L23: Inflammatory bowel diseases

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MED 433

MEDICINE 433

objectives

1. Describe & Distinguish the Inflammatory bowel disease (IBD) is comprised of two major disorders: Ulcerative colitis (UC), rohn'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.

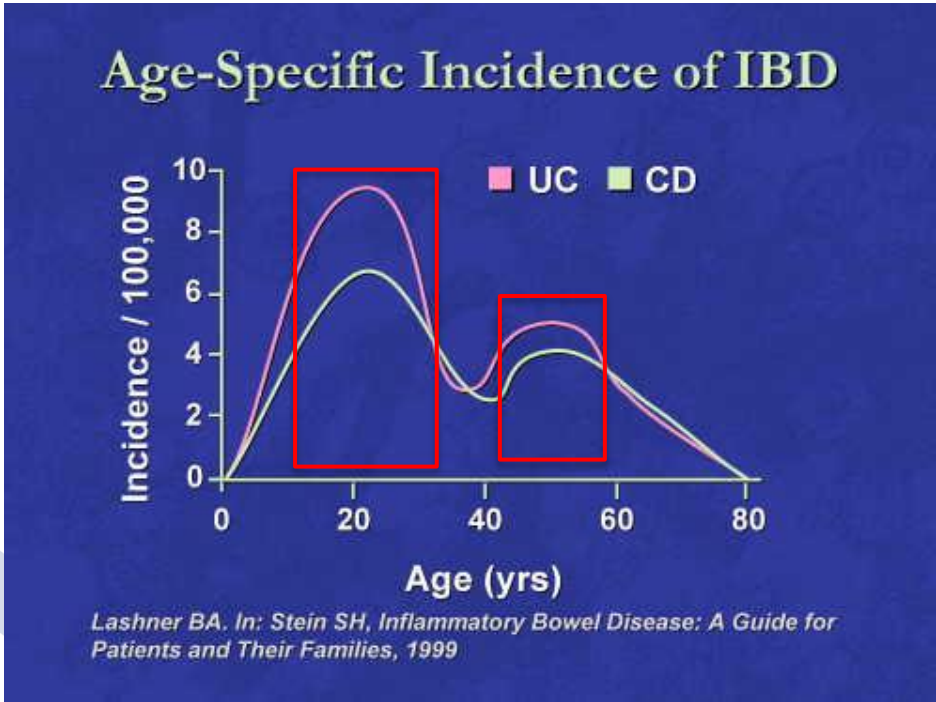
Epidemiology of IBDs

- Inflammatory bowel disease (IBD) is comprised of two major disorders:
  - Crohn's disease (CD).
  - Ulcerative colitis (UC).
- IBD is more common in the West, but the incidence is increasing in the developing countries including Saudi Arabia.
- IBD can present at any age, we have two peaks for the disease:
  1. 15 - 30 years.
  2. The 50s.

• More common in Caucasians than other racial groups

• Particularly common in Jewish populations

Etiological:
Infections (T.B) . 2- dysbiosis: (they noticed the microbial colonies differ between relapse and remission)
3-increase permeability
4- deregulated immune response (in which the immunity in the GIT is decreased when triggered by certain allergies.



-Due to westernization of lifestyle and diet.
-Peaks: means the incident is increasing in these interval. In ksa the first peak is more common
-Diets in the first 10 years of life is a major factor for developing ibd (western diet especially frozen food)

Pathophysiology of IBDs

-Smoking is risk factor in cd but protective factor in uc!
-Appendectomy:in young age it's protective for uc

- Inflammatory bowel disease has both **environmental** and **genetic components**, and evidence from genomewide association studies suggests that genetic variants that predispose to Crohn's disease may have undergone positive selection by protecting against infectious diseases, including tuberculosis. It is thought that IBD develops because these genetically susceptible individuals **mount an abnormal inflammatory response to environmental triggers**, such as intestinal bacteria. This leads to inflammation of the intestine with release of inflammatory mediators, including TNF, IL-12 and IL-23, which cause tissue damage. In both diseases, the intestinal wall is infiltrated with acute and chronic inflammatory cells but there are important differences between the conditions in the distribution of lesions and in histologic.al features.

IMPORTANT

22.71 Factors associated with the development of inflammatory bowel disease

Genetic

- Both CD and UC common in Ashkenazi Jews
- 10% have first-degree relative/≥1 close relative with IBD
- High concordance in identical twins (40–50% CD; 20–25% UC)
- 163 susceptibility loci identified at genome-wide levels of significance; most confer susceptibility to both CD and UC; many are also susceptibility loci for other inflammatory conditions (esp. ankylosing spondylosis and psoriasis)
- UC and CD both associated with genetic variants at HLA locus, and with multiple genes involved with immune signalling (esp. IL-23 and IL-10 pathways)
- CD associated with genetic defects in innate immunity and autophagy (*NOD2, ATG16L1* and *IRGM* genes)
- UC associated with genetic defects in barrier function
- *NOD2* associated with ileal and stricturing disease, and hence need for resectional surgery
- *HLA-DR*103* associated with severe UC

Environmental

- UC more common in non-smokers and ex-smokers
- CD more common in smokers (relative risk = 3)
- CD associated with low-residue, high-refined-sugar diet
- Commensal gut microbiota altered (dysbiosis) in CD and UC
- Appendicectomy protects against UC

(CD = Crohn's disease; HLA = human leucocyte antigen; IL = interleukin; IBD = inflammatory bowel disease; UC = ulcerative colitis)

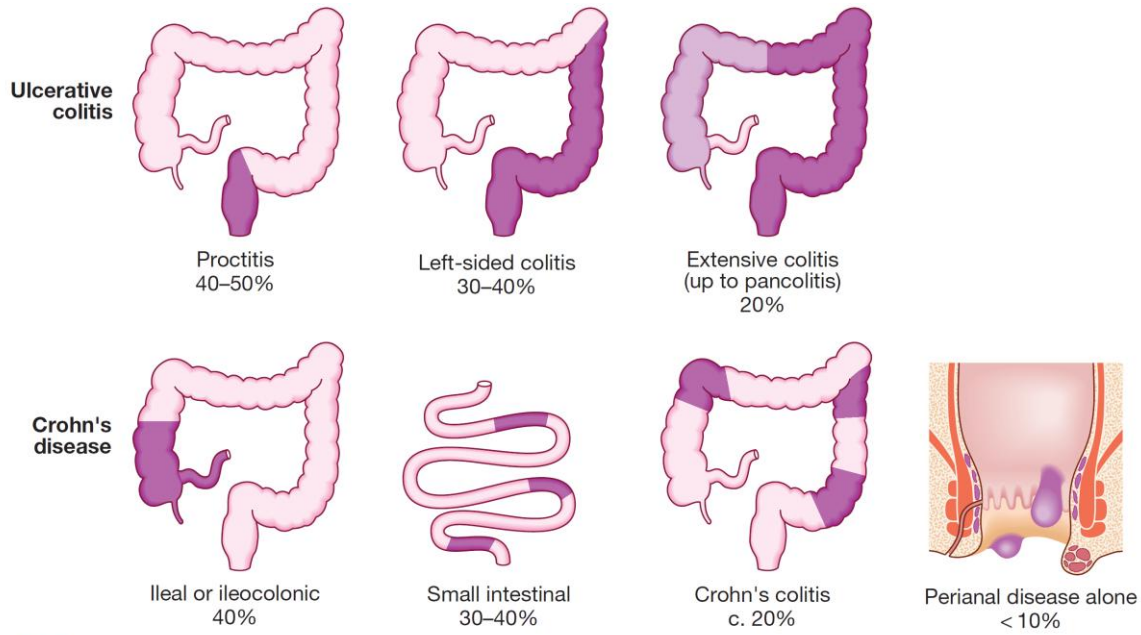
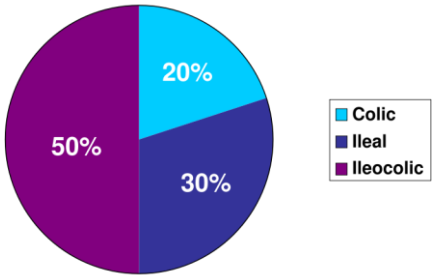


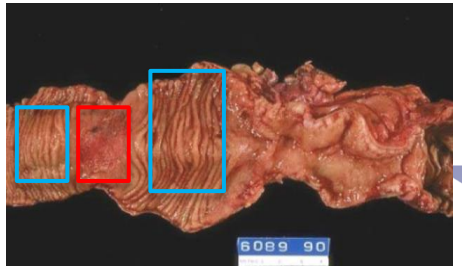
Fig. 22.49 Common patterns of disease distribution in inflammatory bowel disease.

Signs & Symptoms of Crohn's disease

Crohn disease is a chronic transmural inflammatory disease that can affect any part of the GI tract (mouth to anus) but most commonly involves the small bowel (terminal ileum).



- **Distribution of Crohn's disease:**
  - There are three major patterns of disease:
    - 40% of patients have disease in the **terminal ileum and cecum.**
    - 30% of patients have disease confined to the small intestine.
    - 25% of patients have disease confined to the colon.
    - Rarely, other parts of GI tract may be involved (stomach, mouth, esophagus).
- **Pathology of Crohn's disease:**
  - **Terminal ileum is the hallmark location,** but other sites of GI tract may also be involved.
  - Skip lesions - discontinuous involvement.
  - Fistulae.
  - Luminal strictures.
  - Noncaseating granulomas.
  - **Transmural thickening and inflammation** (full-thickness wall involvement)—results in narrowing of the lumen.
  - Mesenteric "fat creeping" onto the antimesenteric border of small bowel.



Skip lesions in Crohn's disease

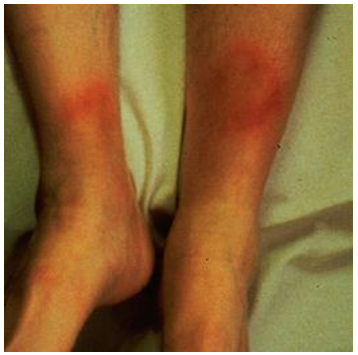
Crohn's disease has a chronic, indolent course characterized by unpredictable **flares and remissions.** The effectiveness of medical treatment decreases with advancing disease, and complications eventually develop, requiring surgery. There is no cure, and recurrence is common even after surgery.

Signs & Symptoms of Crohn's disease

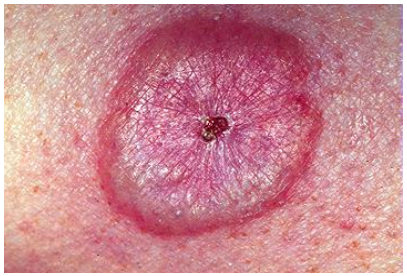
- **Clinical features**
  1. Diarrhea (Usually **without blood**)
  2. Malabsorption and weight loss (Common)
  3. Abdominal pain (usually Right Lower Quadrant), nausea, and vomiting
  4. Fever, malaise
  5. Extraintestinal manifestations in 15% to 20% of cases (uveitis, arthritis[1], ankylosing spondylitis, **erythema nodosum[2]**, **pyoderma gangrenosum[3]**, aphthous oral ulcers, cholelithiasis[4], and nephrolithiasis)
  6. Phlegmon abscess: Inflammatory mass without bacterial infection.

Patients present late because usually affects the small intestine (more proximal)

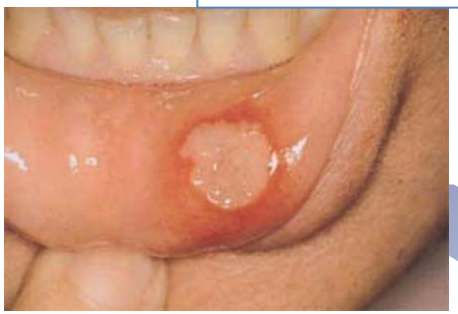
Patients may have vague abdominal pain and diarrhea for years before a diagnosis of Crohn's disease is considered.



Erythema nodosum



Pyoderma gangrenosum



Aphthous oral ulcers

1- Arthritis – Primarily involving large joints in approximately 20% 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.
2- Erythema nodosum: painful nodules.
3- Pyoderma gangrenosum: painless ugly looking ulcers.
4- Why there are gallstones formation? Because of the disruption in the enterohepatic circulation. Bile is absorbed from terminal ileum, terminal ileum absorption will be disturbed because of Crohn's Disease, so they will end up with Gall stones.

pANCA more common in UC
ASCA more common in CD

Diagnosis of Crohn's disease

- **Diagnosis:**
  1. Endoscopy (sigmoidoscopy or colonoscopy) with biopsy—typical findings are aphthous ulcers, **cobblestone appearance**, pseudopolyps, patchy (skip) lesions
  2. Barium enema
  3. Upper GI with small bowel follow-through
  4. Wireless capsule endoscopy" Wireless capsule good in small intestine (coz' colon is wider and dirty)"
  5. Serologic markers
     - Inflammatory marker : Erythrocyte sedimentation rate "ESR" and C-reactive protein"CRP" (used to distinguish between IBD and IBS)
     - Antibody tests :
       - Anti-Saccharomyces cerevisiae antibodies (ASCA) (Used for Crohn's Disease only)
       - Antineutrophil cytoplasmic antibodies (pANCA)
     - Stool markers — **fecal calprotectin** (**This will tell us if there is an inflammation within the GI tract**)

6. **Imaging studies**
   small bowel follow through (SBFT)
   computed tomography: CTS or CT enterography
   Magnetic resonance imaging (MRI) or MR enterography

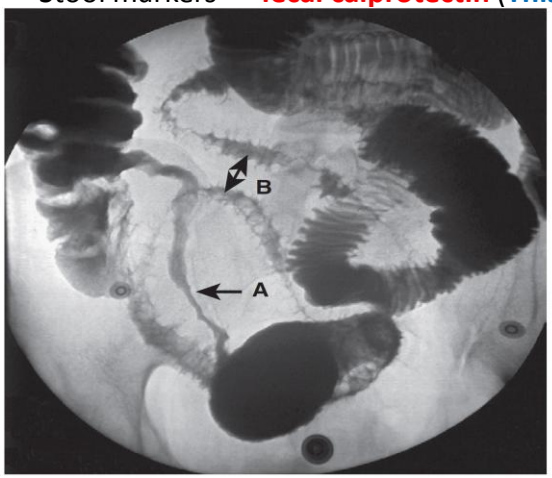
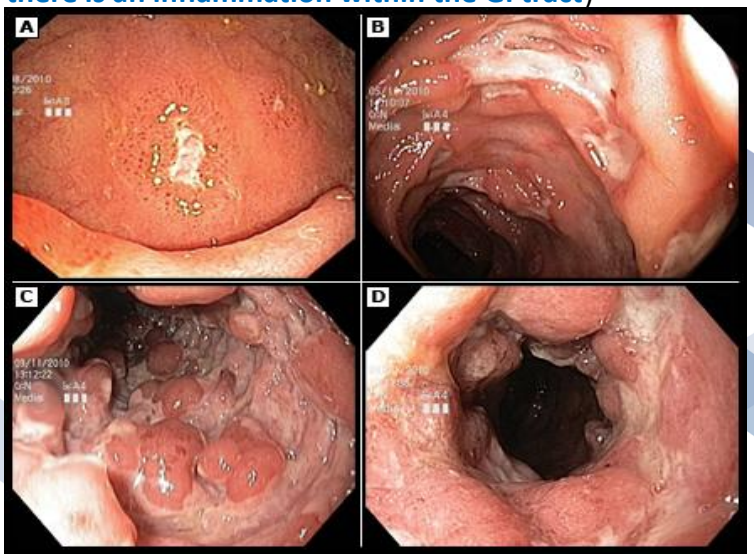


Fig. 22.53 Barium follow-through showing terminal ileal Crohn's disease. A long stricture is present (arrow A), and more proximally there is ulceration with characteristic 'rose thorn' ulcers (arrow B).



Complications of Crohn's disease

1. Fistulae—between colon and other segments of intestine (enteroenteral), bladder (enterovesical), vagina (enterovaginal), and skin (enterocutaneous)
2. Anorectal disease (in 30% of patients)—**fissures, abscesses, perianal fistulas**
3. Small bowel obstruction (in 20% to 30% of patients) is the most common indication for surgery. Initially, it is due to edema and spasm of bowel with intermittent signs of obstruction; later, scarring and thickening of bowel cause chronic narrowing of lumen
4. Malignancy—increased risk of colonic and small bowel tumors* (but less common than in UC)
5. Malabsorption of vitamin B12 and bile acids (both occur in terminal ileum)
6. **Cholelithiasis** may occur secondary to decreased bile acid absorption.
7. Nephrolithiasis—increased colonic absorption of dietary oxalate can lead to calcium oxalate kidney stones.
8. Aphthous ulcers **of lips**, **gingiva**, and **buccal mucosa** (common).
9. Toxic megacolon—**less common in Crohn disease than in UC**
10. Growth retardation
11. Narcotic abuse, psychosocial issues due to chronicity and often disabling nature of the disease

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

Management of Crohn's disease

Doctor said you may be asked about treatment:

First of all, you need to rule out infections, you don't want to reduce the immunity of the patient while he has an infection

- **Medical**
  - Sulfasalazine
    - This is useful if the colon is involved. 5-ASA" 5-aminosalicylic acid" (mesalamine) is the active compound and is released in the colon—**it is more useful in UC than in CD.**
    - 5-ASA compounds block prostaglandin release and serve to reduce inflammation.
    - There are preparations of 5-ASA that are more useful in distal small bowel disease.
  - Metronidazole—if no response to 5-ASA
  - Systemic corticosteroids (prednisone)—for acute exacerbations and if no response to metronidazole

  Local acting: Budosonide.
  - Immunosuppressants (azathioprine, 6-mercaptopurine, Methotrexate)—in conjunction with steroids if the patient does not respond to above agents
  - Bile acid sequestrants (cholestyramine or colestipol)—for patients with terminal ileal disease who cannot absorb bile acids
  - Antidiarrheal agents generally not a good choice (may cause ileus)
- **Surgical** (eventually required in most patients)
  - Reserve for complications of Crohn disease
  - Involves segmental resection of involved bowel
  - Disease recurrence after surgery is high—up to 50% of patients experience disease recurrence at 10 years postoperatively
  - Indications for surgery include Small bowel obstruction, fistulae (especially between bowel and bladder, vagina), disabling disease, and perforation or abscess
  - Limited resection in CD (in UC the whole colon is removed despite the affected area)
- **Nutritional supplementation and support**

parenteral nutrition is sometimes necessary

The drug of first choice in patents with ileal disease is budesonide, since it undergoes 90% first-pass metabolism in the liver and has very little systemic toxicity

o Azithyoprine o Methotrexate and Anti TNF therapy "work better in CD than UC"

o Local acting: Budosonide "Local is better than systemic because it will be absorbed then it will goes immediately to the cecal area + less side effect than systemic"

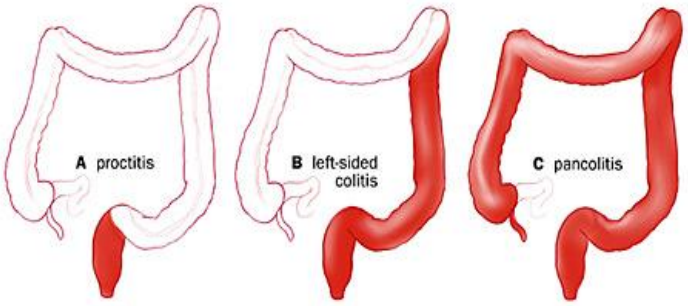
-Immunomodulators : "good only for maintaining remission

Signs & Symptoms of ulcerative colitis

Ulcerative colitis is a chronic inflammatory disease of the colon or rectal mucosa. It may occur at any age (usually begins in adolescence or young adulthood). The course is unpredictable and variable and is characterized by periodic exacerbations and periods of complete remission. Less than 5% of patients have an initial attack without any recurrence.

- **Distribution of Ulcerative colitis:**
  - involves the rectum in all cases and can involve the colon either partially or entirely.
    - 10% of cases will be in the Rectum alone=proctitis
    - 40% of cases will be in the Rectum and left colon=proctosigmoiditis
    - 30% of cases will be in the Rectum, left colon, and right colon.
    - 30% of cases will be Pancolitis.
    - The small bowel is not usually involved in UC, but it may reach the distal ileum in a small percentage of patients ("backwash ileitis" in 10% of cases)

From 432 (The only type present without continues inflammation is cecal patch (which is here the rectum affected then there is a normal mucousa then there is affected base of the cecum near the appendix)



-Ulcerative > affects the mucosa layer
-Colitis> starts usually from the colon
-Continuous inflammation = no skipped area

- **Pathology**
  - **Uninterrupted involvement of rectum and/or colon—no skip lesions**
  - Inflammation is not transmural (as it is in Crohn disease). It is limited to the mucosa and submucosa.
  - PMNs accumulate in the crypts of the colon (crypt abscesses).

Signs & Symptoms of ulcerative colitis

- **Clinical features**
  - **Hematochezia (bloody diarrhea)**
  - **Abdominal pain**
  - **Rectal bleeding**
  - Bowel movements are frequent but small
  - Fever, anorexia, and weight loss (severe cases)
  - Tenesmus (rectal dry heaves)
  - Extraintestinal symptoms (e.g., jaundice, uveitis, arthritis, skin lesions)
  - Patients with proctitis usually pass **fresh blood or blood-stained mucus either mixed with stool or streaked onto the surface** of normal or hard stool
  - When the disease extends beyond the rectum, blood is usually mixed with stool or grossly bloody diarrhea may be noted
  - When the disease is severe, patients pass a liquid stool containing blood, pus, fecal matter

Patients with UC may have nonbloody diarrhea at first, with eventual progression to bloody diarrhea.

Urgency colon can't hold its contents for long time due to the inflammation) first sign

Patients with UC develop symptoms much earlier than patients with Crohn's disease because the disease starts in the rectum.

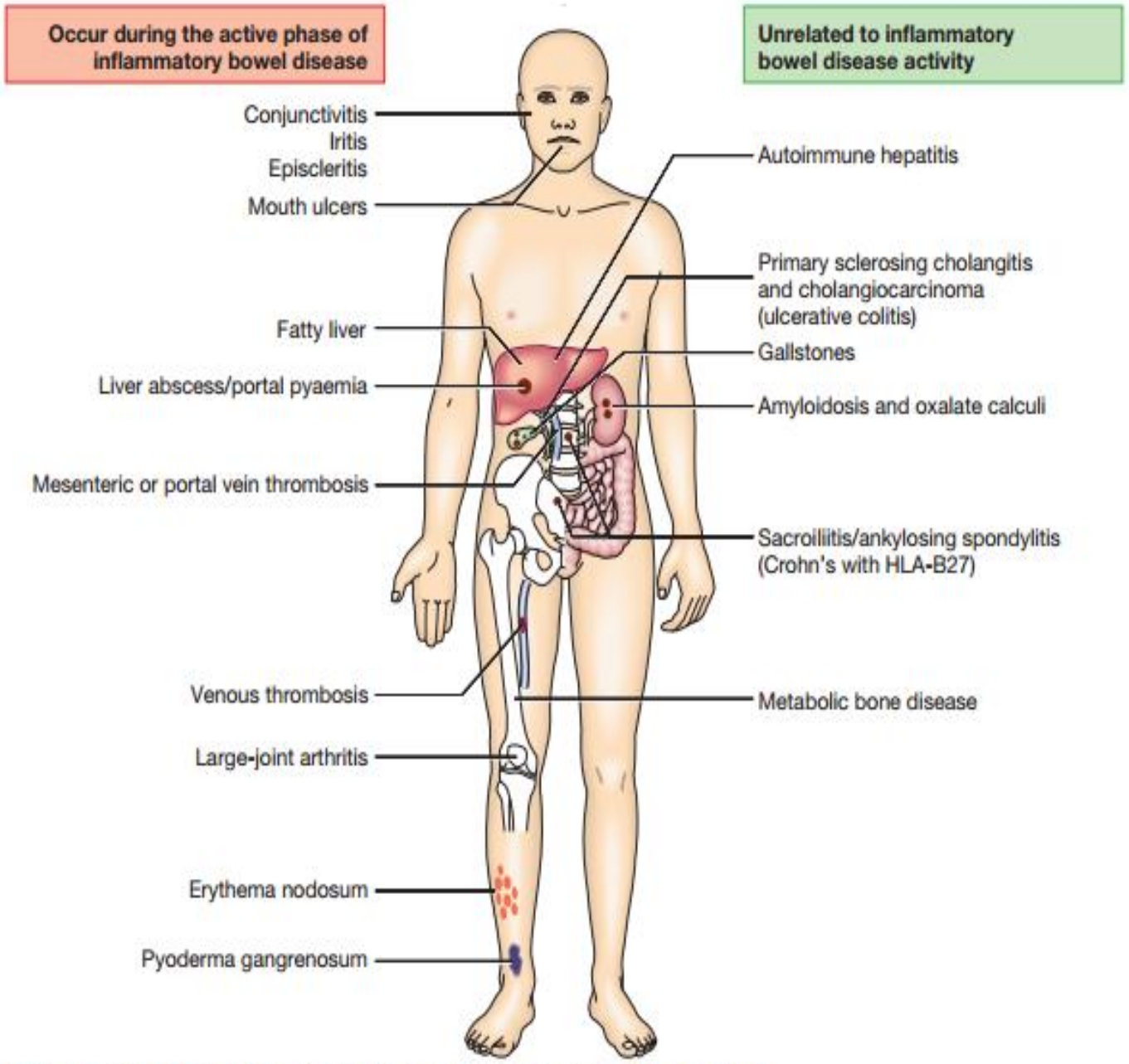


Fig. 22.55 Systemic complications of inflammatory bowel disease. (See also Chs 19 and 20.)

Diagnosis of Ulcerative colitis

- **Diagnosis:**
  - Stool cultures for *C. difficile,* ova, and parasites—to rule out infectious diarrhea
  - Fecal leukocytes
  - WBCs can appear in UC, ischemic colitis, or infectious diarrhea
  - Colonoscopy—to assess the extent of disease and the presence of any complications

* The vascular markings are lost, petechiae, exudates, touch friability, and frank hemorrhage may be present*

In ulcerative colitis, there is loss of vascular pattern, granularity, friability and contact bleeding, with or without ulceration

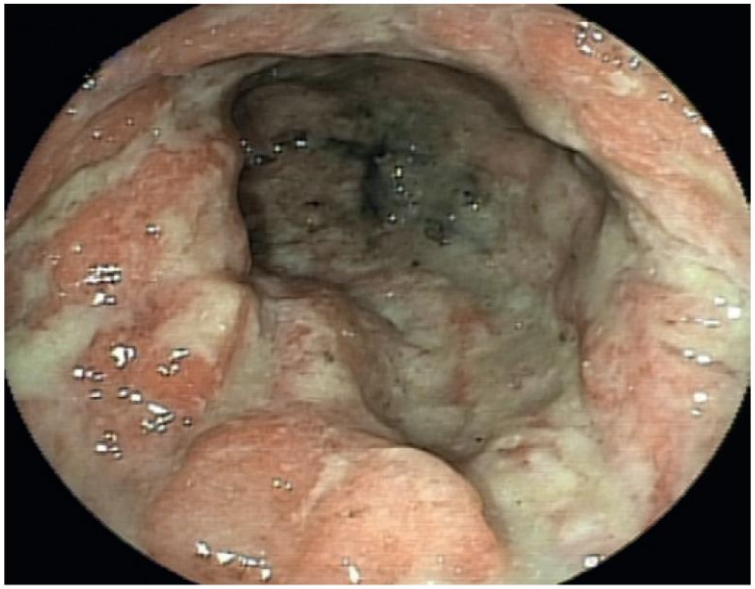


Fig. 22.56 Sigmoidoscopic view of moderately active ulcerative colitis. Mucosa is erythematous and friable with contact bleeding. Submucosal blood vessels are no longer visible.

Crypt abscess is seen under microscope where crohn's abscess is seen under naked eye

Complications of Ulcerative colitis

1. Iron deficiency anemia
2. Hemorrhage
3. Electrolyte disturbances and dehydration secondary to diarrhea
4. Strictures, benign and malignant (usually malignant)
5. **Colon cancer**—The risk correlates with extent and duration of colitis. In distal proctitis there is no increased risk of CRC
6. Sclerosing cholangitis (SC)—The course not parallel with bowel disease and is not prevented by colectomy
7. Cholangiocarcinoma—Half of all bile duct cancers are associated with UC
8. Toxic megacolon* is the leading cause of death in UC and affects <5% of patients. It is associated with the risk of colonic perforation
9. Growth retardation
10. Narcotic abuse
11. Psychosocial issues (e.g., depression) due to chronicity and often disabling nature of the disease

Toxic megacolon: "It is characterized by a very dilated colon (megacolon) accompanied by abdominal distension (bloating) It is a very serious complication and needs immediate surgery to remove the colon. Symptoms include: sepsis, fever, tachycardia & abdominal pain“ from 432

Patients who develop colonic dilatation (> 6 cm), those whose clinical and laboratory measurements deteriorate and those who do not respond after 7–10 days’ maximal medical treatment usually require urgent colectomy.

Management of Ulcerative colitis

Doctor said you may be asked about treatment:

First of all, you need to rule out infections, you don't want to reduce the immunity of the patient while he has an infection

- **Medical**
  - Systemic corticosteroids" Prednisolone" are used for acute exacerbations.
  - 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 maintaining remissions. 5-ASA (mesalamine) is the active component.
    - 5-ASA enemas can be used for proctitis and distal colitis.
  - Immunosuppressive agents" Azithyoprine,Methotrexate" in patients with refractory disease may prevent relapses but are not effective for acute attacks.
- **Surgical**—often curative (**unlike Crohn's disease**) and involves total colectomy.
  - **Severe disease** that is debilitating, refractory, and unresponsive to medical
  - therapy
  - Toxic megacolon (risk of perforation), obstruction (due to stricture), severe hemorrhage, perforation
  - Fulminant exacerbation that does **not respond** to steroids
  - Evidence of colon cancer or increased risk of colon cancer
  - Growth failure or failure to thrive in children
  - Systemic complications
- Anti TNF therapy Infliximab, Adalimumab (Humira), Certolizumab pegol (Cimzia)

Severe ulcerative colitis. Intravenous corticosteroids (methylprednisolone 60 mg or hydrocortisone 400 mg/day) should be given by intravenous infusion or bolus injection.

Sulfasalazine is metabolized by bacteria to 5-ASA and sulfapyridine. 5-ASA is the effective moiety of the drug, and sulfapyridine causes the side effects.

o Oral with Rectal formulations are used in Left-sided colitis and Pancolitis
o Rectal formulations are used in ulcerative proctitis and proctosigmoiditis
Corticosteroids: o Systemic: Prednisolone, cortisone " Try to avoid Corticosteroids as much as you can because of its long term side effects"
o Local acting: enema. "e.g.: Hydrocortisone enema or suppository"* **from 432**

Summary

Davidson's comparison

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	*HLA-DR*103*; colonic epithelial barrier function (*HNF4a, LAMB1, CDH1*)	Defective innate immunity and autophagy (*NOD2, ATG16L1, IRGM*)
Risk factors	More common in non-/ex-smokers Appendicectomy 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

Comparison from the slides

Feature	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
Peri-anal disease	1/3	Rare
Fistulization	Yes	No
Granulomas	30%	No
Mucosal involvement	Discontinuous	Continuous
Aphthous ulcers	Common	Rare
Surrounding mucosa	Relatively normal	Abnormal
Longitudinal ulcer	Common	Rare
Cobble stoning	In severe cases	No
Mucosal friability	Uncommon	Common
Vascular pattern	Normal	distorted
Transmural inflammation	Yes	Uncommon
Fissures	Common	Rare
Fibrosis	Common	No
Submucosal inflammation	Common	Uncommon

MCQs

1- Features of Crohn disease:

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

2- Features of ulcerative colitis:

A. Transmural inflammation
B. Skip lesions
C. Marked pseudo polyps
D. Mouth to anus distribution

3- Morphological features of Crohn disease include:

A. Skip lesions
B. Left-sided disease
C. Broad-based ulcers
D. pseudo polyps

4- Morphological features of ulcerative colitis include:

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

MCQs

5- Initial presentation of Crohn disease:

A. May be a medical/surgical emergency
B. Begins with intermittent attacks of relatively mild diarrhoea
C. 20% present acutely with left lower quadrant pain
D. Never have bloody diarrhoea

6- Complications of ulcerative colitis include all EXCEPT:

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

7- A 35-year-old woman has chronic crampy abdominal pain and intermittent constipation and diarrhea, but no weight loss or gastrointestinal bleeding. Her abdominal pain is usually relieved with defection. Colonoscopy and upper endoscopy with biopsies are normal, and stool cultures are negative. Which of the following is the most likely diagnosis?

A. Infectious colitis
B. Irritable bowel syndrome
C. Crohn disease
D. Ulcerative colitis

8- A 25-year-old man is hospitalized for ulcerative colitis. He has now developed abdominal distention, fever, and transverse colonic dilation of 7 cm on x-ray. Which of the following is the best next step?

A. 5-ASA
B. Steroids
C. Antibiotics and prompt surgical Consultation
D. Infliximab

7- Irritable bowel syndrome is characterized by intermittent diarrhea and crampy abdominal pain often relieved with defecation, but no weight loss or abnormal blood in the stool. It is a diagnosis of exclusion once other conditions, such as inflammatory bowel disease and parasitic infection (eg, giardiasis), have been excluded.

8- With toxic megacolon, antibiotics and surgical intervention are often necessary and life saving. Medical therapy is usually ineffective.

Answers : 1-A 2-C 3-A 4-C 5-B 6-A 7-B 8-C

DONE BY

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Medicine is a science of uncertainty and an art of probability