IBD

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Mbbs.md.fracp(19061)

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Disclosure

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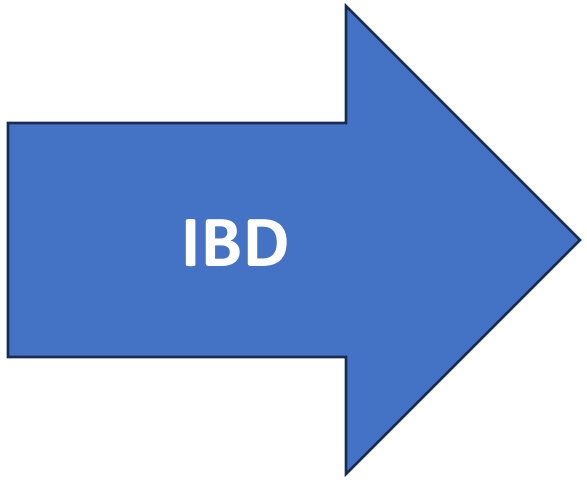


Chronic Remitting relapsing inflammatory diseases that affect the gut

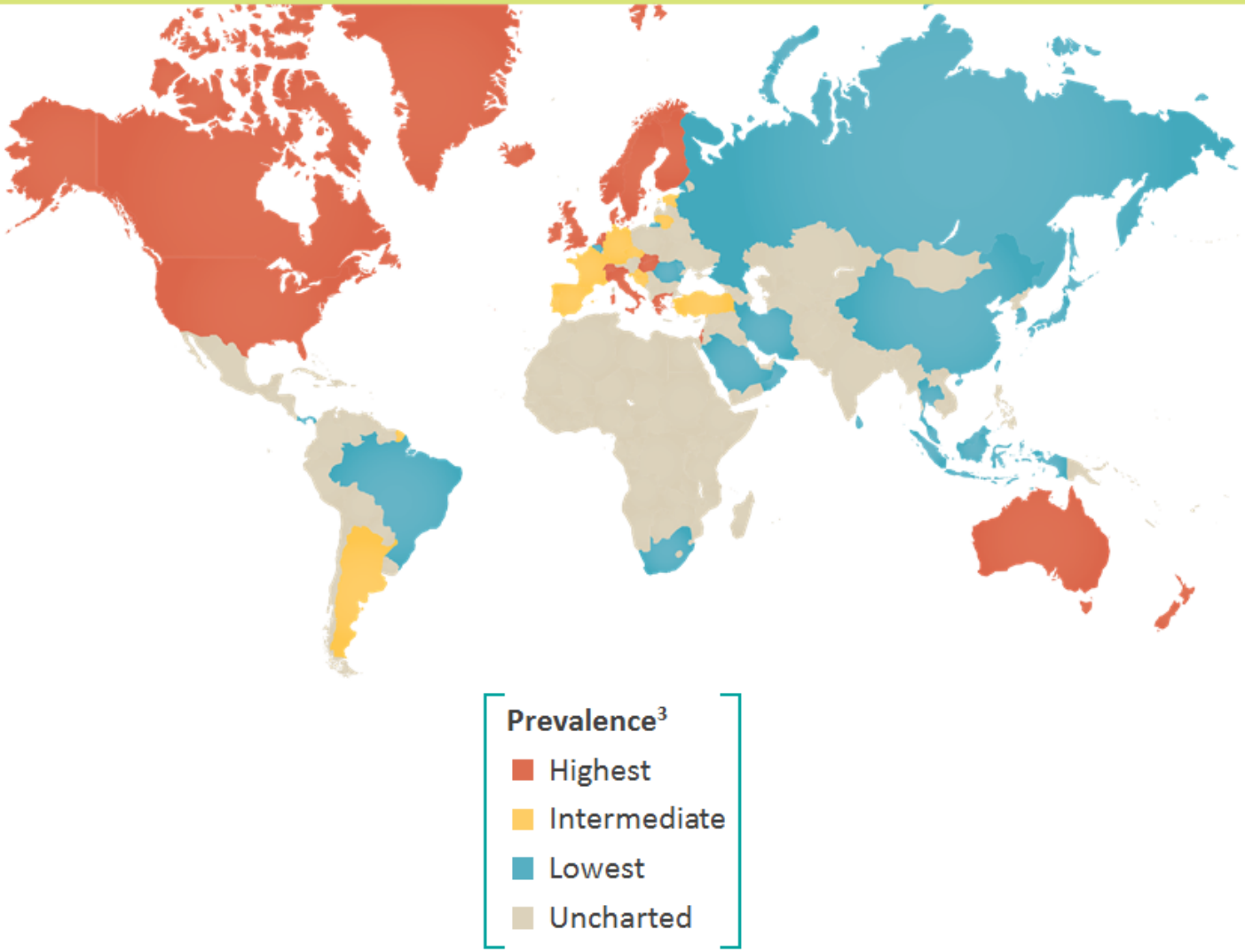
May be associated with other inflammatory diseases.

Ulcerative Colitis

Crohn's disease

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]

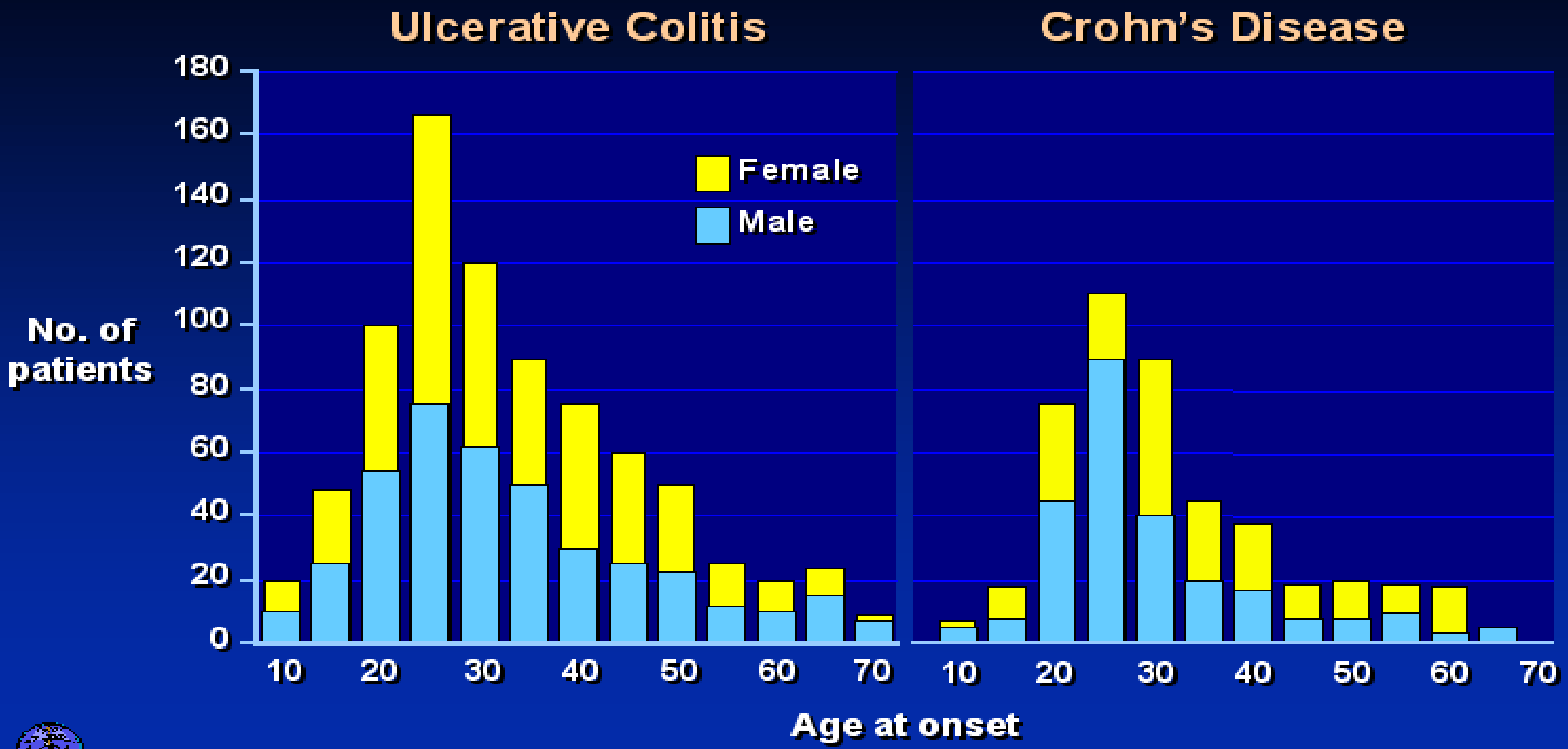


1. Kaplan GG. *Nat Rev Gastroenterol Hepatol.* 2015;12(12):720-7. 2. Kappelman MD, et al. *Dig Dis Sci.* 2013;58(2):519-525. 3. Molodecky NA, et al. *Gastroenterology.* 2012;142(1):46-54.

Distribution of the disease among population

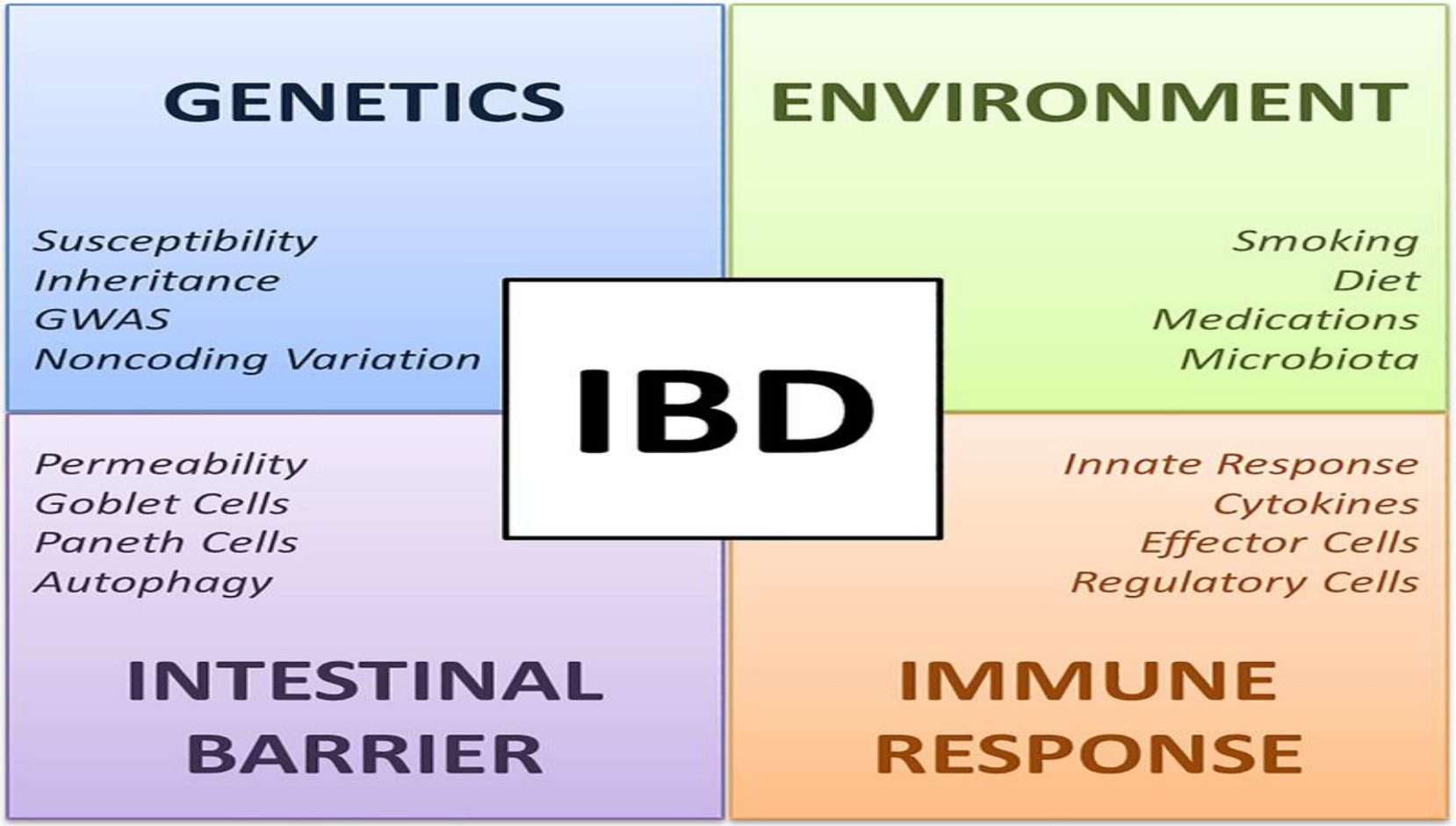
- Age of onset 15-40 years.
- Second peak 50-80.
- Male and females affected equally
- Whites more than blacks.
- Incidence 3-15 (UC), 1-10 (CD)/100,000
- Prevalence: 50-80 (UC), 20-100 (CD)

IBD - Age and Sex Distribution



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

Pathogenesis



Infectious
Immunological
Genetic
Dietary
Environmental
Vascular
Allergic
Psychogenic

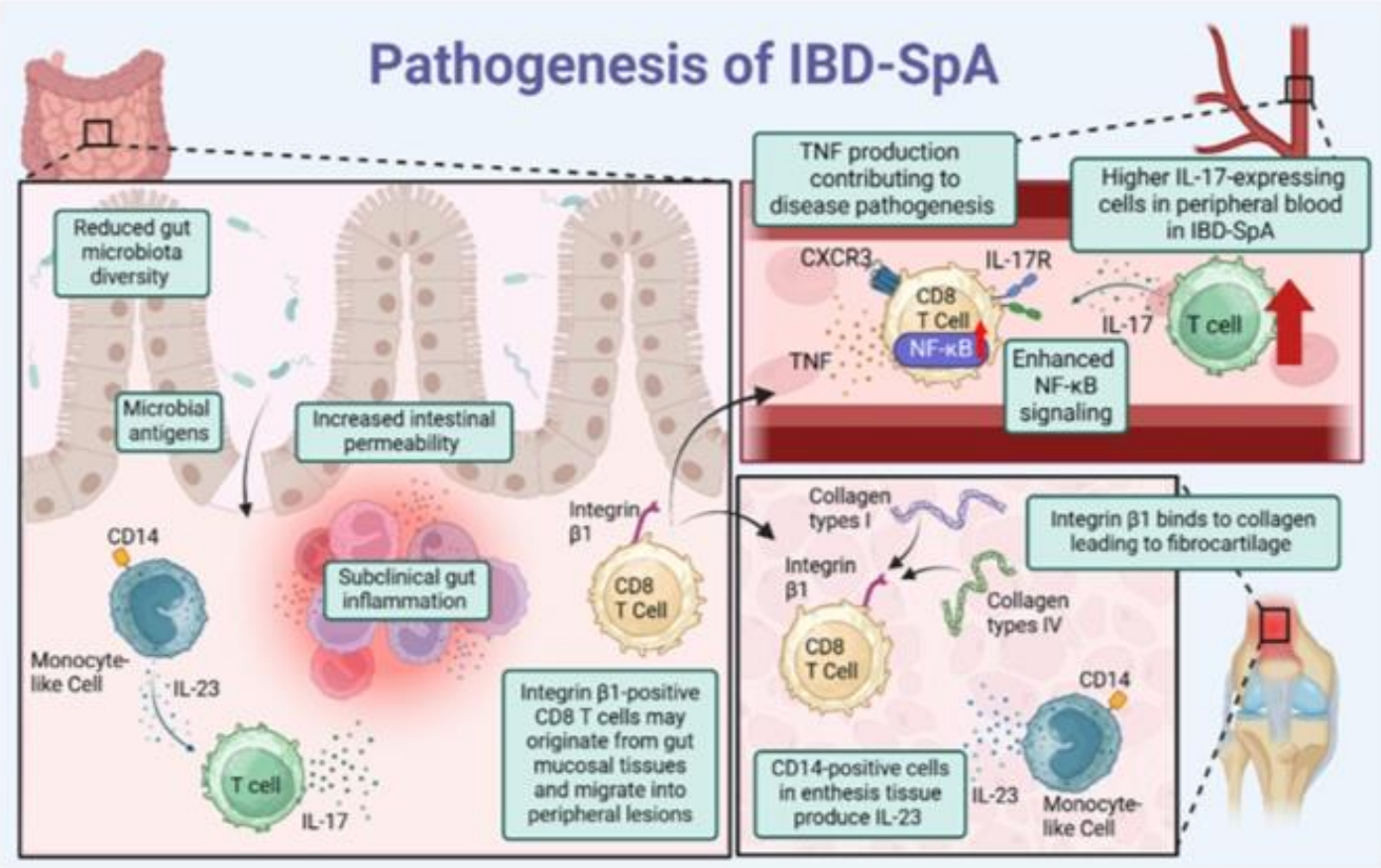
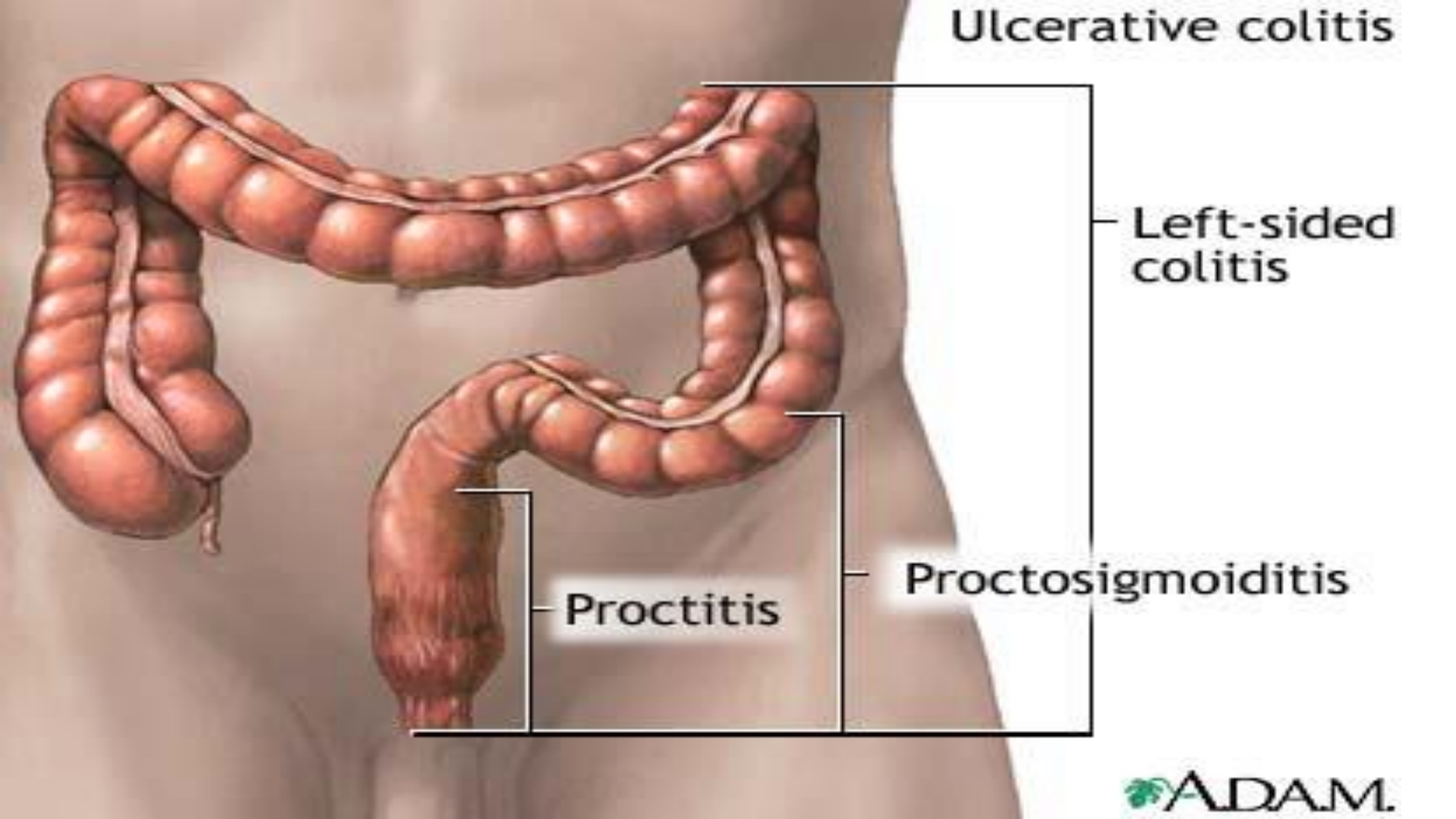


Fig. 5. Schematic representation of IBD-SpA pathogenesis.
This figure represents the current understanding of IBD-SpA pathogenesis. The disease is thought to originate from intestinal inflammation, which triggers the migration of pathogenic immune cells from the gut into the bloodstream and subsequently to enthesitis sites, leading to inflammation.

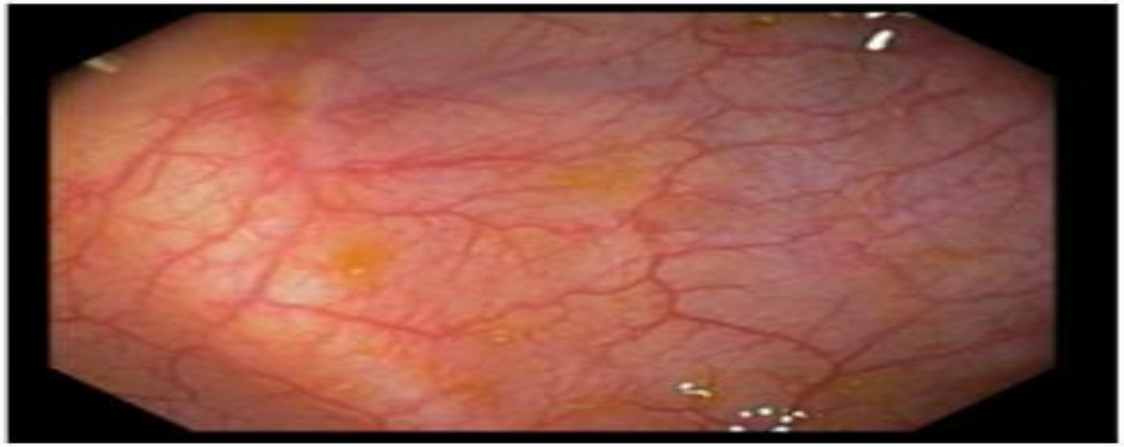
- IBD and share common signaling pathways. Genome-wide association studies have revealed that the IL-23–IL-17 axis is involved in the pathogenesis of both diseases
- TNFα plays a crucial role in the inflammatory processes of IBD
- Increased intestinal permeability is linked to the subsequent development of CD
- IBD are associated with reduced gut microbiota diversity

Distribution of the Disease

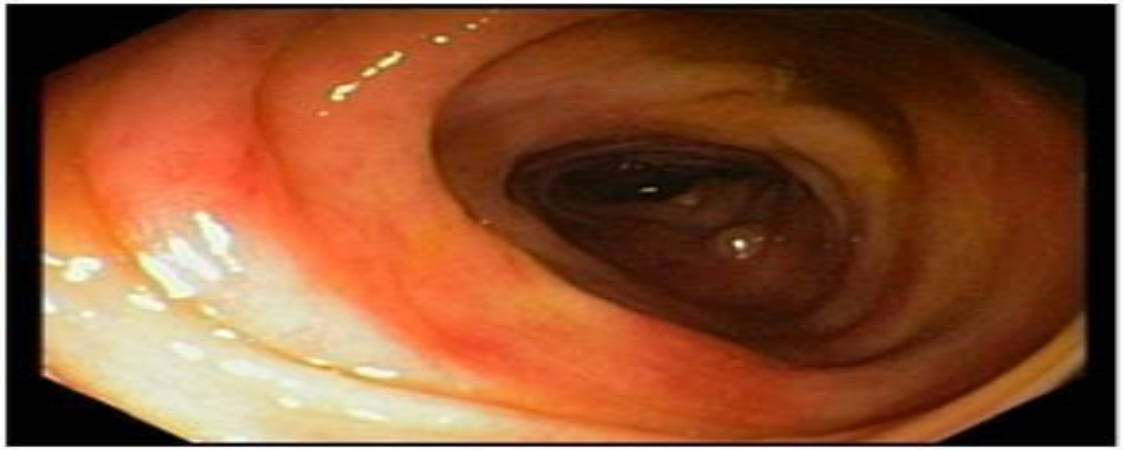
- UC : is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon.
- It almost invariably involves the rectum and may extend in a proximal and continuous fashion to involve other portions of the colon


Ulcerative colitis
Left-sided colitis
Proctosigmoiditis
Proctitis
A.D.A.M.

Normal mucosa

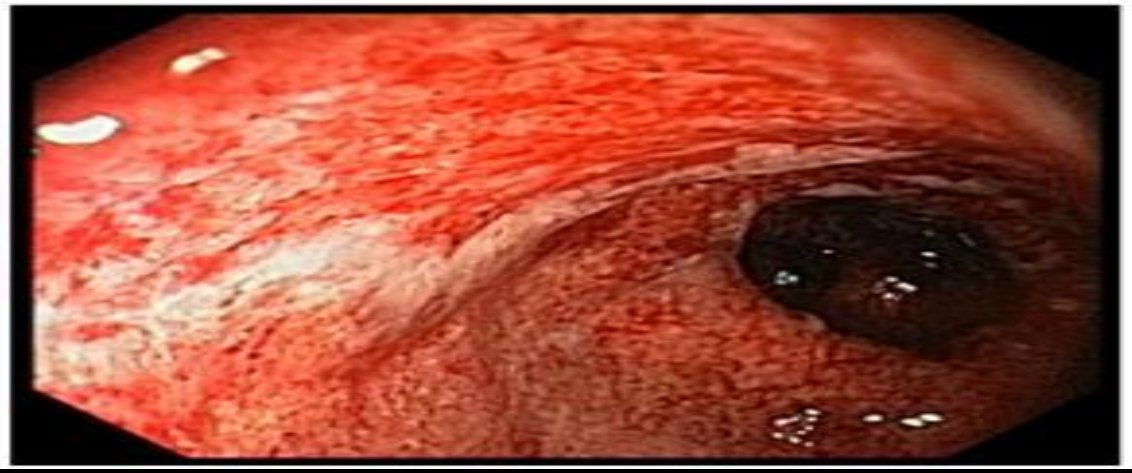


Mild inflammation



Moderate inflammation

Severe inflammation



Presentation

A Young patient presented with loose bowel motion with blood for the last 6 weeks.

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

Severity of the Disease

0-4 Mild, 5-9 Moderate, 9-12 Severe

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

Presentation

- Gradual onset of symptoms, sometimes preceded by a self-limited episode of **rectal bleeding** that occurred more then 4 weeks
- 30% Mild and limited to the rectum or distal colon
- 30% Limitted to the left colon up to the splenic flexure
- 30% pancolitis.
- 10% present with fulminant disease.
- It is important to exclude infectious etiology and CD

Diagnosis

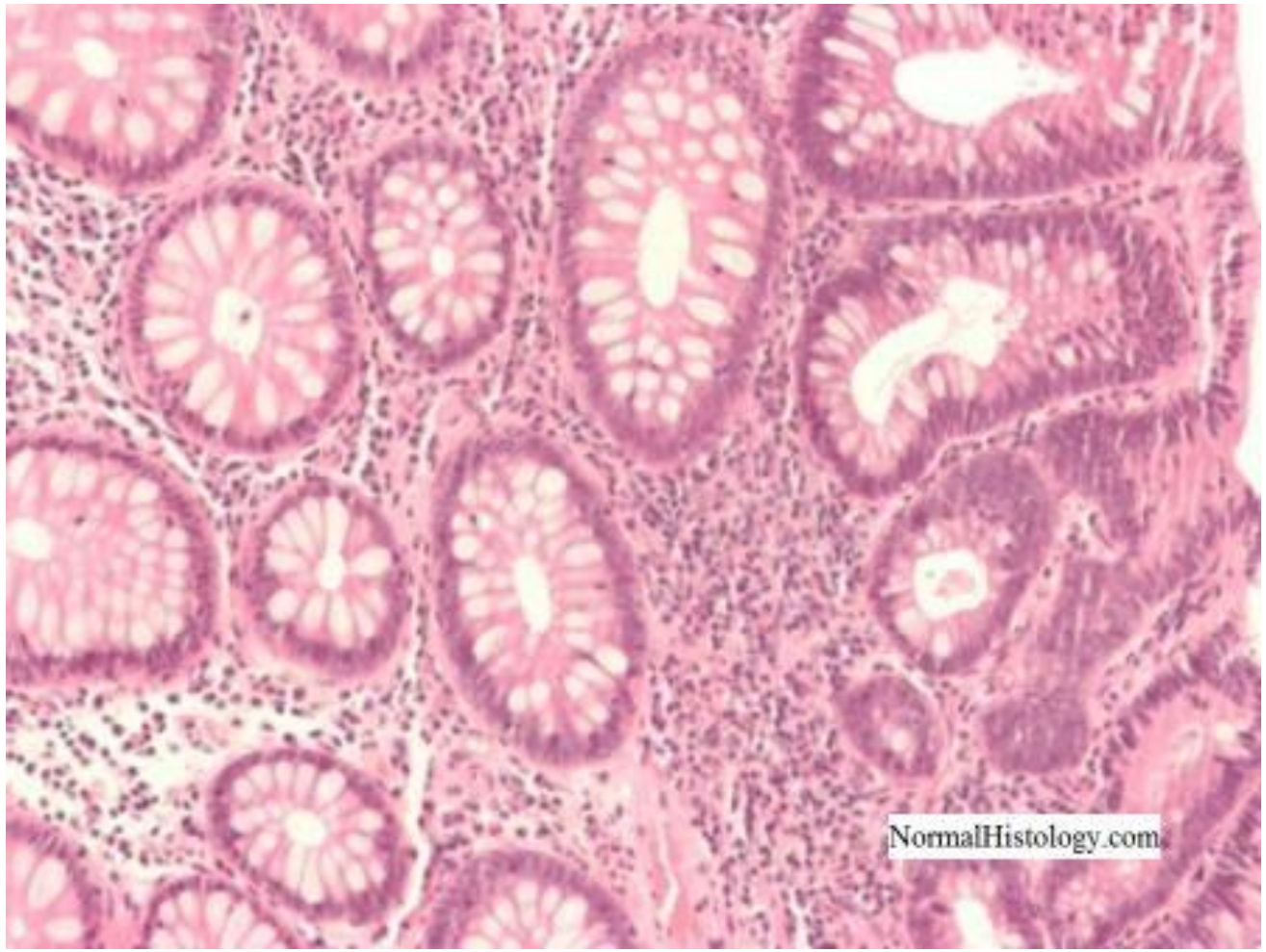
- **Typical History**
- **typical endoscopic appearance**
- **confirmatory histology seen** on **colonic biopsy**
- **Radiological assessment**
- **Serological markers** P-ANCA, ASCA
- **Routine labs: CBC, KFT,LFT,PT**
- **Stool for R&M Culture, Cl Difficle toxines and Faecal calprotectin**

Histopathology

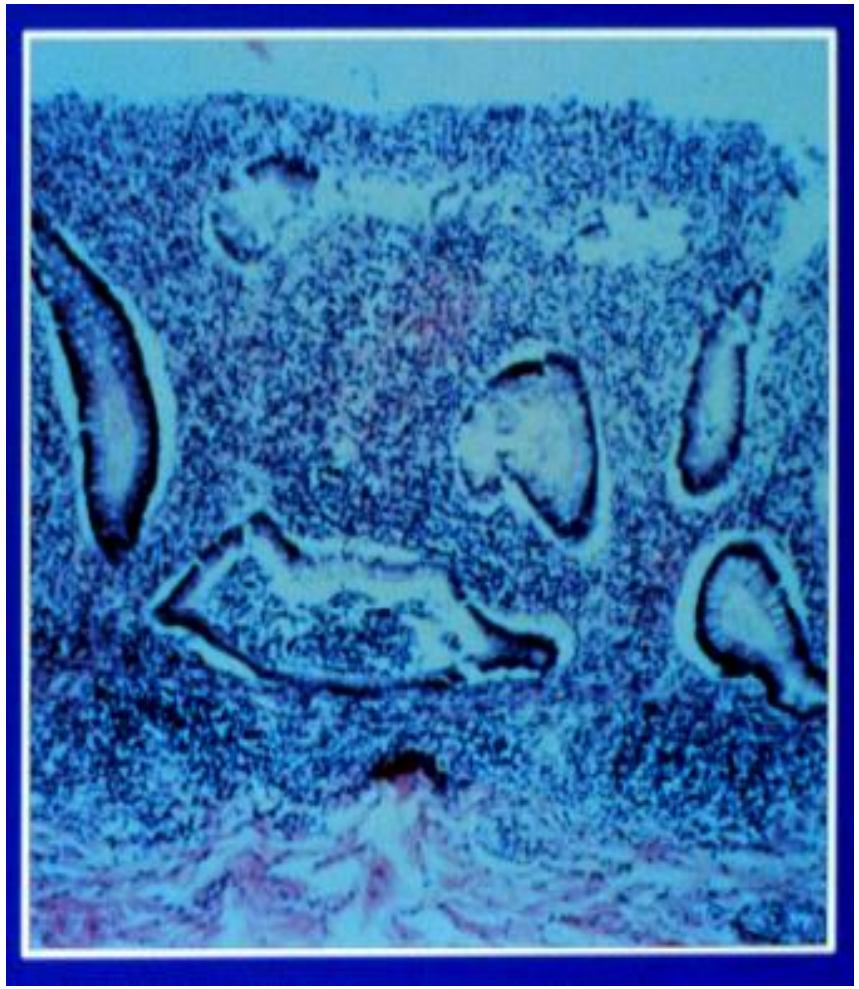
- Changes are limited to mucosa and sub mucosa except in sever cases.
- There is crypt distortion, Cryptitis / crypt abscesses

  Lamina propria expansion with acute and chronic inflammatory cells
- There is basal plasma cells and lymphoid infiltration.

Normal Colon



UC



Course of the Disease

- the typical 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
- Relapses may occur even with treatment
- Overall mortality is only slightly increased compared with the general population.

Goals of Managements

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

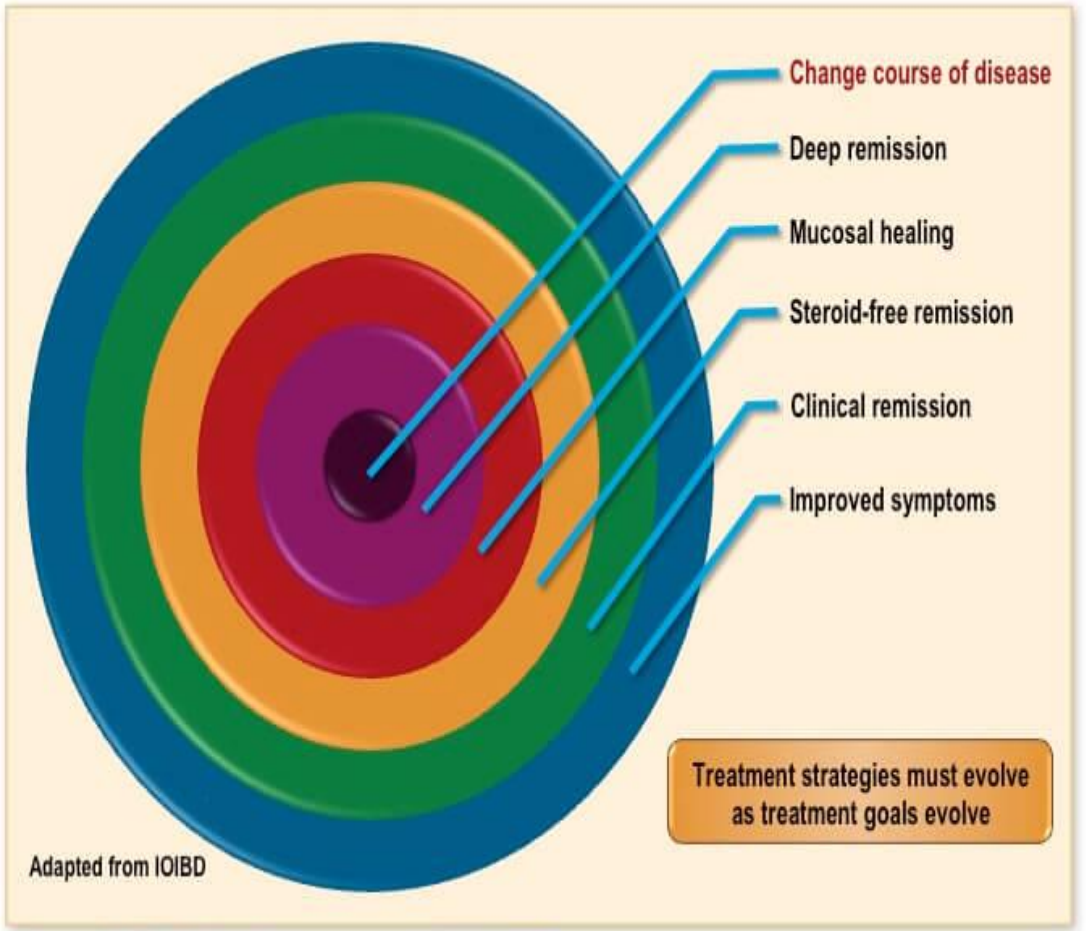


Figure 1. Evolution of treatment goals in IBD.

Colombel JF.Lancet. 2017;390:2779-2789
Turner D. J gastro 2020;12:031

Current available Medical Treatment

- Steroids : used only for induction, no rule for maintenance
- 5 ASA : The main stay of treatment in mild to moderate disease
- Azathioprine/6MP: used for maintenance
- Biological Treatment :

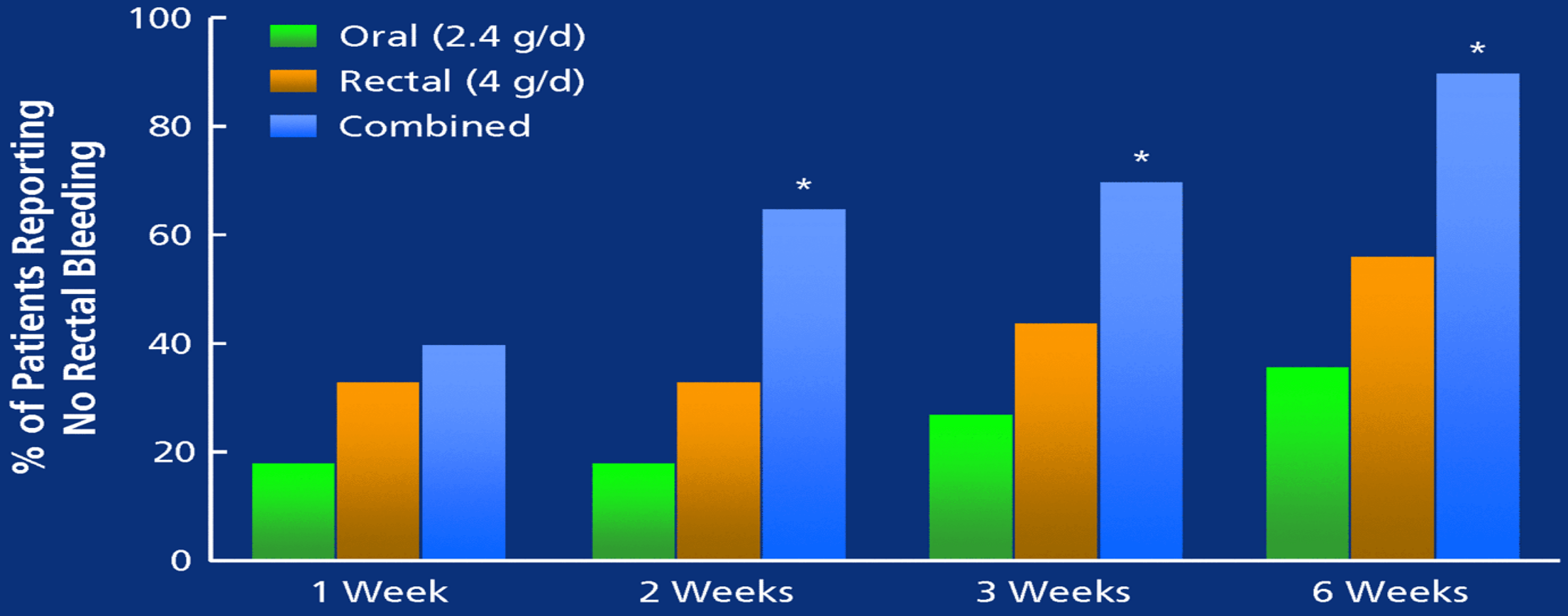
  TNF inhibitors : Infliximab, Adalumumab, Golimumab

  Alpha 4 B7 Integrin inhibitors : Vedlozumab

  JAK Inhibitors: Tofacitinib, Ubadacitinib

  IL 12, 13 Inhibitors: Ustikinomab, Mirkizumab, Gusalkomab

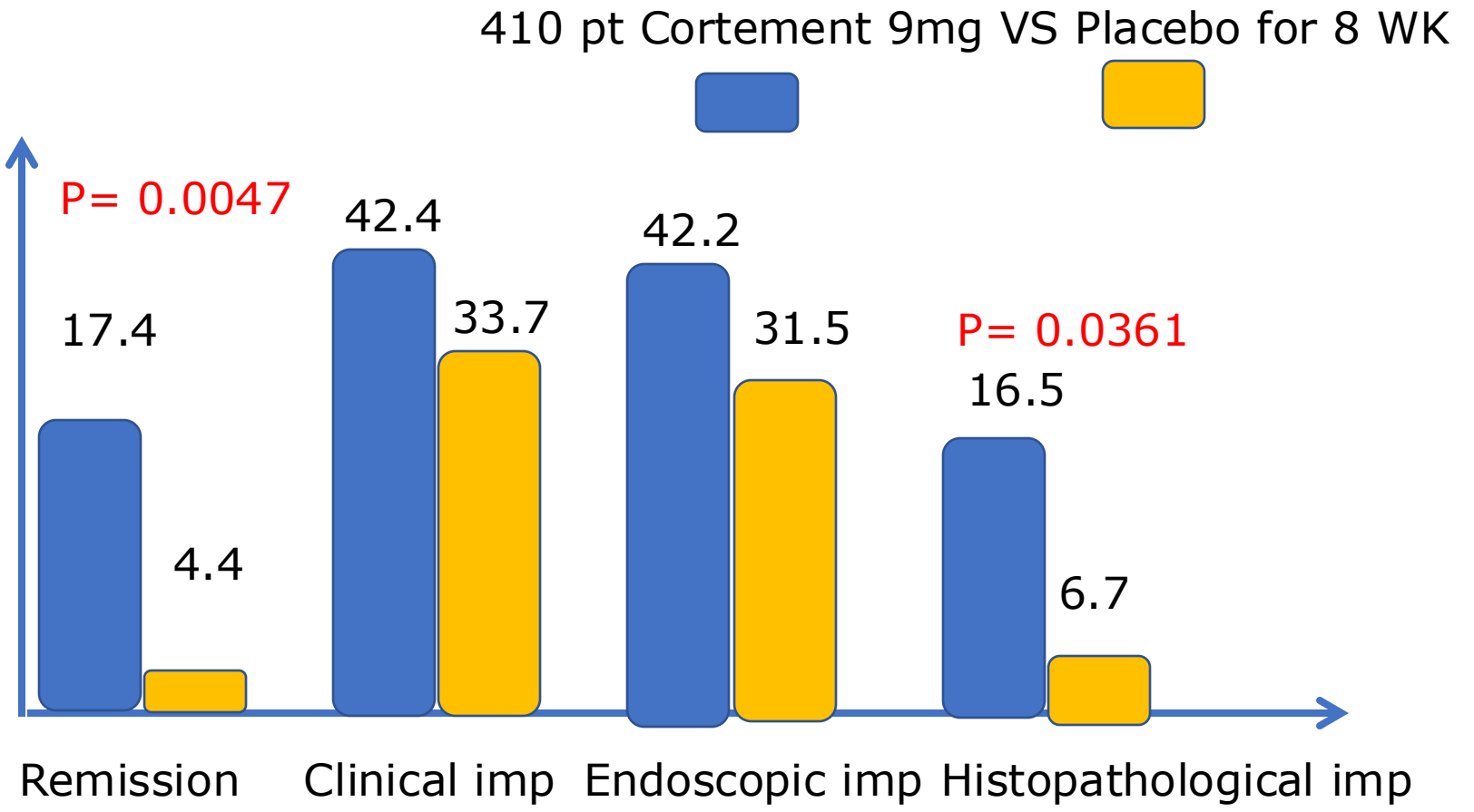
Treatment of Distal UC: Oral and Topical Mesalamine Therapy



*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.

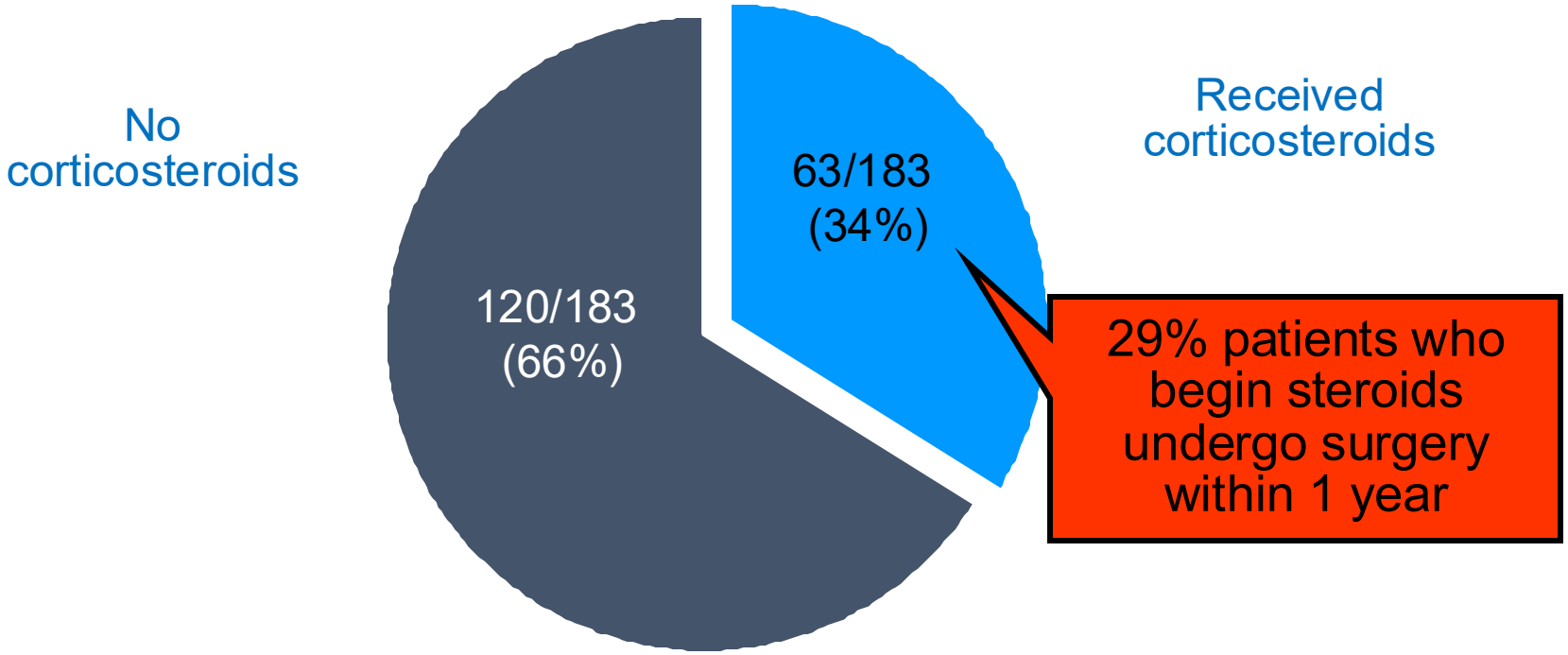
Steroids (new formulation)
Budesonide



Simon Travis Gut 2014

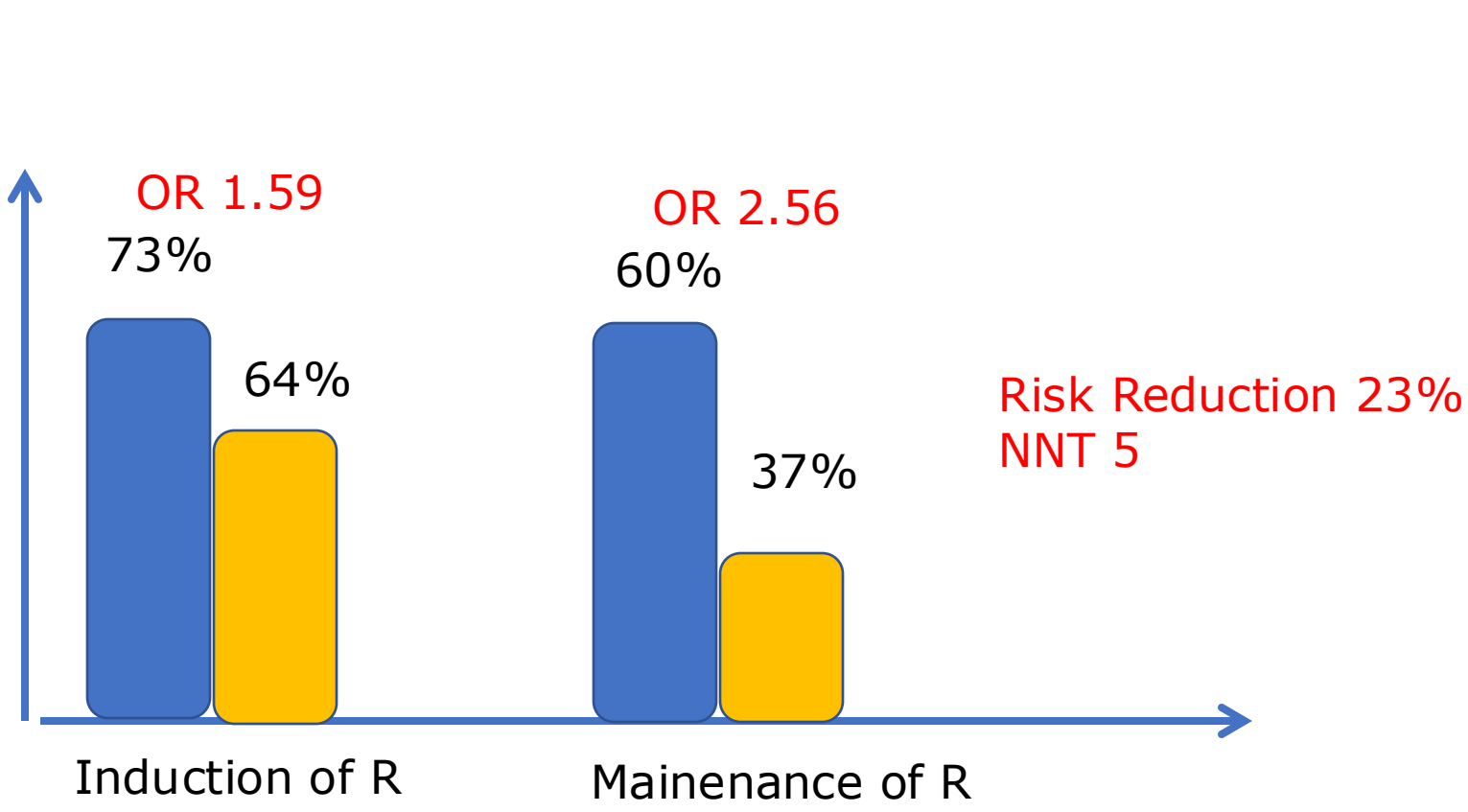
Steroids Need in Ulcerative Colitis

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



Risk Reduction 23%
NNT 5

1632 PT

AZA,6 MP

Standard Rx or Placebo

J.P Gisbert APTh 2009

Ulcerative Colitis and biological 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*
- *Daily Abd Xray, Inflammatory markers and monitoring of symptoms*

Surgery in UC

- Not responding to medical treatment
- complications
- 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：CRC risk increases 8 to 10 years following the onset of symptoms
- Left-sided colitis：risk of CRC increases after 15 to 20 years
- 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

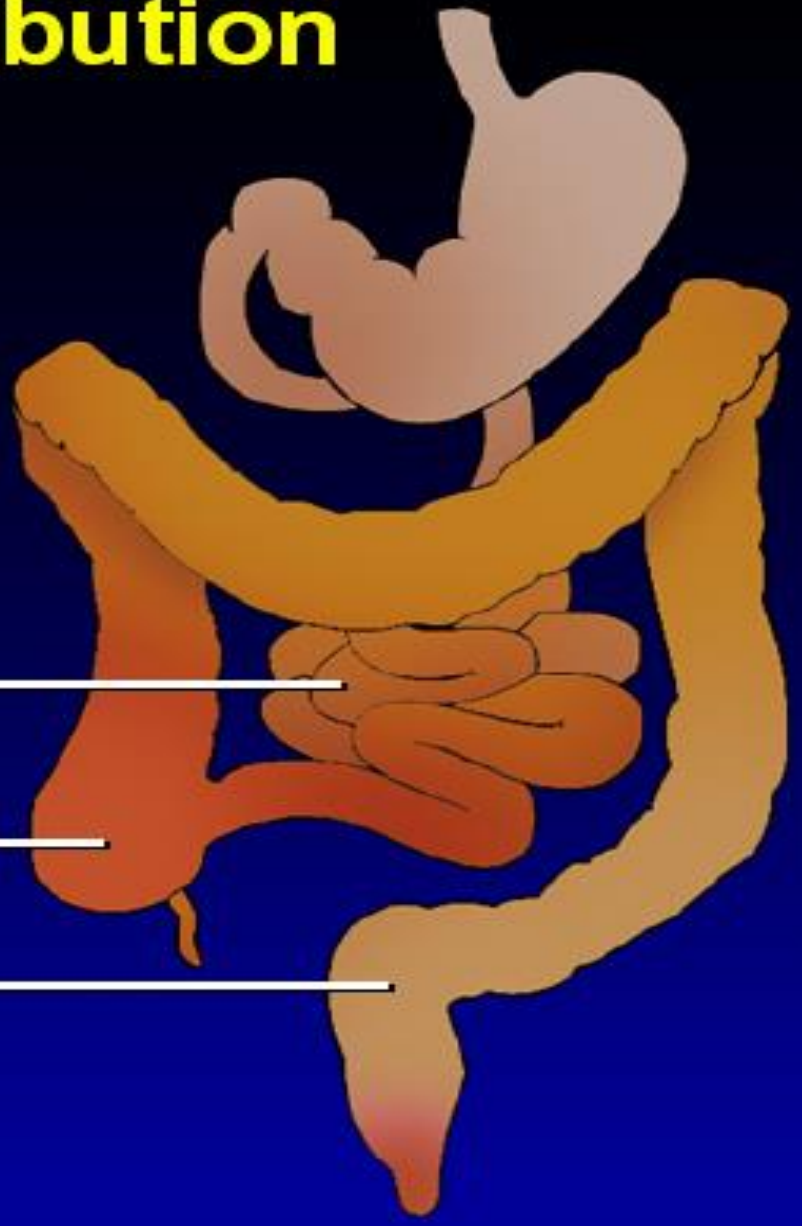
- Crohn's disease is characterized by transmural inflammation and by skip lesions rather than continuous disease.
- Crohn's disease may involve the entire gastrointestinal tract from mouth to perianal area

CD

Anatomic Distribution

Freq. of involvement

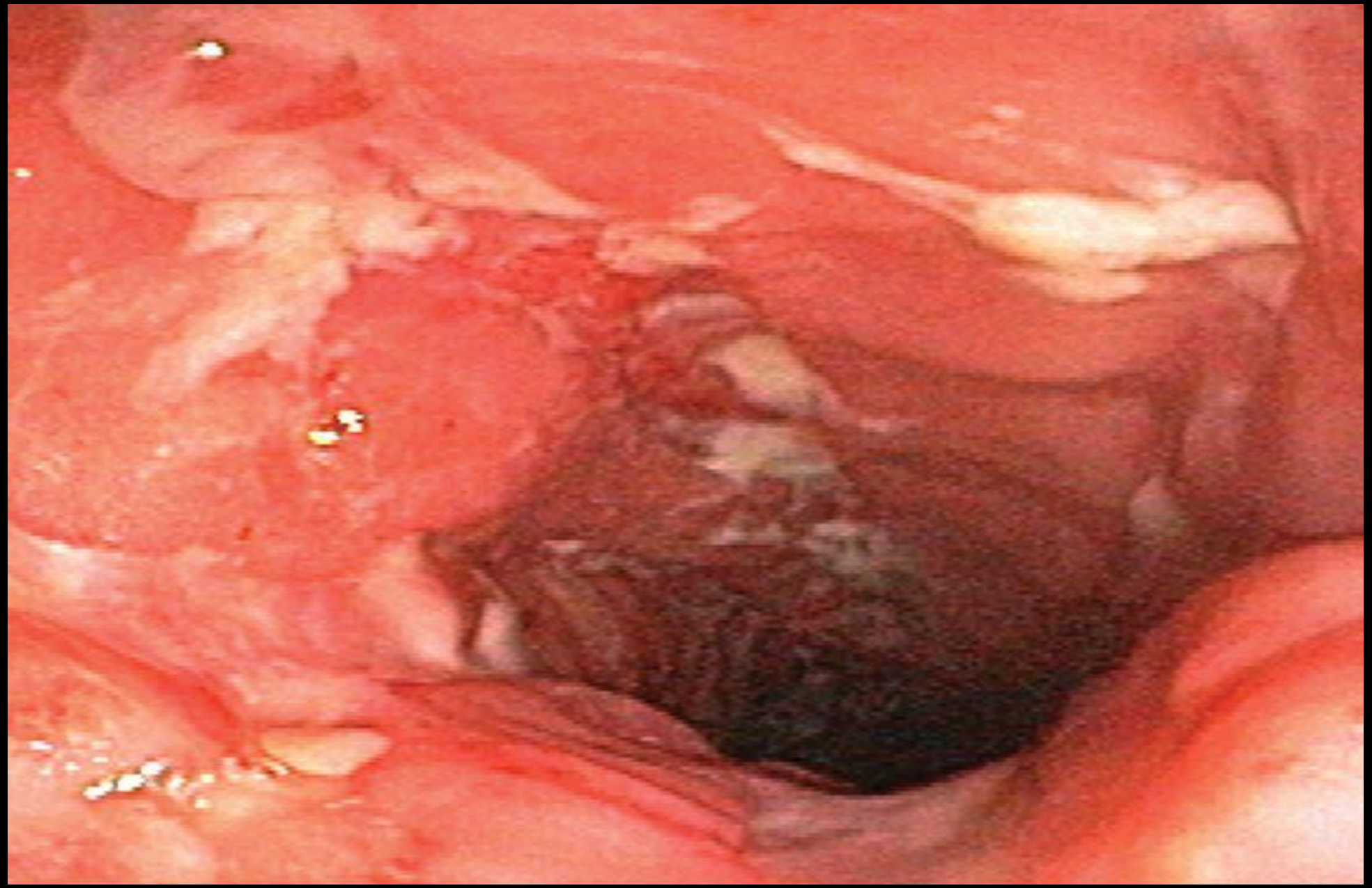
most — least



Small bowel alone 33%

Ileocolic 45%

Colon alone 20%

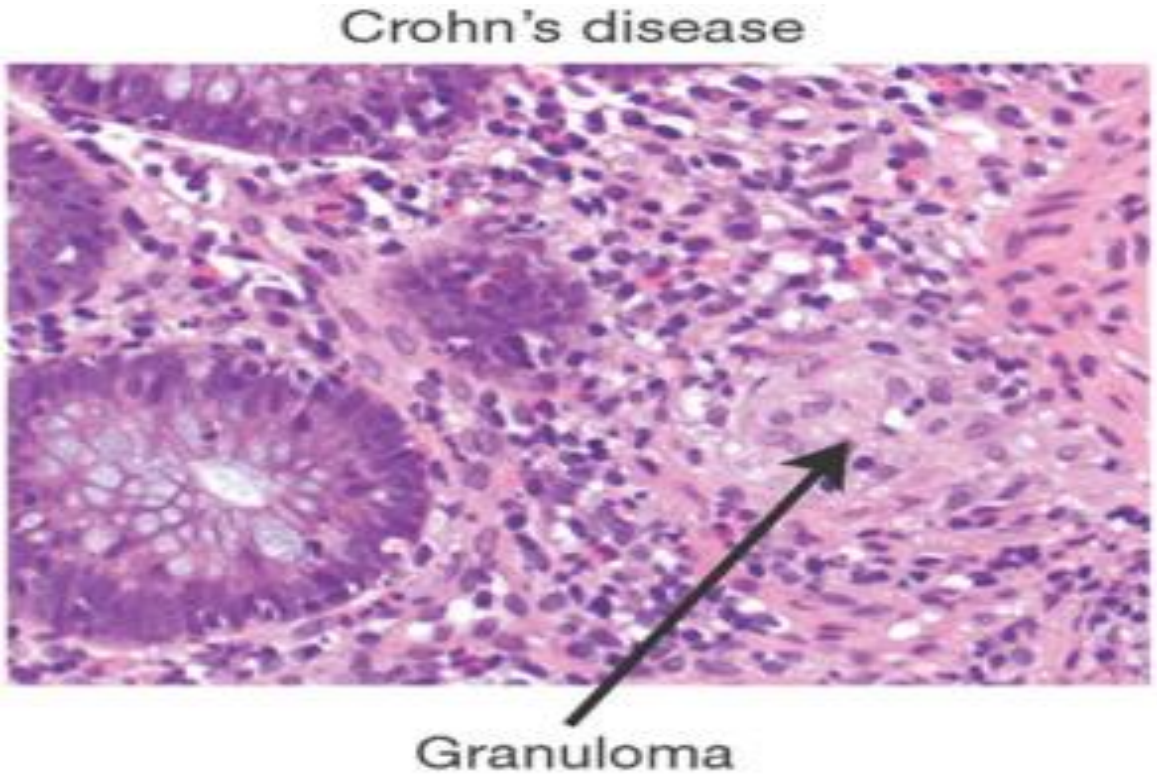


Crohn’s Disease

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

Histopathology

- Epithelioid non-caseating granulomas
- Chronic and acute inflammatory infiltrate, including lymphocytes and plasma cells
- Crypt architectural distortion/Abscess



Presentation

- There are variability of the site& extent of disease
- A young patient presents with dull Abdominal Pain (RIF) and occasional loose bowel motion for more than 4 weeks.

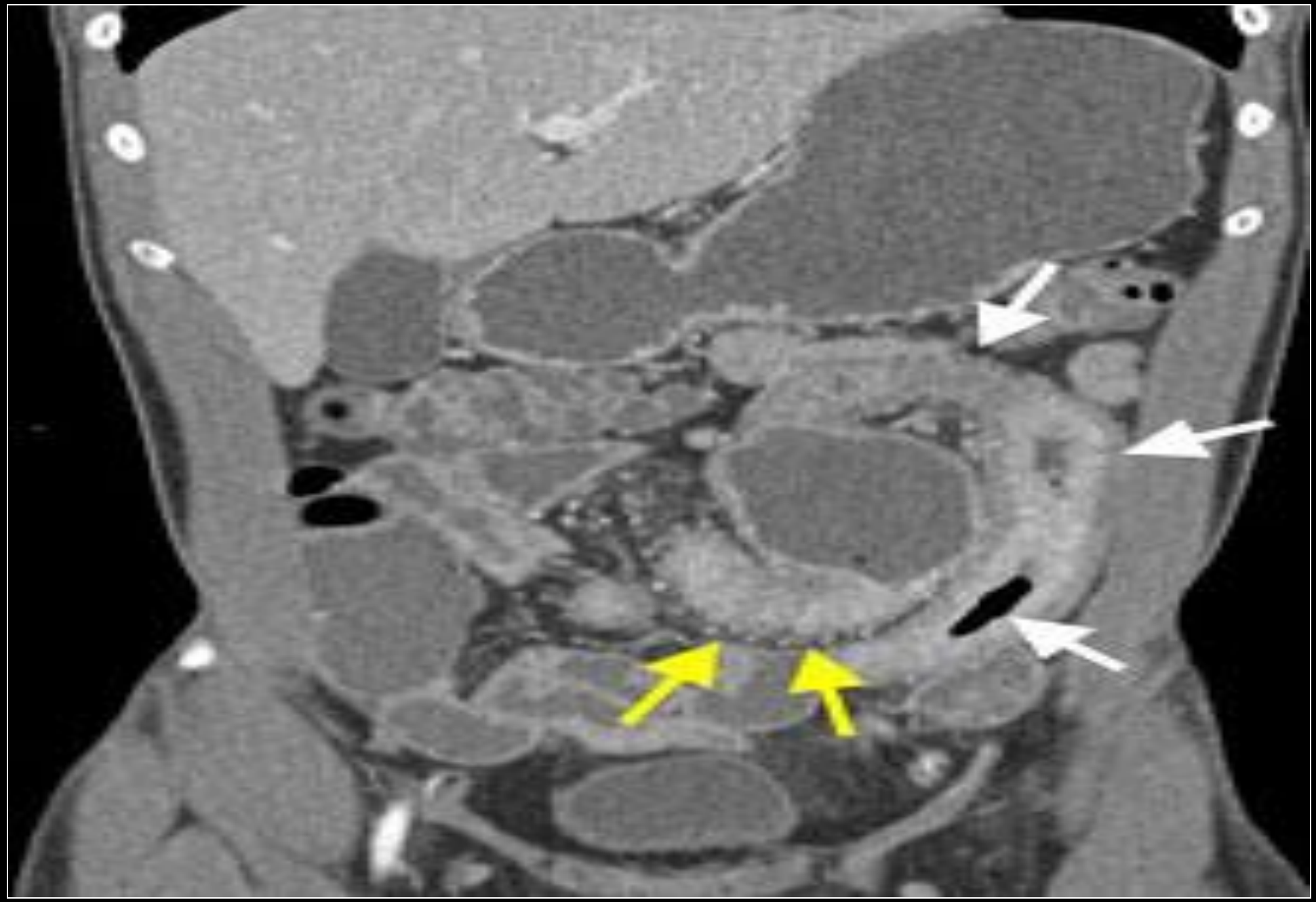
- Additional symptoms include; Fatigue, weight loss, and fever, with or without gross bleeding, are the hallmarks of Crohn's disease
- 10 percent of patients do not have diarrhea.
- Poor growth is common in children

complications

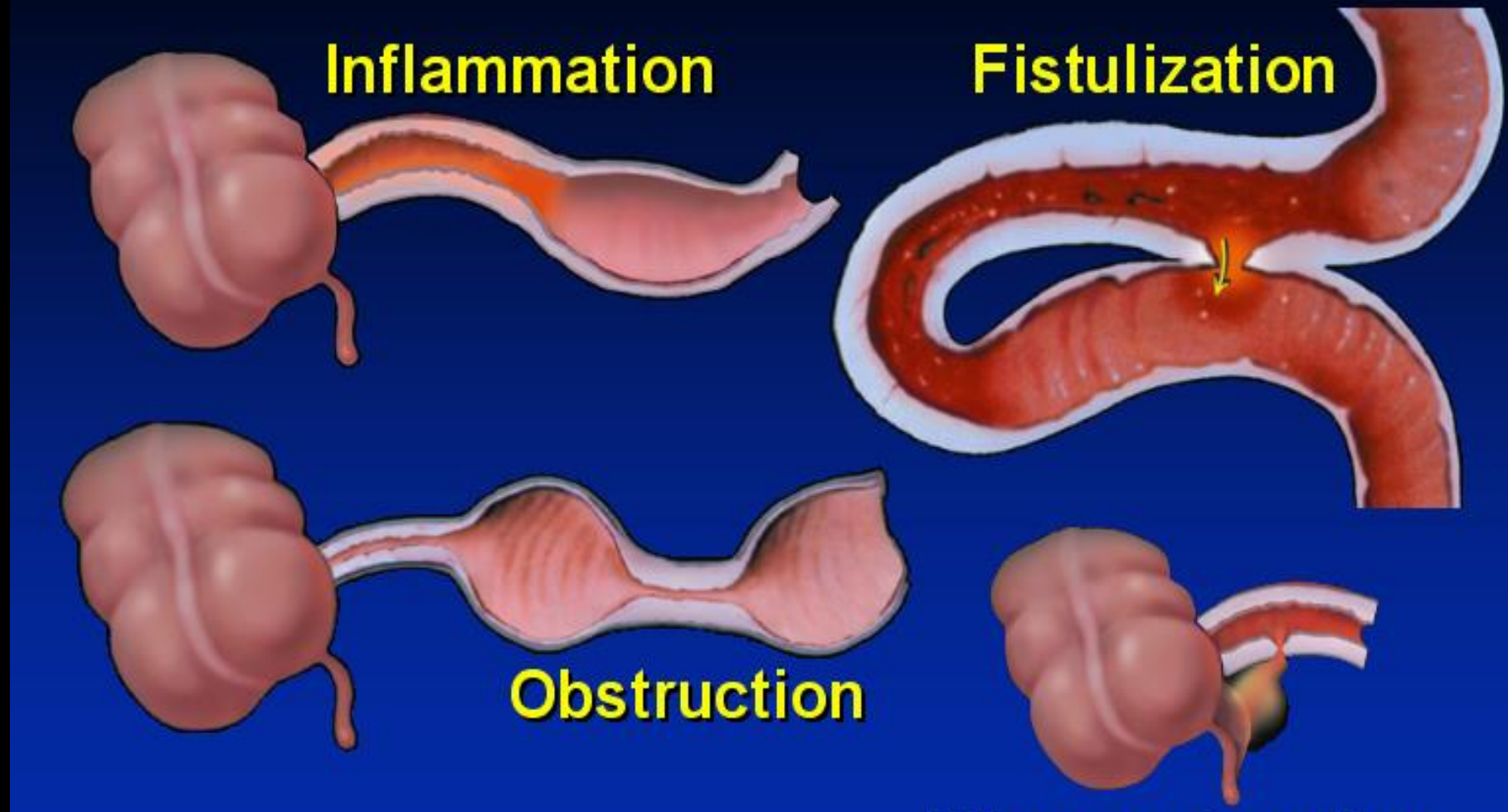
1. *Intestinal obstruction*
2. *Severe hemorrhage*
3. *Acute perforation*
4. *Fistulae*
5. *Abscess formation*
6. *Toxic megacolon.*

Diagnosis

- **Typical History**
- **typical endoscopic appearance**
- **confirmatory histology seen** on **colonic biopsy**
- **Radiological assessment, Capsule endoscopy**
- **Serological markers** P-ANCA, ASCA
- **Routine labs: CBC, KFT,LFT,PT**
- **Stool for R&M Culture, Cl Difficle toxines and Faecal calprotectin**



CD - Clinical Patterns



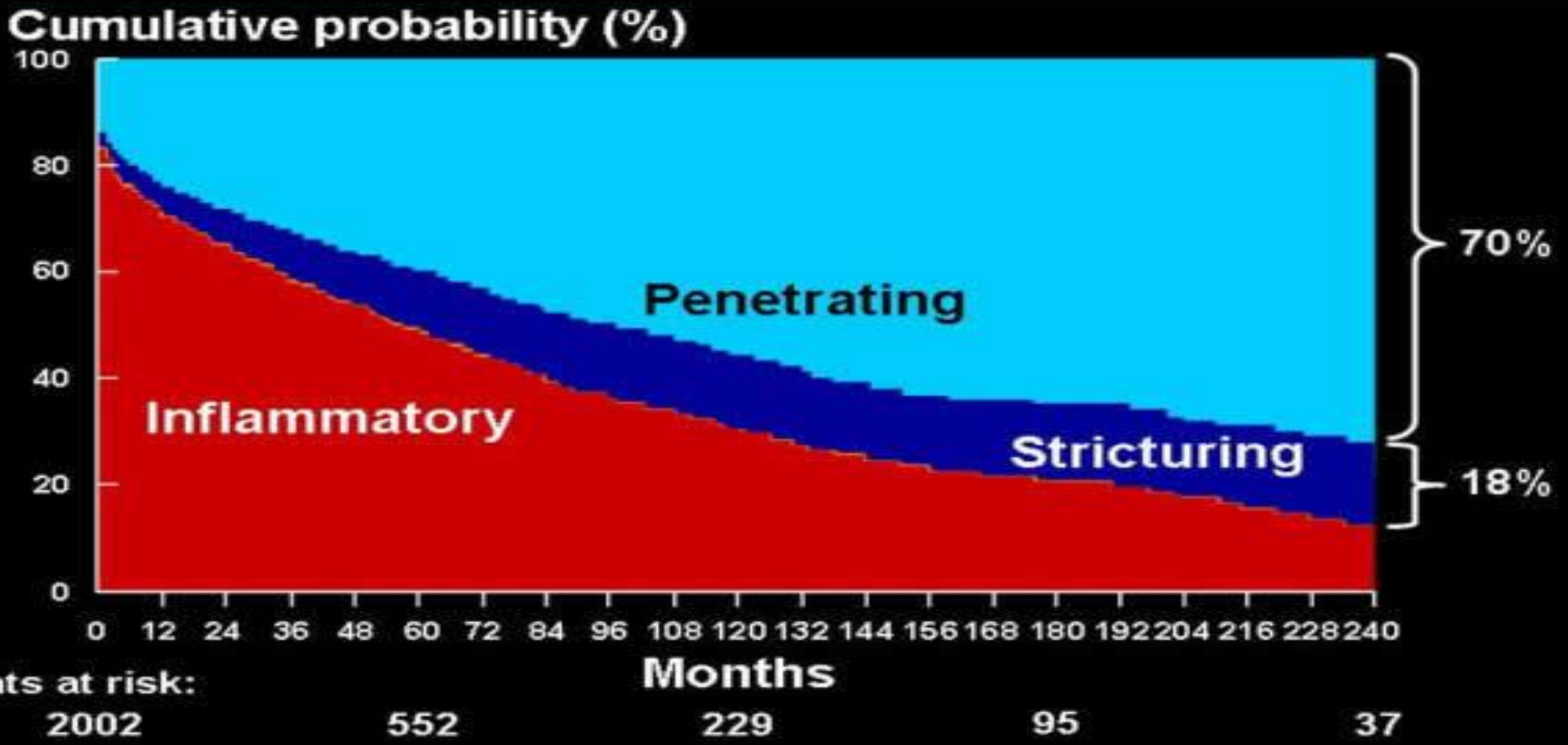
Anastomotic stricture in a patient with Crohn's Disease

Anastomotic fistula in a patient with Crohn's Disease

Adapted from www.vh.org, GI Endoscopy Atlas: Colon: Inflammatory Changes: IBD accessed on April 5, 2004

CLOSE SLIDE X

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

Crohn's Disease Activity Index

Item(day)	Weight
No. liquid or very soft stools(each day for 7days)	×2
Abdominal pain, sum of 7 d rating (0=none,1=mild,2=moderate,3=severe)	×5
General well being (1-4)	×7
Exteraintestinal (1 per finding) Arthritis/arthralgia Mucocutaneous lesion Iritis/uveitis Anal disease (fissure, fistula,etc) External fistula	×20
Fever>36.8	
Antidiarrheal use	×30
Abdomial mass(none-0,equivocal-2,definite-5	×10
Hematocrit (males-47) (Females-42)	×6
Bodyweight (1-body weight/standard weight) ×100	×1
Total CDAI Score	

Management

- Steroids : used only for induction, no rule for maintenance
- 5 ASA : The least effective treatment
- Azathioprine/6MP: used for maintenance
- MTX
- Biological Treatment :

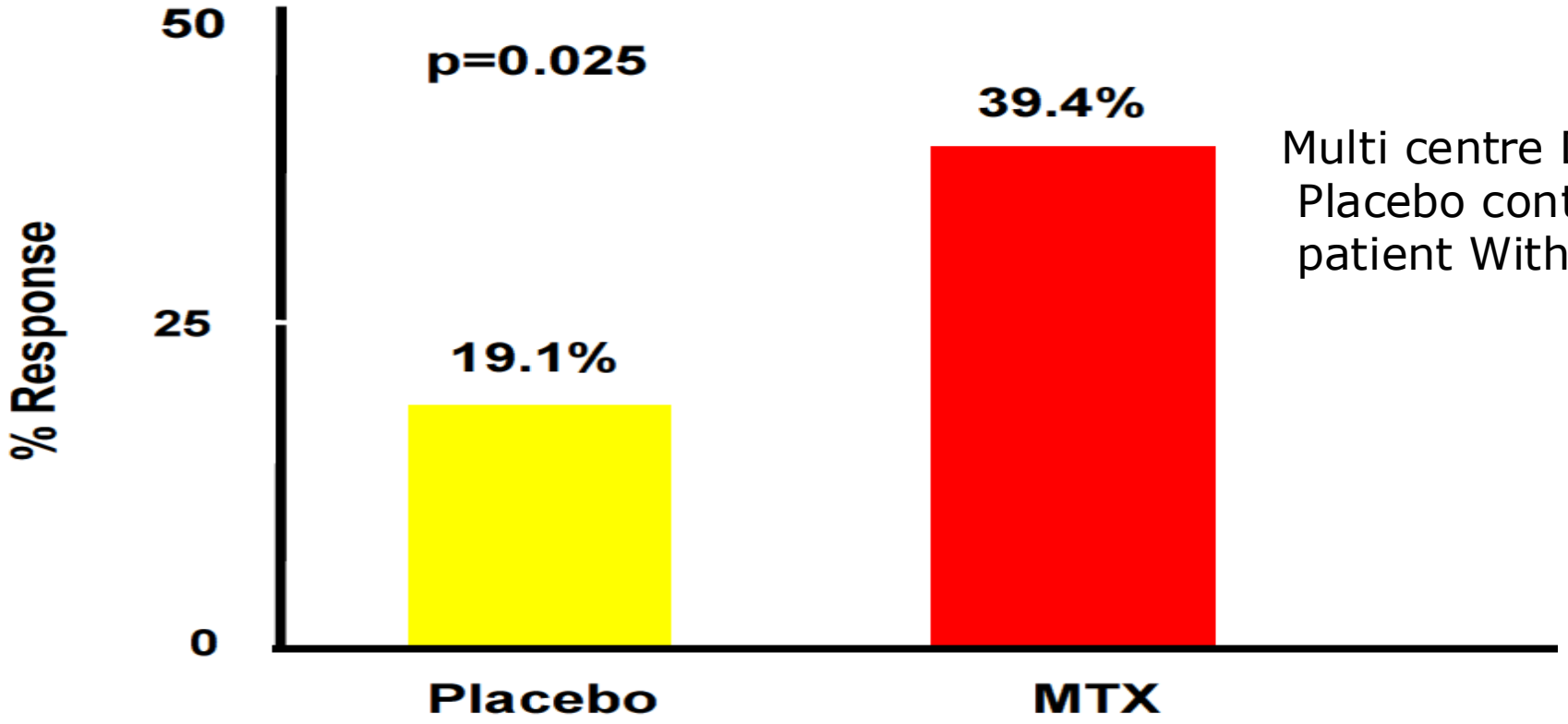
  TNF inhibitors : Infliximab, Adalimumab, Certolizumab

  Alpha 4 B7 Integrin inhibitors : Vedolizumab

  JAK Inhibitors: Ubadacitinib

  IL 12, 13 Inhibitors: Ustikinomab, Rizinkumab, Gusalkomab

MTX Induction of remission



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

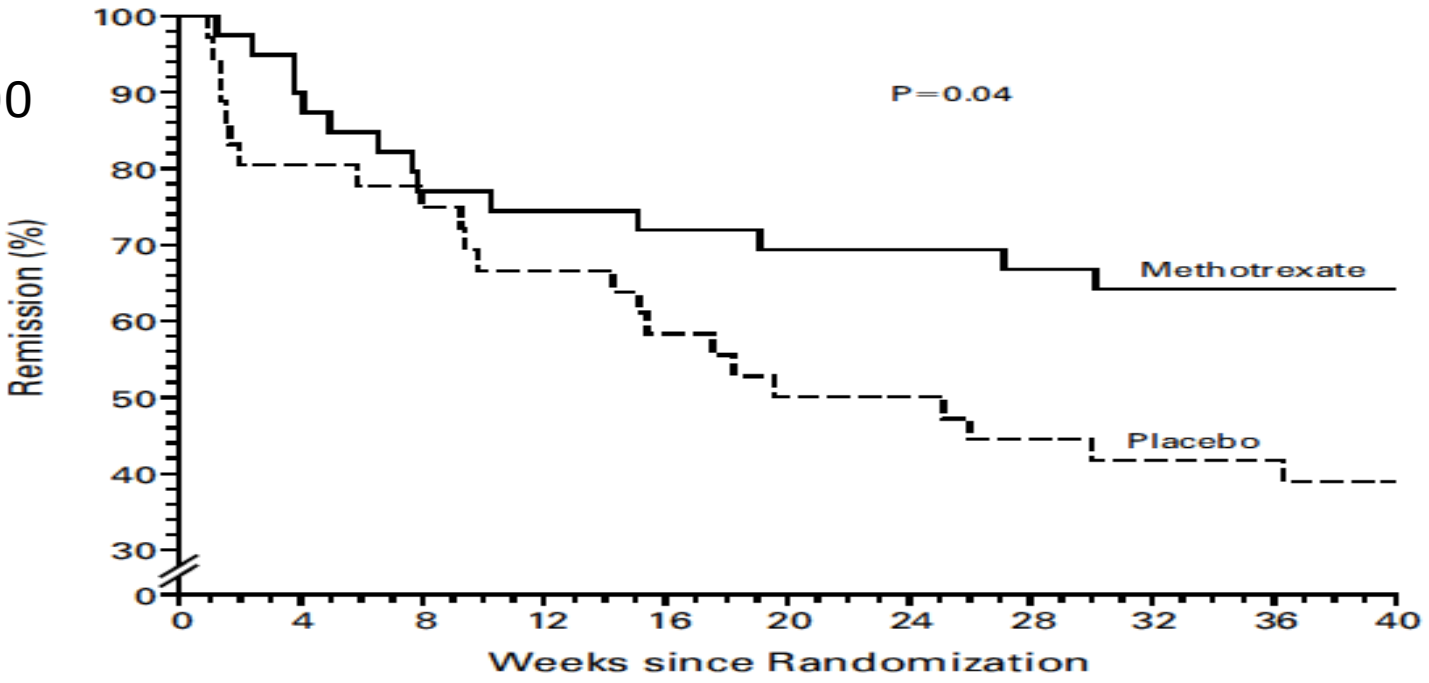
Feagan. N Eng J Med. 1995 Feb 2;332 (5):292-7

MTX For Maintenance of Remission CD

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

Feagan BG NEJM 2000

MTX 15 my I/M Vs Placebo



P= 0.04

25/40 (65%)

14/36 (39%)

No. at Risk

Methotrexate	40	36	30	29	28	27	27	26	25	24	19
Placebo	36	29	28	24	21	18	18	16	15	15	12

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

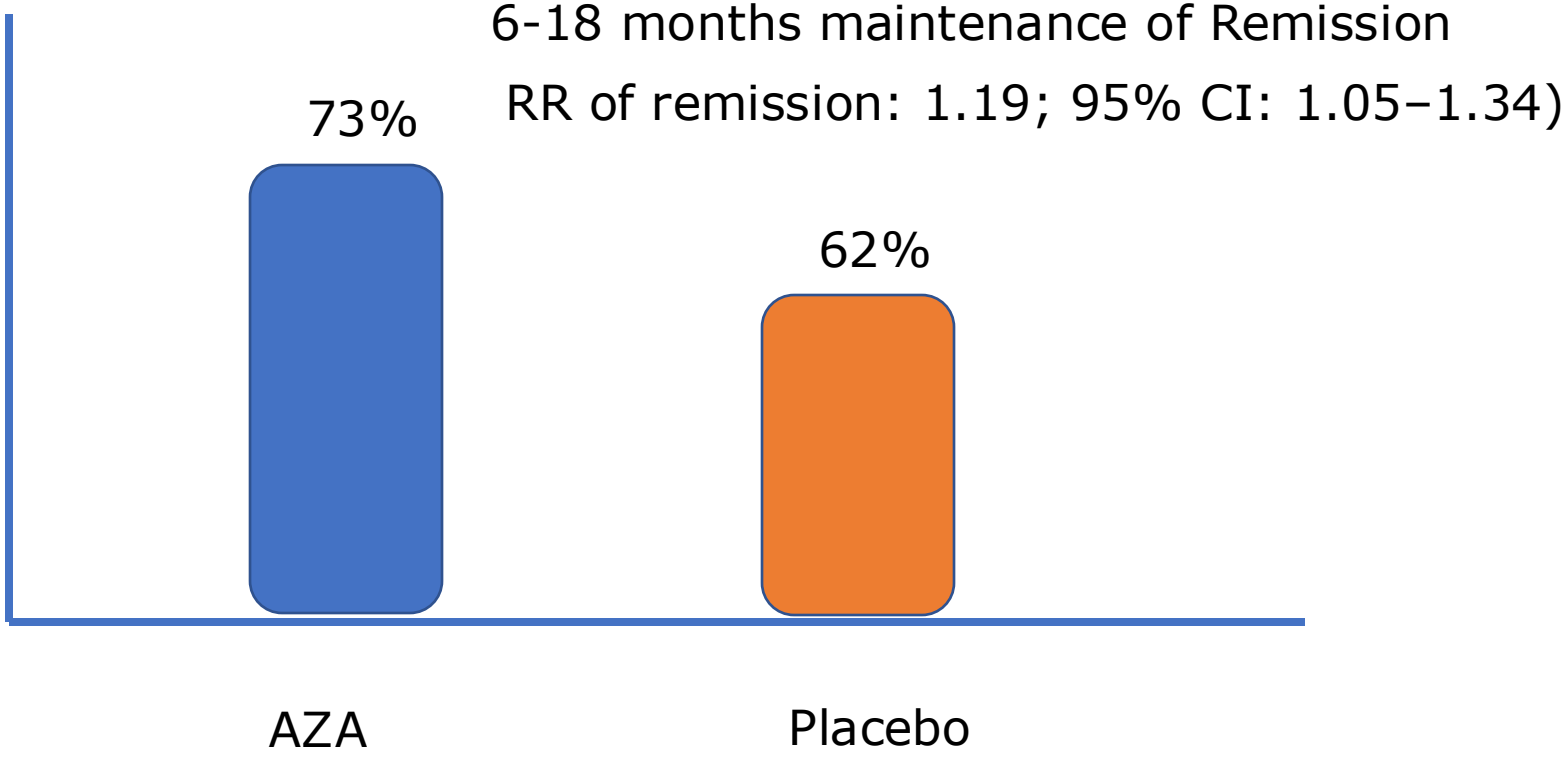
11/40 (28%) MTX vs 21/36 (58%) Placebo used prednislon p = 0.01

Thiopurine in CD

489 Pt from 6 studies

6-18 months maintenance of Remission

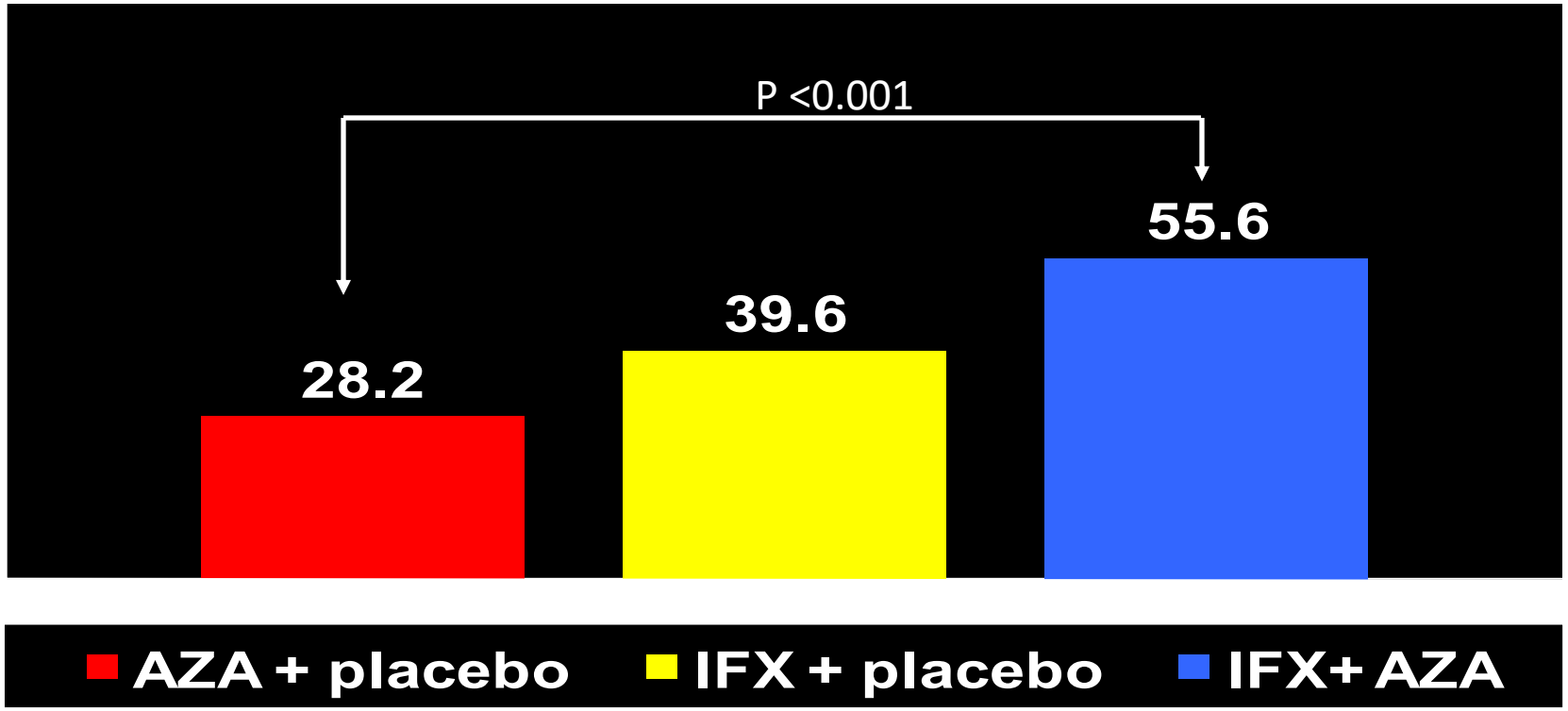
RR of remission: 1.19; 95% CI: 1.05–1.34)



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

Biologics in CD; Corticosteroid-Free Clinical Remission at Week 50 Sonic trial

All Randomized Patients (N=508)*



Medical treatment summery

- **Corticosteroids** *for induction of remission, prednisone is initiated at a dose of 40 to 60 mg/day, other steroids maybe used.*
- **Azathioprine and 6-mercaptopurine** *For most patients the main stay of treatment for maintenance in mild to moderate disease.*
- **5 ASA** *For the patient with mild symptoms, therapy is initiated with sulfasalazine or one of the mesalamine agents NNT 17 Most effective in post op colonic disease*
- A**ntibiotics** — *Antibiotic therapy should be considered in the patient who with infection/abscess,post op.perianal(Metronidazole*
- ***Biological*** treatment in moderate to severe disease refractory to other treatment

Surgical treatment & Risk of CRC

- 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.
- Surgery remove the active disease, it is not a cure
- 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!

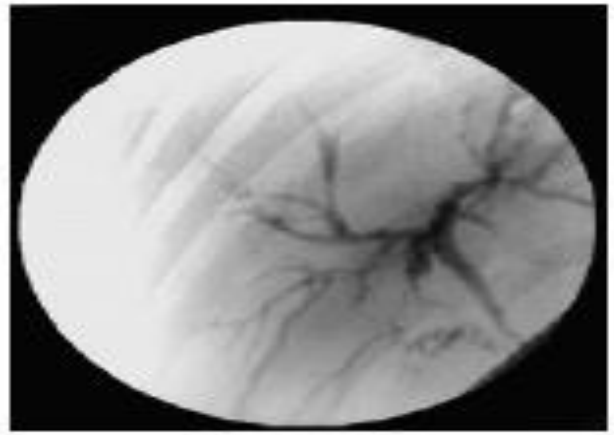
Skin

Eye

Bones and Joints

Kidney

Hepatobiliary



Images courtesy of DT Rubin.

EIM 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

5-ASA (Mesalamine)

- 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 formulations for treatment of CD, high doses of these drugs should be used (4gms)
- The least effective medications in CD (no needed 1/17)