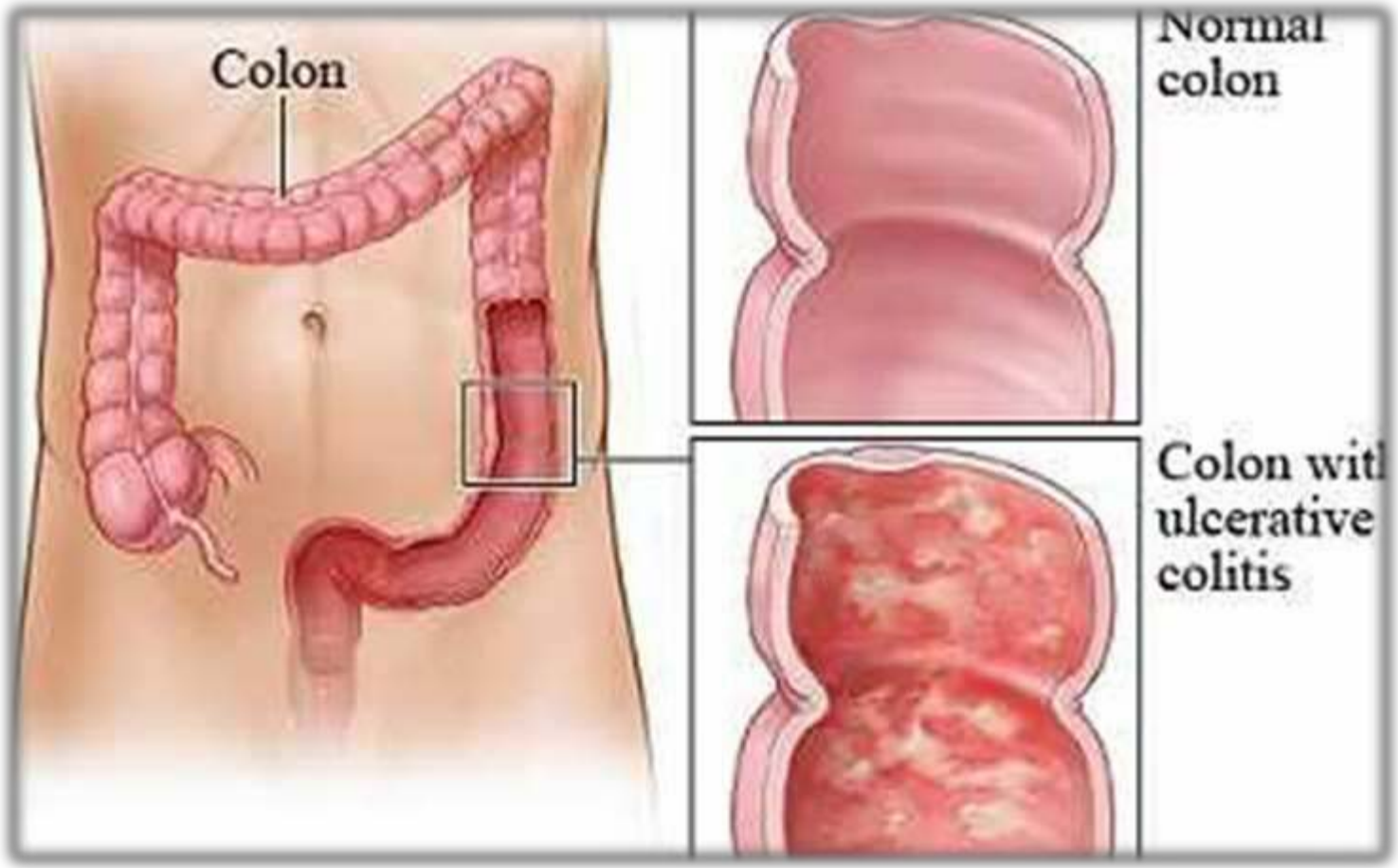


Ulcerative Colitis Update

Wayne Manishen, MD, FRCPC

Outline

- Introduction
- Epidemiology
- Pathophysiology
- Clinical features
- Management
  - Investigation
  - Treatment

Introduction

- UC is a chronic inflammatory condition of the colon that is marked by remission and relapses.
- May involve only rectum, left colon or pan-colitis
- Elevated risk of colon cancer, osteoporosis, thrombotic disease
- It is a form of IBD.
- Risk factors: genetics, western diet; altered microbiome due to AB in early years; appendectomy is protective
- Flares due to stress, NSAIDS, infection C.diff, CMV; stopping smoking

Epidemiology

- The annual incidence is 10.4-12 cases/100,000 people, and the prevalence rate is 35-100 cases/100,000 people. (US)
- UC is 3 times more common than Crohn disease.
- Women > men.
- The age of onset follows a bimodal pattern
  - With a peak at 15-25 years and a smaller one at 55-65 years
  - Although the disease can occur in people of any age.

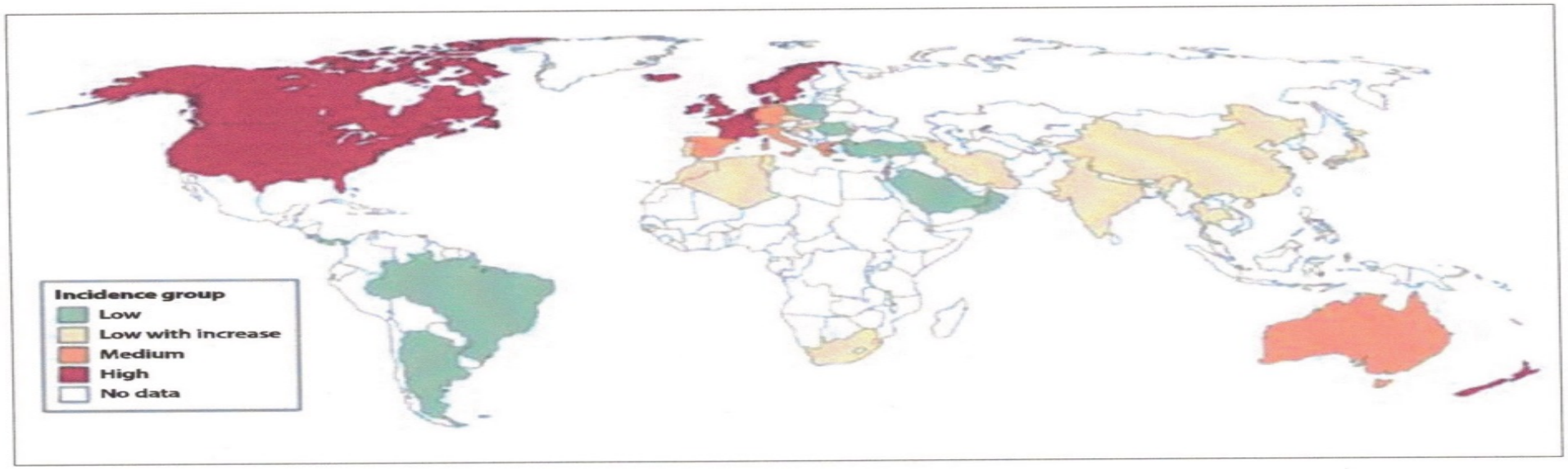


Figure 1. Worldwide incidence of inflammatory bowel disease.
Adapted from Cosnes J et al. *Gastroenterology*. 2011;140(6):1785-1794.[2]

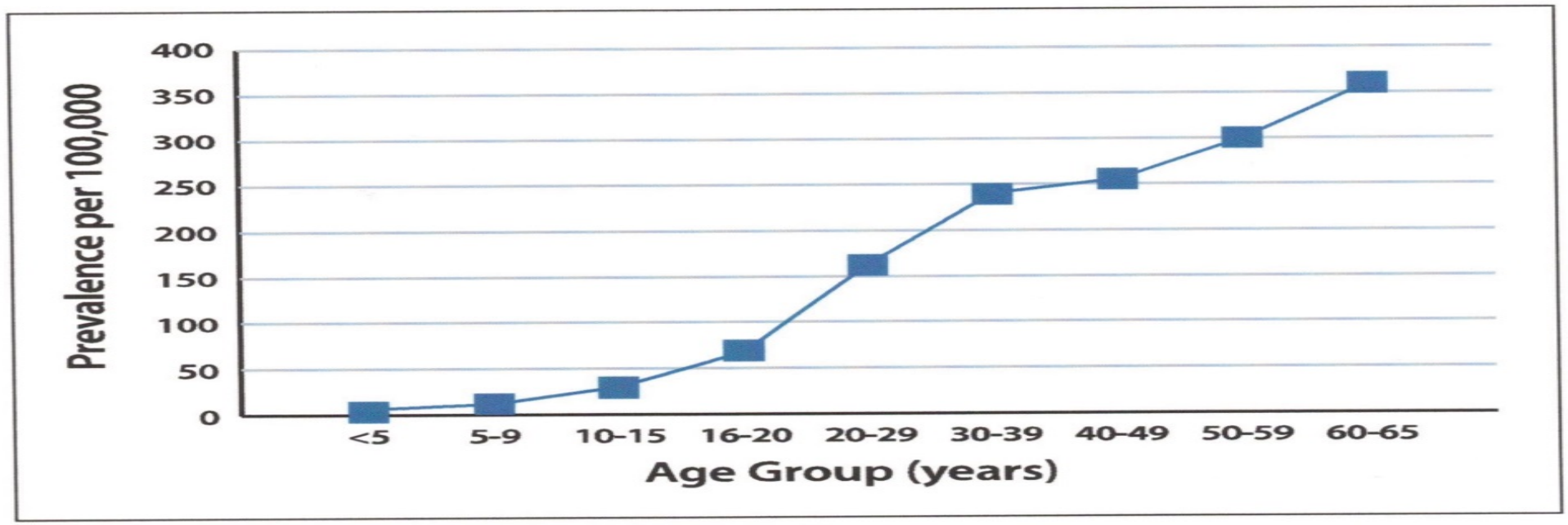
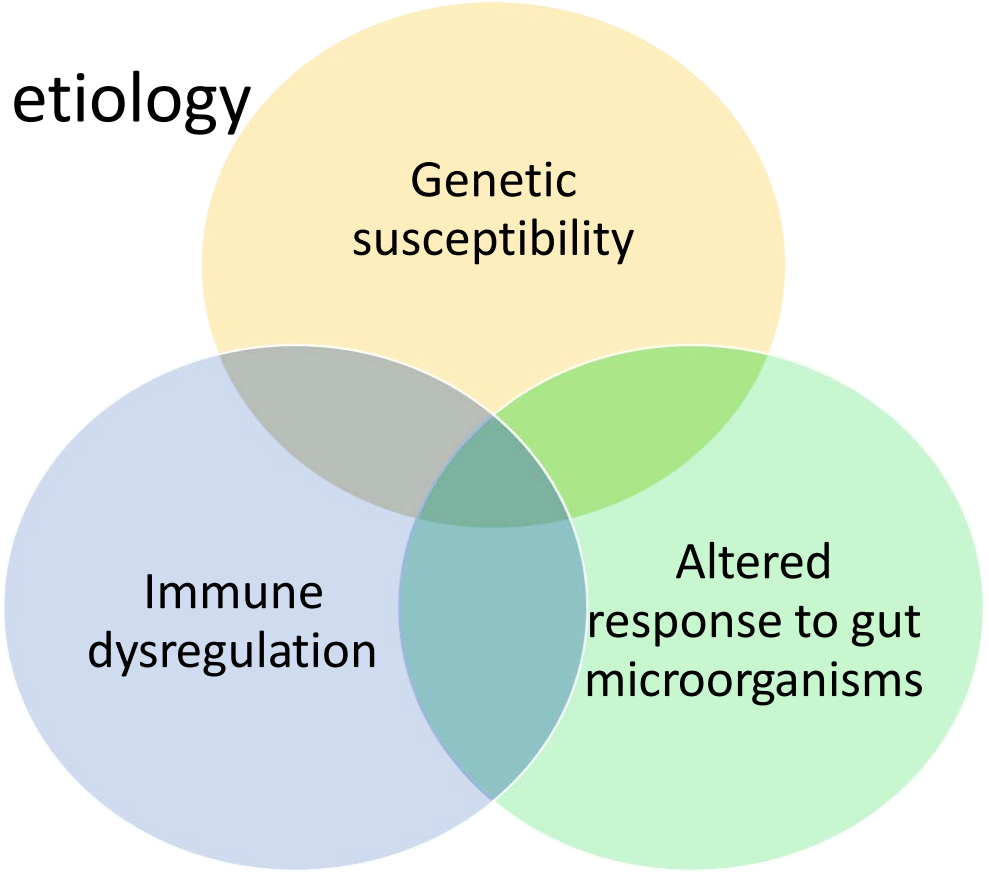


Figure 2. Age-specific prevalence of ulcerative colitis in the United States.
Adapted from Kappelman MD et al. *Dig Dis Sci*. 2013;58(2):519-525.[1]

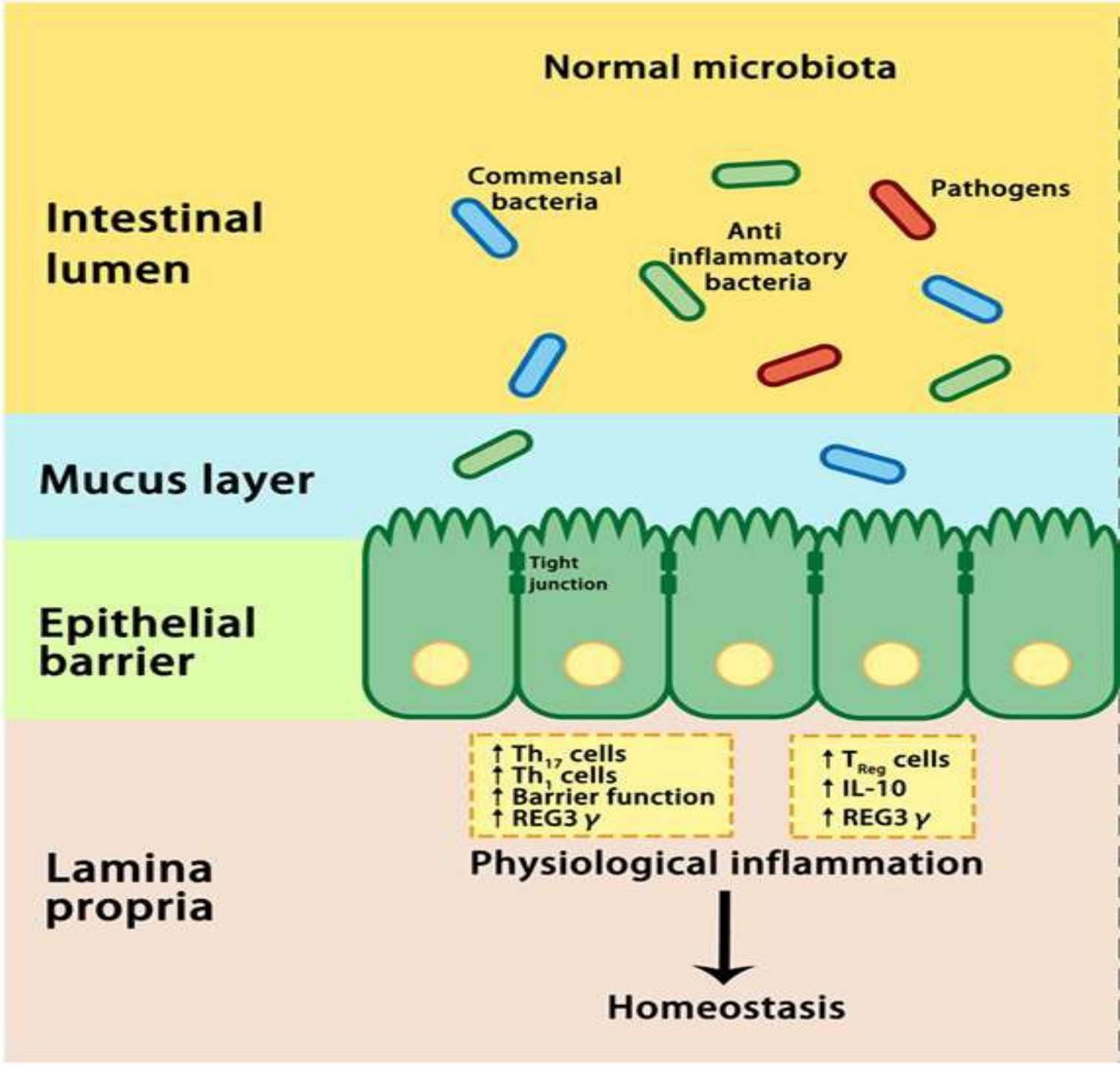
Etiology of UC

- Exact cause of UC remains unclear
- Three characteristics that define the etiology



Pathogenesis

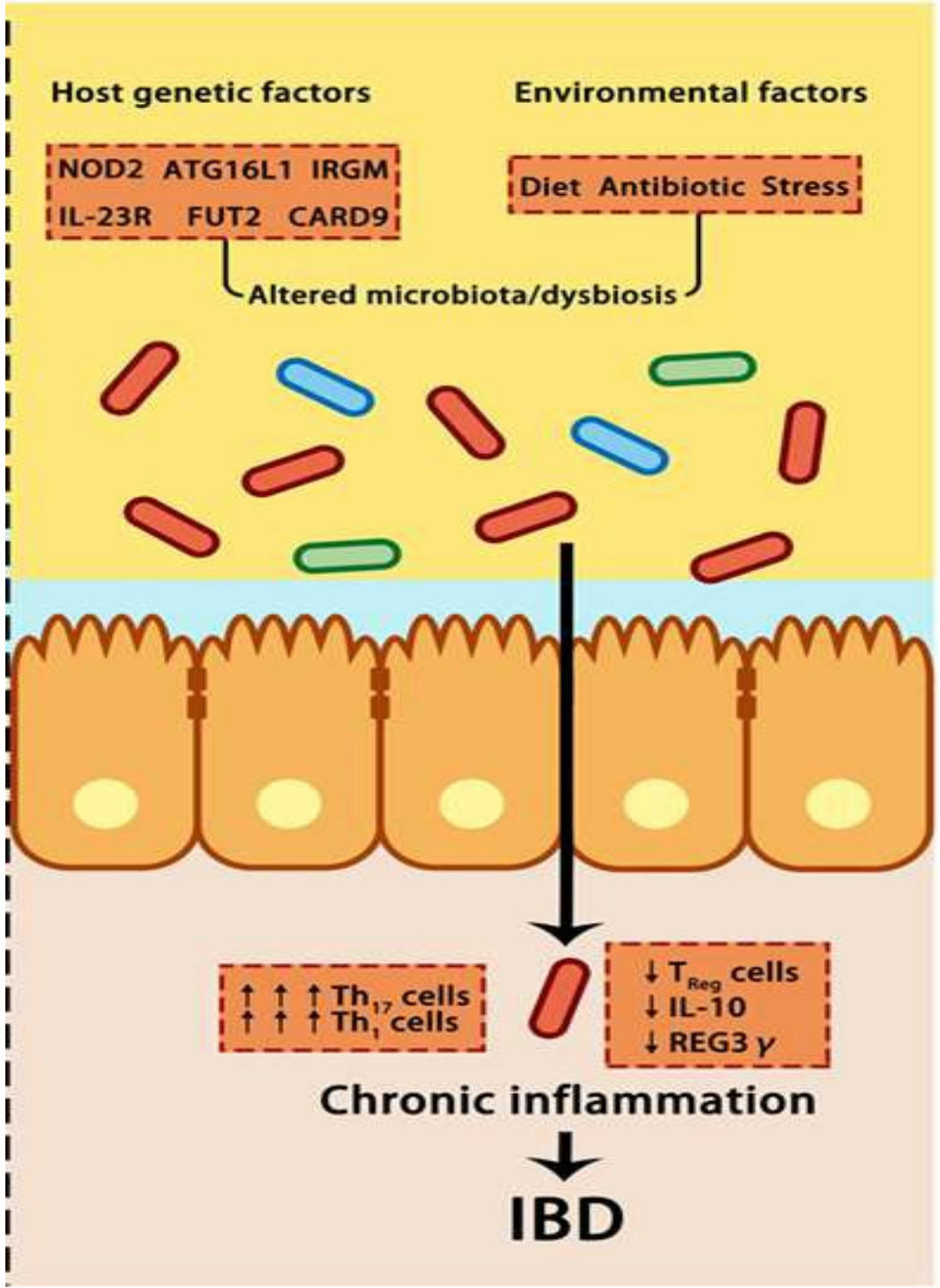
- Under physiologic conditions , homeostasis normally exists between
  - The commensal gut flora
  - Epithelial cells that line the interior of the intestines and
  - Immune cells within the tissues .



- This homeostasis is disrupted in susceptible host by
  - Specific environmental (e.g. diet, antibiotics ,enteropathogens , stress) and
  - Genetic factors

- Resulting in
  - Hyper-activation of T helper 1 (Th1) and Th17 cells,
  - Increase in tight junction permeability.

- Leading to
  - Uncontrolled chronic inflammation (UC)



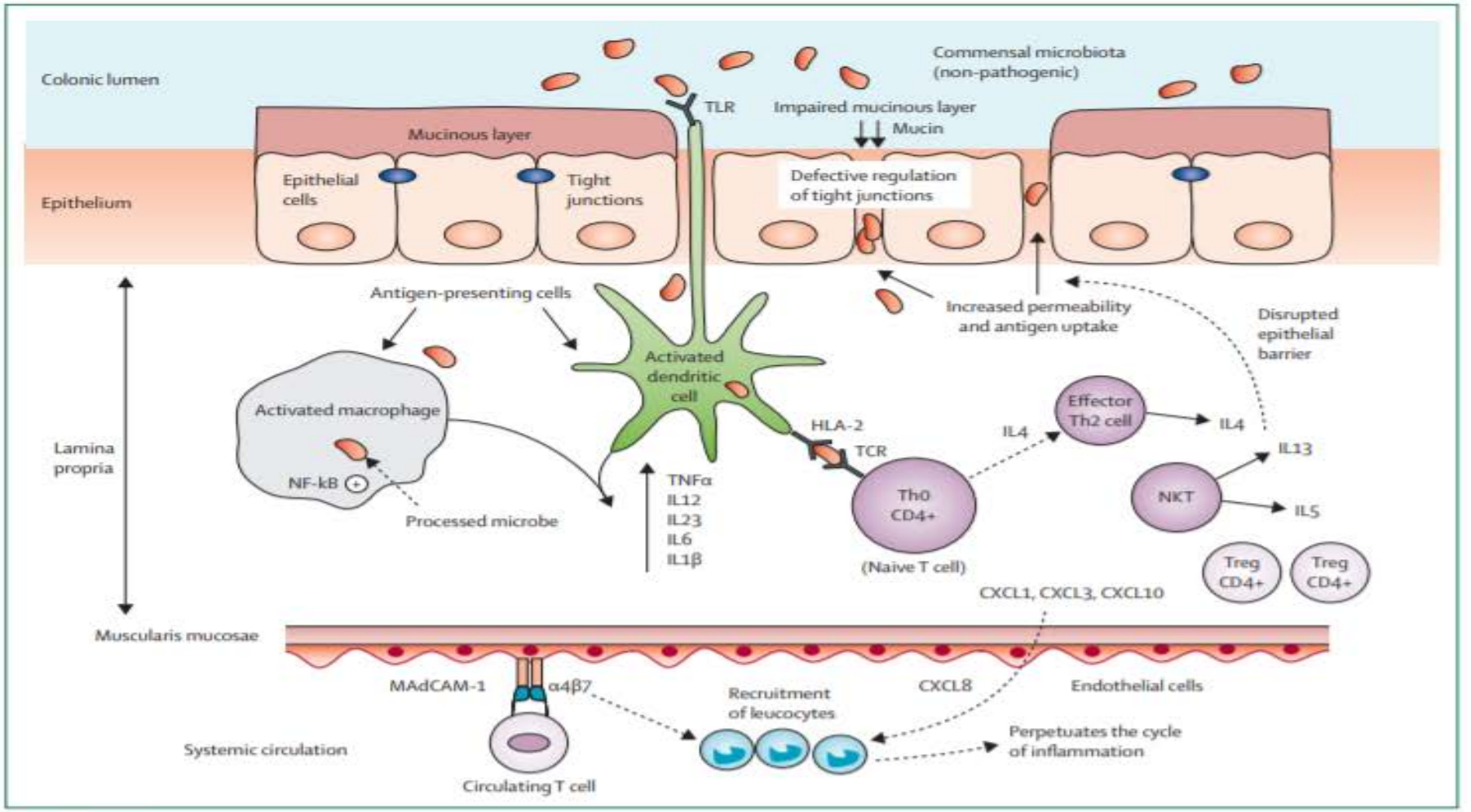
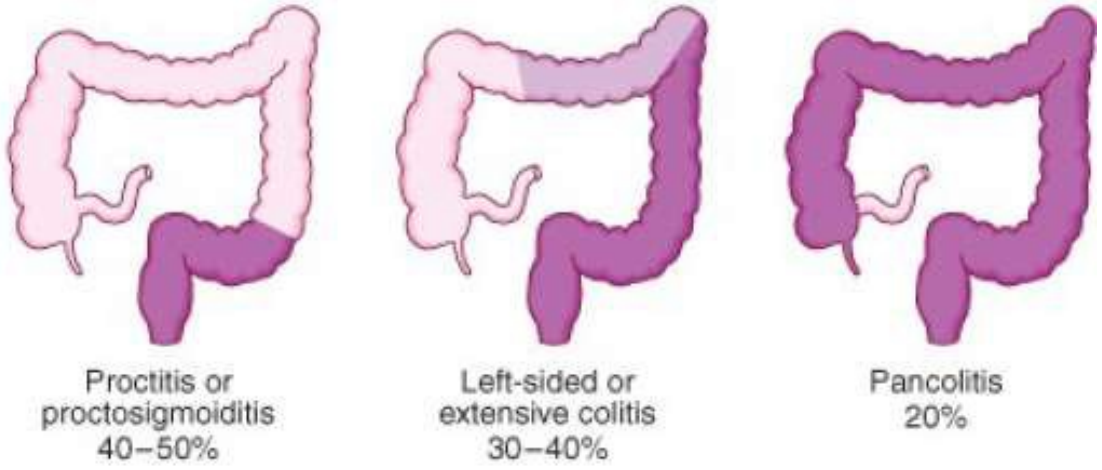


Figure 1: **Pathophysiology of ulcerative colitis**

Disruption of tight junctions and the mucus film covering the epithelial layer causes increased permeability of the intestinal epithelium, resulting in increased uptake of luminal antigens. Macrophages and dendritic cells (innate immune cells), on recognition of non-pathogenic bacteria (commensal microbiota) through molecular pattern-recognition receptors (TLR), change their functional status from tolerogenic to an activated phenotype. Activation of NF-kB pathways stimulates the transcription of proinflammatory genes, resulting in increased production of proinflammatory cytokines (TNF-α, interleukins 12, 23, 6, and 1β). After processing of antigens, macrophages and dendritic cells present them to naive CD4 T-cells, promoting differentiation into Th2 effector cells, characterised by production of interleukin 4. Natural-killer T cells are the main source of interleukin 13, which has been associated with disruption of the epithelial cell barrier. Circulating T cells bearing integrin-α4β7 bind to colonic endothelial cells of the microvasculature through the mucosal vascular addressin-cell adhesion molecule 1, whose expression is enhanced in the inflamed intestine, leading to increased entry of gut-specific T cells into the lamina propria. Upregulation of inflammatory chemokines, such CXCL1, CXCL3, and CXCL8, leads to recruitment of circulating leucocytes which perpetuates the cycle of inflammation. TLR=Toll-like receptor. HLA=human leucocyte antigen. IL=interleukin. TNF=tumour necrosis factor.

Pathology

- The rectum is always involved, with inflammation extending proximally in a confluent fashion.
- The disease typically is most severe distally and less severe proximally.
- According to extent of proximal involvement it is classified into
  - Proctitis/ proctosigmoiditis
  - Left sided colitis/ extensive colitis
  - Pancolitis



Pathology

- Inflammation is limited to the mucosal layer of the colon.

- Except in fulminant disease where inflammation extend beyond the mucosal layer and can develop a toxic megacolon.

Symptoms/ signs

- Predominant symptoms are Rectal bleeding, with frequent stools and mucous discharge from the rectum
- Others
  - Tenesmus
  - Nausea and weight loss
  - In severe cases, purulent rectal discharge causes lower abdominal pain and severe dehydration.
- Constipation may be the main symptom when the inflammation is limited to the rectum (proctitis).
- Although UC can present acutely , symptoms have usually been present for weeks or months.

Signs

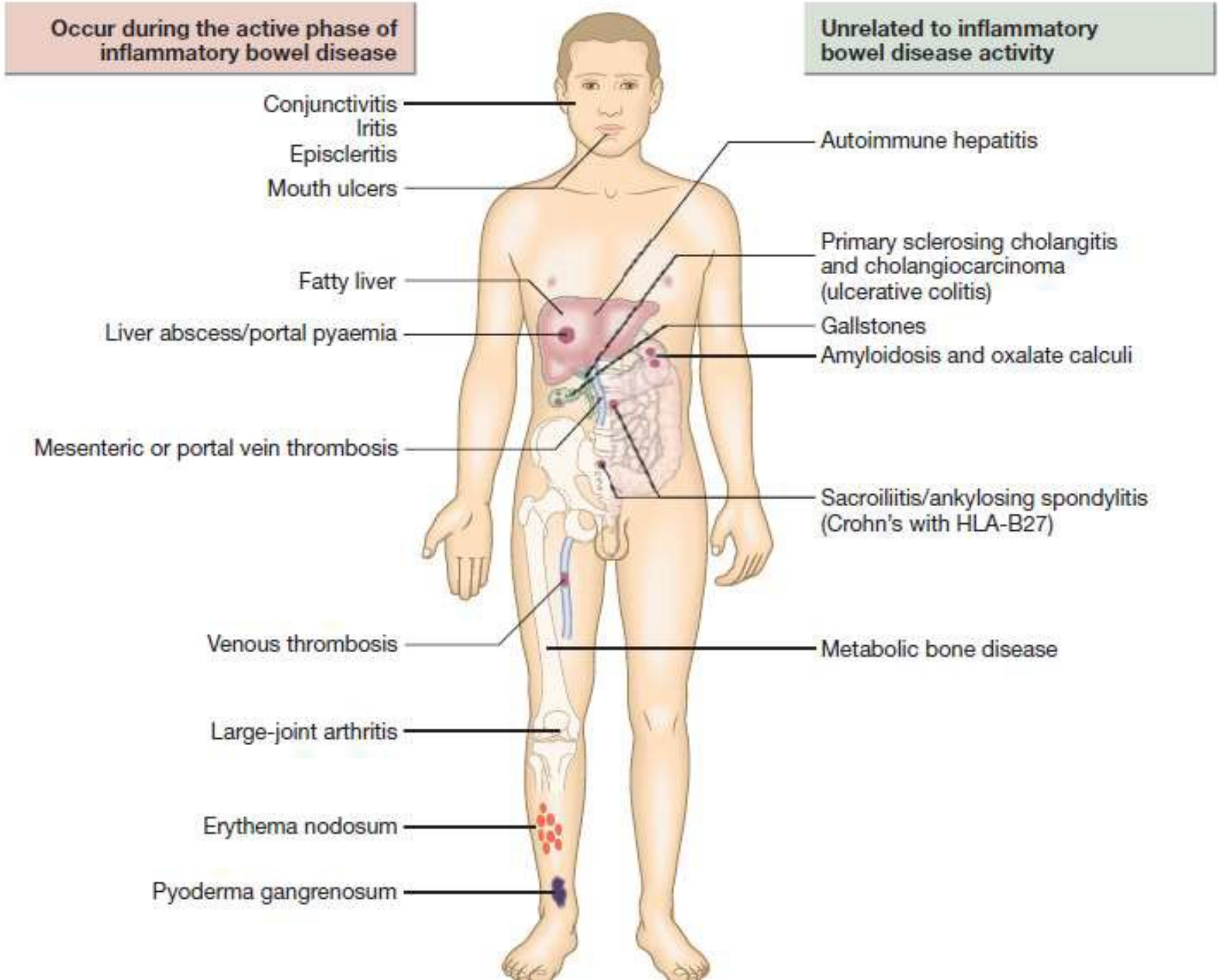
- Pallor may be evident.
- PR examination may disclose visible red blood.
- Signs of malnutrition.
- Severe abdominal tenderness, fever, or tachycardia suggests fulminant disease.

Grading of disease

Mild	• Bleeding per rectum and • <4 bowel motions/day
Moderate	• Bleeding per rectum with • >4-6 bowel motions/day
Severe	• Bleeding per rectum, • >6 bowel motions/day, and a systemic illness with hypoalbuminemia (<30g/l)

Extraintestinal manifestations

- UC (IBD) is not restricted to GI tract, can involve almost any organ system
- Upto 50% of patients can experience at least one EIM
- UC is associated with various extracolonic manifestations
  - Musculoskeletal conditions:- Peripheral or axial arthropathy
  - Cutaneous conditions:- Erythema nodosum, pyoderma gangrenosum
  - Ocular conditions:- Scleritis, episcleritis, uveitis
  - Hepatobiliary conditions:- PSC


Occur during the active phase of inflammatory bowel disease
Unrelated to inflammatory bowel disease
Conjunctivitis
Iritis
Episcleritis
Mouth ulcers
Fatty liver
Liver abscess/portal pyaemia
Mesenteric or portal vein thrombosis
Venous thrombosis
Large-joint arthritis
Erythema nodosum
Pyoderma gangrenosum
Autoimmune hepatitis
Primary sclerosing cholangitis and cholangiocarcinoma (ulcerative colitis)
Gallstones
Amyloidosis and oxalate calculi
Sacroiliitis/ankylosing spondylitis (Crohn's with HLA-B27)
Metabolic bone disease

Complications of UC

- Acute
  - Toxic megacolon – potentially life threatening complication
  - Perforation
  - Haemorrhage
- Chronic
  - Cancer
  - Extra-alimentary manifestations: skin lesions, eye problems and liver disease

Differential diagnosis

Other IBD	INFECTIVE	NON INFEVTIVE

• Crohn's disease	• Bacterial
	  • Salmonella
	  • Shigella
	  • Compylobacter jejuni
	  • Tubercuosis etc
	• Viral – HSV, CMV
	• Protozal - amoebiasis
		• Ischemic colitis
		• Collagenous collitis
		• NSAIDS
		• Diverticulosis
		• Radiation proctitis
		• Behcet's disease
		• Colonic carcinoma

Diagnosis

- Diagnosis relies on a combination of Compatible
  - Clinical features
  - Endoscopic appearances
  - Histologic findings
- Disease mimickers should be excluded

Laboratory studies

- No single test allows the diagnosis of UC with acceptable sensitivity and specificity.
- Useful principally for helping
  - To exclude other diagnoses
  - Assess the patient's nutritional status

CBC

CBC

CHEM

Inflammatory markers

Stool assays

Serological studies

- Leucocytosis
- Anaemia
- Thrombocytosis

CHEM

- CBC
- CHEM
- Inflammatory markers
- Stool assays
- Serological studies

- Hypoalbuminemia (ie, albumin <3.5 g/dL)
- Hypokalemia (ie, potassium <3.5 mEq/L)
- Hypomagnesemia (ie, magnesium <1.5 mg/dL)
- Elevated ALP: >125 U/L suggests PSC (usually >3 times the upper limit of the reference range).

Infammatory markers

- CBC
- CHEM
- Inflammatory markers
- Stool assays
- Serological studies

- ESR and CRP correlates with disease activity.
- Other inflammatory markers
  - Fecal calprotectin
    - Can also be used to determine mucosal healing 3-6 months after treatment initiation.
  - Fecal lactoferrin and alpha-1-antitrypsin studies are used to exclude intestinal inflammation

Stool assays

- CBC
- CHEM
- Inflammatory markers
- Stool assays
- Serological studies

- Used to exclude other causes and to rule out infectious enterocolitis.
- Tests include
  - Evaluation of fecal blood or leukocytes
  - Ova and parasite studies
  - Viral studies
  - Culture for bacterial pathogens
  - *Clostridium difficile* titer

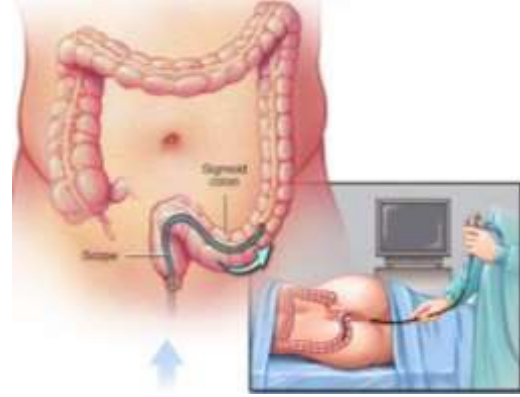
Serological studies

- CBC
- CHEM
- Inflammatory markers
- Stool assays
- Serological studies

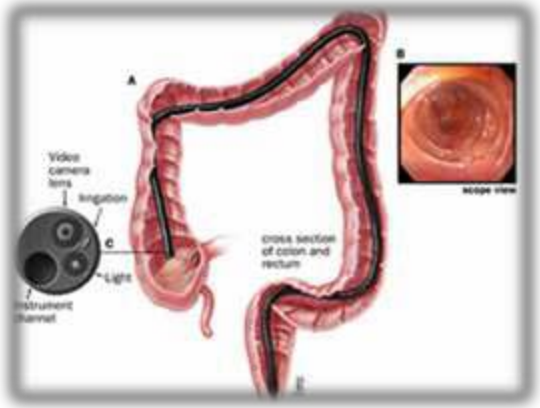
P-ANCA

- colitis associated serologic marker.
- Positive in 60%-80% of patients
- Helpful in predicting disease activity.
- Associated with an earlier need for surgery
- ASCA associated with Crohn's

Colonoscopy/ Sigmoidoscopy

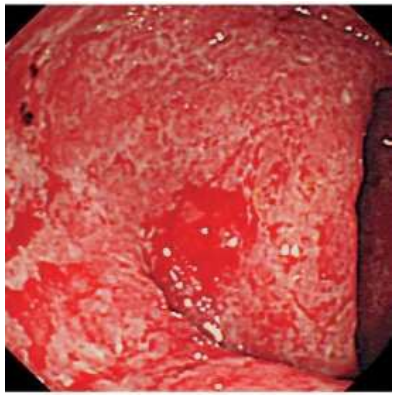


- Essential at initial presentation
  - To establish diagnosis
  - Exclude alternate diagnosis like ischemic and infectious colitis
  - Determine the extent and severity of disease.
- It may also be useful at the time of subsequent attacks
  - To determine recurrence
  - For surveillance for dysplasia.
- Multiple biopsies could be taken
  - Biopsy of the terminal ileum should be attempted to exclude the presence of Crohn's disease



Endoscopy findings include:

- Abnormal erythematous mucosa, with or without ulceration, extending continuously from the rectum to a part or all of the colon
- Contact bleeding may also be observed, with mucus identified in the lumen of the bowel
- Pseudopolyps in patients with long-standing disease.



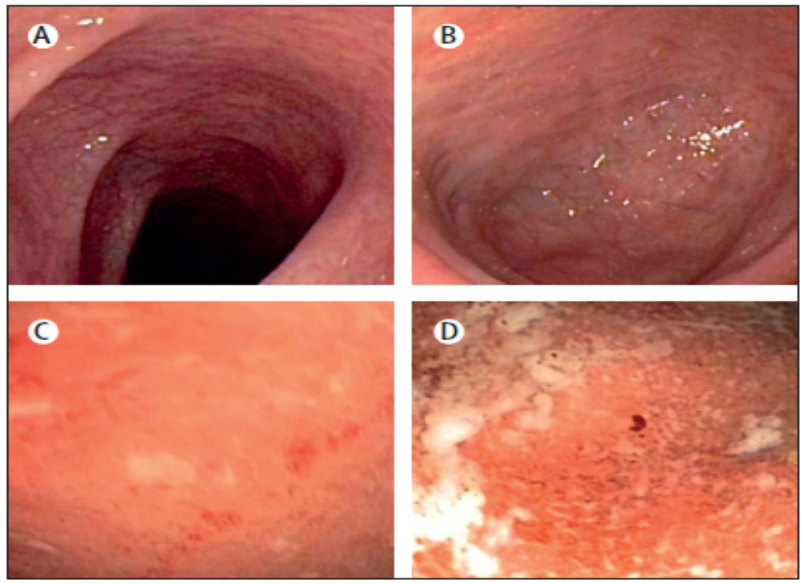


Figure 2: **Mayo endoscopic score for ulcerative colitis**
(A) Score 0=normal; endoscopic remission. (B) Score 1=mild; erythema, decreased vascular pattern, mild friability. (C) Score 2=moderate; marked erythema, absent vascular pattern, friability, erosions. (D) Score 3=severe; spontaneous bleeding, ulceration. Images courtesy of Elena Ricart.

Panel 2: **Montreal classification of extent and severity of ulcerative colitis**

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): four or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): four stools per day, minimum signs of systemic symptoms
- S3 (severe): six or more bloods per day, pulse rate of ≥90 beats per min, temperature ≥37·5°C, haemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/h

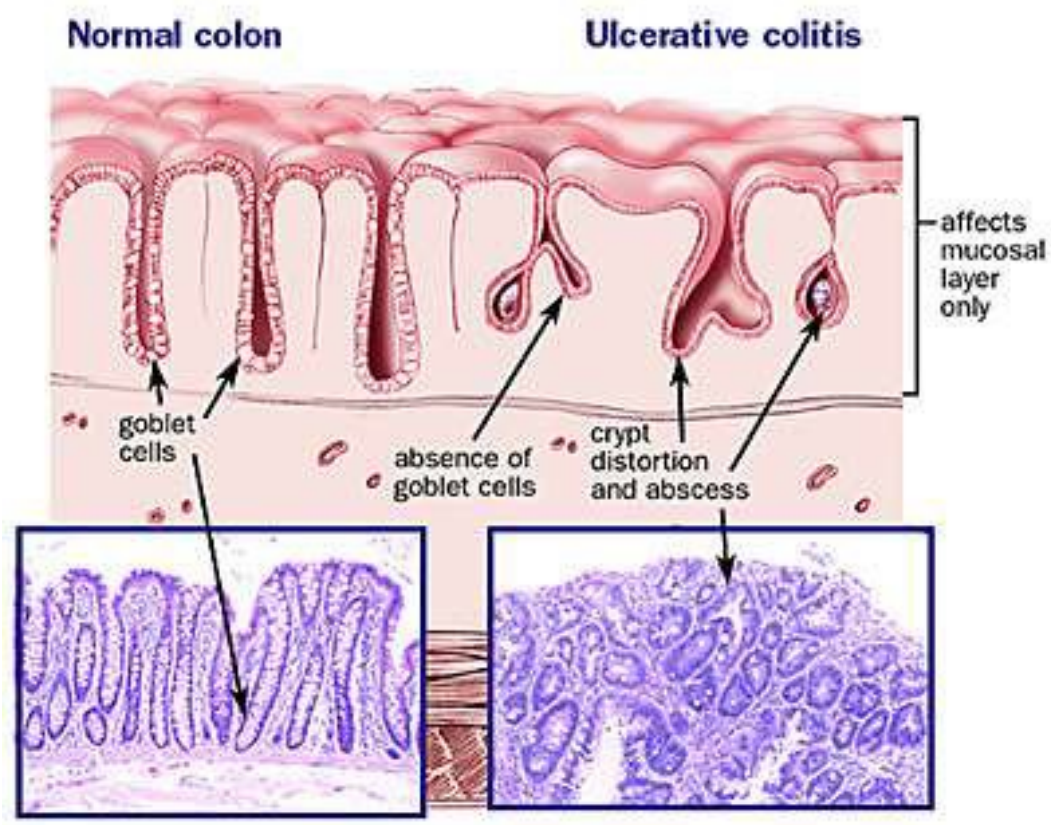
after 10 years of follow-up; in almost 661 (57%) of patients, the disease followed a chronic intermittent course; and 209 (18%) had chronic continuous activity.[71] A short period (2 years) from diagnosis to the first flare, presence of fever or weight loss at diagnosis, and active disease in the preceding year might increase the risk of subsequent relapse.[72]

Extension of colonic disease can occur in time. At diagnosis, 30–50% of patients have disease confined to the rectum or the sigmoid colon (distal colitis), 20–30% have left-sided colitis, and about 20% have pancolitis.[73] Of those with distal colitis, 25–50% progress to more extensive forms of the disease in time.[74] Patients who are diagnosed at a young age (eg, 15–30 years), and those with concomitant primary sclerosing cholangitis, are more likely to have extensive disease at presentation than are those diagnosed later in life. Disease flares associated with progression of anatomic extent (eg, from proctitis to left-sided colitis or pancolitis) usually follow a severe course and require more intensive medical treatment than do non-progressive flares.[75] The anatomical extent of mucosal inflammation is clearly one of the most important factors determining disease course; patients with more severe disease tend to have more extensive forms (pancolitis) than do those with less severe disease. Furthermore, disease extent is an important predictor of colectomy (patients with extensive colitis have a risk of 3·5 to four times greater than those with proctitis)[71,76] and colorectal cancer.[77] Colectomy rates within 10 years of diagnosis are 20–30%, increasing to 40% in patients with long-lasting and extensive disease.[72,78] In time, rates of colectomy decrease, with most done in the first 2 years of disease onset and in patients with pancolitis.[79]

Despite the often severe disease manifestations, patients with ulcerative colitis do not have an increased

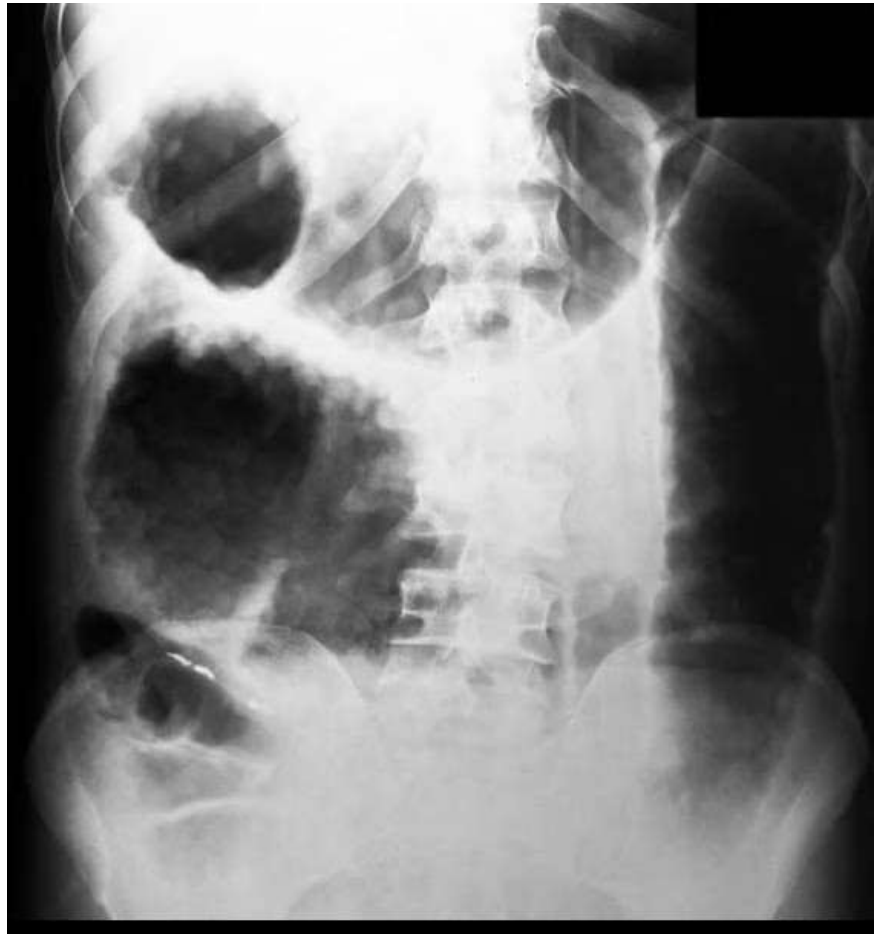
Histologic finding of UC

- Surface ulceration
- Inflammation confined to the mucosa with
- Excess inflammatory cells in the lamina propria
- Loss of goblet cells
- Presence of crypt abscess



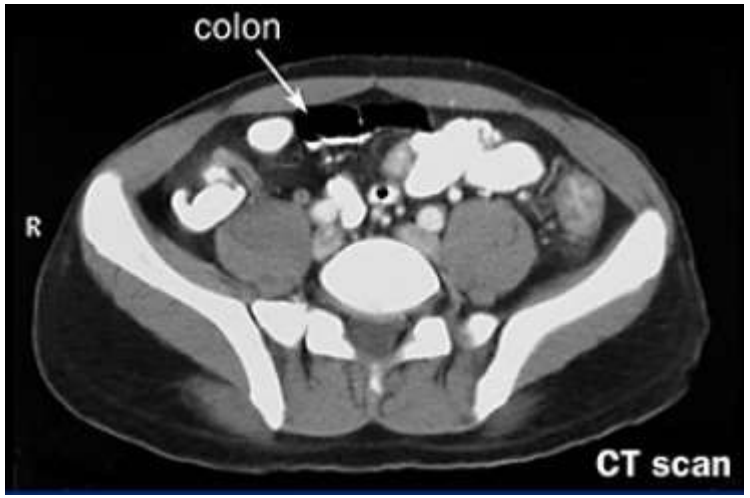
Imaging Studies

- Plain Abdominal X-ray:
  - Useful predominantly in patients with symptoms of severe or fulminant colitis.
  - Images may show
    - colonic dilatation with loss of haustral markings , suggesting toxic megacolon
    - Evidence of perforation; obstruction; or ileus.



CT scan

- Loss of haustra, especially in the distal colon
- Pseudopolyps
- Chronic cases - a narrow , featureless , shortened ‘hosepipe’ colon



Approach Considerations

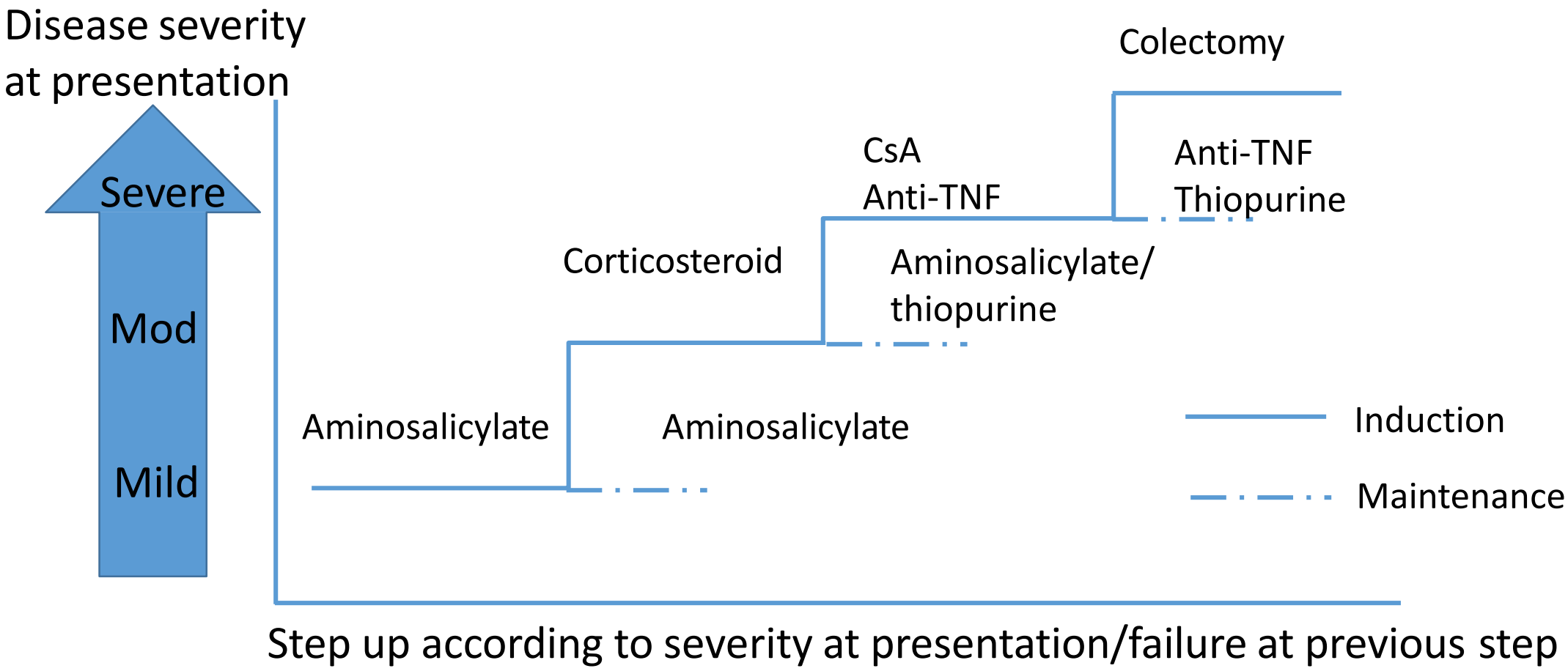
- The treatment of UC is made on the basis of
  - Disease stage (active, remission),
  - Extent (proctitis , distal colitis, left-sided colitis, pancolitis), and
  - Severity (mild, moderate, severe).
- Options
  - Medical
  - Surgical

Treatment goals

- Induction of remission
- Maintenance of remission.

- Prevention of complications
  - Therapy related- allergies/ intolerance, infections, lymphoma, steroid side effects
  - Disease related- EIM’s, neoplasia, toxic megacolon

Sequential therapies of UC



A) Medical Treatment

- 5ASA
- Corticosteroids
- Thiopurine
- Cyclosporine
- Biologics

1) 5-Aminosalicytes

- The mainstay of therapy for mild to moderate UC
- Preparations
  - Sulfasalazine
  - Mesalamine
- Effective at inducing and maintaining remission
- Topical mesalazine given by suppository is the preferred therapy for disease confined to the rectum
- Left-sided colonic disease is best treated with a combination of mesalazine suppository and an oral aminosalicylate.

Rx Strategies

Pharmacological Rx (attack vs. maintenance)

- 5'ASA for minor to moderate episodes or for prevention
  - P.O. ± P.R. (according to topography)
- 5'ASA suppositories for proctitis
- 5'ASA P.O. + enemas more effective than just one of the two
- 5'ASA enemas more effective than topical steroids

Corticosteroids

5ASA

Corticosteroids

Thiopurine

Cyclosporine

Biologics

- Used in acute treatment of moderate to severe colitis.
- Preparations:
  - Oral Prednisone
  - Iv Methylprednisolone
  - Iv Hydrocortisone
- Budesonide - A new glucocorticoid
  - Released entirely in the colon
  - Has minimal to no systemic glucocorticoid side effects.
  - The dose is 9 mg/d for 8 weeks and no taper is required
- Rectally administered steroid enemas provide therapy for flares of distal UC.

Thiopurines

- 5ASA
- Corticosteroids
- Thiopurines
- Cyclosporine
- Biologics

- Effective for the maintenance of remission
- Not appropriate as solo induction agents for patients with severe disease due to their slow onset of action
- Preparations
  - Azathioprine 2 - 2.5 mg/kg/day.
  - 6-mercaptopurine 1 - 1.5 mg/kg/day.

Cyclosporine

- 5ASA
- Corticosteroids
- Thiopurines
- Cyclosporine
- Biologics

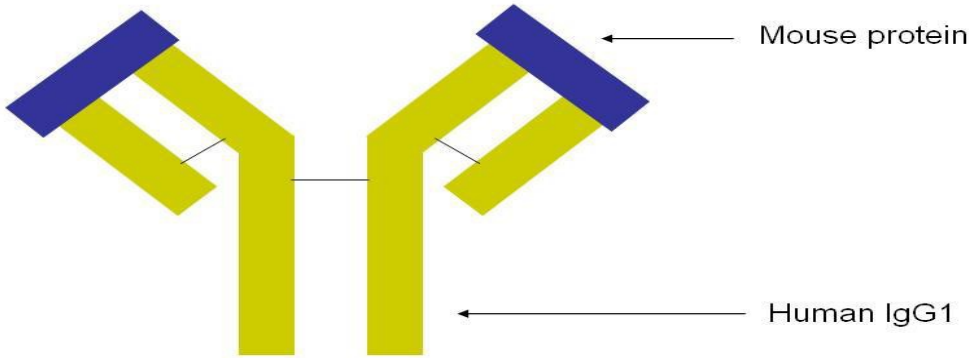
- Used to treat hospitalized patients with severe ulcerative colitis.
- Dose:
  - * 2-4 mg/kg/day given as a continuous infusion.
- Side effects:
  - Nephrotoxicity.
  - Opportunistic infections.
  - Seizures.

Biologics - antiTNF

- 5ASA
- Corticosteroids
- Thiopurines
- Cyclosporine
- Biologics

- Its an IgG monoclonal antibody directed against TNF.
- It is a less toxic alternative to cyclosporine for patients with severe ,steroid refractory disease
- Effective for both induction and maintenance of remission.
- Preparations - infliximab
  - Induction of remission: 5 mg/kg IV at weeks 0, 2, 6.
  - Maintenance: 5 mg/kg IV every 8 weeks.

Pharmacology



- TNF-α = pro-inflammatory cytokine
- Infliximab = chimeric human-murine IgG MAb
- Infliximab binds to TNF-α
  - Neutralizes TNF-α, blocks inflammation
  - Apoptosis of T-lymphocytes and monocytes
  - Down-regulation of other pro-inflammatory cytokines

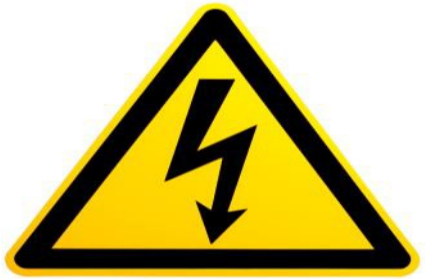
Reference: 2-5

Indications (focus: GI)

- Chronic inflammatory diseases
- Crohn's Disease (Moderate-Severe)
- Ulcerative Colitis (Moderate-Severe)
  - For patients with inadequate response to conventional therapies
  - Induce and maintain remission
  - Maintain fistula closure (in fistulizing Crohn's)
  - Induce and maintain mucosal healing (UC)

Reference: 2

Side Effects / Safety Concerns



Resp	Upper respiratory tract infection (32%)
GI	Nausea (21%) Abdominal pain (12%; Crohn's 26%)
Misc	Antinuclear antibodies (~50%) Infection (36%), joint pain, weight gain Infusion reactions (20%; severe <1%) Malignancies (<5%) (when combined with Azothioprine, 6MP) , non-melanoma skin cancer

Reference: 5-9

Contraindications

- Hypersensitivity to infliximab, any component of the formulation
- Doses >5 mg/kg in patients with moderate or severe heart failure (NYHA Class III/IV)
- Severe infections
  - Sepsis, Abscesses
  - Tuberculosis
  - Opportunistic infections

Reference: 6

Practical: Screening/Preparation

- TB Skin Test ,CXR
- Hepatitis B virus evaluation, Pneumovax, Shingles vaccine
- Rule out infection/abscesses (C. diff, T, WBC)
- Arrange for infusion site
- Pharmacare EDS must be applied before start
- Cost for most biologics (1 yr) $20,000

Reference: 10

Drug class	Ulcerative colitis	Crohn's disease
Anti-TNF alpha	Infliximab (iv) Adalimumab (sc) Golimumab (sc)	Infliximab (iv) Adalimumab (sc)
Anti-integrin	Vedolizumab (iv)	Vedolizumab (iv)
Anti-IL-12 and IL-23		Ustekinumab (iv and sc)

Biologic Tx Efficacy & Effectiveness

Anti-TNF Rx remission in 25 % at 4 weeks, 30% by one year

50-60% may have worthwhile response by 1 year

Healing fistulas in 25% by 1 year

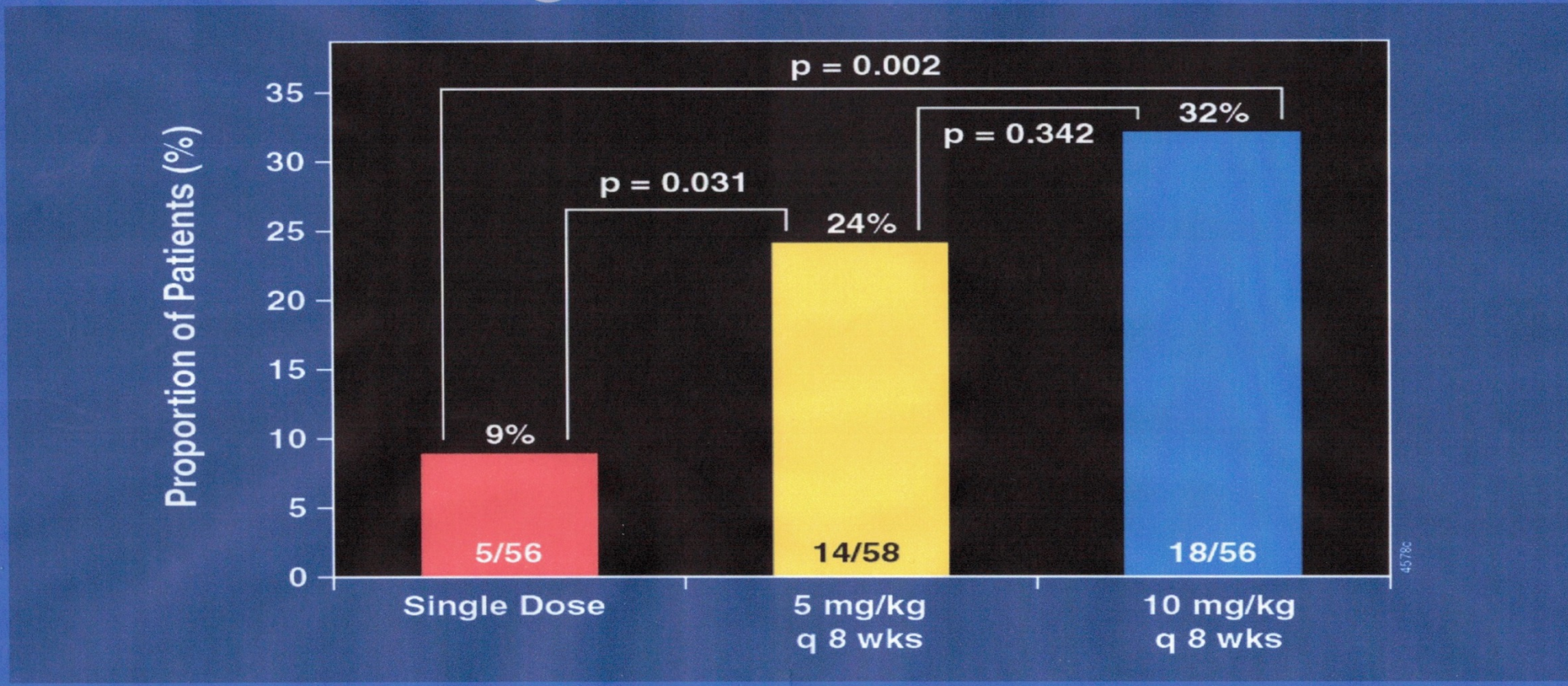
Monitor drug levels and drug-antibody levels

Oral biologic for colitis Tofacitinib –Janus kinase inhibitor
Xeljanz – possoble risk of DVT, PE

ACCENT I

Clinical Remission with Steroid Withdrawal at Week 54

Patients Receiving Steroids at Baseline



Five Things Physicians and Patients Should Question

by
Canadian IBD Network for Research and Growth in Quality Improvement
Crohn's and Colitis Canada
Canadian Association of Gastroenterology
Last updated: May 31, 2017

1 **Don't use steroids (e.g., prednisone) for maintenance therapy in inflammatory bowel disease (IBD).**

2 **Don't use opioids long-term to manage abdominal pain in inflammatory bowel disease (IBD).**

3 **Don't unnecessarily prolong the course of intravenous corticosteroids in patients with acute severe ulcerative colitis (UC) in the absence of clinical response.**

4 **Don't initiate or escalate long-term medical therapies for the treatment of inflammatory bowel disease (IBD) based only on symptoms.**

5 **Don't use abdominal computed tomography (CT) scan to assess inflammatory bowel disease (IBD) in the acute setting unless there is suspicion of a complication (obstruction, perforation, abscess) or a non-IBD etiology for abdominal symptoms.**

How the list was created

Surgical Treatment

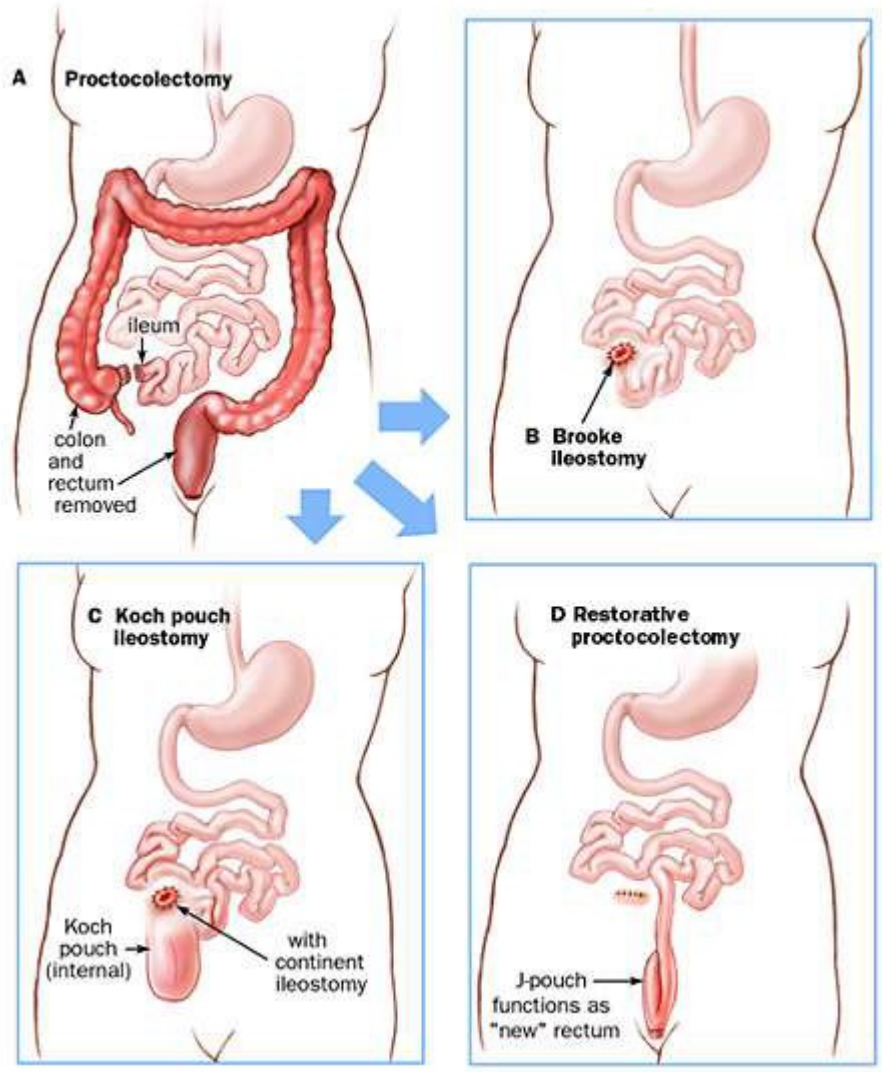
- About 10% to 20% of patients with UC.
- Indications:
  1) Chronic intractable disease
     - Not controlled with medications or
     - Drug side effects are too severe.
  2) Severe acute colitis requiring an urgent procedure.
  3) Presence of dysplasia or cancer.
  4) Colonic perforation

Surgery

- Proctocolectomy

- 2 options after proctocolectomy
  - Permanent end iliostomy
  - J pouch

- Technically, proctocolectomy cures UC and prevents colon Ca.



Take home message

- UC is an idiopathic IBD that affects the colonic mucosa.
- Hallmark of UC is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus.
- The clinical course is marked by exacerbations and remissions.
- The diagnosis of UC is suspected on clinical grounds and supported by the appropriate findings on
  - Proctosigmoidoscopy or colonoscopy
  - Biopsy
  - By negative stool examination for infectious causes

Cont..

- The initial treatment for UC includes corticosteroids, anti-inflammatory agents (like 5ASA) .
- Thiopurines can maintain remission, replace steroids
- Biologics can induce and maintain remission
- Surgery is considered if medical treatment fails or if a surgical emergency develops

Questions

- Which of the following is the most common cause of UC -related mortality?

1. Colonic adenocarcinoma
2. Toxic megacolon
3. Perforated colon
4. Colonic infarction

- Which of the following is *not* a common extracolonic manifestation of UC ?
    1. Erythema nodosum
    2. Uveitis
    3. Primary sclerosing cholangitis
    4. Cholelithiasis

- In mild UC confined to the rectum, which of the following is the preferred treatment?
    1. Steroid Enemas
    2. Rectal steroid foams
    3. Topical mesalamine
    4. Systemic steroids

- Defining characteristic of severe UC is ?
    1. > 4 bowel movements per day
    2. Bleeding from the rectum
    3. A systemic illness with hypoalbuminemia (< 30 g/L)
    4. Fistulae

True or False

1) Fecal Transplantation is an accepted treatment for ulcerative colitis

2) Studies have shown specific diets are helpful in treating IBD

3) Probiotics can be helpful in treating proctitis

4) Antibiotics are useful in treating ulcerative colitis

5) Antibiotic use in childhood raises the risk of IBD

P=0.229, $CI_{95\%}$ 0.35–0.57), physician's rating of disease activity (PP P=0.088, $CI_{95\%}$ 0.34–0.58; ITT P=0.168, $CI_{95\%}$ 0.31–0.53), or mean endoscopy scores (PP P=0.086, $CI_{95\%}$ 0.74–0.92; ITT P=0.366, $CI_{95\%}$ 0.66–0.86) (see Figure 3).

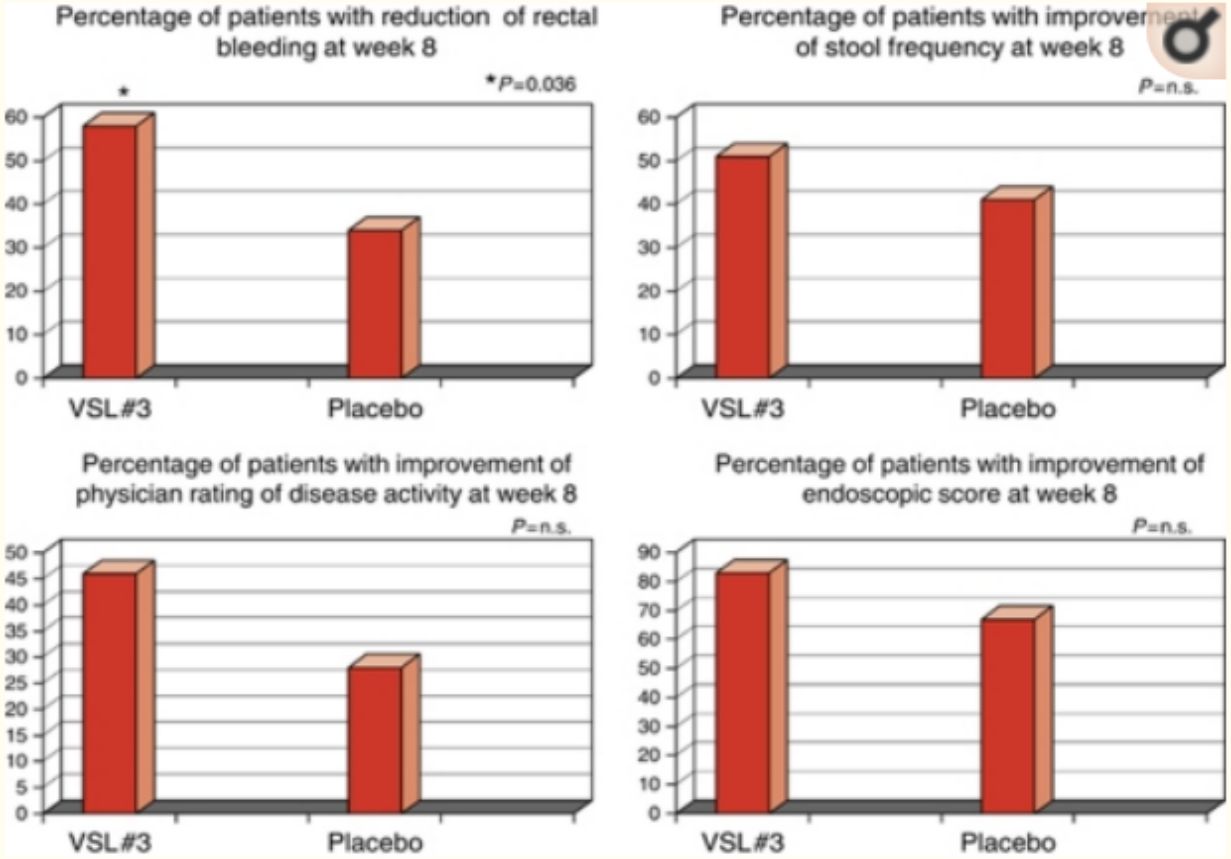


Figure 3

Percentage of patients with improvement in different subgroups of ulcerative colitis disease activity index (UCDAI; rectal bleeding, stool frequency, physician rating of disease activity, and endoscopic score) at week 8 (on intention-to-treat analysis). n.s., not

NPG Open Ac


Promise me that if I die on the toilet you'll flush before calling 911.
yourecards

Thank you