

Inflammatory bowel disease

Objectives:

- ★ Describe & Distinguish the Inflammatory bowel disease (IBD) is comprised of two major disorders: Ulcerative colitis (UC), Crohn's disease (CD).
- ★ Know the disorders have both distinct and overlapping pathologic and clinical characteristics.
- ★ know the Genetic factors: NOD2/CARD15
- ★ Know the ENVIRONMENTAL FACTORS: Smoking, Appendectomy: protect UC, Diet

Color index:

Original text Females slides Males slides
Doctor's notes Text book Important Golden notes Extra

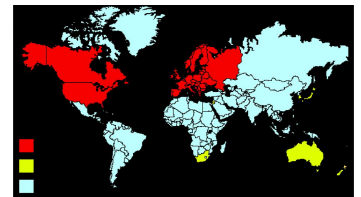
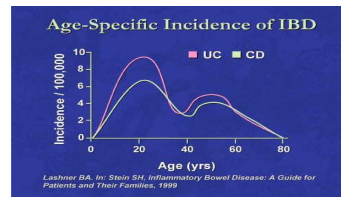


Definition

- **IBD is comprised of two major disorders: Ulcerative colitis (UC) and Crohn's disease (CD)** also include Microscopic Colitis & Indeterminate (Undetermined) Colitis When it's difficult to distinguish between Crohn's Disease & Ulcerative Colitis.
- These disorders have both distinct and overlapping pathologic and clinical characteristics.

Epidemiology

- **More common in the west**, but the incidence is increasing in the developing countries including Saudi Arabia.
- **IBD can present at any age:**
 - The peak: 15-30 years
 - A second peak is 50 years old



Etiology

1 Defective Mucosal integrity

- Altered mucus
- Increased permeability
- Cellular starvation
- Impaired restitution

2 Diet

- Western diet and Frozen food increase the chance of developing IBD, especially in children less than 10 years-old

3 Persistent infection

- Mycobacteria
- Helicobacter sp
- Measles, Mumps
- Listeria
- Toxigenic E. coli

4 Dysbiosis

- **Change in microbiota of the gut:**
 - ↓ protective bacteria
 - ↑ aggressive commensals

5 Dysregulated immune response

- Loss of tolerance
- Aggressive cellular activation
- Defective apoptosis

6 Host factors

- **Major genetic factors¹ for CD: There are more than 300 genes.**
 - Nucleotide Oligomerization Domain 2 (NOD2/CARD15)^{*}

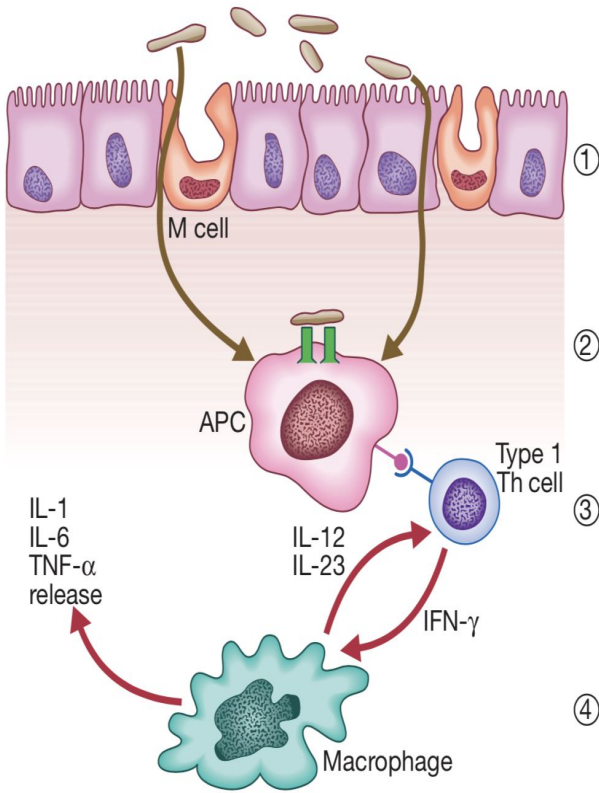
6 Environmental factors

- **Smoking:**
 - Increases the chance for Crohn's disease.
 - It has a protective role in Ulcerative colitis.
- **Appendectomy:**
 - Have a protective role in Ulcerative colitis.

*Genetics of IBD:

- The NOD2 protein on **chromosome 16** is an intracellular sensor of bacterial peptidoglycan, present in bacterial cell walls.
- UC and CD are both associated with genetic variants at HLA locus, and with multiple genes involved with immune signalling (especially IL-23 and IL-10 pathways)
- CD is associated with genetic defects in innate immunity and autophagy (NOD2, ATG16L1 and IRGM genes)
- UC is associated with genetic defects in barrier function
- NOD2 is associated with ileal and stricturing disease, and hence a need for resectional surgery
- HLA-DR*103 is associated with severe UC
- 10% have first-degree relative/1 or more close relative with IBD
- High concordance in identical twins (40–50% CD; 20–25% UC)

Pathophysiology (Hypothesis) of IBD



- 1) Bacterial antigens are taken up by specialised M cells, pass between leaky epithelial cells or enter the lamina propria through ulcerated mucosa.
- 2) After processing, they are presented to type 1 T-helper cells by antigen-presenting cells (APCs) in the lamina propria.
- 3) T-cell activation and differentiation results in a Th1 T cell-mediated cytokine response with secretion of cytokines, including interferon gamma (IFN- γ). Further amplification of T cells perpetuates the inflammatory process with activation of non-immune cells and release of other important cytokines, including interleukin 12 (IL-12), IL-23, IL-1, IL-6 and tumour necrosis factor alpha (TNF- α).
- 4) These pathways occur in all normal individuals exposed to an inflammatory insult and this is self-limiting in healthy subjects. In genetically predisposed persons, dysregulation of innate immunity may trigger inflammatory bowel disease.

Overview on UC and CD

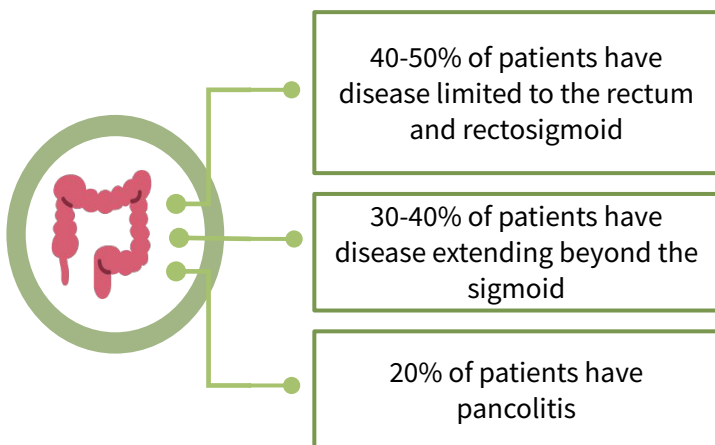
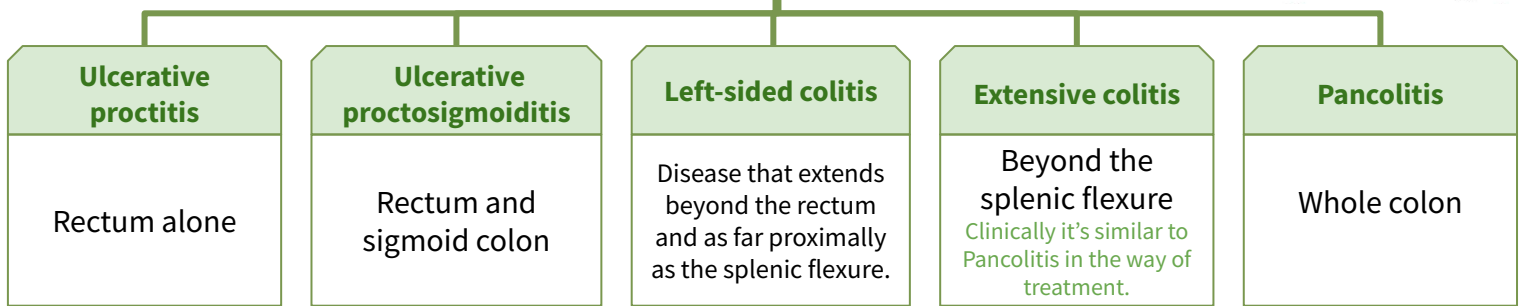
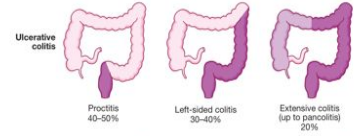
	Ulcerative Colitis	Crohn's disease
Wall involvement	Mucosal, submucosal ulcers	Full-thickness inflammation with knife-like fissures
Location	Begins in rectum and can extend proximally up to cecum	Anywhere from mouth to anus with skip lesions Terminal ileum is the most common site
Symptoms	Left lower quadrant pain (rectum) with bloody diarrhea	Right lower quadrant pain (ileum) with non-bloody diarrhea
Inflammation	Crypt abscess with neutrophils	Lymphoid aggregates with Granulomas
Gross appearance	Pseudopolyps	Cobblestone mucosa, creeping fat and strictures
Complications	Toxic megacolon, Carcinoma	Malabsorption with nutritional deficiency, Calcium oxalate nephrolithiasis, fistula formation and Carcinoma
Smoking	Protects against UC	Increases risk

Ulcerative Colitis

Definition

UC is a **chronic inflammatory disease** characterized by **recurrent episodes** of inflammation **limited to the mucosal layer** of the **rectum** and **colon**. Starts at the rectum then extends proximally

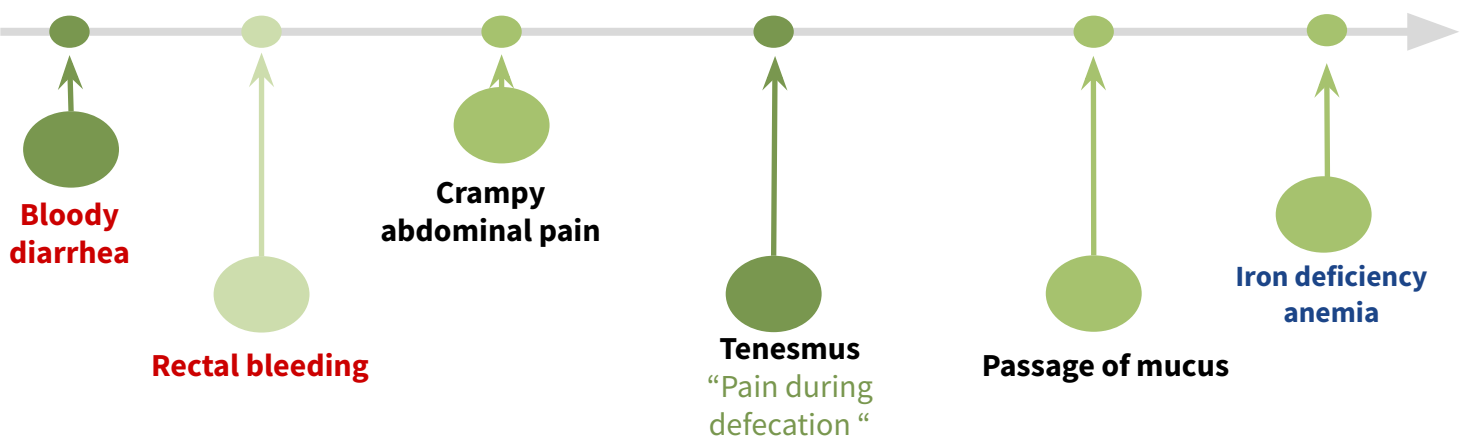
Types / Locations¹



- 1 Patients with proctitis usually pass **fresh blood** or **bloodstained mucus either mixed with stool or streaked onto the surface** of normal or hard stool
- 2 When the disease extends beyond the rectum, blood is usually mixed with stool or grossly bloody diarrhea may be noted
- 3 When the disease is severe, patients pass a liquid stool containing blood, pus, fecal matter
- 4 Other symptoms in moderate to severe disease include: anorexia, nausea, vomiting, fever, weight loss

Signs & Symptoms^{2,3}

How to differentiate between mild and severe UC? [Click here \(EXTRA!!!!\)](#)



1- Inflammation invariably involves the rectum (proctitis) and spreads proximally in a continuous manner to involve the entire colon in some cases (pancolitis). In long-standing pancolitis, the bowel can become shortened and post-inflammatory 'pseudopolyps' develop; these are normal or hypertrophied residual mucosa within areas of atrophy. The inflammatory process is **limited to the mucosa** and spares the deeper layers of the bowel wall.

2- The first attack is usually the most severe and is followed by relapses and remissions. Emotional stress, intercurrent infection, gastroenteritis, antibiotics or NSAID therapy may all provoke a relapse.

3-Ulcerative colitis patients present earlier than Crohn's Disease.

Ulcerative Colitis cont'

◀ Diagnosis

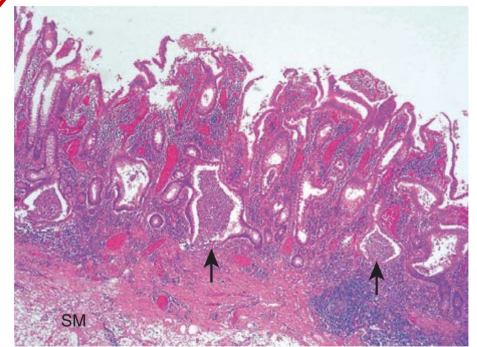
- No single modalities is enough for Diagnosis. Combination of Clinical picture, laboratory, Endoscopy, pathology.
- The most important issue is to distinguish the first attack of acute colitis from infection. In general, diarrhoea lasting longer than 10 days in Western countries is unlikely to be the result of infection.
- ★ **Faecal calprotectin** has a high sensitivity for detecting gastrointestinal inflammation and may be elevated, even when the CRP is normal. It is particularly **useful for distinguishing inflammatory bowel disease from irritable bowel syndrome at diagnosis**, and for subsequent monitoring of disease activity.
- **At initial presentation**, stool microscopy, culture and examination for **Clostridium difficile** toxin or for ova and cysts, blood cultures and serological tests should be performed.
- ESR and CRP are often raised; liver biochemistry may be abnormal, with hypoalbuminaemia occurring in severe disease. **pANCA may be positive**. This is contrary to CD, where pANCA is usually negative

Colonoscopy¹

- The **vascular markings are lost**, petechiae, exudates, **touch friability**, and frank hemorrhage may be present.
- Colonic involvement is **continuous** in ulcerative colitis, in contrast to the patchy nature of Crohn's disease.
- **Endoscopy with mucosal biopsy is the GOLD standard**

Pathology

- **Crypt abscesses²**
- Chronic changes including branching of **crypts**, atrophy of glands, and **loss of mucin in goblet cells³**



UC has 3 main features:

- 1- **Confined to the mucosa** with excess inflammatory cells in the lamina propria
- 2- **Loss of goblet cells**
- 3- **Crypt abscesses** (arrows)

◀ Management⁴

[Click here](#) for more details about the meds (EXTRA!!!!!!)

Medical

- **Rule out infection**
- **Anti TNF therapy** (Induction & maintenance)
- **5 ASA therapy: The 1st line therapy. Used for induction & maintenance of remission.** (Oral/Rectal:Suppository for Disease up to 10 cm while Enema for disease involving 10-20 cm if more than 20 cm then we combine oral with rectal)
- **Corticosteroids: Used for induction ONLY NEVER used for Maintenance of remission.**
 - Systemic: Prednisolone
 - Local acting: enema. Such as Budesonide MMX that acts locally in the colon.
- **Immunomodulators: (Just for maintenance)**
 - Azithyoprine
 - Methotrexate

Surgery

- Severe attacks that fail to respond to medical therapy.
- Complications of a severe attack (e.g., perforation, acute dilatation (**Toxic megacolon**))
- Chronic continuous disease with an impaired quality of life.
- Dysplasia or carcinoma.

Goals of therapy

Induce and maintain remission	Ameliorate symptoms
Improve pts quality of life	Adequate nutrition
Prevent complication of both the disease and medications	

1- Patients who present with **diarrhoea** plus raised inflammatory markers or **alarm features**, such as weight loss, rectal bleeding and anaemia, should undergo ileocolonoscopy. Flexible sigmoidoscopy is occasionally performed to make a diagnosis, especially during acute severe presentations when ileocolonoscopy may confer an unacceptable risk; ileocolonoscopy should still be performed at a later date, however, in order to evaluate disease extent. Barium enema is a less sensitive investigation than colonoscopy in patients with colitis and, where colonoscopy is incomplete, a CT colonogram is preferred.

2- Both acute and chronic inflammatory cells infiltrate the lamina propria and the crypts ('cryptitis'). Crypt abscesses are typical.

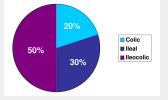
3- Goblet cells lose their mucus and, in long-standing cases, glands become distorted. Dysplasia, characterised by heaping of cells within crypts, nuclear atypia and increased mitotic rate, may herald the development of colon cancer. **When should screening occur?** After 8 to 10 years of colonic involvement, with colonoscopy every 1 to 2 years

4-For mild use **5-ASA agents** (eg, sulfasalazine "not used anymore due to its side effects", mesalamine such as Pentasa & Asacol), topical or oral; **corticosteroids for flare-ups** and **immunomodulators** (eg, azathioprine) or **biologics** (eg, infliximab) for **refractory or moderate to severe disease**. Want more details? [click here](#)

Crohn's disease (CD)

Introduction

- Characterized by **transmural** inflammation of the gastrointestinal tract.
- Involve the **entire gastrointestinal tract** from mouth to the perianal area
 - 80% small bowel , 50% ileocolitis, 30% perianal disease , 20% colon, UGI < 5%
 - Perianal Diseases rarely comes alone & usually combined with other sites such as colon or ileocecal.



Clinical manifestation

- **General:** Fatigue, Diarrhea, Abdominal pain, Weight loss, Fever.

Intestinal manifestations

- **Phlegmon/abscess:** Phlegmon is walled off inflammatory mass without bacterial infection if there's a bacterial infection it's called abscess.
- **Perianal disease** can present with fistula/abscess.
- **Gallstones:** develop because Crohn's Disease can affect terminal ileum and interferes with bile salt absorption
- **Severe oral involvement: aphthous ulcers.**
- **Esophageal involvement:** odynophagia and dysphagia.
- **Gastroduodenal CD:** upper abdominal pain and symptoms of gastric outlet obstruction.
- **Fistulas:** Tracts or communications that connect two epithelial-lined organs.
 - Enterovesical
 - Enterocutaneous
 - Enteroenteric
 - Enterovaginal

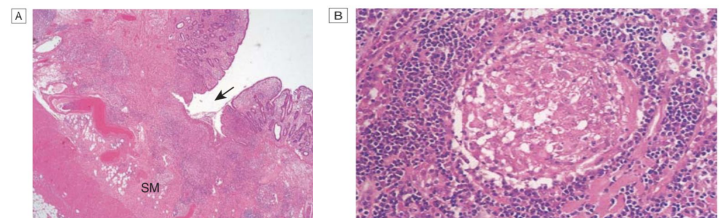
ExtraIntestinal manifestations

CD and ulcerative colitis share a number of extraintestinal manifestations

- **Arthritis:**
 - **Type 1** (Pauci/oligoarticular arthritis): swelling and pain of **5 or fewer joints**, tends to be acute and self-limiting. It particularly affects the **large joints** in the lower extremities. **Type 1 correlates with IBD activity.**
 - **Type 2** (Peripheral arthritis): Has a more polyarticular distribution (**>5 joints**). Lasts longer (Months to years) and it is usually associated with uveitis. **Type 2 is INDEPENDENT of IBD activity.**
- **Skin disorders e.g.** Erythema nodosum & Pyoderma gangrenosum
- **Primary sclerosing cholangitis:** Common with **Ulcerative colitis** & with **increased risk of malignancy "Cholangiocarcinoma"**.
- Bone loss and Osteoporosis & Osteopenia.
- **Venous and arterial thromboembolism**
- **Renal stones**
- **Vitamin B12 deficiency¹**
- **Eye involvement**
 - Uveitis, Iritis, Episcleriti

CD main features

- 1) **Submucosal or transmural inflammation**
- 2) **Deep fissuring ulcers**
- 3) **Fistulae**
- 4) **Patchy changes**
- 5) **Non-caseating granulomas**



1- Anaemia is common and may be the normocytic, normochromic anaemia of chronic disease. However, deficiency of iron and/or folate also occurs. Despite terminal ileal involvement in CD, megaloblastic anaemia due to vitamin B12 deficiency is unusual, although serum B12 levels can be below the normal range.

◀ Diagnosis

Colonoscopy

- Colonoscopy is performed if colonic involvement is suspected, except in patients presenting with severe disease (in whom a limited unprepared sigmoidoscopy should be carried out).

Endoscopic features include:

- Focal ulcerations adjacent to areas of normal appearing mucosa along with polypoid mucosal changes that give a **cobblestone**
- **Wireless capsule endoscopy:** Before doing this step, make sure that the pt doesn't have strictures. To avoid retention of the capsule used in capsule endoscopy (CE), the patency capsule (PC), a self-disintegrating sham capsule, is administered prior to CE in patients suspected of small intestinal strictures. If the PC is excreted intact within 30 hours of ingestion, the patient can undergo CE without retention. However, if the PC is not excreted within 30 hours, its location must be confirmed as in either the small intestine or the colon. The patient swallows it & it takes a picture/second for 8 hours.

Stool tests

- Stool cultures, including C. difficile toxin assay, should always be performed if diarrhoea is present.
- **Faecal calprotectin** and lactoferrin are raised in active intestinal disease

Imaging studies¹

- Small bowel follow through (SBFT)
- Computed tomography: CTS or CT enterography
- Magnetic resonance imaging (MRI) or **MR enterography** it's used more than SBFT & CT.

Markers

Inflammatory marker: ERS, CRP

Antibody tests

Serology may reveal:

- **Negative** Antineutrophil cytoplasmic antibodies (**pANCA**) **more common in ulcerative colitis if Positive.**
- **Positive** Anti-Saccharomyces cerevisiae antibodies (**ASCA**) **more common with Crohn's Disease**

◀ Management



Goals of therapy:

- Induce and maintain remission.
- Ameliorate symptoms.
- Prevent complication of both the disease and medications
- Improve pts quality of life
- Adequate nutrition

➤ **Rule out infection**

➤ **Corticosteroids: only for induction of remission.**

- Systemic: Prednisolone
- Local acting: Budesonide.

➤ **Surgery indicated in:**

- ➔ Obstruction or stenosis.
- ➔ Difficult fistulas or abscess.
- ➔ Major bleeding
- ➔ Severe perianal disease unresponsive to medical therapy
- ➔ Severe disability

➤ **Anti TNF therapy** as well as anti integrins or anti IL-12 & anti IL-23.

➤ **Immunomodulators: used for maintenance of remission.**

- Azithyoprine
- Methotrexate

For more details [Click here](#) (EXTRA)

1- Small bowel imaging is mandatory in patients with suspected CD. An asymmetrical alteration in the mucosal pattern with deep ulceration, and areas of narrowing or structuring may be found. Although disease is commonly confined to the terminal ileum, other areas of the small bowel can be involved, and skip lesions with normal bowel are seen between affected sites. Axial imaging allows the diagnosis of extraintestinal sepsis in patients presenting acutely and is therefore preferred in this situation.

Complications

1- Hemorrhage

→ Haemorrhage due to erosion of a major artery is rare but **can occur in both UC and CD.**

2- Perforation

3- Fistulae

- **These are specific to Crohn's disease.**
- **Enterointestinal fistulae** can cause diarrhoea and malabsorption due to blind loop syndrome.
- **Enterovesical fistulation** causes recurrent urinary infections and pneumaturia.
- **An enterovaginal fistula** causes a faeculent vaginal discharge.
- **Fistulation from the bowel** may also cause perianal or ischiorectal abscesses, fissures and fistulae

4- Toxic megacolon

- Transverse colon with a diameter of more than 5,0 cm to 6,0 cm with loss of haustration. **This can occur in both ulcerative colitis and Crohn's colitis.**
- Toxic megacolon (Dilated colon) is a **serious complication** associated with acute severe colitis. The plain **abdominal X-ray shows a dilated, thin-walled colon** with a diameter of >6 cm; it is gas-filled and contains mucosal islands. It is a particularly dangerous stage of advanced disease, with impending perforation and a high mortality (15-25%). **Urgent surgery is required in all patients in whom toxic dilatation has not resolved within 48 hours.** The differential diagnosis includes an infectious colitis, e.g. with *C. difficile* and cytomegalovirus.

5- Colon cancer

- The risk of dysplasia and cancer increases with the duration and extent of uncontrolled colonic inflammation. Thus patients who have long-standing, extensive colitis are at highest risk
- Oral mesalazine therapy reduces the risk of dysplasia and neoplasia in ulcerative colitis. Azathioprine also seems to reduce the risk of colorectal cancer in ulcerative colitis and Crohn's colitis.
- Cumulative risk for dysplasia in ulcerative colitis may be as high as 20% after 30 years but is probably **lower for Crohn's colitis**
- The risk is particularly high in patients who have concomitant **primary sclerosing cholangitis** for unknown reasons
- Patients with long-standing colitis are therefore entered into surveillance programmes **beginning 10 years after diagnosis**
- If high-grade dysplasia is found, panproctocolectomy is usually recommended because of the high risk of colon cancer.

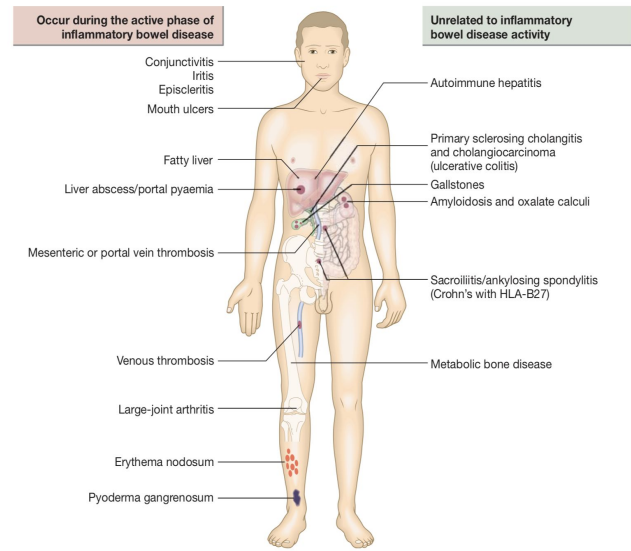


Fig. 21.52 Systemic complications of inflammatory bowel disease. See also Chapters 17 and 18. (HLA = human leukocyte antigen)



◀ Distinguishing characteristics of CD and UC

	Crohn's disease	Ulcerative Colitis
Location	SB or colon	Colon
Anatomic distribution	Skip lesions	Continuous
Rectal involvement	Rectal spare	Involved in 90%
Gross bleeding	Only 25 %	Universal
Perianal disease	1/3	Rare
Fistulization	Yes	No
Granulomas	30%	No

◀ Endoscopic features of CD and UC

	Crohn's disease	Ulcerative Colitis
Mucosal involvement	Discontinuous	Continuous
Aphthous ulcers	Common	Rare
Surrounding mucosa	Relatively normal	Abnormal
Longitudinal cancer	Common	Rare
Cobblestoning	In severe cases	No
Mucosal friability	Uncommon	Common
Vascular pattern	Normal	Distorted

◀ Pathologic features of CD and UC

	Crohn's disease	Ulcerative Colitis
Transmural inflammation	Yes	Uncommon
Fissures	Common	Rare
Fibrosis	Common	No
Submucosal inflammation	Common	Uncommon

Lecture Quiz

Q1: A 35-year-old white man presents with diarrhea, weight loss, and right lower quadrant (RLQ) pain. On examination, a tender mass is noted in the RLQ; the fecal occult blood test is positive. Colonoscopy shows segmental areas of inflammation. Barium small bowel series shows nodular thickening of the terminal ileum?

- A- Ulcerative colitis
- B- Crohn disease
- C- Ischemic colitis
- D- Diverticulosis

Q2: A 75-year-old African-American woman, previously healthy, presents with low-grade fever, diarrhea, and rectal bleeding. Colonoscopy shows continuous erythema from rectum to mid-transverse colon. The cecum is normal.?

- A- Ulcerative colitis
- B- Crohn disease
- C- Ischemic colitis
- D- Diverticulosis

Q3: You are asked to see a 29-year-old woman diagnosed with ulcerative colitis 18 months ago. Over the last 4 days she has been experiencing slight abdominal cramps, opening her bowels approximately 4–5 times a day and has been passing small amounts of blood per rectum. The patient is alert and orientated and on examination her pulse is 67, blood pressure 127/70, temperature 37.3°C and her abdomen is soft with mild central tenderness. PR examination is nil of note. Blood tests reveal haemoglobin of 13.5 g/dL and a CRP of 9 mg/L. The most appropriate management plan for this patient is?

- A- Admission to hospital for intravenous fluid therapy and steroids
- B- Oral steroid therapy + oral 5-ASA + steroid enemas + discharge
- C- Admission and refer to surgeons for further assessment
- D- Oral steroid therapy and discharge home

Q4: A 29-year-old anxious man is diagnosed with mild Crohn's disease. Due to time constraints, the patient was asked to come back for a follow-up appointment to discuss Crohn's disease in more detail. The patient returns with a list of complications he researched on the internet. Which of the following are not associated with Crohn's disease?

- A- Cigarette smoking reduces incidence
- B- Fistula formation
- C- Abscess formation
- D- Non-caseating granuloma formation

Q5: You read a report which was handwritten in a patient's medical notes who you suspect has inflammatory bowel disease. The report reads, '... there is cobblestoning of the terminal ileum with the appearance of rose thorn ulcers. These findings are suggestive of Crohn's disease'. Select the most likely investigation that this report was derived from?

- A- Colonoscopy
- B- Sigmoidoscopy
- C- Barium follow through
- D- Abdominal CT

THANKS!!

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