The Inflammatory Bowel Diseases: an Overview

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Conflicts

- Medical Advisory Board
  - Johnson and Johnson
- Educational Grants
  - J&J, Takeda, Pfizer, Celgene

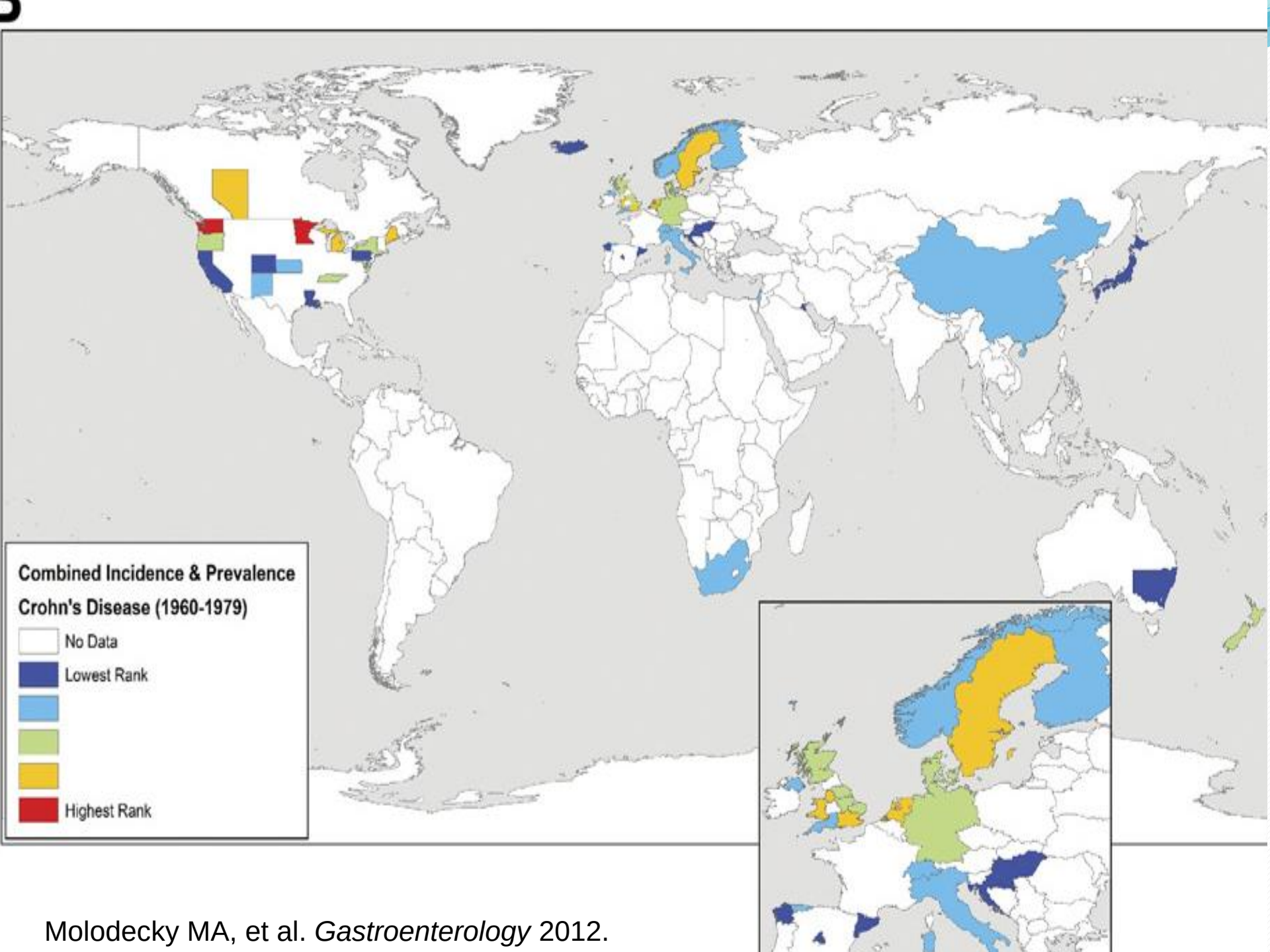
Outline

- Epidemiology
- Pathogenesis
- Diagnosis
- Staging
- Management
- Cases

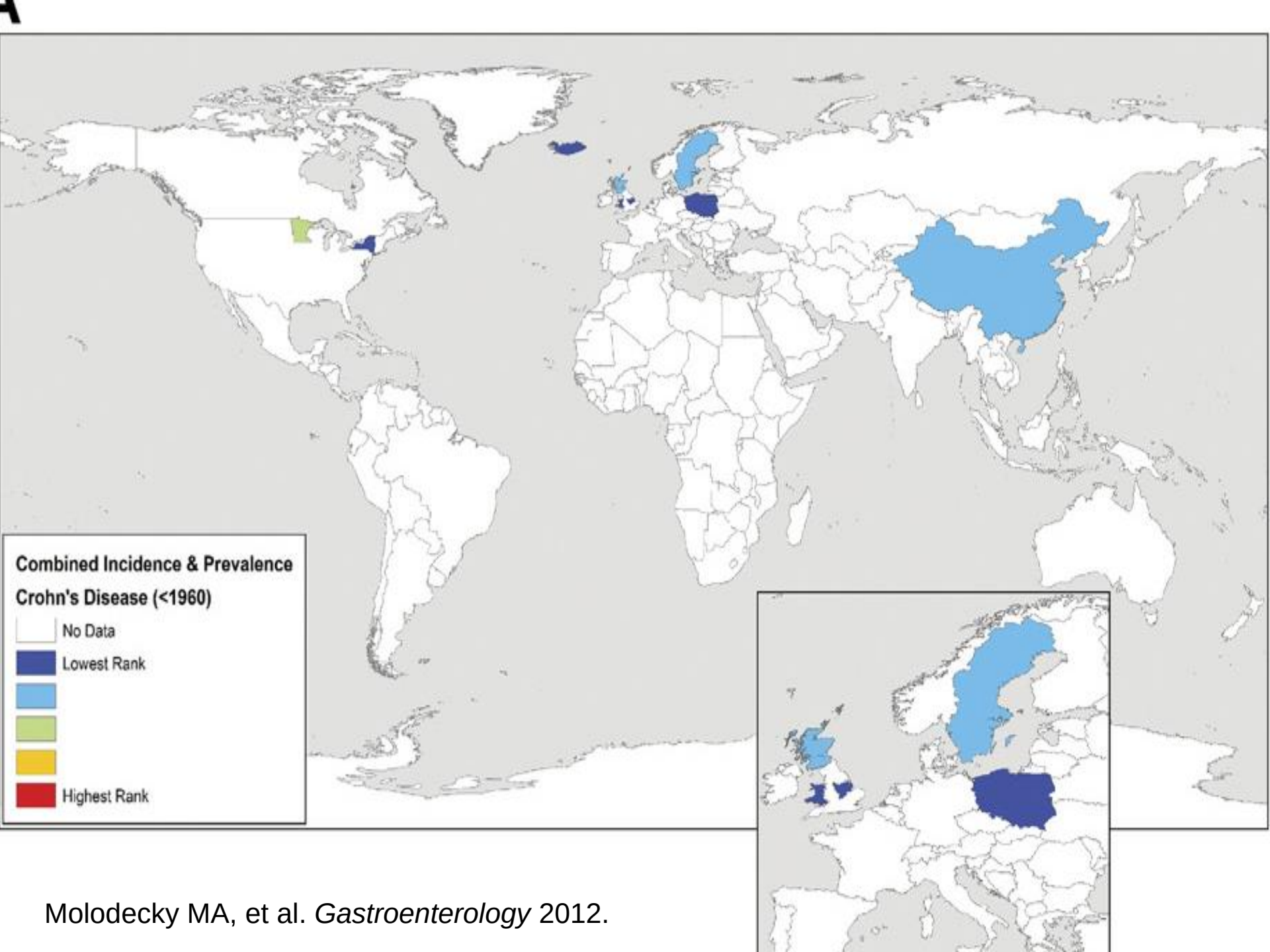
Epidemiology of IBD in North America

- Approximately 1.6 million people in US with IBD
- Most commonly presents in 20s but can present at any age
- Slight male predominance in UC
- Slight female predominance in CD

Loftus EV. *Gastroenterology* 2004.



Molodecky MA, et al. *Gastroenterology* 2012.



Molodecky MA, et al. *Gastroenterology* 2012.

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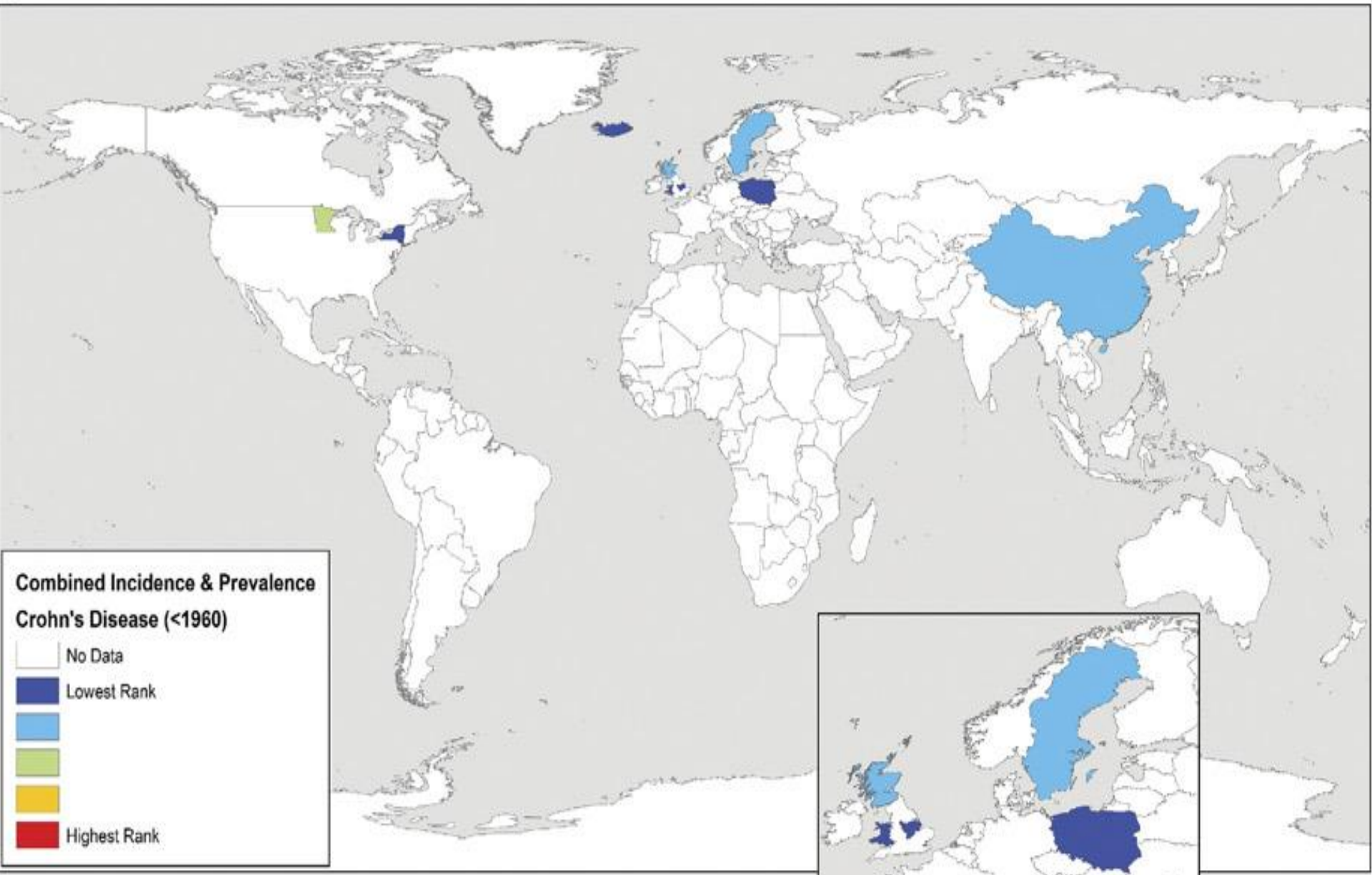
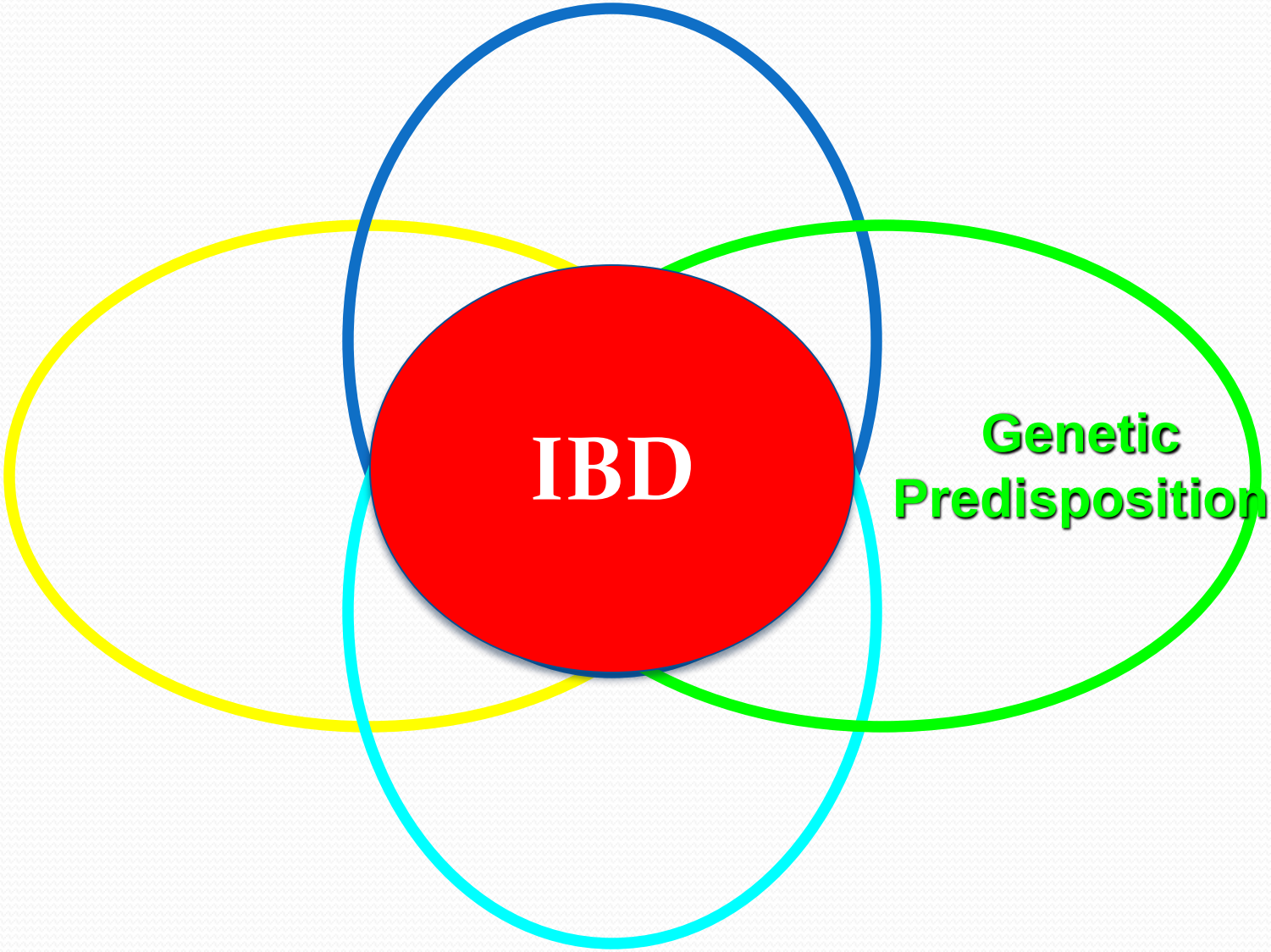


Molodecky MA, et al. *Gastroenterology* 2012.

IBD Pathogenesis



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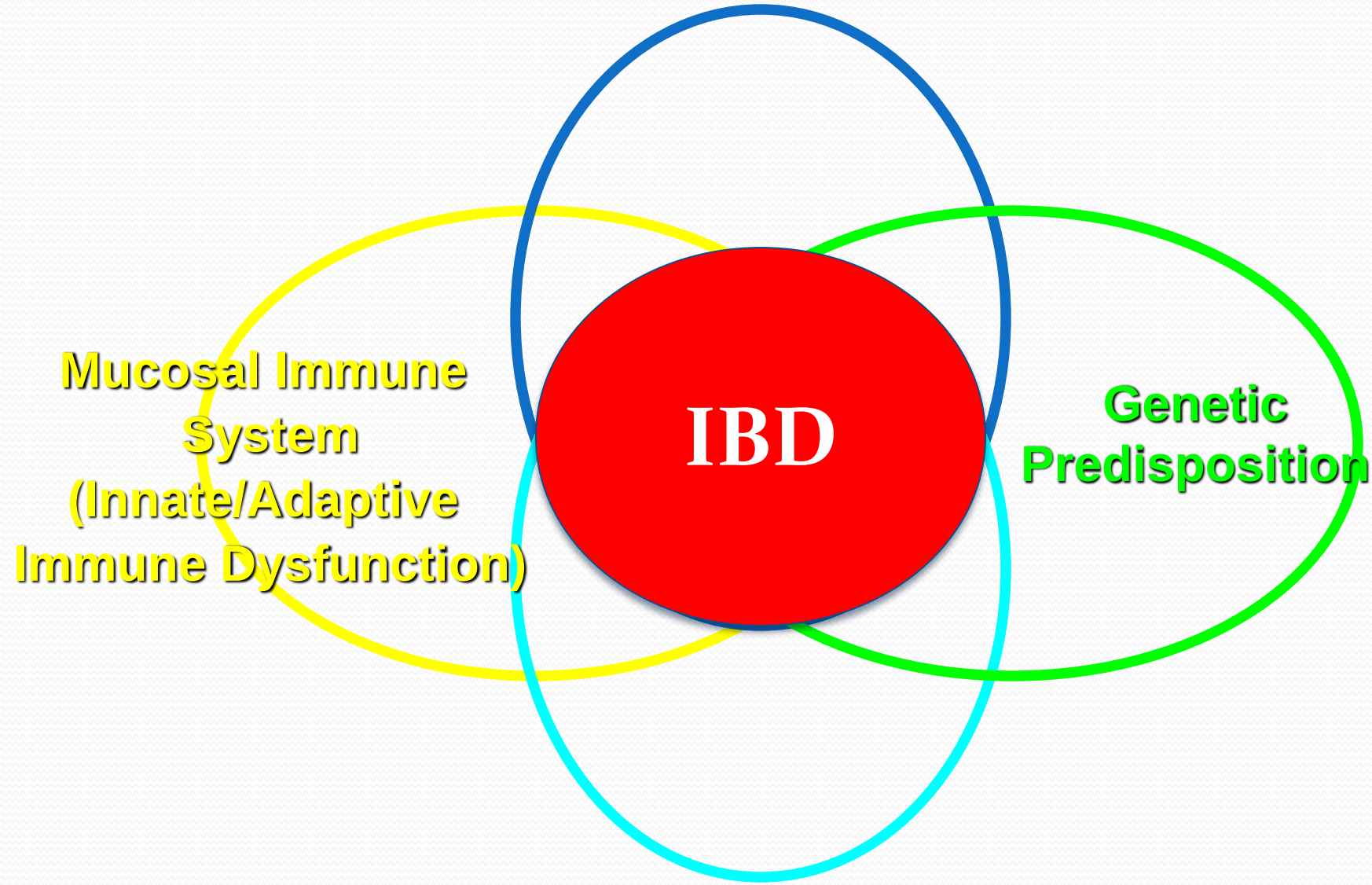

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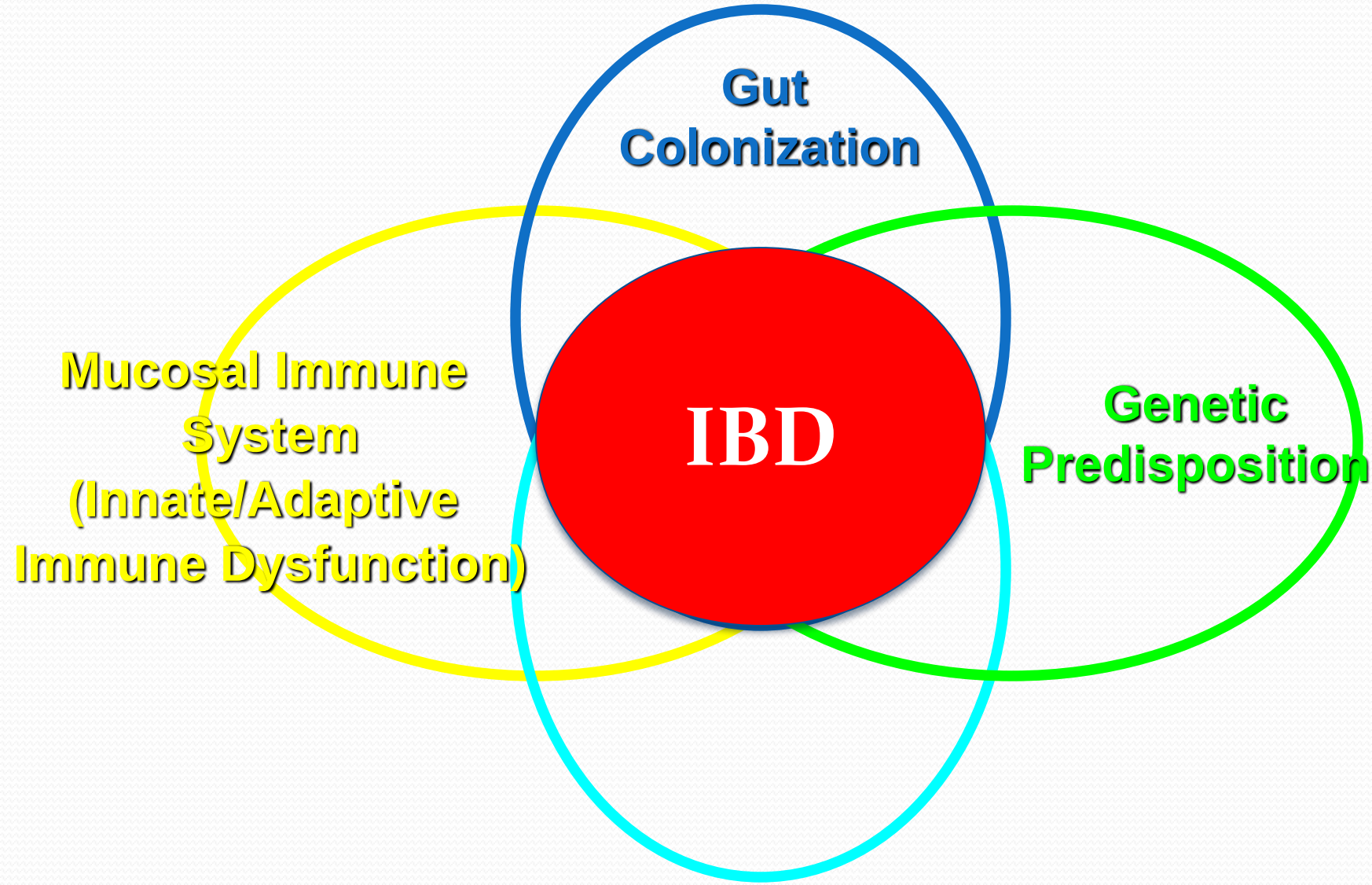

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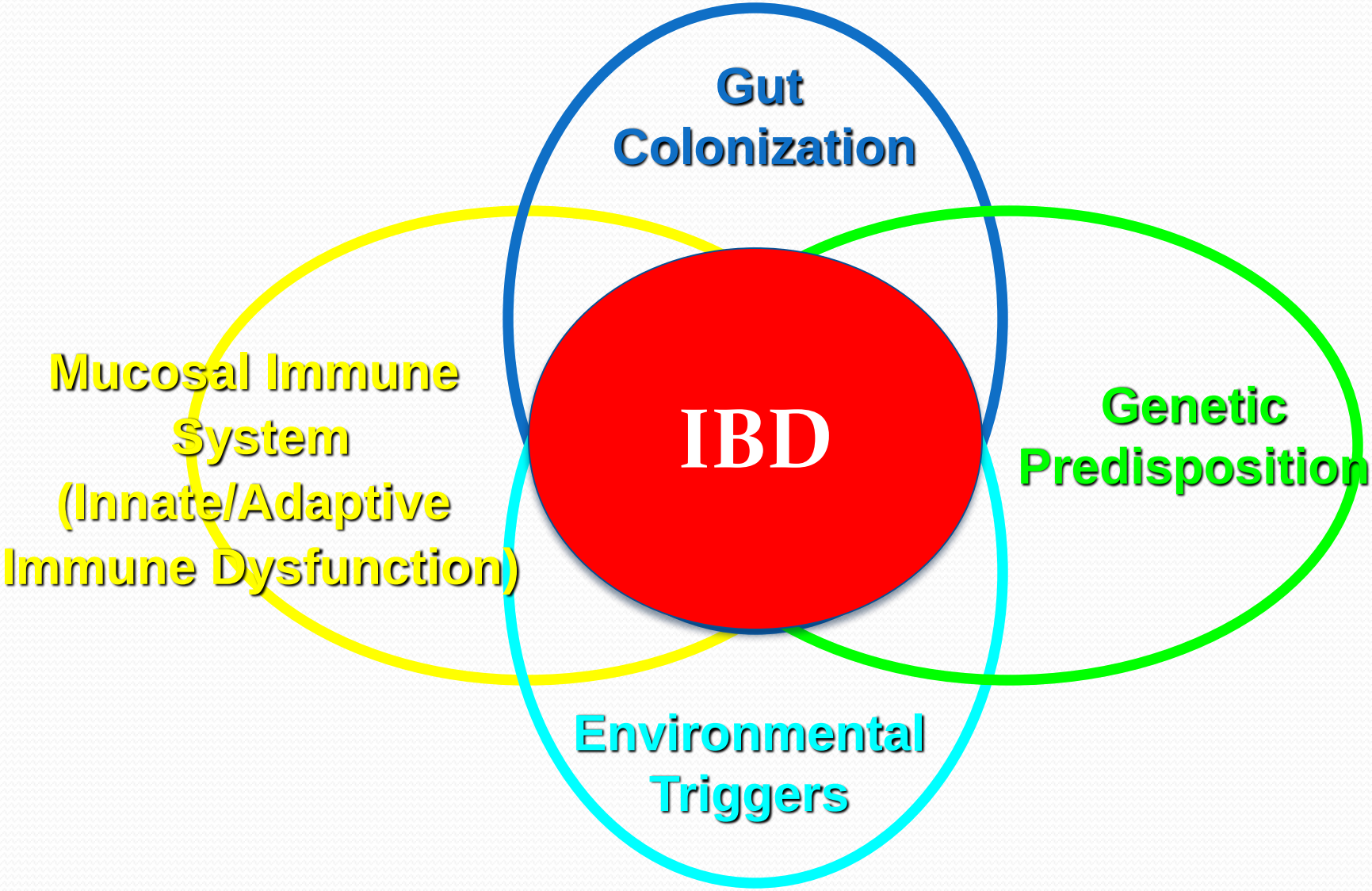
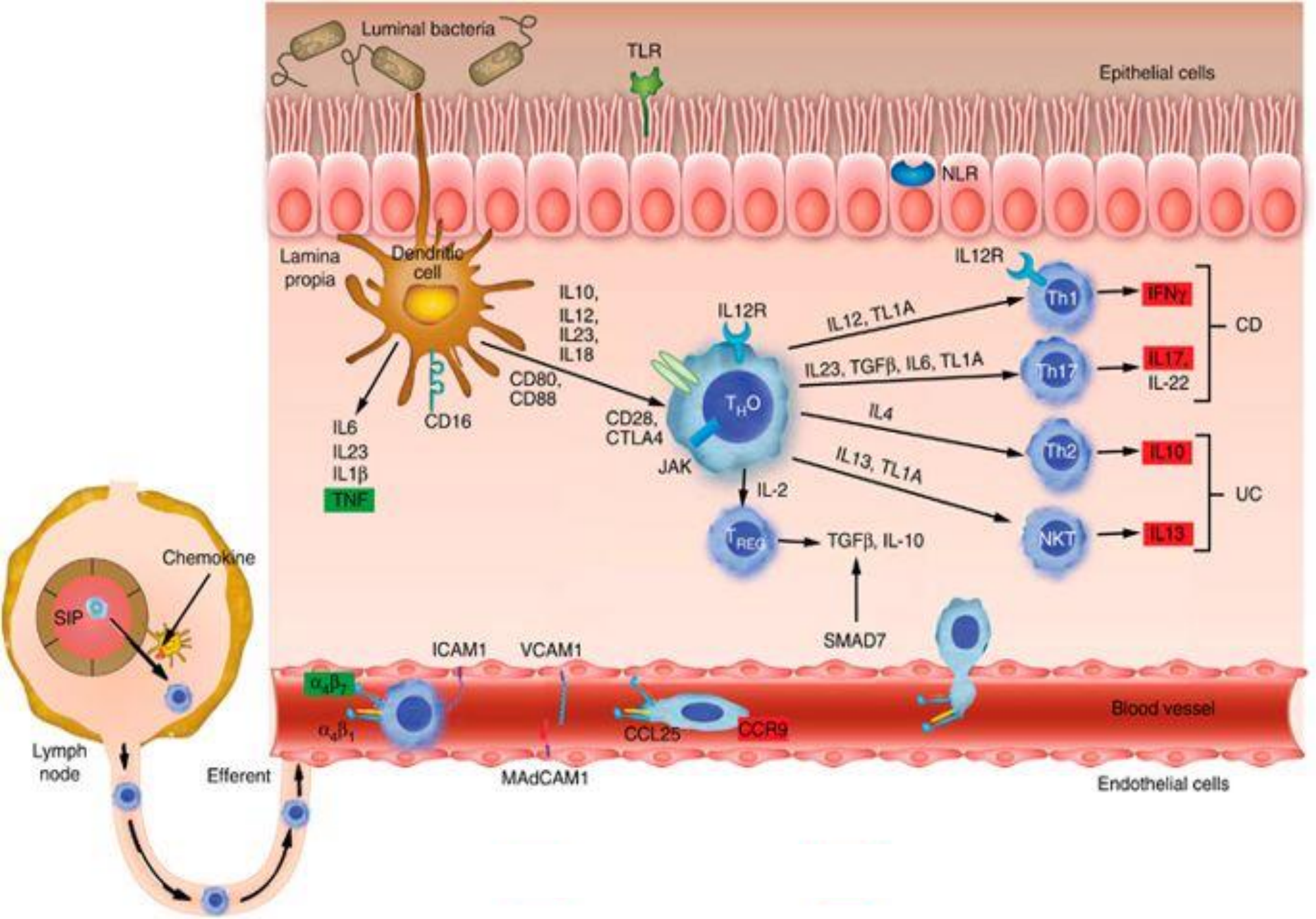




Billsborough J, et al. *Am J Gastroenterol* 2016.

Normal Intestine vs. Intestine with IBD

Normal bowel:
controlled inflammation

Environmental triggers (medications infections, smoking, diet?)

IBD: Genetic Susceptibility
failure to down-regulate inflammation

Normally: inflammation is down-regulated

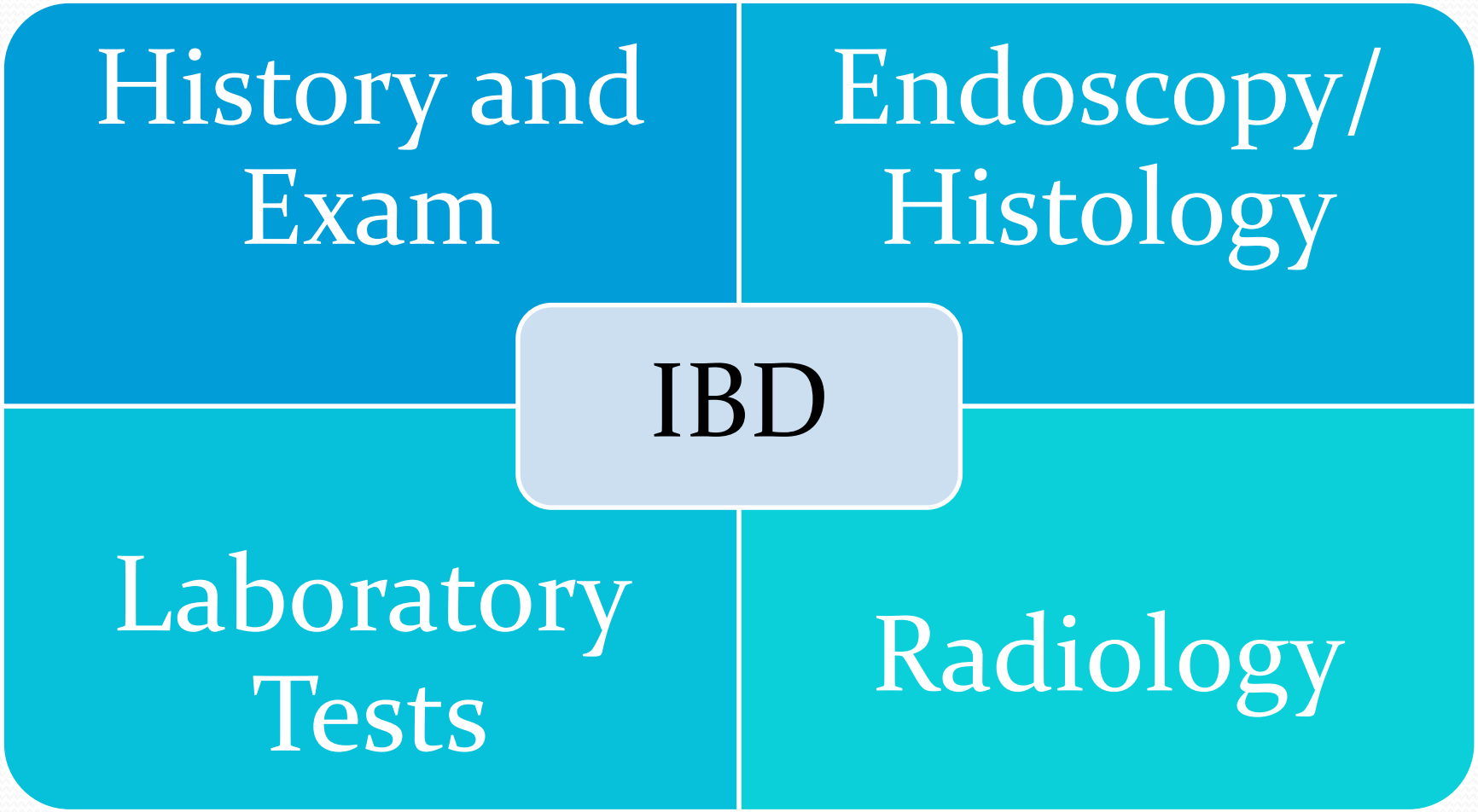
Inflamed bowel

Chronic uncontrolled inflammation = IBD

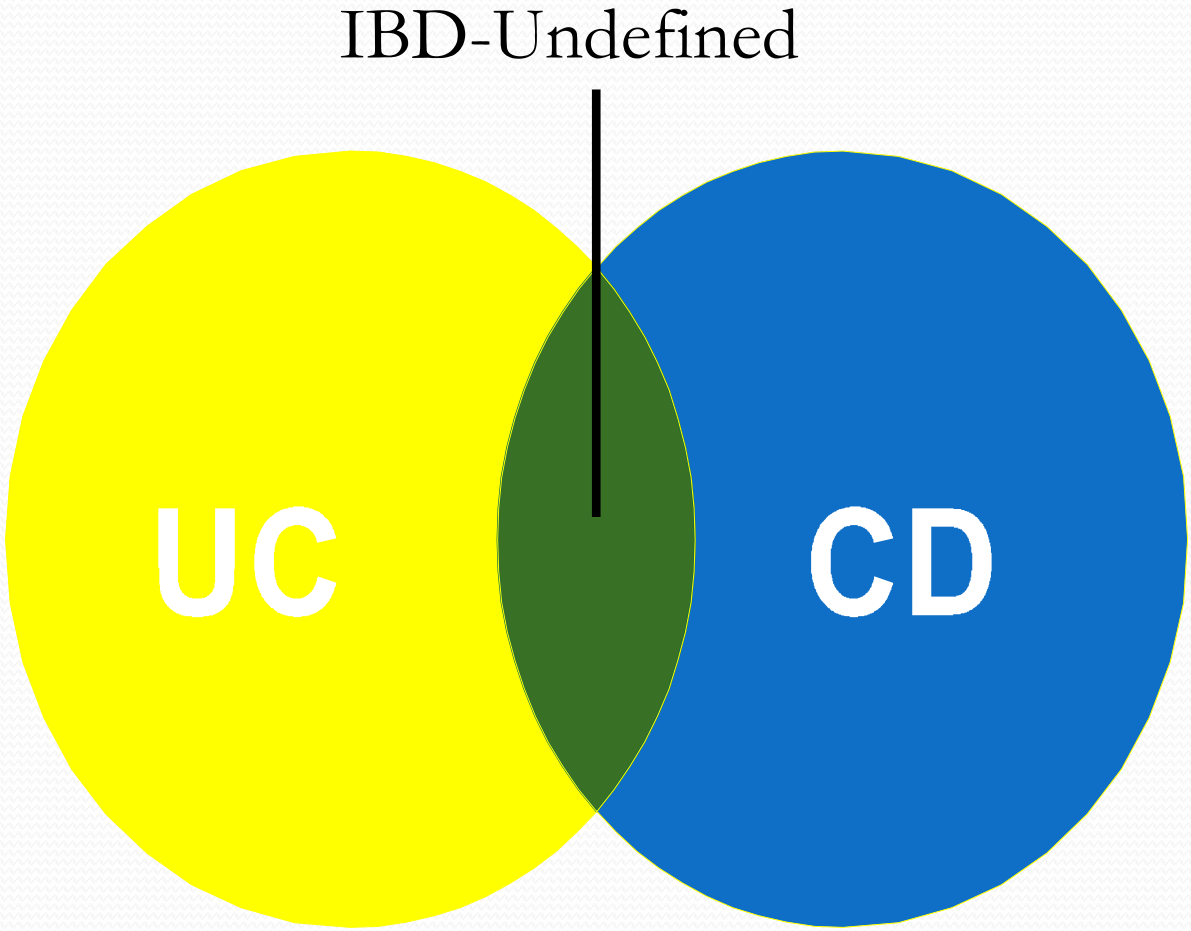
Normal bowel:
controlled inflammation

Farrell JJ, Sands BE. Etiology and pathogenesis of inflammatory bowel disease. In Cohen RD, ed. *Inflammatory Bowel Disease: Diagnosis and Therapeutics*. 2003, Humana Press Inc, Totowa, NJ.

Diagnosis


History and Exam
Endoscopy/ Histology
IBD
Laboratory Tests
Radiology

The Spectrum of IBD



Clinical Symptoms

Crohn's disease

- Nonbloody diarrhea
- Abdominal pain
- Fatigue
- Fever
- Weight loss
- Nausea/Vomiting

- Stunted growth (children)

Ulcerative colitis

- Bloody diarrhea
- Abdominal pain
- Urgency/Tenesmus
- Fever
- Loss of appetite
- Nausea/Vomiting

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Ulcerative colitis

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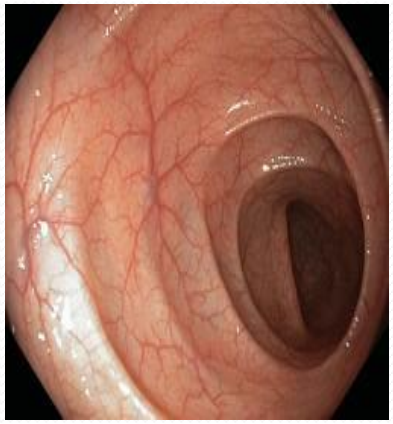
Endoscopic Evaluation of Ulcerative Colitis

Normal



- Tan mucosa
- Normal vascular pattern

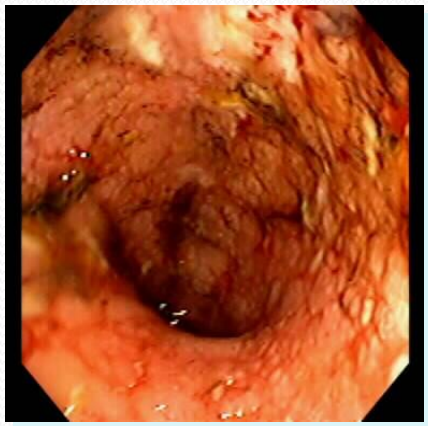
Mild

- Granular mucosa
- Edematous
- Loss of normal vascular pattern

Moderate

- Coarsely granular
- Small ulcerations
- Friable

Severe



- Frank ulcerations
- Spontaneous hemorrhage

Images courtesy of R. Cohen MD.
Modified from Sutherland LR, et al. *Gastroenterology*. 1987;92:1894.

Normal Colon

- Tan mucosa
- Normal vascular pattern

Mild Colitis

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- Edematous
- Loss of normal vascular pattern

Moderate Colitis

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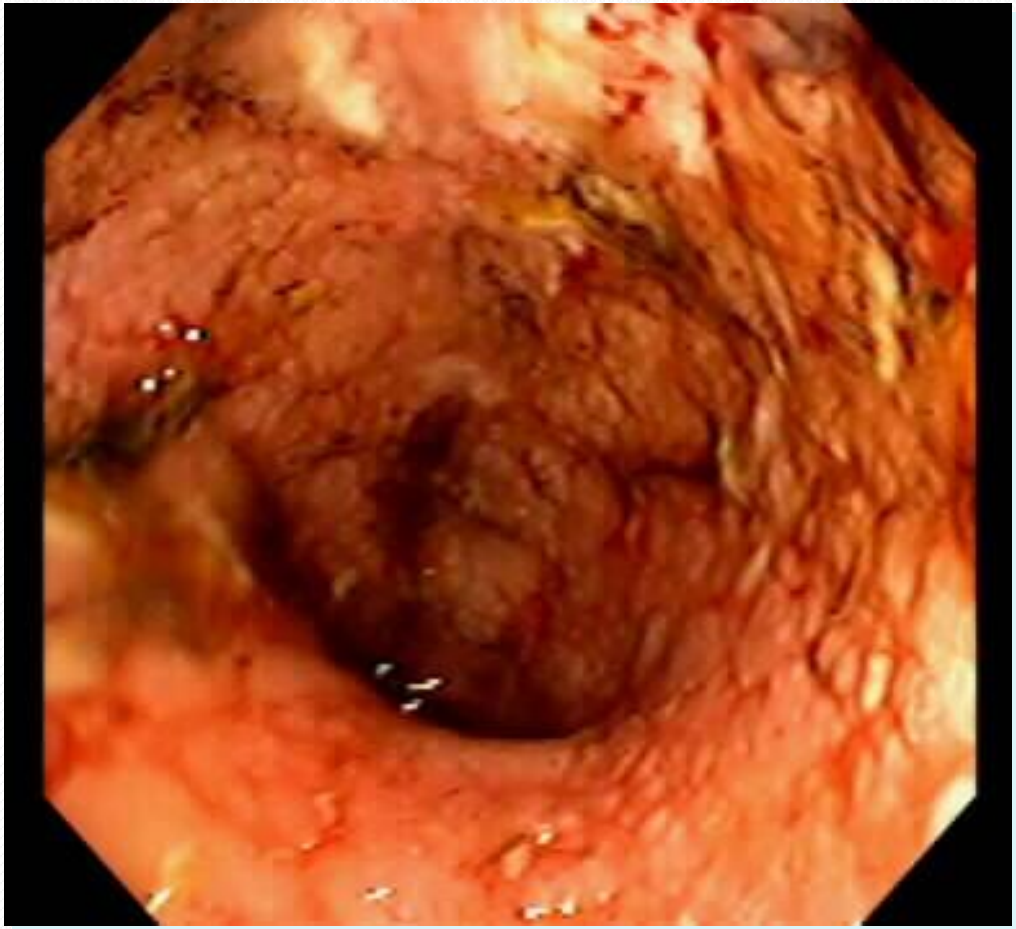
- Small ulcerations
- Friable

Severe Colitis



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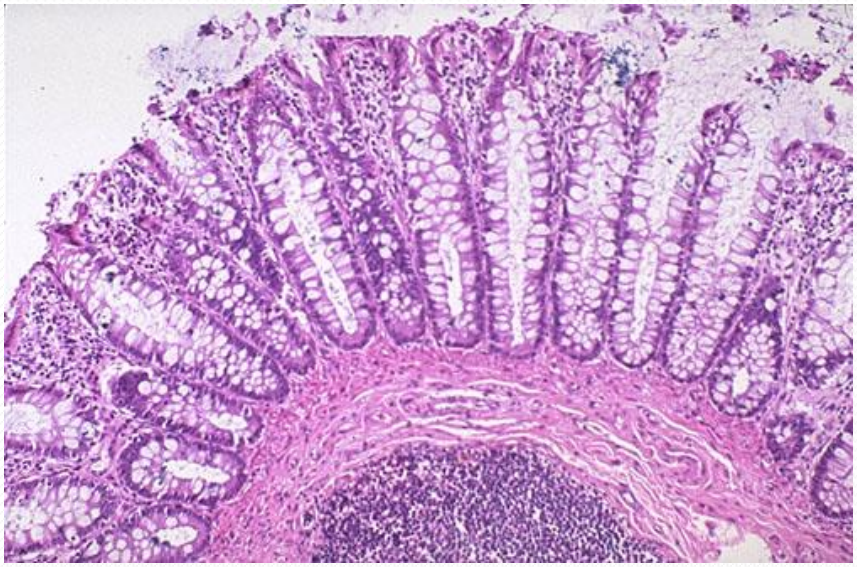
Histology of Patient Without Ulcerative Colitis

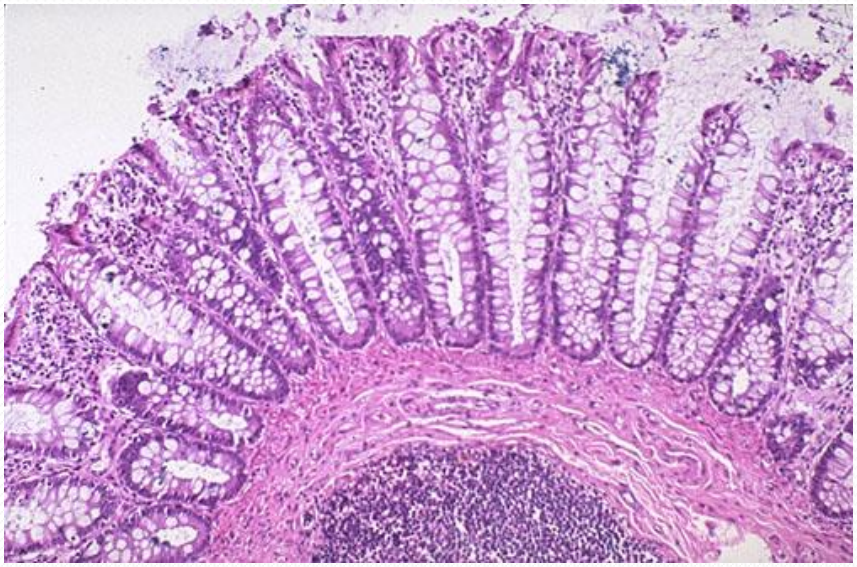


Non-IBD

- Aligned crypts
- No active inflammation

Images courtesy of John Hart, MD.

Histology of Ulcerative Colitis



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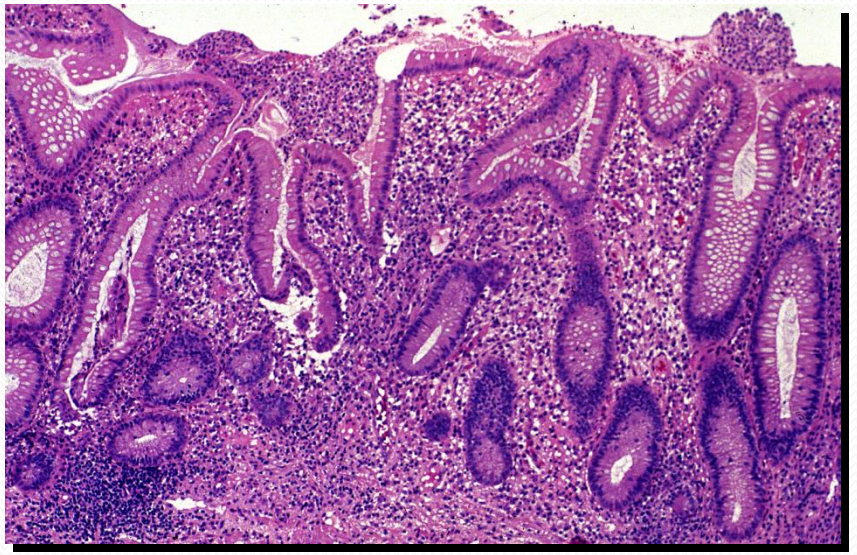
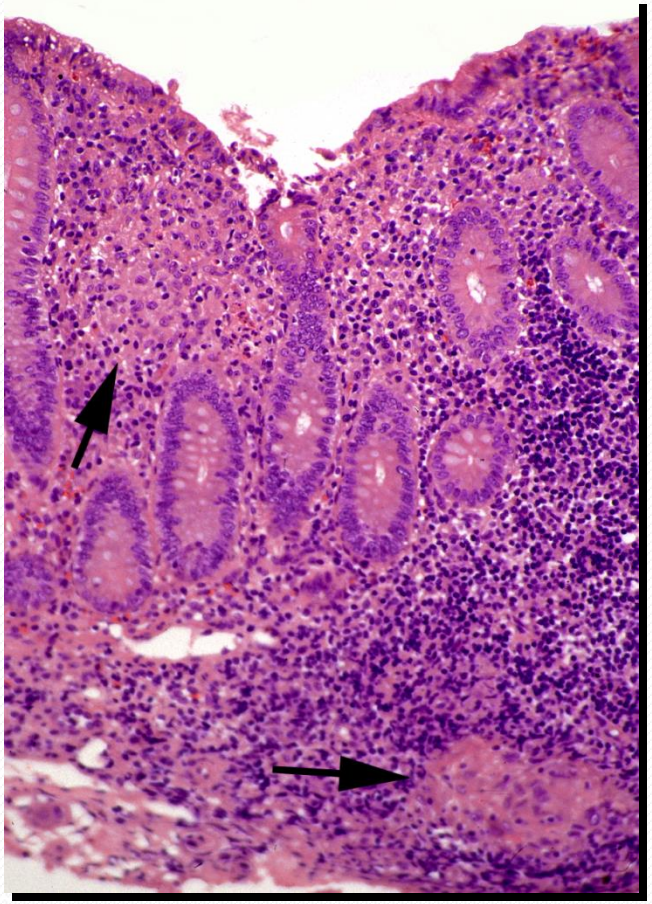


Active

- Crypt distortion
- Inflammation infiltrates
- Crypt abscesses

Images courtesy of John Hart, MD.

Histology of Crohn's Colitis



Crohn's Colitis

(arrows indicate granulomas)

Images courtesy of John Hart, MD.

Case #1

- In the clinic, 67 M with BPH, gout, DJD, and ulcerative colitis in clinical remission for several years presents with abdominal pain and bloody diarrhea over three days
- Vs stable, PE with with mild RLQ pain with no guarding/rebound, otherwise nl
- Meds: finasteride, acetaminophen, sulfasalazine, folate, MVN
- CBC 12.1/12/350, BMP nl, CRP 7

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- CBC **12.1**/**12**/350, BMP nl, CRP **7**

What is the immediate next best step?

- A) MRI of the abd/pelvis
- B) Follow up with GI
- C) Start prednisone
- D) Send stool studies
- E) Transfuse 1 Unit PRBCs

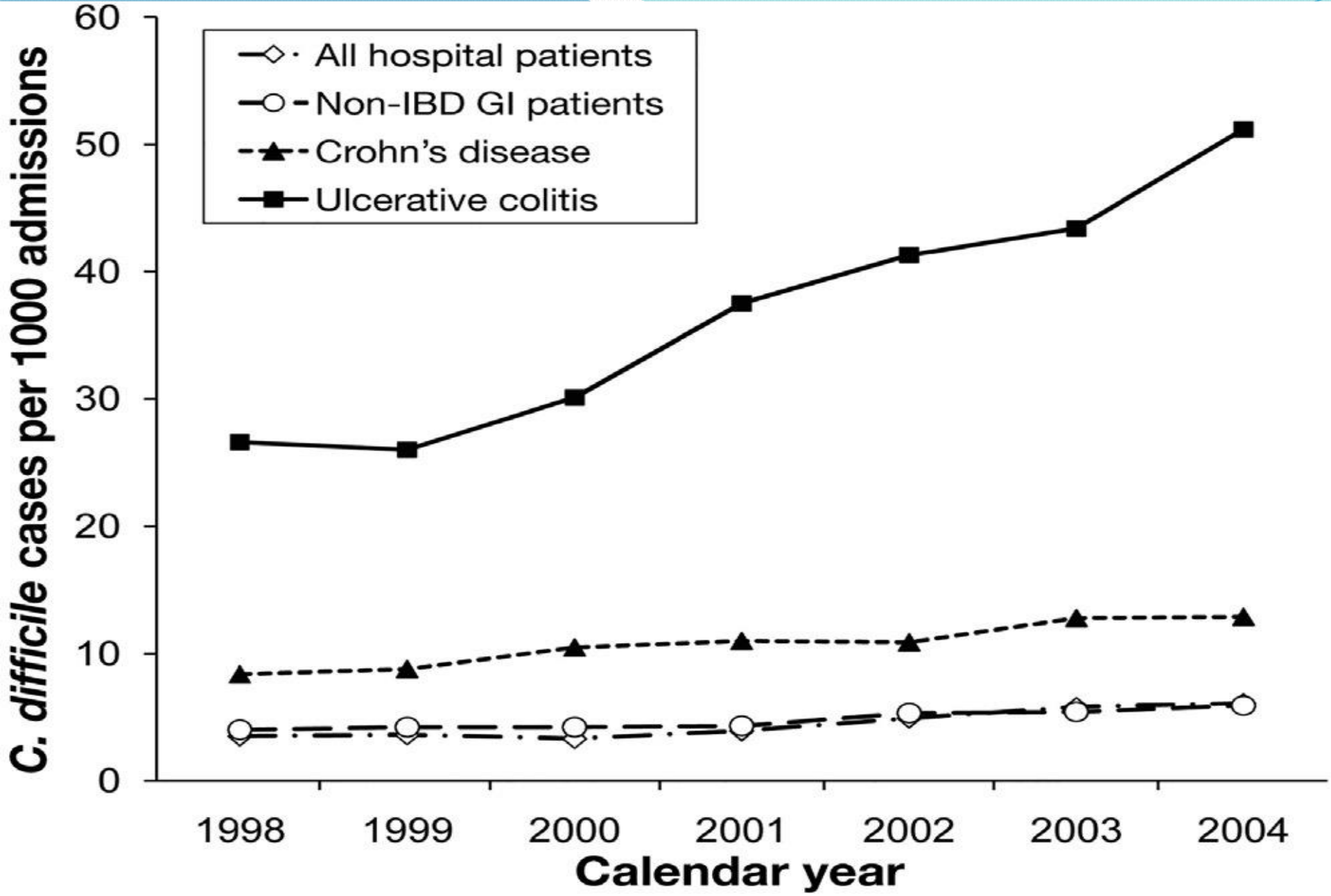
Differential Diagnosis of IBD

- Infectious diarrhea
- Medication-induced injury
- Ischemic colitis
- Segmental colitis associated with diverticula (SCAD)
- Radiation injury
- Microscopic colitis
- Celiac disease
- Irritable bowel syndrome

Intestinal Infections Complicate IBD

- 10-13% of “flares” in IBD are secondary to stool infections
  - Stool infections are much more common in IBD than in non-IBD population

Antoneilli E, et al. *J Crohns Colitis* 2012.



Khanna S, et al. *Clin Gastroentero Hepat* 2017.

Intestinal Infections Complicate IBD

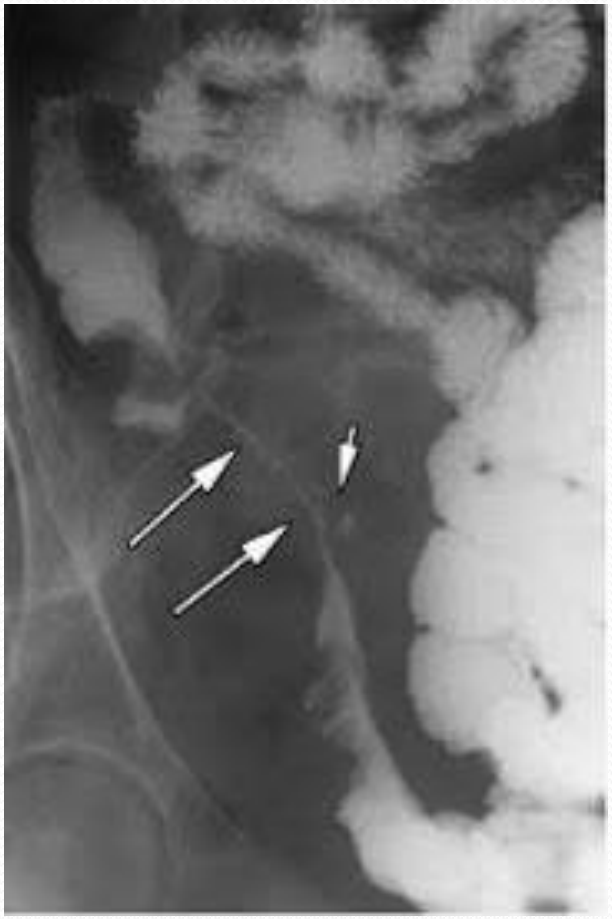
- The most common bacterial infections are:
  - 1) C. difficile
  - 2) C. jejuni
- All patients with IBD flare-like symptoms should undergo stool testing
- All IBD patients with C. diff should be treated with vancomycin

Antoneilli E, et al. *J Crohns Colitis* 2012.

Radiology: early years

Barium Enema

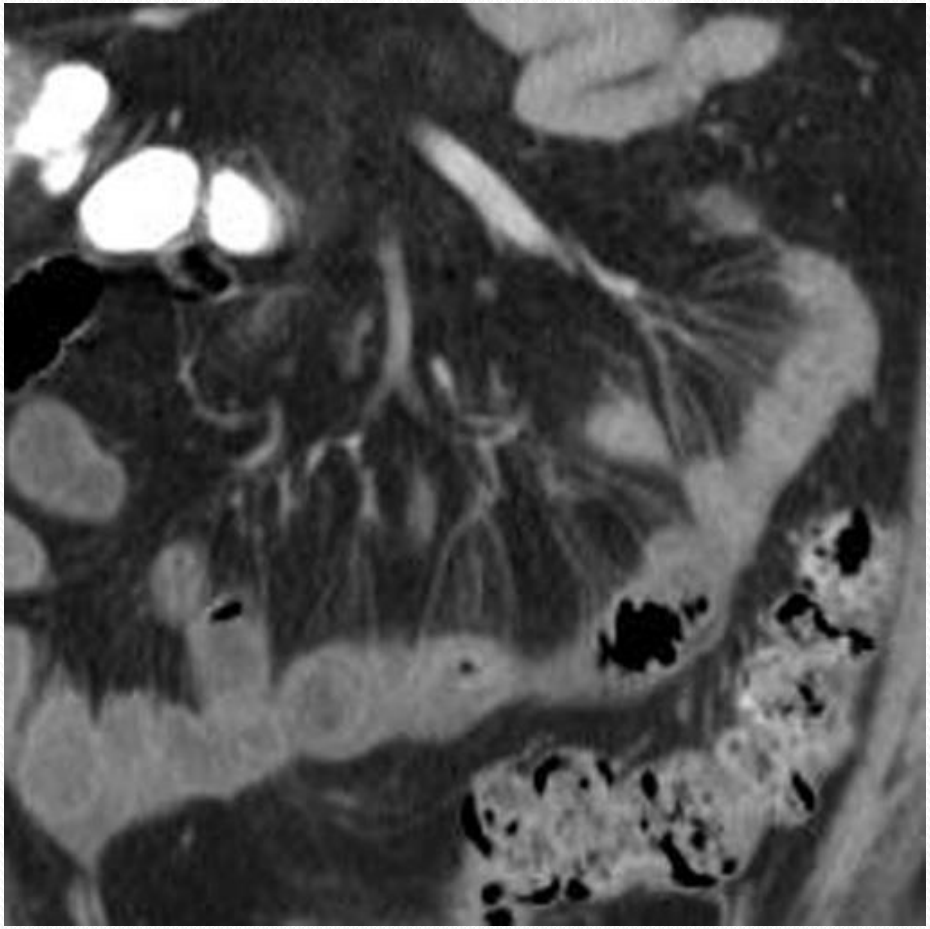
Small Bowel Follow Through



"string sign"

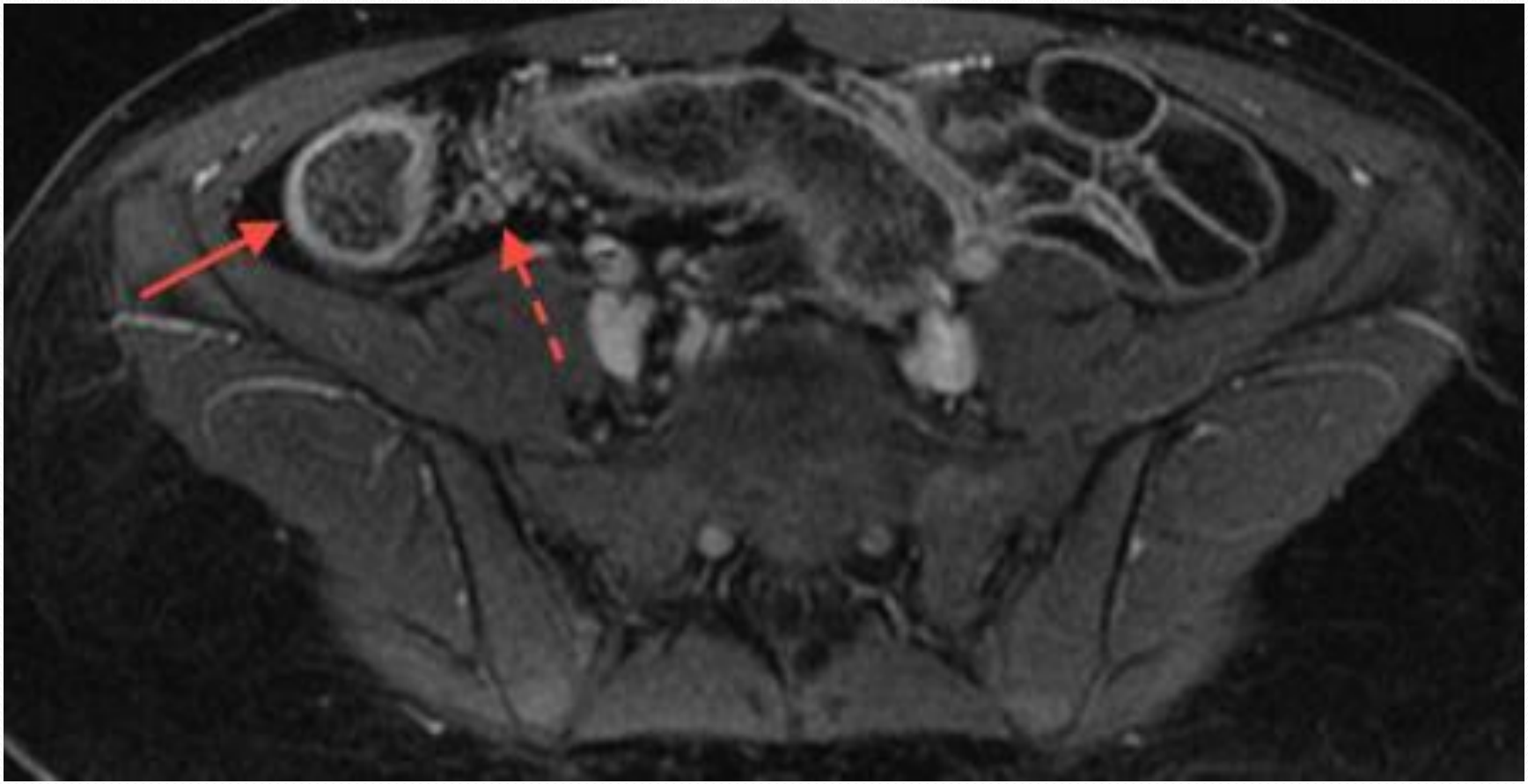
http://emedicine.medscape.com/article/367666-overview#a2

CAT Scan: Comb sign



http://radiopaedia.org/articles/comb-sign

MRI: Active colonic inflammation



https://bodymri.stanford.edu/Gastroenterology

Case #2

- In clinic, a 22 y/o M with migraines, gastroparesis, and long-standing Crohn's disease presents with diffuse abdominal pain and nausea.
- A colonoscopy the previous week showed no active disease. Has had a comprehensive evaluation of his symptoms with no cause found.
- Has had three other presentations in last 2 months with similar symptoms. Each time, a CT A/P has shown no causes.
- Vs: BP 128/72, HR 90; PE: moderate diffuse abd px with no rebound/guarding, BSs present, exam otherwise nl
- CBC 8/16/258, BMP nl, CRP nl
- Meds: Infliximab, Percocet

What is the next best step?

- A) Recommend a MRI instead
- B) Do a CT scan without contrast
- C) Start metronidazole and ciprofloxacin
- D) Consult GI
- E) Start prednisone

Reasons to Perform Imaging in IBD

- Crohn's disease
  - Evaluate active small bowel inflammation
  - Stricture
  - Abscess
  - Perforation
- Ulcerative colitis
  - Toxic megacolon
  - Perforation

RADIATION GUIDE

For this procedure:	Your effective radiation dose is:	Comparable to natural background radiation for:
MRI	None	None
Computed Tomography (CT) - Abdomen and Pelvis	10 mSv	3 years
Computed Tomography (CT) - Body	10 mSv	3 years
Radiography - Lower GI Tract	8 mSv	3 years
Radiography - Upper GI Tract	6 mSv	2 years
Radiography - Spine	1.5 mSv	6 months
Radiography - Extremity	0.001 mSv	Less than 1 day
Computed Tomography (CT) - Head	2 mSv	8 months
Computed Tomography (CT) - Spine	6 mSv	2 years
Myelography	4 mSv	16 months
Computed Tomography (CT) - Chest	7 mSv	2 years
Radiographic Chest	0.1 mSv	10 days
Bone Densitometry (DEXA)	0.001 mSv	Less than 1 day
Mammography	0.7 mSv	3 months

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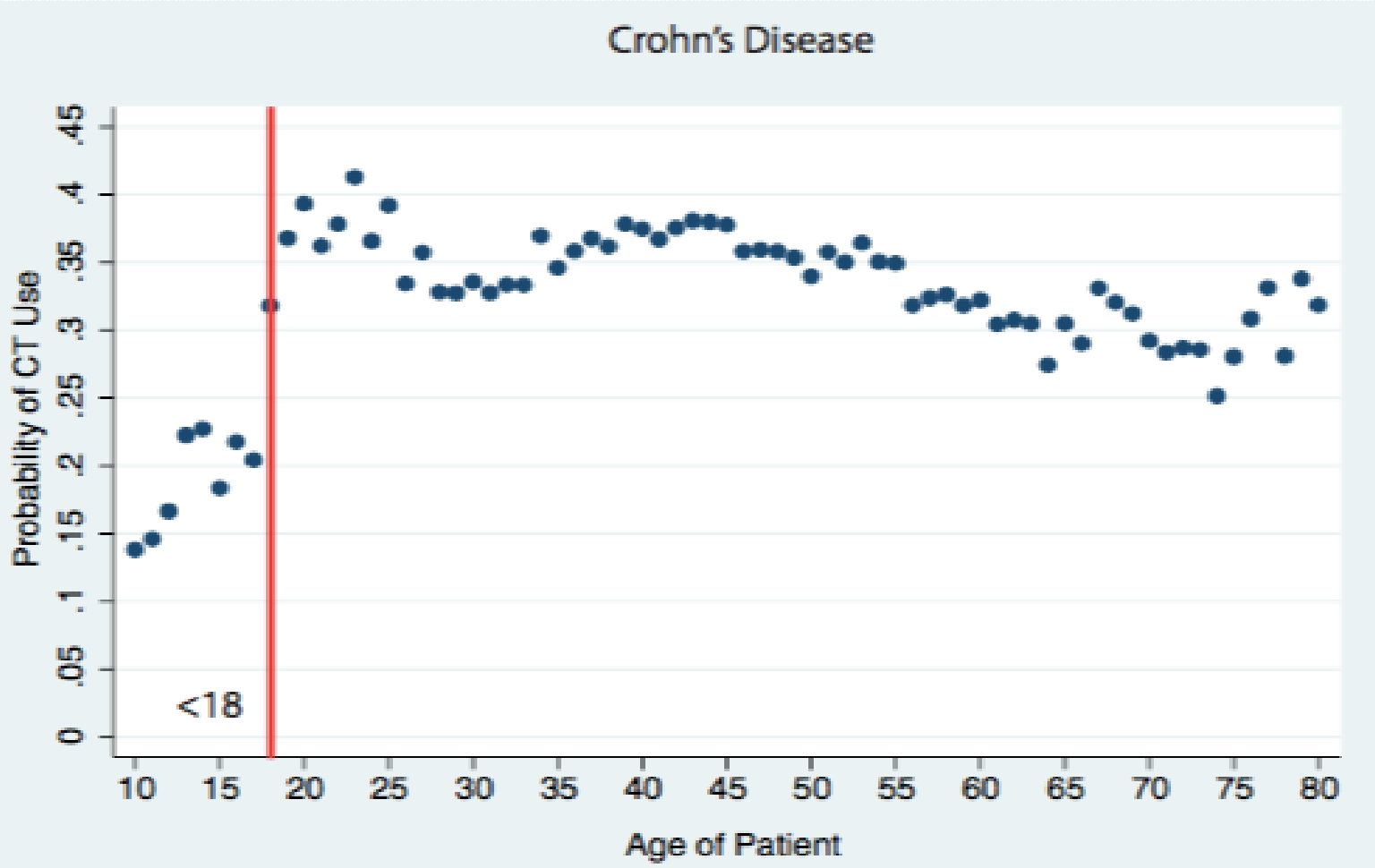
Making the Decision to Perform a CT Scan or X-Ray

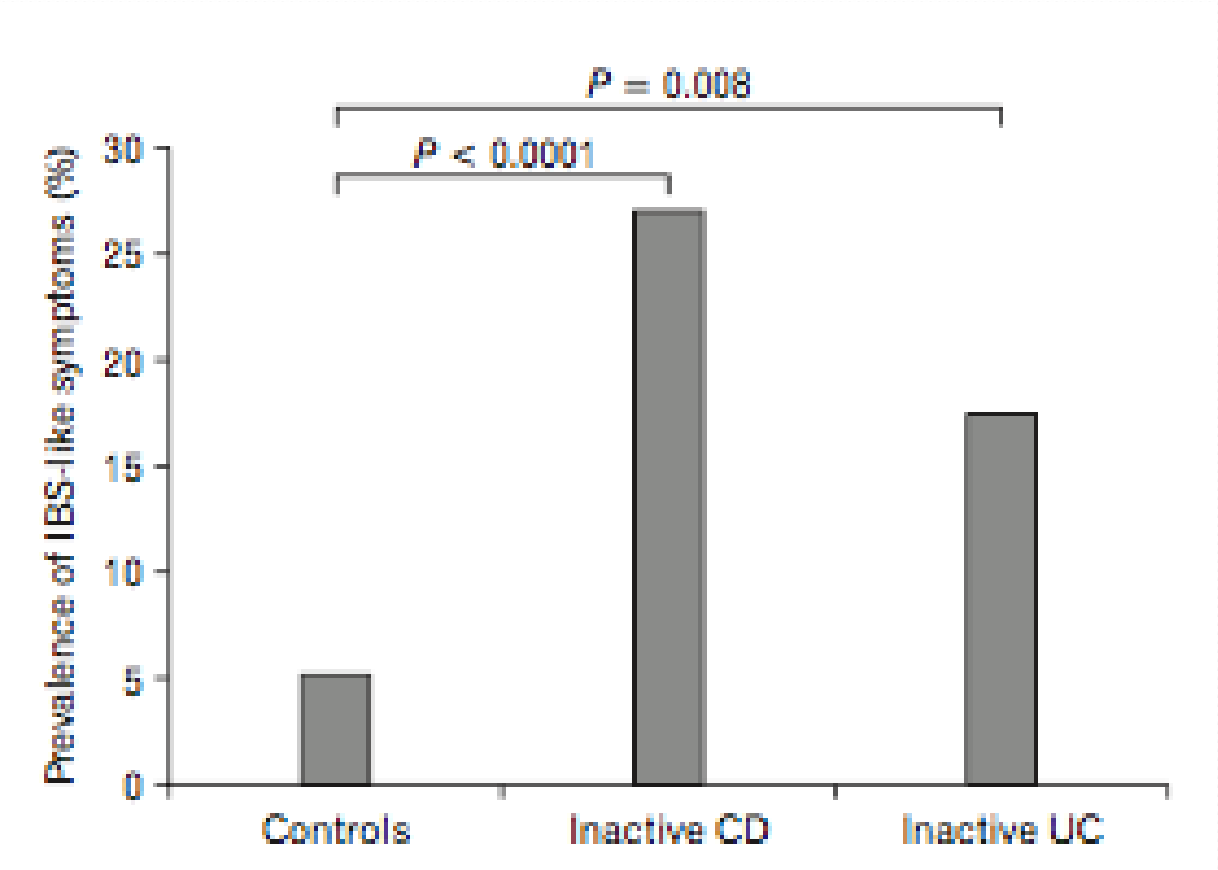
- Consider the risks and benefits of radiation exposure
- 50 mSv is association with increased risk of malignancy
  - 25% of IBD patients have undergone this degree of exposure
  - Most radiation exposure in IBD occurs in hospital

Govani SM, et al. *PLoS One* 2018.



Govani SM, et al. *PLoS One* 2018.

Prevalence of Irritable Bowel Syndrome (IBS) in Inflammatory Bowel Disease (IBD)



Tomita T, et al. *J Neurogastroenterol Motil* 2016.

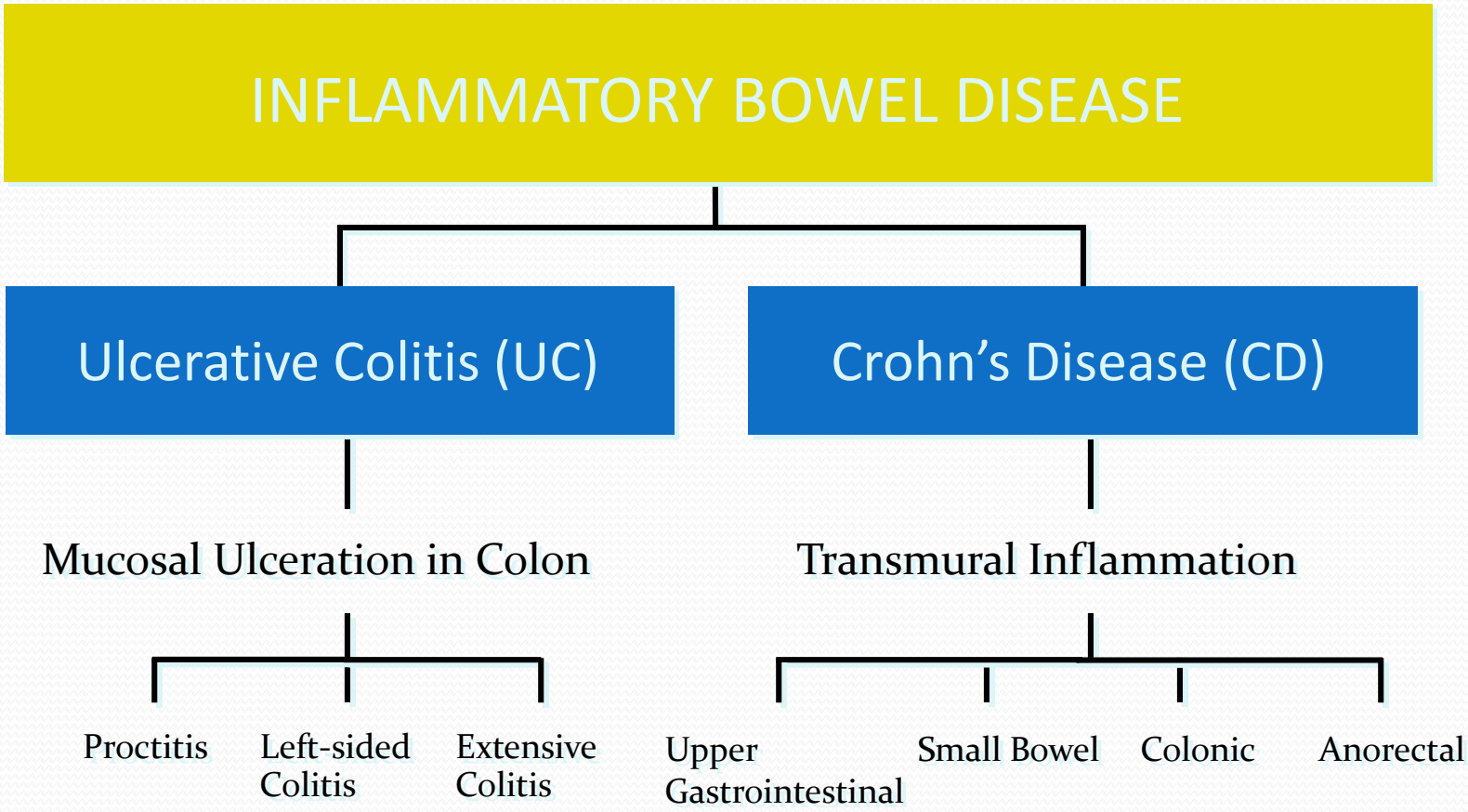
Staging of Disease after Diagnosis

- Extent and behavior
- Complications
- Extraintestinal manifestations

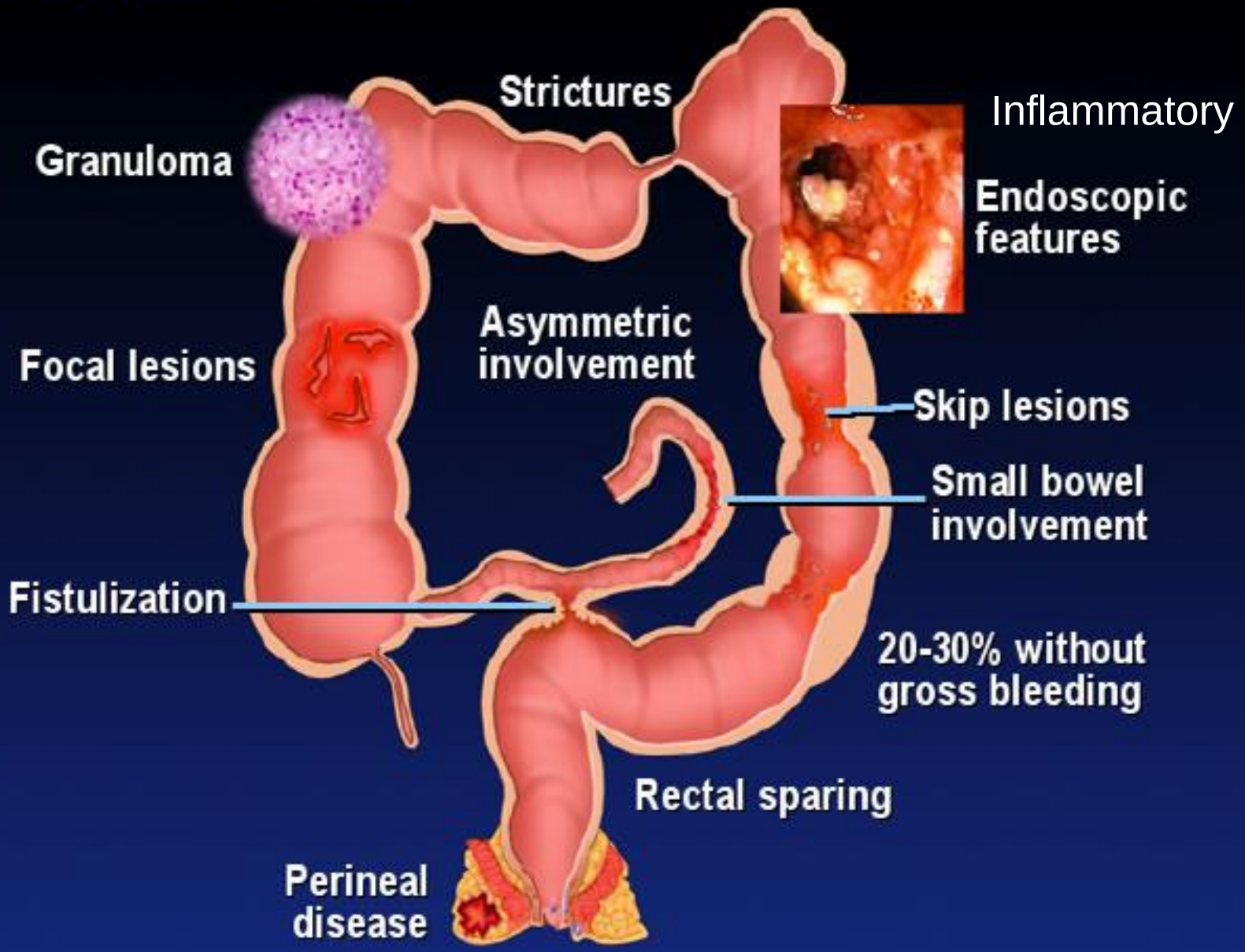
Staging of Disease after Diagnosis

- **Extent and behavior**
- Complications
- Extraintestinal manifestations

Anatomic Distribution of UC and CD



CD - Distinguishing Features



Courtesy of www.mcgillibd.ca

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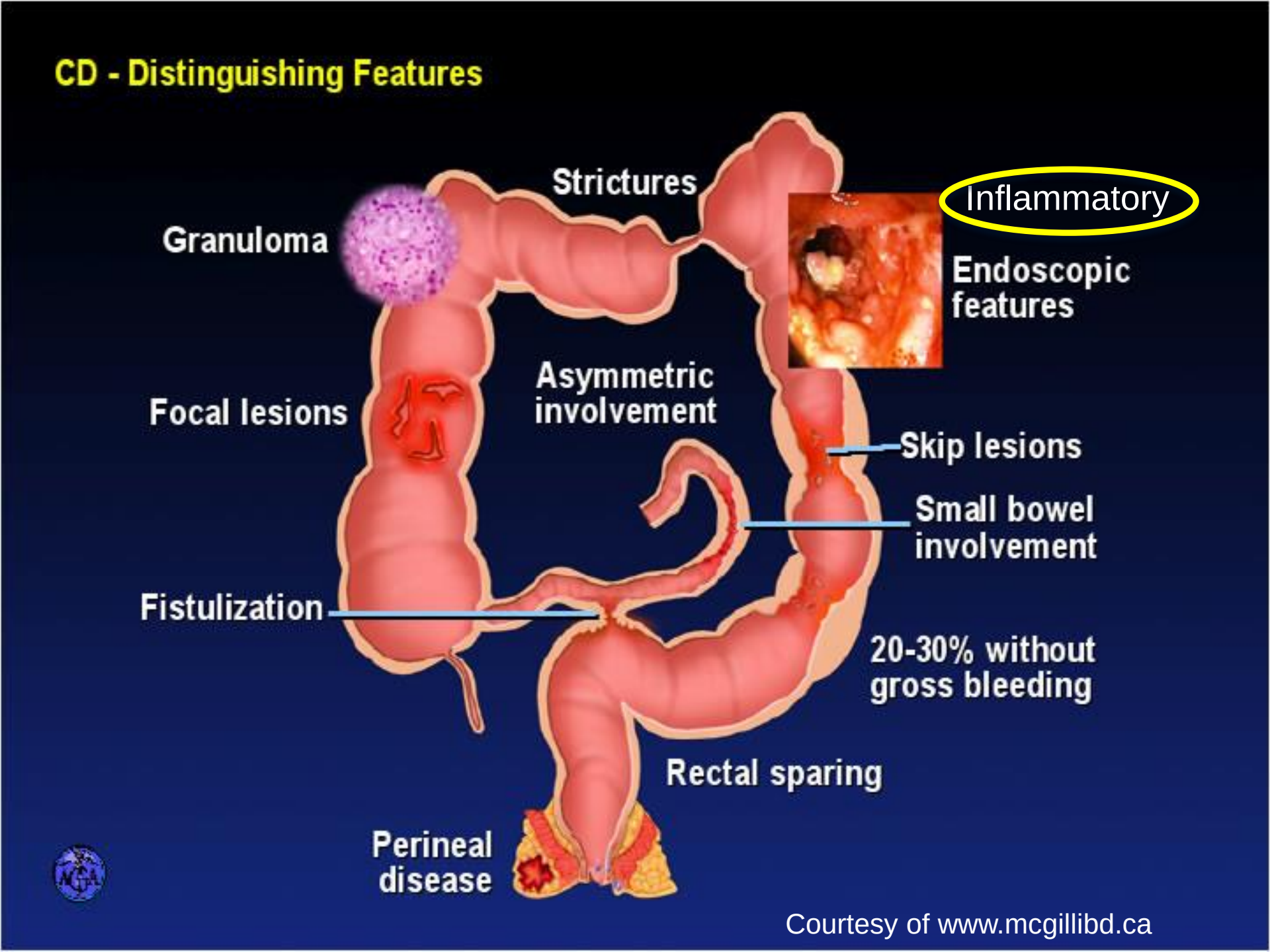

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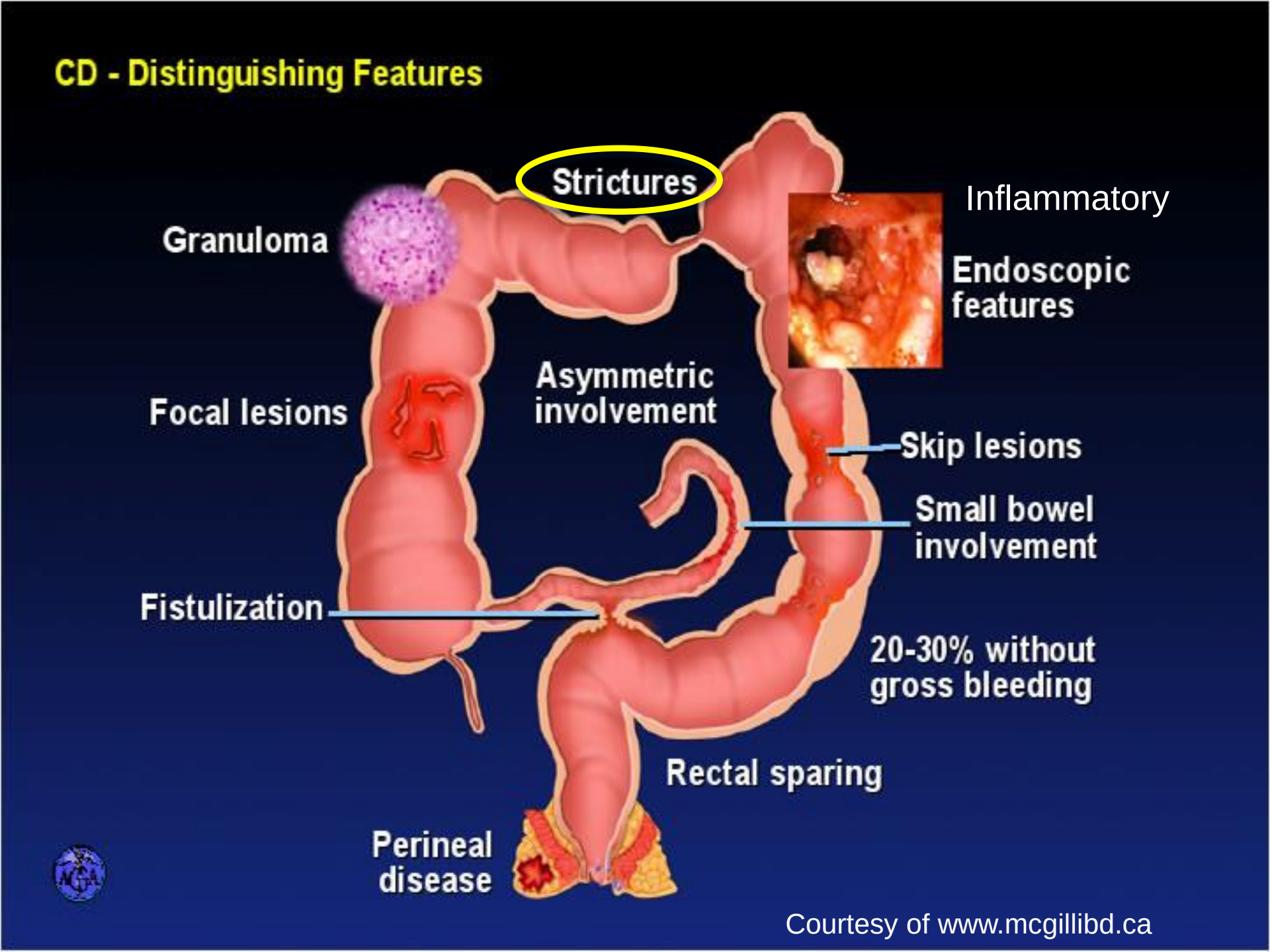

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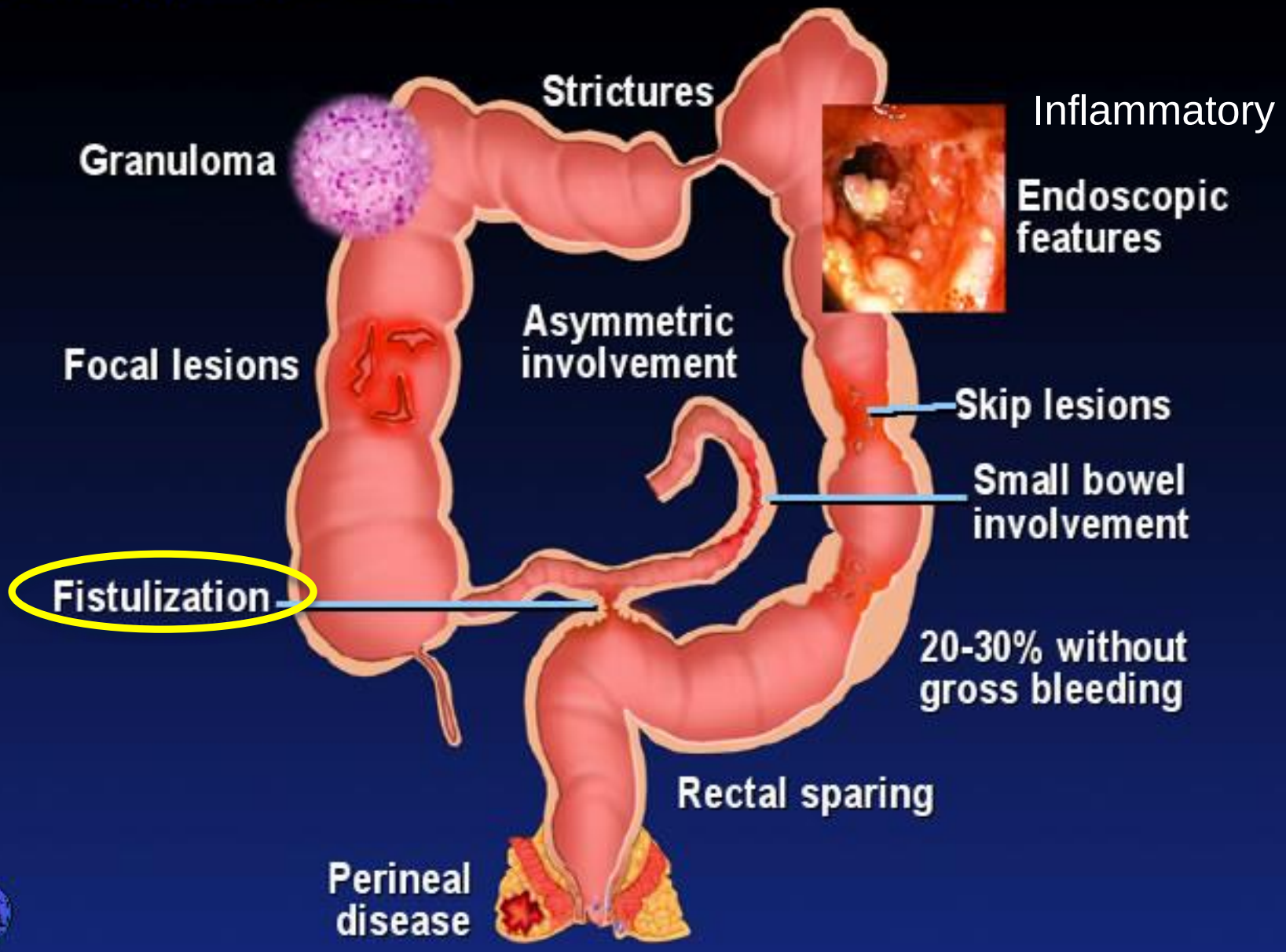
CD - Distinguishing Features



Courtesy of www.mcgillibd.ca

Staging of Disease after Diagnosis

- Extent and behavior
- **Complications**
- Extraintestinal manifestations

Case #3

- 35 y/o F with hypothyroidism and ulcerative colitis presents with 5 days of abdominal pain, bloody diarrhea and severe urgency.
- CBC **14.1**/**9**(previously 12)/480, CRP **25**, Stool studies neg
- T 99.8 otherwise Vs stable, PE: mild lower abd pain, otherwise nl
- CT A/P with diffuse colitis
- Meds: Lialda, Levothyroxine

You are entering the admission orders and start the patient on prednisone. What other medication do you ensure is ordered?

- A) Metronidazole
- B) SQ Heparin
- C) Percocet
- D) Loperamide
- E) Ibuprofen

IBD Related Complications

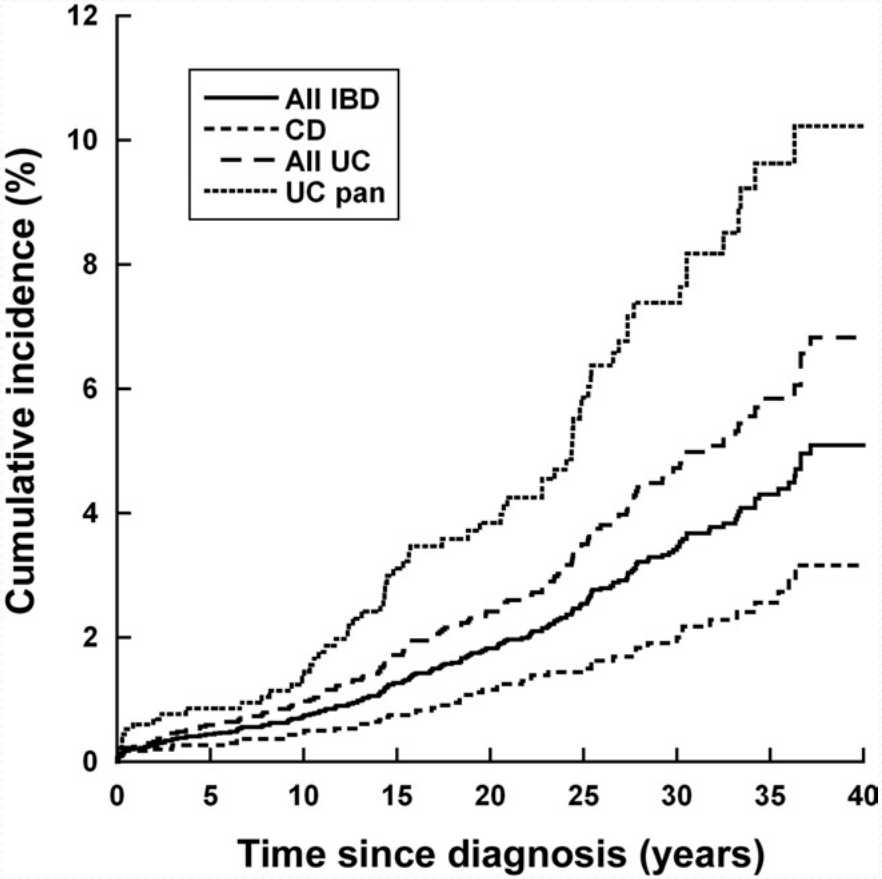
Complications of Crohn's Disease

- Fistulas
- Abscesses
- Intestinal blockage
- Malnutrition
- Gallstones
- Kidney stones
- Thrombosis
- Colon or rectal cancer
- Growth failure in children

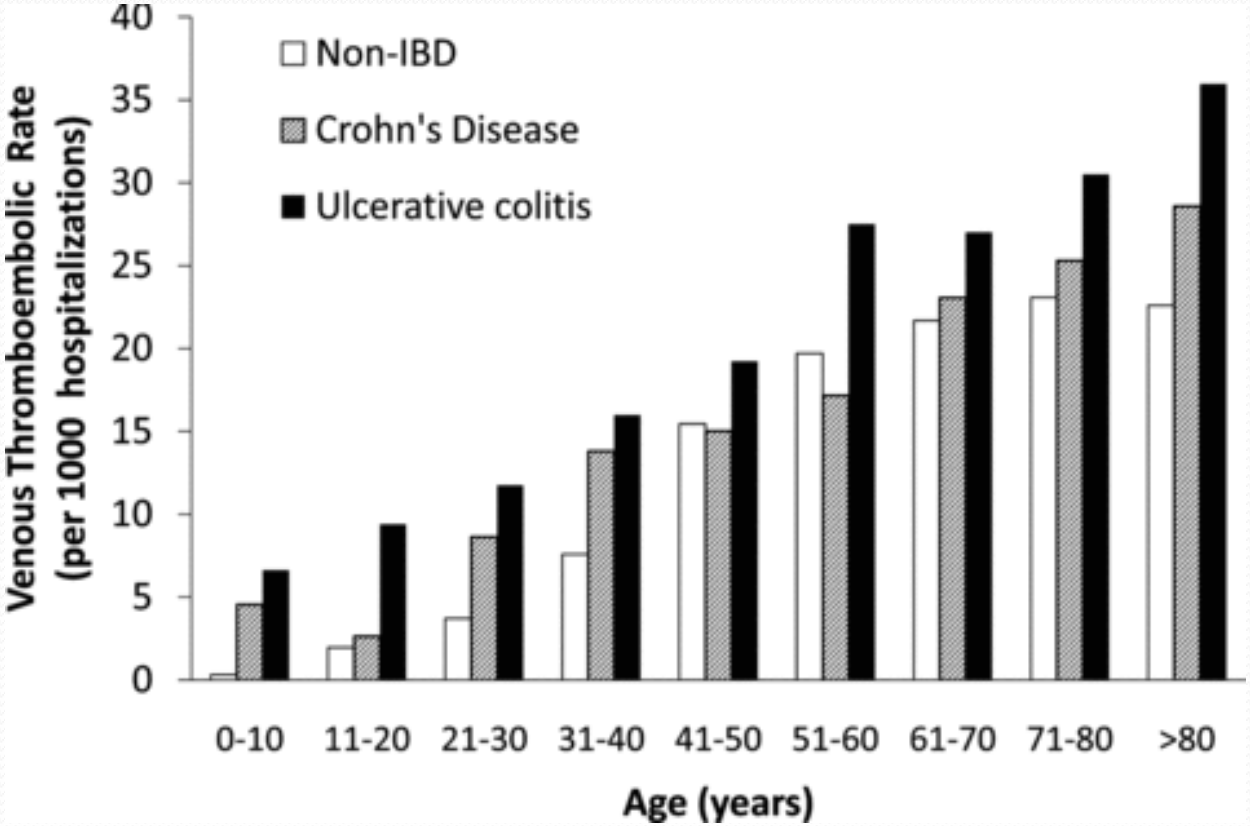
Complications of Ulcerative Colitis

- Toxic megacolon
- Perforation
- Thrombosis
- Colon or rectal cancer

Colorectal Cancer Risk in IBD

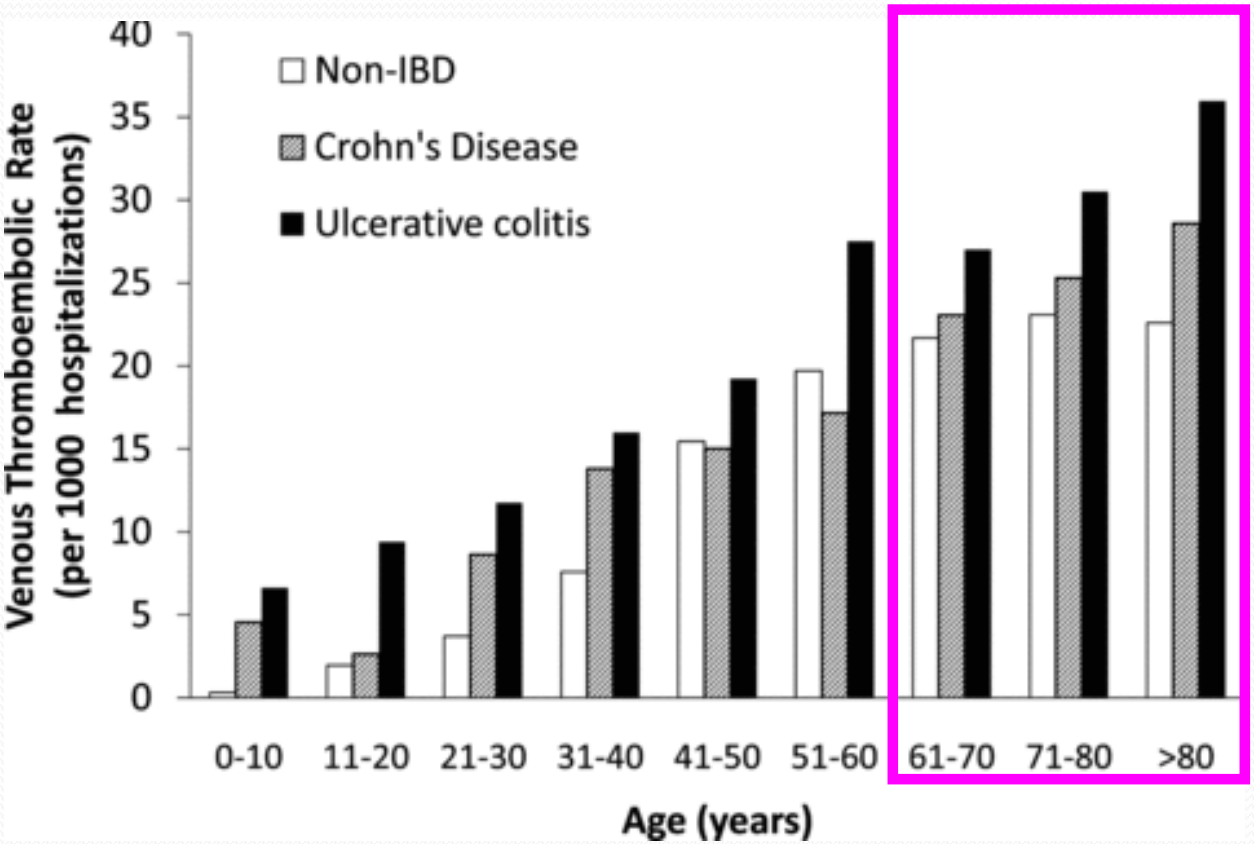


Increased Risk of Venous Thromboembolism



Nguyen GC, et al. *Am J Gastroenterol* 2008.

Increased Risk of Venous Thromboembolism



3% of elderly UC admissions had VTE

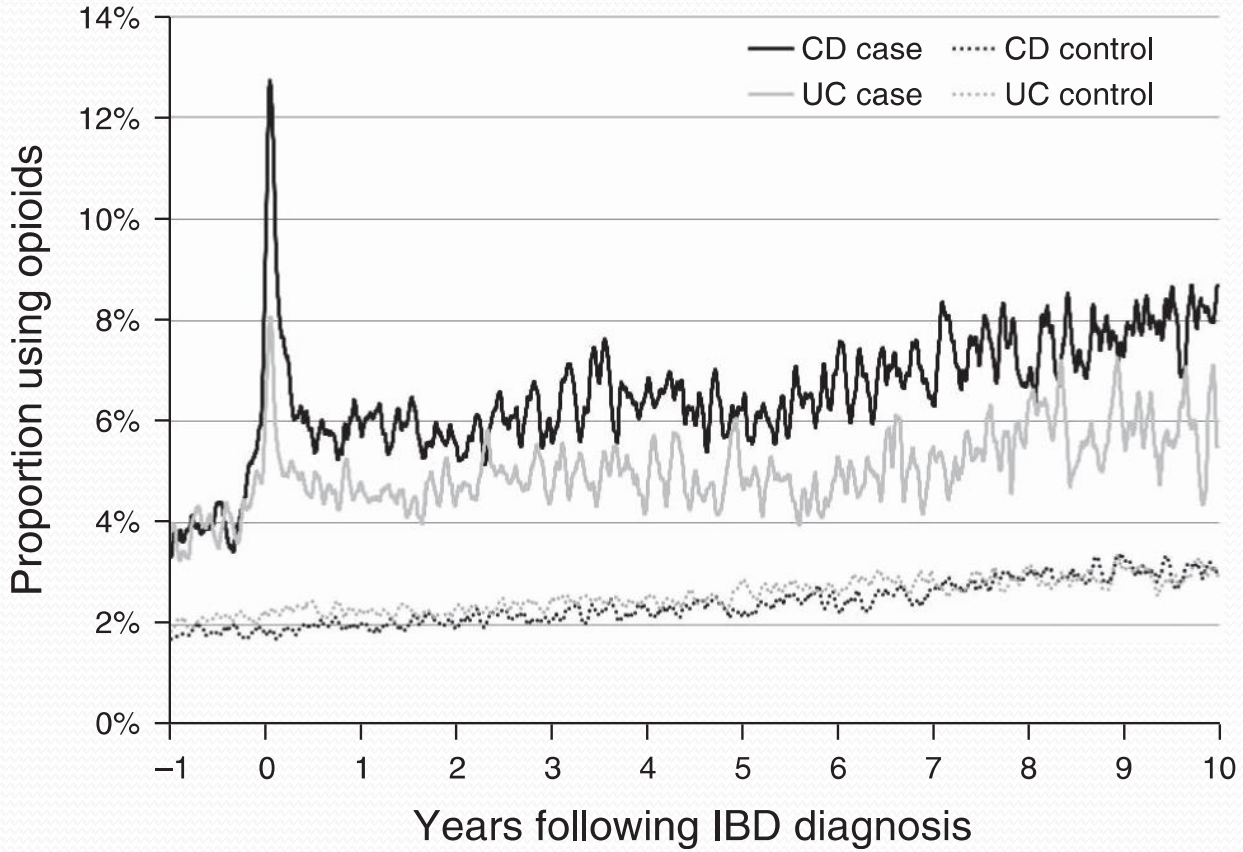
Nguyen GC, et al. *Am J Gastroenterol* 2008.

Safety of DVT Prophylaxis

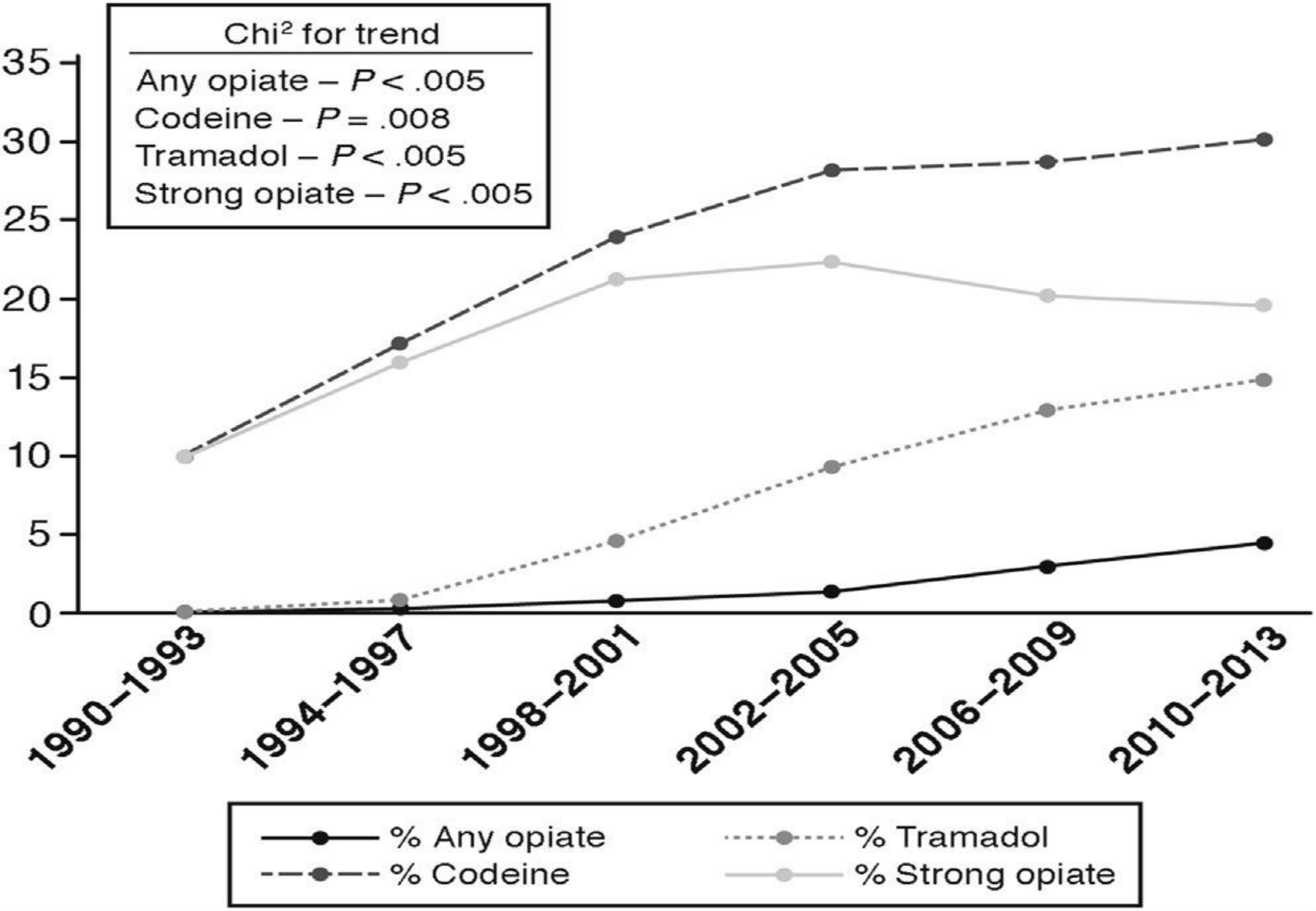
- 2007 Meta-analysis of 8 studies showed no increased risk of complications with the use of heparin in IBD inpatients

Shen J, et al. *Aliment Pharmacol Ther* 2007.

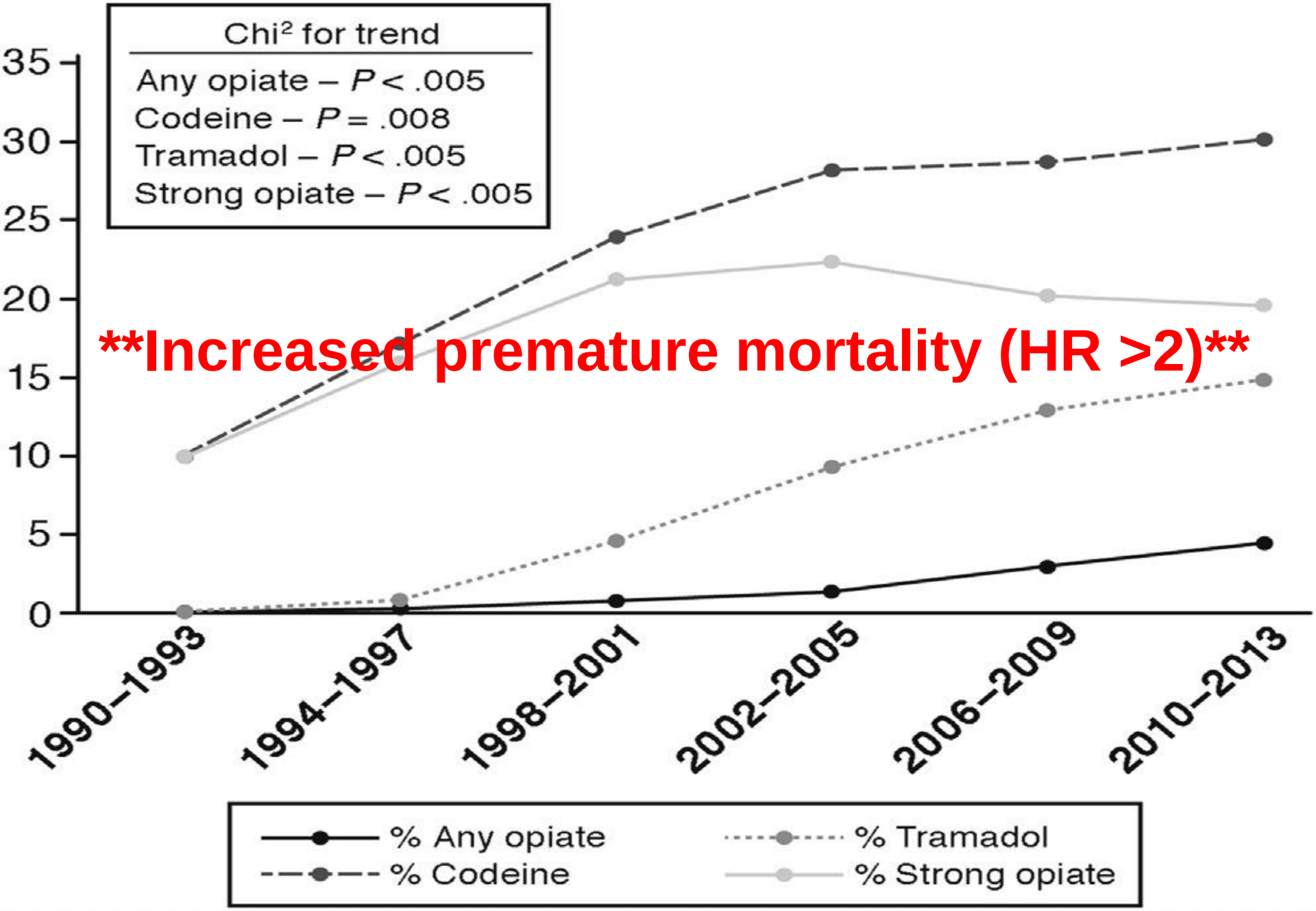
Opioid Use in IBD



Targownik LE, et al. *Am J Gastroenterol* 2014.



Burr NE, et al. *Clin Gastroenterol Hepatol* 2018.



Increased premature mortality (HR >2)

Burr NE, et al. *Clin Gastroenterol Hepatol* 2018.

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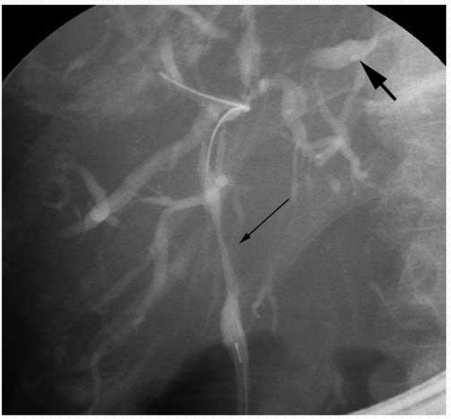
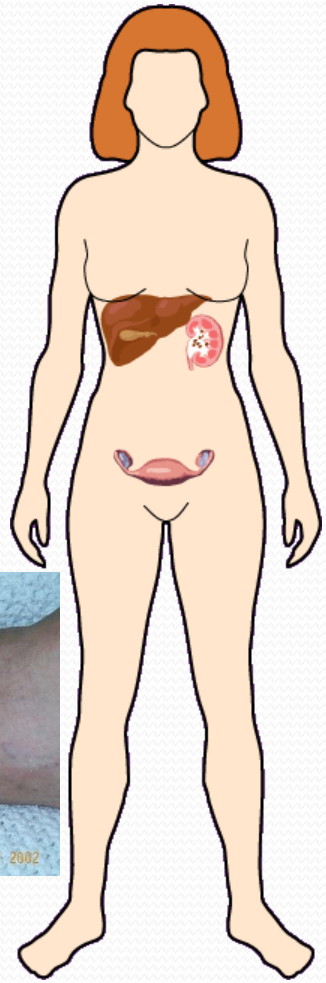
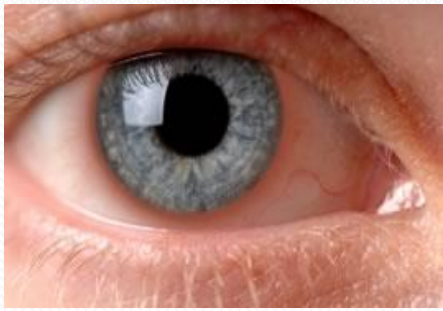
- **Extraintestinal manifestations**

Extraintestinal Manifestations







Extraintestinal Manifestations

- Musculoskeletal
  - Peripheral arthritis*
  - Ankylosing spondylitis
- Skin
  - Erythema nodosum*
  - Pyoderma gangrenosum
- Ocular
  - Episcleritis*
  - Scleritis
  - Anterior uveitis
- Hepatobiliary
  - Primary sclerosing cholangitis

*Follows course of intestinal inflammatory disease

Two Main Management Strategies in IBD

- Medical
- Surgical

Two Main Management Strategies in IBD

- **Medical**
- Surgical

Goals of Medical Therapy in Moderate-Severe Crohn's and UC

- Symptom resolution

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- Symptom resolution
- Mucosal healing

Goals of Medical Therapy in Moderate-Severe Crohn's and UC

- Symptom resolution
- Mucosal healing
- Minimizing complications of therapy

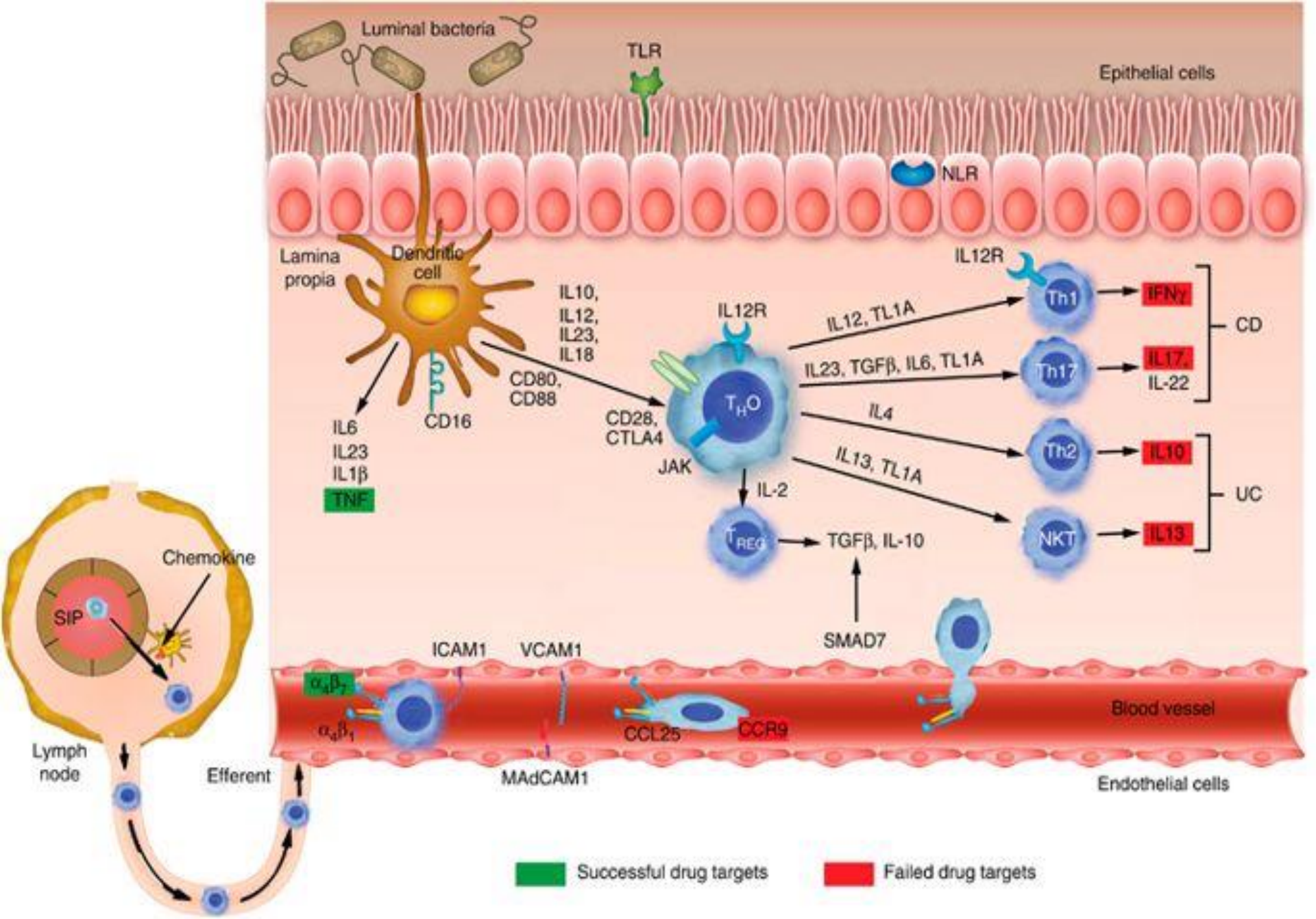
IBD Therapies in 1998

Antibiotics	Ciprofloxacin Metronidazole
Mesalamine	Apriso Asacol
Steroids	Prednisone Hydrocortisone enemas Cortifoam
Immune Modulating Agents	6-Mercaptopurine Azathioprine Methotrexate
Surgery	Ileal pouch-anal anastomosis Small bowel resection Stricturoplasty

IBD Therapies in 2019

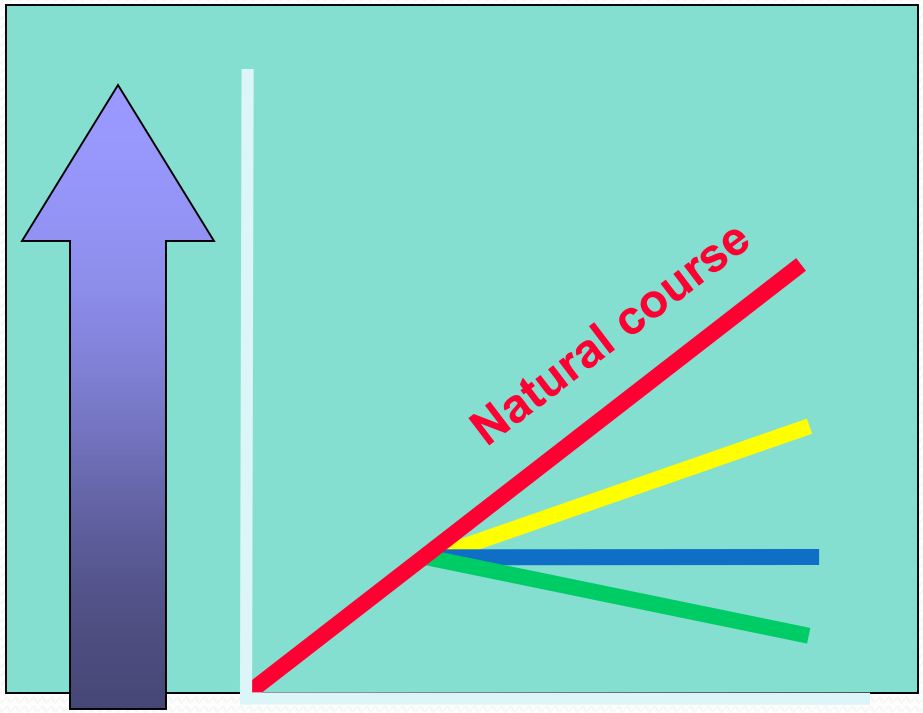
Antibiotics	Ciprofloxacin Metronidazole
Mesalamine	Apriso, Pentasa, Delzicol, Lialda, Rowasa, Canasa
Steroids	Entocort Prednisone Hydrocortisone enemas Cortifoam
Immunomodulators	6-Mercaptopurine Azathioprine Methotrexate
Surgery	Ileal pouch-anal anastomosis Small bowel resection Strictureplasty

Anti-TNF	Infliximab Adalimumab Certolizumab Golimumab
Anti-integrin	Natalizumab Vedolizumab
Anti-IL 12/23	Ustekinumab
JAK Kinase Inhibitor	Tofacitinib



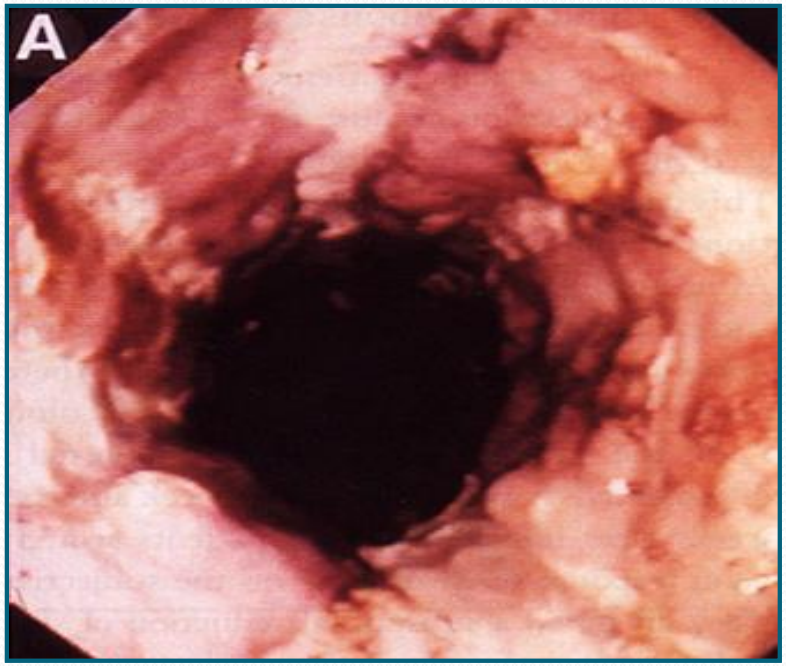
Billsborough J, et al. *Am J Gastroenterol* 2016.

Medical Therapy Alters the Natural History of IBD



- Induce and maintain gastrointestinal healing
- Prevent need for steroids
- Prevent strictures and penetrating complications
- Prevent extra-intestinal complications
- Decrease hospitalization/surgery
- Decrease long-term cost of care

Medical Treatment of Refractory CD in the Age of Biologics



Pretreatment

van Dullemen HM, et al. *Gastroenterol* 1995.
Present DH, et al. *NEJM* 1999.

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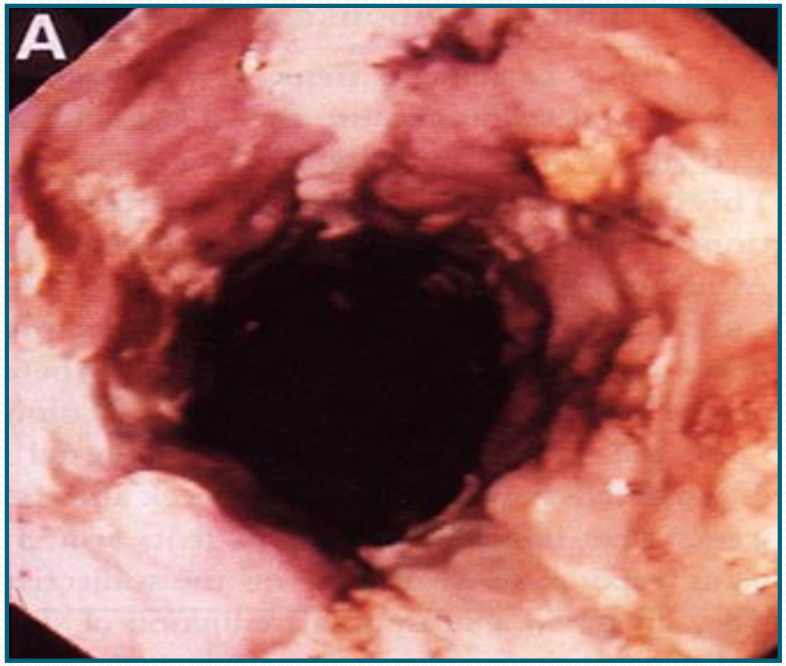

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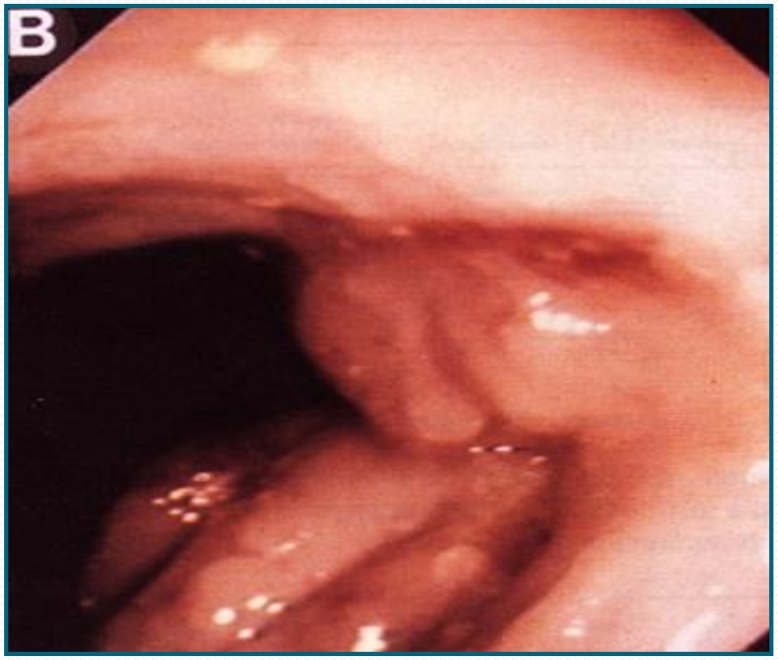

4 Weeks posttreatment

van Dullemen HM, et al. *Gastroenterol* 1995.
Present DH, et al. *NEJM* 1999.

UC Medical Management

Mild-Moderate UC

Induction and Maintenance

5-Aminosalicylic Acids, Topical Steroid

Moderate-Severe UC

Induction

Steroids, Anti-TNF-α Agents, Anti-Integrin, JAK inhibitors

Maintenance

Thiopurines, Anti-TNF-α Agent, Anti-Integrin, JAK inhibitors

CD Medical Management

Mild-Moderate CD

Induction and Maintenance

Enterocort,
Antibiotics

Moderate-Severe CD

Induction

Steroids, Anti-TNF-α Agents, Anti-Integrins Anti-Interleukin 12/23

Maintenance

Thiopurines, Anti-TNF-α Agents, Anti-Integrins, Anti-Interleukin 12/23

Diet and IBD

- Multiple diets have been described for use in IBD including the Paleo diet, FODMAP, and Specific Carbohydrate Diet (SCD)
- No data that any particular diet plays a role in gut inflammation in IBD
- In patients with active inflammation, best to avoid high fiber foods
- Food journal

Fecal Transplant and IBD

- UC: 4 RCTs with 277 patients followed up to 12 weeks
  - Clinical Response: 49 vs 28%*
  - Clinical Remission: 28 vs 9%*
  - Endoscopic Remission: 14 vs 5%*

Levy AN, et al. *Therap Adv Gastroenterol* 2019.

Fecal Transplant and IBD

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**p < 0.05*

Levy AN, et al. *Therap Adv Gastroenterol* 2019.

Fecal Transplant and IBD

- UC: 4 RCTs with 277 patients followed up to 12 weeks
  - Clinical Response: 49 vs 28%*
  - Clinical Remission: 28 vs 9%*
  - Endoscopic Remission: 14 vs 5%*
- CD: 5 uncontrolled cohort studies with 71 patients followed up to 15 months
  - Clinical Response: 63%
  - Clinical Remission: 52%
  - Endoscopic Remission: 0% (6 patients)
- Safety: generally well tolerated but LT effects unclear

*$p < 0.05$

Levy AN, et al. *Therap Adv Gastroenterol* 2019.

Health Care Maintenance Issues

- Vaccines
- Skin cancer screening
- Bone Health/Osteoporosis
- Pyscho-social issues

Vaccines in IBD

- IBD itself should not impact vaccine response
- Generally lives vaccines contraindicated in the immunosuppressed
  - Include Rubella, Varicella, Yellow fever, Zoster
- Annual influenza vaccine
- Pneumococcal vaccine

Sands BE et al. *Inflamm bowel dis* 2004.
Melmed GY. *Inflamm bowel dis* 2009.

Human Papilloma Virus (HPV)

- HPV linked with cervical and anal cancers
- Women with IBD have an increased risk for cervical dysplasia
  - Increased risk with >6 months immune modulator use
- HPV vaccine available and safe in immunosuppression, but no specific guidelines for IBD
- Recommended for women and men ages 9 to 26

Kane et al. *Am J Gastroenterol* 2008.
Bhatia et al. *World J Gastroentol* 2006.
www.cdc.gov

Herpes Zoster Vaccines

- IBD patients are at higher risk of developing shingles, particularly on immune suppression
- Zostavax: live-attenuated zoster vaccine
- Shingrix: inactivated zoster vaccine
  - Approved in 2017 and given in 2 doses: 2nd dose is given 2-6 months after first dose
  - Approved for ≥50 years old
  - Can be given to patients on low levels of immune suppression (prednisone ≤20 mg, methotrexate, azathioprine, 6-MP)
  - Safety with biologics and tofacitinib under study

Skin Cancer

- Increased risk of nonmelanoma skin cancer in patients on azathioprine or 6-MP
- Possible increased risk of melanoma in patients on anti-TNF agents
- Patients on immunosuppression should have a full body skin exam at least once per year

Osteoporosis

- **Risk Factors in general population:**
  - Previous history of osteoporotic related fractures
  - Advanced age
  - Family history of osteoporosis
  - Lack of exercise
  - Smoking
  - Hypogonadal state

Bernstein CD, et al. *Clin Gastroenterol Hepatol* 2006.

Osteoporosis

- **Risk Factors in general population:**
  - Previous history of osteoporotic related fractures
  - Advanced age
  - Family history of osteoporosis
  - Lack of exercise
  - Smoking
  - Hypogonadal state
- **Risk factors specific to IBD patients**:
  - Chronic inflammatory activity
  - Chronic or recurrent corticosteroid use
  - Malnutrition
  - Low body weight
  - Low intake or absorption of Ca & Vit D

Bernstein CD, et al. *Clin Gastroenterol Hepatol* 2006.

Psycho-Social Issues

Variable	Depression	Anxiety Disorder	Bipolar Disorder	Schizophrenia
Cohort				
Matches	1.0	1.0	1.0	1.0
IBD	**1.42 (1.32–1.52)**	**1.24 (1.17–1.31)**	**1.45 (1.19–1.77)**	1.11 (0.76–1.60)
Sex				
Male	1.0	1.0	1.0	1.0
Female	**1.76 (1.64–1.90)**	**1.54 (1.48–1.62)**	**1.58 (1.34–1.87)**	0.75 (0.55–1.02)
Age, y				
18–24	1.0	1.0	1.0	1.0
25–44	**1.95 (1.66–2.30)**	**1.95 (1.70–2.23)**	**1.74 (1.18–2.57)**	0.96 (0.57–1.62)
45–64	**2.34 (1.98–2.76)**	**2.15 (1.87–2.47)**	**2.06 (1.38–3.08)**	1.51 (0.89–2.58)
≥65	**1.99 (1.68–2.36)**	**2.05 (1.78–2.37)**	**1.24 (0.81–1.91)**	0.97 (0.56–1.67)
Socioeconomic status				
Quintile 1 (lowest)	1.22 (1.09–1.36)	**1.27 (1.18–1.36)**	1.24 (0.92–1.66)	**3.25 (1.92–5.51)**
Quintile 2	1.12 (1.04–1.21)	**1.08 (1.02–1.14)**	**1.26 (1.02–1.57)**	**2.73 (1.73–4.31)**
Quintile 3	1.09 (0.99–1.19)	**1.10 (1.03–1.18)**	1.21 (0.99–1.46)	0.86 (0.40–1.87)
Quintile 4	1.03 (0.95–1.11)	**1.07 (1.02–1.13)**	0.99 (0.79–1.24)	1.14 (0.59–2.21)
Quintile 5 (highest)	1.0	1.0	1.0	1.0
Region				
Rural	1.0	1.0	1.0	1.0
Urban	**1.28 (1.19–1.37)**	**1.26 (1.20–1.32)**	**1.88 (1.50–2.35)**	2.28 (1.66–3.12)
No. physician visits	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**
Year[b]	**1.04[c] (1.04–1.05)**	**1.035[d] (1.03–1.04)**	**1.055[e] (1.04–1.07)**	**1.025 (1.01–1.05)**

Bernstein CN, et al. *Inflam Bowel Dis* 2019.

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Management of IBD Requires Multidisciplinary Approach

- Gastroenterology
- Colorectal surgery
- Radiology
- Pathology
- Nutrition
- Social work
- Nursing

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- Gastroenterology
- Colorectal surgery
- Radiology
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- Social work
- Nursing
- Primary Care Provider

Conclusions

- CD and UC tends to occur in younger adults
- Pathogenesis results from a combination of genetics, environmental factors, gut microbiota, and an aberrant immune system
- Diagnosis of IBD is based on history and exam, labs, radiographic imaging, and endoscopy and histology

Conclusions

- IBD is a systemic disease with multiple complications
- New therapies have improved patient outcomes
- Health care maintenance issues in IBD are key

Case #1

- In the clinic, 67 M with BPH, gout, DJD, and ulcerative colitis in clinical remission for several years presents with abdominal pain and bloody diarrhea over three days
- Vs stable, PE with with mild RLQ pain with no guarding/rebound, otherwise nl
- Meds: finasteride, acetaminophen, sulfasalazine, folate, MVN
- CBC **12.1**/**12**/350, BMP nl, CRP **7**

What is the immediate next best step?

- A) MRI of the abd/pelvis
- B) Call a GI consult
- C) Start prednisone
- D) Send stool studies
- E) Transfuse 1 Unit PRBCs

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Case #2

- In clinic, a 22 y/o M with migraines, gastroparesis, and long-standing Crohn's disease presents with diffuse abdominal pain and nausea.
- A colonoscopy the previous week showed no active disease.
- Has had three other presentations in last 2 months with similar symptoms. Each time, a CT A/P has shown no causes.
- Vs: BP 128/72, HR 90; PE: moderate diffuse abd px with no rebound/guarding, BSs present, exam otherwise nl
- CBC 8/16/258, BMP nl, CRP nl
- Meds: Infliximab, Percocet

What is the next best step?

- A) Recommend a MRI instead
- B) Do a CT scan without contrast
- C) Start metronidazole and ciprofloxacin
- D) Consult GI
- E) Start prednisone

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- A) Recommend a MRI instead
- B) Do a CT scan without contrast
- C) Start metronidazole and ciprofloxacin
- **D) Consult GI**
- E) Start prednisone

Case #3

- 35 y/o F with hypothyroidism and ulcerative colitis presents with 5 days of abdominal pain, bloody diarrhea and severe urgency.
- CBC 14.1/9(previously 12)/480, CRP 25, Stool studies neg
- T 99.8 otherwise Vs stable, PE: mild lower abd pain, otherwise nl
- CT A/P with diffuse colitis
- Meds: Lialda, Levothyroxine

You are entering the admission orders and start the patient on prednisone. What other medication do you ensure is ordered?

- A) Metronidazole
- B) SQ Heparin
- C) Percocet
- D) Loperamide
- E) Ibuprofen

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- A) Metronidazole
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- C) Percocet
- D) Loperamide
- E) Ibuprofen

Cases: Major takeaways

- IBD patients with diarrhea should undergo stool studies
- Use of appropriate imaging can prevent unnecessary radiation exposure
- In IBD inpatients, the benefits of DVT prophylaxis almost always outweigh the risks
- Narcotics in IBD are associated with increased mortality

CD and UC Patient Support Groups:

ccfa.org

crohnsforum.com

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(206)992-8114 (cell)