Inflammatory Bowel Disease

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Inflammatory Bowel Disease

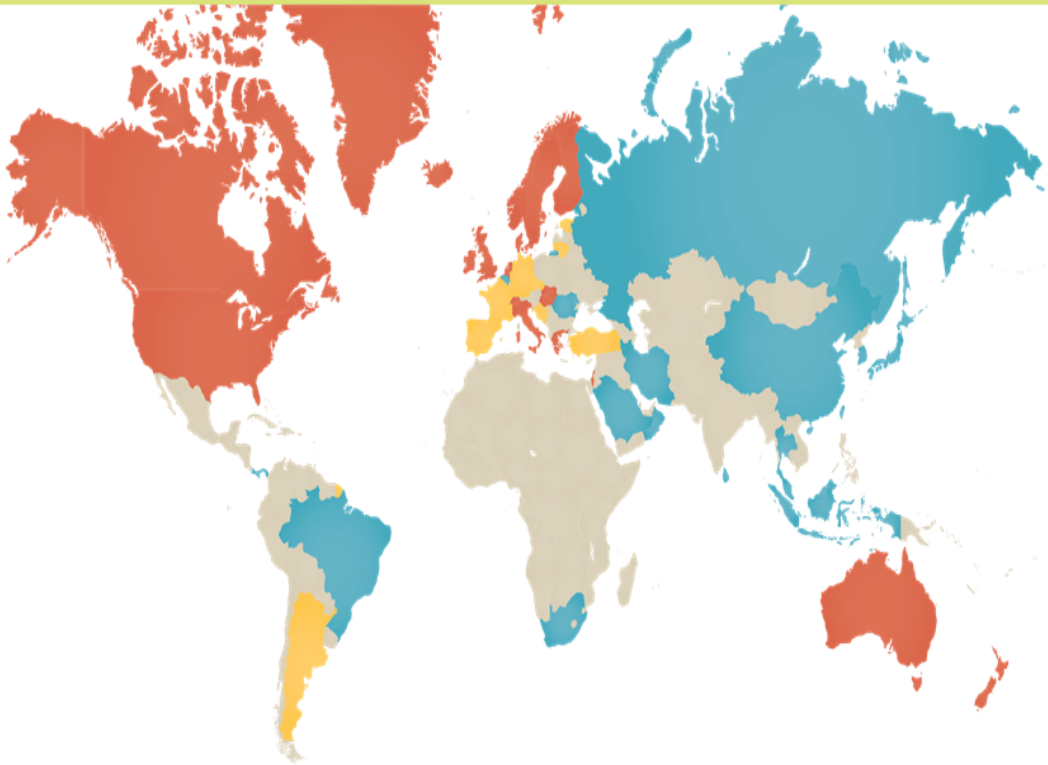
Ulcerative colitis

Crohn's disease

Undeterminate colitis

The Global Burden of Inflammatory Bowel Disease (IBD)

- IBD is a global disease whose prevalence is predicted to increase exponentially within the next decade[1]
- >1 million people in the United States have IBD
  - Prevalence of CD: ~235 cases per 100,000 people[2]



1. Kaplan GG. *Nat Rev Gastroenterol Hepatol.* 2015;12(12):720-7. 2. Kappelman MD, et al. *Dig Dis Sci.* 2013;58(2):519-525. 3. Molodecky NA, et al. *Gastroenterology.* 2012;142(1):46-54.

Epidemiology

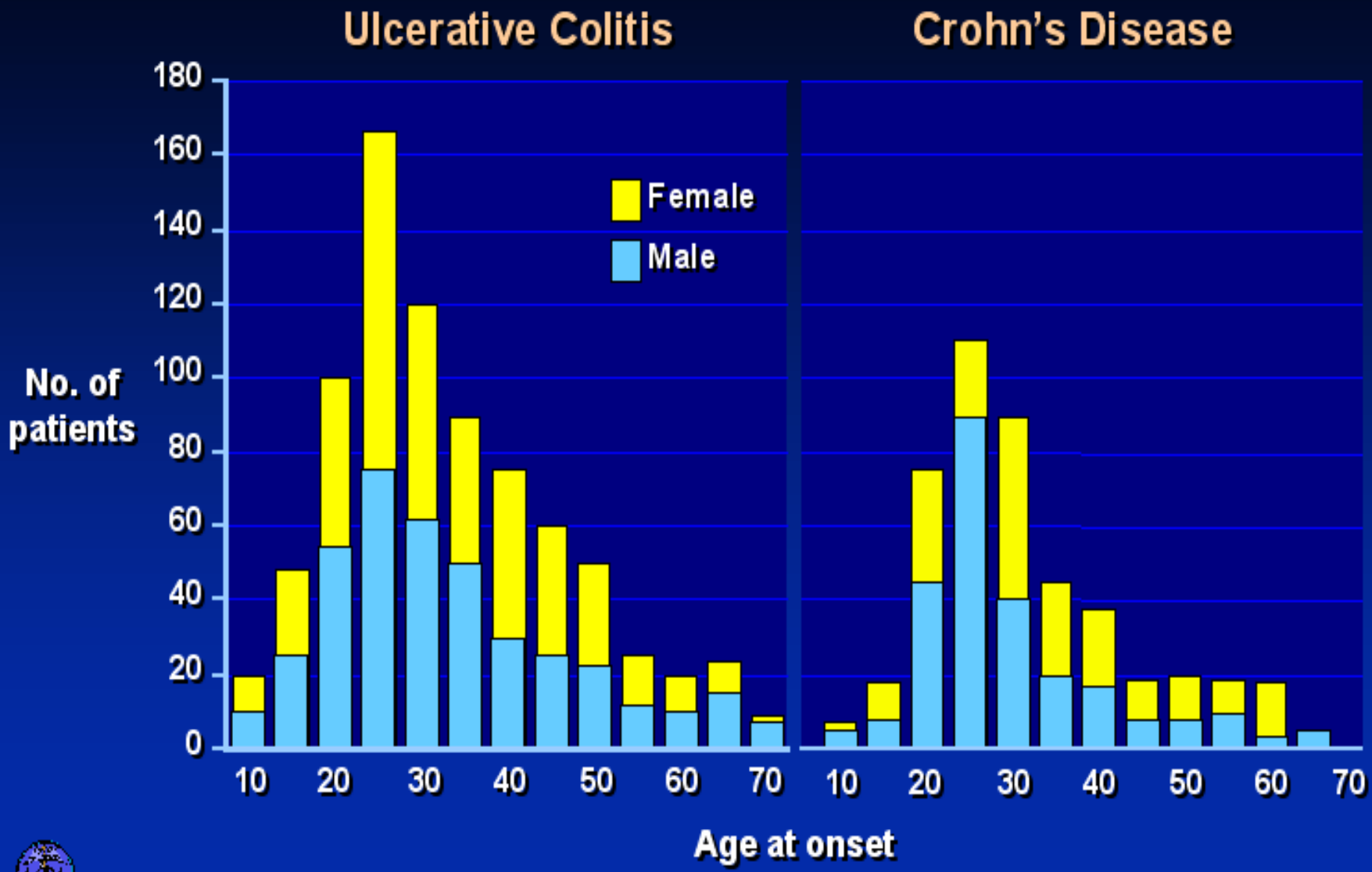
- Most cases of ulcerative colitis and Crohn's disease have their onset between ages 15 and 40.

- bimodal age distribution for both disorders with a second peak between age 50 and 80
- Male = Female
- Whites>Blacks

Epidemiology

- Incidence 1-10 (CD)/1000000
- Incidence 3-15 (UC)/100000
- Prevalence: 20-100 (CD)
- Prevalence: 50-80 (UC)
- Jewish> non Jewish
- Chr 16 (CD)
- Chr 3,5,7,12,19 (CD+UC)
- TNF,IL 1A,HLA A2, HLA DR1,DQW5 (CD), HLA DR2 (UC).

IBD - Age and Sex Distribution



Rogers et al., J. Chronic Dis. 1971; 24:743

Etiological theories of IBD

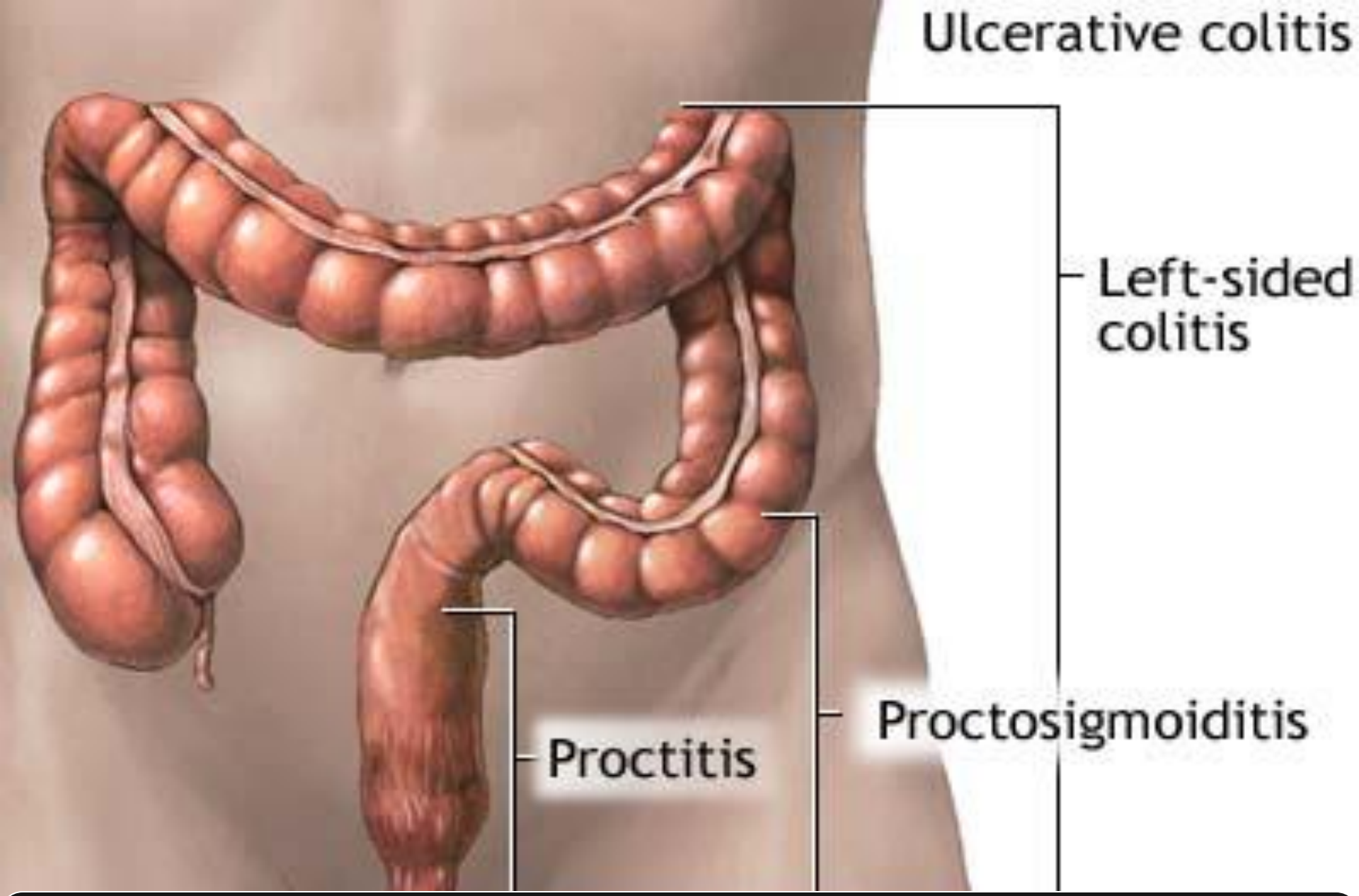
- Infectious
- Immunological
- Genetic
- Dietary
- Environmental
- Vascular
- Allergic
- Psychogenic

Definition UC

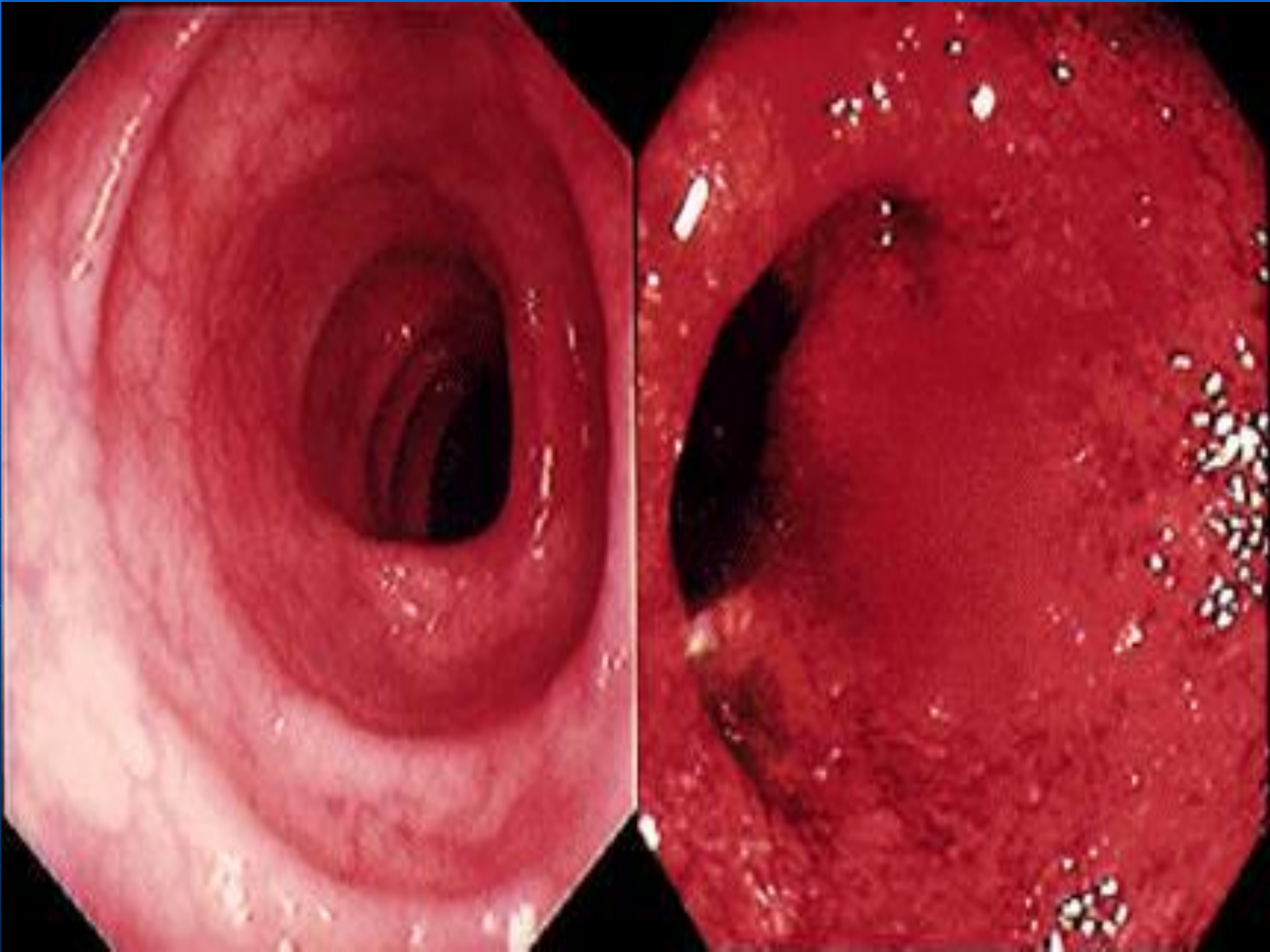
- Ulcerative colitis is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon.
- It almost invariably involves the rectum and may extend in a proximal and continuous fashion to involve other portions of the colon

Ulcerative Colitis
Definitions

- Ulcerative proctitis: Limited to the rectum.
- Proctosigmiditis or Distal colitis: Involving to mid sigmoid area.
- Left sided colitis: up to the splenic flexure proximally.
- Pancolitis: Beyond the splenic flexure proximally



No skip lesions



UC: Signs & Symptoms

- Bloody Diarrhea
- Tenesmus
- Urgency
- Abdominal Pain
- Fever
- Weight Loss
- Joint Pain
- Skin Rash
- Fatigue

SIGNS AND SYMPTOMS

- Mild disease

Proctitis or proctosigmoiditis or distal colitis intermittent rectal bleeding associated with the passage of mucus

*mild diarrhea with fewer than **four** small loose stools per day*

- Moderate disease

*involvement of more than the distal colon, frequent loose, **bloody stools (up to 10 per day)**, mild anemia*

SIGNS AND SYMPTOMS

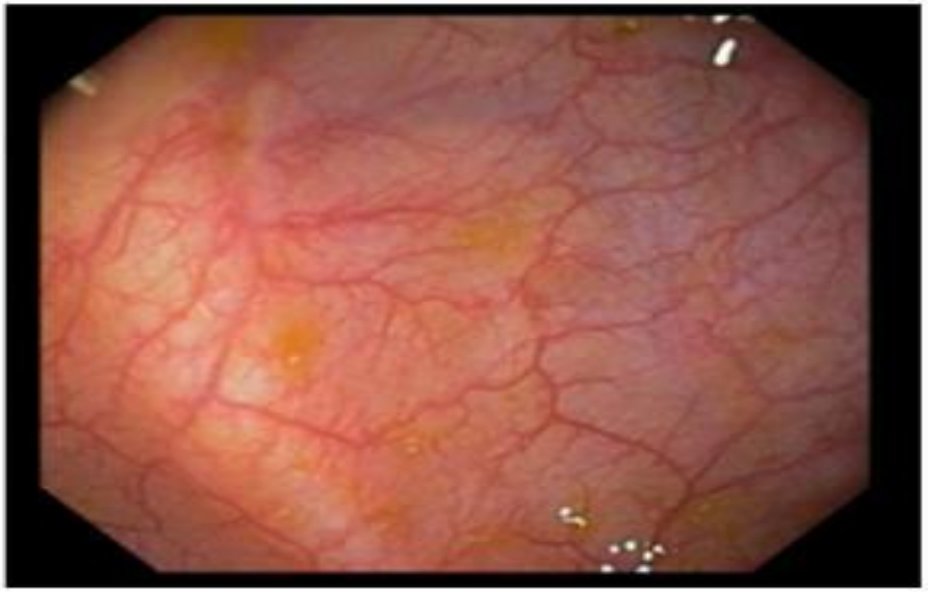
- Severe disease

extensive colonic involvement

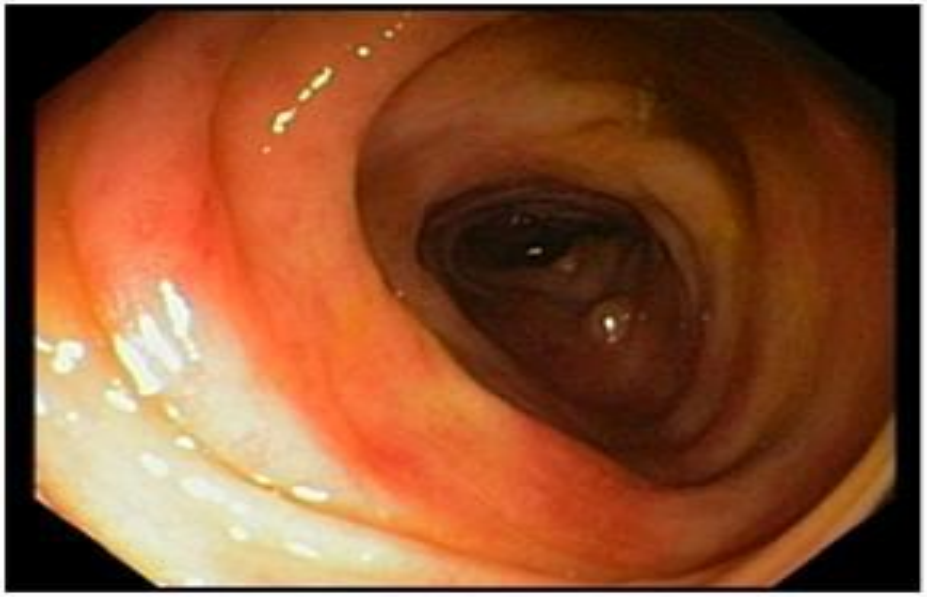
frequent loose stools **(greater than 10 per day) with severe cramps, fever up to 39.5°C**

bleeding often necessitating blood transfusion. They may suffer rapid weight loss, leading to a poor nutritional state.

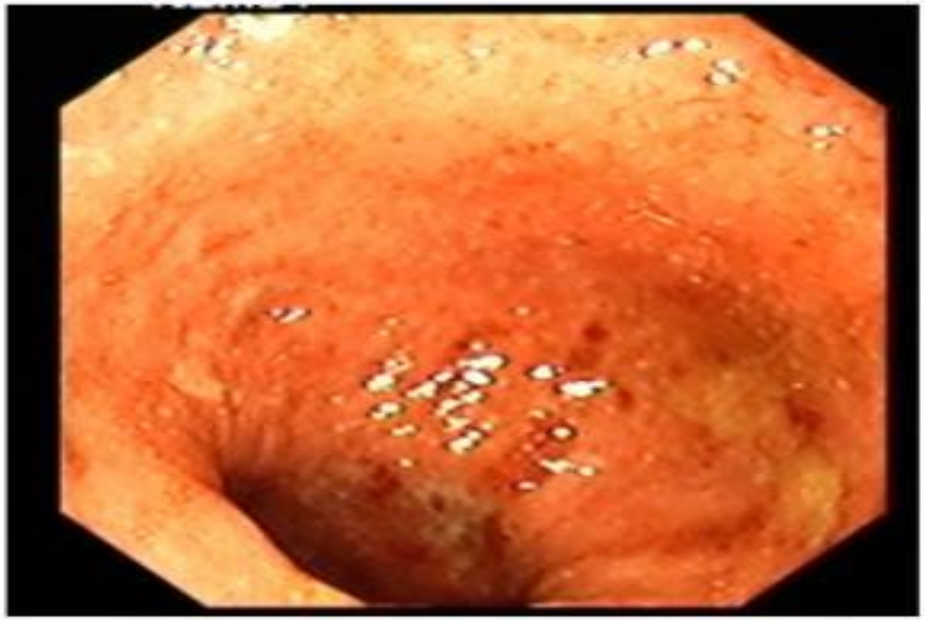
Normal mucosa



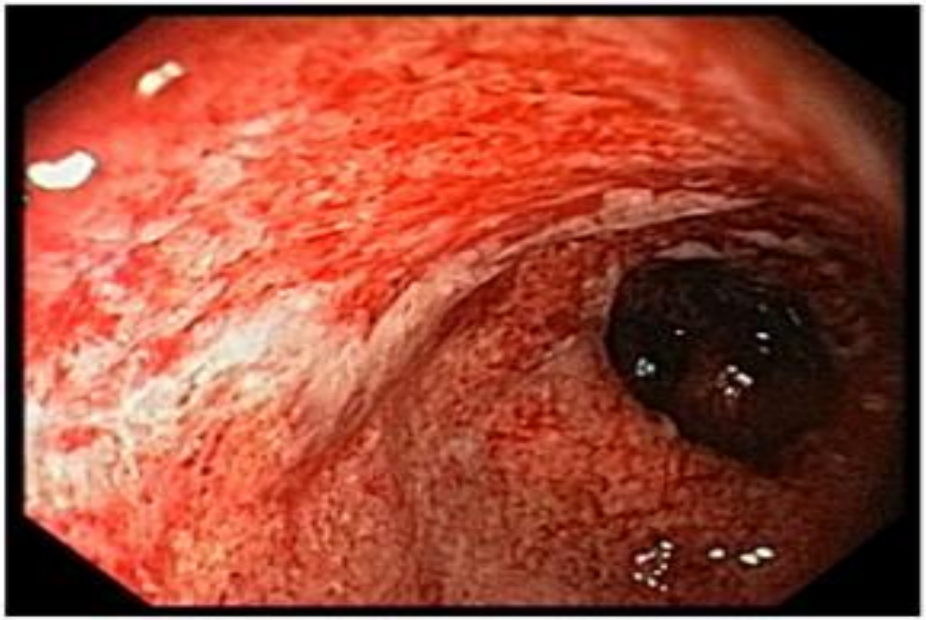
Mild inflammation



Moderate inflammation



Severe inflammation



Initial presentation of UC

- The history is typically one of the gradual onset of symptoms, sometimes preceded by a self-limited episode of **rectal bleeding** that occurred weeks or months earlier.
- The initial episode is limited to the rectum or distal colon in one-third of patients, to the left colon up to the splenic flexure in one-third, and most of the remaining patients have pancolitis.
- Less than 10 percent present with fulminant disease.

Differential D'X of UC

Infectious Mimics of Inflammatory Bowel Disease†

Infectious agents causing colitis

Bacteria

Shigella species
Enterohemorrhagic Escherichia coli
Enteroinvasive Escherichia coli
Campylobacter jejuni
Salmonella species (gastroenteritis and typhoid fever)
Yersinia enterocolitica
Mycobacterium tuberculosis
Clostridium difficile
Vibrio parahaemolyticus
Chlamydia trachomatis (lymphogranuloma venereum serotypes)

Parasites

Entamoeba histolytica
Schistosoma species
Balantidium coli
Trichinella spiralis

Viruses

Cytomegalovirus

Infectious agents causing proctitis

Neisseria gonorrhoeae
Herpes simplex virus
Chlamydia trachomatis
Treponema pallidum
Cytomegalovirus

† Adapted from Guerrant, RL, Lima, AA. Inflammtory enteritides. In: Principles and Practice of Infectious Diseases, 5th ed, Mandell, GL, Bennett, JE, Dolin, R (Eds), Churchill Livingstone, Philadelphia 2000. p.1127.

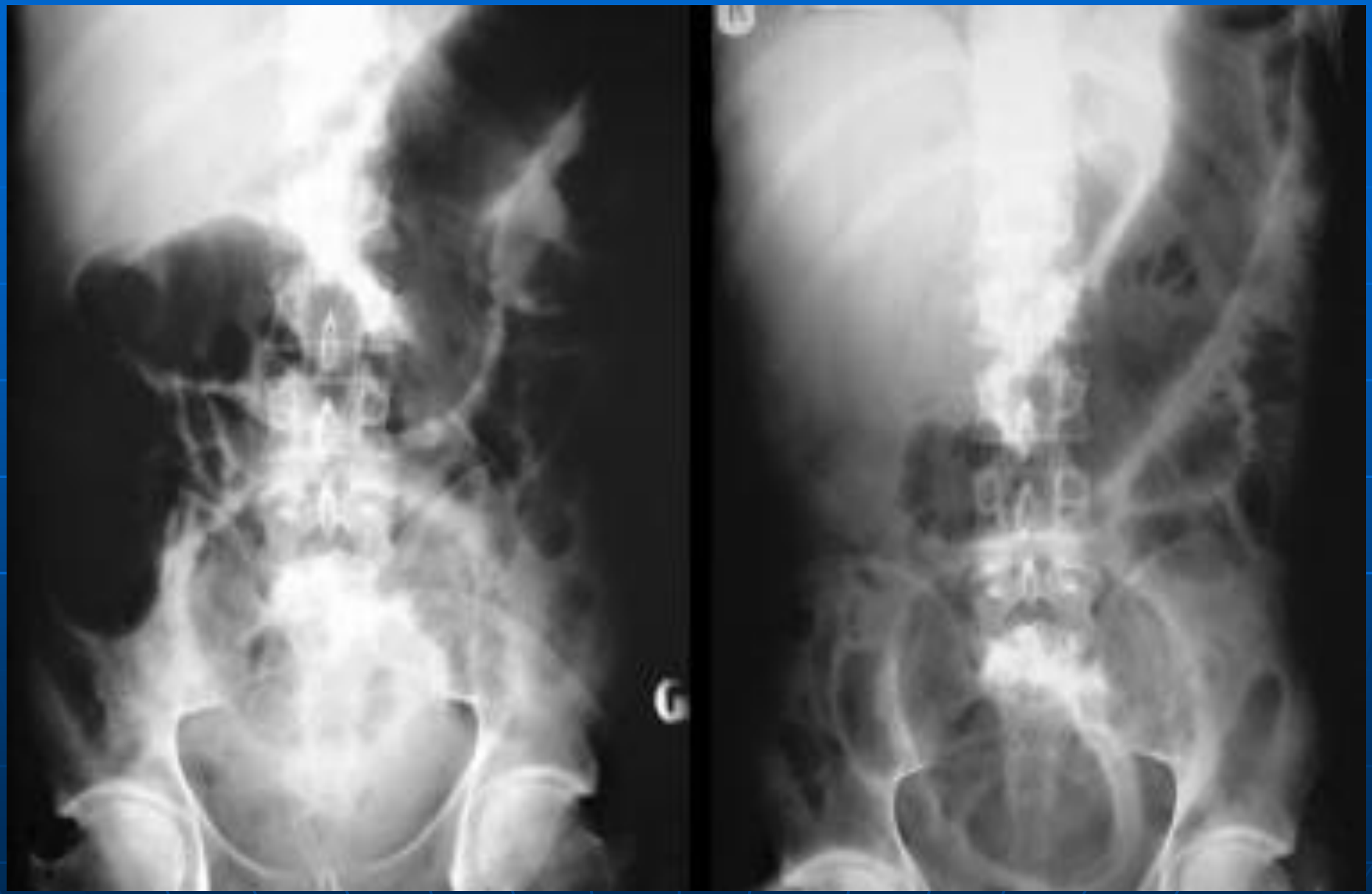
Ulcerative Colitis
Diagnosis

- **History**
- **typical endoscopic appearance**
- **confirmatory histology seen** on **colonic biopsy**

- **Serological markers**
  - pANCA Positive
  - ASCA Negative

Positive predictive value 75%

Routine labs
Stool for R&M Culture, Cl Difficle toxines and Faecal calprotectin.



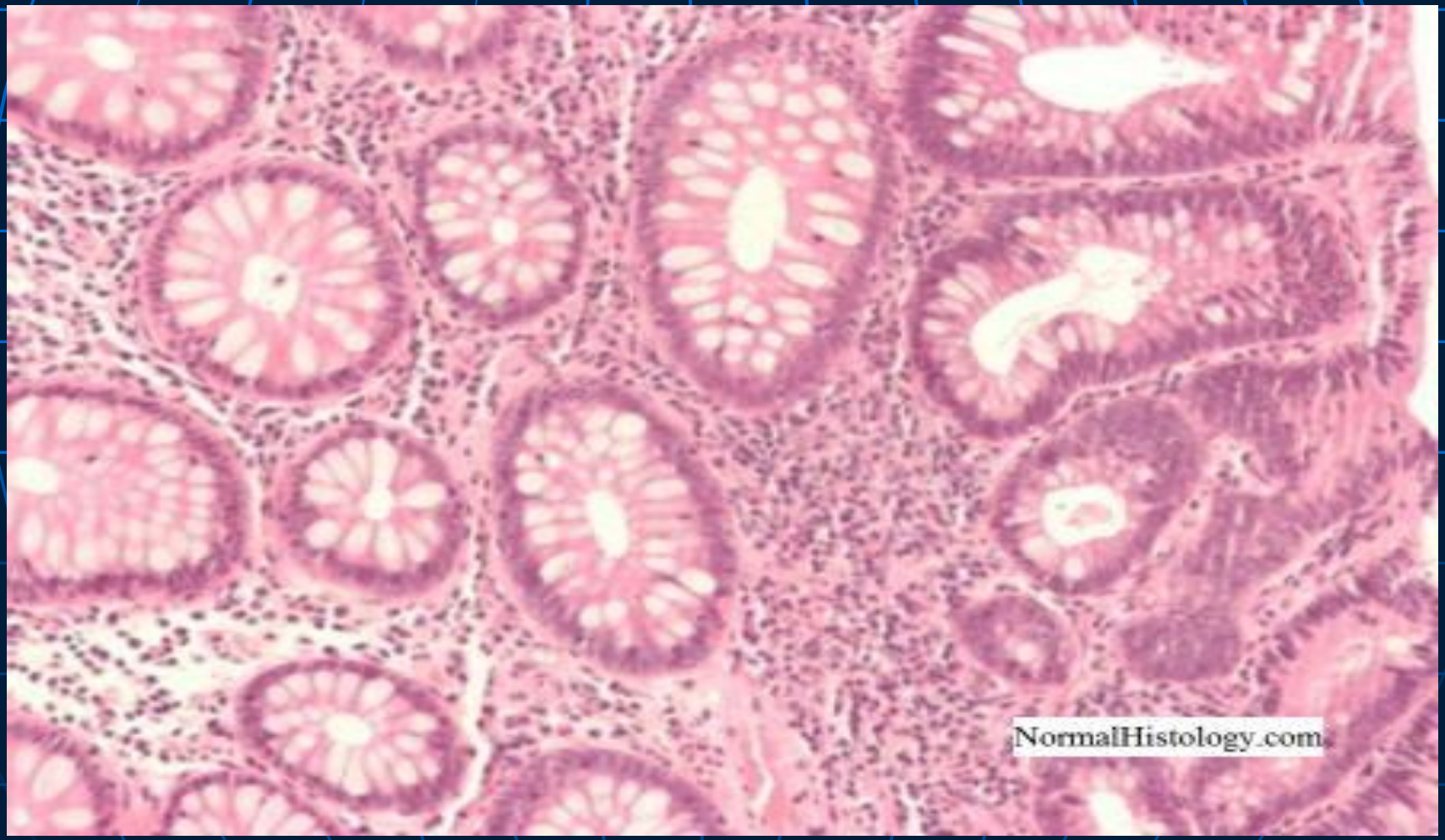
UC Pathology

- Changes are limited to mucosa and sub mucosa except in sever cases.
- There is crypt distoration
- Cryptitis / crypt abscesses

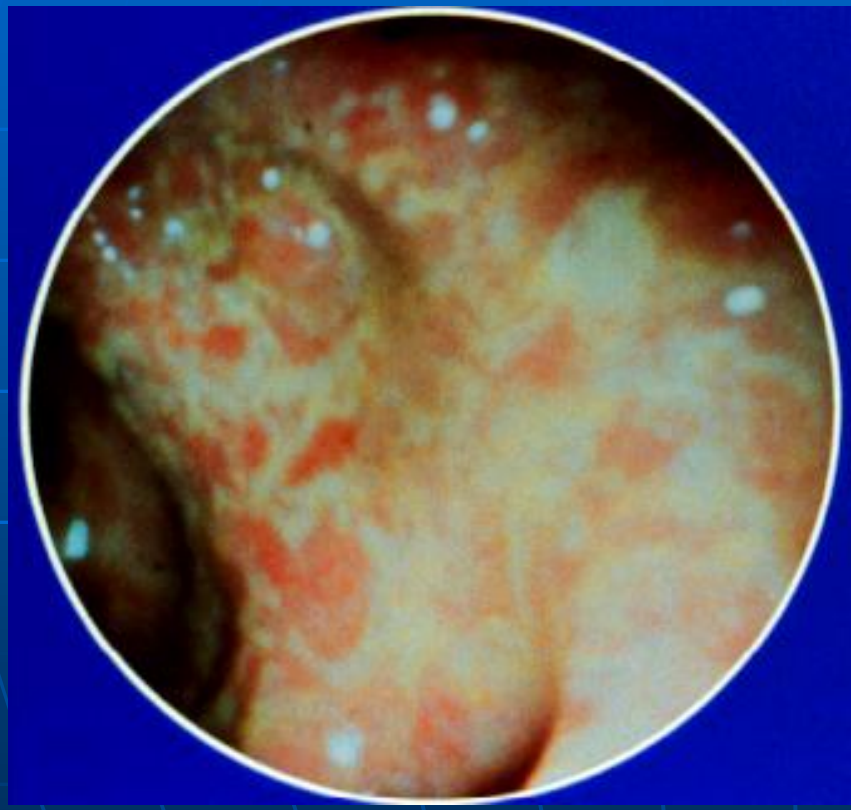
Lamina propria expansion with
acute and chronic inflammatory cells

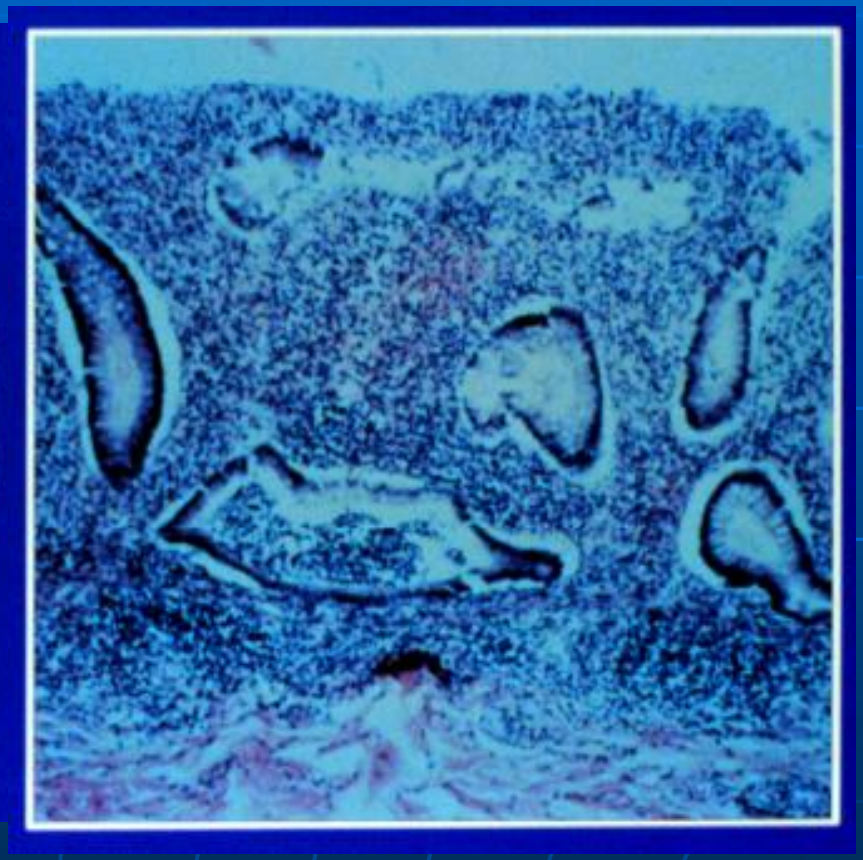
- There is basal plasma cells and lymphoid infiltration.

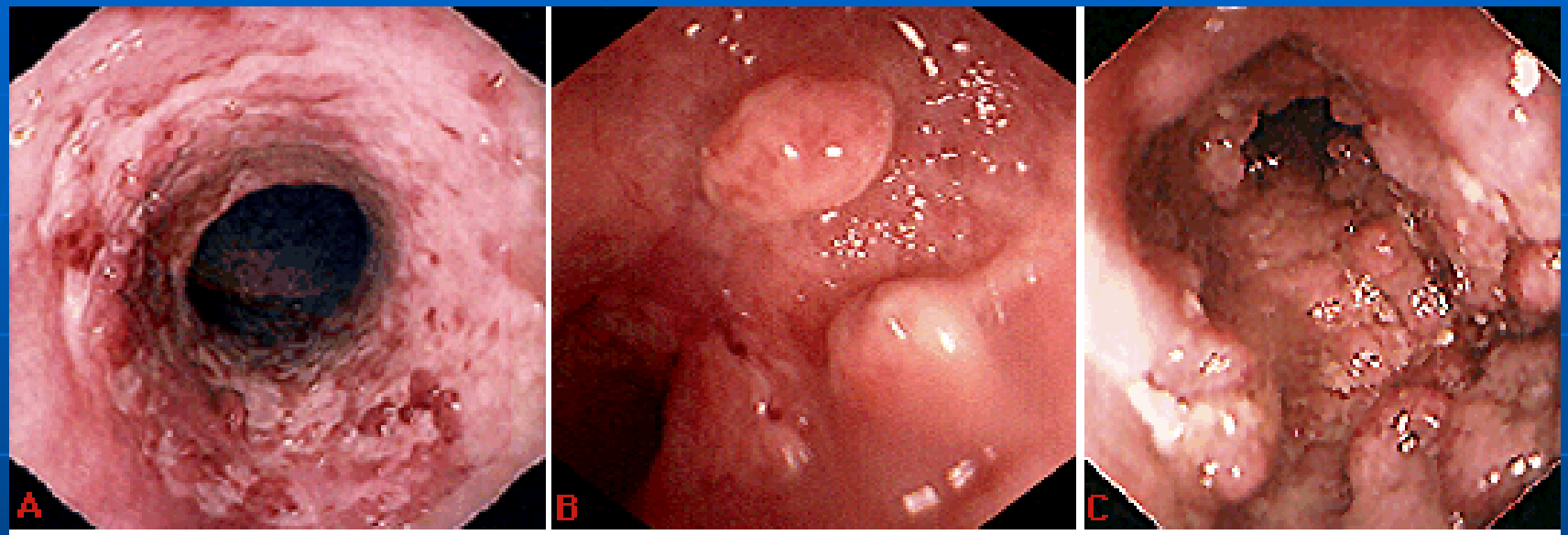
Normal Colon



Severe Ulcerative Colitis
Diagnosis







Ulcerative colitis Endoscopic appearance of ulcerative colitis. Extensive ulceration of the mucosa is the most common endoscopic finding (panel A). The surface is irregular, friable, and erythematous, with loss of the normal vascular markings. Pseudopolyps may form as a reaction to inflammation (panel B); these can become quite extensive (panel C). Courtesy of James B McGee, MD.

NATURAL HISTORY of UC

- the course of ulcerative colitis typically consists of intermittent exacerbations alternating with periods of complete symptomatic remission.
- A small percentage of patients, however, have continuing symptoms and are unable to achieve remission
- Depend on extent of disease

overall mortality is only slightly increased compared with the general population.

Mayo Scoring System for Assessment of UC Activity

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

Goals of IBD Therapy

- Achieve mucosal healing and induce remission
- Maintain **steroid-free** remission
- Prevent / treat complications of disease
- Avoid short and long term toxicity of therapy
- Enhance quality of life

Management Of Ulcerative Colitis

Steroids

5 ASA

Azathioprine/6MP

Biological Treatment :

Infliximab

Adalumumab

Golimumab

Vedlozumab

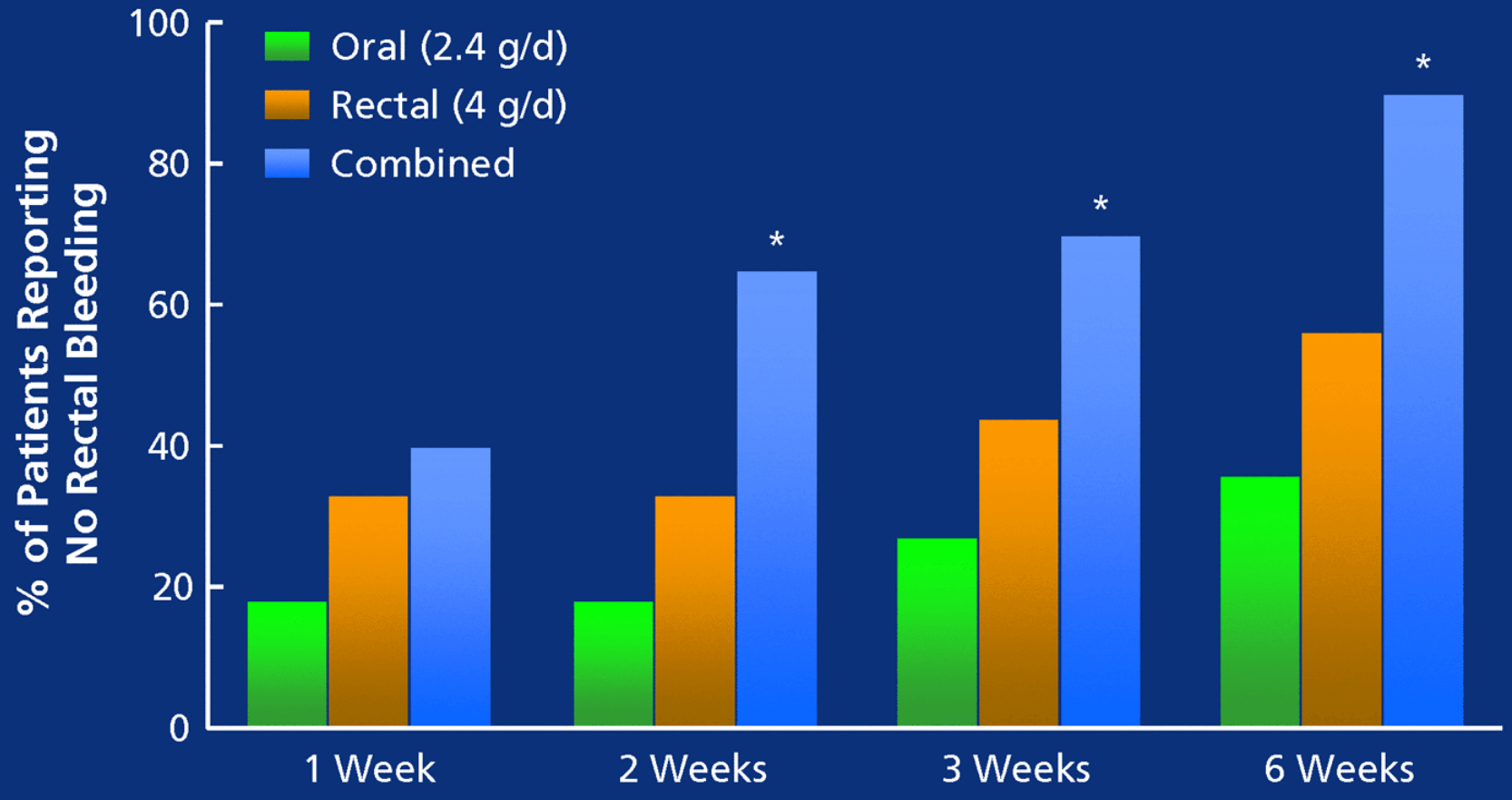
Tofacitinib

Ustikinomab

5 ASA

THE MAIN STAY OF TREATMENT IN UC

Treatment of Distal UC: Oral and Topical Mesalamine Therapy



*P<.002 vs oral alone, P=.04 vs topical alone.

Adapted from Safdi M, et al. *Am J Gastroenterol.* 1997;92:1867-1871 with permission from Blackwell Publishing.

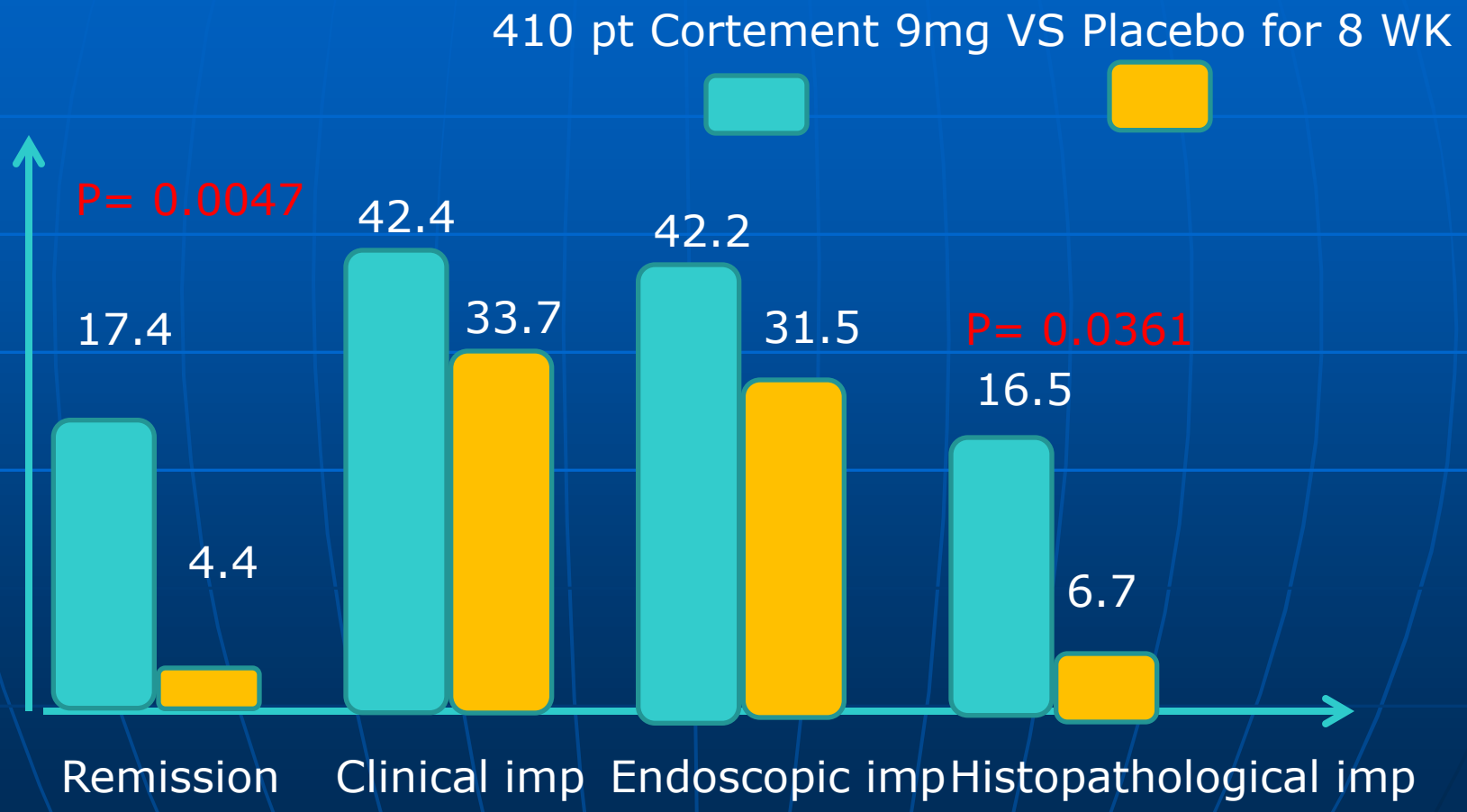
5- ASA in UC

- **Acute-phase oral treatment:** A meta-analysis reported that 5-ASA was superior to placebo with regard to all measured outcome variables.
- **Prevention of relapses of UC with oral treatment:** 5-ASA is statistically significantly better than placebo. 5-ASA and sulfasalazine seemed to have similar efficacy in the long-term (at least 12 months)
- **Acute-phase topical treatment of UC :** Topical 5-ASA were at least as effective, and probably more effective, than topical steroids for the treatment of distal UC

5- ASA in UC

- **Prevention of relapses of UC with topical treatment:** topical 5-ASA formulations were effective not only for the treatment of acute UC but also for maintenance of remission.

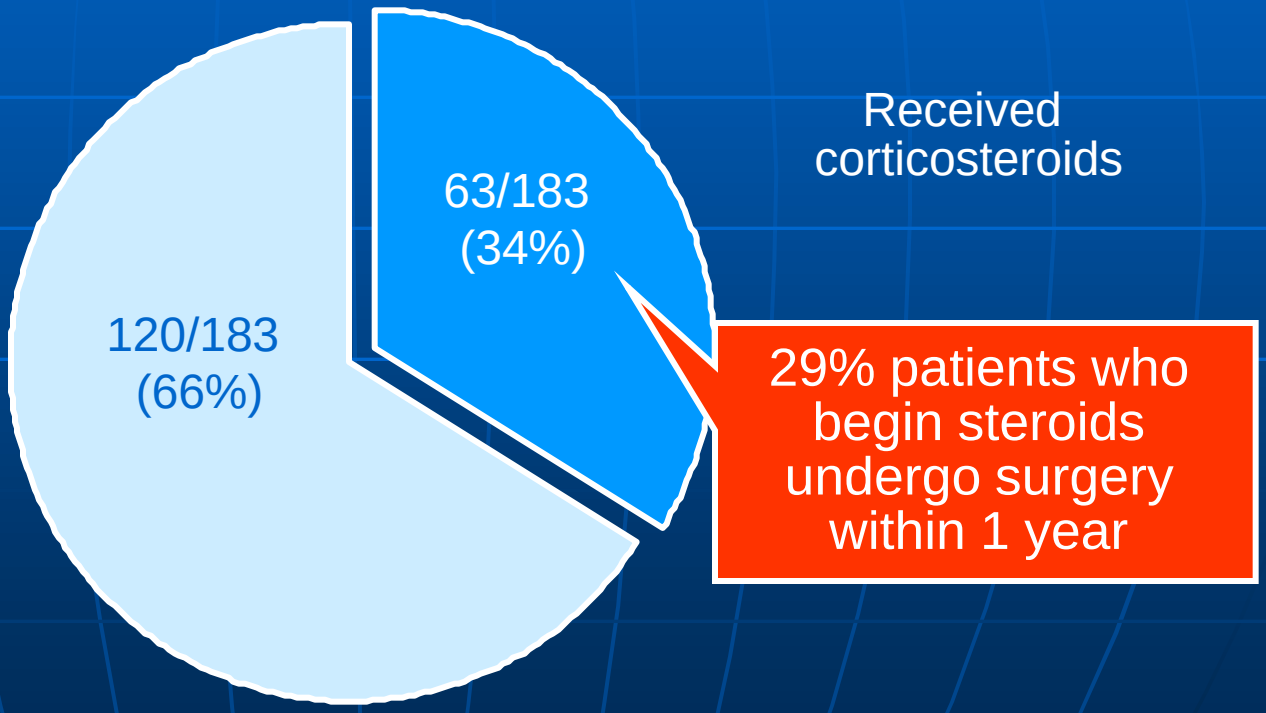
New steroid formulation



Simon Travis Gut 2014

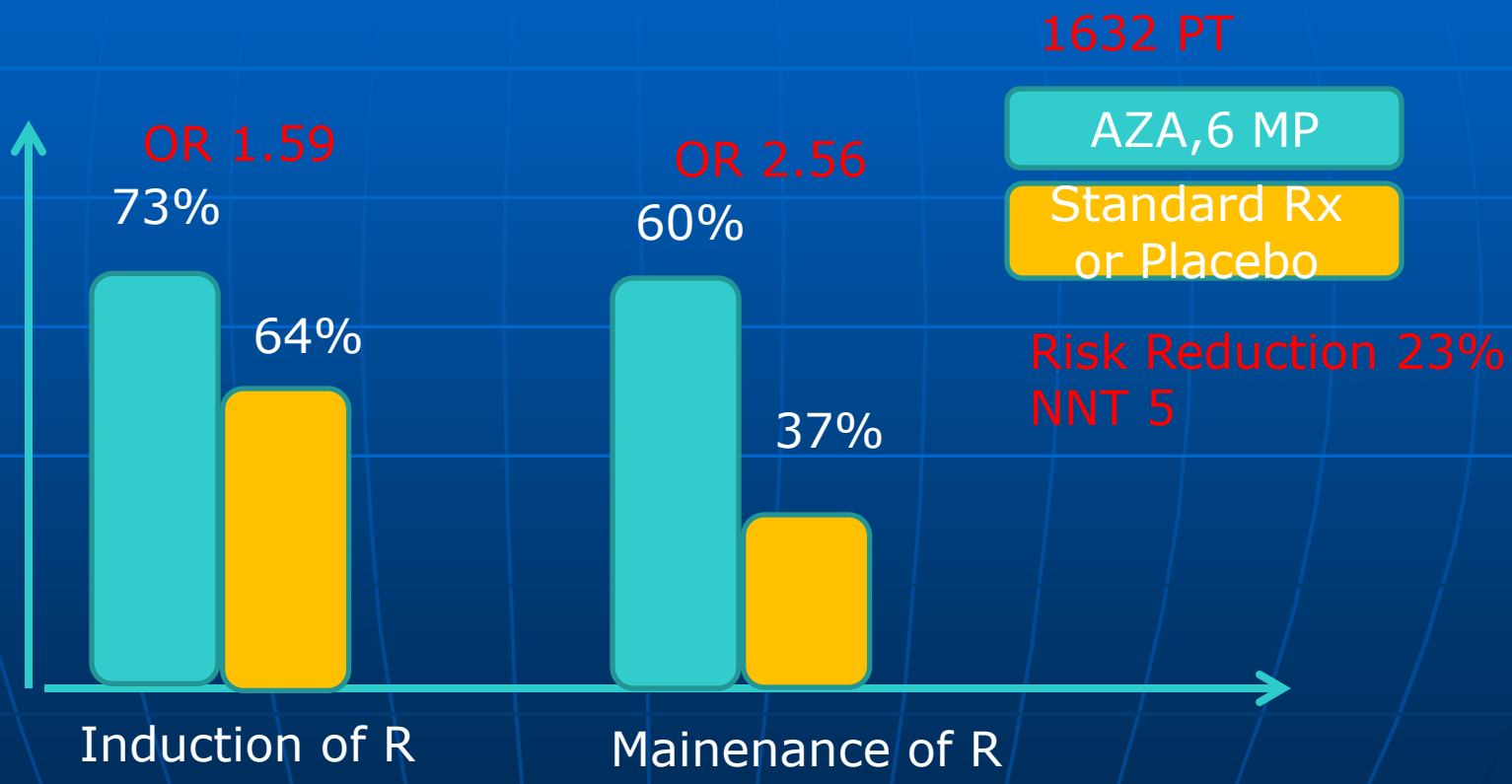
Most UC Patients Do Not Require Corticosteroids

Population-Based Cohort in Olmsted County, MN From 1970–1993
One year Data



Faubion WA et al. *Gastroenterology.* 2001;121:255.

Meta analysis AZA & 6 MP in UC



J.P Gisbert APTh 2009

Ulcerative Colitis and Combination Treatment

Success trial

	IFX + AZA	IFX	AZA
Steroid-free remission	**40%**	24%	24%
Response	**77%**	69%	50%
Mucosal Healing	**63%**	55%	37%

Panccione R et al. DDW 2011. Abstract 835

SEVERE OR FULMINANT COLITIS

Steroid I/V 3-5 days

If No response

cyclosporine?/Infliximab for toxic megacolon

If No response to therapy

Consider colectomy

Consult the surgeon at D1 of admission

INDICATIONS FOR SURGERY IN UC

- Persistent symptoms despite high-dose corticosteroid therapy
- Dependence upon steroids to maintain remission Progression of disease with worsening of the symptoms or new onset of complications while on maximal medical therapy
- Significant treatment-related complications such as severe steroid side effects .
- Detection of unequivocal dysplasia in patients with long-standing colitis during endoscopic surveillance .

Colorectal cancer in UC

- **The risk of colorectal cancer (CRC) is increased in ulcerative colitis**
- Pancolitis — Patients with disease extending to the hepatic flexure or more proximally have the greatest risk of CRCthe risk begins to increase 8 to 10 years following the onset of symptoms
- Left-sided colitis — Most studies have found that the risk of CRC increases after 15 to 20 years
- Proctitis — Patients with ulcerative proctitis and proctosigmoiditis are probably not at increased risk for CRC
- Primary sclerosing cholangitis — An increased risk of CRC has been observed in patients with UC complicated by PSC

Crohn's disease

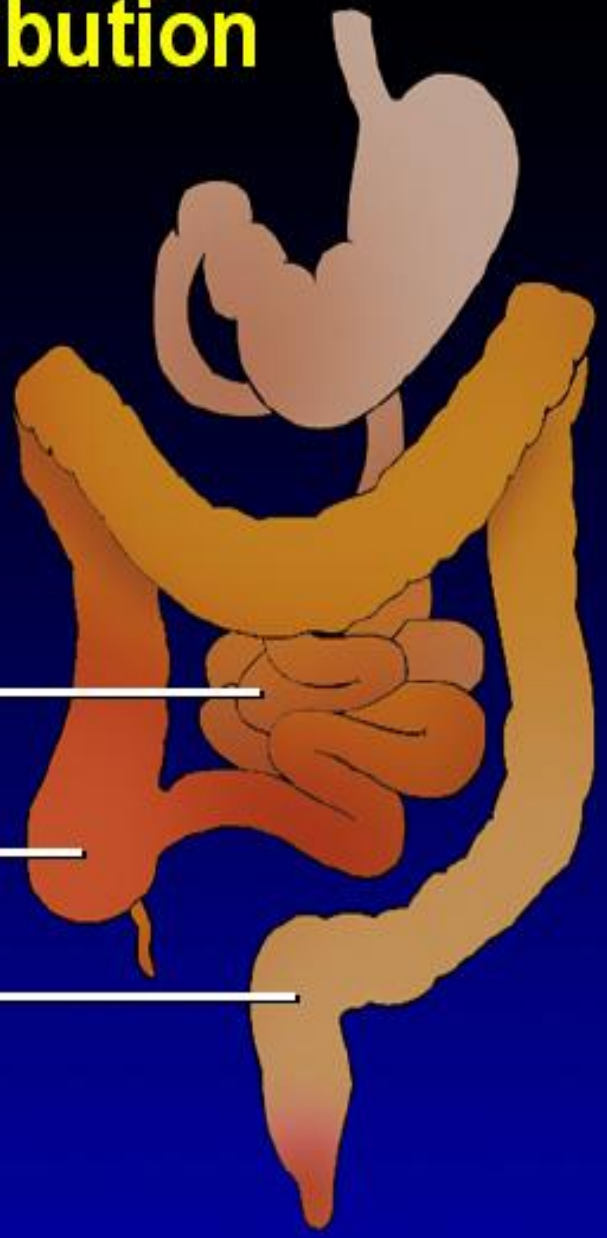
- Crohn's disease is characterized by transmural rather than superficial mucosal inflammation and by skip lesions rather than continuous disease.
- Crohn's disease may involve the entire gastrointestinal tract from mouth to perianal area

CD

Anatomic Distribution

Freq. of involvement

most — least



Small bowel alone 33%

Ileocolic 45%

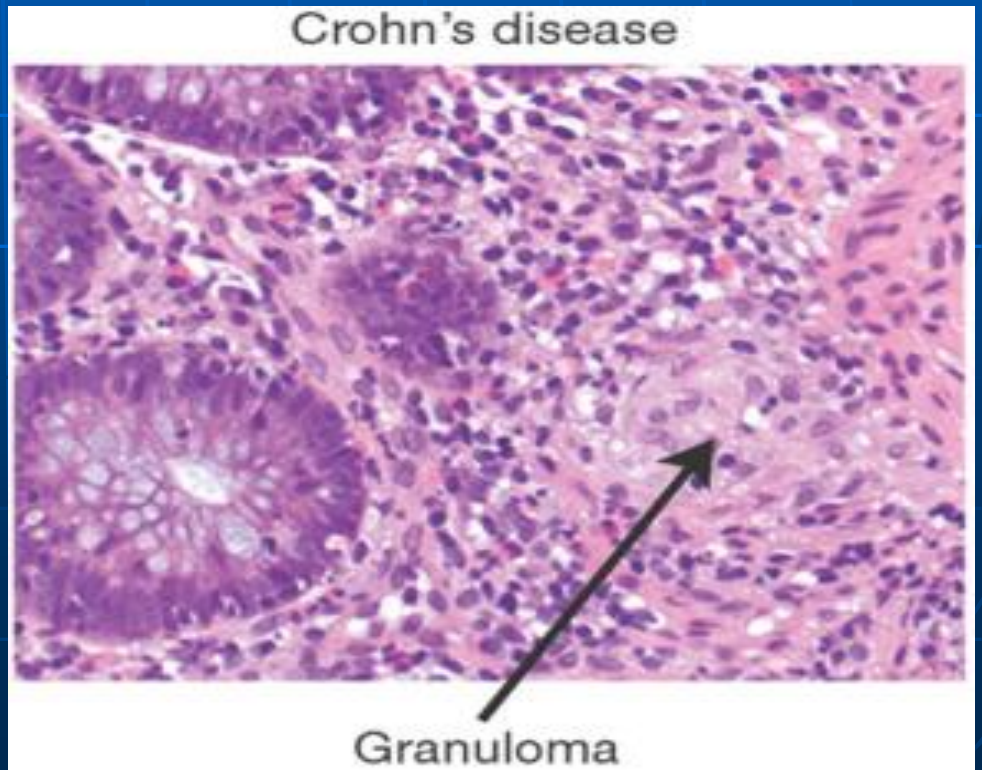
Colon alone 20%

Crohn's Pathology

- The process is transmural.
- Cobble stone appearance of the mucosa.
- The Rectum is spared
- There is skip areas.
- Fistulas fissures, abscess and anal stenosis

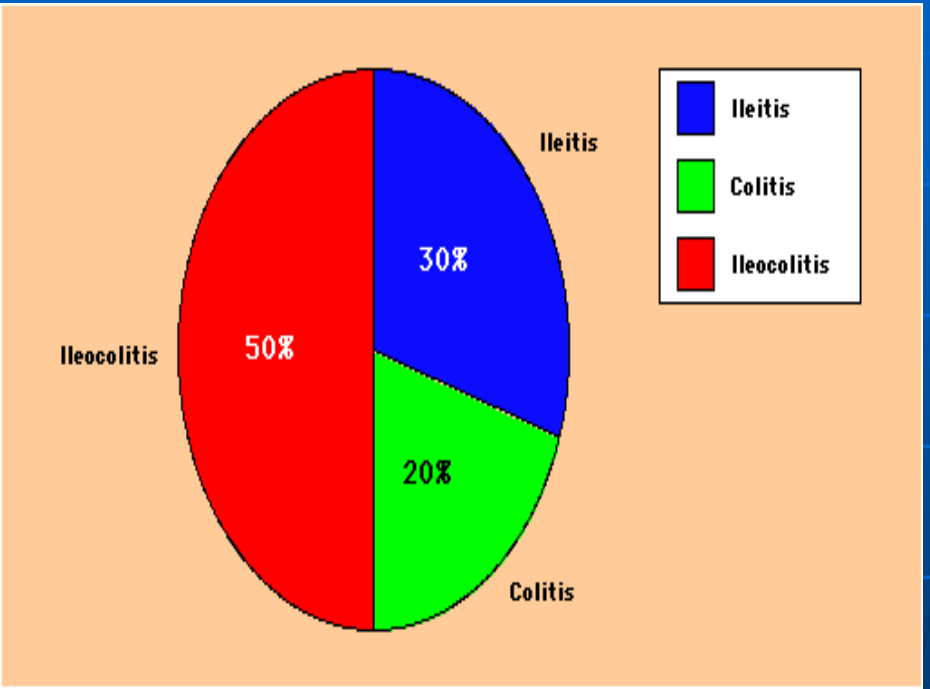
Pathologic Changes

Epithelioid non-caseating granulomas
Chronic inflammatory infiltrate
Crypt architectural distortion



Distribution of Crohns disease

- Approximately 80 percent of patients have small bowel involvement, usually in the distal ileum, with one-third of patients having exclusively ileitis.
- Approximately 50 percent of patients have ileocolitis which refers to involvement of both the ileum and colon.
- Approximately 20 percent have disease limited to the colon
- A small percentage have predominant involvement of the mouth or gastroduodenal area
- Approximately one-third of patients have perianal disease.



Distribution of Crohn's disease Approximate frequency of ileal and colonic involvement in Crohn's disease. Crohn's disease can involve the entire gastrointestinal tract from mouth to perianal area. (Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA through Milner-Fenwick, Inc at 1-800-432-8433.)

CLINICAL MANIFESTATIONS OF CD

- More variable than those of ulcerative colitis because of the transmural involvement and the variability of the extent of disease
- Fatigue, prolonged diarrhea with abdominal pain, weight loss, and fever, with or without gross bleeding, are the hallmarks of Crohn's disease
- 10 percent of patients do not have diarrhea.
- Poor growth is common in children

CLINICAL MANIFESTATIONS

- **Ileitis and colitis** *Diarrhea, abdominal pain, weight loss, and fever are the typical clinical manifestations for most patients with ileitis, ileocolitis, or Crohn's colitis*
- **Abdominal pain**
- **Bleeding** *gross bleeding is much less frequent than in ulcerative colitis*
- **Perforation and fistulae** *Transmural inflammation is also associated with the development of sinus tracts that can lead to serosal penetration and bowel wall perforation*
- **Perianal disease** *perianal pain and drainage from large skin tags, anal fissures, perirectal abscesses, and anorectal fistulae*
- **Other sites of intestinal inflammation** severe oral involvement, *esophageal involvement gastroduodenal Crohn's disease, sprue-like picture*

Complications

- Local complications

1. *Intestinal obstruction*
2. *Severe hemorrhage*
3. *Acute perforation*
4. *Fistulae*
5. *Abscess formation*
6. *Toxic megacolon.*

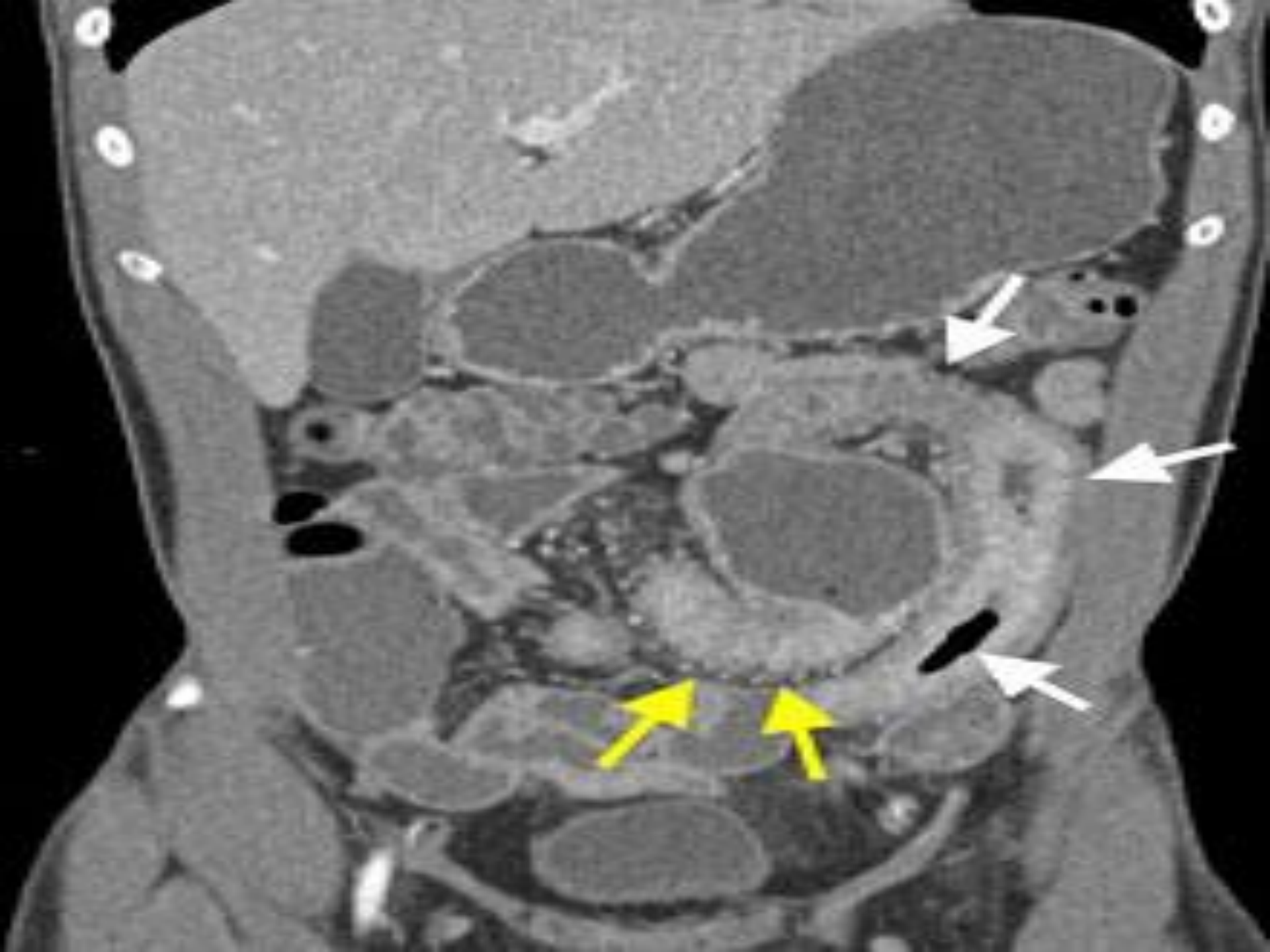
Work up

History and physical exam

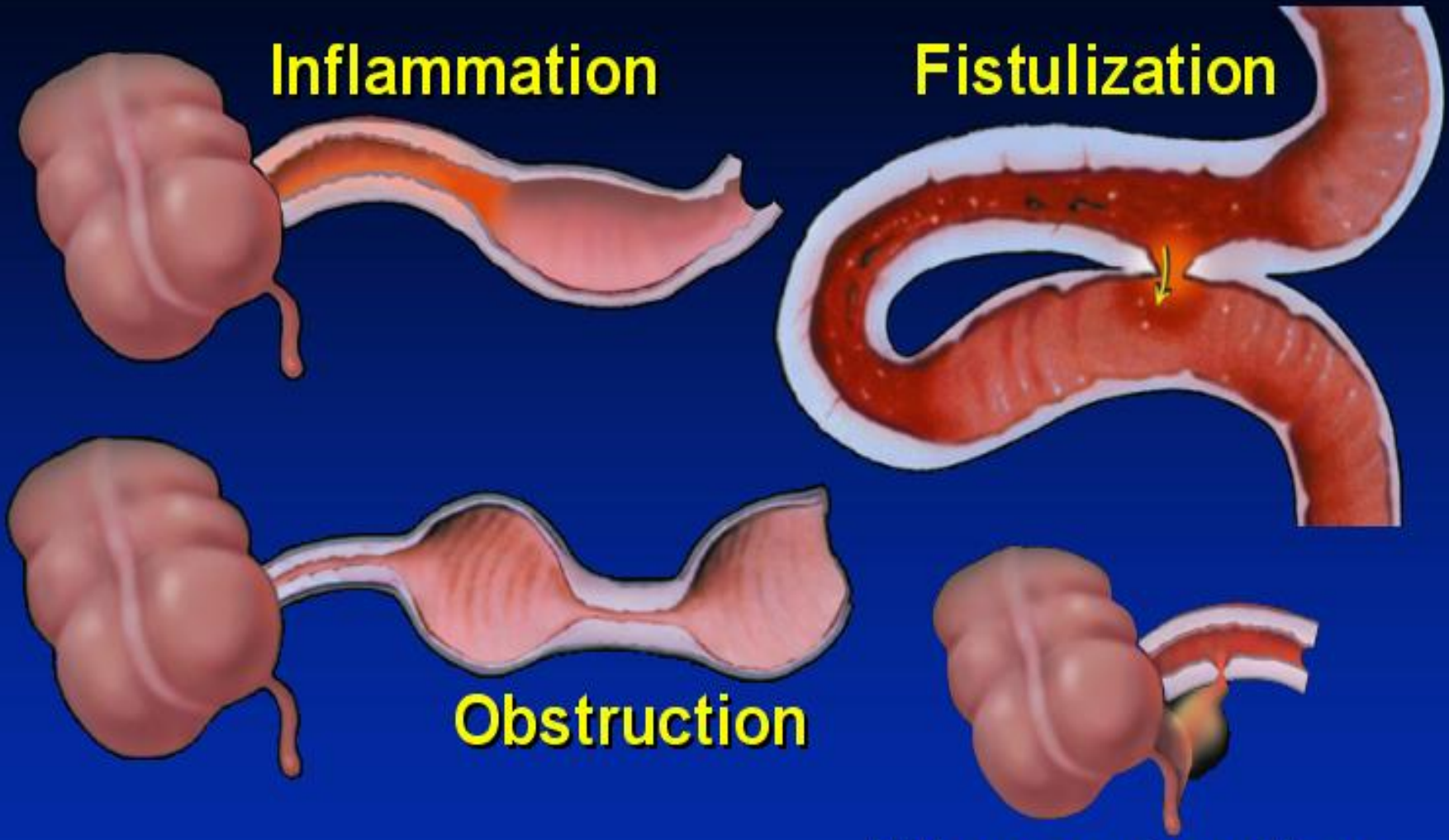
Routine labs CRP, ASCA,ANCA Stool examination

Colonoscopy/Endoscopy

Immaging/capsule endoscopy



CD - Clinical Patterns



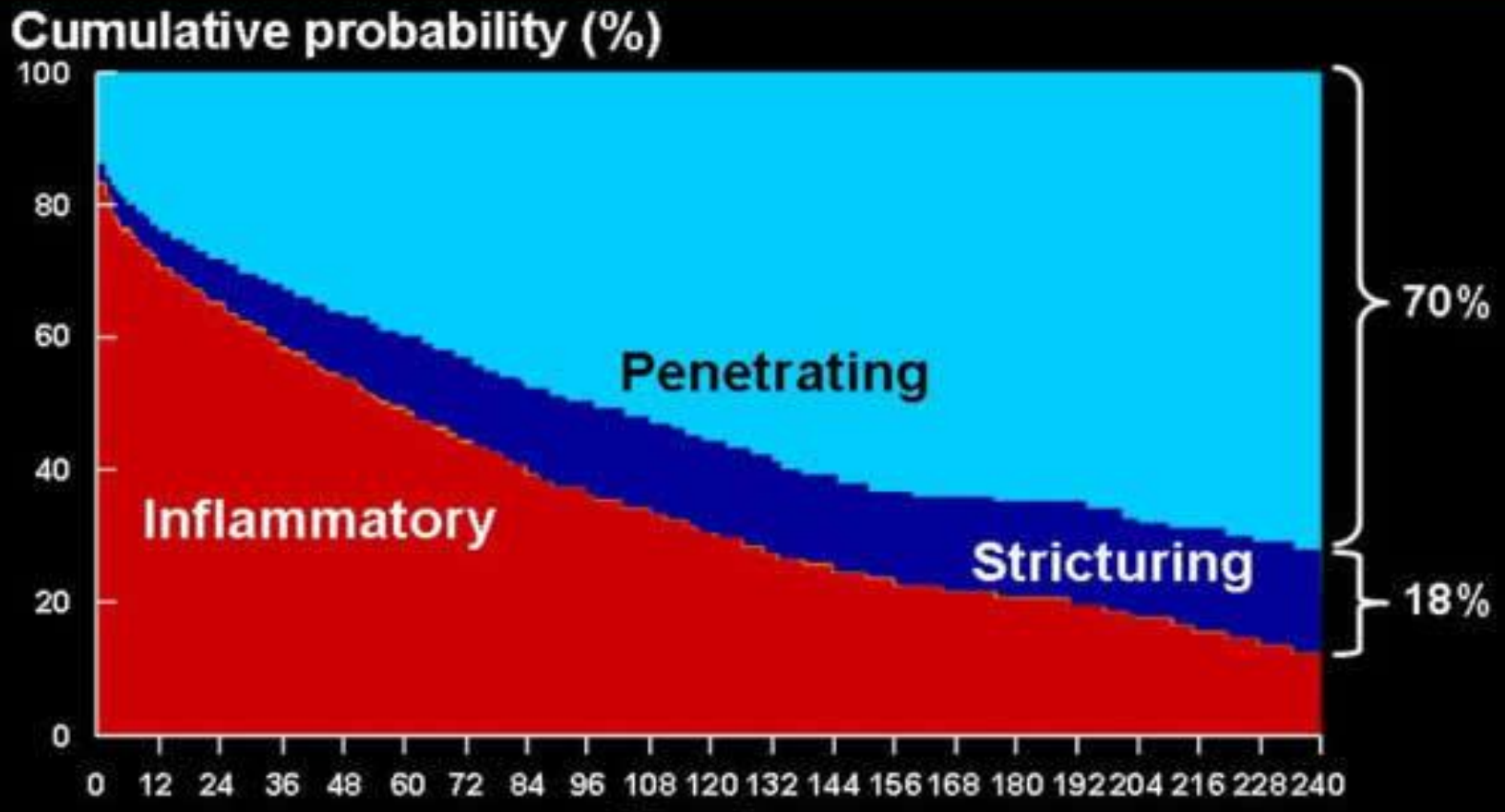
Complications

- Systemic symptoms

Fatigue, weight loss and fever are the primary systemic symptoms in Crohn's disease

- Extra intestinal complications

The evolution of Crohn's disease: Inflammation leads to structural damage



Over a 20 year period, 88% risk of developing stricturing (18%) or penetrating (70%) disease

Cosnes et al, Inflamm Bowel Dis 2002; 8: 244

Severity of CD
CDAI

Crohn's Disease Activity Index†

1	Number of liquid or soft stools (each day for 7 days)	×2
2	Abdominal pain, sum of 7 daily ratings (0=none, 1=mild, 2=moderate, 3=severe)	×5
3	General well-being, sum of 7 daily ratings (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)	×7
4	Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or apphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 100°F	×20
5	Use of diphenoxylate or loperamide for diarrhea (0=no, 1=yes)	×30
6	Abdominal mass (0=no, 2=questionable, 5=definite)	×10
7	Hematocrit (males, 47-HCT; females 42-HCT)	×6
8	Body weight (1-weight/standard weight) × 100 (add or subtract according to sign)	×1

Clinical Meaning of Threshold Scores

		Very poor	Poor	Fair to good	Very well
600	Very severe	67%	6%	0%	0%
450					
300	Active	33%	82%	69%	10%
150					
0	Remission	0%	6%	31%	90%

†Data from Best, WR. Gastroenterology 1976; 70:439.

5 ASA in CD

for the treatment of acute CD, different 5-ASA formulations may be chosen depending on the location of the disease.

the risk of clinical recurrence may be significantly reduced by 5-ASA maintenance treatment in patients with surgically induced remission.

The length of previous remission of CD does not seem to be useful in clinical practice for predicting the response to5-ASA for the maintenance of remission in a particular patient

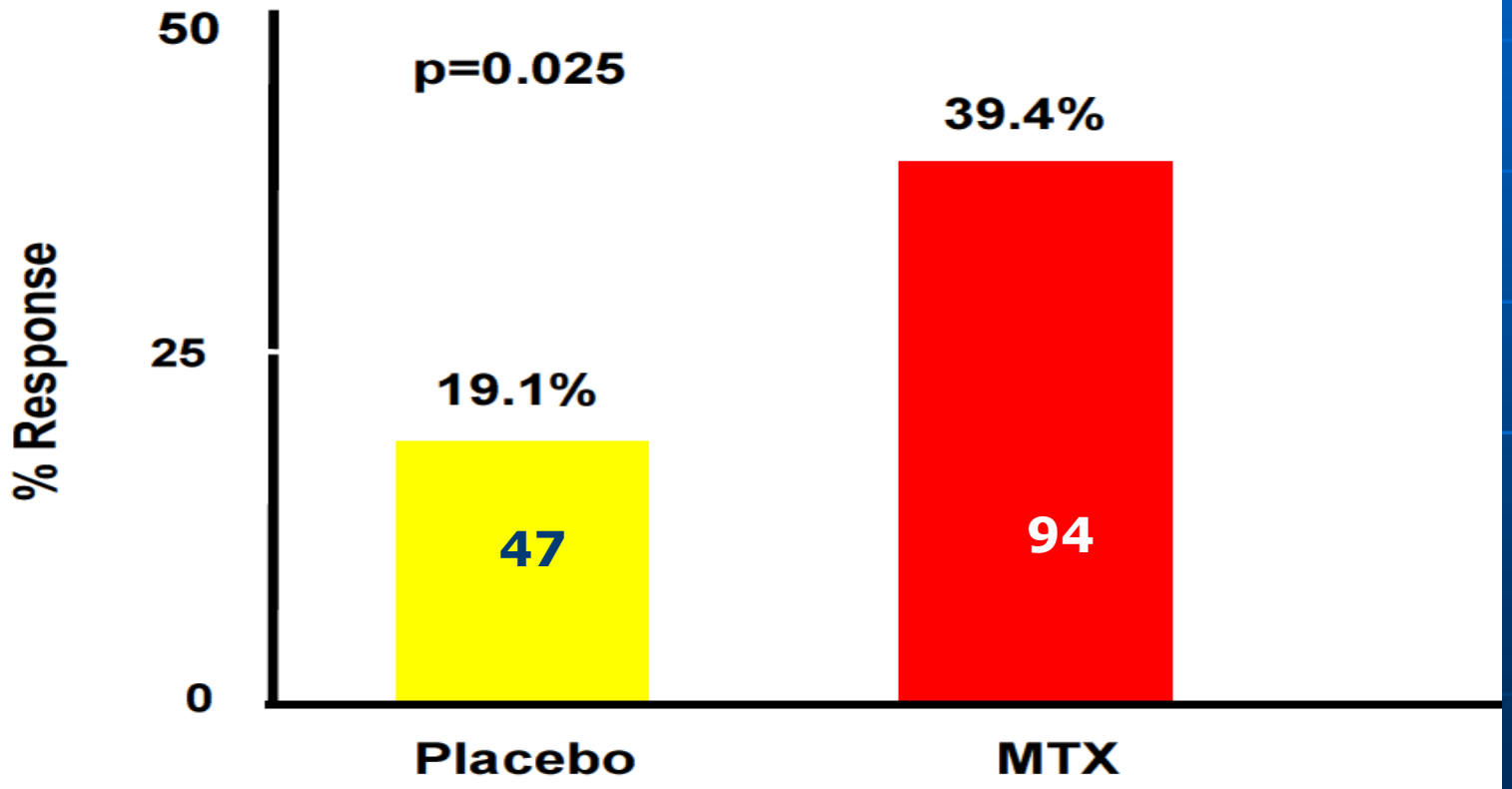
5 ASA in CD

when prescribing 5-ASA formulations for the acute-phase treatment of CD, high doses of these drugs should be used

Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination

MTX For Induction of Remission

Multi centre Double blinded Placebo controlled study patient With Crohn's disease



Feagan. N Eng J Med. 1995 Feb 2;332 (5):292-7

MTX For Maintenance of Remission CD

Multi centre Double blinded Placebo controlled study patient With Crohn's disease

MTX 15 my I/M Vs Placebo

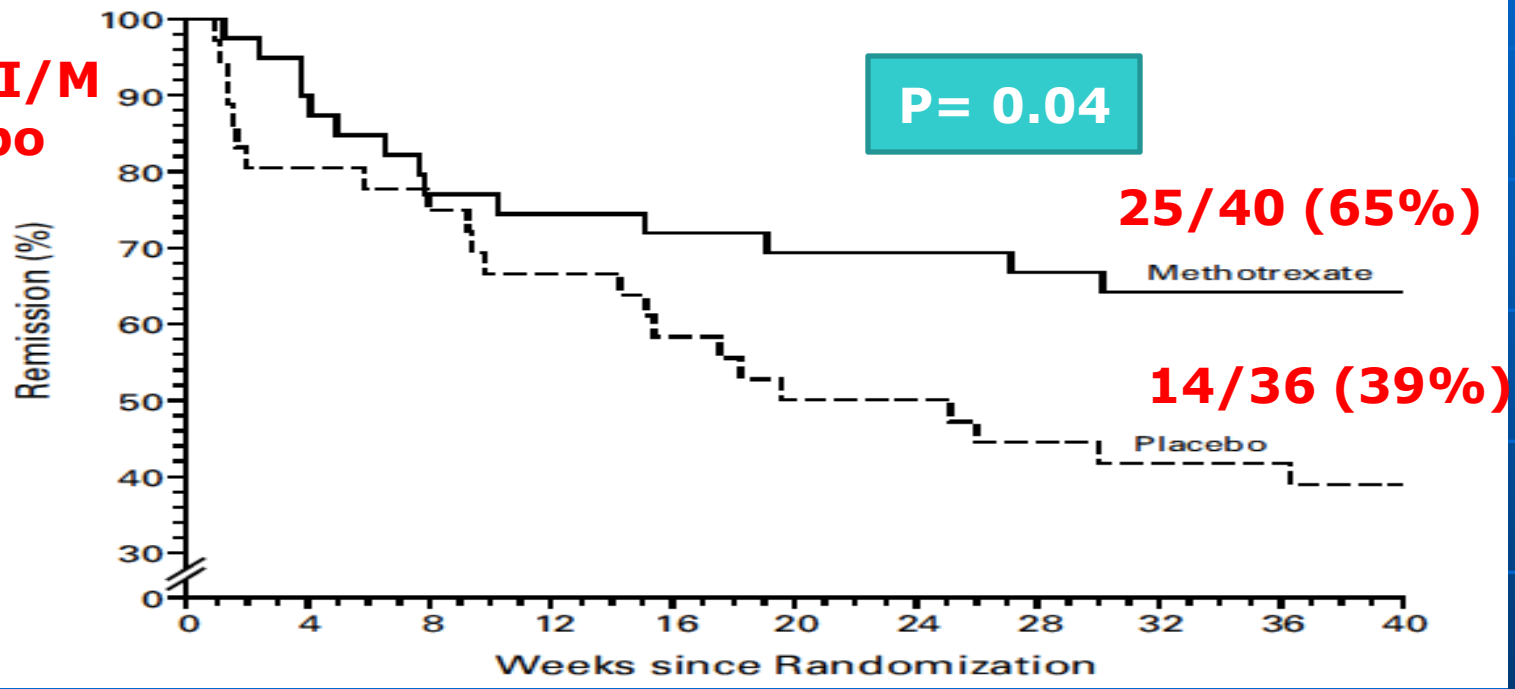


Figure 1. Kaplan–Meier Estimates of the Time to Relapse in the Methotrexate Group and the Plac Group.

11/40 (28%) MTX vs 21/36 (58%) Placebo used prednislon p = 0.01

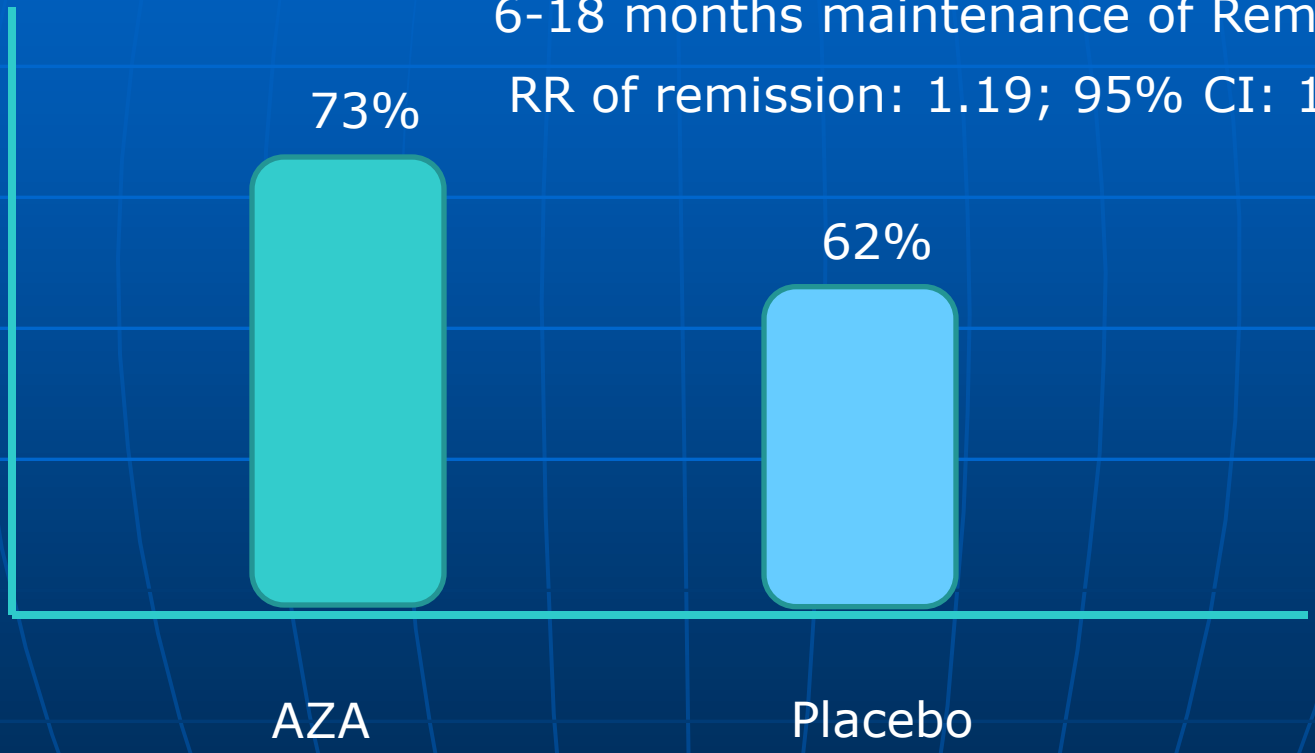
Feagan BG NEJM 2000

Thiopurine in CD

489 Pt from 6 studies

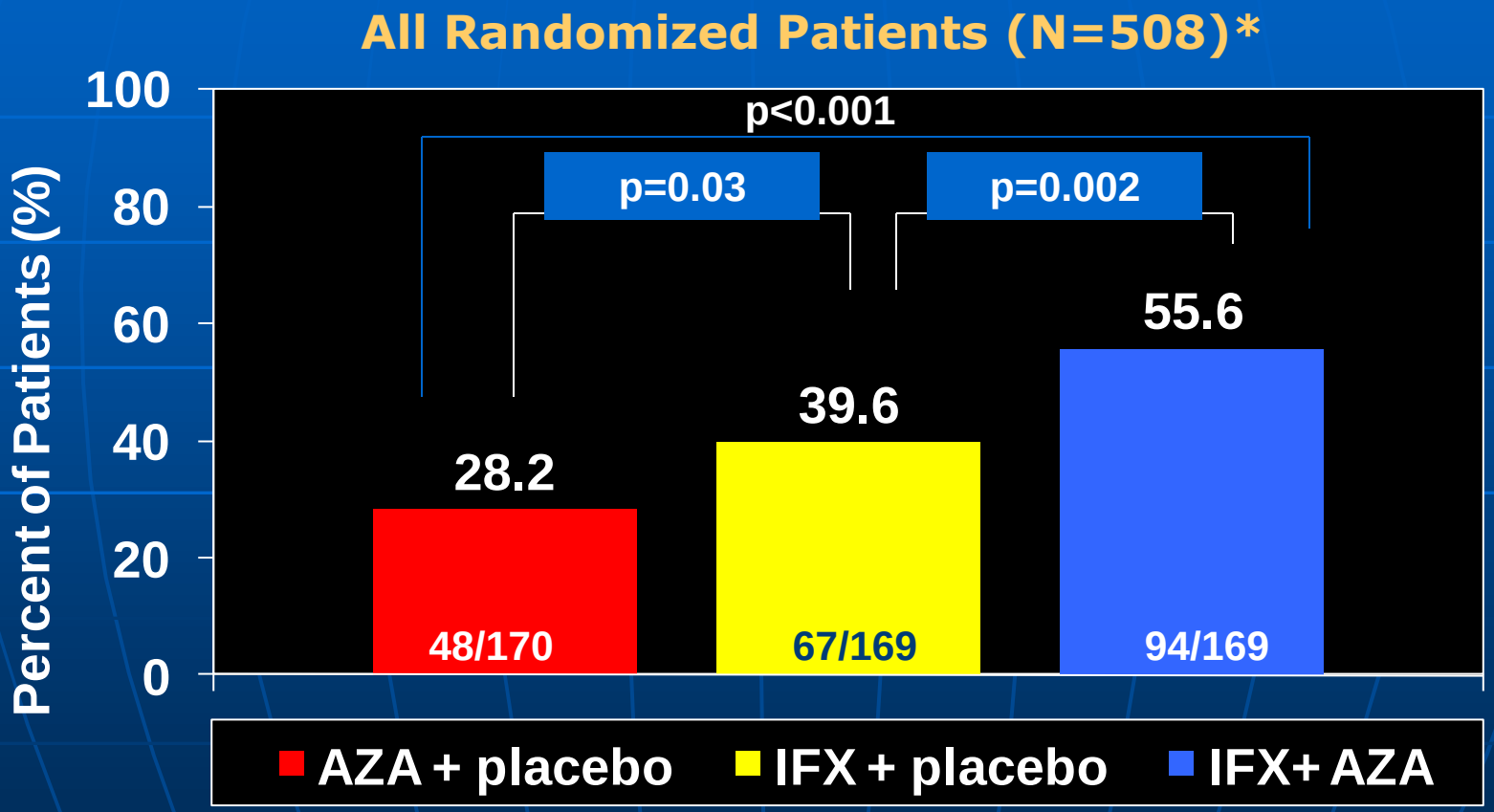
6-18 months maintenance of Remission

RR of remission: 1.19; 95% CI: 1.05–1.34)



Chande N, Patton PH, Tsoulis DJ *et al*. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2015(10):Cd000067

Corticosteroid-Free Clinical Remission at Week 50



* Patients who did not enter the Study Extension had Week 26 values carried forward

ILEOCOLITIS AND COLITIS

- **5 ASA** *For the patient with mild symptoms, therapy is initiated with sulfasalazine or one of the mesalamine agents NNT 17*
- **Antibiotics** *— Antibiotic therapy should be considered in the patient who with infection/abscess,post op.perianal(Metronidazole)*
- **Corticosteroids** *for induction of remission, prednisone is initiated at a dose of 40 to 60 mg/day*
- **Azathioprine and 6-mercaptopurine** *For most patients the main stay of treatment for maintenance.*

REFRACTORY DISEASE
Moderate to severe D

- Remains symptomatic despite adequate doses of steroids (steroid-resistant), and antibiotics or the patient who flares once the prednisone is decreased or stopped (steroid-dependent)
- Azathioprine and 6-mercaptopurine
- Methotrexate
- Infliximab
- Humera
- Vedlozumab
- Ustikinomab

PERINEAL DISEASE

- In those who present with draining **fistulae and small abscesses** not amenable to surgical drainage, therapy is initiated with **metronidazole** at a dose of 10 mg/kg per day
- **Ciprofloxacin (500 mg BID)** can be tried in patients who fail metronidazole or be used as an alternative initial therap
- treatment with azathioprine or 6-MP + Biological Agents
- **surgical management**

FISTULAE

- Infliximab 5mg/kg administered at weeks 0, 2, and 6 and azathioprine 2-2.5 mg/kg or 6-MP 1 to1.5 mg/kg are the drugs with the best established roles for the medical treatment of active Crohn's fistulous disease.
- Adalimumab

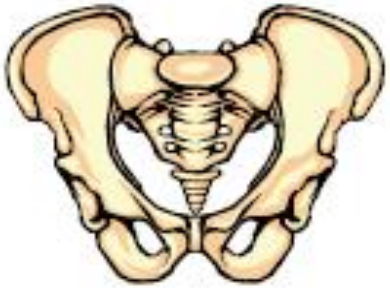
SURGICAL OPTIONS FOR CROHN'S DISEASE

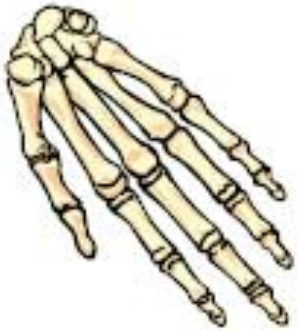
- The major indications for surgery are obstruction and perforation in small intestinal Crohn's disease, and chronic disability and failure to respond to medical therapy in those with colonic involvement.

Colorectal cancer in CD

- The AGA concluded that the risk of colorectal cancer associated with ulcerative colitis and Crohn's colitis is similar for comparable extent, duration, and age of onset of inflammatory disease.

IBD is a Systemic Inflammatory Disorder!





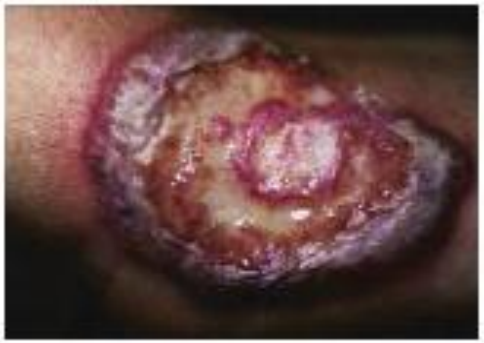
Skin

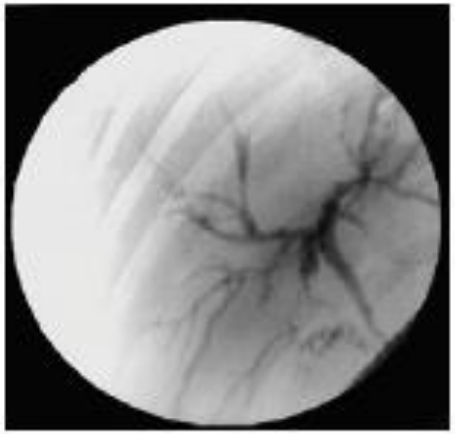
Eye

Bones and Joints

Kidney

Hepatobiliary





Images courtesy of DT Rubin.

Systemic complications of IBD

- Eye involvement with conjuctivitis, uveitis and episcleritis
- ankylosing spondylitis & Sacoilitis
- peripheral arthritis
- Sclerosing cholangitis, steatosis, cholelithasis
- Venous and arterial thromboembolism
- Autoimmune hemolytic anemia
- Skin disorders such as erythema nodosum and pyoderma gangrenosum
- Renal calculi, uretric obstruction, fistulas.
- Metabolic bone disease

The END