

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is an idiopathic disease, probably involving an immune reaction of the body to its own intestinal tract. The 2 major types of IBD are ulcerative colitis and Crohn's disease. As the name suggests, ulcerative colitis is limited to the colon; Crohn's disease can involve any segment of the gastrointestinal tract from the mouth to the anus.



Severe colitis noted during colonoscopy. The mucosa is grossly denuded, with active bleeding noted.



Stricture in the terminal ileum noted during colonoscopy. Narrowed segment visible upon intubation of the terminal ileum with the colonoscope. Relatively little active inflammation is present, indicating that this is a cicatrix stricture.

Although ulcerative colitis and Crohn's disease have significant differences, many (but not all) of the treatments available for one are also effective for the other. Likewise, both diseases share many extra-intestinal manifestations, although some of these tend to occur more commonly with one disease or the other.

Both ulcerative colitis and Crohn's disease usually have waxing and waning intensity and severity. When the patient is actively symptomatic, indicating significant inflammation, the disease is considered to be in an active stage; the patient is having a flare of the IBD.

When the degree of inflammation is less (or absent) and the patient is usually asymptomatic, then the patient's disease is considered to be in remission. In most cases, symptoms do correspond well with the degree of inflammation present for either disease, although this is not

universally true. In some patients, objective evidence for disease activity should be sought before administering medications with significant adverse effects.

Pathophysiology

The pathophysiology of IBD is under active investigation. The common end pathway is inflammation of the mucosal lining of the intestinal tract, causing ulceration, edema, bleeding, and fluid and electrolyte loss.

Persons with IBD have a genetic predisposition (or perhaps susceptibility) for the disease. The triggering event for the activation of the immune response has yet to be identified. Possible factors related to this event include a pathogenic organism (as yet unidentified), an immune response to an intra-luminal antigen (eg, protein from cow milk), or an autoimmune process whereby an appropriate immune response to an intra-luminal antigen and an inappropriate response to a similar antigen is present on intestinal epithelial cells (ie, alteration in barrier function).

A great deal of research has been performed to discover potential genes linked to IBD. One of the early linkages discovered was on chromosome 16 (*IBD1* gene), which led to the identification of the *NOD2* gene (now called *CARD15*) as the first gene clearly associated with IBD (as a susceptibility gene for Crohn's disease).

Studies have also provided strong support for IBD susceptibility genes on chromosomes 5 (5q31) and 6 (6p21 and 19p). *NOD2/CARD15* is a polymorphic gene involved in the innate immune system. The gene has more than 60 variations. Three of these variations play a role in 27% of patients with Crohn's disease, primarily in patients with ileal disease.

One important point to note with all of these potential genes is that they appear to be permissive (ie, allow IBD to occur) but not causative (ie, just because the gene is present does not necessarily

mean the disease will develop).

First-degree relatives have a 5- to 20-fold increased risk of developing IBD compared to subjects from unaffected families. The child of a parent with IBD has a 5% risk of developing IBD. Twin studies show a concordance of approximately 70% in identical twins versus 5-10% in non-identical twins.

None of these mechanisms has been implicated as the primary cause, but they are postulated as potential causes. The lymphocyte population in persons with IBD is polyclonal, making the search for a single precipitating cause difficult. In any case, activation of the immune system leads to inflammation of the intestinal tract, both acute (neutrophilic) and chronic (lymphocytic, histiocytic).

For unclear reasons, research suggests that smoking increases the risk of Crohn's disease but reduces the likelihood of ulcerative colitis.

Appendectomy early in life also reduces the lifetime risk of developing ulcerative colitis.

Many of the mucosal changes seen in persons with IBD are nonspecific in nature; they are seen in any organ system in which active inflammation is occurring. Many inflammatory mediators have been identified; antibodies against these mediators or methods to block the production or receptors for these mediators hold great promise for potential therapy for IBD.

The incidence of IBD is assumed to be highest in developed countries and lowest in the developing regions of the world. A study in Italy showed the incidences of ulcerative colitis and Crohn's disease to be similar to those found in the United States. Persons living in colder climates have a greater rate of IBD than persons living in warmer climates. Persons living in urban areas have a greater rate of IBD than persons living in rural areas.

Mortality/Morbidity

Multiple studies have been conducted from regions throughout the world on mortality in patients with IBD. The mortality from ulcerative colitis has decreased over the past 40-50 years.

- One study suggested decreased mortality for ulcerative colitis (standardized mortality ratio of 0.6 in Florence, Italy), but the vast majority of studies indicate a small but significant increase in mortality associated with IBD. The standardized mortality ratio for IBD generally ranges from approximately 1.4 times the general population (Sweden) to 5 times the general population (Spain). In general, the 95% confidence intervals suggest that the increase in relative risk is real. Ulcerative colitis and Crohn's disease have approximately equal mortality rates.
- The most frequent cause of death in persons with IBD is the primary disease, followed by malignancy and thromboembolic disease.
- A generally accepted postulation is that the risk of colorectal cancer is not significantly higher in persons with ulcerative colitis compared with the general population until several years after diagnosis. Beyond 8-10 years after diagnosis, the risk of colorectal cancer increases by 0.5-1.0% per year. Data suggest that surveillance colonoscopies with random biopsies reduce mortality from colorectal cancer in patients with ulcerative colitis, primarily by allowing the detection of carcinoma at an earlier Duke stage. Data suggest that persons with Crohn's colitis involving the entire colon have a risk of developing malignancy equal to that of persons with ulcerative colitis; however, the risk for most patients with Crohn's disease is much smaller (albeit poorly quantified).

Age

Ulcerative colitis and Crohn's disease are most commonly diagnosed in young adults (ie, late adolescence to the third decade of life). The

age distribution of newly diagnosed IBD cases is bell-shaped; the peak incidence occurs in people in the early part of their second decade of life, with the vast majority of new diagnoses made in people aged 15-40 years. However, children younger than 5 years and elderly persons are occasionally diagnosed. Of patients with IBD, 10% are younger than 18 years.

Clinical History

The manifestations of IBD generally depend on the area of the intestinal tract involved. Patients with ulcerative colitis or Crohn's colitis frequently have bloody diarrhea, occasionally with tenesmus (urge to frequently visit the toilet). Patients with Crohn's disease involving the small intestine frequently have abdominal pain and diarrhea, and occasionally they have symptoms of intestinal obstruction. A variety of intestinal and extra-intestinal manifestations of IBD also may be observed in conjunction with either ulcerative colitis or Crohn's disease.

- Ulcerative colitis
 - The most typical manifestation of ulcerative colitis is bloody diarrhea. Pain is uncommon but may occur.
 - Patients are commonly fatigued, which is often related to the inflammation and anemia that accompany disease activity.
- Crohn's disease
 - The most typical manifestations of Crohn's disease are abdominal pain and diarrhea. Not uncommonly, patients have been diagnosed with irritable bowel syndrome.
 - Pain is particularly common, especially when some degree of obstruction is present. The pain may be almost anywhere within the abdominal cavity, although the classic location is the lower abdomen or right lower quadrant (appendicitis like).

- Patients are commonly fatigued, which is often related to the pain, inflammation, and anemia that accompany disease activity.
- Intestinal complications
 - Strictures and obstructions are not uncommon in persons with Crohn's disease. These strictures are often inflamed and frequently resolve with medical treatment. Fixed (scarred or cicatrix) strictures may require endoscopic or surgical intervention to relieve obstructions. However, in persons with ulcerative colitis, colonic strictures are of significant concern and should be presumed to be malignant unless proven otherwise (usually by resection).
 - Fistulae and perianal disease are not uncommon in persons with Crohn's disease and may be refractory to vigorous medical treatment, including antibiotic therapy. Surgical intervention is often required for fistulae and perianal disease treatment, but both are associated with a high risk of recurrence.
 - Toxic megacolon is a life-threatening complication of ulcerative colitis and requires urgent surgical intervention.
 - Infectious colitis is in the differential diagnosis of ulcerative colitis and must be excluded before the diagnosis of ulcerative colitis can be made. However, in patients with well-established ulcerative colitis, superimposed infection can occur. Infection with *Clostridium difficile* is by far most common. Stools of patients hospitalized for a flare of ulcerative colitis should be tested for *C difficile* toxin. Treatment of *C difficile* (if present) infection generally helps put the flare into remission.
 - Malignancy is the most dreaded long-term intestinal complication of ulcerative colitis. The risk of colon cancer for persons with ulcerative colitis begins to rise significantly above that of the general population approximately 8-10 years after diagnosis. For cancer prevention, surveillance colonoscopy every 2 years after 8

years of disease is recommended, more frequently if areas of pathologic concern are evident. The risk of cancer in persons with Crohn's disease may equal to that of persons with ulcerative colitis if the entire colon is involved, and screening may be beneficial for patients with pancolitis Crohn's disease. The risk of small intestine malignancy is increased in persons with Crohn's disease, but the malignancy is as likely to arise in a previously normal area as in an inflamed area. No screening protocol has ever been demonstrated to be effective for small bowel Crohn's disease.

Physical

- Ulcerative colitis
 - Presenting signs of ulcerative colitis include diarrhea with occult or frank blood loss. Weight loss and anemia are also common. Persons with ulcerative colitis typically do not develop fistulae or perianal disease, although they may have perianal abscesses.
 - Diagnosis can be made endoscopically or radiologically, with contrast radiographs typically showing loss of the normal mucosal pattern and, with more advanced disease, loss of colonic haustrae.
 - Sigmoidoscopy or colonoscopy reveals that the rectum is almost always involved. The disease can be limited to the rectum (proctitis); to the rectum, sigmoid, and descending colon (left-sided colitis); or to the entire colon (pancolitis). Ulcerative colitis does not involve any other segment of the gastrointestinal tract. Colectomy is curative.
- Crohn's disease
 - Presenting signs of Crohn's disease include occult blood loss and low-grade fever; weight loss and anemia are common. Growth retardation is seen in children and may

be the only presenting sign in young patients. Fistulae and perianal disease are not uncommon.

- Diagnosis can be made endoscopically or radiologically, with contrast radiographs typically showing a cobblestone pattern to the mucosa and areas of normal mucosa alternating with areas of inflamed mucosa (skip lesions).
- Sigmoidoscopy or colonoscopy reveals that the rectum is frequently spared and right colonic predominance is common. Ninety percent of patients with Crohn's disease have involvement of the terminal ileum and/or right colon. Pediatric patients are more likely (about 20%) to present with disease limited to the small intestine. Occasionally, gastric or duodenal Crohn's disease manifests as seemingly refractory ulcer disease.

Extra-intestinal complications:

Many complications associated with IBD can occur with either ulcerative colitis or Crohn's disease. In addition, many of the medications used to treat IBD may cause significant adverse systemic effects.

- In addition to medication-induced arthropathies, the arthritides associated with the IBD are of 2 varieties, axial (or central) arthritis and peripheral arthritis.
 - The axial arthritis associated with IBD consists of ankylosing spondylitis and sacroiliitis. Axial arthritis occurs in approximately 5% of patients with IBD (often Crohn's disease) and typically is independent of disease activity. Axial arthritis is often associated with HLA-B27.
 - The peripheral arthritides vary with the activity of the underlying IBD. Peripheral arthritis occurs in approximately 10% of patients with IBD; it is a nondestructive arthritis, and patients have seronegative findings for rheumatoid factor. The

peripheral arthritis typically is asymmetric, and it can be monoarticular or may involve different joints on different sides of the body. The classic peripheral arthritis affects large weight-bearing joints, although any joint may be involved.

- Diseases of the eye associated with ulcerative colitis are episcleritis and iritis (uveitis). Treatment of these complications often requires high-dose systemic steroids or infliximab, and either condition can cause significant vision loss if left untreated.
- The major skin diseases associated with IBD are erythema nodosum and pyoderma gangrenosum.
 - Erythema nodosum is a painful, tender, raised, purplish lesion on the anterior surface of the tibia. Erythema nodosum tends to correlate well with the activity of the underlying bowel disease; with bowel disease treatment, the erythema nodosum usually dissipates.
 - Pyoderma gangrenosum, on the other hand, typically is not associated with disease activity. This skin lesion starts as an inflamed patch of skin ranging from one to several centimeters in diameter that progress until it ulcerates. Upon ulceration, the lesion may persist for many months before healing. Treatments that have been tried that may have some efficacy include dapsone, metronidazole, cyclosporine, and infliximab. Surgical removal of the diseased bowel (eg, colectomy) does not ameliorate pyoderma gangrenosum.
 - Infectious skin lesions related to immune suppression may also be seen (eg, herpetic lesions)
- The urinary complications of IBD are more common in persons with Crohn's disease. Calcium oxalate stones are the most common type of renal calculi associated with Crohn's disease; treatment is to increase hydration and to use oral calcium citrate supplements, which bind the

oxalate within the intestinal tract and prevent its excretion in the urinary tract. Because of its proximity to the ureters, inflammation of the small bowel may involve the ureters, causing obstruction and hydro-nephrosis. Fistulae occasionally occur between the bowel and bladder or ureters.

- Sclerosing cholangitis is most commonly associated with ulcerative colitis. Sclerosing cholangitis is a disease of the biliary tree. Although sclerosing cholangitis typically manifests as fatigue and, perhaps, jaundice, it is far more commonly sought when abnormal LFT results in a cholestatic pattern are found in a patient with ulcerative colitis.
 - Although ursodeoxycholic acid may help improve serum LFT results, this has not been translated into improved survival. If sclerosing cholangitis is diagnosed in the absence of a known history of ulcerative colitis, colonoscopy is indicated.
 - Ulcerative colitis may be expected to be clinically evident within 2 years of diagnosis of sclerosing cholangitis if the colitis is present and has not been diagnosed first. Sclerosing cholangitis may be indolent for many years but may progress to cirrhosis, for which hepatic transplantation may be necessary. The most dreaded complication of sclerosing cholangitis is the development of cholangiocarcinoma.
- Gallstones are common in persons with Crohn's disease, but these persons are usually asymptomatic; occasionally, cholecystectomy is necessary.
- The anemia associated with IBD may be of 2 types:
 - (1) Iron deficiency anemia secondary to chronic blood loss,

(2) Anemia of chronic disease. Because iron is absorbed in the duodenum, patients with Crohn's disease involving the proximal small intestine may have difficulty absorbing oral iron; occasionally, parenteral iron replacement is necessary. IBD is a recognized cause of anemia of chronic disease.

- A hyper-coagulable state is associated with IBD. It is estimated to occur in as many as one third of patients with IBD, but it may go unrecognized until a thrombotic event occurs. Strokes, retinal thrombi, and pulmonary emboli are not uncommon in patients with IBD.

Causes

The causes of IBD are currently unknown.

Genetics: IBD clearly has a familial tendency. First-degree relatives have a 5- to 20-fold increased risk of developing IBD compared to subjects from unaffected families. A parent with IBD has approximately a 5% chance of having a child develop IBD. Of patients with IBD, 10-25% is estimated to have a first-degree relative with the disease. Monozygous twin studies show a high concordance for Crohn's disease but less so for ulcerative colitis; twin studies show a concordance of approximately 70% in identical twins versus 5-10% in non-identical twins.