

Crohn's Disease: Introduction

Inflammatory bowel disease encompasses two idiopathic, chronic, inflammatory diseases: Crohn's disease and ulcerative colitis. Crohn's disease and ulcerative colitis are disorders of unknown cause, involving genetic and immunological influence on the gastrointestinal tract's ability to distinguish foreign from self-antigens. They share many overlapping epidemiological, clinical, and therapeutic characteristics. In some patients it is not possible to distinguish which form of inflammatory bowel disease is present (Figure 2).

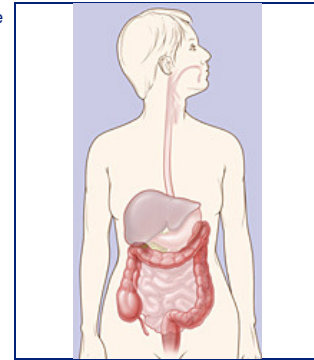


Figure 1. Location of the colon in the body.

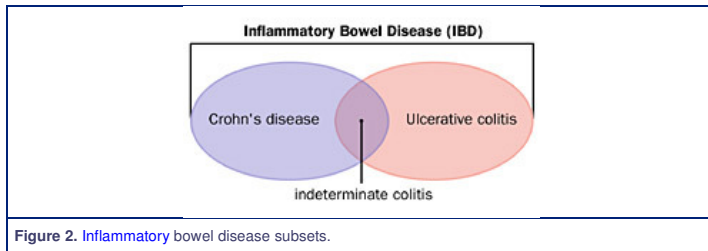


Figure 2. Inflammatory bowel disease subsets.

There are, however, important pathological and clinical differences that distinguish these inflammatory disease processes. Clinically, Crohn's disease tends to present more frequently with abdominal pain and perianal disease, whereas ulcerative colitis is more often characterized by gastrointestinal bleeding. Cobblestoning mucosa and aphthous or linear ulcers characterize the endoscopic appearance of Crohn's disease. Ulcerative colitis presents with diffuse continuous involvement of the mucosa. Radiographic studies of patients with Crohn's disease characteristically show fistulae, asymmetry, and ileal involvement. In contrast, radiographic studies of patients with ulcerative colitis show continuous disease without fistulizing or ileal disease. Pathologically, Crohn's disease features mucosal discontinuity, transmural involvement, and granulomas, whereas ulcerative colitis does not. Crypt abscesses and granulomas are present only in Crohn's disease. Figure 3 compares the anatomic distribution of Crohn's disease and ulcerative colitis.

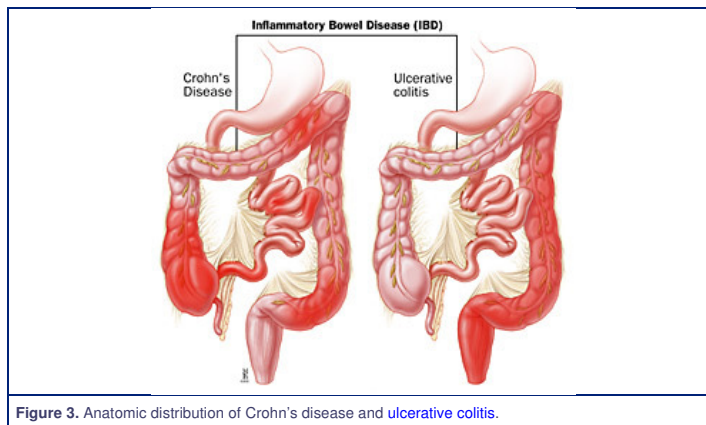


Figure 3. Anatomic distribution of Crohn's disease and ulcerative colitis.

Crohn's disease is a form of inflammatory bowel disease. The term Crohn's disease has replaced older terms, which included regional enteritis, regional or terminal ileitis, and granulomatous colitis. Although the terminal ileum and the right colon are the most commonly involved sites, a similar pathological and clinical disorder can affect any part of the gastrointestinal tract, from the mouth to the perianal area. Only one third of patients with Crohn's disease have granulomatous inflammation. The broad term Crohn's disease does not imply any one cause, site, or pathological response. Crohn's is a chronic illness that requires expensive medications, often hospitalization and/or surgery, and results in a heavy social and economic toll.

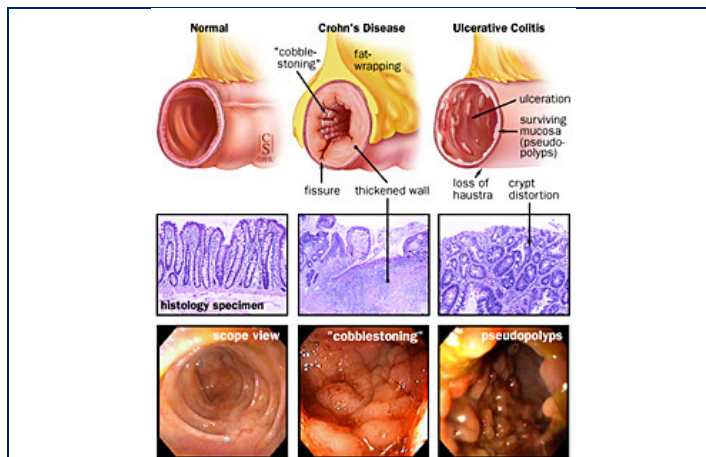


Figure 4. Comparison of the appearance of normal, Crohn's, and ulcerative colitis mucosa; gross (top); histological (center); endoscopic (bottom).

The geographic distribution of Crohn's disease historically suggested a north-south gradient of incidence; however, more recent investigations have reported increased prevalence in temperate regions of North America, South Africa, and Australia. Urban areas have a higher incidence of disease than rural populations, and ethnic minorities (south Asians in the United Kingdom, blacks in South Africa, Bedouin Arabs in Israel) are at lower risk. Jews originating from middle Europe (Ashkenazi Jews) and those individuals of Scandinavian descent are at increased risk (Figure 5).

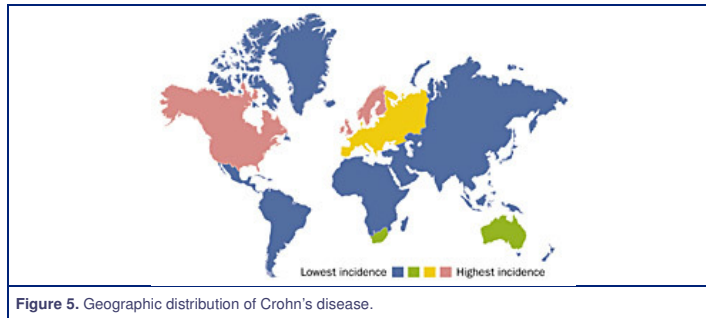


Figure 5. Geographic distribution of Crohn's disease.

What is Crohn's Disease?

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract. Inflammation extends all the way through the intestinal wall from mucosa to serosa. Like ulcerative colitis, Crohn's disease is a relapsing and remitting disease. Initially only a small segment of the gastrointestinal tract may be involved, but Crohn's disease has the potential to progress extensively.

Although surgical resection of inflamed segments may temporarily arrest symptoms, subsequent inflammation is likely to recur. Resection is not curative in Crohn's disease, which is in contrast to ulcerative colitis, where colectomy eliminates the illness.

This illness usually appears early in life; about one-sixth of patients present before the age of 15 and often with severe disease. The average age at diagnosis is 27 years. The cause of Crohn's disease is unknown, although strong genetic influences are suggested by the occurrence of this disease in families, with a higher incidence in Jews than in the general population. Genetic influences are more prominent in the younger onset subgroup of patients than those who present after the age of 40.

In one-third of patients with Crohn's disease, the gross pathologic changes are limited to the terminal part of the ileum. About 40% of patients have ileocolitis, involvement of the distal ileum and proximal colon. About 5% have ileojejunitis, in which there is either continuous involvement throughout the small bowel, or more commonly, several sharply demarcated skip areas separated by normal bowel, sparing the terminal ileum. As many as one-third of young patients with Crohn's disease have subtle microscopic and macroscopic ulceration of the gastric antrum and the duodenum. In these cases, the lesions are not often symptomatic. Up to 20% of patients have involvement limited to the colon (Figure 6).

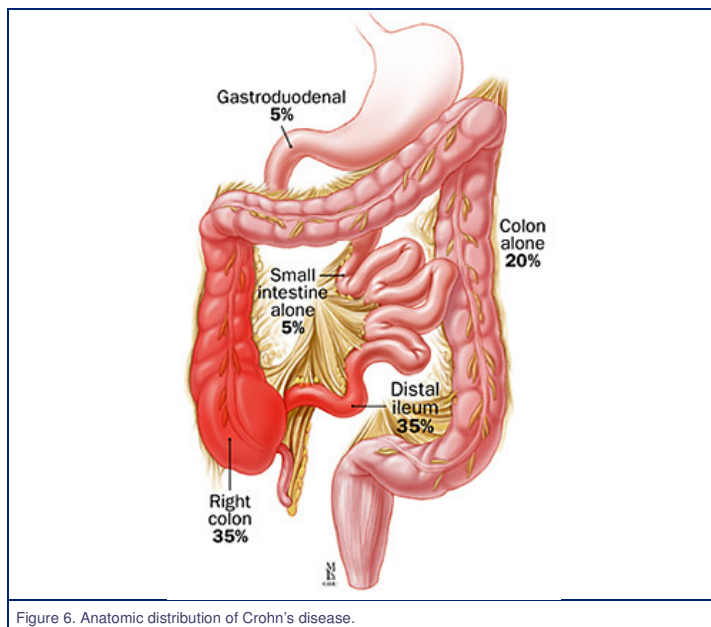
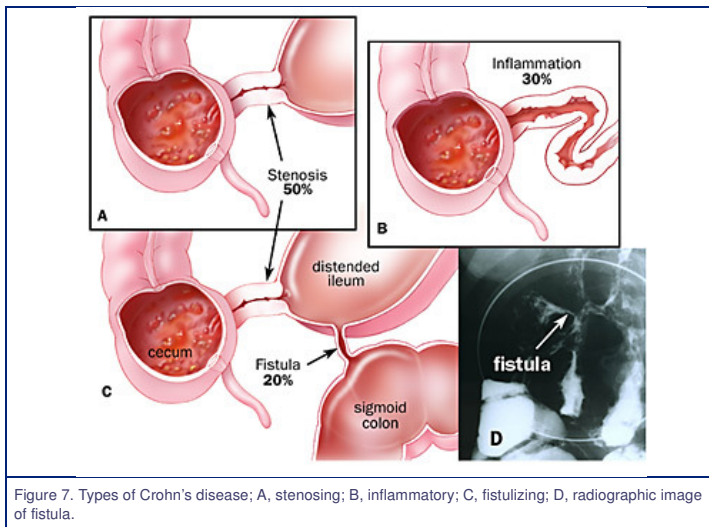


Figure 6. Anatomic distribution of Crohn's disease.

The colonic lesions are often segmental and sometimes spare the rectum; this helps to distinguish them from ulcerative colitis, which always involves the rectum and is continuous rather than segmental. Crohn's disease is also more likely than ulcerative colitis to cause fistula, benign fibrous strictures, and perianal disease. Despite these differences, in about 10% of patients with chronic inflammatory bowel disease confined to the colon both macroscopically and microscopically, the diagnosis must be classified as indeterminate. This distinction becomes important when the clinician is considering surgery. Ulcerative colitis can be cured by total colectomy, and disease does not recur in an ileoanal pouch. However, patients with Crohn's disease can have troublesome recurrences in the ileum. Alternatively, segmental resections of the colon can be helpful in patients with Crohn's disease.

Most patients with Crohn's disease have focal mucosal inflammation seen endoscopically and aphthous ulcers visible macroscopically scattered throughout extensive portions of an otherwise normal bowel. The widespread microscopic disease may partially account for the high rate of recurrence (50% at 5–10 years) after surgical resection of all gross disease. With time, the inflammation extends through most layers of the bowel. In contrast, ulcerative colitis usually remains within the mucosa; in only a few patients does colitis go on to perforate. Noncaseating granulomas are found in 30–50% of resected bowel sections from patients with Crohn's disease. These are usually considered diagnostic, since granulomas are rare in ulcerative colitis.

The pathologic findings in Crohn's disease correlate with three distinct disease courses. The inflammatory type affects 30% of patients, remains localized to the mucosa and submucosa, and causes diarrhea and pain from acute partial obstruction. Fistulizing or perforating disease affects 20% of patients who have ileitis. Aggressive transmural inflammation leads to intra-abdominal fistulae from the diseased bowel wall to another bowel loop, or to a nearby organ like the urinary bladder. Some patients suffer free bowel perforation early in the disease.



Stenosing or stricturing disease characterizes the third course. About 50% of patients with ileitis follow this route. Early in the course of Crohn's disease in the small bowel, patients seem to develop muscle hypertrophy followed by collagen (scar) deposition. After about 7–8 years of ileal disease, patients develop a fixed, scarred obstruction that causes painful cramping and requires surgical management. Most patients go to surgery 8–10 years after the onset of disease or after a previous resection for obstruction. This obstructive process seems to be caused by inflammatory cytokines that are not inhibited by corticosteroids, anti-inflammatory salicylates, or immunomodulator drugs. In the bowels' effort to decompress the obstructed segment, fistula can develop through fissures in the thickened bowel wall in the proximal part of a stenotic area, causing secondary fistula or even perforation.

Symptoms

Crohn's disease usually begins in the teens and twenties; however, one-sixth of patients present before age 15. More than 90% of patients have symptoms before the age of 40. Patients most often present with abdominal cramps, diarrhea, delayed growth (in prepubescent patients), weight loss, fever, anemia, a right lower quadrant abdominal mass (if a complication has developed in the ileal area), or perianal fistula. Typically, patients with ileitis or ileocolitis have an insidious onset and a long course before they receive a specific diagnosis. The average duration of symptoms before diagnosis and initiation of therapy used to be 2–2½ years, but this lag time has been shortened with better imaging techniques such as ultrasonography and computed tomography (CT), and a higher index of suspicion for Crohn's disease.

Crohn's disease can have several patterns of involvement: jejunoileitis, ileitis, ileocolitis and colitis. Each subtype has a distinct clinical presentation and typical course. Patients with inflammation of the jejunum and ileum often present with cramping abdominal pain after meals and eventually develop diarrhea. These patients, many of whom are teenagers or young adults, may have prominent extraintestinal manifestations including arthritis, fever, skin lesions, and delayed growth. Ileitis causes discomfort 1–2 hours after meals. Patients lose weight because they eat less to avoid discomfort. The inflammation in the ileum can extend transmurally into adjacent structures as tracks or fistulae, or can cause perforation of abscesses adjacent to the bowel. This form of Crohn's disease is known as fistulizing or perforating. It has the worst prognosis of all the forms and often requires surgical resection after three or four years. Other patients with ileitis develop intestinal obstruction 8–10 years after the onset of disease because muscle hypertrophy and fibrosis narrow the lumen of the bowel. This form of Crohn's disease is known as stricturing or stenosing. Crohn's disease in the colon causes diarrhea and may be difficult to distinguish from ulcerative colitis.

The clinical picture of Crohn's disease depends on the areas of the bowel that are involved. Patients with ileal involvement may notice a gradual decrease in their sense of well-being, with vague cramping abdominal pain 1–2 hours after meals. This discomfort, caused by partial obstruction and inflammation of the bowel lumen, may be localized to the periumbilical area, or more commonly, to the right lower quadrant. Because of anorexia, nausea, or the fear of abdominal cramps, patients eat less and invariably lose weight. Most patients with small-bowel Crohn's disease have an increase in the number of bowel movements, although rarely more than five per day, with soft and unformed stools. About 80% of patients with ileal disease have diarrhea.

Crohn's disease is associated with extraintestinal manifestations that may be more problematic than the bowel disease. Colitic arthritis is a migratory arthritis that affects knees, ankles, hips, wrists, and elbows that may accompany Crohn's disease (although it is uncommon when Crohn's is confined to the small intestine). Often, joint pain, swelling, and stiffness parallel the course of the bowel disease. Successful treatment of the bowel disease results in improvement in the arthritic symptoms. Pericholangitis, usually associated with primary sclerosing cholangitis (PSC), is the most common hepatic complication of inflammatory bowel disease. PSC is demonstrable by endoscopic retrograde cholangiopancreatography (ERCP) or hepatic magnetic resonance imaging (MRI). Pericholangitis is characterized by inflammation of the portal tracts with lymphocyte and eosinophil infiltrates. Degenerative changes in the bile ductules are also characteristic. Kidney stones (calcium oxalate stones) are seen in patients with small-intestine Crohn's disease. Inflammation from the bowel can result in urinary tract complications. Occlusion of the ureters, leading to obstruction and hydronephrosis, usually involves the right ureter in Crohn's patients. Fistula can form between inflamed bowel and the urinary bladder leading to infection (Figure 8).

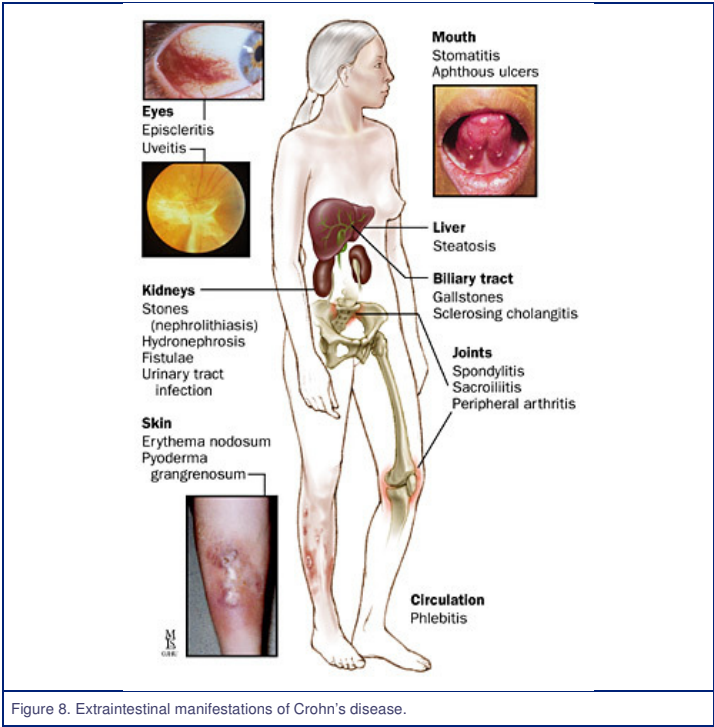


Figure 8. Extraintestinal manifestations of Crohn's disease.

Crohn's Disease: Anatomy

The duodenum extends from the pylorus to the ligament of Treitz in a sharp curve that almost completes a circle. It is so named because it is about equal in length to the breadth of 12 fingers, or about 25 cm. It is largely retroperitoneal and its position is relatively fixed. As the small intestine re-enters the peritoneal cavity at the ligament of Treitz, it becomes the jejunum. Generally the jejunum is considered the proximal two fifths of the small bowel and the ileum the distal three fifths. There is no landmark between these two regions. The jejunum has a thicker wall than the ileum. The circular folds of mucosa and submucosa that comprise the lumen of the duodenum and jejunum gradually disappear in the mid-ileum. In addition to the plicae circulares (circular folds), intestinal villi (or fingerlike projections) protrude into the intestinal lumen and cover the surface of the mucosa. These villi are broad and leaf-like in the duodenum, tall and thin in the jejunum, and short and broad in the ileum. The crypt of Lieberkuhn may be found at the base of the villi where the epithelium enters the lamina propria. The enzymes, receptors, and carriers necessary for digestion and absorption are contained in this complex network of membranes.

The lower gastrointestinal tract may be divided into the cecum, the ascending colon, the transverse colon, the descending colon, and the rectum. The large intestine (colorectum) begins at the cecum, which is a pouch approximately 2–3 inches long. Ileal contents empty into the cecum through the ileocecal valve. The appendix extends from the base of the cecum. The ascending colon rises from the cecum along the right posterior wall of the abdomen and extends under the ribs to the undersurface of the liver. At this point, it turns toward the midline (hepatic flexure) becoming the transverse colon. The transverse portion crosses the abdominal cavity toward the spleen, goes upward into the chest under the ribs and turns downward at the splenic flexure. Continuing along the left side of the abdominal wall to the rim of the pelvis, the descending colon turns medially and inferiorly to form the S-shaped sigmoid (sigma-like) colon. The rectum extends from the sigmoid colon to the pelvic floor muscles, where it continues as the anal canal, terminating at the anus (Figure 9). The anal canal is approximately 4 cm long.

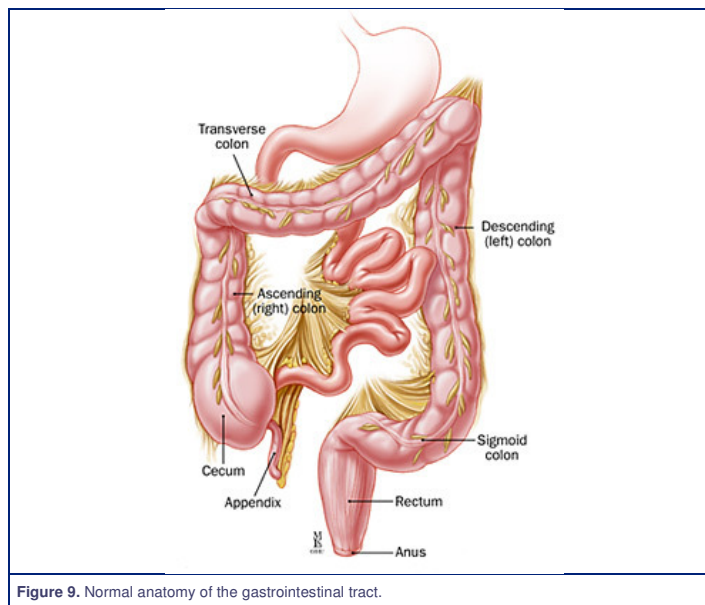


Figure 9. Normal anatomy of the gastrointestinal tract.

The small intestine is the site where digestive enzymes are secreted and digested nutrients are absorbed by osmosis, filtration, and diffusion. The absorption ability of the small intestine is enhanced because of the large surface area created by the villi. Segmenting contractions of the circular muscles keep the "food" moving along the gastrointestinal tract. The process of hydrolysis results in the production of amino acids, simple sugars, glycerol, and fatty acids. Small capillaries and lacteals embedded in the villi allow the products of digestion to be absorbed into the circulatory and/or lymphatic systems.

The large intestine is approximately 4–6 feet long and 2 ½ inches in diameter. It is the site of salt and water absorption. Glands secrete large quantities of alkaline mucus that lubricates the intestinal contents and neutralizes acids formed by bacteria in the intestine. These bacteria aid in decomposition of undigested food residue, unabsorbed carbohydrates, amino acids, cell debris, and dead bacteria through the process of segmentation and putrefaction. Short-chain fatty acids that are formed by bacteria from unabsorbed complex carbohydrates provide an energy source for the cells of the left colon. Maintenance of potassium balance is also assigned to the colon, where the epithelium absorbs and secretes potassium and bicarbonate.

Crohn's Disease: Causes

Risk Factors

No unified hypothesis explains the pathogenesis of Crohn's disease and its characteristic inflammatory pattern. Typically, focal inflammatory collections and aphthous ulcers in the mucosa progress to transmural inflammation (Figure 10). It is not known whether patients with fistulizing disease have a distinct type of disease or whether their cytokine response is simply unable to confine the inflammatory process to the bowel wall. It is known that after ileocolonic resection, disease recurs at the neoterminal ileum only when it has contact with the luminal stream and colonic contents, and perhaps the bacteria therein. Conversely, inflammation decreases when the fecal stream is diverted or the bowel is rested with an elemental diet or total parenteral nutrition (TPN). It is possible that an infectious agent or antigen from the lumen, perhaps in concert with the intestinal bacterial flora, sets up an inflammatory response in a genetically predisposed host who cannot down-regulate it. Also as yet unexplained are the segmental distribution of the inflammatory process, its predilection for the terminal part of the ileum and the right colon, the tendency to recur years after remitting or being resected, and the frequency of perianal disease.

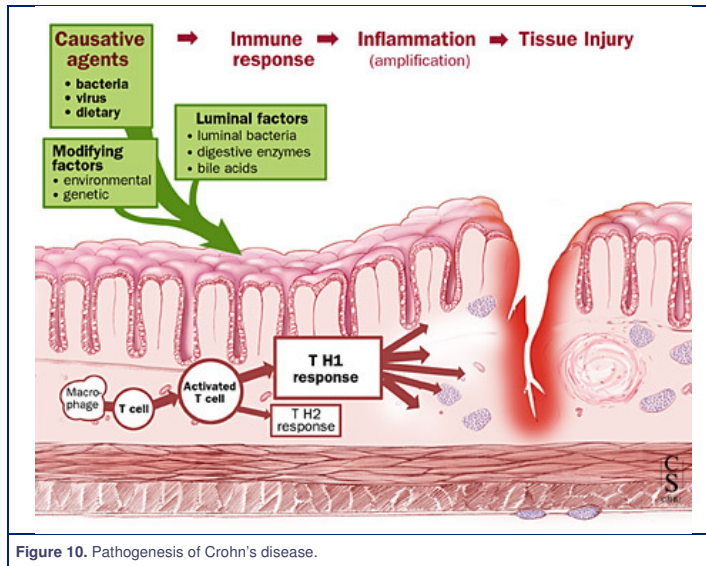


Figure 10. Pathogenesis of Crohn's disease.

Genetic Factors

Several factors influence the expression of Crohn's disease. Genetic factors are the most obvious. About 10–15% of patients with Crohn's disease have a family history of the disorder; another 5–7% have a family history of ulcerative colitis. Identical twins have at least a 53% concordance for Crohn's disease; fraternal twins have the same concordance as patients with a family history. The fact that children of two Ashkenazi Jewish parents with inflammatory bowel disease have a greater than 50% risk of developing Crohn's disease suggests involvement of only a limited number of genes. Recent genome-wide screening studies in both Crohn's disease and ulcerative colitis families have identified susceptibility loci on chromosomes 1, 3, 4, 6, 12, 14, and most significantly on chromosome 16 (in Crohn's disease) (Figure 11).

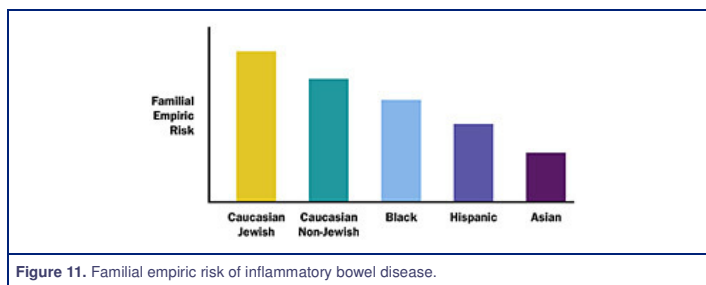
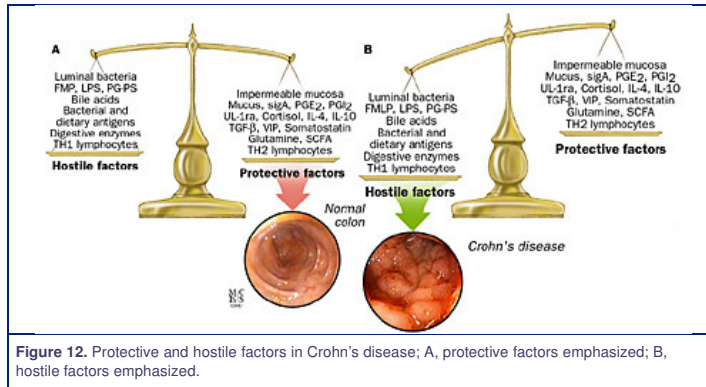


Figure 11. Familial empiric risk of inflammatory bowel disease.

Immune System

The immune system clearly takes part in the response to the initial insult. It has been proposed that instead of responding normally to an offending antigen by activating suppressor T cells, the patient with inflammatory bowel disease mounts an exaggerated helper (T4) lymphocyte response, which then is not physiologically down-regulated. The activated T4 lymphocyte in turn releases lymphokines, including tumor necrosis factor-alpha (TNF-alpha), which activate and recruit monocytes, macrophages, polymorphonuclear leukocytes, and mast cells. These cells amplify the inflammatory response. This is the basis for anti-TNF-alpha therapy. T-cell lymphapheresis has also produced remission in some patients whose illness did not respond to medication. Antigen-antibody reactions in the joints, skin, and eyes are probably responsible for the arthritis, erythema nodosum, iritis, and other extraintestinal manifestations seen in patients with Crohn's disease or with ulcerative colitis.



Crohn's Disease: Diagnosis

Clinical, Endoscopic, Histological and Radiological Findings in Patients with Inflammatory Conditions of the Colon				
	Ulcerative Colitis	Crohn's Disease	Diverticulitis	Collagenous Colitis
Age	20-30 and 50+	15-35	50+	50+
Diarrhea	In most	Very frequent	None	In most
Bleeding	Very frequent	May occur	May occur	None
Mucus	Frequent	Occurs	May occur	Variable
Pain	Variable	Frequent	Frequent	Variable
Anal lesions	Occasional	Common	None	None
Scope appearance	Mucosa inflamed w/edema, Contact bleeding, Mucopus, Ulceration	Mucosa inflamed or normal, +/- aphous ulcers	Abnormal sharp angulation at rectosigmoid area, Luminal narrowing, Erythematous mucosa, Congestion, Hyperemia, Bleeding	Lamina propria normal or inflamed, Intestinal secretions
Histology	Mucosal inflammation, Goblet cell depletion, Crypt abscess, Superficial ulceration	Transmural inflammation, Deep ulceration, Fissuring, Granuloma, Patchy involvement	Intramural abscess, Diverticula, Peridiverticular abscesses	Intraepithelial lymphocytes, Subepithelial collagen band > 10 µm thick
Barium contrast studies	Rectal involvement w/extension, Superficial ulceration w/collar stud ulcer in severe, Pseudopolyps	Rectal sparing, Mucosal infolding, Fistulae, Fixed eccentric defect in wall, Longitudinal sinus tracts, Extraluminal stricture, Hyperemia	Normal	Normal

Table 1. Overview

Physical Exam

The intestinal nature of the disease may be difficult to assess. A patient may have a completely normal physical examination of the right lower quadrant. For months, the only objective evidence of disease may be unexplained low-grade fever, polyarthralgia, iron deficiency anemia, hypoalbuminemia, guaiac-positive stools, elevated C-reactive protein, or an elevated erythrocyte sedimentation rate. Children and teenagers who present with fever and arthralgia may be given a misdiagnosis of rheumatic fever or juvenile rheumatoid arthritis. Prepubescent patients may have a slowing of growth 1–2 years before weight gain slows or gastrointestinal symptoms begin. This is because inflammatory mediators impair bone growth and mineralization before the intestinal lesions are extensive enough to cause cramping or diarrhea.

The diagnosis of Crohn's disease is established by a combination of clinical, radiographic, endoscopic and pathological findings. The physician gains confidence in the diagnosis by observing the patient's course. Laboratory evidence of inflammation, such as an elevated C-reactive protein, an elevated erythrocyte sedimentation rate or hypoalbuminemia, can support a diagnosis of Crohn's disease, but its absence does not exclude the illness. In addition, multiple investigations have confirmed the association between serum anti-Saccharomyces cerevisiae antibodies and Crohn's disease in about two-thirds of patients, although the reasons are poorly understood.

Radiographic Diagnosis

The availability of excellent imaging techniques such as barium contrast x-rays (Figure 13) and computed tomography (CT) should make it unusual for Crohn's disease to be diagnosed unexpectedly at exploratory laparotomy. A double-contrast barium enema x-ray can show the right colon and the terminal part of the ileum, the areas most often involved in Crohn's disease. The examiner looks for aphthous ulcers (seen as small filling defects with an opaque center), loss of mucosal detail, cobblestone filling defects, segmental areas of involvement, fistula, and an asymmetric appearance. Spasm or scarring, producing the classic string sign, may narrow the ileal lumen. Abdominal CT is the preferred technique for suspected intra-abdominal abscesses.

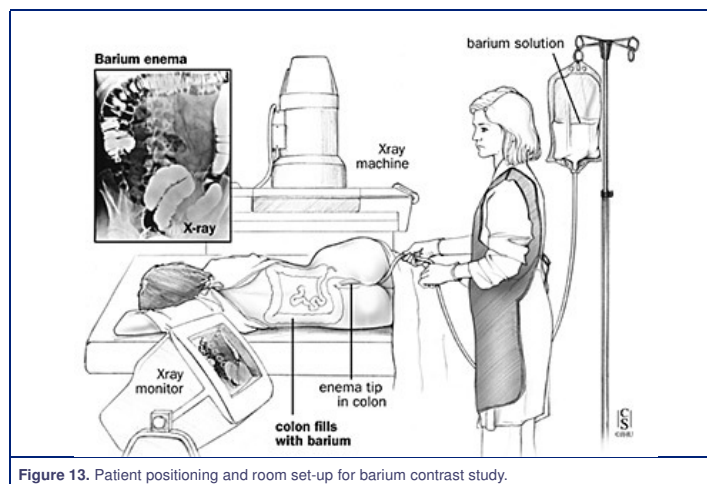


Figure 13. Patient positioning and room set-up for barium contrast study.

Small Bowel Series

This is a fast, safe procedure for visualization of the small bowel. The patient drinks a barium suspension and overhead abdominal radiographs are taken at 20–30 minute intervals. When the barium reaches the right colon, fluoroscopy is performed while moving the patient in various positions to unwind superimposed bowel

loops. Compression spot radiographs are obtained with attention to the terminal ileum. Small-bowel x-rays reveal the proximal extent of disease, skip areas, and stenosis and dilation, indicating partial obstruction.

Enteroclysis

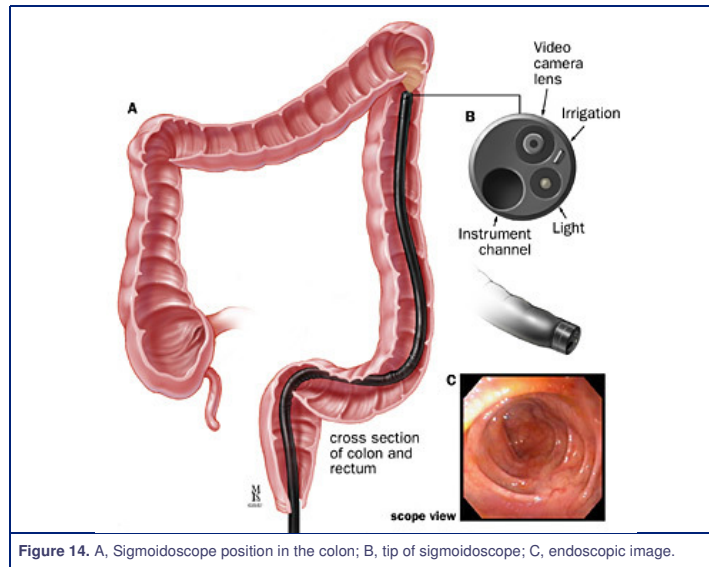
Enteroclysis is more sensitive for focal lesions (such as adhesions), but has a higher rate of complications and technical difficulty. With the patient mildly sedated, a tube is passed through the nose and advanced into the jejunum. Under constant fluoroscopic imaging, barium is infused through the tube with a methylcellulose solution, resulting in distension and coating of small-bowel loops. The appearance is similar to a double-contrast enema.

Endoscopic Diagnosis

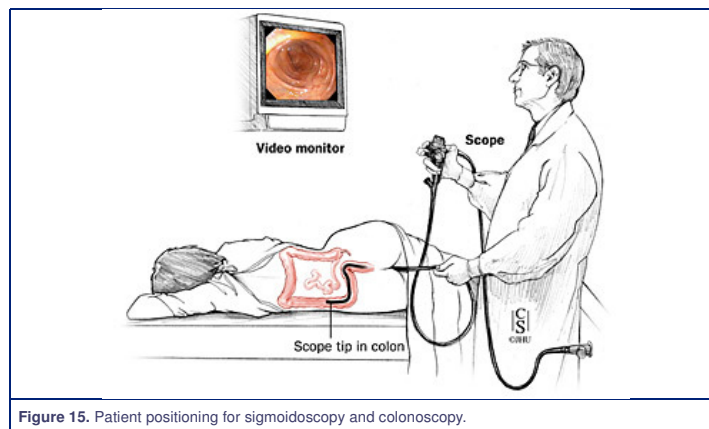
Flexible sigmoidoscopy or colonoscopy with colorectal biopsies can reveal focal inflammation granulomas even when the patient has no gross findings. However, the preparation for colonoscopy or barium enema x-rays can be risky for acutely ill patients with fulminant colitis. For these patients, flexible sigmoidoscopy and a small bowel series with colon follow-through may give the clinician enough information to make diagnostic and therapeutic decisions.

Flexible Sigmoidoscopy

The flexible sigmoidoscopy is an examination of the rectum and the lower colon. It is performed with a lighted, flexible, hollow tube. The sigmoidoscope is inserted into the anus through the rectum and into the sigmoid colon (Figure 14). Before sigmoidoscopy, the colon must be clear of stool to ensure good visibility. The patient must undergo a preparation that may include a liquid diet, enema, and laxatives to clear stool from the colon.

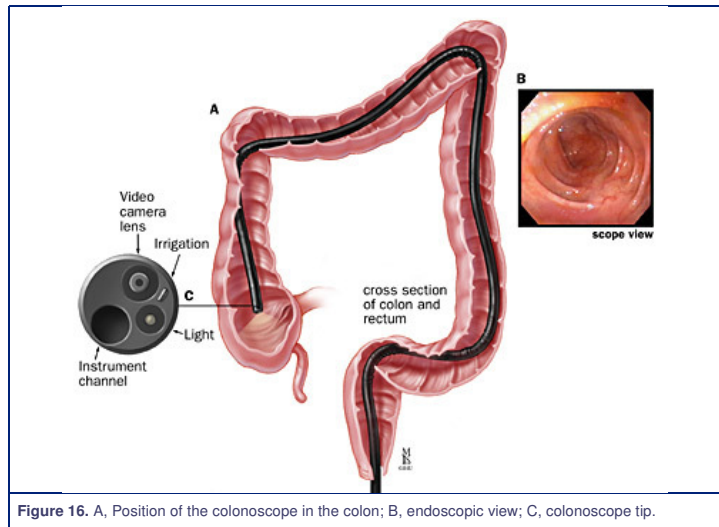


The physician is able to visualize the lower part of the colon. Biopsy forceps may be inserted through a channel of the scope to remove a small sample of tissue for microscopic examination. Sometimes it is necessary for the doctor to introduce air into the colon to improve visibility. Most patients feel a little cramping or discomfort when having a flexible sigmoidoscopy (Figure 15).

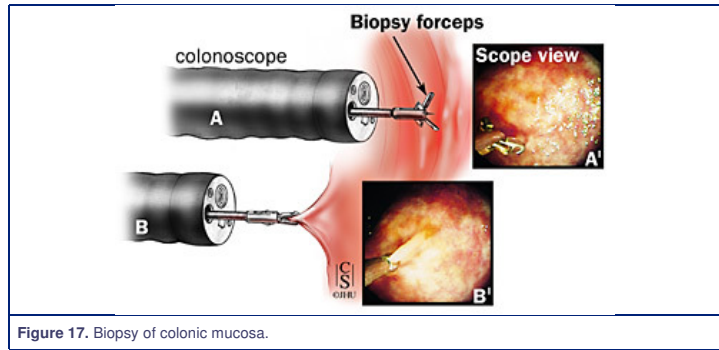


Colonoscopy

A colonoscopy involves the examination of the rectum and the entire colon. It is performed with a lighted, flexible, hollow tube. Colonoscopy permits the physician to visualize the entire colon. The colonoscope allows the doctor to assess the disease progress and to ascertain the effectiveness of therapy (Figures 15 and 16).



Biopsy forceps may be inserted through the colonoscope to remove a small sample of tissue for microscopic examination (Figure 17). Before having a colonoscopy, the colon must be clear to ensure good visibility. The patient must undergo a preparation that may include a liquid diet, enema, and laxatives to clear stool from the colon.



The patient is sedated before the colonoscopy begins. Many people sleep through the entire procedure and feel little or no discomfort. The insertion of air during the procedure may cause some discomfort.

Differential Diagnosis

Other diseases that have the same distribution as Crohn's disease are ileal or ileocecal tuberculosis, yersiniosis, lymphoma, carcinoid tumors, amyloidosis, actinomycosis, histoplasmosis (usually in immunocompromised hosts), carcinoma of the cecum, and amebic involvement of the cecum. Tuberculosis deserves special mention. About 50% of patients with intestinal tuberculosis have evidence of pulmonary tuberculosis. The cecum is usually fibrotic and narrowed, and a few patients have typical calcified abdominal nodes. Culture and histological studies should be done on colonoscopic biopsy specimens and material from fistulae to rule out tuberculosis and actinomycosis. When a positive tuberculin skin test and other clinical features make tuberculosis a possibility, the physician may want to initiate anti-tuberculous drugs, especially if corticosteroid or immunomodulator drugs are being considered as treatment for presumed Crohn's disease. In a small minority of cases, laparotomy is required to distinguish Crohn's disease from tuberculosis, or most importantly, lymphoma before therapy can be started.

Crohn's Disease: Therapy

Medical Therapy

Overview

Therapeutic regimens are based upon the severity of Crohn's disease and the extent of gastrointestinal tract involvement. These factors may vary during the course of the disease but accurate assessment of both is crucial in determining treatment. The severity of the disease impacts the use of anti-inflammatory drugs and risk of future complications. The extent of disease is relevant in the determination of what kind of therapy will be most efficacious, e.g., topical or targeted therapy.

The aims of therapy include the treatment of active disease followed by maintenance of remission. Treatment should successfully suppress active inflammatory disease medically and attempt to conserve the small bowel. Surgery should be reserved for managing complications (fistulae and abscesses) as well as treating obstruction.

Symptoms such as fever, anorexia, crampy pain, and abdominal tenderness should abate within the first few days or weeks of treatment. If symptoms do not respond promptly, the physician must suspect obstruction, abscess, or an error in diagnosis. As soon as the patient begins to improve, the corticosteroids should be tapered.

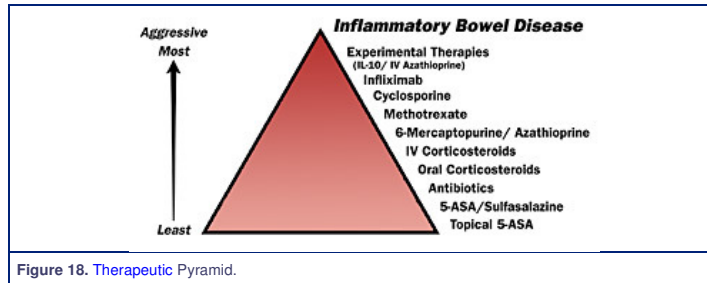


Figure 18. Therapeutic Pyramid.

Anti-Inflammatory Drugs

Mild to moderate Crohn's disease has a good response to 5-aminosalicylate-containing agents. 5-aminosalicylic acid (5-ASA) derivatives (mesalamine, mesalazine and sulfasalazine) provide anti-inflammatory actions for connective tissue. Aminosaliclates can be targeted to sites along the gastrointestinal tract. Asacol, coated with a pH-sensitive acrylic polymer, releases 5-ASA in the distal ileum and colon at pH of 7.0. Sulfasalazine acts as the transport mechanism to carry the 5-ASA component to the colon tract. Pentasa is comprised of coated granules that release 5-ASA in the upper gastrointestinal tract, as well as the ileum and colon.

Aminosaliclates have multiple anti-inflammatory effects that are primarily topical (mucosal), not systemic. They also inhibit oxygen radical production and are scavengers of free radicals. Sulfasalazine and 5-ASA preparations inhibit the function of lymphocytes, monocytes, and plasma cell production of immunoglobulins (Figure 19).

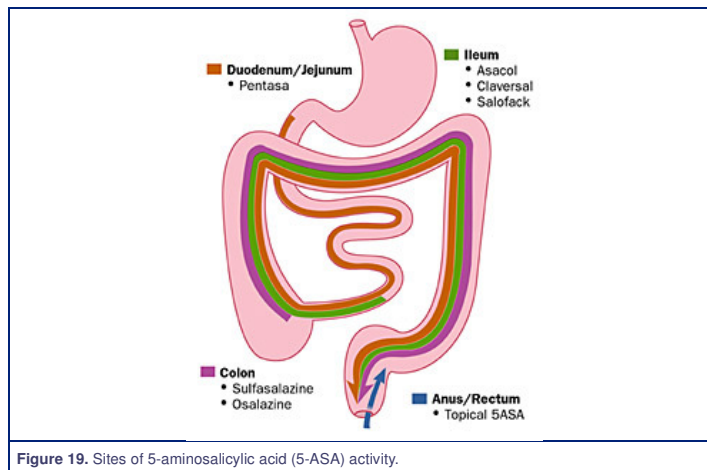


Figure 19. Sites of 5-aminosalicylic acid (5-ASA) activity.

The side effects associated with sulfasalazine therapy are common and related to the sulfapyridine component of the drug. These side effects, which include headache, dyspepsia, malaise, nausea, vomiting and anorexia, are often dose related with the exception of osalazine (dipentum), which can cause diarrhea. The other 5-ASA products have very few adverse effects.

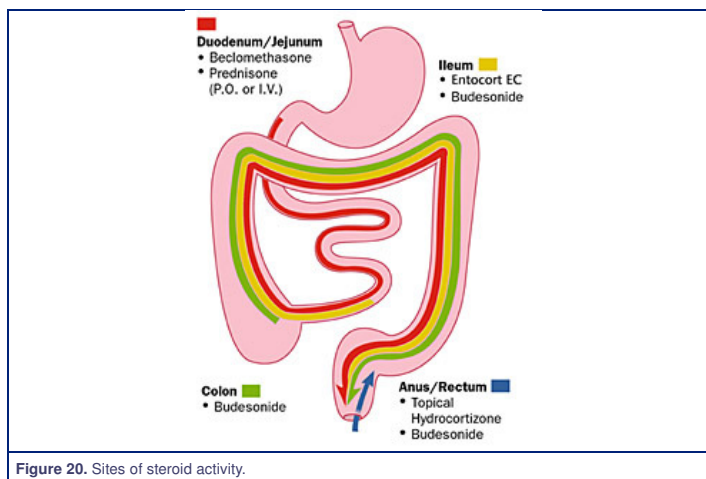
Continuous-release mesalamine (5-ASA products) has been shown to induce clinical improvement or remission. These drugs have also been evaluated for use in maintenance therapy with inconsistent results. Benefit has been demonstrated, however, with 3 g doses in reducing endoscopic and clinical evidence of disease process in postoperative recurrence studies.

Antibiotics

Antibiotic treatment has been used in Crohn's disease despite the fact that microbial agents have not been identified as specific etiological factors. Metronidazole is the most commonly used antibiotic and its efficacy is comparable to sulfasalazine. Metronidazole has been effective in treatment of perianal disease and has transiently reduced recurrence of the disease process after ileal resection. Ciprofloxacin has been as effective as mesalamine in mild to moderate Crohn's disease and has been used in combination with metronidazole for ileal and perianal disease. Studies of combination therapies with antimicrobial therapies in Crohn's disease have been inconsistent in terms of their effectiveness for active disease and maintenance of remission.

Steroid Drugs

Adrenocorticosteroids (e.g., prednisone 40–60 mg/d), in combination with other anti-inflammatory drugs (e.g., sulfasalazine or mesalamine), improve symptoms in over 75% of patients who are treated during the first 4–5 years of uncomplicated disease or during a post-resection recurrence. Patients with predominantly ileal involvement are the most responsive (Figure 20).



Corticosteroids are an integral part of therapy for moderate to severe Crohn's disease. Significant benefit was noted in a large controlled study in steroid-treated patients for all disease locations. It is essential to monitor patients on chronic steroid therapy for evidence of bone degradation with a dual-photon bone density scan (even those on low-dose alternate-day therapy or budesonide—Entocort EC). If there is evidence of osteopenia or osteoporosis, therapy with a bisphosphonate or calcitonin is indicated. Weight-bearing exercise, supplemental calcium, and vitamin D are also used, but care must be taken in patients with a history of nephrolithiasis.

Topical steroid drugs (budesonide) have been used in oral delayed-release formulations for site-specific delivery of active steroids. They have been shown to be effective in treatment of ileocecal Crohn's disease and have demonstrated benefits similar to systemic prednisone. For example, 9 mg budesonide was statistically similar to 40 mg of prednisone in patients with ileocecal Crohn's disease. Low-dose budesonide has not yet been proven efficacious for the prevention of relapse. These preparations are currently available in Canada and Europe but not in the United States.

Immunomodulator Drugs

Immunomodulator therapy (azathioprine and 6-mercaptopurine [6-MP]) has been used for over 25 years for the treatment of inflammatory bowel disease. These drugs are thought to alter the immune response by inhibition of natural killer cell activity and suppression of T-cell function. Immunomodulator therapy has been shown to be more effective than steroids as a maintenance therapy and is generally well tolerated. Remission or steroid sparing can be achieved in 70% of patients. However, potential side effects include fever, rash, nausea, leukopenia and hepatitis. Pancreatitis may occur in 3–15% of patients with prompt resolution with drug cessation.

Immunomodulators are indicated for patients with disease refractory to conventional therapy and as a mechanism for steroid sparing. Two or three months of therapy are usually needed before results are seen.

Another potent T cell inhibitor, cyclosporine, has demonstrated rapid onset of action. Cyclosporine has been successfully used in patients with steroid-refractory and fistulizing Crohn's disease with response rates around 60–80%. Low oral dosages had poor results in long-term maintenance trials. Continuous infusion, however, has proven to be efficacious in the treatment of Crohn's fistulae. The use of this drug remains controversial and requires further investigation and comparison trials.

Methotrexate given intramuscularly is effective for 9–12 months, in about half of the patients that are unresponsive to azathioprine or 6-MP. Methotrexate results in impaired DNA synthesis and IL-1 inhibition with anti-inflammatory properties. The drug is well tolerated and potential toxicity (hepatic fibrosis and bone marrow suppression) is uncommon with consistent monitoring of liver enzymes and blood counts. Common side effects may include diarrhea, nausea, or vomiting, which can be reduced with folic acid supplementation. In a multicenter trial using weekly intramuscular or subcutaneous injections, clinical remission was maintained during a 16-week trial and half of the patients continued to show sustained responses at one year.

Biologic Therapies

Infliximab (Remicade) is a potent new biologic agent that offers potential for the treatment of inflammatory bowel disease. The Food and Drug Administration has currently approved Infliximab specifically for Crohn's disease. For patients with disease refractory to immunomodulators and those with perianal fistulizing disease, benefit may be achieved from therapy with this new chimeric monoclonal antibody that targets tumor necrosis factor-alpha. Preliminary evidence indicates that more than 60% of patients receiving a single infusion will have a clinical response. This drug has also shown utility in sustaining clinical remission with re-infusion at 8-week intervals. Drawbacks include the need for multiple dosing, a concern for developing lymphoma, and limited long-term follow-up information.

Diet

For patients with small-bowel Crohn's disease, elemental diets (composed of simple sugars and amino acids that do not require digestion) alter intestinal luminal contents and can give temporary relief while medical therapy is being started. Enteral nutrition—involving monomeric, oligomeric, or polymeric diets—used for 1–2 months may provide short-term remissions in approximately 70% of patients. There is no particular difference between the diets themselves. Total parenteral nutrition therapy instituted for 2–3 weeks in medically refractory patients can induce remission in approximately 60% of cases (although most patients relapse). This helps correct nutritional deficits in patients with chronically active Crohn's disease. This improvement, however, must be supported by additional medical therapy such as an immunomodulator; without it, most patients relapse when they resume enteral feeding. Late in the disease, medical treatment may provide patients with partial obstruction a several-month reprieve from surgery, but they will eventually require resection. Surgical results are improved if nutritional deficits and active disease have been managed preoperatively. Laparoscopically assisted surgery may be possible in patients with adequate nutrition repletion and the absence of phlegman fistulae or numerous adhesions.

Maintenance Therapy

Clinical studies have demonstrated that maintenance approaches for Crohn's disease can reduce clinical relapse when appropriate therapy is matched with the clinical scenario.

5-Aminosalicylates have been shown to be useful in maintenance regimes when continued after inductive therapy (although they have little value after steroids). Azathioprine, or 6-MP, has been shown to be effective after 3–4 months. Blood levels should be monitored every 3 months, including white blood cell count to avoid leukopenia and bone marrow suppression. Many clinicians report that the antibiotics used to induce remission continue to maintain remission (although no data are available to support this).

Mesalamine, instituted shortly after surgery in 3 g doses, has been suggested to prevent postoperative recurrence of Crohn's disease. Metronidazole (at a rate of 20 mg/kg) administered for 3 months after surgical resection has also been shown to be effective postoperatively for up to 12 months. 6-Mercaptopurine (50 mg/day) has been shown to be effective in maintaining remission for at least two years following surgery.

Infusion of Infliximab at 8-week intervals also has shown promising results in maintaining remission. It is not yet clear how long this expensive therapy should be maintained. Addition of azathioprine or methotrexate may influence long-term success rates.

Surgical Therapy

About 40–60% of patients with ileal Crohn's disease need surgery during the first 10 years of symptoms, most often at 8–10 years. Patients require surgery earlier if they develop intra-abdominal abscesses or the rare free perforation. Unfortunately, 50–60% of patients who undergo surgery develop recurrent disease within 10 years. Aggressive transmural disease (abscesses or free perforation) tends to recur sooner. Most abscesses require percutaneous or operative drainage. Physicians usually delay definitive resection of the involved bowel and fistulous tracts (Figure 21) until they have controlled the inflammatory reaction and corrected malnutrition. In these cases, total parenteral nutrition can be helpful. In the presence of a severe protein-losing enteropathy, surgery should not be delayed. If the bowel is resected when the disease is active, the recurrence rate (within 3–4 years) approaches 50%.

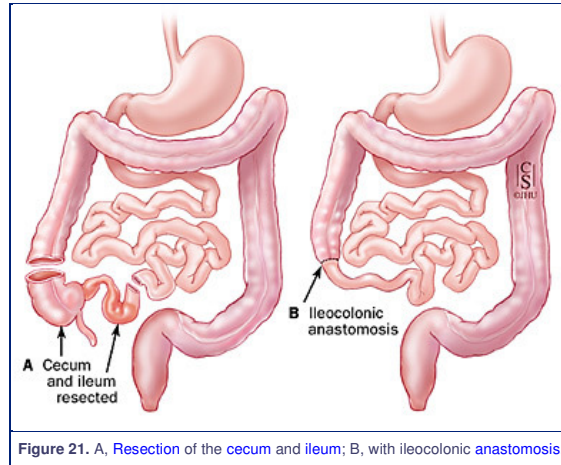


Figure 21. A, Resection of the cecum and ileum; B, with ileocolonic anastomosis.

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Abscesses and Fistulae

Abscesses and fistulae are the products of extension of a mucosal fissure or ulcer through the intestinal wall into another loop of bowel or into extra-intestinal tissue. Abscesses are caused by the leakage of intestinal contents through a tract into the peritoneal cavity. The infection is walled off by surrounding tissue, unlike free perforation, which causes generalized peritonitis. Extension of this tract through adjacent viscera, or through the abdominal wall to the skin, results in a fistula.

The terminal ileum is the most likely point of origin for abscesses and occurs in 15–20% of patients with Crohn's disease. The typical clinical presentation is fever and abdominal pain, often with tenderness and abdominal mass. Leukocytosis is the most common laboratory abnormality.

Computed tomography (CT), barium enema, and ultrasonography are useful in the diagnosis of abdominal mass. Broad-spectrum antibiotic treatment and drainage are indicated.

Simple drainage of an abscess may not provide adequate therapy because of persistent communication between the abscess cavity and intestinal lumen. In such circumstances, drainage may result in the formation of an enterocutaneous portion of the intestine containing the abscess (see Figure 21). Percutaneous drainage is usually carried out first under ultrasound or CT guidance. After adequate drainage and reduction of inflammation, often accompanied by bowel rest and total parenteral nutrition, the involved bowel segment is resected. Communication sites are not always obvious and may require radiographic identification after oral administration or injection of contrast into the abscess cavity.

Fistulae occur in 20–40% of patients with Crohn's disease. Most of these are enteroenteric or enterocutaneous. Regardless of the location, the mechanism of formation appears similar. A deep abscess penetrates into an adjacent organ or the skin. The terminal ileum is the segment most frequently involved. Enteroenteric fistulae seldom cause symptoms and are often incidentally discovered. Symptoms such as malabsorption, diarrhea, and weight loss are present with larger fistulae, or those in more distal locations.

Asymptomatic fistulae do not require treatment except, in cases where there are significant symptoms. Administration of total parenteral nutrition or immunosuppressive therapy, including Remicade, may induce closure. There may be recurrence, however, after the cessation of therapy. Surgery is indicated for cases of nonhealing or recurrent fistulae. Resection of the active disease and fistulae, as well as closure of the distal fistula site, may be performed (Figure 22). Fistulae commonly develop in zones of high pressure proximal to a stricture. If the stricture is resected, eliminating this high-pressure zone, management, and prevention are more likely to be achieved.

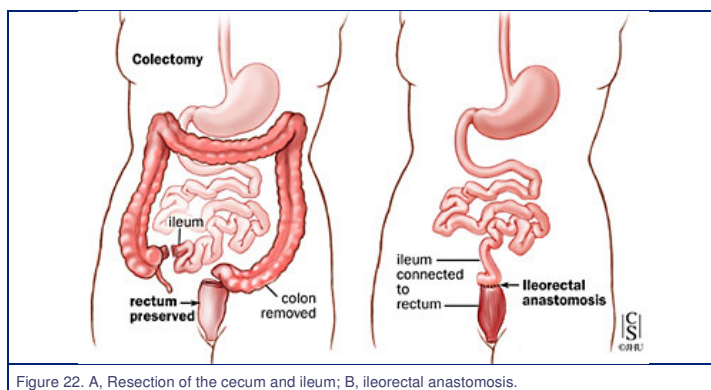


Figure 22. A, Resection of the cecum and ileum; B, ileorectal anastomosis.

Enterocutaneous fistulae commonly occur as a result of anastomotic leaks after resection and intestinal anastomosis. The scar is often the cutaneous end of the fistula and the anastomotic site the enteric end. These fistulae may also occur spontaneously. Fistulae often require surgical resection when there is persistent drainage.

Obstruction

Obstruction, particularly in the small intestine, is a common complication of Crohn's disease and one of the major indications for surgical intervention. Mucosal thickening from acute inflammation, adhesions, or muscular hyperplasia and scarring may cause obstruction. Patients with obstruction present with complaints of abdominal pain, borborygmi, and diarrhea that worsens postprandially. Nausea and vomiting may accompany episodes of prolonged pain and diarrhea. The symptoms may abate with fasting. Barium studies or colonoscopy are useful to evaluate strictures, depending on the anatomic location.

Initial therapy for obstruction is to give nothing by mouth, apply nasogastric suction, and provide intravenous fluids. Parenteral corticosteroids may help reduce acute inflammation. If the obstruction does not resolve with this treatment, endoscopic balloon dilation of long-standing anastomotic strictures or short strictures not associated with fistulae can be attempted. However, surgical intervention (either resection or stricturoplasty) is preferable. Stricturoplasties are especially useful in the duodenum, for jejunoileitis, and to preserve bowel length in patients who have undergone previous bowel resections (Figure 23).

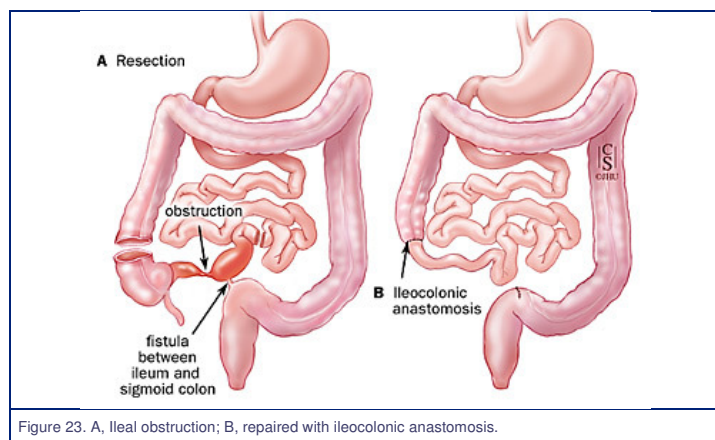


Figure 23. A, Ileal obstruction; B, repaired with ileocolonic anastomosis.

Crohn's Colitis

Crohn's colitis is characterized by abscesses and fistulae. Fistulae often tract through the mesocolon and may enter the small intestine or vagina. Long-standing inflammation often results in scarring and fibrosis and consequently in bowel obstructions. Although most strictures are benign, stricture formation may reflect carcinoma in chronically diseased intestinal segments. Medical management of patients with Crohn's colitis begins with dietary modification to eliminate foods that stimulate bowel activity (dairy products and highly seasoned food). Initially medical therapy consists of sulfasalazine, corticosteroids, and aminosalicylates orally or as retention enemas. In refractory cases, metronidazole and azathioprine or 6-mercaptopurine are added. Cyclosporine is an additional immunosuppressive for those patients with intractable disease. Patients with Crohn's colitis often require surgery for palliation of symptoms. Intractability to medical therapy is the most common indication for surgery. Other indications include inability to sustain clinical remission, or the management of complications such as fistula, abscesses, obstructions, and cancer. Proctocolectomy with Brooke ileostomy is the conventional treatment for Crohn's colitis with rectal involvement (Figure 24).

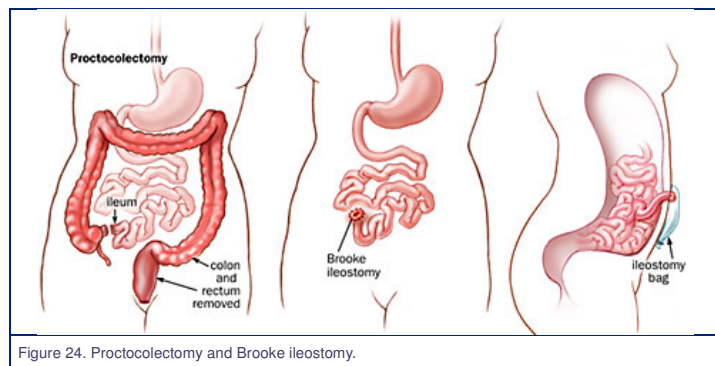
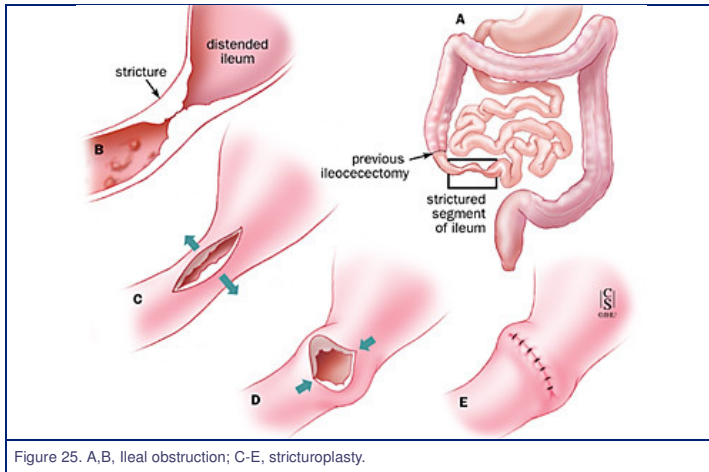


Figure 24. Proctocolectomy and Brooke ileostomy.

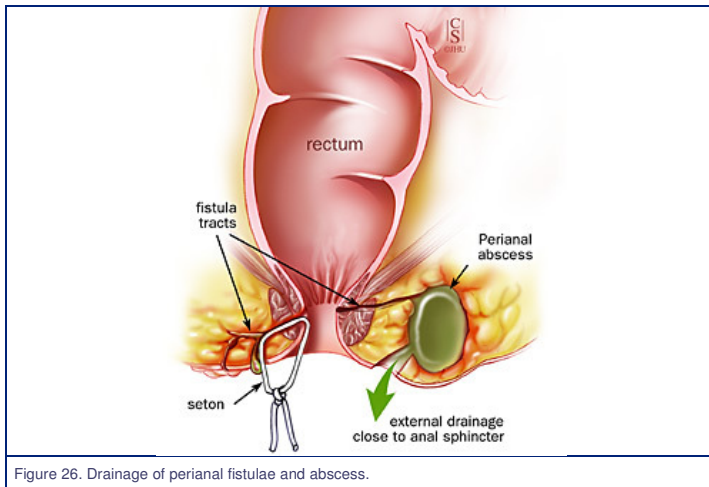
In cases of Crohn's colitis with rectal sparing, colectomy with ileorectal anastomosis is the procedure of choice (Figure 25).



Isolated segments of Crohn's colitis may be treated with segmental colectomy and anastomosis.

Perianal Disease

Anal fissures, as well as ulcers in the anal canal resulting in perirectal abscesses or fistulae, are a difficult complication of Crohn's disease. The fistulous openings are commonly in the perianal skin but may also appear in the groin, the vulva, or the scrotum. Single rectal ulcers may give rise to a fistulous tract with multiple openings.



Perianal abscesses present with pain exacerbated by defecation, sitting, or walking. Fever may be the sole presenting symptom or it may accompany redness and pain in the perianal region.

Perianal disease often requires proctoscopic examination under anesthesia. Barium enema and CT scans are also useful. Severe persistent perianal disease leading to repeated surgical procedures can result in anal sphincter destruction and fecal incontinence.

Therapy for perianal disease should be aimed at the relief of symptoms and the preservation of the anal sphincter. Fistulae that are not causing problems do not require therapy. Therapeutic decisions should be made according to the severity of the disease. Sitz baths for local cleansing should be included in the first therapeutic measures along with antibiotics. Drains or setons in the fistulous tracts promote continual drainage. Efforts should be made to minimize intestinal disease activity because successful management of the disease process reduces episodes of diarrhea passing through the perianal area. A trial of metronidazole or ciprofloxacin may be helpful, although discontinuation of the drug results in recurrence of perianal disease in many patients. Azathioprine or 6-mercaptopurine may be helpful in one third of patients. Remicade has led to healing of fistulae in 50% of patients and improvement in 60%. Long-term results are pending.

A number of surgical approaches may be performed if drainage and medical therapies are not successful. Surgical drainage with seton placement and placement of mushroom catheters, which may be left in place for prolonged periods during the healing process, have been successful. Alternative approaches include partial internal anal sphincterotomy to remove cryptoglandular epithelium as well as fecal diversion by colostomy. Rectal advancement flaps may also be used.

Neoplasia

Like ulcerative colitis, the risk of colonic neoplasia in patients with Crohn's disease is a recognized complication of the disease. The risk of colon cancer appears to be related to the severity and the duration of the disease, the age at disease onset, stricture formation and the presence of primary sclerosing cholangitis. Unlike ulcerative colitis, there are no standardized guidelines for surveillance in Crohn's disease patients. However, in those patients with Crohn's Disease for 8–10 years, colonoscopic surveillance should be undertaken at 2–3 year intervals and at 1–2 year intervals for patients with a disease history of over 20 years. Dysplasia is the precursor to cancer in these patients and therefore a total of 30 biopsies are recommended at 10-cm intervals throughout the colon. If there is a stricture, a pediatric

colonoscopy may allow examination of the bowel proximal to the stricture. Patients with indefinite dysplasia should receive aggressive therapy to control inflammation. Finding dysplasia on surveillance colonoscopy is sufficient to recommend surgical intervention (colectomy).

Prognosis

Patients with Crohn's disease today have an excellent prognosis for long-term survival and an acceptable quality of life. New drugs, nutritional therapies, advances in surgical techniques, improved postoperative care, and recognition of cancer risk have improved the outlook. In particular, stricturoplasties are used to prevent short-bowel syndrome, a severe malabsorption syndrome resulting from repeated long resections. Patients with short-bowel syndrome may require long-term home parenteral alimentation or even a small-bowel transplant. Mortality from Crohn's disease is now not much greater than in the general population and is generally related to septic complications from perforation or short-bowel syndrome. Suicide remains a problem, especially among young people with extensive disease, ostomies, or a need for long-term hyperalimentation. Although primary psychiatric illness is no more common in patients with inflammatory bowel disease than in the general population, patients are prone to reactive depression and have the potential to abuse pain medications. Physicians must be cognizant of these problems and patients should be treated appropriately.

Most patients managed with current standard medical and surgical approaches report a good quality of life, but many patients with severely compromised small intestine function are discontented. Patient support groups and educational materials, such as those supplied by the Crohn's and Colitis Foundation of America (www.cdfa.org), help improve overall patient management and satisfaction. Advanced Therapy of Inflammatory Bowel Disease, although written for physicians, has many chapters that were designed with patients in mind. Additionally, information gained from the Internet can be very helpful in patient education.