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Ulcerative Colitis: Diagnosis and Management

Case Study and Commentary: Paul T. Kefalides, MD, and Stephen B. Hanauer, MD, MC

DR. LIANG:

Ulcerative colitis, also known as chronic ulceration of the intestines, is a common disorder estimated to have an incidence of 1 in 1000 persons in western countries.[1] Effective treatment relies on accurate and timely diagnosis. Various factors contribute to the disease's clinical manifestations, including psychiatric and physical components, but the etiology of the disease remains poorly understood.[2–4]

In patients with bloody diarrhea, such as the patient in this case study, there are many differential diagnoses to consider. Diagnoses to be excluded at the outset of illness, based on patients' risk factors, include radiation injury, diversion colitis, and ischemia. The presence of pancolitis should increase a physician's suspicion of disorders with potential infectious etiologies, such as amebic colitis, which is similar in presentation to ulcerative colitis.[5,6] Additionally, it is often difficult to distinguish between ulcerative colitis and Crohn's disease in patients with pancolitis; roughly 10% of affected patients will have only an indeterminate diagnosis of colitis until further work-up determines the specific type.[7–9]

Bloody diarrhea, an important presenting symptom, is generally (but not always) characteristic of ulcerative colitis, whereas Crohn's disease usually presents as nonbloody diarrhea. Moreover, ulcerative colitis often begins in the rectum and spreads proximally and continuously, whereas Crohn's disease often skips some areas of the bowel and spares the rectum in as many as 50% of cases.[10] These findings are apparent on endoscopic examination—a necessary component of any investigation of colitis.

An area of increasing concern is pediatric ulcerative colitis, which has an incidence of 2 to 4 per 100,000 children; median age at diagnosis is 10 years.[11] In general, pediatric ulcerative colitis presents as a chronic inflammation of the colonic and rectal mucosal lining. However, it is currently not known whether the disease has a genetic and/or autoimmune etiology or is related to a broad array of contributing factors, such as diet and infection.[12] Because of the symptomatic effect the disease has on children, they often will also have poor oral intake and concomitant malnutrition. Growth delays, poor development, and delayed sexual maturity can result and contribute to a high risk for depression in these patients.[13]

Of particular concern in children with severe disease is whether or not it is appropriate to use corticosteroids. Besides possible adverse effects (eg, Cushing's syndrome, metabolic abnormalities, adrenal suppression, osteoporosis, cataracts), use of corticosteroids places children at high risk for growth and developmental delays and greater severity of varicella infections, if and when they occur.[14] Thus, the primary care physician must be fully aware of the potential negative effects of treatment when managing the case of a pediatric patient.

Overall, a timely and accurate diagnosis is essential to benefit patients with ulcerative colitis, because effective treatments for the disease exist. A risk-benefit assessment must be carefully made prior to initiating any therapy, however, in light of the potentially significant adverse effects of some treatments, particularly in a pediatric population. With appropriate diagnosis, education, treatment, and patient compliance, ulcerative

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colitis can be successfully addressed, and patients can successfully participate in their activities of daily living.

DRS. KEFALIDES AND HANAUER:

Ulcerative colitis is a chronic inflammatory bowel disease of the colon that has become increasingly common in first-world countries. Ulcerative colitis and Crohn's disease comprise the spectrum of inflammatory bowel disease. These diseases affect approximately 400,000 individuals in the United States, and their economic impact has been estimated at $2 billion annually.[15]

Ulcerative colitis and Crohn's disease share many epidemiologic features. They can affect persons of any age group, although they typically begin in the second or third decade of life. They are most common in developed countries and can occur in persons, or more commonly their descendants, who have moved from second- or third-world countries to more industrialized environments. These disorders have a genetic component and occur more often in families in which another individual has the diagnosis. Approximately 10% to 30% of patients with inflammatory bowel disease report having a family member with inflammatory bowel disease.[16] Certain environmental factors, particularly cigarette smoking, affect the development and course of these diseases.

In order to diagnose inflammatory bowel disease and to distinguish ulcerative colitis from other diarrheal disorders, the physician must review the patient's history and integrate historical information with physical examination, laboratory, endoscopic, and pathologic findings. Inflammatory bowel disease in general, and ulcerative colitis specifically, are lifelong disorders that greatly influence overall health, health care utilization, and quality of life. Several studies have shown, however, that life expectancy in patients with ulcerative colitis is normal, especially in those with mild or limited disease.[17] Therefore, the goals of management of this chronic inflammatory disease are to induce and then maintain clinical remission while minimizing the risk for complications related to the disease or the medications used to treat it. Currently, ulcerative colitis can be cured only by surgery.

CASE STUDY

Initial Presentation and History

A 23-year-old woman with a history of dysmenorrhea associated with abdominal cramping goes to her primary care physician because of a 1-year history of episodic diarrhea and blood-streaked stools; symptoms have become more bothersome over the past 4 weeks. She reports loose stools with increasing amounts of blood and abdominal cramping over the past 4 days. She reports no fever or chills. Her appetite has been poor for the past 3 days. She has no history of recent travel and has been eating at home.

- **What information should be sought when a patient presents with diarrhea?**

For any patient presenting with chronic diarrhea, the primary care physician must try to distinguish between pathologic causes and irritable bowel syndrome. Irritable bowel syndrome is the most common cause of loose bowel movements associated with abdominal cramping; in this condition, loose bowel movements often alternate with constipation. In contrast to inflammatory bowel disease, irritable bowel syndrome is not associated with blood in the stool, nocturnal bowel movements, weight loss, or other inflammatory sequelae (eg, fever, arthritis, skin or eye lesions, perianal disease). The presence of blood or pus (fecal leukocytes) is associated with inflammation or neoplasia; in contrast, mucus is a normal constituent of stool, and neither its presence nor its absence has any specificity for either condition. In addition, specific risk factors for diarrheal illness should be sought, such as recent antibiotic use (with its risk for *Clostridium difficile* infection), other contacts who have acute or chronic diarrhea, or recent travel.

Further History

On further questioning, the patient reports that her bowel movements are sometimes dark and watery. She reports moving her bowels about 5 times per day and about 2 to 3 times during the night. She has seen blood mixed with the stool but believes the blood is coming from a hemorrhoid, although she has never noted anal skin tags. Her only medications are vitamins and occasional ibuprofen for menstrual cramps. She has no allergies and no history of hospitalization or surgery. Family history is notable for spastic colon in her mother and colitis in her father's brother. The patient has 2 siblings, both of whom are well. She is a graduate student in the humanities and works part-time in an office. She was a smoker while in high school and undergraduate college but quit approximately 6 months ago. She typically has 1 to 3 alcoholic drinks on the weekends but reports no drug use or HIV risk factors.

- **What additional risk factors for inflammatory bowel disease are present in this history?**

The patient's report of blood in the stool or at the time of bowel movements is highly suggestive of

inflammatory diarrhea with loss of mucosal integrity. The diarrhea may be infectious or may represent inflammatory bowel disease. Nocturnal bowel movements are almost never seen in irritable bowel syndrome but are common in inflammatory bowel disease. Recent cessation of smoking is a known risk factor for development of ulcerative colitis. For an as yet unknown reason, cigarette smoking protects against the development of ulcerative colitis but is associated with the development of Crohn's disease.[18] Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen disrupt gastrointestinal mucosal integrity and may precipitate or cause a flare of inflammatory bowel disease. Because there is a genetic predisposition for inflammatory bowel disease, a family history of colitis may reflect either irritable bowel syndrome or inflammatory bowel disease, depending on the validity of the described family history. All these factors should heighten the suspicion of inflammatory bowel disease as the cause of this patient's symptoms.

Physical Examination

On physical examination, the patient is slim and slightly pale. Her temperature is 37.8°C (100°F), heart rate is 90 bpm, and blood pressure is 110/60 mm Hg. Her oral mucosa is dry. There is no adenopathy in the cervical chain. She has a midsystolic click on cardiac examination and clear lungs. Her abdomen is flat, with normal bowel sounds. There is mild tenderness diffusely but no rebound tenderness or guarding. The rectal examination shows no external lesions and no stool is obtainable, but the mucus on the glove is positive for occult blood. The patient's skin appears normal. Musculoskeletal examination shows no joint swelling or tenderness.

- **What physical findings are important in a patient with ulcerative colitis?**

Results of physical examination in patients with ulcerative colitis may be normal or may represent subtle changes caused by the presence of colitis. The subtle findings to note in a patient with suspected inflammatory bowel disease include pallor (anemia), ocular inflammation (episcleritis or iritis), oral ulcers, skin lesions (erythema nodosum, pyoderma gangrenosum), perianal skin tags or fistulae (associated with Crohn's disease), or large-joint arthritis. In cases of severe ulcerative colitis, weight loss, fever, and tachycardia may be seen. Results of abdominal examination may show generalized tenderness in the setting of active disease or may be normal. In cases of severe colitis, the abdomen will have decreased or absent bowel sounds, distension, and tympany. The latter are ominous changes that can reflect the development of toxic megacolon, a dilation of the colon with thinning of the colonic wall that can lead to perforation.

Laboratory Examination

The physician orders a comprehensive metabolic profile, complete blood count with differential, and erythrocyte sedimentation rate (ESR). Stool samples are sent for testing for microbial pathogens. The results of laboratory testing are shown in **Table 1**. Testing of stool for ova and parasites and culture for *C. difficile* toxin have negative results. A test for fecal leukocytes is positive.

- **How do these laboratory findings help focus the differential diagnosis?**

The presence of fecal leukocytes is diagnostic for inflammatory diarrhea, whereas the negative cultures and absence of *C. difficile* toxin, along with the long duration of symptoms, exclude many acute infectious causes of diarrhea. The anemia and thrombocytosis are indicative of a chronic process with a high likelihood of inflammation and/or iron deficiency. The electrolyte values confirm the physical examination findings of volume depletion, and the hypokalemia is consistent with the history of chronic diarrhea. The hypoalbuminemia may reflect loss of protein from damaged colonic mucosa or may be a consequence of malnutrition in the setting of systemic inflammation.

- **What are the indications for endoscopy in a patient presenting with diarrhea?**

Flexible sigmoidoscopy or colonoscopy is indicated for evaluation of diarrhea when diarrhea is persistent, when noninvasive tests do not reveal a pathogen, or when inflammatory symptoms or signs are present. A recent study showed that for patients with diarrhea, examination and biopsy of the distal colon is 99% sensitive for colonic pathology.[19] Endoscopic examination can provide supportive evidence of colonic inflammation, allow for tissue or stool sampling, and evaluate the extent and severity of disease. Severity in ulcerative colitis can be judged by the extent and degree of the colonic injury as seen on endoscopy. In mild cases of ulcerative colitis, only a small area of the distal colon is involved; in severe cases, there can be pancolitis. The inflammatory injury in the colon progresses from a loss of vascular pattern with granularity and friability in mild

Table 1. Laboratory Test Results in the Case Patient

Serum values	
Sodium	39 mEq/L
Potassium	3.4 mEq/L
Chloride	101 mEq/L
Bicarbonate	21 mEq/L
Creatinine	0.7 mg/dL
Albumin	3.2 g/dL
Total protein	6.7 g/dL
Alkaline phosphatase	110 U/L
Total bilirubin	0.7 mg/dL
Aspartate aminotransferase (AST, SGOT)	45 U/L
Blood urea nitrogen	30 mg/dL
Hematologic values	
Leukocyte count	$10.9 \times 10^3/mm^3$
Hemoglobin	11.3 g/dL
Hematocrit	33.2%
Platelet count	$368 \times 10^3/mm^3$
Erythrocyte sedimentation rate	73 mm/hr

cases, to superficial ulceration in patients with moderate severity, and then to deep ulceration with overlying mucopus in extremely severe cases. Clinically, there may be markers for severe inflammation. Generally, patients with a more rapid onset of symptoms and more impressive signs of systemic inflammation are noted to have more severe colitis at endoscopy.

Although flexible sigmoidoscopy is an efficient way to evaluate a patient with diarrhea, if the sigmoidoscopy leads to a diagnosis of inflammatory bowel disease, a full colonoscopy is indicated to examine the entire colon for discontinuous areas of inflammation (known as *skip lesions*) and to visualize the terminal ileum.

Endoscopic Evaluation and Biopsy

The physician performs a flexible sigmoidoscopy examination that reveals a diffuse pattern of erythema, superficial ulceration, friability, and mucopus extending in a continuous pattern from the anal verge to the splenic flexure. A demarcation is noted 55 cm from the anal verge. The mucosa proximal to this point appears normal. Biopsies are taken from both the affected and normal-appearing areas.

Pathologic examination of the biopsy samples reveals diffuse, continuous crypt architectural distortion with crypt abscesses and expanded acute and chronic inflammatory cells in the lamina propria from the macroscopically involved areas. The biopsy samples taken from normal-appearing mucosa are entirely normal.

- **What are the pathologic features of ulcerative colitis?**

Pathology

Histologic examination for ulcerative colitis in a patient with acute symptoms usually shows an inflammatory infiltrate consistent with acute colitis with polymorphonuclear cells and background findings of chronic inflammation. These features of chronic inflammation—cryptitis and crypt abscesses—indicate the presence of concomitant chronic inflammation and help distinguish inflammatory bowel disease from acute self-limited colitis (a sudden inflammatory injury to the colon that spontaneously remits, such as infectious colitis, ischemic colitis, and NSAID colitis). None of these features is specific for ulcerative colitis—they can be present in infectious colitis or other inflammatory conditions, such as Crohn's disease.[20] A pathologist's experience with inflammatory bowel disease will determine how easily he or she can differentiate it from acute self-limited colitis. The conditions most commonly confused with inflammatory bowel disease are *Campylobacter* and *Yersinia* infections, amebic infections of the colon, and ischemic colitis.[21] The differential diagnosis of ulcerative colitis is shown in **Table 2**.

Distinguishing ulcerative colitis from Crohn's disease is also essential, because treatments and anticipated complications will differ. Because it is sometimes not possible to make this distinction early in the course of disease, some patients are given a diagnosis of "indeterminate colitis." As the disease develops, it will likely begin to fit a pattern that is more consistent with either ulcerative colitis or Crohn's disease. Differentiating infectious colitis from inflammatory bowel disease or ischemic colitis by endoscopy alone may not be possible, although the endoscopic impression may be consistent with the clinical diagnosis. Affected mucosa in ulcerative colitis can regenerate and heal to a virtually normal appearance; therefore, for longstanding cases, biopsies are useful to identify histologic changes of chronic inflammatory bowel disease (crypt architectural distortion) or other forms of "microscopic colitis" (eg, collagenous colitis). Biopsy of normal and abnormal mucosa is required to reveal quiescent colitis and to determine if skip lesions are present. Skip lesions are seen in Crohn's disease, but the inflammation of ulcerative colitis is usually in a continuous pattern.[21]

Histology can also help predict the future severity of a patient's ulcerative colitis course. A recent study that evaluated clinical factors that predict frequent relapses

Table 2. Differential Diagnosis of Ulcerative Colitis

Disease	Clinical Characteristics	Histologic Characteristics
Ulcerative colitis	Bloody diarrhea	Distortion of crypts; acute and chronic diffuse inflammatory infiltrate; goblet cell depletion; crypt abscesses; lymphoid aggregates
Crohn's colitis	Perianal lesions common; frank bleeding less frequent than in ulcerative colitis	Focal inflammation; submucosal involvement; granulomas; goblet cell preservation; transmural inflammation; fissuring
Ischemic colitis	Older age groups; vascular disease; sudden onset, often painful	Mucosal necrosis; ballooning of capillaries; red blood cell congestion; hemosiderin and fibrosis (chronic disease)
Collagenous colitis	Watery diarrhea; rectal bleeding rare	> 10 µm–thick subepithelial collagen band; chronic inflammatory infiltrate
Microscopic (lymphocytic) colitis	Watery diarrhea; often seen in older women; macroscopically normal colonic mucosa	Chronic inflammatory infiltrate; increased intraepithelial lymphocytes; crypt distortion unusual
Infective colitis	Sudden onset usual; identifiable source with other cases (eg, *Salmonella*); pain may predominate (eg, *Campylobacter*); pathogens present in stool	Crypt architecture usually normal; edema; superficial neutrophil infiltrate; crypt abscesses
Pseudomembranous colitis	May be a history of antibiotics; "membrane" may be seen on sigmoidoscopy; *Clostridium difficile* toxin detectable in stools	Similar to acute ischemic colitis but may show "summit" lesions of fibrinopurulent exudate
Amebic colitis	Travel in endemic area; amebae in fresh stool	Similar to ulcerative colitis; amebae in lamina propria or in flask-shaped ulcers; identified by periodic acid–Schiff stain
Gonococcal colitis	Rectal pain; pus	Intense neutrophil infiltration; purulent exudate; gram-positive cocci

Adapted with permission from Jewell DP. Ulcerative colitis. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Gastrointestinal and liver disease. Vol. 2. Philadelphia: W.B. Saunders; 1998:1748.

of ulcerative colitis identified heavy infiltration of plasma cells into the lamina propria as an independent predictor of more frequent flares.[22] Microscopic erosions seen in macroscopically intact mucosa also have been cited as a predictor of relapse.[23] Further research that identifies such histologic criteria may allow subgroups of patients who are at high risk of relapse to be targeted with more aggressive medical therapy.

- **What serologic tests can be performed to distinguish ulcerative colitis from Crohn's disease?**

Serology Tests

In the past 10 years, the perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and antisaccharomyces cerevisiae antibody (ASCA) serum assays have emerged as useful adjuncts in the classification of patients with indeterminate colitis. In the clinical context of idiopathic colitis, a positive p-ANCA test predicts ulcerative colitis with high specificity.[24] Similarly, a patient with indeterminate colitis who has ASCA-positive serum is likely to experience a clinical course consistent with Crohn's disease. These markers are not sensitive enough to allow them to be used as screening tests in the general population. Determining p-ANCA and ASCA status may be more useful as a confirmatory test in a pediatric population, in which they have been shown to have high specificity[25] and in which endoscopic evaluation is more difficult. In adults, serologic tests can help predict the type of course a patient will experience and thereby aid with medical and surgical decision making. Moreover, several studies have shown that p-ANCA titers correlate with disease activity

Table 3. Medications Commonly Used to Treat Ulcerative Colitis

Class/Drug	Distal Colitis	Mild-Moderate	Moderate-Severe	Maintenance
5-ASA				
Enema	+†	+*	–	+
Oral	+†	+†	–	+
Corticosteroids (classic and novel)				
Enema, foam, suppository	+†	+*	–	–
Oral	+†	+	+†	–
Intravenous	+†	–	+†	–
Immunomodulators				
6-MP/AZA	+†	–	+†	+†
Methotrexate	–†	–	–	–
Cyclosporine	+†	–	+†	–

Adapted with permission from Sands BE. Therapy for inflammatory bowel disease. Gastroenterol 2000;118:S71.

ASA = aminosalicylic acid; AZA = azathioprine; 6-MP = 6-mercaptopurine.

*For adjunctive therapy.

†Selected patients.

or may predict the postsurgical complication of pouchitis in patients with ulcerative colitis who undergo colectomy and ileoanal J-pouch anastomosis.[26,27]

Diagnosis

The physician makes a diagnosis of ulcerative colitis based on the following findings: The patient is a young woman with recent onset of inflammatory diarrhea symptoms. Her physical examination is notable for pallor, dry oral mucosa, abdominal tenderness, and heme-positive stool. Laboratory data show leukocytosis, hypoalbuminemia, and fecal leukocytes. Endoscopic evaluation shows a left-sided colitis and biopsies reveal acute and chronic inflammation. The patient's disease is judged to be moderately severe.

- **What is the approach to therapy in inflammatory bowel disease?**

Therapy for ulcerative colitis or Crohn's disease occurs in 2 steps. The first step is to induce remission and resolve all inflammatory symptoms, and the second is to maintain remission. Published literature reviews of severe ulcerative colitis suggest that approximately two thirds of patients achieve clinical remission with medical therapy; remission is maintained in up to 80% of treatment-compliant patients.[28]

Induction

Aminosalicylates that contain 5-aminosalicylic acid (5-ASA [mesalamine]) are the first-line agents for inducing remission in ulcerative colitis for patients with mild to moderate symptoms (**Table 3**). Mesalamine is the active moiety that acts topically (from the lumen) to suppress the production of numerous proinflammatory mediators.[29] Aminosalicylates are available in pills, suppositories, and enemas.

The selection of an aminosalicylate agent is determined by the specific sites in the large intestine to which the mesalamine must be delivered; the dose must be optimized to achieve clinical benefits. Fortunately, these formulations have low toxicity and are generally well tolerated (**Table 4**). When aminosalicylates are inadequate or when symptoms of ulcerative colitis are moderate to severe, oral or topical administration of corticosteroids must be used to induce remission. Prednisone 40 mg or 60 mg daily is the usual starting corticosteroid. Full-dose therapy is continued until symptoms abate and bowel movements normalize. The dose is tapered only after the patient improves to the extent that he or she is experiencing no visible blood with bowel movements and no frequency, urgency, or nocturnal bowel movements.

When orally administered prednisone is not effective, patients must be hospitalized and started on

corticosteroids, intravenously (usually methylprednisolone sodium succinate 40 mg daily). If the flare has not responded after 5 to 7 days of intravenous therapy, 2 options remain: intravenously administered cyclosporine or colectomy.[30] A retrospective study of 85 consecutive patients with severe ulcerative colitis, many of whom had failed therapy with orally administered corticosteroids, showed that those with symptoms lasting more than 6 weeks or with severe endoscopic lesions had the highest failure rate on intravenously administered corticosteroids (85%).[31] This patient subset required colectomy or intravenously administered cyclosporine.

Maintenance

Once a patient is in remission, the goal of continued therapy is to prevent recurrence. The level of therapy that induced remission dictates the selection of therapy for maintenance. If, for example, 5-ASA compounds successfully controlled symptoms, then 5-ASA compounds will likely be adequate for maintenance therapy.[32] Patients with ulcerative colitis limited to the distal colon often require topical administration of mesalamine to induce remission. Many clinicians have found that to maintain remission in these patients, the combination of oral and intermittent rectal mesalamine treatments with enemas or suppositories are necessary on a long-term basis.[33] If corticosteroids are necessary to induce remission, larger doses (up to 4.8 g daily) of mesalamine may be required to prevent relapse as corticosteroids are tapered.

Corticosteroids can induce remission in ulcerative colitis but are not effective in preventing relapse. Once a disease is in remission, the daily dose of prednisone can be tapered on an individualized basis according to the time required to achieve a complete resolution of symptoms. In general, prednisone can be reduced weekly in 5-mg increments.

At referral centers for inflammatory bowel disease, clinical researchers have studied immunomodulator therapy with 6-mercaptopurine (6-MP) or azathioprine to maintain remission in ulcerative colitis patients who have been unable to taper corticosteroids, despite mesalamine maintenance therapy. In a long-term outcome study, complete remission was attained in 65% of patients taking 6-MP and partial remission was seen in 24%.[34] Complete responders who discontinued immunomodulator therapy, however, had a high relapse rate (87%).

If intravenously administered cyclosporine was used to induce remission, a transition to orally administered cyclosporine is performed at the time of hospital discharge. Over the next several months, many experts suggest further transition to 6-MP or azathioprine as long-term maintenance therapies, because cyclosporine has not been an effective maintenance treatment. Long-term toxicities of cyclosporine include hypertension, renal insufficiency, headaches, gingival

Table 4. Selected Adverse Effects of Medications Commonly Used to Treat Ulcerative Colitis

Agent	Adverse Effects
5-ASA	
Sulfasalazine	Anorexia, dyspepsia, nausea/vomiting; hemolysis, neutropenia, agranulocytosis; folate malabsorption; reversible male infertility; neuropathy; *see also* sulfa-free 5-ASAs
Sulfa-free (mesalamine, olsalazine, balsalazide)	Headache; drug fever, rash; paradoxical exacerbation of colitis; pancreatitis; hepatitis; pericarditis; pneumonitis; nephritis; secretory diarrhea (olsalazine)
Corticosteroids	
Classic	Sleep disturbance, mood disturbance, acne, striae, hirsutism, adrenal suppression, proximal myopathy, glucose intolerance, hypertension, narrow angle glaucoma, cataracts, pseudo-tumor cerebri, infection, edema, impaired wound healing, growth retardation, osteoporosis, aseptic necrosis
Novel	Budesonide CIR: adrenal suppression at doses of 9 mg/day in 2 divided doses and higher, but occurrence of classic corticosteroid adverse effects similar to placebo
Immunomodulators	
6-MP/AZA	Nausea; drug fever, rash, arthralgia; leukopenia; thrombocytopenia; pancreatitis; hepatitis; infection
Methotrexate	Anorexia, nausea/vomiting; bone marrow suppression; megaloblastic anemia; alopecia; abortifacient; hepatic fibrosis; interstitial pneumonitis; neuropathy
Cyclosporine	Reversible or irreversible decrease in renal function; hypertension; tremor, headache, paresthesia, seizure; hypertrichosis; hepatotoxicity; infection; lymphoma; gingival hyperplasia

Adapted with permission from Sands BE. Therapy for inflammatory bowel disease. Gastroenterol 2000;118:S72.

ASA = aminosalicylic acid; AZA = azathioprine; CIR = controlled ileal release; 6-MP = 6-mercaptopurine.

hyperplasia, and hyperkalemia. The antimetabolites 6-MP and azathioprine are generally better tolerated, although they are associated with a 3% to 15% incidence of pancreatitis. Monitoring of a patient's complete blood count is required at least quarterly because of the risk for leukopenia.[35]

Treatment and Follow-up

Therapy with orally administered mesalamine at a dose of 2.4 g daily is started in the patient, and she is instructed to avoid NSAIDs. She is seen for follow-up 10 days later. At this visit, she reports that her symptoms have improved slightly, but her bowel movements have not normalized. She still has 3 or more soft or sometimes liquid bowel movements daily with visible blood. The pain has resolved, and the patient has begun to eat more. The fever has resolved as well.

The dose of orally administered mesalamine is increased to 4.8 g daily, and a mesalamine enema is prescribed to be taken at night. After several weeks, symptoms of morning urgency and bleeding continue, and the patient reports at least 6 trips to the toilet daily. She is begun on orally administered prednisone 40 mg daily and is continued on mesalamine 4.8 g daily.

After 3 weeks her diarrhea has completely resolved. She feels well. She reports that she has no abdominal pain and that her bowel movements are formed, occur once daily, and have no apparent blood.

- **How long must maintenance therapy be continued in ulcerative colitis?**

The optimum duration of medical maintenance therapy is not known. In one study, patients with ulcerative colitis were stratified according to their duration of remission and randomized to receive mesalamine or placebo for 1 year.[36] Mesalamine was more effective at maintaining remission in patients who had a shorter duration of remission (mesalamine 23% recurrence, placebo 49% recurrence). However, among the patients with a longer duration of remission at study entry, there was no statistical difference in the rate or relapse. This research suggests that patients with mild ulcerative colitis may not need indefinite maintenance therapy once they have been in remission for several years. In general, however, patients with inflammatory bowel disease must be compliant with maintenance medical therapy in order to decrease the likelihood of recurrent flares.

- **How is alternative or complementary medicine changing the management of ulcerative colitis?**

Complementary Medicine Use

Use of complementary medicine therapies has become increasingly common among patients with inflammatory bowel disease. Vitamins and herbal therapies appear to be the most popular choices. Because some remedies may interfere with conventional medicines, it has become necessary for clinicians to question patients about self-medication. In a 1998 survey of 134 patients with Crohn's disease or ulcerative colitis, 51% of patients used an alternative therapy within the prior 2 years.[37] Patients were motivated by dissatisfaction with adverse effects and ineffectiveness of conventional treatments. Patients who were ill for more than 10 years and those with a history of hospitalization for inflammatory bowel disease were most likely to have used complementary medicine. A large percentage of patients surveyed did not report the complementary medicine use to their doctor, mostly because they perceived their physicians to be ignorant or intolerant of alternative therapies.

Moser and colleagues reported similar conclusions from a study that correlated alternative medicine use with results from a questionnaire on patients' concerns about inflammatory bowel disease.[38] Approximately 1 in 3 patients with inflammatory bowel disease used an unconventional therapy. Most used the alternative treatments in conjunction with conventional medicines prescribed by their doctors. Users of complementary medicine tended to have longer disease duration and were more preoccupied by the prospect of surgery and feeling out of control.

At this time, when most herbal supplements have not been rigorously studied and their efficacy in inflammatory bowel disease is unknown, clinicians must be aware of these trends in patients with a chronic illness such as ulcerative colitis. These studies reinforce the importance of taking a thorough medication history and allowing inflammatory bowel disease patients to actively participate in medical decision making.

- **What surgical procedures are used in ulcerative colitis, and when is surgery indicated?**

Surgery

Surgery is curative in ulcerative colitis and has been shown to lead to durable improvements in quality of life.[39] Several surgical options exist. The 2 most common choices today are proctocolectomy with ileostomy and total colectomy with ileoanal anastomosis. In previous years, total colectomy with ileorectal anastomosis has been performed as well as proctocolectomy with the Kock pouch—a continent ileostomy.

Elective surgery in ulcerative colitis can be done laparoscopically. The advantages of the laparoscopic approach are a shorter postoperative ileus and less narcotic requirement. Patients can generally be fed sooner, and shorter hospital stays have been reported.[40]

Colectomy is indicated in ulcerative colitis that is refractory to medical therapies or when it is fulminant and toxic megacolon or perforation is suspected. Approximately 25% of patients with severe colitis will fail to improve from therapy with intravenously administered corticosteroids and will require urgent colectomy.[41] Clinical signs that suggest failing medical therapy include cessation of bowel movements, abdominal distension, progressive leukocytosis, and progressive hypoalbuminemia. Surgery should be offered to all patients with severe symptoms who do not improve within a week of treatment with intravenously administered corticosteroids. A final indication for surgery is the development of dysplasia or cancer.

Two Years Later

At a follow-up visit 2 years after diagnosis of ulcerative colitis, the patient reports having mild flares of her symptoms that she manages with short-term treatment with nightly mesalamine enemas. In general, the ulcerative colitis has remained well controlled with orally administered mesalamine. She has new symptoms of hip and knee pain that correlate with her flares of colitis. In addition, her aunt was recently diagnosed with colon cancer, and she is concerned about her own risk.

- **What are the complications of ulcerative colitis?**

Complications of Ulcerative Colitis

There are several extraintestinal manifestations of ulcerative colitis. Inflammatory changes can be seen in the oral mucosa, where aphthae are seen in approximately 10% of patients experiencing an acute flare. The skin may also be involved in ulcerative colitis. Erythema nodosum may complicate ulcerative colitis or herald a flare of the disease. Pyoderma gangrenosum is an ulcerating skin condition that affects the trunk and limbs of only 1% to 2% of these patients. The skin lesions parallel the severity of colonic inflammation and only rarely persist in the setting of quiescent colitis or after colectomy. Episcleritis or anterior uveitis is seen in 5% to 8% of patients. Scleral inflammation is most commonly associated with flares of colitis, whereas uveitis (iritis) is associated with HLA B-27 and runs a course independent from colitis activity. Asymmetric, large joint arthritis with swelling but without erosion complicates approximately 10% to 15% of patients with acute symptoms. In general, these extraintestinal manifestations of ulcerative colitis respond to the treatment of the disease.[20]

The principal long-term complications of ulcerative colitis are colorectal cancer and primary sclerosing cholangitis. The risk for colon cancer in a patient with ulcerative colitis rises exponentially as the duration of disease increases. The annual rate of development of colorectal cancer has been estimated to be 2% after 20 years of disease and 8% after 30 years. Persons who develop ulcerative colitis later in life are thought to be at an even higher risk.[42]

Current practice guidelines recommend that surveillance for colorectal cancer begin after the tenth year of disease, regardless of the level of disease activity. Colonoscopy with random biopsies is recommended at 2-year intervals. If there is any microscopic evidence of dysplasia in areas of the colon affected by ulcerative colitis, the patient should undergo prophylactic colectomy.[43]

Cancerous lesions in ulcerative colitis may be occult, and some experts advocate consideration of elective prophylactic colectomy in any patient with a long disease duration. In a series of 493 patients with an average duration of illness of 18.5 years who underwent colectomy and were found to have cancer, 12% had no preoperative evidence of malignancy.[44] Our preference is to enroll patients with disease in a surveillance program that consists of colonoscopy every 2 years with multiple random biopsies at 10-cm intervals throughout the colon. This screening begins 10 years after diagnosis. We do not advocate routine prophylactic colectomies.

Primary sclerosing cholangitis occurs in approximately 3% of ulcerative colitis patients. Chronic inflammation of the biliary system leads to cholestasis, intrahepatic and extrahepatic biliary obstruction, and, eventually, cirrhosis. Endoscopic cholangiography and liver biopsy can confirm the diagnosis. Treatments include endoscopic decompression of dominant extrahepatic biliary strictures and supportive care for complications of liver disease. Therapy with ursodeoxycholic acid can provide symptomatic relief from pruritus and may slow the progression of the biliary inflammation. Interestingly, a recent cross-sectional study showed that patients with ulcerative colitis who had primary sclerosing cholangitis treated with ursodeoxycholic acid had less colonic dysplasia, suggesting that ursodeoxycholic acid may have a chemopreventive effect in the colon.[45] Primary sclerosing cholangitis is a strong risk factor for the development of cholangiocarcinoma. All dominant biliary strictures should be sampled cytologically or evaluated by intraductal endosonography to afford early diagnosis of malignancy.

Physician's Recommendations

The physician reassures the patient that the joint pains she is feeling is related to her intestinal inflammation and should improve with treatment of the colitis. He also explains that her risk of colorectal cancer will ultimately be even higher than that of other patients with ulcerative colitis because she has a first-degree relative with colorectal cancer. The physician recommends full colonoscopy after 10 years of ulcerative colitis, or sooner if the patient has new symptoms or a clinical change such as weight loss.

CONCLUSION

Ulcerative colitis is a chronic inflammatory condition of the colon that does not shorten a patient's life span but can cause significant morbidity and lead to considerable expense. Before establishing the diagnosis of ulcerative colitis, a physician must carefully consider other inflammatory intestinal processes that resemble the disease. The goals of therapy are to suppress all inflammatory symptoms, both intestinal and extraintestinal, and then to choose the least toxic but most effective maintenance treatment to prevent flares. Over the long term, screening for neoplastic and cholestatic complications as well as complications of medical therapy take on greater importance. **HP**

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