

## **Ulcerative colitis and Crohn's disease**

<b>Key features of Inflammatory Bowel Diseases (IBDs)</b>		
	<b><i>Crohn's disease (CD)</i></b>	<b><i>Ulcerative colitis (UC)</i></b>
Location	Entire GI tract; mostly small intestine and colon	Limited to colon
Rectum	Often spared	Almost always involved
History	Abdominal pain, weight loss	Bloody diarrhoea
Colonoscopy	Skip lesions, "cobblestone" mucosa	Continuous involvement, pseudopolyps
Treatment	Metronidazole, immunomodulators	Sulfasalazine, immunomodulators
Complications	Bowel obstruction, abscesses, fistulae	Toxic megacolon, colon carcinoma

The Inflammatory Bowel Diseases (IBDs) – Ulcerative colitis (UC) and Crohn's disease (CD) – are both idiopathic, chronic, inflammatory conditions of the bowel, but their clinical and pathologic features are quite different.

UC is a relapsing and remitting inflammatory disorder of the colonic mucosa (muscular and adventitia are spared). It may affect just the rectum (proctitis) or extend proximally to involve part or all of the colon (pancolitis). It "never" spreads proximally to the ileocaecal valve (except for "backwash" ileitis). The lesions are continuous.

CD is characterized by transmural granulomatous inflammation and may affect every part of the gut (from mouth to anus), but favours the terminal ileum and proximal colon (most of the time the rectum is spared). Unlike UC, the lesions are transmural (that is, they affect the mucosa, the muscular and the adventitia) and there is unaffected bowel between areas of active disease (skip lesion).

### **Prevalence**

- Developed countries (4-11/100,000 for UC, 100/100,000 for CD)
- Whites > blacks
- Ages: 15-30 years

### **Etiology**

For both diseases, the etiology is unknown. They may involve adhesion-expressing strains of *E. coli*, capable of inducing interleukin-B production and transepithelial migration of WBCs.

- The increased relative risk of disease (4- to 20-fold) in first-degree relatives of IBD patients suggests a genetic predisposition.
- No infectious agents have been isolated, but the effectiveness of antibiotics in treatment suggests that the intestinal microflora is involved.
- The pathology of the disease, with inflammation and granuloma formation, supports the concept of a dysregulated immune response as a key factor in the development of IBDs. This inappropriate and chronic inflammatory immune response is hypothesized to be due to an intrinsic (genetic) defect in immune regulation and driven by elements of the intestinal microflora.
- In CD mutations of the NOD2/CARD15 gene increase the risk.
- UC is twice as common in non-smokers, whereas the opposite is true for CD.

### **Signs and symptoms**

IBDs have a slow onset of signs and symptoms.

- Typical UC patient presents with a
  - gradual onset of crampy abdominal discomfort and diarrhoea with or without blood and/or mucus.
  - The frequency of bowel movements is related to severity of disease.
  - During attacks, systemic symptoms are common: fever, malaise, anorexia, weight loss, tachycardia, orthostatic hypotension. There can also be urgency and tenesmus (due to rectal disease).
- In CD the situation is similar, but diarrhoea is less frequent.
  - There can also be abdominal tenderness, palpable masses (representing adherent loops of bowel), perianal abscesses/fistulae/skin tags.

Both the diseases may present with extra-intestinal signs:

- Clubbing
- Aphthous oral ulcers
- Erythema nodosum (violaceous subcutaneous nodules located most often on the lower legs)
- Pyoderma gangrenosum (an ulcerating lesion usually located on the trunk)
- Conjunctivitis, episcleritis, uveitis, iritis
- Large joint arthritis, sacroilitis, ankylosing spondylitis
- Fatty liver, primary sclerosing cholangitis, cholangiocarcinoma
- Very rarely: renal stones, osteomalacia, nutritional deficiencies and systemic amyloidosis.

### **Complications**

The complications are very common, since both diseases have a chronic evolution. There can be small intestinal obstruction, perforation and rectal hemorrhage.

- Typical complications of UC are:
  - Toxic dilatation of the colon (fever and pain + colonic diameter >6 cm on abdominal x-ray → parenteral nutrition, steroids, empiric antibiotics, surgery only if needed)
  - Colonic cancer (the risk is high after 10 years of active disease; 15% with pancolitis for 20 years → screening with colonoscopy every 1-2 years; colectomy if high-grade dysplasia).
- Characteristic of CD are:
  - Abscess formation (abdominal, pelvic or ischiorectal)
  - Fistulae (entero-vesical, entero-vaginal, entero-enteric or entero-cutaneous)

### **Differential diagnosis**

The differential diagnosis depends on the patient's chief complaint.

In the patient with lower GI bleeding, we have to consider:

- Diverticulosis
- Colon cancer or polyps
- Arteriovenous malformations
- Hemorrhoids.

In the patient with bloody diarrhoea, consider:

- Infectious etiologies such as *Yersinia*, *Campylobacter*, *Shigella*, *Salmonella*, amebiasis, or *C. difficile*.

In the elderly patient with a presentation suggesting of IBDs consider:

- The above diagnoses and diverticulitis or ischemic bowel.

### **Diagnostic evaluation**

The diagnostic evaluation of IBDs takes advantage of many tests.

For both diseases, we order:

- Full blood count (FBC)

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Urea & creatinine & electrolytes (U&E)
- Liver function tests (LFT)
- Blood cultures

In the stool we perform:

- microscopy and culture
- we look for *C. difficile*'s toxin, to exclude infective diarrhoea (*C. difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, Amoebae).

In CD we measure also serum iron, vit B<sub>12</sub> and folate (→ anemia). CD markers of activity are ↓Hb, ↑ESR and ↑CRP (→ inflammation), and ↓albumin (→ malabsorption).

Increased alkaline phosphatase level may represent underlying liver disease, which occurs at a higher frequency in patients with IBD. Hepatobiliary diseases associated with IBDs include primary sclerosing cholangitis (mostly UC), cholangiocarcinoma, cholelithiasis (mostly CD), fatty liver, autoimmune hepatitis.

Two interesting laboratory findings are the presence of:

- perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) in the majority of patients with UC
- anti-*Saccharomyces cerevisiae* antibodies (ASCA) in the majority of patients with CD.

By the way, definitive diagnosis in IBDs is made by direct visualization of the GI tract and biopsy.

- Abdominal x-ray reveals no fecal shadows, mucosal thickening/islands, colonic dilatation, perforation.
- Colonoscopy and sigmoidoscopy reveal inflamed and friable mucosa, with longitudinal ulcerations with a “cobblestone” appearance in CD, or regeneration of the mucosa around a diseased colon that gives the appearance of pseudopolyps in UC. Colonoscopy and sigmoidoscopy also show disease extent and allow biopsies to be taken.
- Biopsy can be significant: in UC we have inflammatory infiltrate, goblet cell depletion, glandular distortion, mucosal ulcers and crypt abscesses; in CD the typical finding is the presence of granulomas.
- Barium enema may be helpful, showing loss of haustra, granular mucosa, shortened colon (but never do a barium enema during an acute attack!). In CD barium enema may show “cobblestoning”, “rose thorn” ulcers, colonic strictures with rectal sparing. Small bowel enema may help to detect ileal disease (strictures, proximal dilatation, inflammatory mass or fistula).

### **Natural history**

The natural history of IBDs varies with the type of disease and severity of the initial presentation. In UC, disease limited to the rectum has a relatively benign course. In fact, 20% of patients with UC are relapse-free a decade after the initial presentation. CD, however, tends to be more severe, with frequent relapses.

### **Management**

The management of both diseases is complicated.

#### **UC**

- In mild UC (<4 bowel movements/day and the patient is otherwise well) we prescribe:
  - Prednisolone (20 mg/day PO or PR)
  - Mesalazine (500-1000 mg/day).
  - Twice-daily steroid foams PR or prednisolone 20 mg retention enemas

If no improvement after two weeks, treat as moderate UC.

- In moderate UC (4-6 bowel movements/day and the patient is otherwise well), we give:
  - Prednisolone (40 mg/day for one week, then 30 mg/day for one week, then 20 mg for four more weeks)
  - Sulfasalazine (1 g/12 h PO) (sulfasalazine is a combination of 5-aminosalicylic acid and sulfapyridine, which carries the 5-ASA to the colon; 5-ASA is then activated by bacterial enzymatic cleavage)
  - Twice-daily steroid (budesonide) enemas

If no improvement after two weeks, treat as severe UC.

- In severe UC (>6 bowel movements/day and patient systematically unwell), we prescribe:
  - Nil by mouth
  - IV hydration (1 l or 0.9% saline + 2 l of dextrosesaline/24h, + 20 mmol K<sup>+</sup>/l).
  - Hydrocortisone 100 mg/6h IV
  - Rectal steroids (hydrocortisone 100 mg in 100 ml 0.9% saline/12h PR).
  - Monitor temperature, pulse and blood pressure; record stool frequency/character
  - Consider the need for blood transfusion (if Hb <10 mg/dl) and parenteral nutrition (if severe malnutrition); give IV vitamins.

If improving in five days, transfer to oral prednisolone (40 mg/24h) and sulfasalazine (1 g/12h) to maintain remission.

Topical therapies for:

- Proctitis include suppositories (prednisolone 5 mg or mesalazine 250 mg/8h)
- Procto-sigmoiditis may respond to foams (prednisolone 20 mg/12-24h or 5-ASA 1 g/day).

Indications for surgery are:

- Perforation
- Massive haemorrhage
- “Toxic” dilatation of colon (>6 cm)
- Failure to respond to drugs
- Prophylactic resection to prevent colon cancer.

Typically a proctocolectomy with terminal ileostomy or a colectomy with ileo-anal anastomosis are performed.

Novel therapies include:

- Cyclosporine A (for patients refractory to UC; 2-4 mg/kg IV; side effects: nephrotoxicity, ↑K<sup>+</sup>, seizures, ↑BP).
- New trials suggest that tacrolimus (FK-506) could be superior to cyclosporine in maintaining remission.
- Azathioprine (2-2.5 mg/kg/day PO; side effects: bone marrow suppression, pancreatitis) and
- Methotrexate (25 mg/week IM; side effects: bone marrow suppression, diarrhoea, stomatitis, hepatic fibrosis) are used in those patients that manifest steroid side effects or in those who relapse quickly when steroid are reduced (steroid-dependent patients).

To maintain remission, the first line treatment is:

- Sulfasalazine (1 g/12 h PO) for life. Side effects of sulfasalazine are nausea, headache, allergic reaction, hepatitis, bone marrow suppression (→ monitor periodically full blood count).
- In case of intolerable side effects due to sulfasalazine, we can prescribe olsalazine (500 mg/12 h PO) or mesalazine (400-500 mg/8 h PO).

## CD

In CD, severity is more difficult to assess than in UC.

- In mild attacks (patients are symptomatic but systemically well). We give:

- Prednisone 30 mg/day PO for one week, then 20 mg/day for a month. If symptoms resolve, reduce steroids by 5 mg/2-4 weeks.
- In severe attacks the patient is admitted to hospital, and we give:
  - IV steroids
  - Nil by mouth
  - Hydration (1 l 0.9% saline + 2 l dextrose-saline/24 h + 20 mmol K<sup>+</sup>/l)
  - Hydrocortisone 100 mg/6 h IV
  - Metronidazole 400 mg/8 h PO helps in perianal disease or superinfection (there are no evidences that antibiotics are effective in UC)
  - Monitor temperature, pulse and blood pressure; record stool frequency/character
  - Consider the need for blood transfusion (if Hb <10 mg/dl) and parenteral nutrition (if severe malnutrition)
  - Infliximab (a chimeric monoclonal anti-TNF $\alpha$  antibody) is being tested. A single dose of infliximab is given by IV infusion over two hours on a day ward, under expert guidance
  - Azathioprine (2-2.5 mg/kg/day PO) is used in those patients that manifest steroid side effects or in those who relapse quickly when steroids are reduced.

If improving in five days, transition to oral prednisolone (40 mg/day). If there is no response (or deterioration) during IV therapy, we seek surgical advice.

- Surgery is never curative, the aim is limited resection of the worst areas, but the disease will recur around the surgical resection.