Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an idiopathic disease caused by a dysregulated immune response to host intestinal microflora.

Types of inflammatory bowel disease

The two major types of inflammatory bowel disease are:

Crohn disease	It can affect any segment of the gastrointestinal tract from the mouth to the anus, involves "skip lesions," and is transmural.
Ulcerative colitis	It affects the colon and rectum only.

Other types include:

Indeterminate colitis	It originally referred to those 10–15% of cases of inflammatory bowel disease (IBD) in which there was difficulty distinguishing between ulcerative colitis and Crohn disease in the colectomy specimen.
Microscopic colitis	It refers to two related medical conditions which cause diarrhea: ***collagenous colitis*** and ***lymphocytic colitis***. The main feature is watery diarrhea in the presence of a normal colonoscopy and chronic inflammation in the absence of crypt architectural distortion on mucosal biopsies. Drugs such as NSAIDs and proton pump inhibitors are implicated as the cause in up to 50% of cases of microscopic colitis.
Diversion colitis	It is when inflammation occurs in the defunctioned loop of a colostomy causing a mucous discharge.
Infectious colitides	*Pseudomembraneous colitis* is caused by *Clostridium difficile*, usually after prolonged or multiple antibiotics.
	Cytomegalovirus colitis is caused by *cytomegalovirus* (CMV).
Others: include ischemic colitis and medication-induced colitis.	

Pathophysiology:

Factors involved in cause of inflammatory bowel disease include infectious agents, genetics, the environment and the immune system.

- The ***microflora*** of the GI tract may provide an environmental trigger to activate inflammation and are highly implicated in the development of inflammatory bowel disease.
- Several ***genetic markers*** and loci have been identified that occur more frequently in patients with inflammatory bowel disease.
- The ***inflammatory response*** with inflammatory bowel disease may indicate abnormal regulation of the normal immune response or an autoimmune reaction to ***self-antigens***.
- ***Smoking*** appears to be protective for ulcerative colitis but associated with increased frequency of Crohn disease.
- The use of ***NSAIDs*** may trigger disease occurrence or lead to disease flares.

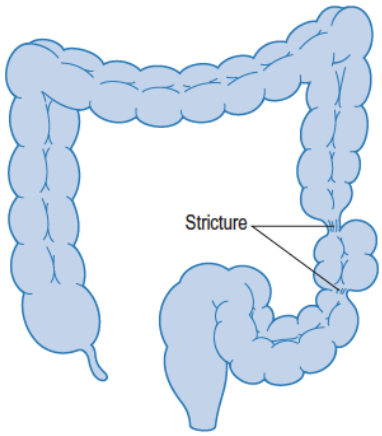
Diagnosis

IBD is frequently diagnosed in late-teen and young-adult patients. Due to the nonspecific gastrointestinal symptoms of Crohn disease and ulcerative colitis, several other diagnoses must be considered before establishing a diagnosis, particularly in the absence of typical endoscopic findings and in populations at higher risk for other diagnoses.

Imaging studies

The following imaging studies may be used to assess patients with IBD:

- Abdominal/pelvic computed tomography scanning/magnetic resonance imaging
- Chest and abdominal radiography
- Barium double-contrast enema radiographic studies
- Abdominal ultrasonography
- Computed tomography enterography
- Colonoscopy, with biopsies of tissue/lesions
- Flexible sigmoidoscopy
- Upper gastrointestinal endoscopy
- Enteroscopy (Capsule or double balloon)



Ulcerative colitis

In ulcerative colitis, the inflammation begins in the rectum and extends proximally in an uninterrupted fashion to the proximal colon and could eventually involve the entire length of the large intestine. The rectum is always involved in ulcerative colitis.

The disease remains confined to the rectum in approximately 25% of cases, and in the remainder of cases, ulcerative colitis spreads proximally and contiguously. Pancolitis occurs in 10% of patients. The distal terminal ileum may become inflamed in a superficial manner, referred to as distal ileitis. Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As ulcerative colitis becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead-pipe appearance.

Clinical Presentation

- There is a wide range of presentation in ulcerative colitis, ranging from mild abdominal cramping with frequent small-volume bowel movements to profuse diarrhea. Many patients have disease confined to the rectum (proctitis).
- Most patients with ulcerative colitis experience intermittent bouts of illness after varying intervals of no symptoms.

Severity	*Signs & symptoms*			
	Bowel motion		systemic disturbance	ESR
	Frequency	*Blood in stool*		
Mild UC	< 4 / day	with or without	no	normal
Moderate UC	> 4 / day	with or without	minimal	normal
Severe UC	> 6 / day	with blood	fever, tachycardia, anemia	> 30

Complications:

- Local complications occur in the majority of patients with ulcerative colitis. Relatively minor complications include hemorrhoids, anal fissures, and perirectal abscesses.
- A major complication is toxic megacolon, a severe condition that occurs in up to 7.9% of ulcerative colitis patients admitted to hospitals. The patient with toxic megacolon usually has a high fever, tachycardia, distended abdomen, elevated white blood cell count, and a dilated colon.
- The risk of colonic carcinoma is much greater in patients with ulcerative colitis as compared with the general population.

- Approximately 11% of patients with ulcerative colitis have hepatobiliary complications, including fatty liver, pericholangitis, chronic active hepatitis, cirrhosis, sclerosing cholangitis, cholangiocarcinoma and gallstones.
- Arthritis commonly is typically asymptomatic and migratory. Arthritis typically involves one or a few large joints, such as the knees, hips, ankles, wrists and elbows.
- Ocular complications occur in 2% to 29% of patients.
- Skin and mucosal lesions include erythema nodosum, pyoderma gangrenosum, aphthous ulceration and Sweet syndrome (acute febrile neutrophilic dermatosis).

Treatment of ulcerative colitis

The expected outcomes of treatment are resolution of acute inflammatory processes, resolution of attendant complications, alleviation of systemic manifestations, maintenance of remission from acute inflammation, or surgical palliation or cure.

Induction therapy:

Aminosalicylates	*mesalamine (mesalazine), sulfasalazine, olsalazine, balsalazide*
	Most patients with mild to moderate active ulcerative colitis can be managed on an outpatient basis with oral (tablet) and/or topical (enema or suppository) of an aminosalicylate.
Steroids ○ *Oral* ○ *I.V.* ○ *Rectal*	Steroids have a place in the treatment of moderate to severe ulcerative colitis or in those who are unresponsive to maximal doses of oral and topical aminosalicylate.
	Oral *prednisone* 40 to 60 mg daily is recommended for adult. Budesonide is available in oral and rectal dosage forms.
	Patients with uncontrolled severe colitis or incapacitating symptoms require hospitalization for effective management. • IV *hydrocortisone* 100 mg t.i.d. • IV *methylprednisolone* 60 mg q.d.
Immune-suppressive agents	*cyclosporine, 6-mercaptopurine, azathioprine, or tacrolimus*
	They are used for patients are unresponsive to parenteral corticosteroids after 3 to 7 days
anti-TNF agents	*infliximab, adalimumab, golimumab, certolizumab pegol*
	They viable option for patients with moderate to severe active ulcerative colitis who are unresponsive to steroids or other immunosuppressive agents.

Maintenance therapy

Once ***remission*** from active disease has been achieved, the goal of therapy is to maintain the remission.

Aminosalicylates		All oral agents are effective options.
Steroids		They have no role. They are ineffective.
		They are continued for up to 8 weeks for remission induction then should be gradually withdrawn after remission is induced.
Thiopurines		azathioprine or 6-mercaptopurine (6-MP)
		They are alternatives with proven effectiveness for maintenance of remission, particularly for those who are steroid dependent or unable to maintain remission with 5-ASA preparations.
Anti-TNF agents		*infliximab, adalimumab, golimumab, certolizumab pegol*
		They are effective for induction of remission in steroid-refractory or steroid-dependent moderate to severe ulcerative colitis.
New agents	Vedolizumab	It is an integrin inhibitors are emerging as options for moderate-to-severe active IBD in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.
	Tofacitinib	It is a JAK inhibitor indicated for adults with moderately to severely active ulcerative colitis. An induction dose for at least 8 weeks is administered orally, followed by a maintenance dose, depending on the patient's therapeutic response.
	Ustekinumab	inhibits IL-12 and IL-23. It is indicated for adults with moderately to severely active ulcerative colitis.

Crohn Disease

- Crohn disease is a transmural inflammatory process. The terminal ileum is the most common site of the disorder, but it may occur in any part of the GI tract. Most patients have some colonic involvement.
- Complications of Crohn disease may involve the intestinal tract or organs unrelated to it. Small bowel stricture with subsequent obstruction is a complication that may require surgery. Fistula formation is common and occurs much more frequently than with ulcerative colitis.
- Systemic complications of Crohn disease are common and similar to those found with ulcerative colitis.
- Nutritional deficiencies are common with Crohn disease (weight loss, iron deficiency anemia, vitamin B12 deficiency, folate deficiency, hypoalbuminemia, hypokalemia and osteomalacia).

Clinical Presentation

- The presentation of Crohn disease is highly variable. A patient may present with diarrhea and abdominal pain or a perirectal or perianal lesion.
- The course of Crohn disease is characterized by periods of remission and exacerbation. Some patients may be free of symptoms for years, whereas others experience chronic problems despite medical therapy.
- Signs and symptoms include malaise, fever, abdominal pain, frequent bowel movements, hematochezia (bloody stool), fistula, arthritis, weight loss and malnutrition.
- Oral involvement may present with aphthous ulcers or pain in the mouth and gums.
- Esophageal involvement may present with odynophagia or dysphagia.
- Gastroduodenal involvement is seen in up to 15% of patients and may present with upper abdominal pain, nausea, and/or postprandial vomiting.
- Under physical examination, signs of abdominal mass and tenderness may appear in addition to possible perianal fissure or fistula.
- Laboratory tests show increased white blood cell count and erythrocyte sedimentation rate (ESR). Anti–*Saccharomyces cerevisiae* antibodies test is positive.
- Extraintestinal manifestations of Crohn disease are generally related to inflammatory disease activity. (see: *Complications of Crohn disease*)

Complications of Crohn disease

Most complications of Crohn disease are similar to the complications of ulcerative colitis.

Bone and joints	Primarily involving large joints in approximately 20% of patients without synovial destruction, arthritis is the most common extraintestinal manifestation.
	Metabolic bone disease may occur as a result of glucocorticoid use and impaired vitamin D and calcium absorption.
Eye	Eye manifestations occur in approximately 5% of patients and include uveitis, iritis, and episcleritis.
Skin	Dermatologic manifestations occur in approximately 10% of patients and include erythema nodosum and pyoderma gangrenosum.
Lung	Pulmonary manifestations of IBD include bronchiectasis, chronic bronchitis, interstitial lung disease, bronchiolitis obliterans with organizing pneumonia, sarcoidosis, necrobiotic lung nodules, and pulmonary infiltrates with eosinophilia syndrome.
Liver and Gallbladder	Primary sclerosing cholangitis typically occurs in approximately 5% of patients.
	Other hepatobiliary disorders are often related to IBD medications rather than the disease itself.
Metabolic	Secondary amyloidosis is very rare but may lead to renal failure and other organ system involvement.
Kidney	Calcium oxalate and uric acid kidney stones can result from steatorrhea and diarrhea. Uric acid stones can result from dehydration and metabolic acidosis.

Treatment of Crohn disease

Induction therapy

- First-line options for induction therapy include a biologic agent with or without an immunomodulator (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate). For example, for patients who are naïve to biologics, anti-TNF agents are typically given as combination therapy with an immunomodulator to prevent immunogenicity.
- For most patients with fistulizing moderate to severe Crohn disease (e.g., perianal or intestinal fistula), a combination therapy consisting of a TNF inhibitor and an immunomodulator.

TNF inhibitors	infliximab, adalimumab and certolizumab pegol
	They are used for moderate to severe active Crohn disease in patients failing immunosuppressive therapy, in those who are corticosteroid dependent, and for treatment of fistulizing disease.
Oral corticosteroids	**Prednisone** 40 - 60 mg/day, are generally considered first-line therapies and are frequently used for the treatment of moderate to severe Crohn disease.
	Budesonide is a viable first-line option for patients with mild to moderate ileal or right-sided (ascending colonic) disease.
	Once remission is achieved, the agent is slowly tapered.
	For relapse after steroid withdrawal, other treatment options are required.
Methotrexate	Weekly injection of 25 mg has demonstrated efficacy for induction of remission in Crohn disease.
Integrin inhibitors	Natalizumab and vedolizumab
	• They used for moderate-to-severe active IBD in patients who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. • They are generally given as monotherapy. • Vedolizumab may be given with an immunomodulator.
Ustekinumab	It is used for adults with moderately to severely active Crohn disease who have failed or were intolerant to standard therapy (immunomodulators or corticosteroids), but naïve to biologics (never failed treatment with anti-TNF agents), or failed or were intolerant to treatment with 1 or more anti-TNF agents. It is generally given as monotherapy.
Thiopurines	azathioprine or 6-mercaptopurine (6-MP)
	They are ***not recommended*** to induce remission in moderate to severe Crohn disease. They are generally limited to use for patients not achieving adequate response to standard medical therapy or in the setting of steroid dependency.
Cyclosporine	It is ***not recommended*** for Crohn disease except for patients with symptomatic and severe perianal or cutaneous fistulas.
Aminosalicylates	They are not significantly effective in Crohn disease.

Maintenance therapy

For patients who achieve remission following induction therapy, long-term treatment with a biologic agent and immunomodulator is continued for one to two years. many high-risk patients with moderate to severe Crohn disease will require life-long therapy with at least one agent.

TNF inhibitors	infliximab, adalimumab and certolizumab pegol
	They are indicated for maintaining clinical response in patients with moderate to severe active disease who had an inadequate response to conventional therapy.
Integrin inhibitors	Natalizumab and vedolizumab
	They are used every 8 weeks as maintenance therapy.
Ustekinumab	It is used as subcutaneous injection 8 weeks after the initial IV infusion, then every 8 weeks thereafter.
Thiopurines	azathioprine or 6-mercaptopurine (6-MP)
	They are effective in maintaining steroid-induced remission.
	Maintenance therapy with thiopurine monotherapy is an alternative for patients who have achieved clinical remission with glucocorticoids or for patients who are no longer responding to biologic agents.
Methotrexate	It is an alternative for maintenance therapy for the patient who does not tolerate thiopurines, and may be preferable to azathioprine or 6-MP in patients with Crohn disease-related arthropathy.
Steroids	They are not indicated for maintenance, because of serious complications.

Other treatments for ulcerative colitis and Crohn disease:

Antidiarrheals	• Chronic diarrhea in Crohn disease and ulcerative colitis responds well to antidiarrheal agents such as ***loperamide*** and ***diphenoxylate/atropine***. • Such agents may be administered up to 4 times daily. • They prolong GI transit time and decrease secretion. • They should not be given to patients with active colitis, because of the risk of developing toxic megacolon.
Ulcer healing drugs	H_2-receptor antagonist or a proton pump inhibitor (PPI)
	They reduce gastric acid secretion.
Antispasmodics	• They may reduce abdominal cramps. • These drugs should not be used if there is the possibility of a bowel obstruction.
Bile acid sequestrants	cholestyramine, colestipol, and colesevelam
	Their use may be beneficial as patients with terminal ileal disease may not absorb bile acids normally, which can lead to secretory diarrhea in the colon.
Aspirin NSAIDs Corticosteroids	Arthritis is a systemic complication. It can be managed by aspirin or another NSAID as well as a corticosteroid. However, NSAIDs may exacerbate IBD and predispose patients to GI bleeding.
Oral iron Vitamin B_{12} Folic acid	Anemia can be treated with oral iron. Vitamin B_{12} or folic acid may be required.
Antibiotics	• Antibiotics are less effective in persons with ulcerative colitis, except in fulminant toxic megacolon or pouchitis. • They are usually administered on an empiric basis in patients with severe colitis in whom they may help by averting a life-threatening infection. They have been shown to be effective for the treatment of pouchitis after an ileal pouch-anal anastomosis (IPAA) procedure. • Metronidazole and ciprofloxacin are the most commonly used antibiotics in persons with IBD. • Rifaximin is a broad-spectrum antibiotic that may also help treat patients with IBD.
Heparins	• Patients with IBD are at increased risk of VTE and PE. • Prophylaxis with LMWH is recommended in all hospitalized patients with IBD.

Surgery

Urgent surgery is indicated in patients with ulcerative colitis in the following cases:

1. Toxic megacolon refractory to medical management
2. Fulminant attack refractory to medical management
3. Uncontrolled colonic bleeding.

Elective surgery in ulcerative colitis is indicated in:

1. long-term steroid dependence
2. dysplasia or adenocarcinoma found on screening biopsy
3. the presence of disease for 7-10 years.

Unlike ulcerative colitis, Crohn disease has no surgical cure. Most patients with Crohn disease require surgical intervention during their lifetime. Within 15 years of diagnosis, 70% of patients with Crohn disease have required 1 or more surgical procedures, and many require multiple procedures.

The most common complication of surgical treatment of Crohn disease is the development of intraperitoneal adhesions. Patients with Crohn disease undergoing abdominal surgery are also at increased risk for the development of enterocutaneous fistulae as a result of their surgery. Those who are being treated with steroids or immunosuppressive agents may be at increased risk of wound or intra-abdominal infections.

Toxic megacolon

Toxic megacolon is the clinical term for an acute toxic colitis with dilatation of the colon. The dilatation can be either total or segmental. A more contemporary term for toxic megacolon is simply toxic colitis, because patients may develop toxicity without megacolon.

It is usually a complication of inflammatory bowel disease, such as ulcerative colitis and, more rarely, Crohn's disease, and of some infections of the colon, including *Clostridium difficile* infections, which have led to pseudomembranous colitis. Other forms of megacolon exist and can be congenital (present since birth, such as Hirschsprung's disease). Also, it can be caused by *Entamoeba histolytica* and *Shigella*.

Toxic megacolon may complicate any number of colitides, including inflammatory, ischemic, infectious, radiation, and pseudomembranous.

Treatment of toxic megacolon includes 3 main goals:

1. reduce colonic distention to prevent perforation
2. correct fluid and electrolyte disturbances, and
3. treat toxemia and precipitating factors.

The patient should be started on IV steroids. IV hydrocortisone is necessary for patients who are taking corticosteroids or who have been recently treated with corticosteroids.

Some reports indicate that cyclosporine may be beneficial in the treatment toxic megacolon.

Early surgical consultation is essential for cases of toxic megacolon. Colectomy is recommended if persistent dilatation is present or if no improvement is observed on maximal medical therapy after 24-72 hours.

In a case report, infliximab was successful in the treatment of toxic megacolon in a patient whose condition failed to respond to usual treatment and who refused surgery.