

# Inflammatory Bowel Disease

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## Educational Goals:

By the completion of this lecture, you should be familiar with

1. Epidemiology and pathogenesis of inflammatory bowel disease (IBD)
2. Differentiation of Crohn's disease (CD) and ulcerative colitis (UC) from a clinical, pathologic, and radiographic perspective
3. Differential diagnosis of idiopathic inflammatory colitis and ileitis
4. Extraintestinal manifestations of IBD
5. Pharmacologic and surgical therapy for IBD

## Key Words:

- 5-aminosalicylates (5-ASA)
- 6-mercaptopurine
- Abscess
- Anemia (iron and B12 deficiency)
- Ankylosing spondylitis
- Antibiotics
- Anti-TNF $\alpha$  antibody
- Aphthae
- Arthropathy (peripheral, axial)
- ASCA, ANCA
- Azathioprine
- Backwash ileitis
- Budesonide
- Cobblestoning
- Colectomy
- Colon cancer
- C-reactive protein
- Creeping fat
- Crohn's disease
- Crypt abscess
- Cyclosporine
- Dysplasia
- Episcleritis
- Erythema nodosum
- Extraintestinal manifestations of IBD
- Fissure
- Fistula
- Gallstones
- Glucocorticosteroids
- Granuloma (non-caseating)
- Hematochezia
- Ileopouch anal anastomosis
- J-pouch
- Malabsorption
- Methotrexate
- Microscopic colitis (collagenous, lymphocytic)
- Natalizumab
- Nephrolithiasis
- NOD2/CARD15
- Osteoporosis
- Pancolitis
- Perforation
- Perianal disease
- Primary sclerosing cholangitis
- Proctitis
- Pseudopolyps
- Pyoderma gangrenosum
- Sacroiliitis
- Sinus tract
- Skip areas
- Stricture
- String sign
- Sweet's syndrome
- Tenesmus
- Toxic megacolon
- Transmural inflammation
- Ulcerative colitis
- Urgency
- Uveitis
- Vitamin deficiency

## Introduction and Summary

1. Inflammatory bowel disease (IBD) refers to idiopathic chronic inflammation involving the luminal gastrointestinal tract. The two most common subtypes are Crohn's disease (CD) and ulcerative colitis (UC). The pathogenesis of IBD is multifactorial, resulting from immune dysregulation, environmental influences and genetic mutations.
2. CD may involve any part of the GI tract, although most commonly the terminal ileum & colon. Symptoms depend on disease location and subtype, but include diarrhea, abdominal pain, fever, and weight loss. Inflammation is transmural and patchy; noncaseating granulomas are the hallmark histologic finding. Strictures, fistulas & abscesses may complicate CD.
3. UC involves only the colon, and always extends proximally from the rectum: extent of disease ranges from proctitis to pancolitis. Inflammation is limited to the mucosa. Patients generally present with frequent bloody loose stools, urgency, tenesmus, and lower abdominal cramping. UC may be complicated by toxic megacolon, hemorrhage, perforation & in more long-standing disease, colon dysplasia and/or carcinoma.
4. In the proper clinical setting, diagnosis of IBD is generally made by endoscopy and histology; while disease proximal to the terminal ileum in CD has traditionally been

evaluated by barium studies (small bowel series), CT and MR enterography as well as capsule endoscopy are now utilized with increasing frequency.

5. Extraintestinal manifestations (EMI) of IBD may parallel or manifest independently of disease activity. EMI include uveitis, episcleritis, ankylosing spondylitis, sacroiliitis, arthropathy, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, nephrolithiasis & primary sclerosing cholangitis.
6. Treatment of UC and CD varies depending on subtype and severity, but significant overlap is seen. The goals of treatment are two-fold: induction and maintenance of remission. 5-ASA agents are efficacious in UC, but data is weaker in CD. Antibiotics appear somewhat effective in patients with perianal and colonic CD. Glucocorticosteroids induce but do not maintain remission in IBD and have many deleterious effects. The non-systemic steroid budesonide induces remission in ileal and right colonic CD. Immunomodulators and biologic agents including anti-tumor necrosis factor- $\alpha$  (anti-TNF $\alpha$ ) antibodies and natalizumab (an anti alpha-4 integrin antibody) are also effective in IBD.
7. Total proctocolectomy (TPC) is curative in UC, but is generally reserved for those with medically-refractory disease or with a complication or neoplasia. As many as 30% of patients will require this surgery over their lifetime. Surgery in CD is not curative, but up to 70% of patients require  $\geq 1$  operation, the most common being an ileocecectomy.
8. Microscopic colitis (MC) is divided into lymphocytic and collagenous colitis. It will not be the focus of this lecture. Inflammatory changes are not seen macroscopically, only histologically. MC typically affects women in their 5<sup>th</sup> and 6<sup>th</sup> decades, who present with non-bloody diarrhea. NSAIDs increase the risk. Treatment may include anti-diarrheal agents, bismuth salicylate and 5-ASAs, though budesonide is the most effective medication.
- 9.

TABLE 1: UC vs. CD

	Ulcerative Colitis	Crohn's Disease
Anatomic location	Colon	Entire GI tract (ileum/colon), perianal disease
Distribution	Continuous from rectum proximally	Skip areas, patchy
Granulomas	Absent	May be present
Inflammation	Mucosal	Transmural
Fistula, Abscess, Stricture	Absent	May be present
Serologies	pANCA	ASCA, OmpC, CBir1
Smoking	May be protective	Increases risk, worsens disease
Appendectomy	May be protective	May increase risk
Clinical presentation	Small volume bloody diarrhea, tenesmus, urgency	Variable: abdominal pain, diarrhea, weight loss, fever
Surgery	Curative (total proctocolectomy)	Not curative
Monozygotic Twin concordance	15-20%	20-50%

I. Definition: IBD is chronic uncontrolled inflammation of the intestinal mucosa

II. Subtypes:

- A. Ulcerative Colitis (UC)
- B. Crohn's Disease (CD)
- C. Microscopic Colitis (lymphocytic and collagenous): not focus of lecture; covered briefly

III. Epidemiology

- A. Prevalence/Incidence
  - a. Prevalence: UC 214/100K + CD 174/100K = IBD 388/100K: ~ 1.1 million in US
- B. Incidence: UC 8.8/100K, CD 7.7/100K
- C. Overall, rates continue to trend upward
- D. Geographic Distribution:
  - a. Northern-hemisphere, industrialized countries > southern-hemisphere, developing countries, although increasing rates being seen in latter

- E. Age onset: peak 16-35; possible “2<sup>nd</sup> peak” in later decades
- F. Gender: overall, equal rates between females and males
  - a. CD: slight female predominance                      UC: slight male predominance
- G. Ethnicity:
  - a. Caucasians (especially Ashkenazi Jews) > non-Caucasians
  - b. Increasing rates: African-Americans, Hispanics, Asians

#### IV. Pathogenesis (Fig 1)

Multifactorial: Environmental, Genetic, Immunologic

##### A. Environmental Factors

1. Hygiene Hypothesis: less sanitary, more crowded living conditions possibly protective
2. Diet: no conclusive data
3. Appendectomy: possibly protective in UC, but increased risk for CD
4. Role of Microbial Flora
  - a. Abnormal response to commensal bacteria
  - b. Germ-free animals do not develop colitis; IBD onset after enteric infection
  - c. Specific pathogens?: e.g., mycobacterium paratuberculosis
  - d. Acute infections: e.g., Clostridium Difficile
  - e. Therapeutic role of certain antibiotics, probiotics, diversion of fecal stream
5. Medications: NSAIDs, antibiotics, OCPs
6. Cigarette Smoking
  - a. UC: protective, older pts with new disease often ex-smokers, nicotine as putative ingredient?
  - b. CD: doubles risk of developing disease, worsens clinical course; quitting improves disease, associated with ileal and inflammatory subtypes

##### B. Genetics

###### 1. The Clues

- a. Twins concordance: monozygotes      dizygotes

CD	20-50%	0-7%
UC	14-19%	0-7%
- b. 1st degree family members: CD RR ≤ 35, UC RR ≤ 15
- c. 75% familial concordance of IBD subtype
- d. Higher rates in Ashkenazi Jews

###### 2. IBD Susceptibility Genes

###### NOD2/CARD15

- i. 1st gene associated with IBD, chromosome 16q12
- ii. 3 major risk alleles in/near leucine-rich repeat region (LRR)
- iii. 27-39% CD patients with mutation (vs. ~15% UC and controls)
- iv. Product expressed inside macrophages, dendritic cells, and intestinal epithelial cells. The NOD2 protein = intracellular sensor for a bacterial product known as muramyl-dipeptide (MDP).
- v. Bacteria interact with NOD2 → induces inflammatory pathways, production of inflammatory cytokines, and secretion of antimicrobial substances into GI lumen.
- vi. Paradox: ?compensatory upregulation adaptive immune response, loss tolerance to commensal microflora, decreased regulatory T-cells
- vii. Relative Risk (CD only): heterozygotes 4, homozygotes 40
- viii. NOD2 knockout mice do not develop intestinal inflammation

###### a. IL23R

- i. IL-12 & IL-23: common p40 subunit and B1 receptor
- ii. Multiple independent risk alleles increase IBD susceptibility, except Arg381Gln, which confers protection against IBD development
- iii. IL23 stimulation: perpetuation and expansion of T<sub>H</sub>17 (CD4<sup>+</sup> subset mediating intestinal inflammation).
- iv. Animal models now suggest that IL-23, not IL-12, is major cytokine implicated in intestinal inflammation

- v. Anti p40 neutralizing Abs block IL23 & IL12 function
- C. Immune Dysregulation
  1. T cell Subsets: Naïve T-cells are stimulated to differentiation
    - a. Th1: stimulated by IL-12 → IFN $\gamma$  (Crohn's)
    - b. Th2: stimulated by IL-4 → IL-4,5,13, 25 (UC)
    - c. Th17: stimulated by IL-23 → IL-17 (CD)
  2. Defects in Innate Immunity
    - a. Intestinal barrier defect: increased permeability→continuous stimulation of mucosal immune system; disturbed electrolyte transport→diarrhea
    - b. Neutrophil/macrophage defects: altered function, NOD2 mutation
    - c. Paneth cell defects: impaired defensin production
    - d. Therapeutic targets: epidermal growth factor enemas; GMCSF
  3. Defects in Adaptive Immunity: continued production of cytokines/chemokines after innate immune response may perpetuate inflammation in IBD
  4. Inflammatory Mediator Imbalance
    - a. Overactive Proinflammatory Cytokines: TNF, IL-1, IL8, IL-12, IFN $\gamma$
    - b. Ineffective Downregulatory cytokines: TGF $\beta$ , IL-10, IL-4
    - c. Therapeutic Targets: anti-TNF $\alpha$  Ab, anti IL-12/IL-23 Ab, Trichuris suis ova (induce Tregs, blunt T<sub>h</sub>1 cells)
  5. Activated Effector Cell/regulatory cell Imbalance
    - d. Overactive/overabundance of effector cells: macrophages/granulocytes/Tcells (Th1, Th2, Th17)→inflammatory cytokines, chemokines
    - e. Underactive/too few regulatory cells (Tr1, Th3)
    - f. Therapeutic Targets: immunomodulators, 5-ASAs, steroids inhibit activated effector cells
  6. Ineffective apoptosis of activated effector cells  
Therapeutic Targets: Azathioprine/6-MP, infliximab → induce apoptosis
  7. Failure to downregulate leukocyte trafficking to the intestine
    - a. Therapeutic Targets: glucocorticosteroids, natalizumab inhibits  $\alpha$ 4 integrin (mediates leukocyte adhesion to activated endothelium)

V. Diagnosis: suggested by clinical presentation, supported by endoscopic and radiographic findings, confirmed by histology. Of note, ~ 10-15% cases of colitis are "indeterminate" (ie, cannot distinguish between UC and Crohn's of the colon)

	Ulcerative Colitis	Crohn's Disease
Symptoms	Hematochezia, diarrhea, constipation, tenesmus, urgency, incontinence, nocturnal awakening, abdominal cramps	<u>Variable with disease location/subtype</u> : Colon: similar to UC Ileum: RLQ pain, diarrhea, fever Perianal: pain, drainage <u>Fistulizing</u> : Entero-enteric: diarrhea, malabsorp Rectovaginal: air/stool per vagina Rectovesicular: fecaluria, pneumaturia <u>Strictureing</u> : emesis, obstipation
Physical Exam	Pallor, abdominal tenderness, red blood on rectal exam. Toxic Megacolon: abd distention, hypoactive bs, tympany Perforation: hypoactive bs, rebound, guarding EMI: conjunctival erythema, skin lesions (tender nodules, ulcers), joint tenderness	Fever, orthostatic hypotension, tachycardia, pallor, cachexia Abdominal tenderness (esp RLQ), fistula Perianal: fissure, fistula, abscess Intraabd Abscess: RLQ mass, psoas sign Obstr: distention, hyperactive bs, tympany Perforation/EMI: see UC
Laboratory Tests	Iron deficiency anemia (low Hgb/Hct, low MCV, low ferritin, high platelets), elevated CRP/ESR/WBC, low	Iron and/or B12 deficiency anemia, elevated CRP/ESR, low K <sup>+</sup> ; low fat soluble vitamins (A, D, E, K), elevated PT,

	K <sup>+</sup> /albumin; +pANCA	low albumin; + ASCA, OmpC, CBir1
Endoscopic (Fig 3,4)	*Continuous from rectum proximally* <u>Distribution:</u> Rectosigmoid 46% Left colon 37% Pancolitis 17% <u>Mild:</u> erythema, edema, abnormal vascular pattern <u>Moderate:</u> granularity, erosions, ulcers, friability <u>Severe:</u> coalescence of ulcers, mucopurulent exudate, spontaneous bleeding, pseudopolyps <u>Chronic:</u> featureless → mucosal atrophy, muscular hypertrophy, loss of haustra, shortened/narrowed	*Patchy, “skip” lesions, rectal sparing <u>Distribution:</u> Ileum + colon: 35% Ileum: 28% Colon: 32% Perianal: ≤ 30% Esophageal: <1% Gastroduodenal: 1-4% (Peds: 30-40%) <u>Mild:</u> aphthoid ulcers, edema, hyperemic spots, loss of vascular pattern <u>Moderate/Severe:</u> deep, linear, stellate, coalescing “bear-claw” ulcers, pseudopolyps; cobblestoning
Histologic (Fig 5,6)	<u>Early:</u> mucosal infiltration by neutrophils, lymphocytes, plasma cells, macs → cryptitis, crypt abscesses <u>Chronic:</u> key to distinguish from acute colitides → Paneth cell metaplasia, crypt distortion/atrophy, basal lymphoid aggreg, chr. inflamm. infiltr.	<u>Histology:</u> sim to UC; additionally, non-caseating granulomas <u>Gross pathology:</u> transmural inflammation, fistulas, strictures; creeping fat
Radiographic	<u>Barium Enema:</u> granularity, ulcers, thickened folds → loss of haustra from relaxation taeniae coli → “lead-pipe”/shortened colon, strictures/ca, dilation, widening of presacral space <u>CT:</u> diffuse/symmetric thickening, dilation, perforation, EMI <u>MR/CT colonography</u>	<u>Small bowel series/Enteroclysis:</u> lymphoid hyperplasia, granularity, fold/wall thickening, ulceration, cobblestoning, polyps, fistulae, stricture (“string sign”) <u>CT:</u> ileal/colon thickening, fat stranding, “halo” sign, abscess, obstruction, EMI <u>CT/MR enterography</u> (negative/neutral contrast): greater mucosal detail <u>MRI:</u> perianal/rectovaginal fistulae

#### VI. Differential Diagnosis: UC

Inflammatory	CD, diversion or diverticula-associated colitis, GVHD
Neoplastic	Polyps, adenocarcinoma, metastasis, lymphoma
Vascular	Ischemia, radiation, vascular ectasias, SRUS, vasculitis (Behçet’s)
Infectious	Bacterial, Amebic, viral (CMV/HSV)
Drugs	NSAIDs, OCP, antibiotics, gold, K <sup>+</sup>
Miscellaneous	IBS, factitious diarrhea

#### VII. Differential Diagnosis: Ileitis

Inflammatory	Appendicitis, cecal diverticulitis, GVHD
Neoplastic	Adenocarcinoma, carcinoid, lymphoma, metastasis
Gynecologic	Endometriosis, PID, TOA, ovarian cyst
Infiltrative	Amyloid, eosinophilic enteritis
Vascular	Mesenteric ischemia, radiation enteritis
Infectious	Mycobacterium, Yersinia, Campylobacter, Anisakis
Functional	IBS
Congenital	CVID, chronic granulomatous disease
Miscellaneous	Meckel’s diverticulum, adhesions, NSAIDs

#### VIII. Extraintestinal Manifestations of IBD (EMI)

##### A. Rheumatologic

1. Peripheral arthropathies: 5-20% IBD (CD>UC); asymmetric, migratory, nondeforming, seronegative RF; colonic disease increases risk
    - a. Pauciarticular (type I): ≤4 joints; large joints (knee/ankle), <5 wks
    - b. Polyarticular (type II): ≥5 joints; small joints; median 3 yrs duration
  2. Axial arthropathies (3-5%)
    - a. Ankylosing spondylitis (AS): low back pain, morning stiffness, improved with exercise; 75% HLA-B27 pos
    - b. Sacroiliitis: may be asymptomatic, usually does not progress to AS; HLA-B27 neg
  3. Metabolic Bone Disease:
    - a. Osteopenia/osteoporosis: 23-59%, CD>UC; a/w corticosteroids, decreased physical activity, SB resection, Ca<sup>++</sup>/vit D def., smoking, inflammatory cytokines
    - b. Osteonecrosis = avascular necrosis; rare; a/w steroids
- B. Mucocutaneous**
1. Pyoderma gangrenosum (1-10%, UC>CD): pustule/nodule → ulcer with irregular violaceous edges; sites: LE or stoma; pathergy
  2. Erythema Nodosum (10-20%): tender, red nodules, extensor surfaces of LE
  3. Sweet's syndrome: rare; tender, erythematous plaques/nodules arms/legs/trunk/hands/face; leukocytosis; neutrophilic infiltrate with leukocytoclasia
  4. Oral lesions: aphthous ulcers and angular stomatitis are nonspecific, most common
  5. Psoriasis: up to 10% of CD patients
  6. Metastatic CD: rare, characterized by granulomatous lesions at extraintestinal sites
- C. Ocular (1-6%)**
1. Anterior uveitis/iritis: serious; photophobia, blurred vision, HA, eye pain
  2. Scleritis/episcleritis: less serious; burning, watering, itching, erythema
- D. Hematologic**
1. Anemia: iron def (blood loss), B12 def (ileal CD/resection), chronic disease, autoimmune hemolytic anemia
  2. Hypercoagulable states (1-39%): inflammatory state, thrombocytosis, other
- E. Nephrolithiasis:**
1. Calcium oxalate: non-absorbed fats in ileum saponify Ca<sup>++</sup> → not available to bind oxalate → absorbed in colon → binds Ca<sup>++</sup> in kidney → Ca<sup>++</sup>/oxalate stones
  2. Uric acid: abnormal urate excretion, decreased intestinal absorption of Na<sup>++</sup>/H<sub>2</sub>O → vol depletion → oliguria
- F. Hepatobiliary:**
1. Primary Sclerosing Cholangitis: 2.4-7% (UC>CD), up to 90% PSC with IBD (UC>CD); M>F; chronic cholestatic stricturing disease of bile and liver ducts → cirrhosis
  2. Other: gallstones, granulomatous hepatitis
- G. Other: Amyloidosis (rare), pericarditis/myocarditis (5-ASA); pulmonary**

EMI Paralleling Disease Activity: Pauciarticular arthropathy, erythema nodosum, Sweet's syndrome, episcleritis

EMI Independent of Disease Activity: Polyarticular arthropathy, axial arthropathy, pyoderma gangrenosum, uveitis

## VII. Treatment

### A. Current Medical Treatment

	Mechanism of Action	Efficacy	Safety Profile
5-Aminosalicylates (PO, rectal)	Inhibits cyclooxygenase, lipoxygenase, B cells, inflammatory cytokines; activates PPAR-γ	UC: +induct/maint CD: +induct (weak), ?maint	Sulfasalazine: folate-depletion anemia, oligospermia; All: ?interstitial nephritis
Antibiotics (PO, IV)	Cipro (quinolone; Gram neg) Metronidazole (anaerobes)	CD: colonic, perianal (cipro/metronidazole),	C: tendon rupture M: metallic taste,

	Rifaximin (min absorption)	ileocolonic (high dose Rifaximin)	peripheral neuropathy
Glucocorticosteroid (PO, IV, rectal)	Inhibits recruit/prolif of lymphs, monos, macs; dec migration neutrophils to inflamm sites; dec prod cytokines, leukotrienes, prostaglandins	UC: +Induction CD: +Induction <hr/> NOT EFFECTIVE for MAINTENANCE	Moon face, wt gain, acne, hirsutism, irritability, HTN, DM, bone metabolism, infection, cataracts, adrenal insufficiency, ecchymoses, osteonecrosis
Budesonide (PO)	Non-sys steroid, pH-dep. rel TI, high 1 <sup>st</sup> pass metabolism	CD (R colonic, TI): + induction	<10% side effects of systemic steroids
6-MP/Azathioprine (PO)	Purine analogs → 6-TG → interferes with nucleic acid synthesis → anti-proliferative effect on active lymphocytes; induces apoptosis	CD/UC: steroid withdrawal; maintenance	Leukopenia, hepatotoxicity, pancreatitis, infection (viral), lymphoma, non-melanoma skin cancer
Methotrexate (IM, PO)	Folate analog: reversible competitive inhibitor of DHFR → decreased DNA synthesis, multiple anti-inflammatory effects	CD: + induction, maintenance UC: ?	Bone marrow suppression, hepatotoxicity, pneumonitis
Cyclosporine (IV → PO)	Lipophilic peptide: downregulation of IL2 → inhibition of prolifer/active T <sub>H</sub> cells	UC: induction for severe, steroid-refractory patients	Infection, hypertension, neurotoxicity, renal toxicity
Natalizumab	Alpha 4 Integrin Ab	CD: +induc/maint	PML
Anti-TNF antibodies Infliximab (IV) Adalimumab (SQ) Certolizumab (SQ)	Inhibits TNFα (Fig 2 re: TNF roles)	CD/UC: induction, maintenance (Adalim and certolizumab: only CD)	Infection (opportunistic/TB), demyelination, SLE-like reaction, CHF, infusion reaction, lymphoma

#### B. Medical Treatment "Pipeline":

1. Biologics: MLN02, Anti IL-12
2. Other: Probiotics/Helminths; Growth factors; Apheresis; Curcumin

#### C. Surgical Treatment:

1. Crohn's Disease:
  - a. Indications: fibrotic stricture, perforating disease (abscess, fistula, free perforation), refractory disease, hemorrhage, cancer. Intraabdominal/pelvic abscesses may be amenable to percutaneous drainage, which in combination with antibiotics, is preferred initially over surgery.
  - b. Most common types: ileocectomy, stricturoplasty; perianal fistulotomy/setons
  - c. ~ 60-70% patients will have ≥ 1 surgery over lifetime
2. Ulcerative Colitis:
  - a. Indications: refractory disease, dysplasia or cancer, fulminant colitis, toxic megacolon, obstruction, hemorrhage
  - b. Types: total proctocolectomy (TPC) with either end-ileostomy or ileal pouch anal anastomosis (IPAA)
  - c. Up to 30% patients will have TPC over lifetime

### VIII. Special Considerations

#### A. Pregnancy

1. Fertility rates: no differences, except in women after TPC/IPAA (up to 30%)
2. Effect of pregnancy on IBD: ~ 1/3 flare, ~ 2/3 same/improve
3. Effect of IBD on preg/fetus: preterm delivery, low-birth wt, small for gestational age

4. Medications: most are safe during pregnancy (NOT methotrexate)
5. Mother & baby do better when patient conceives during, and remains in, remission

#### B. Colon Cancer

1. Increased Risk: duration of disease (up to 30% at 35 years), extent of disease, PSC, severity of inflammation, pseudopolyps, family history, smoking, ?young age at onset, ?backwash ileitis
2. Likely similar risk in patients with Crohn's of the colon, depending on extent of disease.
3. Decreased risk: 5-aminosalicylates
4. Colonoscopy Surveillance: begin after 8-10 yrs duration, q1-2 yrs depending on extent of disease, 4-quadrant biopsies every 10 cm
  - a. Indefinite dysplasia: treat underlying inflammation, repeat colonoscopy 3-6 mos
  - b. Flat low-grade dysplasia: repeat colonoscopy 3 months (vs. colectomy)
  - c. Multifocal low-grade dysplasia, dysplastic-associated lesion/mass (DALM), high-grade dysplasia, adenoca: TPC

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Figures

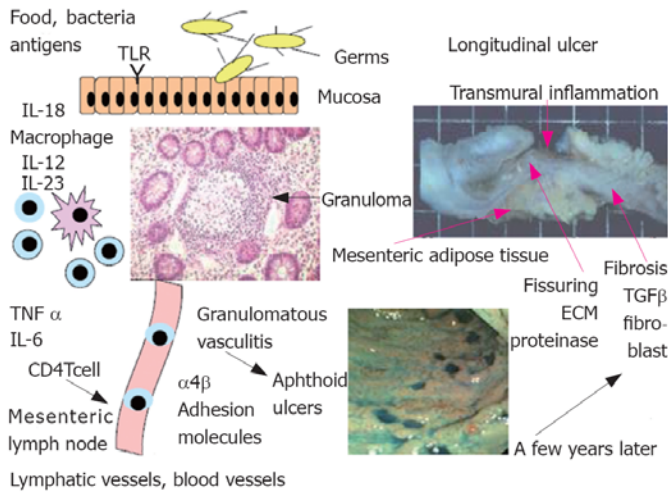


Figure 1: IBD pathogenesis

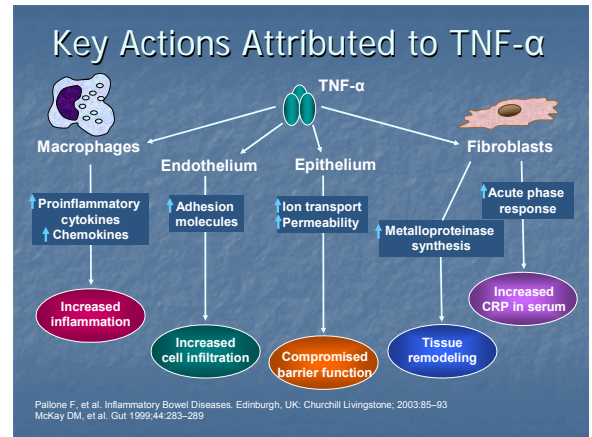


Figure 2: Role of TNF



Figure 3: CD



Figure 4: UC

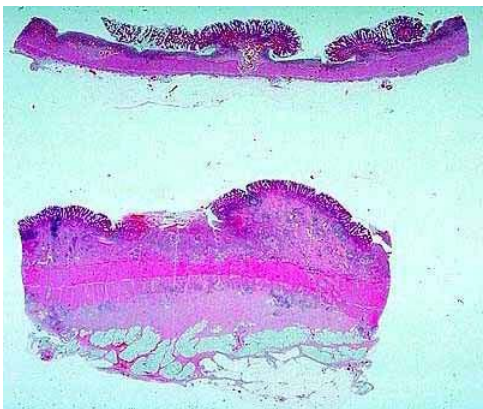


Figure 5: pseudopolyps  
Transmural inflammation CD

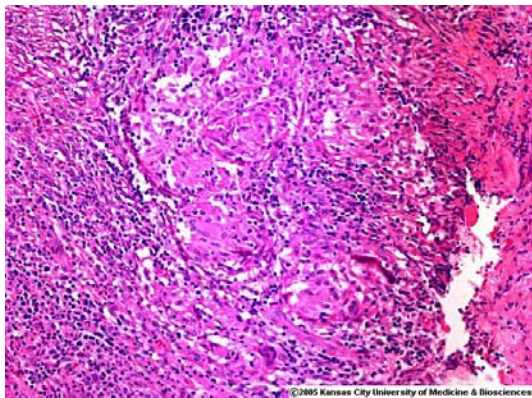


Figure 6: non-caseating granuloma