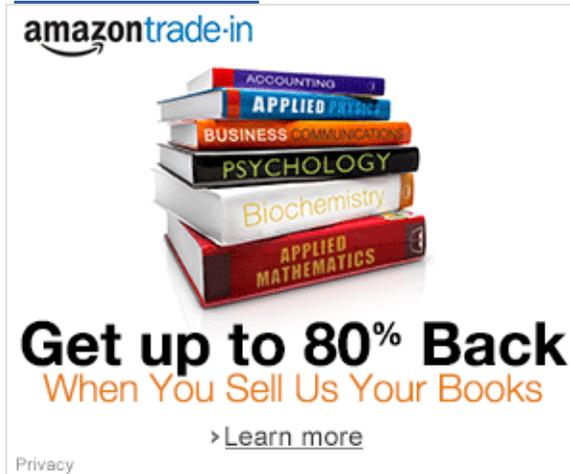


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Center for Continuing Education

Ulcerative Colitis

[Bret A. Lashner](#)

Definition

Ulcerative colitis, one of the inflammatory bowel diseases, is characterized by recurring episodes of inflammation of the mucosal layer of the large bowel not related to an intestinal infection or the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The inflammation always involves the rectum and can extend proximally in a continuous fashion. *Ulcerative proctosigmoiditis* refers to inflammation extending into the sigmoid colon. *Left-sided colitis* refers to inflammation extending up to, but not beyond, the splenic flexure. *Pancolitis* refers to disease that extends proximally to the splenic flexure. Approximately 50% of patients present with proctosigmoiditis, 30% with left-sided colitis, and 20% with pancolitis. Interestingly, about 50% progress to more extensive disease over the first 5 years of disease.¹ The inflammation is characterized by superficial ulcerations, granularity, and a distorted vascular pattern ([Figure 1](#)). Histologic features include an expansion of the lamina propria with inflammatory cells and crypt abscesses ([Figure 2](#)). There are usually no fistulae or granulomas, the usual histologic features of Crohn disease.

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Epidemiology

The annual incidence of ulcerative colitis is between 1 and 10 cases per 100,000 people, depending on the region studied. The peak age-specific incidence occurs near 20 years, and a second smaller peak occurs near age 50 years. The prevalence of ulcerative colitis ranges from 10 to 70 per 100,000 people, but some North American studies have shown prevalence as high as 200 per 100,000 people.² In the United States, males and females are

equally affected, but both whites and Ashkenazi Jews are at much higher risk of developing inflammatory bowel disease than the general population. Ulcerative colitis patients are most often never smokers or non-smokers, with no more than 10% being current cigarette smokers. Worldwide, ulcerative colitis cases are concentrated in North America, Europe, and Australia, and a north-south gradient exists, with higher incidence rates in higher latitudes. For unknown reasons, a history of appendectomy is protective against the development of ulcerative colitis.

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Pathophysiology

The pathogenesis of ulcerative colitis is believed to be related to a dysregulated proinflammatory response to commensal gut bacteria. Due to mutations, some mucosal defense mechanisms are disrupted. MUC2 is the most abundant protective mucin that coats the epithelium and prevents entry of microbes. Genome-wide association studies have shown that mutations in the MUC2 gene are associated with ulcerative colitis.³ Other mucosal defense mechanisms include the presence of tight junctions, IgA secretion, and defensins (naturally-occurring antibiotics that are produced by Paneth cells to maintain sterility of the crypt). When defense mechanisms are depressed, uncontrolled microbial proliferation can occur, and NF- κ B-dependent genes are stimulated to produce pro-inflammatory cytokines like tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, and the chemokine IL-8. *Cytokines* is a collective term for a group of low-molecular-weight peptides that are active at low concentrations and bind to specific receptors to produce autocrine, paracrine, and endocrine effects; chemokines are peptides that attract inflammatory cells. Cytokine and chemokine production attract T-cell infiltration, which in ulcerative colitis patient are principally Th-2 cells, which in turn amplify the inflammatory response.

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Clinical Presentation

Ulcerative colitis patients typically present with rectal bleeding, diarrhea, tenesmus (urgent desire to evacuate the bowels but with passage of little stool), and lower abdominal pain. The severity of disease at clinical presentation is important in determining the appropriate therapy ([Table 1](#)).⁴ Patients with mildly active disease will have fewer than 4 bowel movements daily and no signs of toxicity. Patients with moderate disease have more frequent bowel movements with bleeding. Approximately 70% of patients with ulcerative colitis will have moderately active disease at presentation.⁵ Patients with severely active disease will have signs of toxicity with fever, tachycardia, and anemia. Patients with fulminant or toxic colitis, or toxic megacolon often have more than 10 bowel movements in a day, continuous bleeding, abdominal distention and tenderness, and radiologic evidence

of edema and, in some cases, bowel dilation. These patients most often require immediate colectomy because fully 10% suffer perforated colon at the time of surgery.

Table 1: Classification of disease severity in ulcerative colitis patients⁴

Mild	<4 stools/day ± blood Normal ESR No signs of toxicity
Moderate	4-6 stools/day Minimal signs of toxicity
Severe	>6 bloody stools/day + fever, tachycardia, anemia, elevated ESR
Fulminant	>10 stools/day, continuous bleeding, toxicity, abdominal tenderness/distention, transfusion requirement, colonic dilation on x-ray

ESR, erythrocyte sedimentation rate

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Diagnosis

The diagnosis of ulcerative colitis is established by finding characteristic intestinal ulcerations and excluding alternative diagnoses, such as enteric infection, ischemia, diverticulitis, or NSAID-induced enteropathy ([Table 2](#)). The most common diagnosis that mimics ulcerative colitis is that of the infectious colitides. It is imperative to check stool for enteric pathogens, including ova and parasites, *Escherichia coli* O157:H7, cytomegalovirus, and *Clostridium difficile*. Active disease in ulcerative colitis is characterized by the endoscopic appearance of superficial ulcerations, friability, a distorted mucosal vascular pattern, and exudates ([Figure 1](#)). Patients with severely active disease can have pseudopolyps, and deep ulcers and friability that result in spontaneous bleeding. The typical distribution of disease is continuous from the rectum proximally. However, patients with partially treated ulcerative colitis might have discontinuous or patchy involvement. Histologic features of ulcerative colitis include disease limited to the mucosa and submucosa with an expansion of inflammatory cells in the lamina propria, mucin depletion, ulcerations, exudate, and crypt abscesses ([Figure 2](#)).

Table 2: Principal Alternatives in the Differential Diagnosis of Ulcerative Colitis

- Infectious colitis
- Antibiotic-associated colitis
- Amyloidosis
- Solitary rectal ulcer syndrome

Diarrhea of HIV infection

Clostridium difficile -associated colitis

Cytomegalovirus

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Natural History

Extraintestinal manifestations

Ulcerative colitis is a systemic disease; there are many extraintestinal manifestations. Approximately 2% of ulcerative colitis patients develop primary sclerosing cholangitis (PSC), a cholestatic liver disease diagnosed by the appearance of extrahepatic and intrahepatic strictures on a cholangiogram.⁶ About 3 times as many PSC patients have ulcerative colitis than Crohn disease. Anti-inflammatory medications are not effective for the liver disease in patients with PSC. Other hepatobiliary manifestations of inflammatory bowel disease include fatty liver, chronic active hepatitis, amyloidosis, and complications from medications used to treat inflammatory bowel disease (eg, azathioprine, 6-mercaptopurine [6-MP], sulfasalazine, or infliximab).

Erythema nodosum, seen in up to 3% of patients, is characterized by raised, tender, erythematous nodules appearing typically on the extremities that respond to anti-inflammatory medications. Pyoderma gangrenosum, a rare ulcerating necrotic lesion, is seen in both Crohn disease and ulcerative colitis, and about 50% of affected patients respond to anti-inflammatory medications. Arthritis usually is seronegative, mono- or pauciarticular, and asymmetrical. The large joints are most often affected, and there is no synovial destruction. Peripheral arthritis, but not axial arthritis (ankylosing spondylitis or sacroiliitis), responds to anti-inflammatory agents. Ocular manifestations include blurred vision, eye pain, photophobia, and keratitic precipitates. Patients with uveitis often have human leukocyte antigen B27 (HLA-B27), whereas patients with episcleritis and iritis usually do not. Cerebrovascular accidents and other thromboembolic events can result from the hypercoagulability that results from chronic inflammation or to other inherited syndromes, such as the factor V Leiden mutation.

Colorectal Cancer Risk

Patients with ulcerative colitis are at increased risk of colonic epithelial dysplasia and carcinoma with age-specific risk that is at least 3 times greater than that in the general population. This risk of colon cancer is related to increased duration and extent of disease, a positive family history of colorectal cancer, and the presence of PSC.⁷ Entering a patient into a cancer surveillance program is important, but the exact method and timing of

surveillance are subjects of debate. Most guidelines recommend beginning surveillance colonoscopies after 8 years of disease. Multiple biopsies are taken at regular intervals throughout the colon and of polypoid lesions. Biopsies are read by pathologists for the benign, but premalignant neoplastic lesion of dysplasia. All specimens with any grade of dysplasia should be reviewed by an expert gastrointestinal pathologist to confirm the findings.

It is generally agreed that high-grade dysplasia is an absolute indication for a colectomy, because these patients have a 42% risk for concurrent cancer. Low-grade dysplasia in flat mucosa also is an indication for colectomy, because progression to more advanced neoplasia often occurs.⁸ The frequency with which colonoscopic surveillance should be performed varies according to the extent of colitis, the duration of disease, and the history of PSC. Because the risk of cancer is low throughout the first decade after the diagnosis of ulcerative colitis, surveillance need not be performed more frequently than every 3 years. As the cancer risk increases, the testing interval should shorten.⁹ One reasonable approach is to test every 3 years for 12 years, then every 2 years for 10 years, and annually thereafter. Patients with primary sclerosing cholangitis have an increased risk of colorectal cancer, so endoscopic surveillance examinations should be performed annually. Some studies suggest that 5-aminosalicylic acid (5-ASA) agents, folic acid, and ursodeoxycholic acid (in ulcerative colitis patients with PSC) have a cancer chemopreventive effect and should be considered as maintenance therapy in patients with ulcerative colitis.

Ileal Pouch—“Anal Anastomosis

Ulcerative colitis patients who require surgery are frequently offered an ileal pouch—anal anastomosis. At surgery, a total proctocolectomy is performed, the distal small bowel is fashioned into a J-shaped reservoir, and the ileal pouch is stapled to the anal verge. Following surgery, patients usually have 4 to 7 bowel movements daily and occasional or minimal incontinence. Acute pouchitis, the most common complication, occurs in about 25% to 50% of patients within 5 years. Acute pouchitis usually is successfully treated with antibiotics such as metronidazole or ciprofloxacin.¹⁰ Other, less-common complications of the ileal pouch include chronic pouchitis (inadequate response of pouchitis to multiple rounds of antibiotics), irritable pouch syndrome (bowel symptoms without endoscopic inflammation), cuffitis (recrudescence of colitis in the retained rectal cuff), or even unsuspected Crohn disease. Irritable pouch syndrome often responds to anticholinergics or antidepressants, cuffitis responds to 5-ASA suppositories, chronic pouchitis responds to long-term antibiotics, probiotics, or immunosuppressive therapy, and Crohn disease of the ileal pouch requires immunosuppressive therapy for treatment.

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Treatment

Management of ulcerative colitis is described in practice guidelines published in 2010.⁴ The severity of the ulcerative colitis flare is based on patient symptoms and on the extent of colitis, not on the histologic severity of inflammation ([Table 1](#)).

For patients with mild to moderate distal or left-sided colitis, therapy includes oral or topical 5-ASA agents, or both. The combination of oral and topical mesalamine is more effective than either alone for active disease.¹¹ Mesalamine (5-ASA) enemas are commonly used topical agents and given at a dose of 4 g nightly. This therapy is effective for both active colitis and for maintaining remission, and it is superior to rectal corticosteroids for distal disease. Steroid enemas are effective in active disease, but they are not useful in maintaining remission. Mesalamine suppositories are also useful for patients with proctitis.

Mesalamine therapy is not considered to have failed until a patient has been given maximum doses of the drug or has experienced intolerable side effects. Oral 5-ASA doses of up to 4.8 g per day are given for active disease and 2.4 g per day for maintenance of remission. Sulfasalazine 2 g per day is given for maintenance, and up to 8 g per day for active disease ([Table 3](#)). Balsalazide 6.75g daily is particularly effective for left-sided colitis. Once-daily formulations of mesalamine are effective in inducing and maintaining remission. Although sulfasalazine is less expensive than the other 5-ASA agents, it has a high incidence of side effects, such as nausea, vomiting, anorexia, dyspepsia, malaise, and headache. Some rare idiosyncratic reactions include fever, rash, hepatitis, pancreatitis, pneumonitis, and agranulocytosis. Folate supplementation is recommended, because sulfasalazine can inhibit folate absorption. The other 5-ASA agents can be more expensive but generally are better tolerated.

Table 3. Aminosalicylates and intestinal activity

Medication	Dosage (g/day)	Colon Activity		
		Distal	Proximal	Small Bowel Activity
Sulfasalazine	2-8	++	+++	-
Olsalazine	1-3	++	+++	-
Balsalazide	6.75-13.50	+++	+++	-
Mesalamine (Pentasa)	2-4	++	++	++
Mesalamine (Asacol)	2.4-4.8	++	+++	+
Mesalamine (Asacol HD)	2.4-4.8	++	++	+
Mesalamine (Lialda)	2.4-4.8	++	++	-

Mesalamine (Apriso)	1.5	++	++	++
Mesalamine rectal suspension enema (Rowasa enema)	4	+++	-	-
Mesalamine suppository	2-4	+	-	-

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For patients with mild to moderate pancolitis, first-line therapy involves oral 5-ASA agents. If this therapy is ineffective, oral steroids can be used for active disease, with the usual starting prednisone dose of 40 mg/day. Long-term steroid use has many intolerable side effects, such as osteoporosis, hypertension, weight gain, adrenal suppression, diabetes, and myopathy, so duration of steroid use must be limited. For patients with mild to moderate disease who do not completely respond to or are dependent on oral steroids, immunosuppressives such as 6-MP or azathioprine can be used. These purine analogues act by causing chromosome breaks and blunt the proliferation of rapidly dividing cells, such as lymphocytes. These agents are mildly effective for active disease, but excellent for maintaining remission. Thiopurine methyltransferase (TPMT) activity should be measured before initiating 6-MP or azathioprine therapy to determine the optimal starting dose.¹² Metabolite levels of 6-MP (6-thioguanine [6-TG] and 6-methylmercaptopurine [6-MMP]) can be measured to determine the optimal therapeutic dose with the minimal risk of toxicity. Measurements of metabolite levels are best performed in patients who are not responding but who are taking adequate doses. Metabolite levels can be used to distinguish between those who are nonresponders, those who are not compliant with medication, and those in whom the dose can be safely increased. One shortcoming, however, is that 6-MP and azathioprine usually require 3 to 6 months to become maximally effective. In addition, they have the rare side effects of allergy (eg, abdominal pain, fever, rash), pancreatitis, and bone marrow suppression.

Infliximab, a monoclonal chimeric anti-TNF antibody, has been approved for use in ulcerative colitis and is especially helpful in patients with moderately active disease that does not respond to 5-ASA agents, immunosuppressive medications, or corticosteroids.¹³ Adalimumab, a fully human monoclonal anti-TNF antibody, also has been shown to be effective in ulcerative colitis patients.¹⁴

For ulcerative colitis patients with severely active colitis refractory to maximal oral therapy, admission to the hospital and intravenous steroids are required. The usual dosage of intravenous steroids is 0.5 to 0.75 mg/kg/day of prednisone equivalents. Usual regimens include intravenous hydrocortisone 100 mg every 8 hours or intravenous methylprednisolone 40 mg daily. It is important to rule out toxic megacolon by checking a radiograph of the abdomen, as well as CMV infection with serologic and histologic studies, and *C. difficile* with stool PCR. A colorectal surgery consultation should be obtained, because a significant number of these patients require surgery during hospitalization.

Indications for a colectomy during a colitis flare include massive hemorrhage, perforation, toxic megacolon, or active disease unresponsive to medical therapy. Surgery is also indicated for patients with persistently active moderate disease that is medically refractory or for those with steroid-dependence and intolerable steroid side effects.

Cyclosporine has been shown to be useful in the treatment of patients with severely active ulcerative colitis who do not completely respond to IV steroids.¹⁵ However, because cyclosporine has many side effects and has not been shown to be effective in maintaining long-term remission, this medication is not widely used in the treatment of severe ulcerative colitis. Infliximab can be used as salvage therapy to induce remission in severely active cases.¹⁶ Maintenance therapy with infliximab and an immunosuppressive agent should be considered in patients whose remission was induced with infliximab.

Prior to initiating immunosuppressive therapy, a thorough vaccine history should be recorded.¹⁷ Vaccines given prior to immunosuppression will be more effective than those initiated after the start of such therapy. In general, live vaccines (ie, live attenuated influenza vaccine, measles-mumps-rubella, varicella-zoster vaccine, and oral polio live vaccine) should be avoided. Fortunately, alternatives exist for the influenza vaccine, and some others. Pneumococcus vaccine, meningococcus vaccine, human papillomavirus vaccine, and hepatitis B virus vaccine are all inactive vaccines and, therefore, should be administered when appropriate.

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Conclusions

Ulcerative colitis occurs in genetically predisposed individuals, usually in the second or third decade of life. It is a systemic disease and patients often develop extra-intestinal manifestations, as well as diarrhea and rectal bleeding. Medical therapy with aminosalicylates, corticosteroids, immunosuppressives, and biologic agents will usually induce and maintain remission, but fully 30% of patients will eventually require total proctocolectomy.

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Summary

- Ulcerative colitis is characterized by mucosal inflammation of the large bowel, but has a variety of extra-intestinal manifestations.
- The diagnosis of ulcerative colitis is based on a constellation of clinical, endoscopic, and histologic features, including negative stool cultures and no history of nonsteroidal anti-inflammatory drug use.

- The differential diagnosis ulcerative colitis includes infectious colitis, antibiotic-associated colitis, and solitary rectal ulcer syndrome.
- First-line therapy for ulcerative colitis patients includes 5-aminosalicylic agents, and some patients also need corticosteroids, immunosuppressive medications, and biologic agents.
- Colorectal cancer risk is an important concern for patients with ulcerative colitis.

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Suggested Readings

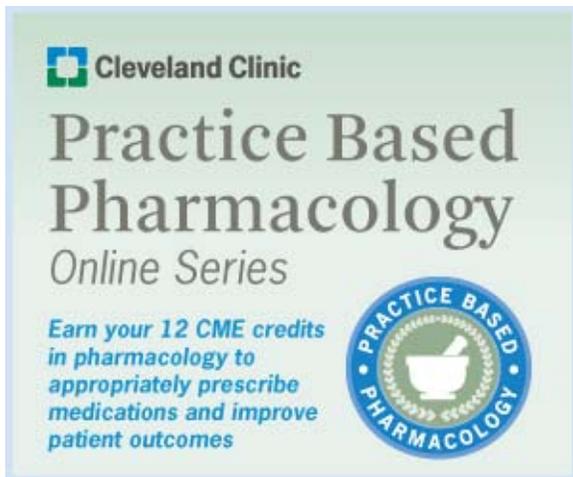
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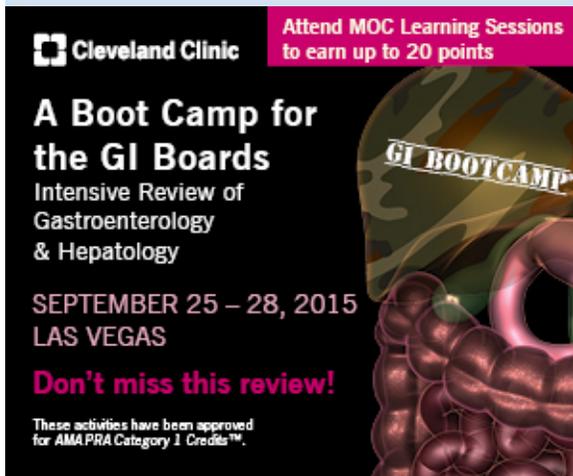
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