Clinical Roundtable Monograph

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# Optimizing Patient Outcomes in the Treatment of Ulcerative Colitis

## Faculty

Patrick G. Brady, MD
Director of the Division of Digestive Diseases and Nutrition
University of South Florida
Tampa, Florida

Gary R. Lichtenstein, MD
Director of the Inflammatory Bowel Disease Program
University of Pennsylvania
Philadelphia, Pennsylvania

Paul J. Rutgeerts, MD, PhD, FRCP, AGAF
Professor of Medicine
Head of the Endoscopy Unit
Leuven University Hospital
Leuven, Belgium

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## Abstract

With a prevalence of approximately 500,000 cases in the United States alone, ulcerative colitis (UC) has a major impact on patient health and quality of life. Currently, clinicians use a range of medications to treat this condition. Patients with mild or moderate UC often respond well to 5-aminosalicylic acid and/or corticosteroids, while patients with severe or fulminant UC may require intravenous corticosteroids, antibiotics, and/or immunosuppressant agents. Because of the chronic nature of this disease, however, patients are likely to experience repeated symptomatic flares and often become refractory to particular treatments. Mounting evidence suggests that the degree of response patients achieve following treatment largely dictates their ability to maintain long-term remission: Patients who achieve both symptomatic and endoscopic remission tend to experience better clinical outcomes than patients who achieve symptomatic remission but still show mucosal inflammation. Importantly, clinical trials have shown that the anti–tumor necrosis factor agent infliximab can induce both symptomatic and endoscopic remission, suggesting that it may provide significant benefits in the treatment of UC. This roundtable addresses several topics that physicians should consider when treating patients with UC, including the importance of successfully differentiating between UC and Crohn's disease, the association between mucosal healing and improved patient outcomes, and data regarding which therapies can best achieve these outcomes.

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**Course Description:** This monograph discusses advances in the treatment and understanding of ulcerative colitis (UC), including diagnosis, predictors of response, and strategies for maximizing patient outcomes.

**Accreditation:** This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of USF Health, BioMed Media, and *Gastroenterology & Hepatology*. USF Health is accredited by the ACCME to provide continuing medical education (CME) for physicians.

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**Statement of Need:** The clinical roundtable monograph *Optimizing Patient Outcomes in the Treatment of Ulcerative Colitis* discusses the most recent updates emerging in the management of UC. Advances in diagnosis, evaluation, treatment, predictors of response, definitions of remission, and emerging data regarding current and novel therapies for UC continue to evolve. Physicians need to be aware of all these variables that can influence treatment choices and outcomes. This program is designed to meet those needs with the latest data, information, and practical recommendations from renowned experts.

**Target Audience:** This activity is intended for gastroenterologists, nurses, and other healthcare professionals involved in the treatment of patients with UC.

**Learning Objectives:** At the conclusion of this activity, participants should be able to:

1. Communicate the therapeutic goals of treatment in patients with UC.
2. Outline the benefits of achieving mucosal healing in patients with UC.
3. Access the current evidence for the use of therapies in altering the course of disease and improving long-term outcomes.
4. Articulate effective, individualized treatment strategies for patients with UC.
5. Characterize the latest developments in the treatment of UC.

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# Diagnosis of Ulcerative Colitis

Gary R. Lichtenstein, MD

Ulcerative colitis (UC) is a chronic, lifelong, idiopathic inflammatory disorder of the colon limited to the mucosa of the intestinal tract.[1] The clinical course of UC generally involves repeated symptom exacerbations, or flares, which alternate with periods of remission. While remission may occur in response to therapy, patients can also achieve remission spontaneously, as occurs in some placebo-treated patients in clinical trials.[2,3] In the United States, UC is a significant health issue; it affects approximately 500,000 individuals and is associated with an adjusted incidence of 8.8–12.0 cases per 100,000 individuals per year.[4,5] UC also has a major impact on productivity and medical costs, and it is a major reason for physician visits and hospitalizations.[6-8]

## Establishing a Diagnosis of UC

UC is an idiopathic inflammatory disorder that spares no age (although it typically occurs in the 2nd to 3rd decade of life), gender, or socioeconomic group. Classical clinical features of UC include persistent bloody diarrhea and tenesmus. However, diarrhea is not a compulsory symptom; individuals may present with a change in bowel habits or even constipation.

Clinical scenarios that may exacerbate UC symptoms include use of nonsteroidal anti-inflammatory drugs or recent smoking cessation. Recent epidemiologic data have linked the use of the acne prescription medication isotretinoin with the development of inflammatory bowel disease (IBD); among 85 IBD cases reported to the US Food and Drug Administration, isotretinoin was suggested to be a highly probable, probable, or possible cause in 5%, 68%, and 27% of patients, respectively.[9] A more recent case-control study likewise found a strong association between prior isotretinoin exposure and UC (odds ratio [OR], 4.36; 95% confidence interval [CI], 1.97–9.66), and this risk was found to increase with higher doses (OR per 20-mg increase, 1.50; 95% CI, 1.08–2.09).[10] This same study failed to show an association between isotretinoin exposure and Crohn's disease (CD). The association between isotretinoin and IBD is not universally supported, however; a population-based, case-control study found no significant association between isotretinoin use and IBD.[11]

The diagnosis of UC is first suspected based upon clinical grounds and then supported by appropriate findings on endoscopy; pathogens or infectious causes of inflammation must also be excluded with negative stool studies.[1] In a patient who presents with suspected UC, a diagnosis is established with either a proctosigmoidoscopy or colonoscopy. These procedures are used to view the intestinal lining and look for characteristic mucosal changes indicative of UC, which include loss of the characteristic vascular pattern, ulceration, granularity, and friability.[12-14] The prototypic presentation of UC involves changes in the distal rectum that proceed proximally in a symmetric and circumferential continuous pattern to involve part or all of the colon.[15] However, some individuals with distal colonic disease exhibit only associated patchy cecal inflammation.[15,16]

In addition to endoscopic findings, histology can help to establish the diagnosis in a patient with suspected UC. Histologic findings are especially important when differentiating UC from infectious colitis.[17-20] Unlike infectious colitis, UC is more frequently associated with distorted crypt architecture, including crypt atrophy, separation, and distortion. Chronic inflammatory cells in the lamina propria are also more frequently observed in UC. Additionally, neutrophils infiltrate the crypt epithelium preferentially in UC, and lymphocytes and plasma cells appear in increased numbers at the crypt bases. Other characteristic histologic features observed in the mucosa of UC patients include crypt shortfall (in which the crypt does not reach the muscularis mucosae) and basal lymphoid aggregation. Paneth cell metaplasia may also be observed and is typically more common on rectal biopsy in UC patients. In contrast, crypt abscesses do not help to differentiate between UC and infectious colitis. When distinguishing between CD and UC, clinicians should note that patients with CD may have noncaseating granulomas or microscopic focality; however, the absence of these findings does not exclude a diagnosis of CD.

Determining whether an infectious etiology may explain the clinical symptoms in a presenting patient is sometimes difficult, particularly when the patient lacks histologic findings such as distorted crypt architecture. To be certain of the diagnosis in these cases, clinicians may need to perform a repeat endoscopy to determine if changes are persistent. The presence of persistent endoscopic findings suggests that an infectious etiology is not responsible for the presence of the colitis.

The natural history of UC involves a sequence of progression in association with the mucosal inflammation. Characteristically, in the early phases, the lamina propria

is edematous, capillaries become more dilated and congested, and clinicians may observe the presence of inflammatory infiltrates and extravasates, including neutrophils, plasma cells, macrophages, lymphocytes, eosinophils, and mast cells. In early active disease, crypt epithelial lining infiltrates form crypt abscesses, which are associated with mucus coming out of the goblet cells and an increase in cell turnover.[21] Goblet cell dropout eventually occurs and is followed by more progressive changes.[22] For example, the surface epithelium begins to flatten out and form ulcerations as the inflammation increases. These ulcerations can be deep and may go around the surface epithelium, and some inflammation and vascular congestion are commonly present in the submucosa. Clinicians should recognize that histology can become completely normal as the disease goes into remission. Additionally, treatment can cause the mucosa to exhibit a patchy disease distribution, in which some areas appear completely normal and intervening areas are abnormal.

## Distinguishing UC from CD and Other Conditions

A variety of factors are used to differentiate UC and CD, including endoscopic, histologic, and radiographic features.[23] For example, UC classically appears as continuous disease on endoscopy, with mucosal changes beginning in the rectal area at the anal verge and proceeding proximally. In contrast, CD causes discontinuous changes and characteristic "skip" lesions. Further differentiating these 2 conditions, the mucosa appears more granular and friable in UC, while in CD it contains serpiginous ulcerations. Also, fistulae may be present in CD, but they do not appear in UC. Finally, the ileum is ulcerated and inflamed with aphthous ulcers in CD, but these ulcers do not classically appear in UC.

Depending upon which study is cited, indeterminate colitis is present in approximately 5–20% of patients, although there is a paucity of data regarding the incidence of indeterminate colitis among adults in the United States.[24] In cases of indeterminate colitis, clinicians cannot distinguish between UC and CD at presentation. Fortunately, this diagnostic uncertainty does not represent a major concern in terms of short-term disease management, as the initial treatment remains the same regardless of the diagnosis. Distinguishing between the 2 conditions becomes a more pressing issue when clinicians are trying to determine if a colectomy is needed, as data show that patients with indeterminate colitis have a higher risk of pouch complications compared to patients with definitive UC.[25,26] If the clinician is unable to distinguish between UC and CD, then he or she must acknowledge the higher risk of complications associated with an ileal pouch-anal anastomosis.

If a patient with acute, self-limited, infectious colitis is misdiagnosed as having UC, the patient will likely receive unnecessary corticosteroid treatment. Unfortunately, the array of complications that may ensue from such treatment can be significant, potentially including bacteremia. Because corticosteroids may supress the immune system, they can make an individual more susceptible to complications of sepsis; thus, bacteremia may result in cases where a pathogen is responsible for the inflammation.

Another possible consequence of misdiagnosis is the potential for unnecessary or inappropriate surgery. If infectious colitis is misdiagnosed as UC, patients may undergo unnecessary surgery. On the other hand, if a patient is misdiagnosed as having CD instead of UC, the surgeon might withhold the option of an ileal pouch-anal anastomosis and instead require the patient to undergo an end ileostomy (also referred to as a Brooke ileostomy). This latter procedure represents a less desirable outcome for patients, who generally prefer to undergo the ileal pouch-anal anastomosis so that they can remain capable of functioning without an external ostomy.

## Imaging and Diagnostic Assays for Diagnosis of UC

When attempting to distinguish UC from CD, clinicians may find imaging studies of the small intestine to be helpful, as they can aid in determining the presence or absence of small bowel disease. These imaging studies may include computed tomography (CT) enterography, magnetic resonance enterography, and video capsule endoscopy; in addition, various forms of enteroscopy (including spiral or double-balloon enteroscopy) can be used when a biopsy may be necessary and to visualize any areas that may appear abnormal on small bowel imaging.[27-29] Colonoscopic intubation of the terminal ileum may allow clinicians to visualize at least a portion of the small bowel, and small bowel barium radiographic studies or CT enterography may also be useful in some cases. Additionally, an upper endoscopic evaluation may be helpful if the patient has aphthous ulcerations or other features characteristic of CD.

The laboratory values commonly assessed in UC patients—including complete blood count, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR)—are all nonspecific and thus are not helpful in establishing a diagnosis of UC. However, the presence or absence of enteric pathogens in the stool is an important criterion for ruling out infectious colitis. For example, clinicians should test for *Clostridium difficile* infection, especially in patients who were recently treated with antibiotics or admitted to the hospital. Viral infections may also be responsible for a patient's symptoms, as in the case of cytomegalovirus (CMV) colitis, so serologic testing and mucosal histologic assessment may sometimes be necessary to search for a viral etiology. While CMV colitis occurs more frequently in immunocompromised hosts, it can occur in a normal host as well.

In the absence of imaging features characteristic of either UC or CD, it has been hoped that serologic evaluation may help to differentiate between the 2 conditions. In patients with known diagnoses, the presence of perinuclear antineutrophil cytoplasmic antibody (pANCA) combined with a negative anti–*Saccharomyces cerevisiae* antibody (ASCA) result has a sensitivity of 57% and a specificity of 97% in UC patients.[30] Another study demonstrated that positivity for pANCA alone was associated with a sensitivity of 40% and a specificity of 82% in UC patients.[31] However, pANCA is not found exclusively in UC; it has been reported in up to 40% of CD patients.[32] In addition, CD patients with pANCA-positive disease typically have a clinical phenotype that resembles left-sided UC, so pANCA alone is not very useful in distinguishing between UC and CD.[33] However, reactivity to anti-flagellin antibody (CBir1) is observed at higher rates in pANCA-positive CD patients compared to pANCA-positive UC patients (44% vs 4%).[34]

In a meta-analysis of 60 studies (comprising 3,841 UC patients and 4,019 CD patients) in which researchers evaluated the performance characteristics of ASCA and pANCA, specificity for pANCA in UC was 88.5%, but the sensitivity of this marker was only 55.3%. A positive ASCA test combined with a negative pANCA result showed a specificity of 92.8% for CD, but the sensitivity of this combination was only 54.6%. Thus, the low sensitivity of pANCA for UC restricts its usefulness as a diagnostic tool.[35] However, the specificities of combination results may make these tests helpful for distinguishing between CD and UC in patients who have no other clinical or pathologic features.

Unfortunately, when assessed prospectively, ASCA and pANCA are not very helpful for assessing whether patients with indeterminate colitis have UC or CD.[36] The addition of other serologic markers, such as *Escherichia coli* outer membrane porin C (OmpC) and *Pseudomonas fluorescens*–related protein (I2), adds no further benefit.[37]

## Summary

Unfortunately, clinicians do not yet have a definitive serologic test for the diagnosis of UC. Instead, a suspected diagnosis of UC must be confirmed with endoscopic and histologic mucosal findings. These findings must be considered in conjunction with pathogen testing to exclude the possibility of infectious colitis. In addition, clinicians must evaluate patients for a history of exposure to environmental factors that might explain the observed inflammation (such as ischemia, radiation, or drugs) as well as for conditions in which colitis is caused by some other etiology (such as solitary rectal ulcer syndrome or segmental colitis with diverticulitis). Endoscopy, radiology, and histology remain the mainstays of our clinical diagnostic armamentarium. Microscopic findings and disease distribution help to classify patients as having UC, CD, or indeterminate colitis.

## References


1. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105:501-523.
2. Meyers S, Janowitz HD. The "natural history" of ulcerative colitis: an analysis of the placebo response. *J Clin Gastroenterol*. 1989;11:33-37.
3. Kornbluth AA, Salomon P, Sacks HS, Mitty R, Janowitz HD. Meta-analysis of the effectiveness of current drug therapy of ulcerative colitis. *J Clin Gastroenterol*. 1993;16:215-218.
4. Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996-2002. *Am J Gastroenterol*. 2008;103:1998-2006.
5. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis*. 2007;13:254-261.
6. Nguyen GC, Tuskey A, Dassopoulos T, Harris ML, Brant SR. Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004. *Inflamm Bowel Dis*. 2007;13:1529-1535.
7. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology*. 2008;135:1907-1913.
8. Sonnenberg A, Chang J. Time trends of physician visits for Crohn's disease and ulcerative colitis in the United States, 1960-2006. *Inflamm Bowel Dis*. 2008;14:249-252.
9. Reddy D, Siegel CA, Sands BE, Kane S. Possible association between isotretinoin and inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:1569-1573.
10. Crockett SD, Porter CQ, Martin CF, Sandler RS, Kappelman MD. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. *Am J Gastroenterol*. 2010;105:1986-1993.
11. Bernstein CN, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. *Am J Gastroenterol*. 2009;104:2774-2778.
12. Leighton JA, Shen B, Baron TH, et al. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointest Endosc*. 2006;63:558-565.
13. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. *Clin Gastroenterol Hepatol*. 2005;3:11-24.
14. Simpson P, Papadakis KA. Endoscopic evaluation of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14:1287-1297.
15. Robert ME, Skacel M, Ullman T, Bernstein CN, Easley K, Goldblum JR. Patterns of colonic involvement at initial presentation in ulcerative colitis: a retrospective study of 46 newly diagnosed cases. *Am J Clin Pathol*. 2004;122:94-99.
16. Joo M, Odze RD. Rectal sparing and skip lesions in ulcerative colitis: a comparative study of endoscopic and histologic findings in patients who underwent proctocolectomy. *Am J Surg Pathol*. 2010;34:689-696.
17. Dundas SA, Dutton J, Skipworth P. Reliability of rectal biopsy in distinguishing between chronic inflammatory bowel disease and acute self-limiting colitis. *Histopathology*. 1997;31:60-66.
18. Surawicz CM, Belic L. Rectal biopsy helps to distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. *Gastroenterology*. 1984;86:104-113.
19. Jenkins D, Balsitis M, Gallivan S, et al. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol*. 1997;50:93-105.
20. Nostrant TT, Kumar NB, Appelman HD. Histopathology differentiates acute self-limited colitis from ulcerative colitis. *Gastroenterology*. 1987;92:318-328.
21. Strugala V, Dettmar PW, Pearson JP. Thickness and continuity of the adherent colonic mucus barrier in active and quiescent ulcerative colitis and Crohn's disease. *Int J Clin Pract*. 2008;62:762-769.
22. Faure M, Moënnoz D, Montigon F, et al. Mucin production and composition is altered in dextran sulfate sodium-induced colitis in rats. *Dig Dis Sci*. 2003;48:1366-1373.
23. Geboes K, De Hertogh G. Indeterminate colitis. *Inflamm Bowel Dis*. 2003;9:324-331.
24. Meucci G. What is the incidence, prevalence, and natural history of indeterminate colitis? *Inflamm Bowel Dis*. 2008;14(suppl 2):S159-S160.
25. Mitchell PJ, Rabau MY, Haboubi NY. Indeterminate colitis. *Tech Coloproctol*. 2007;11:91-96.
26. Brown CJ, Maclean AR, Cohen Z, Macrae HM, O'Connor BI, McLeod RS. Crohn's disease and indeterminate colitis and the ileal pouch-anal anastomosis: outcomes and patterns of failure. *Dis Colon Rectum*. 2005;48:1542-1549.

27. Mensink PB, Aktas H, Zelinkova Z, West RL, Kuipers EJ, van der Woude CJ. Impact of double-balloon enteroscopy findings on the management of Crohn's disease. *Scand J Gastroenterol*. 2010;45:483-489.
28. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol*. 2006;101:954-964.
29. Fiorino G, Bonifacio C, Peyrin-Biroulet L, et al. Prospective comparison of computed tomography enterography and magnetic resonance enterography for assessment of disease activity and complications in ileocolonic Crohn's disease. *Inflamm Bowel Dis*. 2011;17:1073-1080.
30. Quinton JF, Sendid B, Reumaux D, et al. Anti-*Saccharomyces cerevisiae* mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut*. 1998;42:788-791.
31. Bahari A, Aarabi M, Aarabi M, et al. Diagnostic value of antineutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibody in Iranian patients with inflammatory bowel disease. *Acta Gastroenterol Belg*. 2009;72:301-305.
32. Vasiliauskas EA, Plevy SE, Landers CJ, et al. Perinuclear antineutrophil cytoplasmic antibodies in patients with Crohn's disease define a clinical subgroup. *Gastroenterology*. 1996;110:1810-1819.
33. Abreu MT, Vasilliauskas EA, Kam LR, et al. Use of serologic tests in Crohn's disease. *Clin Perspect Gastroenterol*. 2001;4:155-164.
34. Targan SR, Landers CJ, Yang H, et al. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology*. 2005;128:2020-2028.
35. Reese GE, Constantinides VA, Simillis C, et al. Diagnostic precision of anti-*Saccharomyces cerevisiae* antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol*. 2006;101:2410-2422.
36. Joossens S, Reinisch W, Vermeire S, et al. The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology*. 2002;122:1242-1247.
37. Joossens S, Colombel JF, Landers C, et al. Anti-outer membrane of porin C and anti-I2 antibodies in indeterminate colitis. *Gut*. 2006;55:1667-1669.

# Predictors of Treatment Response in UC

Patrick G. Brady, MD

In order to appropriately manage UC, clinicians must determine the severity and extent of a patient's disease, as these factors will serve as a guide when selecting the initial therapy. Traditionally, assessment of disease severity and extent has been based mainly on clinical symptoms, physical findings, and laboratory values, which together have been used to categorize cases as mild, moderate, or severe. This scheme is based on original studies performed by Truelove and Witt that were first published in 1955.[1]

More recently, criteria for UC severity have been modified to utilize composite scores based on symptoms (such as stool and/or rectal bleeding frequency), endoscopic findings, and the physician's global assessment. Although these formal assessment scores are most useful in the clinical trial setting, assessment of disease severity is important for anyone who is treating IBD, as this information is necessary to select the appropriate therapy for a given patient.

A simplified approach to classifying severity is provided by the American College of Gastroenterology UC practice guidelines.[2] Using this system, patients are classified as having mild, moderate, severe, or fulminant disease; the majority of patients will have mild-to-moderate disease at initial presentation.[2-5] Mild disease is defined as fewer than 4 stools daily (with or without blood), no systemic signs of toxicity, and a normal ESR. Moderate disease is characterized by more than 4 stools daily, but with minimal signs of toxicity. Severe disease is defined as more than 6 bloody stools daily plus evidence of toxicity as shown by fever, tachycardia, anemia, or an elevated ESR. Fulminant disease is defined as more than 10 bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, need for blood transfusions, and observation of colonic dilation on abdominal plain films.

In terms of prognosis, patients with mild disease are likely to have proctitis or proctosigmoiditis and are unlikely to require colectomy during the following 5–10 years. In contrast, patients classified as having severe UC are more likely to have extensive disease and are likely to eventually require colectomy. In addition, certain factors predict conventional treatment failure in over 80% of patients, including persistence of severe diarrhea with 6 or more bowel movements daily and marked elevation of CRP levels (≥30 mg/L) despite 3 days of intensive therapy.[6] If these patients can be identified at an earlier time point, more aggressive medical therapy can be used in an attempt to avoid colectomy.

## Importance of Endoscopy with Biopsy

Endoscopy with biopsy is necessary to confirm a diagnosis of UC and determine the extent of disease. Several studies have shown that endoscopic predictors of severity generally correlate well with overall symptom severity, and endoscopic findings can also predict the need for intensive therapy. Detection of severe, extensive disease is particularly important, as this type of disease is associated with a higher rate of treatment failure.[6] Endoscopic findings in severe UC include extensive and deep ulcerations (down to the muscularis

propria); mucosal detachment on the edges of ulcerations; well-like or very deep ulcerations; and large mucosal adhesions, such as mucosal islands or bridges.[7] These findings are associated with disease that is refractory to treatment with corticosteroids, and they predict conventional treatment failure and a high rate of colectomy. Conversely, the absence of deep ulcerations predicts the success of medical treatment, even in patients with severe symptoms.[8]

Endoscopic and histologic findings on biopsy are also important when assessing response to treatment and predicting relapse in patients who have achieved symptomatic remission. The persistence of mucosal abnormalities or histologic evidence of acute inflammation is associated with a higher rate of symptomatic relapse.[8] In a retrospective analysis of the Active Ulcerative Colitis Trials (ACT 1 and ACT 2), patients with moderate-to-severe colitis who had endoscopic evidence of mucosal healing at Week 8 were found to have a lower risk of symptomatic relapse than patients with persistent mucosal abnormalities.[9] Similarly, in a study of patients with mild-to-moderate UC who received mesalamine treatment followed by mesalamine maintenance therapy, patients with normal mucosa or only mild mucosal erythema had a lower relapse rate after 1 year than patients who achieved symptomatic remission but still had persistent mucosal disease.[10] Together, this evidence suggests that therapy should aim to achieve complete mucosal healing—not just symptomatic control—in order to prevent relapse, avoid complications, and improve patients' quality of life.

Finally, endoscopy may also be indicated if patients relapse or continue to have symptoms despite receiving appropriate therapy. Relapses may be related to therapeutic failure, in which case mucosal abnormalities will remain, or they may be the result of superimposed infection, such as CMV or *C. difficile* infection. Notably, the pseudomembranes typically observed with *C. difficile* infection may not be observed in UC patients. Therefore, diagnosis of this infection requires a high index of suspicion and appropriate stool testing for the *C. difficile* toxin. CMV infection in UC patients typically occurs in the setting of immunosuppression, which may result from UC patients' underlying disease or their therapy. In either case, endoscopic biopsy is the usual method of diagnosis. If UC patients are found to have CMV infection, clinicians must taper and stop immunosuppressant therapies such as corticosteroids, immunomodulatory agents, and anti–tumor necrosis factor (TNF) agents. Also, clinicians should be aware that some patients who experience continued symptoms—especially abdominal pain or nonbloody diarrhea—may actually have irritable bowel syndrome (IBS) rather than UC. Unlike patients with UC, patients with IBS will exhibit a normal mucosa on endoscopy, and their biopsies will not show acute inflammatory changes.

## Preventing Long-Term Disease Sequelae

Patients with UC are at an increased risk of developing colorectal cancer. Approximately 2%, 8%, and 18% of UC patients develop colorectal carcinoma within 10, 20, and 30 years after disease diagnosis, respectively.[11] This risk usually begins 8–10 years after developing UC, and it is further increased if patients have a diagnosis of primary sclerosing cholangitis and/or a family history of colorectal cancer.

While the relationship between UC and development of colorectal cancer needs to be further studied, the risk of colorectal cancer in UC patients is thought to be due to long-standing inflammatory changes. In a controlled series, Rutter and colleagues found that increased microscopic and macroscopic inflammatory changes increased the risk of colorectal cancer and dysplasia.[12] Microscopic inflammation alone increased the risk of colorectal dysplasia 5-fold. Similarly, another cohort study using a surveillance dataset of 400 patients showed that an increase in microscopic inflammation was associated with a 3-fold increase in the risk of colorectal carcinoma.[13] Given these data, achieving mucosal healing and controlling inflammation should help to reduce colorectal cancer risk. Thus, mucosal healing is important not only for the prevention of relapse but also for prevention of colorectal cancer among UC patients.

Current guidelines for detecting dysplasia in UC patients call for endoscopic surveillance with multiple biopsies at 1–2-year intervals beginning 8–10 years after disease diagnosis. Surveillance generally involves taking 4 quadrant biopsies at 10-cm intervals to sample the colonic mucosa. A number of newer endoscopic techniques—including magnifying chromoendoscopy, confocal laser microscopy, and optical coherence tomography—are currently being investigated as possible methods of increasing the detection rate of dysplasia, but recent evidence suggests that most dysplasia is visible using current technology. In 1 study, per-patient sensitivities for detection of dysplasia and cancer were 72% and 100%, respectively.[14] Improvements in image resolution with standard endoscopy likely account for recent improvements in the detection of dysplasia. While most neoplastic change is visible using standard technology, random biopsies still need to be taken, since approximately one quarter of neoplastic lesions may not be visible.

In addition to endoscopy, imaging procedures play a minor role in assessing UC patients. Imaging is most useful when the clinician has reason to suspect a complication, such as toxic megacolon, a colonic perforation, or an abscess. Clinicians should note that CT scans are not an adequate substitute for endoscopic surveillance for dysplasia, as these lesions are generally flat or only slightly elevated and therefore would be difficult or impossible to detect using CT. Also, unnecessary CT scans should be avoided, particularly in children and young adults, as even a low level of radiation

exposure may be associated with an increase in the long-term risk of colorectal cancer.[15]

## Summary

The most important determinants of response to medical therapy include disease severity and extent. These factors should be assessed using both symptomatology and endoscopic findings, and therapy should be based on disease severity. As evidenced by recent controlled trials of mesalamine and anti-TNF agents, assessment of disease severity is useful for predicting a patient's response to initial treatment and maintenance therapy, and this approach can help to minimize treatment risks in patients with mild disease. A new paradigm for determining response to therapy is placing increased emphasis on mucosal healing, as assessed by endoscopy and histology; this paradigm should reduce the short-term risk of relapse and the long-term risk of colorectal cancer.

## References

1. Truelove SC, Witt LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J*. 1955;2:1041-1048.
2. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105:501-523.
3. Hanauer SB. Inflammatory bowel disease. *N Engl J Med*. 1996;334:841-848.
4. Sands BE, Kilgore KM, Bloomfeld RS, Sandborn W. Variation in severity assessment and initial mesalamine dose for ulcerative colitis in community practice. *J Clin Gastroenterol*. 2006;40:587-591.
5. Langholz E, Munkholm P, Nielsen OH, et al. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. *Scand J Gastroenterol*. 1991;26:1247-1256.
6. Gelbmann C. Prediction of treatment refractoriness in ulcerative colitis and Crohn's disease—do we have reliable markers? *Inflamm Bowel Dis*. 2000;6:123-130.
7. Carbonnel F, Lavergne A, Lemann M, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci*. 1994;39:1550-1557.
8. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. *Clin Gastroenterol Hepatol*. 2005;3:11-24.
9. Lichtenstein GR, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis*. 2010;16:338-346.
10. Meccui G, Fasoli R, Saibeni S, et al. Prognostic significance of endoscopy remission in patients with active ulcerative colitis treated with oral and topical mesalamine: preliminary results of a prospective, multicenter study. *Gastroenterology*. 2006; 130:A-197.
11. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48:526-535.
12. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology*. 2004;126:451-459.
13. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology*. 2007;133:412-422.
14. Rubin DT, Rothe JA, Hetzel AB, et al. Are dysplasia and colorectal cancer endoscopically visable in patients with ulcerative colitis? *Gastrointest Endosc*. 2007;65:998-1004.
15. Benner D, Hall EJ. Computed tomography an increasing source of radiation exposure. *N Engl J Med*. 2007;357:2277-2284.

# Strategies for Maximizing Patient Outcomes

Paul J. Rutgeerts, MD, PhD, FRCP, AGAF

The anti-inflammatory agent 5-aminosalicylic acid (5-ASA) is the standard therapy for inducing and maintaining remission in patients with mild-to-moderate active UC. 5-ASA can be effectively delivered both orally and rectally, and a number of formulations have been developed over the years to deliver 5-ASA specifically to the colonic mucosa. These formulations include prodrugs, delayed-release formulations, controlled-release formulations, and formulations that combine delayed-release and sustained-release strategies.

Corticosteroids are also frequently used for the treatment of mild-to-moderate UC; they can be delivered orally, topically, or intravenously. However, studies have shown that corticosteroids provide only short-term benefit; thus, these agents are not recommended for maintenance of remission.[1] A population-based study of 63 UC patients in Olmsted County, Minnesota showed that corticosteroid treatment could immediately achieve complete or partial remission in 54% and 30% of patients, respectively; however, 22% of patients were found to be corticosteroid-dependent after 1 year.[2] Similarly, a study from the United Kingdom evaluated 86 UC patients who required corticosteroid therapy and found that 51% and 31% achieved an immediate complete or partial remission, respectively.[3] However, 17% of patients were corticosteroid-dependent after 1 year.

For patients who are unresponsive to corticosteroids, the immunomodulators 6-mercaptopurine (6-MP) and azathioprine are effective alternatives, but these agents have a slow onset of action, and their benefit must be weighed against their potential adverse events. Additionally, the effi-

cacy of these therapies may be limited in some patients. A recent systematic review and meta-analysis of parallel group, randomized controlled trials assessed azathioprine treatment in 130 UC patients with active disease and found that the benefit of this therapy did not reach statistical significance (relative risk=0.85; 95% CI, 0.71–1.01).[4] However, 6-MP and azathioprine are used in clinical practice and can be successful for treatment of UC.

The use of cyclosporine in the treatment of acute UC is controversial; this drug is associated with a risk of significant toxicities, and there is a paucity of data to support its use in this setting.[4] Intravenous cyclosporine is used in cases of severe active UC that are not immediately responsive to intravenous corticosteroids.[1] However, a long-term, retrospective study suggested that the efficacy of cyclosporine is not long-lasting.[5] This study evaluated 142 patients admitted to a single institution with a UC attack who were treated with cyclosporine between 1992 and 2004. Of these 142 patients, 83% had an initial response to cyclosporine therapy and thus were able to avoid colectomy during their initial hospitalization. However, 54% of these patients required a colectomy by the end of the follow-up period. A second retrospective study of 61 UC patients treated with cyclosporine between 1991 and 1999 demonstrated similar results.[6] In this study, 63% of patients initially responded to cyclosporine therapy, but all had relapsed by 7 years, and 65% required a colectomy by 7 years.

Finally, infliximab can be an effective treatment for UC patients who are corticosteroid-refractory or corticosteroid-dependent. ACT 1 and ACT 2 were the largest randomized, placebo-controlled trials to evaluate infliximab in UC; together, these studies included 728 patients.[7] Both studies enrolled patients who were refractory to treatment: In ACT 1, patients had failed corticosteroid and/or thiopurine therapy; in ACT 2, patients had failed standard treatment with 5-ASA, corticosteroids, or thiopurines. Patients were randomized to 5 mg/kg infliximab, 10 mg/kg infliximab, or placebo. The percentage of patients who achieved a clinical response was 64–69% with 5 mg/kg infliximab and 61–69% with 10 mg/kg infliximab, compared to 29–37% with placebo ($P$<.001 for both comparisons). A quality-of-life analysis from these 2 trials also showed a significant improvement with infliximab compared to placebo, both at Week 8 and at a later time point (Week 54 in ACT 1 and Week 30 in ACT 2).[8] While therapy with infliximab lowers the need for colectomy, a proportion of patients who become refractory to medical treatment must still undergo this procedure.[9]

## Goals for Treatment of UC

The UC treatment algorithm—indeed, physicians' overall approach to the treatment of UC—has changed over the past 5 years following the introduction of infliximab. Specifically, this change is due to the observation that many patients treated with an ileal pouch-anal anastomosis often have a poor long-term prognosis; these patients generally have a lowered quality of life, and complications such as pouchitis occur in many individuals. Infliximab provides a new approach to treatment of UC in patients whose disease is refractory to treatment with 5-ASA, corticosteroids, and/or immunomodulators. Now, the goals of treatment are not only to improve patient symptoms but also to induce and maintain corticosteroid-free remission and mucosal healing.[1] Achieving these goals helps patients avoid colectomy and may also help to prevent dysplasia and development of colorectal cancer in patients with long-standing disease by providing long-term control of inflammation.

An important point to consider is how these newer treatment goals correlate with the goals of UC patients themselves. In a European, questionnaire-based, telephone survey of 294 UC patients, avoiding surgery was ranked as the most important goal of therapy 73% of the time, and healing of the damage to the intestinal lining was ranked as most important 74% of the time.[10] From the patient's perspective, other important therapeutic goals include stopping symptoms from worsening (66%), achieving corticosteroid-free remission (57%), and fast relief of symptoms (52%). Factors that patients considered to be less important include the treatment having minimal side effects (48%), it being recommended by a doctor (38%), the route/type of administration (23%), and the cost of the copayment (19%).

## Treatment Paradigms in UC

Many physicians now use an accelerated "step-up" approach for the treatment of CD, while others believe that a "top-down" strategy may change the outcome of the disease. This debate is also ongoing regarding the treatment of UC.[11] In UC, 5-ASA is the mainstay of therapy. Traditionally, patients who fail 5-ASA have been treated with the more conservative step-up strategy, which advocates beginning treatment with the least aggressive therapy and sequentially progressing to more aggressive therapies until an adequate response is attained. Although this approach is potentially cost-effective and may be able to limit the adverse events associated with more aggressive therapies, evidence suggests that the step-up strategy is not associated with mucosal healing or improved quality of life in many patients.[12] For this reason, the top-down strategy is also currently being explored as a treatment paradigm for UC. A more aggressive approach, the top-down strategy advocates initiating therapy with immunosuppressive agents or the biologic agent infliximab, as this drug is associated with a rapid clinical response, enhanced quality of life, improved rates of

mucosal healing, and reduced need for colectomy; together, these results may lead to indirect savings in the cost of treatment, but more studies are needed.[7,13-15]

Overall, the success of treatment depends on whether it can achieve mucosal healing. If a patient does not achieve mucosal healing in response to the chosen treatment, there is little chance that long-term benefit will be achieved. Regardless of when infliximab is initiated, clinicians should look for mucosal healing early in the course of therapy in order to predict the outcome of the patient's disease. To achieve this goal, endoscopic assessments need to be incorporated into the routine clinical follow-up examination.

Whichever treatment approach is selected, clinicians need to optimize therapy for the individual patient in order to improve the overall treatment outcome. Clinicians should ensure that patients receive the optimal dose, duration, and schedule of treatment. Over the long term, therapeutic adjustments may be required if the patient loses response or develops low blood levels of the drug.

## Role of Mucosal Healing in Patient Outcomes

Population data have demonstrated that mucosal healing is a predictive factor for better long-term outcomes. Using data from an inception cohort of UC patients, Frøslie and colleagues showed that the proportion of patients who required colectomy was significantly lower in UC patients who achieved mucosal healing in response to traditional therapy (including oral or topical 5-ASA, sulfasalazine, antibiotics, corticosteroids, and/or immunomodulatory agents) compared to patients who did not achieve mucosal healing with traditional therapies.[16]

Building on this finding, ACT 1 and ACT 2 found that infliximab could achieve mucosal healing in a significant percentage of patients.[7] In these studies, endoscopic healing was defined as a Mayo endoscopic subscore of 0 or 1 (0=complete healing with a normal vascular pattern; 1=some friability but no erosions, ulcers, or subcutaneous bleeding). Using this definition, approximately 60% of the infliximab-treated patients in ACT 1 and ACT 2 achieved mucosal healing at Week 8 (62% and 59% in the 5 mg/kg and 10 mg/kg groups, respectively), compared to 33.9% in the placebo group ($P$<.001 for both infliximab arms vs placebo). Similarly, a significant difference in the proportion of patients who achieved mucosal healing was observed at Week 30 (50.4% and 49.2% in the 5 mg/kg and 10 mg/kg infliximab groups, respectively, vs 24.8% in the placebo group; $P$<.001 for both infliximab arms vs placebo). In ACT 1, this effect remained significant at Week 54, with mucosal healing achieved by 45.5% and 46.7% of patients in the 5 mg/kg and 10 mg/kg infliximab groups, respectively, compared to 18.2% of patients in the placebo group ($P$<.001 for both infliximab arms vs placebo).

The importance of mucosal healing as a predictor of treatment response was also evaluated in a post-hoc analysis of data from ACT 1 and ACT 2; this study evaluated endoscopic scores at Week 8 as a predictor of later symptomatic outcome.[17] This analysis found that patients with an endoscopic score of 0 at Week 8 had a 70.8% chance of achieving symptomatic remission at Week 30 and a 73.7% chance of achieving symptomatic remission at Week 54. In patients with an endoscopic score of 1, indicating minor friability, the proportion of patients achieving symptomatic remission was reduced to 50.9% and 47.3% at Weeks 30 and 54, respectively. Likewise, patients with endoscopic scores of 2 or 3 at Week 8 had even lower chances of achieving symptomatic remission at Weeks 30 and 54: only 22.8% and 24.2%, respectively, among patients with an endoscopic score of 2, and only 9.7% and 10%, respectively, among those with an endoscopic score of 3.

This same analysis demonstrated a similar association between mucosal healing at Week 8 and corticosteroid-free remission at Weeks 30 and 54. Corticosteroid-free remission at Week 30 was achieved in 61.5%, 46.1%, 19.7%, and 9.7% of patients with Week 8 endoscopic scores of 0, 1, 2, and 3, respectively. For corticosteroid-free remission at Week 54, these proportions were 62.5%, 46.3%, 15.8%, and 5.3%, respectively. This study demonstrates the importance of assessing mucosal healing via endoscopy in clinical trials, as this short-term finding appears to be predictive of long-term remission.

In another study of mucosal healing in UC, Panaccione and colleagues evaluated patients treated with single-agent azathioprine, single-agent infliximab, or a combination of infliximab plus azathioprine.[18] In this study, patients treated with the combination of infliximab plus azathioprine achieved the highest rate of mucosal healing (63%) at 16 weeks, although 55% of patients treated with infliximab monotherapy also achieved mucosal healing ($P$=.295). Azathioprine monotherapy was significantly less effective; only 37% of patients treated with azathioprine alone achieved mucosal healing ($P$=.001 for azathioprine monotherapy vs combination therapy; $P$=.028 for azathioprine monotherapy vs infliximab monotherapy).

Given these findings, mucosal healing appears to be a key therapeutic target. Patients who achieve mucosal healing are more likely to have a long-term benefit from therapy and will have a better chance of avoiding colectomy. Patients who achieve and maintain mucosal healing may also have a lower risk of developing dysplasia and colorectal cancer. Thus, clinicians need to design a treatment algorithm that allows patients to achieve mucosal healing early in the course of their disease. Mounting evidence now shows that the success of this endeavor will predict patient outcomes, including long-term symptomatic outcomes. Once mucosal healing is achieved, it should be maintained over time.

## References


1. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105:501-523.
2. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121:255-260.
3. Ho GT, Chiam P, Drummond H, Loane J, Arnott ID, Satsangi J. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. *Aliment Pharmacol Ther*. 2006;24:319-330.
4. Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:630-642.
5. Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2006;4:760-765.
6. Actis GC, Fadda M, David E, Sapino A. Colectomy rate in steroid-refractory colitis initially responsive to cyclosporin: a long-term retrospective cohort study. *BMC Gastroenterol*. 2007;7:13.
7. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462-2476.
8. Feagan BG, Reinisch W, Rutgeerts P, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. *Am J Gastroenterol*. 2007;102:794-802.
9. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology*. 2009; 137:1250-1260; quiz 1520.
10. Thompson HC, Kelly J, Rahman MI. Important factors when considering treatment for ulcerative colitis. *J Crohns Colitis Supp*. 2008;2:57.
11. Cui DJ. Early aggressive therapy for severe extensive ulcerative colitis. *World J Gastroenterol*. 2009;15:4218-4219.
12. Travis SP, Stange EF, Lémann M, et al. European evidence-based consensus on the management of ulcerative colitis: current management. *J Crohns Colitis*. 2008; 2:24-62.
13. Tsai HH, Punekar YS, Morris J, Fortun P. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther*. 2008;28:1230-1239.
14. Wilhelm SM, McKenney KA, Rivait KN, Kale-Pradhan PB. A review of infliximab use in ulcerative colitis. *Clin Ther*. 2008;30:223-230.
15. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2006;3:CD005112.
16. Frøslie KF, Jahnsen J, Moum BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology*. 2007;133:412-422.
17. Colombel JF, Rutgeerts P, Reinisch W, et al. Mucosal healing in patients with ulcerative colitis associates with a reduced colectomy risk, high incidence of symptomatic remission, and corticosteroid-free state. Presented at the 18th Congress of the United European Gastroenterology Federation; October 23–27, 2010; Barcelona, Spain.
18. Panaccione R, Ghosh S, Middleton S, et al. Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: the UC SUCCESS trial. Presented at the 6th Congress of the European Crohn's and Colitis Organisation; February 24–26, 2011; Dublin, Ireland.

# Question-and-Answer Forum

## In patients with severe UC, especially those with signs of toxic megacolon, what factors should be considered when choosing between infliximab and cyclosporine?

**Paul J. Rutgeerts, MD, PhD, FRCP, AGAF** Most patients with toxic megacolon require colectomy. For patients with severe acute colitis who are refractory to steroids, the data on treatment options are scarse. The Lichtiger study showed that cyclosporine is effective in this setting; likewise, a Scandinavian study comparing infliximab with placebo showed that a single infliximab infusion is an effective rescue therapy that allows patients with acute, severe, steroid-refractory colitis to avoid colectomy.[1,2] A 2-year follow-up study showed that this effect is maintained long term.[3]

There is only 1 randomized trial comparing infliximab with cyclosporine in patients with acute severe colitis. The primary endpoint of this study was the rate of treatment failure, which was found to be 54% in the infliximab group and 60% in the cyclosporine group.[4] Immediate response to treatment (approximately 80% in both groups) and rates of colectomy also did not differ between groups. Importantly, there was also no significant difference in the rate of adverse events between the 2 groups.

These results suggest that infliximab and cyclosporine have similar efficacy in the treatment of acute severe UC. Due to the complexity of cyclosporine and the potential for serious adverse events associated with its administration, however, use of this agent should be restricted to settings in which an expert is available to administer treatment.

## Have any fecal biomarkers been identified that could assist in the diagnosis of UC?

**Gary R. Lichtenstein, MD** Several fecal markers have been investigated that may play a role in the diagnosis of UC. They include fecal calprotectin, fecal myeloperoxidase activity, interleukin-1β, eosinophil granule-derived proteins, and tryptase. In general, these markers are indicative of mucosal inflammation and disease activity in UC. None of these markers have been associated with a high degree of either sensitivity or specificity, but they have some ability to help differentiate between IBD and IBS.

For example, a study of 30 patients by El Saadany and colleagues showed that fecal calprotectin could be helpful in differentiating IBS from other organic intestinal diseases.[5] Although the mean levels of fecal calprotectin did not differ between IBS and control patients (30.3 µg/g vs 22 µg/g, respectively), mean levels were significantly different between IBS and IBD patients (30.3 µg/g vs 99.4 µg/g, respectively; $P<.05$). Overall, this study found that fecal calprotectin testing had a positive predictive value of 85%, a sensitivity of 100%, and a specificity of 92%.

In another study, rapid tests for fecal calprotectin and lactoferrin were found to be as good as enzyme-linked immunosorbent assays for detecting colonic inflammation.[6] Specifically, both the sensitivity and negative predictive value of the rapid test for fecal calprotectin were 100%. This study suggested that these rapid tests could provide a noninvasive way to help exclude IBD, especially in a primary care setting.

Finally, a meta-analysis found that fecal calprotectin could help to identify patients who should undergo endoscopy for suspected IBD.[7] Among the 13 studies included in this meta-analysis, 6 involved adults and 7 involved children or teenagers. Interestingly, the pooled sensitivities and specificities for fecal calprotectin testing were 93% and 96%, respectively, in the adult studies and 92% and 76%, respectively, in the studies involving children and/or teenagers; the differences in sensitivity and specificity between adults and children/teenagers were significant ($P=.048$). The authors of this meta-analysis concluded that measuring fecal calprotectin levels in adults could lower the number of individuals requiring endoscopy by 67%.

## References

1. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med*. 1994;330:1841-1845.
2. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology*. 2005;128:1805-1811.
3. Gustavsson A, Järnerot G, Hertervig E, et al. A 2-year follow up of the Swedish-Danish infliximab/placebo trial in steroid resistant acute ulcerative colitis. *Gastroenterology*. 2007;132:A-146.
4. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in acute severe ulcerative colitis refractory to intravenous steroids: a randomized study. Presented at the 6th Congress of the European Crohn's and Colitis Organisation; February 24–26, 2011; Dublin, Ireland.
5. El Saadany S, Mohamed WF, Mohamed AA, Hammoudah SAF. Fecal calprotectin as a marker in differentiating irritable bowel syndrome from organic intestinal disease. Knol. 2008 Aug 20. Available online at http://knol.google.com/k/sherif-el-saadany/fecal-calprotectin-as-a-marker-in/i2p6c6e8rrui/7.
6. Otten CM, Kok L, Witteman BJ, et al. Diagnostic performance of rapid tests for detection of fecal calprotectin and lactoferrin and their ability to discriminate inflammatory from irritable bowel syndrome. *Clin Chem Lab Med*. 2008;46:1275-1280.
7. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ*. 2010;341:c3369.

# Slide Library

## Diagnosis of IBD

- Clinical diagnosis
- No single test is pathognomonic
- Clinician needs to integrate information from multiple sources to arrive at a diagnosis
  - History and physical
  - Colonoscopy and ileoscopy
  - Small bowel and colonic biopsies
  - Small bowel follow-through or computed tomography enterography
  - Serologies?
  - Fecal markers?
  - Capsule endoscopy?

## Most Common "Imposters" in the Differential Diagnosis of IBD

- Infectious colitis (including *Clostridium difficile*)
- Ischemic colitis
- Drug-induced (NSAID) enterocolitis
- Solitary rectal ulcer syndrome
- Radiation enterocolitis
- Diversion colitis
- Endometriosis
- Malignancy
- Functional IBS
- Diverticular disease

IBS=irritable bowel syndrome; NSAIDs=nonsteroidal anti-inflammatory drug.

Adapted from Farndon DG, Sands BE. In: Sachar DB, Sandborn WJ, Ahnen D, eds. *Inflammatory Bowel Diseases*. 2nd ed. New York, NY: Saunders; 2004:359-379 with permission from Elsevier.

## Endoscopic Features of UC and CD

| Feature | UC | CD |
|---|---|---|
| Mucosal Involvement | • Diffuse<br>• Continuous superficial ulceration | • Focal<br>• Asymmetric<br>• Aphthoid or linear ulcerations or cobblestoning |
| Strictures | Rare (commonly neoplastic) | Common |
| Rectal Involvement | Always present at diagnosis | Rectal sparing is common |

## Serologic Tests for IBD

- Anti-neutrophil cytoplasmic antibody with perinuclear staining (pANCA)
- Anti-*Saccharomyces cerevisiae* antibody (ASCA)
- Antibody to *Escherichia coli* Outer membrane porin C (OmpC)
- Antibody to *Pseudomonas fluorescens* transcription factor (I2)
- Anti-flagellin antibodies (CBir1)

## Levels of Disease Severity in UC

**Mild**
- <4 stools daily, with or without blood; no signs of toxicity; normal ESR

**Moderate**
- >4 stools daily; minimal signs of toxicity

**Severe**
- >6 bloody stools daily; toxicity evidenced by fever, tachycardia, anemia, or elevated ESR

**Fulminant**
- >10 stools daily; continuous bleeding; toxicity; abdominal tenderness and distension; need for blood transfusions; colonic dilation seen on radiography

ESR=erythrocyte sedimentation rate

Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 2010;105:501-523.

## Role of Colonoscopy in UC

- Determine disease extent and severity on presentation
- Reassess refractory disease
  - Failure of therapy
  - Superimposed infection
  - Mucosal healing with irritable bowel syndrome symptoms
- Determine the degree of mucosal healing
- Dysplasia surveillance

## Endoscopic Factors Predicting Severe Disease in UC Patients

- Extensive deep ulcers
- Well-like ulcers
- Mucosal detachment at the edges of ulcers
- Mucosal islands or bridges

## Risk Factors for Neoplasia in UC

- Disease duration ≥8 years
- Macroscopic or microscopic inflammation
- Primary sclerosing cholangitis
- Family history of colorectal cancer

## Treatment Goals in UC

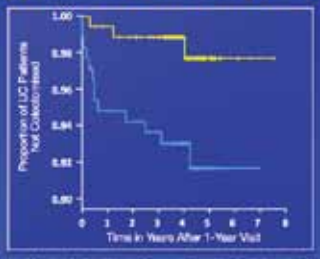
- Induction and maintenance of steroid-free remission
- Induction and maintenance of mucosal healing
- Avoidance of colectomy
- Prevention of dysplasia and cancer in long-standing disease

## Important Factors for Patients When Considering Treatment for UC

Telephone survey of 294 patients with UC

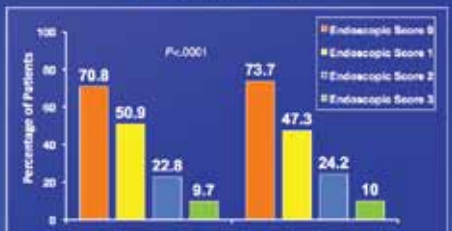
| What patients want | Percent of time ranked as most important |
|---|---|
| Healing the damage to the intestinal lining | 74 |
| Avoiding surgery | 73 |
| Stopping symptoms from getting worse | 66 |
| Achieving steroid-free remission | 57 |
| Fast relief of symptoms | 52 |
| Minimal side effects | 48 |
| Recommended by doctor | 36 |
| Route of administration | 33 |
| Cost of the copayment | 18 |

## Mucosal Healing With Conventional Therapy Reduces Colectomy Rate in UC




## Symptomatic Remission at Weeks 30 and 54

Infliximab-treated patients stratified by Week 8 Mayo Endoscopic Subscore

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# USF Health CB2011 208 Post-Event Questionnaire
# Optimizing Patient Outcomes in the Treatment of Ulcerative Colitis

**This Post-Event Questionnaire may be:**
**1.) Completed and submitted online: http://www.expertscan.autodata.com/Default.aspx?webid=69B458F7-2ED3-4F31-8F04-E65468107703**
**2.) Printed, completed, and faxed to: 813-974-3217**
**3.) Mailed to USF Health, 12901 Bruce B. Downs Blvd, MDC 46, Tampa, FL 33612 (Attn: AJ Bott)**

1. Which of the following endoscopic findings would **NOT** be observed in a patient with ulcerative colitis (UC)?
   - ○ Changes in the distal rectum which proceed proximally in a symmetric and circumferential continuous pattern
   - ○ Discontinuous changes and characteristic "skip" lesions
   - ○ Associated patchy cecal inflammation in patients with distal colonic disease
   - ○ Normal mucosa in patients who are in remission
2. Which of the following must be excluded when establishing a diagnosis of UC?
   - ○ Crohn's disease ○ Infectious colitis ○ Segmental colitis with diverticulitis ○ All of the above
3. Which of the following methods are used to confirm a suspected diagnosis of UC?
   - ○ Serology testing alone
   - ○ Endoscopic and histologic mucosal findings plus pathogen testing
   - ○ Endoscopic and histologic mucosal findings without pathogen testing
   - ○ Small bowel imaging alone
4. What is the disease severity classification for a UC patient with 8 bloody stools daily plus an elevated erythrocyte sedimentation rate?
   - ○ Mild ○ Moderate ○ Severe ○ Fulminant
5. Which of the following endoscopic findings are associated with severe, extensive disease in patients with UC?
   - ○ Extensive and deep ulcerations ○ Mucosal detachment on the edges of ulcerations
   - ○ Large mucosal adhesions such as mucosal islands or bridges ○ All of the above
6. Current guidelines for detecting dysplasia in UC patients call for endoscopic surveillance with multiple biopsies at which intervals?
   - ○ Every 1-2 years beginning immediately after diagnosis
   - ○ Every 1-2 years beginning 8-10 years after diagnosis
   - ○ Every 1-2 years for the first 10 years after diagnosis and every 5 years thereafter
   - ○ Every 5 years beginning immediately after diagnosis
7. Which medication is the standard therapy for inducing and maintaining remission in patients with mild-to-moderate, active UC?
   - ○ 5-aminosalicylic acid ○ Corticosteroids ○ Cyclosporine ○ Infliximab
8. Which of the following statements is true regarding the step-up and top-down approaches for treatment of UC?
   - ○ The step-up approach is more conservative while the top-down approach is more aggressive
   - ○ The top-down approach is more conservative while the step-up approach is more aggressive
   - ○ Both the top-down and step-up approaches involve initiating therapy with immunosuppressive agents and/or infliximab
   - ○ Neither the step-up nor the top-down approach is effective for the treatment of UC
9. Which of the following is true of patients who achieve mucosal healing?
   - ○ They are less likely to require colectomy
   - ○ They are more likely to achieve symptomatic remission and/or corticosteroid-free remission
   - ○ They may have a lower risk of developing dysplasia and colorectal cancer
   - ○ All of the above

10. Which of the following is a benefit of fecal biomarker testing?

- ○ These markers have a high sensitivity for UC
- ○ These markers have a high specificity for UC
- ○ These markers have some ability to help differentiate between IBD & IBS
- ○ Fecal calprotectin can readily distinguish between patients with IBS and control individuals

| | Y | N |
|---|---|---|
| Were ***YOUR*** objectives met in reviewing this material? | ○ | ○ |

If no, please explain.

| | Y | N |
|---|---|---|
| Were the ***PROGRAM'S*** objectives met when reviewing this material? | | |
| Communicate the therapeutic goals of treatment in patients with UC | ○ | ○ |
| Outline the benefits of achieving mucosal healing in patients with UC | ○ | ○ |
| Access the current evidence for the use of therapies in altering the course of disease and improving long-term outcomes | ○ | ○ |
| Articulate effective, individualized treatment strategies for patients with UC | ○ | ○ |
| Characterize the latest developments in the treatment of UC | ○ | ○ |

**Response Definition: 1=Not useful 2=Somewhat useful 3=Quite useful 4=Very useful**

**Rate the usefulness of the following topics:**

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Diagnosis of ulcerative colitis | ○ | ○ | ○ | ○ |
| Predictors of treatment response in UC | ○ | ○ | ○ | ○ |
| Strategies for maximizing patient outcomes | ○ | ○ | ○ | ○ |

Of the information presented in this monograph, what percentage is useful to you?

○ 0 - 20% ○ 21 - 40% ○ 41 - 60% ○ 61 - 80% ○ 81 - 100%

**Response Definition: 1=Strongly Disagree 2=Disagree 3=Neutral 4=Agree 5=Strongly Agree 6=No Opinion 7=N/A**

**As a result of reading this monograph...**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| I increased my knowledge of treatment strategies for UC | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| I am more aware of ways to optimize outcomes when treating patients with UC | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| I learned information relevant to my practice | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| My most pressing questions were answered | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

The material was free of commercial bias or influence

○ Yes ○ No

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Please enter the required information in the space below: ***Full name & credentials - Address - City, State, Zip - Phone - Email***