

# Pathophysiology of Inflammatory Bowel Disease: An Overview

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Inflammatory bowel disease, Crohn's disease, and ulcerative colitis are considered idiopathic diseases affecting the gastrointestinal tract. These two diseases are often considered together because of multiple similarities, including gastrointestinal inflammation, waxing and waning severity and symptoms, and unknown etiology. However, they have separate symptoms and microscopic characteristics as well as patterns within the gastrointestinal tract (Table 1).

The incidence of inflammatory bowel disease varies according to geographic location. Higher rates are typically found in the more developed countries of Scandinavia, northern Europe, and North America, with lower rates in Asia, Africa, and South America. However the incidence is increasing in the less-developed countries as they become more industrialized, implicating environment, diet, and cultural practices as potential risk factors. Other epidemiologic studies have shown that inflammatory bowel disease typically affects young people; however, there is a bimodal incidence with a large peak in the second or third decade of life followed by a smaller peak later in life. The bimodal distribution is seen more consistently with ulcerative colitis than with Crohn's disease [1].

## Etiology

Numerous environmental factors have been studied that influence inflammatory bowel disease, including smoke exposure, diet, oral contraceptives, and nonsteroidal anti-inflammatory agents. There also may be microbial

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Table 1  
Key features of ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Area affected	Colon only	Mouth to anus
Distribution	Continuous	Skip lesions
Histologic features	Mucosa/submucosa, crypt abscesses; superficial ulcers	Transmural granulomas, aphthoid ulcers
Macroscopic features	Mucosal friability, pseudopolyps, loss of haustra (chronic)	Cobblestoning, fistulas fissures
Typical symptoms	Rectal bleeding Diarrhea—often bloody, abdominal pain, weight loss	Abdominal pain, diarrhea, fever, weight loss, fistulas

influences along with immunologic dysregulation. In addition, there is evidence that genetic factors also play a role. Finally, the combination and interaction of genetics, environmental influences, and immunologic abnormalities may play the most important role.

### *Genetics*

Studies comparing the prevalence of inflammatory bowel disease among different ethnic groups suggest genetic tendencies. Inflammatory bowel disease is seen two to four times greater in the Jewish population as compared with other ethnic groups. Ashkenazi Jews have the greatest risk within the Jewish population. Other epidemiologic studies have shown higher rates in whites, lower rates in African Americans, and the lowest rates in Asians [2].

The prevalence of inflammatory bowel disease is also increased in relatives of those who have Crohn's disease and ulcerative colitis. A Danish study found that the risk increases 2 to 13 times for offspring of patients who have inflammatory bowel disease as compared with the general population. For patients who have ulcerative colitis, the occurrence of inflammatory bowel disease in their offspring was 6.26%; for patients who have Crohn's disease, the occurrence was 9.2% [3]. The increased familial risk is similar to other diseases including type 1 and type 2 diabetes, schizophrenia, and celiac disease; the genetic risk ratio is higher for Crohn's disease than ulcerative colitis [4].

Twin studies are another way to determine a genetic contribution for a disease. If a disease were entirely due to genetics, the concordance rates in monozygotic/identical twins would be higher (and should be approaching 100%) than dizygotic/nonidentical twins (which should be approaching 50%). If the disease was dependent only on extrinsic or acquired factors, the concordance rates would be similar among both types of twins. For Crohn's disease, studies have found concordance rates of 20% to 50% in monozygotic twins and less than 10% in dizygotic twins, emphasizing a definite genetic component. With ulcerative colitis, this genetic component was

found to be weaker but still present with concordance rates of 16% in monozygotic twins and 4% in dizygotic twins [4].

Numerous studies have demonstrated that genetics do play a role in the manifestation of inflammatory bowel disease. However, classic Mendelian inheritance patterns are not seen. Thus inflammatory bowel disease cannot be credited to a single gene locus. Numerous areas of possible linkage have been identified. Some of the main areas of linkage being studied are chromosomes 16 (IBD1), 12 (IBD2), 6 (IBD3—the HLA region), and 14 [2]. The IBD1 locus on chromosome 16 contributes to susceptibility to Crohn's disease only [5]. Further studies have shown associations with mutations in a gene located in this area of linkage, which encodes for a protein, NOD2 (also known as CARD 15—capsase activating recruitment domain). This protein activates NF- $\kappa$ B and also responds to bacterial lipopolysaccharides. When mutated and in the presence of bacterial lipopolysaccharides, NOD2 no longer activates NF- $\kappa$ B, and the response to bacterial lipopolysaccharides is greatly reduced [6]. These studies not only show the genetic association but also a possible disease mechanism. Another region studied extensively is IBD3 on chromosome 6. This is an area that includes the HLA complex and has been linked with Crohn's disease and ulcerative colitis. This region has several genes involved in the host inflammatory response [7]. Another area linked specifically to Crohn's disease is on chromosome 5q (IBD5). This area contains the cytokine gene cluster [8]. Studies continue to look for further areas of linkage as well as identifying significant genes in the disease process.

### *Environmental influences*

Smoking is one environmental factor that has been shown to have an effect on inflammatory bowel disease. Cigarette smoking has different effects with Crohn's disease than ulcerative colitis. For ulcerative colitis, the risk for current smokers is less than for those who have never smoked. The risk decreases further with an increasing number of cigarettes smoked [9]. Upon smoking cessation, however, the risk increases to higher than that of nonsmokers. An opposite effect is seen with Crohn's disease. Smoking doubles the risk of Crohn's disease. No dose-dependent response is seen, and ex-smokers continue to carry a slightly lower but increased risk [10].

Another relationship is seen with appendectomies. There have been reports of a low rate of appendectomy among patients who have ulcerative colitis. A Swedish study found that there was an inverse relationship between ulcerative colitis and appendectomy when the appendectomy was done for inflammatory conditions. This relationship did not hold true when appendectomies were performed for nonspecific abdominal pain. This was also only true for patients who underwent appendectomies before 20 years of age [11]. Because of this observation, there have been proposals that

appendectomy has immune-modulating effects and protects against ulcerative colitis. A possible explanation for this finding is that the appendix is largely lymphoid, and removing it may alter the balance of regulatory and effector T cells.

### *Infectious possibilities*

It has been proposed that another contribution to inflammatory bowel disease is one of infectious origin. Many different bacteria have been suspected of being involved in the pathogenesis of inflammatory bowel disease. The inflammation seen with the disease may be a result of a dysfunctional but appropriate response to an infectious source. Numerous bacteria have been proposed as being causes, but most of these have not been fully supported in studies. In Crohn's disease, *Mycobacterium paratuberculosis*, *Pseudomonas* species, and *Listeria* species have all been suggested as probable causes; however, convincing evidence is lacking. In ulcerative colitis, other bacteria have been implicated. These include *Bacillus* species, adhesive *E. coli*, and *Fusobacterium varium*. Again there is not enough compelling evidence for any of these species [12]. Further organisms are continuing to be studied in regard to contributing to the pathogenesis of the two diseases.

### *Immunologic factors*

In Crohn's disease and ulcerative colitis, there are chronic inflammatory changes in the gastrointestinal tract. These are mediated by different immunologic factors for each disease, although they are both a consequence of T-cell activation. Crohn's disease inflammation is thought to be triggered by Th1 cells, which organize cell-mediated immune response. The cytokine IL-12 is increased in the mucosa in Crohn's disease. This leads to increased Th1 response as well as increase IFN- $\gamma$ . IFN- $\gamma$ , in turn, further up-regulates macrophages leading of a cycle of uncontrolled inflammation [13]. Loss of regulation of these excessive activated Th1 cells and macrophages also leads to activation of matrix metalloproteinases, by way of IFN- $\gamma$  and TNF- $\alpha$ , which cause tissue damage [14]. Another explanation for this unregulated inflammation is that the T cells in Crohn's disease are resistant to normal apoptosis, leading to further development of the inflammatory cycle [15]. The cytokine expression is different comparing ulcerative colitis and Crohn's disease. In ulcerative colitis, the inflammation is thought to be regulated by Th2-cells, which mediate B cells and antibody responses; however this has not been proven. It has been shown that there is increased expression of IL-5, which is a Th2 cytokine, but IL-4, another Th2 cytokine, is not increased [16]. The Th2 contribution may be helping the antibody response, because in ulcerative colitis, there is an increase in IgG plasma cells presumably mediated by T cells [17].

## Clinical features of Crohn's disease

The hallmark of Crohn's disease is one of chronic inflammation of the gastrointestinal tract without evidence of infection. It is generally a chronic condition with a relapsing nature. There are often periods of remission, but it may also manifest as chronic continuous symptoms. Unlike ulcerative colitis, Crohn's disease can occur anywhere along the gastrointestinal tract from the mouth to the anus. However, there are three main sites of involvement: the small intestine alone, the colon alone, or combined small and large intestine involvement. The terminal ileum is the most commonly affected area and is involved in two thirds of the patients. Numerous studies have been done regarding the clinical patterns. Overall, the combined small and large intestine pattern is seen in 26% to 48%. The small intestine only pattern is seen in 11% to 48%, and the colon only involvement is seen in 19% to 51% [18]. Further breaking down the patterns, one study found that involvement of the terminal ileum and colon together was the most common pattern, occurring in 55% of patients. Other areas of the small intestine excluding the terminal ileum were involved in only 3% of the cases studied [19]. The duodenum, esophagus, stomach, and mouth may also be involved. However, these are uncommon and rarely occur without concurrent disease activity in the small bowel and/or colon. The different patterns of disease can then lead to different patterns of clinical manifestations as described below.

### *Clinical symptoms by location*

The clinical symptoms of Crohn's disease can vary significantly depending on the disease location. The predominant symptoms in Crohn's disease are typically abdominal pain and diarrhea. These are present in more than 70% of all patients at diagnosis [18]. Other common symptoms include fever and weight loss. Other symptoms that may depend on location of disease are bloody stools, strictures, and fistula to skin or adjacent organs.

Esophageal involvement is rare and has been reported in 0.2% of patients who have Crohn's disease. It is almost always seen with disease elsewhere in the gastrointestinal tract. Esophageal involvement includes aphthous ulcers or deeper ulcerations, stenosis, or pseudopolyps. These patients generally have esophageal symptoms, including dysphagia, odynophagia, heartburn, or chest pain [20].

Gastroduodenal involvement is slightly more common than esophageal involvement but is still rare. It has been reported in 0.5% to 4% of patients who have Crohn's disease. The large majority of patients have coexisting distal disease, and the duodenal disease generally has a more benign course than distal disease [21]. The most common site is the duodenal bulb, which is usually associated with disease proximally in the antrum or distally in the latter parts of the duodenum [22]. Common symptoms include upper abdominal pain, weight loss, nausea and vomiting, and occasionally

hematemesis. The abdominal pain is usually epigastric and can mimic peptic ulcer disease symptoms. Stricture is the main pathologic finding, which can subsequently lead to obstruction. Fistulas are fairly rare and, when seen within the duodenum, usually originate from distal disease. Histologically, acute and chronic inflammation is usually seen. Granulomatous inflammation is also often seen [21]. Other common features are edema, aphthous ulcerations, and irregular mucosal thickening [21,22].

Similar clinical patterns are seen in the three main patterns of disease: small intestine alone, the colon alone, or combined small and large intestine involvement. However there may be significant differences in the clinical symptoms [23]. Patients who had colonic disease had more rectal bleeding: 46% compared with 22% for ileocolic and 10% for small intestine alone. Another difference noted was in rectal fistula. Also, those who had ileocolic and colonic alone disease had more rectal fistula: 21% and 19% compared with only 5% in those who had small intestine only involvement. Other common symptoms with no statistical difference between the three main patterns of disease include diarrhea, abdominal pain, and malnutrition.

This same study also found differences in complications between the three main patterns of disease [23]. Internal fistulas occurred more in those who had ileocolic disease (34%) as compared with small intestine alone (17%) and colon alone (16%). Perianal fistulas were also seen more commonly in the ileocolic pattern (38%) as well as the colonic pattern (36%) compared with only 14% in those who had a small intestine pattern. Intestinal obstruction was found in 44% of those who had ileocolic disease and 35% in those who had with small intestine pattern, but only 17% in those who had colon only disease. Another more rare complication was megacolon, which was seen mostly in those who had only colonic disease. The extraintestinal manifestation of arthritis was also seen more in those who had colonic disease.

Weight loss in patients who have Crohn's may have multiple causes. Partial obstruction can lead to food avoidance due to pain, which contributes to the weight loss. Occasionally there may be persistent pain, and this is due to acute inflammation or abscesses rather than partial obstruction. Another mechanism of weight loss is malabsorption and malnutrition if the small bowel is extensively involved. Other complications of small bowel disease are fistulas that often involve the vagina, skin, or bladder.

Crohn's colitis can manifest as rectal bleeding with other common symptoms of abdominal pain along with diarrhea. Also, strictures may occur, leading to obstruction and distention. Toxic megacolon may also occur; however, this is more commonly seen in ulcerative colitis.

Perianal involvement occurs with inflammation and fistulization within anal crypt glands. Skin tags, fissures, and perianal scarring occur. Symptoms include pain, purulent drainage, and difficulties with defecation.

Extraintestinal manifestations may also occur involving the dermatologic system, ocular system, joints, or the hepatobiliary system. Dermatologically,

patients can have erythema nodosum and pyoderma gangrenosum. Eye involvement can include uveitis and episcleritis. Ankylosing spondylitis, sacral ileitis, and peripheral polyarthropathy are possible joint manifestations. In the hepatobiliary system, primary sclerosing cholangitis can occur, but this is more often seen with ulcerative colitis. Most of these symptoms correlate with bowel disease activity except for primary sclerosing cholangitis and ankylosing spondylitis.

### *Histologic features*

Crohn's disease is characterized microscopically by transmural inflammation anywhere along the gastrointestinal tract. Lymphoid aggregates spread across all layers of the bowel wall but primarily in mucosa and submucosa, which is practically diagnostic for Crohn's disease. Mucosal inflammation is seen with neutrophils infiltrating into the epithelial layer, which overlay these mucosal lymphoid aggregates. Progression leads to neutrophils infiltrating into crypts, forming crypt abscess, and finally destructing the crypt. The crypt destruction leads to atrophy of the colon. Chronic damage may also been seen in the form of villus blunting in the small intestine. Ulcerations are common and are often seen on a background of normal mucosa. Noncaseating granulomas are also characteristic. These are sarcoid-like granulomas, which may be found within areas of active disease or areas of uninvolved bowel.

### *Gross features*

A main feature of Crohn's disease is aphthous ulcers. These are small areas of mucosal ulceration that develop over lymphoid aggregates and are seen as red spots or mucosal depressions. They may enlarge and become stellate. These may also combine and become longitudinal ulcerations usually along the mesenteric side of the bowel wall. They may then further develop into a network of long ulcerations surrounding spared edematous mucosa leading to cobblestone appearance. These ulcerations may also perforate the submucosa and make channels through the bowel wall, leading to fistulas, sinuses, or abscesses. Acute inflammation of the bowel wall is seen as boggy and edematous. Chronic inflammation results in a thickened and leathery appearance due to fibrotic scarring. The bowel lumen may be narrowed due to the edema and inflammation. Because of its transmural nature, strictures may also form due to fibrosis within the bowel wall. Fistulas may also form to adjacent organs or skin. The inflammation extending through the bowel wall may also involve the mesentery and surrounding lymph nodes. Creeping fat may be seen when the mesentery wraps around the bowel surface. There may also be a sharp demarcation between the involved areas and uninvolved areas leading to skip lesions.

## Clinical features of ulcerative colitis

Ulcerative colitis is characterized as noninfectious inflammation of the gastrointestinal tract, limited to the rectum and colon. It is a relapsing and remitting disorder with disease-free intervals alternating with periods of symptomatic inflammation. Although usually grouped together with Crohn's disease, there are many differences between the two. In ulcerative colitis, the inflammation is limited to the mucosa and submucosa, rather than the transmural inflammation seen in Crohn's disease. Unlike Crohn's disease, ulcerative colitis is a continuous disease with no skip lesions between areas of disease. The rectum is almost always involved, and the disease may continue proximally from there. Although the small intestine may be involved in cases of "backwash ileitis," ulcerative colitis is confined to the colon. Four major categories of colonic involvement have been defined. *Proctitis* is rectum-only involvement. *Proctosigmoiditis* includes the rectal involvement with extension into the sigmoid region. *Left-sided colitis* refers to disease extending from rectum continuously to the splenic flexure. *Pancolitis* is inflammation past the splenic flexure, potentially extending to the cecum [24]. In adults, 55% present with proctitis, 30% with left-sided colitis, and 15% with pancolitis [25].

### *Clinical features*

Patients may have differing symptoms based on the extent of their disease. In general, there is a relapsing pattern whereby symptoms may persist for days, weeks, or months and then subside with asymptomatic periods lasting for months, years, or even decades. Typical symptoms include rectal bleeding or bloody diarrhea, abdominal pain, fever, weight loss, and malaise. Proctitis symptoms include bloody stools, tenesmus, and/or painful straining. Urgency and frequency may also be present as well as incontinence of stool. Those who have disease extending more proximal generally have similar symptoms but may also have lower abdominal pain and, in more severe cases, nausea, vomiting, and weight loss. Other signs of chronic disease include malnutrition, weight loss, and anemia.

Extraintestinal manifestations may also be seen with ulcerative colitis, similar to Crohn's disease. These include ocular lesions like iritis and uveitis. Dermatologic symptoms include pyoderma gangrenosum and erythema nodosum. Typically pyoderma gangrenosum is more often associated with ulcerative colitis than Crohn's disease and erythema nodosum more with Crohn's disease. However this is not evident in all studies [26]. Joint symptoms may also be seen ranging from peripheral arthralgias and arthritis to ankylosing spondylitis. Primary sclerosing cholangitis is another major extraintestinal manifestation that is more commonly seen in ulcerative colitis.

Toxic megacolon is a severe life-threatening complication of ulcerative colitis. It occurs more often in ulcerative colitis than Crohn's disease and

is mostly seen in patients who have proctitis. It is often seen within the first few months of diagnosis. It is characterized by nonobstructive colonic dilatation with systemic toxicity. Symptoms include abdominal distension, abdominal tenderness, fever, increased white blood cell count, anemia, hypotension, or altered level of consciousness [27]. Inflammation is seen throughout the bowel wall with necrosis and degeneration of the myocytes. When the disease progresses, the bowel wall may become so thin due to distension and necrosis that it perforates.

The development of colorectal cancer is seen more in ulcerative colitis than Crohn's disease. Ulcerative colitis increases the risk of colorectal cancer compared with the noninflammatory bowel disease population. The risk of cancer increases with an increase in the extent of the disease. One Swedish population study found that the relative risk was increased for pancolitis (14.8) as compared with left-sided colitis (2.8). Those who had proctitis alone did not have a significant increased risk of cancer. A younger age at diagnosis of ulcerative colitis also seems to increase the risk of cancer [28].

### *Histologic features*

In ulcerative colitis, the inflammation is limited to the mucosa and submucosa. In active disease, neutrophils can be found infiltrating the crypts, forming crypt abscesses. Superficial erosions or ulcerations occur and can penetrate deeper into the submucosa in more severe disease. Active disease also results in decreased goblet cell mucin, whereas crypts become more indistinct, shorter, and decreased in number. The destroyed crypts of the active diseased state regenerate with Paneth's cells, which normally are not seen past the hepatic flexure.

### *Gross features*

On gross examination, the main feature noted in ulcerative colitis is that of continuity. The inflammatory changes extend continuously from the rectum. There are no skip lesions as in Crohn's disease. In active disease, the mucosa is generally erythematous and friable. Superficial ulcers are often observed and pseudopolyps are characteristic of severe disease. These are areas of normal but edematous mucosa bulging around the diseased inflamed mucosa. Chronic changes may also be seen. Loss of haustra and mucosal folds are evidence of chronic inactive disease. With repeated outbreaks of active disease, there may be layering of the muscularis mucosa. This leads to hypertrophy of the muscularis mucosa with fibrosis and a decrease in the diameter of the colon, which may eventually lead to stricture. In patients who have pancolitis, backwash ileitis may also be seen consisting of inflammatory changes seen in the terminal ileum in conjunction with inflammation extending to the cecum.

## Summary

Ulcerative colitis and Crohn's disease are two distinct diseases with similar characteristics and symptoms. As of now, they are linked together under the heading of inflammatory bowel disease. **Table 1** details the major pathologic differences between the two disease entities.

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