

Inflammatory bowel disease

Objectives :

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

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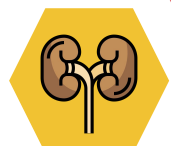
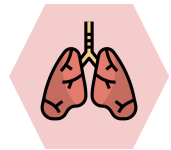
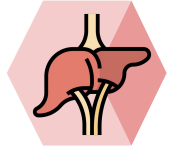
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Resources :

- Doctor 's slides - Team 436

Lecturer: Dr. Othman AlHarbi
Same 436 lecture Slides: Yes



Definition:

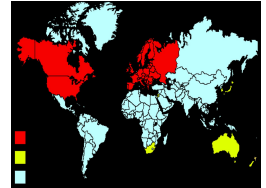
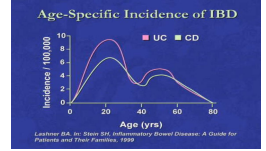
- IBD is comprised of two major disorders: ulcerative colitis (UC) and crohn's disease(CD) .
- These disorders have both distinct and overlapping pathologic and clinical characteristics.
- *So it's clinically useful to distinguish between these two conditions because of differences in their management.*

Epidemiology:

- More common in the west, but the incidence is increasing in the developing countries including saudi arabia.

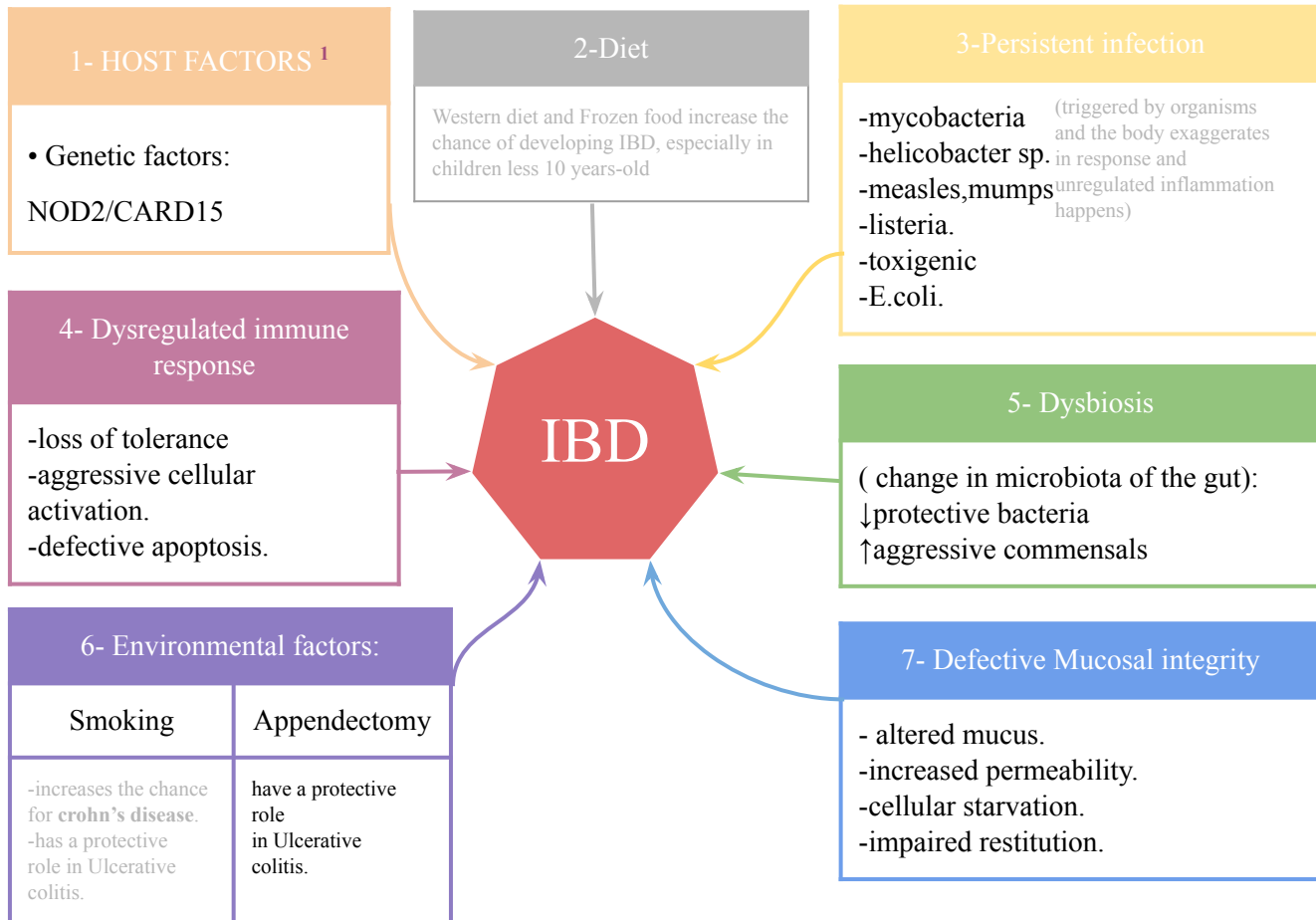
- IBD can present at any age:

- The peak: 15-30 years .
- A second peak is 50 years old in our community we just see the peak of (15-30) cus people who are at age of 50 did not live in the environment that promotes the disease .



Etiology:

Both diseases has no clear cause, but there are multiple factors which hypothesized to Play Role:



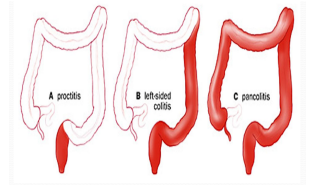
1- The major genetic factors for CD include the NOD2 (CARD 15) gene (nucleotide oligomerization domain 2), the autophagy genes and the Th17 pathway (IL-23–type 17 helper T cells). The NOD2 protein on chromosome 16 is an intracellular sensor of bacterial peptidoglycan, present in bacterial cell walls. NOD2 is expressed in epithelial cells, macrophages and endothelial cells. Individuals who are homozygote or compound heterozygote for one of several mutations in the NOD2 gene have a significantly increased risk of developing ileal CD.

Ulcerative Colitis:

- ❖ 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.

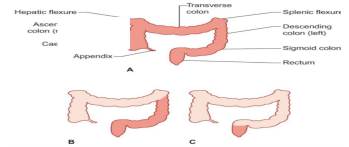
General characteristics:

- Involves the rectum in all cases and can involve the colon either partially or entirely:
 - A. Ulcerative proctitis: rectum alone .
 - B. Ulcerative proctosigmoiditis: rectum and sigmoid colon.
 - C. Left-sided colitis: disease that extends beyond the rectum and as far proximally as the splenic flexure.
 - D. Extensive colitis: beyond the splenic flexure.
 - E. Pancolitis: whole colon. *Treatment of Pancolitis and Extensive colitis is the same.*
 - Ulcerative proctitis and **Ulcerative proctosigmoiditis** ” most common” “A+ B” = 40-50% of patients
 - Extending beyond the sigmoid “C+ D” = 30-40% of patients
 - Pancolitis “E” = 20% of patients



Ulcerations are not deep . from a clinical point of view we just divide them into (A+B+C) , for example if someone gets extensive colitis , he will be treated as if he got pancolitis .

- The course is unpredictable and characterized by periodic exacerbation and periods of complete remission.



Blood in the stool could be:

Proctitis: fresh blood or blood-stained mucus that is either mixed with the stool or streaked on the surface. The stool could be normal or hard.

If the disease extends beyond the rectum, blood is usually mixed with stool or grossly bloody diarrhea may be noted

If the disease is severe, patients pass liquid stool containing blood, pus, or fecal matter.

Clinical features

- **Diarrhea** (bloody diarrhea). Also called large bowel diarrhea , (they will present with frequency and small amounts) because ulcerations is usually in the rectum , so the rectum cant hold the stool that's why they have urgency) **Since it's almost always associated with bloody diarrhea it is more accompanied with anemia.**
- **Rectal bleeding** (Hematochezia)
- **Crampy abdominal pain.** Start when the patient develop “left sided colitis“.
- **Tenesmus** recurrent need to evacuate the bowel.
- **Passage of mucus.**
- Extraintestinal symptoms: skin lesions, jaundice, arthritis.
- In moderate to severe disease: anorexia, nausea, vomiting, fever, weight loss.
- When its only limited to the rectum or sigmoid, the patient won't have severe symptoms

Diagnosis

❖ NO SINGLE MODALITY IS ENOUGH FOR DIAGNOSIS!

→ Combination of clinical picture, laboratory, endoscopy, pathology are required for the diagnosis of UC.

→ Colonoscopy and mucosal biopsy are the gold standard investigation for the diagnosis of UC :

1- stool culture for *C. difficile*, ova and parasites - to rule out infectious diarrhea.

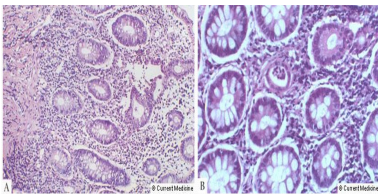
2- fecal leukocytes.

3- Colonoscopy:

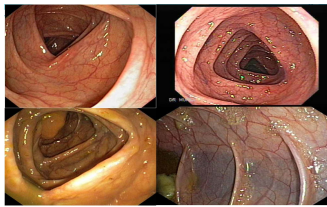
- Vascular markings are lost. colon mucosa will disappear
- Petechiae, exudates, touch friability and frank hemorrhage “rectal bleeding” may be present.
- Colonic involvement is continuous in ulcerative colitis, in contrast to the patchy nature of Crohn's disease. Superficial ulcerations

Pathology

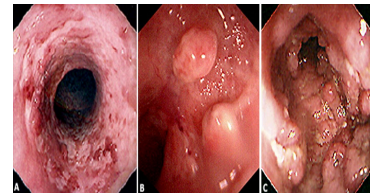
- Inflammation is not transmural, it is limited to the mucosa. Chronic inflammation
- PMNs accumulate in the crypts of the colon (crypt abscesses)
- Chronic changes including branching of crypts, atrophy of glands, and loss of mucin in goblet cells.
- They have pseudo-polyps (that's the mucosa trying to re-generate)



U.C



Normal



Complications

- Hemorrhage.
- Perforation.
- Colon cancer: The risk correlates with extent and duration of colitis. However, in distal proctitis there is no increased risk for colorectal cancer.
- Toxic megacolon: is the leading cause of death in UC and affects <5% of patients. It is associated with a risk of colonic perforation. (It is a transverse colon with a diameter of more than 5-6 cm with loss of haustration) The patient is toxic, he is having tachycardia, fever, abdominal pain and hypotension. There is a distension of the colon itself this is mainly because of paralysis of colonic movement can't rid of gases and feces
- Iron deficiency anemia
- Electrolyte disturbances and dehydration secondary to diarrhea
- Sclerosing cholangitis (SC)
- Cholangiocarcinoma—Half of all bile duct cancers are associated with UC.
- Growth retardation.
- Psychosocial issues (e.g., depression) often due to chronicity and the disabling nature of the disease.

Management

Goals of therapy In both CD and UC :

Induce and maintain remission.

Ameliorate symptoms

Improve pts quality of life.

Adequate nutrition.

Prevent complication of both the disease and medications.

1- Medical: **Rule out infections before start treatment**

(always First thing to do even if it's not the first visit) How? Stool culture. E.g. Salmonella gastroenteritis Even if the patient is a known case of UC , because you don't want to start with steroids and suppress their immune response while they have infection .

a. 5-ASA Aminosalicylates :

give two give two forms (oral and rectal) if its beyond the rectum like rectosigmoiditis , more effective . if 5ASA didn't work you give steroids for induction and immunomodulators for maintenance.

(oral, rectal) work very well with

UC but no rule in Crohn's, Sulfasalazine (topical application as a suppository) is the mainstay of treatment. Preferred over topical steroids because they are effective as maintenance therapy. Remission rates as high as 93% have been reported

- It is effective in **induction and maintaining remissions**. 5-ASA (mesalamine) is the active component.
- 5-ASA enemas can be used for proctitis and distal colitis

b. Systemic corticosteroids

used for acute exacerbations . Good for induction of remission ONLY. never for maintenance, because of the side effects.

- Systemic: Prednisolone
- Local acting: enema.

c. Immunomodulators

agents in patients with refractory disease may prevent relapses but are not effective for acute attacks. (Azithyoprine - Methotrexate) just for maintenance.

d. Anti TNF therapy:

Biological therapy

(infliximab, adalimumab, golimumab), if not responding. induction and maintaining remissions. **Contraindicated** in the presence of infections.

2- Surgical: often curative (unlike Crohn's disease) and involves total colectomy because there is great chance they will get the cancer in another area Indications for surgery include:

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

Crohn's disease (CD):

Is a disorder of uncertain that is characterized by chronic transmural inflammation of the gastrointestinal tract. It is called (regional enteritis).

Location:

CD may involve the entire gastrointestinal tract from mouth to the perianal area.

- 80% small bowel
- 50% ileocolitis. Most common base of crohn's
- 20% colon
- 30% perianal disease
- UGI < 5% Upper GI (mouth, stomach, esophagus)

Clinical manifestation:

Because it is in the terminal ileum they usually present late. As the result of that they will present with fatigue, weight loss and anemia

- Fever, fatigue and malaise. Early manifestation.
- Abdominal pain (usually RLQ pain), nausea and vomiting. Early manifestation.
- Weight loss and Malabsorption. late manifestation
- Non-bloody diarrhea. Late manifestation less frequent than large bowel diarrhea (UC) but more in the amount.
The pain is often associated with diarrhea, which usually watery and does not contain blood or mucus.

◆ Extraintestinal manifestation:

CD and ulcerative colitis share a number of extraintestinal manifestation.

- **Arthritis**, Primarily involving large joints in approximately 20 percent of patients without synovial destruction, arthritis is **the most common extraintestinal manifestation**. Central or axial arthritis, such as sacroiliitis, or ankylosing spondylitis, may also occur. An undifferentiated spondyloarthropathy or ankylosing spondylitis may be the presenting manifestation of CD. Type 1 arthritis and it is called also polyarthritis affecting around 5 large joints and it is associated with the activity of the disease. Type 2 is small arthritis affecting small joints but it is not related to the disease activity, so the gut could be normal but they have severe back pain, severe arthritis in the small joints of the hand
- **Eye involvement** (Anterior uveitis “independent course”, iritis, episcleritis), in approximately 5 percent of patients
- **Skin**, in approximately 10 percent of patients and include:
 - Erythema nodosum: especially in Crohn's disease; parallels bowel disease activity. (Painful)
 - Pyoderma gangrenosum: especially in UC; parallels bowel disease activity in 50% of cases. (Painless)
- **primary sclerosing cholangitis** more with UC, This typically presents in approximately 5 percent of patients with an elevation in the serum alkaline phosphatase or gamma glutamyl transpeptidase (GGT) concentration.
- **Venous and arterial thromboembolism**, resulting from hypercoagulability
- **Renal stones**, Increased risk of renal stones (calcium oxalate calculi), inflammation of the small bowel result in accumulation of oxalate in the blood. Uric acid stone, there is turnover of cells (cell death) so more uric acid get in urine. Oxalate stone, Oxalate normally goes to the colon usually attach to calcium and goes to the stool so there is no absorption of oxalate. Because they have the disease in the terminal ileum so the bile salts won't be absorbed and goes to colon. It will consume all the calcium in the colon so there will **be no enough calcium** to be attached with oxalate to go away, As a result of that oxalate will be reabsorbed from colon and get excreted from urine.
 - Calcium oxalate and uric acid kidney stones can result from steatorrhea and diarrhea. Uric acid stones can result from dehydration and metabolic acidosis.
- **bone loss and osteoporosis**, may result related to glucocorticoid use and impaired vitamin D and calcium absorption
- **Vitamin B12 deficiency**, A clinical picture of pernicious anemia can result from severe ileal disease since vitamin B12 is absorbed in the distal 50 to 60 cm of ileum.
- **Secondary amyloidosis** is very rare but may lead to renal failure and other organ system involvement

Key points in CD:

1-Phlegmon/abscess: walled off inflammatory mass without bacterial infection. Crohn's patients are more prone to have fistulas and abscesses than UC patients. Phlegmon=without pus. Abscess= with pus.

2-Fistula: are tracts or communications that connect two epithelial-lined organs

a-With other loop of the intestines (enteroenteric).

c-Vagina (enterovaginal)

b-With bladder (enterovesical)

d-With skin(enterocutaneous)

e-Severe oral involvement aphthous ulcers. Rarely

C- small bowel to large bowel (enterocolonic)

f-Esophageal involvement odynophagia and dysphagia.

g-Gastroduodenal CD upper abdominal pain and symptoms of gastric outlet obstruction.

h-Gallstones: usually the inflammation affects the ileum and the reabsorption of bile salts happens there, normally bile salts bind to cholesterol and make it water soluble, so without enough bile salts, cholesterol can form stone.

3-Perianal disease.

Perianal diseases (in 30%) include fissures, abscesses, perianal fistulas (almost exclusively to crohn's) Chrons colitis presents in an identical manner to ulcerative colitis, but rectal sparing and the presence of perianal disease are features which favour a diagnosis of CD

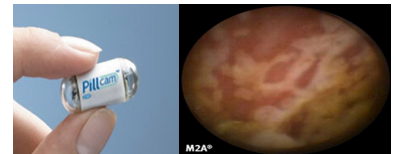
Diagnosis

- The diagnosis of CD is usually established with endoscopic findings or imaging studies in a patient with a compatible clinical history.

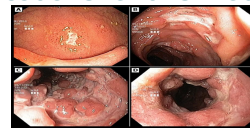
1-Compatible clinical history.

2-Endoscopic findings: (the most accurate test) :

- Colonoscopy: Endoscopic features include focal ulcerations Adjacent to areas of normal appearing mucosa along with polypoid mucosal changes that give a **cobblestone**. -You would also see non-caseating granulomas.

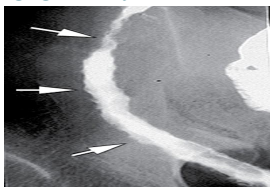


- Wireless capsule endoscopy. (helpful in pediatrics, and useful for identification of small bowel inflammation Stricture or extreme narrowing are contraindications for this modality)



3-Imaging studies in a patient:

- small bowel follow through (SBFT) not done anymore
- computed tomography: CTS or CT enterography
- Magnetic resonance imaging (MRI) or **MR enterography** best imaging modality for CD.



4- Serologic markers: (used when the diagnosis still unclear) :

- Inflammatory marker: ESR, CRP
 - a- Antineutrophil cytoplasmic antibodies(pANCA): positive in UC
 - b- Anti-Saccharomyces cerevisiae antibodies (ASCA) : positive in CD
- Stool markers: fecal calprotectin. done very often, it detects any inflammation in the small bowel (it won't tell us if its crohn's or gastroenteritis) but at the very least it would tell us there is an inflammation ongoing, meaning it has good sensitivity and not specific. Inflammation would give a positive fecal calprotectin.
- It CAN differentiate between IBS and (IBD or any inflammation)**

Management:

1- Medical: Rule out infections (again. First thing to do) How? Stool culture. C.diff

a. corticosteroids

Systemic: prednisone or local acting: budesonide. for acute exacerbations and if no response to metronidazole. **Good for induction of remission ONLY not maintenance**

b. Immunomodulators

1-azathioprine 2-methotrexate

in conjunction with steroids if the patient does not respond to above agents. **Good for induction of remission AND maintenance**

c. Anti TNF therapy

infliximab

d. Bile acid sequestrants

(cholestyramine or colestipol): for patients with terminal ileal disease who cannot absorb bile acids

e. Antidiarrheal agents

generally not a good choice (may cause ileus)

- 5-ASA has NO role in treating Crohn's disease

2- Surgical: eventually required in most patients,

we don't want the patient to have short bowel syndrome

Indications for surgery include:

- | | |
|----------------------------|------------------------|
| A. Obstruction, | C. difficult fistulas, |
| B. severe perianal disease | D. major bleeding, |
| unresponsive to medical | E. severe disability. |
| therapy, | |

3- Nutritional supplementation and support:
Parenteral nutrition is sometimes necessary.

- Conservative surgery, just resect that one affected part, unlike ulcerative colitis you resect the whole bowel.
- Ileostomy is very helpful, it evacuates the stool if the condition is so severe. because the biggest problem which causes more pain and inflammation is that when the feces gets trapped inside the ulcers.

Feature	UC	CD
Characteristics of CD and UC		
Location	colon	SB or colon
Anatomic distribution	Continuous	Skip lesions
Rectal involvement	Involved in >90%	Rectal spare
Gross bleeding	Universal	Only 25%
Peri-anal disease	rare	1/3
Fistulization	No	Yes
Granulomas	No	30%
Endoscopic features of CD and UC		
Mucosal involvement	Continuous	Discontinuous
Aphthous ulcers	Rare	Common
Surrounding mucosa	Abnormal	Relatively normal
Longitudinal ulcer	Rare	Common
Cobble stoning	No	In severe cases
Mucosal friability	Common	Uncommon
Vascular pattern	distorted	Normal
Pathologic features of CD and UC		
Transmural inflammation	Uncommon	Yes
Granulomas	No	30%
Fissures	Rare	Common
Fibrosis	No	Common
Submucosal inflammation	Uncommon	Common



22.70 Comparison of ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Age group	Any	Any
Gender	M = F	Slight female preponderance
Incidence	Stable	Increasing
Ethnic group	Any	Any; more common in Ashkenazi Jews
Genetic factors	<i>HLA-DR*103</i> ; colonic epithelial barrier function (<i>HNF4a</i> , <i>LAMB1</i> , <i>CDH1</i>)	Defective innate immunity and autophagy (<i>NOD2</i> , <i>ATG16L1</i> , <i>IRGM</i>)
Risk factors	More common in non-/ex-smokers Appendectomy protects	More common in smokers
Anatomical distribution	Colon only; begins at anorectal margin with variable proximal extension	Any part of gastrointestinal tract; perianal disease common; patchy distribution, skip lesions
Extra-intestinal manifestations	Common	Common
Presentation	Bloody diarrhoea	Variable; pain, diarrhoea, weight loss all common
Histology	Inflammation limited to mucosa; crypt distortion, cryptitis, crypt abscesses, loss of goblet cells	Submucosal or transmural inflammation common; deep fissuring ulcers, fistulae; patchy changes; granulomas
Management	5-ASA; corticosteroids; azathioprine; biological therapy (anti-TNF); colectomy is curative	Corticosteroids; azathioprine; methotrexate; biological therapy (anti-TNF); nutritional therapy; surgery for complications is not curative; 5-ASA not effective

(5-ASA = 5-aminosalicylic acid; TNF = tumour necrosis factor)

Summary

	<i>Ulcerative colitis</i>	<i>Crohn's disease</i>
Age of onset	- The peak :15 - 30 years - A second peak 50	
Etiology	-Genetic factors: NOD2/CARD15 -↑ aggressive commensals -Environmental factors	
Involvement	-limited to the mucosal layer of the colon -Start rectum then extend proximally -can be presented as: 1- proctitis 2- proctosigmoiditis / Left-sided colitis 3- Extensive colitis / Pancolitis	-Transmural inflammation may involve the entire gastrointestinal tract. -the most common presentation is ileocolitis
Clinical features	-diarrhea -rectal bleeding -tenesmus -passage of mucus -crampy abdominal abdominal pain -blood – stained mucus Streaked onto the surface of stool → in case of proctitis -blood is usually mixed with stool or grossly bloody diarrhea → disease extends beyond the rectum -anorexia, nausea, vomiting, fever, weight Loss -complications : (Hemorrhage-Perforation -Toxic megacolon - cancer)	-Fatigue -Diarrhea and Weight loss -Abdominal pain -Fever -Phlegmon/abscess -fistulas -Perianal disease -aphthous ulcers -Esophageal involvement →odynophagia and dysphagia. -Gastroduodenal CD → upper abdominal pain and gastric obstruction symptoms -gallstones - Extraintestinal mnifestation: (Arthritis - Eye involvement - Skin disorders - Primary sclerosing cholangitis - thromboembolism - Renal stones - osteoporosis ,Vitamin B12 deficiency).
Investigation: CD need different modalities and it difficult to be diagnosed	-Colonoscopy	-Colonoscopy -Wireless capsule endoscopy -SBFT -CT -MRI -Serologic markers

Findings:	<ul style="list-style-type: none"> -The vascular markings are lost -continuous involvement -pathology : 1- crypt abscesses 	<ul style="list-style-type: none"> -skip lesions -cobblestone -Serologic markers: 1- ERS , CRP 2- antibodies : (pANKA) , (ASCA) 3 -stool markers : fecal calprotectin
Management: To induce and maintain remission, improve quality of life and prevent complications	<ul style="list-style-type: none"> -Role out infection -5 ASA therapy -corticosteroid -Immunomodulators : 1-Azathioprine 2 -Methotrexate -biological therapy: 1- Anti TNF therapy 	<ul style="list-style-type: none"> -Role out infection -corticosteroid -Immunomodulators : 1-Azathioprine 2 -Methotrexate -biological therapy: 1- Anti TNF therapy
Surgery indications	<ul style="list-style-type: none"> -Severe attacks that fail to respond to medical therapy -Complications -impaired quality of life -Dysplasia or carcinoma 	<ul style="list-style-type: none"> -Obstruction, -severe perianal disease unresponsive to medical therapy -major bleeding -severe disability

Questions

Q1: All of the following are complication of Crohn's disease, Except :

- A. Arthritis
- B. Uveitis
- C. pyoderma gangrenosum
- D. Toxic Megacolon

Q2: A 27-year-old man undergoes a sigmoidoscopy for long standing diarrhoea and weight loss. On visualization of the rectum, the mucosa appears inflamed and friable. A rectal biopsy is taken and the histology shows mucosal ulcers with inflammatory infiltrate, crypt abscesses with goblet cell depletion. which is the most likely diagnosis

- A. Ulcerative colitis
- B. Crohn's disease
- C. Irritable bowel syndrome
- D. Pseudomembranous colitis

Q3: One of the Features of Crohn disease:

- A. Transmural inflammation
- B. Diffuse distribution
- C. No granulomas
- D. Associated with toxic megacolon

Q4: A 35-year-old white man presents with diarrhea, weight loss, and RLQ pain. On examination, a tender mass is noted in the RLQ; the stool is guaiac-positive. Colonoscopy shows segmental areas of inflammation. Barium small bowel series shows nodular thickening of the terminal ileum

- A. Ulcerative colitis
- B. Crohn's disease
- C. Ischemic colitis
- D. Diverticulosis

Q5: What is the most effective diagnostic tool for IBD?

- A. Blood test
- B. Stress test
- C. Colonoscopy
- D. Faecal analysis

Questions

Q6: A 28-year-old woman is evaluated for an 8-week history of increasing lower abdominal crampy pain and diarrhea. She now has 6 to 10 bowel movements per day with one or two nocturnal stools. Stools are loose to watery with intermittent blood streaking. The pain is in the lower abdomen and has increased to 6 to 8 out of 10 in severity over the past week. She has anorexia and nausea but no vomiting or fever. She takes no medications, including NSAIDs. colonoscopy findings seen in a patchy distribution throughout the ascending, transverse, and descending colon . The terminal ileum and rectum show no inflammation. Which of the following is the most likely diagnosis?

- A. Collagenous colitis
- B. Crohn colitis
- C. Ischemic colitis
- D. Ulcerative colitis

Q7: Morphological features of ulcerative colitis include:

- A. Skip lesions
- B. Cobblestone appearance of mucosa
- C. No granulomas
- D. Noncaseating granulomas

Q8: 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's disease
- C. Ischemic colitis
- D. Diverticulosis

Q9: Complications of ulcerative colitis include all Except:

- A. Fistulae
- B. Neoplasia
- C. Primary sclerosing cholangitis
- D. Toxic megacolon

Answers : D , A , A ,B, C , B ,C , A , A