

ULCERATIVE COLITIS

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[Abstract](#)

[Introduction](#)

[Epidemiology](#)

[Etiology](#)

[Pathophysiology](#)

[Symptoms, signs, and laboratory findings](#)

[Diagnostic methods](#)

[Differential diagnosis](#)

[Therapy](#)

[Prognosis](#)

[Surgery](#)

[References](#)

Abstract

Ulcerative colitis (UC) is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable. In its most limited form it may be restricted to the distal rectum, while in its most extended form the entire colon is involved. UC belongs to the inflammatory bowel diseases (IBD), which is a general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract. UC is usually associated with recurrent attacks with complete remission of symptoms in the interim. In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100.000 populations and an estimated prevalence of approximately 70 to 150 per 100.000 populations. The leading initial symptom of UC is diarrhea with blood and mucus, sometimes with pain. Fever and weight loss are less frequent. Extra intestinal symptoms can be an initial manifestation or can occur later in the course of the disease. Eighty percent of the patients have only proctitis or proctosigmoiditis, and only 20% have extensive colitis. However, in about 50% of patients with initial proctosigmoiditis, proximal extension occurs later, and in some patients the opposite takes place. Depending of the stage of the disease, endoscopy reveals reddening of the mucosa, increased vulnerability, mucosal bleeding, irregular ulcers, pseudopolyps, granularity, and loss of vascular architecture. Several drugs interacting with various points along the immune and inflammatory cascades are currently available for the treatment of UC. Corticosteroids, aminosalicylates, immunomodulators are the mainstay of medical treatment.

Keywords

Ulcerative colitis, inflammatory bowel diseases, colonic mucosa, gastrointestinal tract, proctitis, proctosigmoiditis, corticosteroids, aminosalicylates, immunomodulators

Introduction

Inflammatory bowel disease (IBD) is a general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract. Chronic IBD may be divided into two major groups, **ulcerative colitis** (UC) and **Crohn's disease** (CD), clinically characterized by recurrent inflammatory involvement of intestinal segments with several

manifestations often resulting in an unpredictable course.

Ulcerative colitis is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable. In its most limited form it may be restricted to the distal rectum, while in its most extended form the entire colon is involved. However, 80% of the patients present with

disease extending from the rectum to the splenic flexure, and only 20% have pancolitis.

Although the causes of IBD remain unclear, considerable progress has been made recently in the identification of important pathophysiologic mechanisms, and further and newer knowledge has been obtained from recent studies concerning their epidemiology, natural history, diagnosis and treatment.

Epidemiology

Ulcerative colitis is usually associated with recurrent attacks with complete remission of symptoms in the interim. The disease is more common in Caucasians than in Blacks or Orientals with an increased incidence (three to six fold) in Jewish. Both sexes are equally affected. In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100.000 populations and an estimated prevalence of approximately 70 to 150 per 100.000 populations. While peak occurrence of both diseases (UC and CD) is between ages 15 and 35, it has been reported in every decade of life. A familial incidence of IBD is currently recorded.

Etiology

The cause of UC is unknown. Although less evident than in CD, it is clear from twin studies that a genetic background is also present in UC. Indeed, a stronger association exists between genes of the human leucocyte antigen region - involved in regulating the immune response - and UC. Despite unclear effects due to ethnic origin and disease heterogeneity, this association is strongest in patients with extensive UC; a positive association with *DR2* (in particular, *DRB1*1502* subtype) and the rare alleles *DRB1*0103* and *DRB1*12*, and a negative association with *DR4* and *Drw6* have been reported. However, genes associated with susceptibility to UC are probably not within the human leucocyte antigen region, and genome-wide scanning studies have shown a linkage between UC and regions of chromosomes 3, 7, and 12. Moreover, there are genes that appear to affect the severity and extent of the disease, steroid response, steroid requirements, and extra - intestinal manifestations. Finally, polymorphisms of the IL-1 receptor antagonist that might affect severity and extent of disease have been reported, particularly in patients positive for pANCA, as well as for *MUC3*, a gene encoding intestinal mucins that might also be associated with the pathogenesis of UC.

Among the many puzzles concerning IBD etiology, one of the least understood and, perhaps, most difficult to tackle, presently, is the

role of environmental factors in the appearance and progression of CD and UC.

The effect of cigarette smoking or the opposite effect of this factor on the outcome of each form of IBD represents the most intriguing connection between environmental factors and IBD. Most reports have shown that non-smoking is a feature of patients with UC, whereas smoking is a feature of patients with CD. Smoking is an independent risk factor for clinical, surgical, and endoscopic recurrence in CD but influences disease activity after surgery. On the contrary, the relative risk of developing UC in heavy ex-smokers, all ex-smokers, non-smokers, and smokers has been evaluated to be respectively 4.4, 2.5, 1.0 and 0.6. Nicotine is probably the main active ingredient in this association, but the mechanisms remain unknown. Cigarette smoking has been shown to affect cellular and humoral immunity, and increase colonic mucus production; both smoking and nicotine have been shown to reduce colonic motility. Finally, results from *in vivo* studies have shown that nicotine also has an inhibitory effect on T-helper-2 cell (Th2) function, which predominates in UC, but has no effect on Th-1 cells, predominant in CD.

Epidemiological data indicate that non-steroidal anti-inflammatory drugs can trigger exacerbations of UC and even, occasionally, induce *de novo* disease. Possible mechanisms include decreased production of protective mucosal prostanoïd and increased leukocyte adherence and migration. Although these effects were initially thought to be due to inhibition of cyclo-oxygenase-1 (COX-1), selective COX-2 inhibitors seem as potent as indomethacin in this context.

Psychological stress by some 40% of patients with UC, has been reported to be a potential trigger. Substantial evidence links psychological stress with increased illness and, possibly, increased susceptibility to infection through stress-related impairment of functional immune responses. Duration of stress might also be important since long-term but not short-term stress seems to increase the risk of exacerbations of disease.

Another very interesting environmental factor conditioning UC is appendectomy. Indeed, appendectomy, at a young age, has the strongest preventive effect on the development of UC. This finding has been corroborated by case-control studies, and a very large population-based study recently confirmed the inverse relationship between appendectomy and UC in patients submitted to surgery before age 20 years. In the latter study, the risk of UC was reduced only in patients who underwent appendectomy for appendicitis or mesenteric

lymphadenitis, but not in those who underwent incidental appendectomy or appendectomy for non-specific abdominal pain. This finding suggests that an inflammatory condition at a young age that results in appendectomy, rather than appendectomy itself protects against later development of UC. Another possible explanation for this inverse association is that genetic predisposition to UC might protect against development of appendicitis.

Pathophysiology

While the cause of UC remains unknown, a number of findings in recent years point to an over stimulation or inadequate regulation of the mucosal immune system as a major pathophysiologic pathway, and particular emphasis has been given to either the study of mucosal inflammation or immunologic reactions. When the disease is active, the lamina propria of the mucosa becomes heavily infiltrated with a mixture of acute and chronic inflammatory cells. There is a predominant increase in mucosal IgG production, evidence of complement activation, and activation of macrophages and T cells. This immunological activity is associated with the release of a vast array of cytokines, kinins, leukotriens, platelet activating factor (PAF) and reactive oxygen metabolites. These mediators not only serve to amplify the immune and inflammatory response, but they also have direct effects on epithelial function, on endothelial function (which may increase permeability and lead to ischaemia), and on repair mechanisms, thus increasing collagen synthesis. In addition, many of the cytokines (interleukins 1 and 6, tumor necrosis factor) will activate an acute phase response, resulting in fever and a rise in serum acute phase proteins. Some of the clinical features of acute ulcerative colitis may explain by these mechanisms. It follows, therefore, that any treatment which is able to inhibit the activation of these immunological and inflammatory effector mechanisms is likely to lead to an improvement in the patient's symptoms and to a decrease in the inflammatory activity.

Symptoms, signs, and laboratory findings

The leading initial symptom of UC is diarrhea with blood and mucus, sometimes with pain (Table 1). Fever and weight loss are less frequent. Extra intestinal symptoms can be an initial manifestation or can occur later in the course of the disease (Table 2). In proctitis, rarely, obstipation can be the initial symptom. Eighty percent of the patients have only proctitis or proctosigmoiditis, and only 20% have extensive colitis. However, in about 50% of patients with initial proctosigmoiditis, proximal

extension occurs later, and in some patients the opposite takes place. A change in the extent of disease should be suspected when new symptoms arise. The course of the disease can vary widely. Spontaneous remission from a flare-up occurs in 20 to 50% of the patients, but 50 to 70% have a relapse during the first year after diagnosis.

Table1: Initial symptoms of UC

Diarrhea	96.4%
Blood in stool	89.3%
Pain	81;3%
Generally unwell	40.2%
Weight loss	38.4%
Arthralgia	27.7%
Fever	20.5%
Skin changes	20.5%
Loss of appetite	15.2%
Ophthalmopathies	7.1%
Nausea	6.3%
Vomiting	4.5%
Abscesses	3.6%
Fistulae	3.6%
Lymph node swelli	1.8%

The relapse rate is higher in the younger patients and seems to decrease with increasing age. In a large cohort analysed over 25 years, 50% of the patients were able to work after 10 years.

Table 2: Frequency of extraintestinal manifestations of the course of UC

All	64-66%
Skin	15.9%
Erythema nodosum	8.0%
Pyoderma gangrenosum	7.1%
Aphthae	6.2%
Eyes	9.7%
Conjunctivitis	5.3%
Iritis	4.4%
Uveitis	0.9%
Joints	39%
Arthralgia	38.4%
Arthritis	11.3%
Ankylosing spondylitis	0.8%
Liver/pancreas	16.8%
Fatty liver	10.6%
Hepatitis	1.8%
Pericholangitis primary	3.5%
Sclerosing cholangitis	
Pancreatitis	2.7%

In all patients with severe UC an acute phase response is present, including an elevated erythrocyte sedimentation rate, elevated C-reactive protein level, microcytic anaemia, and, less frequently, thrombocytosis. Until a few years ago no specific laboratory abnormalities were known. More recently it has been found that about 65% of patients with UC have positive perinuclear antineutrophil cytoplasmic antibodies (pANCA). These antibodies also occur in almost all patients with primary sclerosing cholangitis. It is not clear whether they have a pathophysiologic role, are subclinical genetic markers, or are simply an epiphenomenon.

Diagnostic methods

Depending of the stage of the disease, endoscopy reveals reddening of the mucosa, increased vulnerability, mucosal bleeding, irregular ulcers, pseudopolyps, granularity, and loss of vascular architecture. The changes are continuous, and the rectum is always involved if no effective local treatment has been applied. Biopsy specimens show crypt irregularity, crypt abscess, and destruction of the epithelial border in addition to immune cell migration. Histology is however, not specific, and can be used only as a supplementary diagnostic finding.

Abdominal transcutaneous ultrasonography may demonstrate bowel wall thickening of the involved area, but it is non-specific. The same applies for computed tomography and magnetic resonance imaging.

Since the advent of the endoscopy, double blind contrast barium enema is rarely used. It does, however, show typical findings and can be prescribed if endoscopy is not possible or is not accepted by the patient.

Because inflammation in UC is limited to the colon, no imaging studies of the upper gastrointestinal tract and small bowel are necessary once the diagnosis has been established.

Treatment options for extensive colitis are different from those in distal colitis, and therefore the extent of the disease should be assessed. This best done by endoscopy with biopsy. Once the extent of disease has been defined, repeat endoscopy is necessary only in the advent of new symptoms. However, after 10 years, endoscopy surveillance for carcinoma development should be considered.

Disease activity can be assessed clinically and endoscopically. Since the rectum is invariably involved, flexible rectosigmoidoscopy is sufficient.

Differential diagnosis

Diagnosis of UC should not be established before excluding a large number of intestinal inflammatory disorders (Table 3).

Table 3: Differential diagnosis of IBD

Infections (classic)	<i>Invasive: Salmonella, Shigella, Campylobacter species, Yersina enterocolitica, mycobacteria</i> <i>Toxic: C. difficile, E. Coli</i> <i>Parasitic: Entamoeba H, Balantidium coli, Giardia I.</i> <i>Sexual transmitted: Neisseria gonorrhoeae, T. pallidum, Herpes simplex, CMV, C. thachomatis</i>
Infections (new)	Immunocompromised (HIV) Histoplasma, CMV, M avium
Vasculolar	Ischemia, vasculitides, Behcet disease
Malignant	Lymphoma, sarcoma, leukemias
Drug-induced	Pseudomembranous, colitis, contraceptive-induced colitis, NSAID-induced colitis
Others	Radiation and chemically induced colitis, collagenous colitis , sarcoidosis

This can be achieved by microbiologic analysis of fecal samples and by biopsy analysis. Sometimes serologic analysis - for example, for *Yersinia enterocolitica* - is helpful.

Table 4: Differential diagnosis between CD and UC according to endoscopic findings

	CD	UC
Involvement Rectal	Discontinuous 20%	Continuous Always
Involvement Vessels	Often normal	Abnormal/lacking
Erythema/edema	++	+++
Vulnerability	(+)	+++
Bleeding	(+)	+++
Pus/mucus	+	+++
Local ulcers	+++	(+)
Fissural ulcers	+++	(+)
Granularity	(+)	+++
Clobestone pattern	+++	---
Pseudopolyps	++	+++
Strictures	++	(+)

It should be kept in mind that a flare-up of UC can be induced by a microbial superinfection.

Thus, infection should be excluded before treatment is instituted.

The differentiation between UC and CD can usually be done using endoscopic, radiologic, and histologic criteria (Table 4 and Table 5). In particular, continuous of the mucosal and rectal involvements are critical to the diagnosis.

Table 5: Differential diagnosis between CD and UC according to histologic findings

	CD	UC
Crypt Injury	++	++
Granuloma	++	--
Transmural inflammation	+++	--
Mucosal inflammation	--	+++
Lymphoid hyperplasia	++	--
Deep ulcers	++	(+)
Microscopic focality	+++	--
Crypt abscess	(+)	+++
Globet cells depletion	+	+++
Flat ulcers	(+)	++

Histologic differentiation without clinical information is difficult and rarely used. Testing for pANCA can be helpful, since a positive reaction is found in only 10% of patients with CD but in 60 to 70% of those with UC.

Biopsy specimens sometimes show typical findings. However, this is not always the case, and the analysis of the same specimen by different pathologists may lead to different results.

Involvement of the small bowel as seen at endoscopy or small bowel X-ray excludes UC, since the small bowel is not involved in this disease.

Therapy

To reduce toxicity and maximize the therapeutic benefit of the different drugs available for the treatment of UC, thus improving their risk/benefit ratio, several important criteria should be considered when choosing the most appropriate therapeutic approach: a) aims of the treatment; b) extent and the localization of disease; c) disease activity; d) clinical pattern, and e) proven efficacy of the current therapies.

Aims of therapy

The clinical status of a patient with active UC reflects many different factors:

- the primary disease process of gut inflammation, confined to the mucosa in ulcerative colitis;
- metabolic consequences, such as protein-losing enteropathy and hypoalbuminemia,

anemia, hypokalemia, hypocalcemia and hypomagnesemia;

- structural abnormalities such as strictures and perforations.

Priority of therapy is usually to control the consequences of inflammation by transfusion, replacement of losses, minerals, vitamins and so on.

For a disease such as UC, characterized by recurrent attacks of symptoms with complete or partial remission of clinical manifestations, the primary aims of medical treatment must be the induction of remission of inflammatory activity and the prevention of recurrences. Moreover, considering the frequent development of extraintestinal complications, often severely affecting the patient's quality of life, another important objective of the medical therapy is to control the impact of these complications on the patient's life.

Extent and anatomic distribution of UC

Establishing the extent and localization of UC is an important diagnostic and clinical step in the evaluation of patients suffering from UC, because of its therapeutic implications and relative tolerability. Colonoscopy and radiology (barium enema) are the primary diagnostic tools used to define the extent and anatomic distribution of the disease.

In UC, the extent of colon involvement during the first attack has been found to be reasonably uniform in several large series of patients. As mentioned before, approximately 30% of UC patients have disease that is limited to the rectum, in about 40% the disease extends above the rectum but not beyond the hepatic flexure (so-called sub-total colitis), and the remaining 30% develop total colitis. However, in some population-based surveys, more than half of the patients present with disease extending from the rectum to the splenic flexure. In this context, while UC may be classified into proctitis, proctosigmoiditis, or left-sided colitis, the term "distal colitis" is a working classification, which implies that the inflammation is amenable to topical treatment, by means of intrarectal drug administration. Thus, giving pharmacological therapy, this way may reduce potential toxicity. Establishing the extent and localization of UC is an important diagnostic and clinical step in the evaluation

Grading of disease activity

Disease activity indices are prediction rules used to measure the activity of disease objectively in order not only to judge response in clinical trials, but also and especially to choose which drug to administer and its optimal dose

regimen. However, the use of these indices in clinical practice is limited, since they are intended to make the clinical global assessment objective, a prerogative most clinicians do not agree with.

In UC, the activity of the disease is usually assessed primarily on the basis of clinical features. The Truelove and Witts classification in mild, moderate or severe disease, based on the some clinical parameters and laboratory findings (number of bowel movements, fever, presence of tachycardia, anemia, sedimentation rate) is the most widely used clinical activity index in gastroenterological practice. However, although clinically useful, these criteria do not allow sufficient discrimination for the purpose of clinical studies. Expansion of the clinical profile by Powell-Tuck *et al* has improved clinical trials but lacks correlation with sigmoidoscopic appearance. Sutherland *et al* have proposed a useful disease activity index for UC including a grading of clinical and endoscopic signs (Table 6). However, other clinical, endoscopic, and histological indices are available for grading disease activity in UC.

Table 6: Ulcerative colitis disease activity index.

1. Stool frequency	0-3: normal 1-3: 1-2 stools daily > normal 2-3: 3-4 stools 3-3: 4 stools
2. Rectal bleeding	0-3: None 1-3: Streaks of blood 2-3: Obvious blood 3-3: Mostly blood
3. Mucosal appearance	0-3: Normal 1-3: Mild friability 2-3: Moderate friability 3-3: Exudation, spontaneous bleeding
4. Physician's rating of disease activity	1-3: Normal 2-3: Mild 3-3: Moderate 4-3: Severe
Maximum score 3	13

Drug classes

Several drugs interacting with various points along the immune and inflammatory cascades, are currently available for the treatment of UC. Corticosteroid, sulfasalazine and its derivatives the 5-amino salicylic acids (5-ASA) and immunosuppressants are the mainstay of medical treatment. Effective in inducing remission, some of them are largely used to prevent disease recurrence. Other drugs may also have a potential role in this context (anti-

tumor necrosis factor, nicotine, heparin, etc.) but their effectiveness needs to be established in controlled clinical trials. In order to limit toxicity and optimize the therapeutic effects of the current pharmaceutical treatment, thorough understanding of the indications of drug therapy is essential.

Practical guide to the management of UC (see table 3)

Based on the data available, patients with *mild to moderate* distal UC colitis may be treated with either oral 5-ASA, topical 5-ASA, or topical steroids. Patients *refractory* to all of the above agents may require treatment with oral prednisone in doses up to 40-60 mg/day. For *maintenance* of remission, 5-ASA suppositories or enemas are effective, as well as oral 5-ASA or sulfasalazine (SSZ), whereas topical corticosteroids have not proven effective for maintaining remission in distal UC.

Patients with *mild to moderate extensive* UC should begin therapy with oral SSZ or 5-ASA. Oral corticosteroids are generally useful for patients who are *refractory* to oral 5-ASA with or without topical therapy. 6-Mercaptopurine (6-MP) or azathioprine (AZA) are effective for patients who do not respond to oral prednisone but are not so acutely ill as to require intravenous therapy. In these patients, when the acute attack is controlled, a *maintenance* regimen is usually required. SSZ or 5-ASA are effective in reducing relapses. As a rule, patients should not be treated chronically with corticosteroids. AZA or 6-MP may be useful as steroid-sparing agents for steroid-dependent and steroid-resistant patients, and for maintenance of remission not adequately sustained by 5-ASA.

Patients with *severe* UC refractory to maximal oral treatment with prednisone, oral salicylates, and topical medications, or patients who present with toxicity, should be treated for 7-10 days with intravenous corticosteroids. Failure to demonstrate significant improvement within 7-10 days is an indication for either colectomy or treatment with intravenous cyclosporine A (Cy A) in specialized centers.

Complications

Major complications of UC include toxic megacolon, intestinal perforation, mostly in the setting of the toxic megacolon, and massive bleeding. Toxic megacolon is characterized by a sepsis-like syndrome and extensive distension of the colon (>6 cm). It usually appears later in the course of the disease, but it can also occur early. Chronic blood loss leads to microcytic anemia, which may be severe. Drug-induced bone marrow suppression and sulphasalazine-induced hemolytic or folate deficiency can cause anemia

as well. No other deficiency states have been described, in contrast to CD. Severe extraintestinal complications or manifestations include primary sclerosing cholangitis, and pyoderma gangrenosum. An important problem is the increased cancer risk in patients with long-standing and extensive colitis. The risk increases statistically after 10 years in patients with pancolitis, and to a lesser degree in those with left-sided colitis. Rarely, carcinoma can be the initial symptom in patients with unrecognized UC.

Toxic or drug-induced megacolon can be treated for up to 3 days conservatively. High doses of glucocorticoids in combination with total parenteral nutrition and antibiotics are used. If no improvement occurs or the patient's condition deteriorates, immediate surgery is required. Endoscopy and barium enema should not be used because of the high risk of perforation. In patients in whom toxic megacolon has been treated successfully, elective colectomy should be discussed, since this complication seems to carry an increased risk of recurrence.

Severe refractory bleeding also must be treated by surgery; interventional endoscopic treatment generally is not useful, since bleeding is diffuse in almost all patients. For the indication of surgical treatment of bleeding, the amount of daily necessary blood substitution and the time to response on medical treatment must be known.

There is no proven treatment of primary [sclerosing cholangitis](#). The administration of ursodeoxycholic acid may improve laboratory values but does not seem to have any effect on long-term prognosis. If extrahepatic duct stenosis occurs, this can be treated endoscopically. However, cholangiocarcinoma must be considered. Liver transplantation is the final treatment of choice if liver function deteriorates or recurrent complications of bile duct stenosis occur.

[Pyoderma gangrenosum](#) normally is treated with glucocorticoids, and in refractory cases other immunosuppressants such as azathioprine or cyclosporine are used. Most other extraintestinal manifestations react to improvement of disease activity in the colon and therefore are not treated independently.

Surveillance for carcinoma development is widely used after 10 years of disease. The need for surveillance is underscored by the fact that 25% of strictures in patients with UC have been found to be malignant. However, it is not entirely clear whether the current strategy of yearly colonoscopy can indeed improve the outcome, though carcinoma-related mortality has been reduced in some studies. Maintenance therapy after remission, regular patients visits, and a

relatively wide indication for colectomy have led to reduction of carcinoma risk.

Prognosis

The prognosis for UC has improved significantly over the past 60 years. This is the result of an increased rate of colectomy and better timing of surgery as well as of improved surgical knowledge of complications and a better understanding of prophylaxis. The long-term study of Copenhagen group showed that after 10 years 25% of the patients had been colectomized; 93% were able to work, and there was no increased carcinoma risk. Ten-year survival was in the range of 96% of that of the normal population; it was better for those with proctitis (98%) than for those with pancolitis (93%). The risk is particularly high for the rare patients who develop UC later in life and initially present with a complication such as toxic megacolon. The good long-term prognosis in the majority of patients requires that we focus on quality-of-life aspects and on choosing treatment options with regard to all aspects of daily life and not only to medical outcomes.

Surgery

In UC, three situations are absolute indications for surgery: exsanguinating hemorrhage, frank perforation, and documented or strongly suspected carcinoma, i.e., high grade dysplasia or low grade dysplasia in a mass lesion. Massive hemorrhage in UC is due to diffuse mucosal ulceration. If the hemorrhage is exsanguinating or even persisting despite maximal medical therapy, it is an indication for surgical treatment. Perforation (occurring in only 2-3 % of hospitalized UC patients at tertiary referral centers), is the most lethal complication of toxic megacolon. When colon cancer is identified, the need for surgery is obvious; similarly, the coloscopic biopsy diagnosis of high grade dysplasia is often indicative of a concomitant or future cancer and is an indication for colectomy. Severe UC unresponsive to an intensive medical regimen, or toxic megacolon, are other indications for surgery.

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