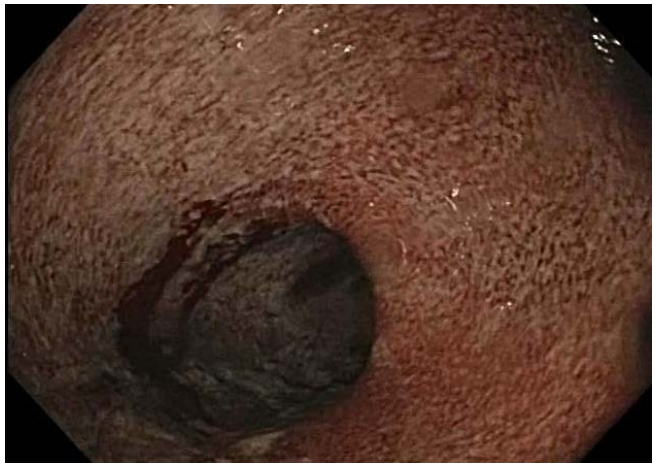
- CRP 63.8 mg/L
- Negative C.Difficile

## Clinical Assessment:

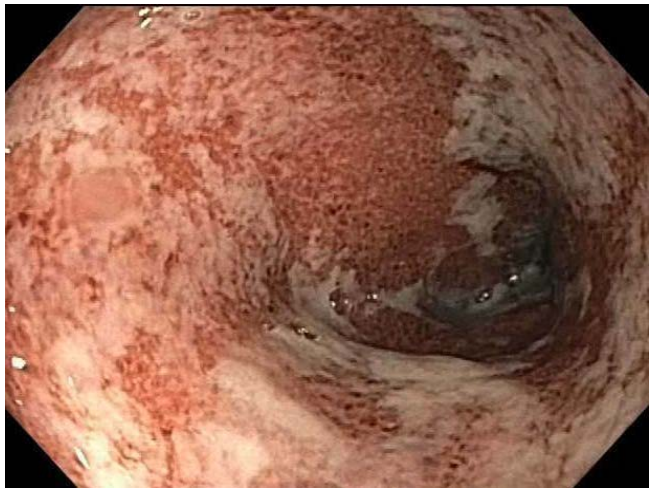
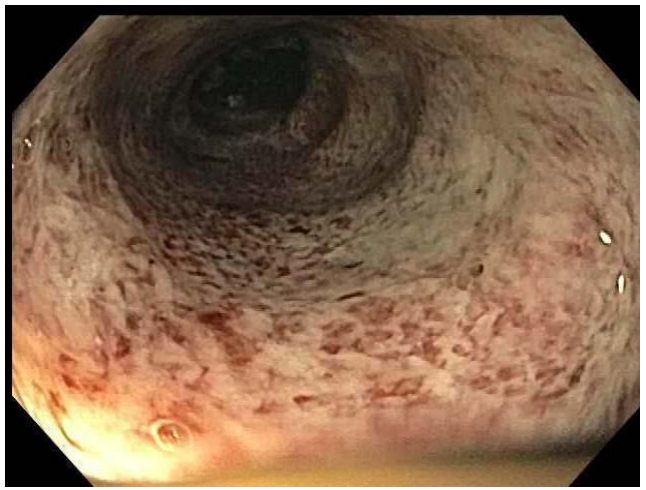
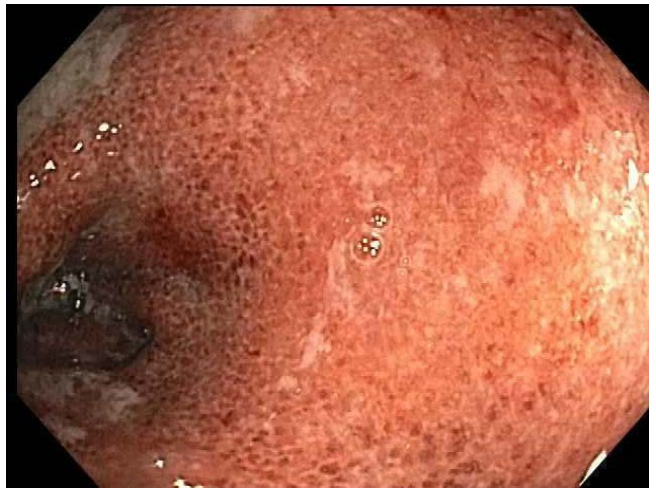
- Pulse 96/min
- 12- 15 BMs per day.
- 100% blood in the stools.

# Flexible sigmoidoscopy

## Rectum

## Sigmoid colon

# Presentation

## Patient Information

- 44 year old Male
- Left sided UC diagnosed 6 years ago
- Symptoms worse over 6 months with acute worsening 3 weeks

## Treatment history

- Oral Colazal 2.25 g bid
- 75 mg 6-MP
- 5 days of Prednisone 20 mg

## Lab Tests

- CRP 63.8 mg/L
- Albumin 3.1
- Negative C.Difficile

## Clinical Assessment: Mayo Score

- Mayo clinical subscore 6
- Endoscopic subscore: 3
- Global Physician Assessment: Severe

# Treatment and follow-up

- Initially 60 mg IV solumedrol x 3 days with ~ 8 BMs a day, CRP 35.6 mg/L.
- Started inpatient Infliximab 10 mg/kg x 1 dose, CRP 12.2 mg/L.
- Continued 40 mg prednisone and 75 mg 6-MP.
- Day 16: After 2nd Infliximab at 5 mg/kg, 1st formed stool.
- Day 42: 3rd Infliximab infusion at 5 mg/kg, daily 1 stool, CRP 0.5 MG/l, 20 MG prednisone and 75 mg 6-MP.

# Case 2: Moderate Ulcerative Colitis


Inflammatory Bowel Diseases Center

# Presentation

## Patient Information

- 25 year old Female
- Moderate Left sided UC diagnosed 4 years ago
- Concerned about repeated steroid use
- Currently symptoms worse after attempting to paper steroids

## Treatment history

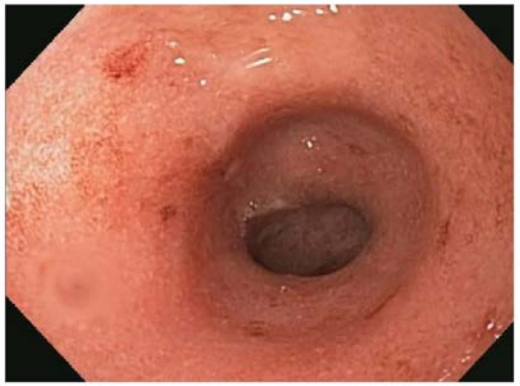
- Oral and Rectal mesalamine since diagnosis
- 3 courses of prednisone over last 18 months

## Lab Tests

- Fecal Calprotectin 400 ug/g
- CRP 13 mg/L
- Negative C.Difficile

## Clinical Assessment: Mayo Score 8

- 5 BMs per day
- Occasional Blood in Stool
- Global Physician Assessment: Moderate
- Colonoscopy: Erosions, Erythema, Friability, Abscent Vacular Pattern



# Management Options

- Mesalamines
- Steroids
  - Topical
  - Oral/Systemic
- Biologics
  - TNFα
  - Integrin
- Surgery

# Learning Objectives

Part I

1. What are the Inflammatory Bowel Diseases (IBD)?
2. What causes IBD?
3. How does IBD affect other organ systems?

Part II

1. What are the current medical therapies for IBD?
2. What is the role for complementary and nutritional therapies in IBD?

Part III

1. Patient Stories and Questions

MODULE IV
GASTROENTEROLOGY:
THE CROSSROADS OF HEALTH

# Inflammatory Bowel Disease

**Matthew Ciorba, MD**
**Associate Professor of Medicine**
**Director, IBD Center**
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