Inflammatory Bowel Disease

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Inflammatory Bowel Disease

- Two major forms of non-specific inflammatory bowel disease are recognized: Crohn's disease and Ulcerative colitis
- Crohn's disease can affect any part of the GI tract while ulcerative colitis affects only the large bowel
- There is overlap between these two conditions in their clinical features, histological and radiological abnormalities; in 10% of cases of colitis a definitive diagnosis of either one is not possible
- Three additional forms of microscopic inflammatory bowel disease (microscopic colitis) are also recognized
- Although the aetiology of IBD is unknown, it is becoming clear that IBD represents the outcome of three essential interactive co-factors: genetic susceptibility, the environment and host immune response

Epidemiology

- The incidence of CD varies from country to country but is approximately 4–10 per 100 000 annually, with a prevalence of 27–106 per 100 000. The incidence of UC is stable at 6–15 per 100 000 annually, with a prevalence of 80–150 per 100 000
- Although both conditions have a world-wide distribution, the highest incidence rates and prevalence have been reported from northern Europe, the UK and North America
- Both race and ethnic origin affect the incidence and prevalence of CD and UC. Jewish people are more prone to inflammatory bowel disease than any other ethnic group
- Prevalence rates also change after migration
- Crohn's disease is slightly more common in females (M : F = 1 : 1.2) and occurs at a younger age (mean 26 years) than UC (M : F = 1.2 : 1) (mean 34 years)

Factors associated with the development of inflammatory bowel disease

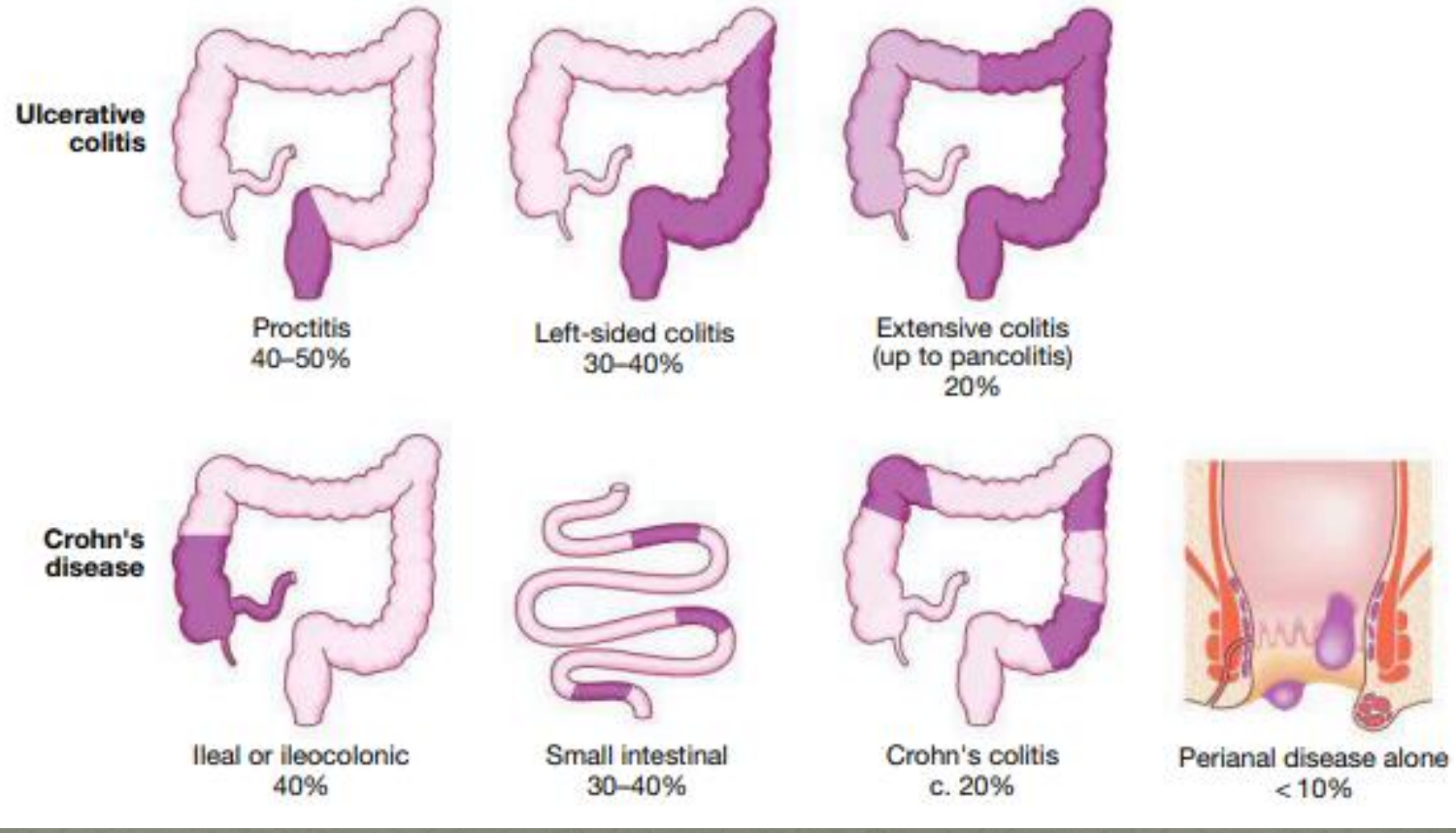
Genetic

- 10% have first-degree relative/one or more close relative with IBD
- High concordance in identical twins (40%–50% CD; 20%–25% UC)
- 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 resection surgery
- HLA-DR*103 is associated with severe UC

Factors associated with the development of inflammatory bowel disease

Environmental

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


Ulcerative colitis
Proctitis 40–50%
Left-sided colitis 30–40%
Extensive colitis (up to pancolitis) 20%
Crohn's disease
Ileal or ileocolonic 40%
Small intestinal 30–40%
Crohn's colitis c. 20%
Perianal disease alone <10%

Crohn's Disease

Pathology

- Crohn's disease is a chronic inflammatory condition that may affect any part of the gastrointestinal tract from the mouth to the anus
- It has a particular tendency to affect the terminal ileum and ascending colon (ileocolonic disease)
- The disease can involve one small area of the gut such as the terminal ileum, or multiple areas with relatively normal bowel in between (skip lesions)
- It may also involve the whole of the colon (total colitis) sometimes without small bowel involvement
- In Crohn's disease the involved small bowel is usually thickened and narrowed
- There are deep ulcers and fissures in the mucosa, producing a cobblestone appearance

- In Crohn's disease the inflammation extends through all layers (transmural) of the bowel, whereas in UC a superficial inflammation is seen
- In CD there is an increase in chronic inflammatory cells and lymphoid hyperplasia
- In 50–60% of patients granulomas are present, these granulomas are non-caseating epithelioid cell aggregates with Langhans' giant cells
- Fistulae and abscesses may be seen in the colon

Clinical Features

- The major symptoms are diarrhea, abdominal pain and weight loss
- Constitutional symptoms of malaise, lethargy, anorexia, nausea, vomiting and low-grade fever may be present and
- In 15% of these patients there are no gastrointestinal symptoms
- The disease may present insidiously or acutely
- The abdominal pain can be colicky, suggesting obstruction, but it usually has no special characteristics
- Diarrhea is present in 80% of all cases and in colonic disease it usually contains blood, making it difficult to differentiate from UC
- Steatorrhea can be present in small bowel disease
- Crohn's disease can present as an emergency with acute right iliac fossa pain mimicking appendicitis. If laparotomy is undertaken, an edematous reddened terminal ileum is found

- Up to 30% of patients presenting with acute ileitis turn out eventually to have CD
- Crohn's disease can be complicated by anal and perianal disease and this is the presenting feature in 25% of cases, often preceding colonic and small intestinal symptoms by many years
- Enteric fistulae, e.g. to bladder or vagina, occur in 20– 40% of cases, equally divided between internal and external fistulae; the latter usually occurring after surgery
- Aphthous ulceration of the mouth is often seen
- Abdominal examination is often normal although tenderness or a right iliac fossa mass are occasionally found. The mass is due either to inflamed loops of bowel that are matted together or to an abscess
- The anus should always be examined to look for edematous anal tags, fissures or perianal abscesses

Extraintestinal Manifestations

- **Eye**: Uveitis, Episcleritis, Conjunctivitis
- **Joints**: Pauci-articular arthropathy, Polyarticular arthropathy, Arthralgia, Ankylosing spondylitis, Inflammatory back pain
- **Skin**: Erythema nodosum, Pyoderma gangrenosum
- **Liver and biliary tree**: Sclerosing cholangitis, Fatty liver, Chronic hepatitis-rare, Cirrhosis-rare, Gallstones(crohn's)
- **Nephrolithiasis**: (oxalate stones)
- **Venous thrombosis**

Investigations

- Anemia is common and is usually normocytic, normochromic of chronic disease
- Deficiency of iron or folate also occurs
- Despite terminal ileal involvement in CD, megaloblastic anemia due to B12 deficiency is unusual, although serum B12 levels can be below the normal range
- Raised ESR and CRP and a raised white cell count
- Hypoalbuminemia is present in severe disease
- Serological tests: Saccharomyces cerevisiae antibody is usually present while pANCA antibody is negative
- The reverse is true in UC but the clinical value of these tests is limited

- A barium follow-through examination or CT scan with oral contrast should be performed in patients suspected of having CD
- The findings include an asymmetrical alteration in the mucosal pattern with deep ulceration, and areas of narrowing or stricturing
- Although 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
- Colonoscopy is performed if colonic involvement is suspected except in patients presenting with severe acute disease
- The findings vary from mild patchy superficial ulceration to more widespread larger and deeper ulcers producing a cobblestone appearance
- High-resolution ultrasound and CT scanning are both helpful techniques in defining thickness of the bowel wall and mesentery as well as intra-abdominal and para-intestinal abscesses

Management

- The aim of management is to induce and then maintain remission
- Patients with mild symptoms may require only symptomatic treatment
- Cigarette smoking should be stopped
- Diarrhea can be controlled with loperamide or codeine phosphate
- Diarrhea in longstanding inactive disease may be due to bile acid malabsorption and should be treated with colestyramine
- Anemia, if due to vitamin B12, folic acid or iron deficiency, should be treated appropriately
- Patients with active (moderate/severe) attacks may have to be admitted to hospital

Induction of Remission

- Steroids are commonly used to induce remission in moderate and severe attacks of CD (oral prednisolone 30–60 mg/day)
- In patients with ileocecal, CD, slow-release formulations of budesonide are as efficacious as oral prednisolone
- Budesonide has high topical potency and because of its extensive hepatic inactivation has low systemic availability, which induces less suppression of endogenous cortisol and reduces frequency and intensity of steroidal side-effects
- Overall remission/response rates vary from 60% to 90% depending on the site and extent of disease
- Enteral nutrition
- In unresponsive patients, remission is sometimes induced and maintained by raising the dose of immunosuppressive drugs

Maintenance of Remission

- Flare ups commonly occur after steroid dosages are tapered and alternative treatment strategies have to be introduced
- Remission in patients with Crohn's colitis, but not in those with small intestinal involvement, can be maintained with aminosalicylates
- Remission in other patients can be maintained with azathioprine (AZA, 2.5 mg/kg/day), 6-mercaptopurine (6MP, 1.5 mg/kg/day), methotrexate (25 mg i.m./week) and mycophenolate mofetil (1 g/day)
- These drugs have steroid sparing properties. Long-term treatment with these drugs is necessary as the rate of relapse on discontinuation is high (70%)
- Azathioprine is the most widely used drug to maintain remission
- Careful early monitoring is required as hypersensitivity reactions can occur. The key enzyme involved in AZA and 6MP metabolism is thiopurine methyl transferase (TPMT). This enzyme has a significant genetic variation and deficiencies can result in high circulating levels of drugs with increased risk of bone marrow depression
- 3-monthly blood counts should be performed on all patients
- In patients in whom remissions can't be induced or maintained with corticosteroid/immunosuppressive therapy, treatment with a biological agent will be indicated

Biological agents

- Infliximab, a chimeric anti TNF-α monoclonal antibody, is the most widely used biological agent. Successful at inducing remission in corticosteroid/immunosuppressive resistant patients, it can also be used to reinduce and maintain remission
- Up to 60% of patients will form antibodies against infliximab which can shorten duration of response and predispose to an infusion reaction
- Other adverse effects include opportunistic infections. The incidence of neoplasms and lymphoma is not increased on treatment
- Adalimumab is a fully human anti-TNF monoclonal antibody that is administered subcutaneously and is effective in patients who have failed to respond to infliximab
- New anti TNF-α antibody therapies include CDP571, etanercept and onercept

Surgical management of Crohn's disease

- Approximately 80% of patients will require an operation at some time during the course of their disease
- Surgery should be avoided if possible and only minimal resections undertaken, as recurrence (15% per year) is almost inevitable
- Patients undergoing their second surgery for CD should be treated with AZA or 6MP to reduce the chance of recurrence
- The indications for surgery are:

1. Failure of medical therapy, with acute or chronic symptoms producing ill-health
2. Complications (e.g. toxic dilatation, obstruction, perforation, abscesses, enterocutaneous fistula)
3. Growth failure in children despite medical treatment

Ulcerative Colitis

Pathology

- Ulcerative colitis can affect the rectum alone (proctitis), can extend proximally to involve the sigmoid and descending colon (left-sided colitis), or may involve the whole colon (total colitis)
- In a few of these patients there is also inflammation of the distal terminal ileum (backwash ileitis)
- In ulcerative colitis the mucosa looks reddened, inflamed and bleeds easily
- In severe disease there is extensive ulceration with the adjacent mucosa appearing as inflammatory polyps
- In fulminant colonic disease of either type, most of the mucosa is lost, leaving a few islands of edematous mucosa (mucosal islands), and toxic dilatation occurs
- On healing, the mucosa can return to normal, although there is usually some residual glandular distortion

- In ulcerative colitis the mucosa shows a chronic inflammatory cell infiltrate in the lamina propria
- Crypt abscesses and goblet cell depletion are also seen
- The differentiation between these two diseases can usually be made not only on the basis of clinical and radiological data but also on the histological differences seen in the rectal and colonic mucosa obtained by biopsy
- It is occasionally not possible to distinguish between the two disorders, particularly if biopsies are obtained in the acute phase, and such patients are considered to have an indeterminate inflammatory colitis

Clinical Features

- The major symptom in UC is diarrhea with blood and mucus, sometimes accompanied by lower abdominal discomfort
- General features include malaise, lethargy and anorexia with weight loss. Aphthous ulceration in the mouth is seen
- When the disease is confined to the rectum (proctitis), blood mixed with the stool, urgency and tenesmus are common
- In an acute attack of UC, patients have bloody diarrhea, passing up to 10–20 liquid stools per day. Diarrhea also occurs at night, with urgency and incontinence
- Occasionally blood and mucus alone are passed
- With severe attacks the patient is often very ill and needs urgent treatment in hospital
- Toxic megacolon is a serious complication. The plain abdominal X-ray shows a dilated thin-walled colon, 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

Investigations

- In moderate to severe attacks an iron deficiency anemia is commonly present and the white cell and platelet counts are raised
- The ESR and CRP are often raised, with hypoalbuminemia occurring in severe disease
- pANCA may be positive. This is contrary to CD, where pANCA is usually negative
- Stool cultures should be performed to exclude infective causes of colitis
- A plain abdominal X-ray with an abdominal ultrasound are the key investigations in moderate to severe attacks. The extent of disease can be judged by the air distribution in the colon and the presence of colonic dilatation
- The presence of free fluid within the abdominal cavity can also be assessed
- Colonoscopy should not be performed in severe attacks of disease for fear of perforation. In more longstanding and chronic disease it is useful in defining extent and activity of disease, and excluding the onset of dysplasia and carcinoma in patients with disease of 10 years duration or more
- Radionuclide scans can be used to assess colonic inflammation

Management

- All patients with UC should be treated with an aminosalicylate. The active moiety of these drugs is 5-aminosalicylic acid (5-ASA) which is absorbed in the small intestine
- The design of the various aminosalicylate preparations is based on the binding of 5-ASA by an azo bond to sulfapyridine(sulfasalazine), 4-aminobenzoyl-β-alanine (balsalazide) or to 5-ASA itself (olsalazine)
- The azo bonds are broken down by colonic bacteria to release 5-ASA within the colon. The pH-dependent forms are designed to release 5-ASA in the terminal ileum
- Luminal pH profiles in patients with inflammatory bowel disease are abnormal and in some patients capsules of 5-ASA coated with pH-sensitive polymer may pass through into the feces intact
- The mode of action of 5-ASA in inflammatory bowel disease is unknown, but the aminosalicylates have been shown to be effective in inducing remission in mild to moderately active disease and maintaining remission in all forms of disease
- Sulfasalazine is being used less frequently because of its wider side-effect profile from the sulphonamide component.

Proctitis

- Oral aminosalicylates plus a local rectal steroid preparation (10% hydrocortisone foam; prednisolone 20 mg enemas or foam) are the first-line treatment
- Mesalazine enemas and budesonide enemas can be tried
- Some cases of proctitis can be resistant to treatment. In these, oral corticosteroids alone or in combination with azathioprine are used

Left-sided proctocolitis

- Oral aminosalicylates plus local rectal steroid preparations may be effective but in moderate to severe attacks oral prednisolone will be required
- If patients do not respond within 2 weeks they should be admitted to hospital

Total Colitis

- Patients should be admitted to hospital and treated initially with hydrocortisone 100 mg i.v. 6-hourly with oral aminosalicylates
- Full investigations should be performed initially and full supportive therapy administered (i.v. fluids, nutritional support via the enteral (not parenteral) route)
- A persistent fever, tachycardia, falling Hb, rising white cell count, falling potassium, falling albumin and persistently raised stool weights (> 500 g/day) with loose blood-stained stool are all signs that the patient is not responding to treatment and that surgery may be indicated
- In patients responding to i.v. hydrocortisone treatment, oral prednisolone therapy should be substituted and doses slowly tailed off (5–10 mg weekly)
- Maintenance of remission is with aminosalicylates
- In patients in whom it is not possible to reduce the dose of prednisolone without flare-up, azathioprine is used

Indications for surgery

- Impaired quality of life
- Loss of occupation or education
- Disruption of family life
- Failure of medical therapy
- Dependence on oral glucocorticoids
- Resistant to drug therapy
- Intolerable side-effects of drug therapy
- Fulminant colitis
- Life-threatening bleeding
- Toxic megacolon
- Perforation
- Colon cancer or severe dysplasia

23.61 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 (*HNF4α*, *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; glucocorticoids; azathioprine; biologic therapy (anti-TNF, anti-α4β7 integrin, anti-p40, Janus kinase inhibitor); colectomy is curative	Glucocorticoids; azathioprine; methotrexate; biologic therapy (anti-TNF, anti-α4β7 integrin, anti-p40); nutritional therapy; smoking cessation; surgery for complications is not curative; 5-ASA is not effective

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

Cancer in inflammatory bowel disease

- Patients with UC and Crohn's colitis have an increased incidence of developing colon cancer
- Patients with CD of the small intestine have a small increase in incidence of small bowel carcinoma
- A screening colonoscopy with multiple biopsies should be done every 2 years in patients with total UC and Crohn's colitis of 10 years' standing and annually after 20 years.
- Patients with UC and primary sclerosing cholangitis are particularly at risk of developing colon cancer and should have a yearly screening colonoscopy

Thank You