



# Ask the Experts: UPDATES IN ULCERATIVE COLITIS

CURRENT APPROACHES TO MEDICAL THERAPY

2009 VOLUME 1, ISSUE 2



**David T. Rubin, MD, FACG, AGAF**  
Associate Professor of Medicine  
Co-Director, Inflammatory Bowel Disease Center  
The University of Chicago Medical Center  
Chicago, Illinois

Dr Rubin earned his doctor of medicine degree with honors from the University of Chicago Pritzker School of Medicine. He completed his residency in internal medicine and fellowships in gastroenterology and clinical medical ethics at the University of Chicago, where he is currently an investigator in the Cancer Research Center. His research interests include clinical outcomes of inflammatory bowel disease (IBD), colon cancer screening and prevention, teaching medicine, and clinical medical ethics. Dr Rubin has contributed numerous peer-reviewed publications to the medical literature, including a handbook for the hospitalized IBD patient and *Curbside Consultation in IBD*.



**Beth-Ann Norton, MS, RN, CS, ANP**  
Adult Nurse Practitioner  
Crohn's and Colitis Center  
Massachusetts General Hospital  
Boston, Massachusetts

Ms Norton received a master of science degree in nursing from Boston College Graduate School of Nursing in Chestnut Hill, Massachusetts. She is certified by the American Nurses Credentialing Center as a nurse practitioner. She has been the principal investigator and subinvestigator for numerous studies and clinical trials in treatments for Crohn's disease and ulcerative colitis. Ms Norton recently presented a poster at the Crohn's and Colitis Foundation of America Advances in Inflammatory Bowel Disease Conference and is the author of several articles on inflammatory bowel disease.



## Disclosures

All faculty and planners participating in continuing education activities sponsored by the University of Nebraska Medical Center College of Nursing Continuing Nursing Education are expected to disclose to the audience any significant support or substantial relationship(s) with providers of commercial products and/or devices discussed in this activity and/or with any commercial supporters of the activity. In addition, all faculty are expected to openly disclose any off-label, experimental, or investigational use of drugs or devices discussed in this activity. The faculty and planning committee have been advised that this activity must be free from commercial bias, and based upon all the available scientifically rigorous data from research that conforms to accepted standards of experimental design, data collection, and analysis.

**Ms Norton:** honorarium: Abbott Laboratories, Salix Pharmaceuticals, Shire Pharmaceuticals Inc., UCB Pharma.

**Dr Rubin:** consultant: Abbott Immunology, Centocor, Inc., Given Imaging, Millennium Pharmaceuticals, Inc., Procter & Gamble Pharmaceuticals, Prometheus Pharmaceuticals, Shire Pharmaceuticals Inc., UCB Pharma; grants: Procter & Gamble Pharmaceuticals, Prometheus Pharmaceuticals, Salix Pharmaceuticals.

The Planning Committee for this activity included Catherine A. Bevil, RN, EdD, and Lisa Anzai, RN, MA, of the University of Nebraska Medical Center College of Nursing Continuing Nursing Education, and Ruth Cohen and Christine Olsen, PhD, of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose.

## Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) in primary care practice.

## Activity Goal

To familiarize NPs and PAs in primary care practices with practical strategies for managing ulcerative colitis (UC) with medical therapy.

## Learning Objectives

After completing this activity, participants should be better able to:

1. Incorporate current therapeutic options into effective treatment plans for patients with UC, based on the severity and anatomic extent of the disease and evolving goals for management.
2. Integrate colorectal cancer screening recommendations into the overall management plan for UC.
3. Formulate strategies for educating patients with UC on the benefits of long-term maintenance therapy.

## Accreditation Information

The University of Nebraska Medical Center College of Nursing Continuing Nursing

Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board of Registered Nursing, Provider #13699 for 1.2 contact hours.



This program has been reviewed and is approved for a maximum of 1.0 hour of AAPA Category I CME credit by the Physician Assistant Review Panel. Approval is valid for one year from the issue date of September 15, 2009. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

This program was supported by an educational grant from Shire Pharmaceuticals Inc.

## How to Receive Credit

Participants wishing to earn CME/CE credit must:

1. Read the newsletter.
2. Relate the content material to the learning objectives.
3. Complete the self-assessment questions and the evaluation form online at: <http://www.unmc.edu/nursing/oe>. Successful completion of the self-assessment is required

to earn CME/CE credit.

Successful completion is defined as a cumulative score of at least 70%.

The estimated time to complete this activity is 1 hour.

**Release date:** September 15, 2009

**Expiration date:** September 15, 2010

## Disclaimer

The opinions or views expressed in this continuing education activity are those of the faculty and do not necessarily reflect the opinions or recommendations of Practicing Clinicians Exchange; the University of Nebraska Medical Center College of Nursing Continuing Nursing Education; or Shire Pharmaceuticals Inc.

Please contact Practicing Clinicians Exchange at [inquiries@cealliance.org](mailto:inquiries@cealliance.org) for questions regarding this activity.

©2009 Practicing Clinicians Exchange  
SHPCE52308-2

## INSIDE THIS ISSUE

Therapeutic Options . . . . .	3
Evolving Treatment Goals . . . . .	5
Colon Cancer Screening Recommendations . . . . .	6
Case Study Discussion . . . . .	7

Ulcerative colitis (UC) is associated with a significant clinical and economic burden. It accounts for approximately 250,000 clinician office visits, 20,000 hospitalizations, and more than 1 million lost workdays each year.<sup>1</sup> Annual direct medical costs are 3 times higher in patients with UC than in patients without the disease (\$15,020 vs \$4982); indirect costs related to absenteeism and short-term disability also are higher in patients with UC.<sup>2</sup>

Patients with UC often experience substantial impairment in their ability to function in work or school environments and declines in their psychological well-being.<sup>3,4</sup> Clinicians, however, may underestimate the real-life impact of UC. In the New Observations on Remission Management and Lifestyle (NORMAL) surveys, 62% of patients with UC said their disease made it difficult for them to lead normal lives, compared with 36% estimated by the gastroenterologists surveyed.<sup>5</sup> The number of relapses during the preceding year is the strongest predictor of a reduction in health-related quality of life in UC patients,<sup>4</sup> under-

scoring the need for effective management of the disease.

Practice guidelines are available for UC, but patients do not always receive optimal care.<sup>6</sup> One retrospective review of the records of patients with UC or Crohn's disease found suboptimal dosing of medications, prolonged use of corticosteroids, failure to use steroid-sparing agents, inadequate measures to prevent metabolic bone disease, and inadequate screening for colorectal cancer (CRC).<sup>7</sup>

This issue of *Ask the Experts: Updates in Ulcerative Colitis* is the second of 3 continuing education newsletters on UC. The first issue focused on key strategies for early diagnosis. Here we highlight current approaches to medical therapy.

## Medical Management

The current goals of medical management include relieving the signs and symptoms of UC, inducing and maintaining remission of the disease, promoting mucosal healing, and improving patients' quality of life.<sup>1,8,9</sup> However, these management goals are evolving to focus also on durable steroid-free remission of the disease and modified long-term outcomes. The current treatment approach is guided by the clinical severity of an acute attack and the anatomic extent of disease rather than the histologic severity of inflammation.<sup>1,8,9</sup>

The evaluation of clinical severity of disease usually is based on a clinical activity index, such as Truelove and Witt's index (Table 1)<sup>1,10</sup> or the Simple Clinical Colitis Activity Index.<sup>11</sup> These indices define disease severity as mild, moderate, severe, or fulminant.<sup>1,10</sup> Patients with mild or moderate disease generally are managed as outpatients, whereas those with severe or fulminant disease definitely need hospitalization.<sup>8</sup>

The anatomic extent of disease is determined endoscopically and may be broadly defined as the proximal margin of macroscopic inflammation.<sup>8</sup> However, the more accurate marker of disease extent for treatment choices and risk stratification is likely the microscopic extent of inflamma-

**TABLE 1. Severity Classification of UC**

Severity	Characteristics
Mild	<4 stools daily with or without blood Absence of systemic signs of toxicity <sup>a</sup> Normal ESR
Moderate	>4 stools daily Minimal signs of toxicity
Severe	>6 bloody stools daily Evidence of toxicity or elevated ESR <sup>b</sup>
Fulminant	>10 stools daily Continuous bleeding Toxicity Abdominal tenderness and distension Blood transfusion requirement Colonic dilation on abdominal plain films

ESR = erythrocyte sedimentation rate.

<sup>a</sup>Signs of toxicity include fever, tachycardia, and anemia.

<sup>b</sup>Note: some patients with severe disease may not have elevated ESR.

Kornbluth A, et al.<sup>1</sup>

**Table 2. 5-ASA Therapy Options: Available Oral and Topical Agents**

Agent	Formulation	Route	Site of Delivery	FDA-Approved Indication
<b>Azo-bonded Formulations</b>				
Sulfasalazine	5-ASA linked to sulfapyridine by azo-bond	Oral	Colon	Treatment of mild to moderate UC and as adjunctive therapy in severe UC Prolongation of the remission period between acute attacks of UC
Olsalazine	5-ASA dimer linked by azo-bond	Oral	Colon	Maintenance of remission of UC in patients who are intolerant of sulfasalazine
Balsalazide	5-ASA linked to inert carrier by azo-bond	Oral	Colon	Treatment of mildly to moderately active UC in patients ≥5 years of age
<b>Mesalamine Formulations</b>				
Mesalamine (Asacol®)	Delayed-release, pH-dependent, soluble pH ≥7	Oral	Distal ileum, colon	Treatment of mildly to moderately active UC and maintenance of remission of UC
Mesalamine (Lialda™)	Delayed-release, multimatrix system, pH-dependent, soluble pH ≥7	Oral	Distal ileum, colon	Induction of remission in patients with active, mild to moderate UC
Mesalamine (Pentasa®)	Controlled-release via ethylcellulose membrane	Oral	Distal stomach, small intestine, colon	Induction of remission and treatment of patients with mildly to moderately active UC
Mesalamine (Apriso®)	Delayed-release, pH-dependent, extended-release matrix core	Oral	Colon	Maintenance of remission of UC in adults
Mesalamine (Canasa®)	Suppository	Rectal	Rectum	Treatment of active ulcerative proctitis
Mesalamine (Rowasa®)	Liquid enema	Rectal	Proximal sigmoid colon up to splenic flexure	Treatment of active mild to moderate distal UC, proctosigmoiditis, or proctitis

Adapted from Howell HR<sup>14</sup>; Baumgart DC, et al.<sup>15</sup> Indications were obtained from the prescribing information for each agent.

tion. In patients with distal disease (proctitis and proctosigmoiditis), topical therapy with or without oral therapy is the preferred treatment. In patients with more extensive disease (left-sided colitis or pancolitis), oral or parenteral therapy is the mainstay of treatment, but the addition of topical therapy, focusing on the inflamed distal colon and rectum, which drive most symptoms of UC, may provide additional benefits in many patients.<sup>1,8</sup>

## Therapeutic Options

**Aminosalicylates:** Compounds containing 5-aminosalicylate acid (5-ASA) have been and continue to remain first-line therapy for both the induction and maintenance of remission of mild-to-moderate UC.<sup>1,8,9,12</sup> 5-ASA exerts its therapeutic effects topically on the inflamed colonic mucosa, but its exact anti-inflammatory mechanism of action is not fully understood, and studies of mucosal concentrations or serum levels of 5-ASA have not been correlated to clinical outcomes.<sup>13</sup> 5-ASAs are available in oral and

rectal (suppositories and enemas) formulations. When taken orally, 5-ASA is absorbed readily in the small intestine. Thus, delivery systems that release 5-ASA in the colonic mucosa have been developed (Table 2).<sup>14,15</sup>

There are 2 categories of oral 5-ASA preparations—the azo-bonded prodrugs (sulfasalazine, olsalazine, and balsalazide) and mesalamine formulations using delayed-, extended-, or controlled-release mechanisms to deliver 5-ASA to the colon.<sup>15</sup> Sulfasalazine, the first azo-bonded 5-ASA prodrug, has been widely prescribed for the last 40 years.<sup>16</sup> In placebo-controlled trials, it has been shown to be effective in relieving signs and symptoms of UC, inducing remission, maintaining remission, and mucosal healing.<sup>17</sup> However, sulfasalazine is associated with multiple adverse effects that are believed to be due to its sulfapyridine moiety.<sup>16,17</sup> Adverse effects in patients with inflammatory bowel disease (IBD) who were treated with sulfasalazine include headache, epigastric pain, nausea and vomiting, cyanosis, skin rash, fever, hepatitis, autoimmune hemolysis,

transient reticulosis, aplastic anemia, leukopenia, agranulocytosis, folate deficiency, pancreatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pulmonary dysfunction, and male infertility.<sup>17</sup> Many of these side effects are dose-related, which limits administration of high concentrations of this therapy. One of the reasons for developing the newer 5-ASAs (olsalazine, balsalazide, and mesalamine) was to avoid the adverse effects of sulfasalazine while retaining its therapeutic benefits and the ability to provide higher doses of mesalamine without producing toxicity.<sup>18</sup>

A meta-analysis confirmed the efficacy of the nonsulfa oral 5-ASAs in mild-to-moderate UC.<sup>18</sup> This analysis found no significant difference in efficacy among the oral 5-ASA formulations studied. However, it was suggested that the results demonstrated a dose effect, with higher doses being more effective than lower doses. This long-standing principle of UC management recently has been clarified; the dose effect with mesalamine appears significant in the treatment of moderately active disease, but not in the treatment of mildly active disease.<sup>19</sup> No differences in adverse events or withdrawals due to adverse events were found between the non-sulfa 5-ASAs and placebo with the exception of olsalazine. Sulfasalazine had greater withdrawal rates than the other 5-ASAs.<sup>18</sup> Because olsalazine is associated with a higher incidence of diarrhea in patients with pancolitis, it is recommended for patients who have left-sided disease or who are intolerant of other 5-ASAs,<sup>8</sup> but it is rarely used today. Serious adverse effects, including pulmonary toxicity, pericarditis, hepatitis, and pancreatitis, are attributable to olsalazine, balsalazide, and mesalamine, but they rarely occur.<sup>17</sup> Interstitial nephritis has been reported in patients receiving mesalamine therapy, but it rarely occurs.<sup>17</sup>

Mesalamine also is available in formulations for rectal use. Although oral and rectal therapies are effective in distal disease, rectal preparations are preferred whenever possible.<sup>8</sup> The advantages of rectal preparations include direct delivery of the drug to the area of disease (hence, a quicker response time) and reduction of systemic adverse effects. However, patients may find these therapies impractical and uncomfortable. Common complaints, including leakage and abdominal bloating, lead to poor compliance.<sup>20</sup> It is important to educate patients about the reasons for prescribing topical therapies, emphasizing the benefits and explaining how they fit within the overall management plan (ie, possibly for short-term use, when the disease is active, transitioning to oral therapy after achieving remission).

**Corticosteroids:** Although 5-ASAs are effective in mild-to-moderate UC, approximately 35% of patients will require corticosteroids to control symptoms.<sup>21</sup> Corticosteroids are highly effective as acute treatment for UC and are used, not only as sec-

ond-line therapy for 5-ASA–refractory mildly-to-moderately active disease, but as first-line therapy for moderately-to-severely active disease.<sup>1,12</sup> Because corticosteroids are associated with significant systemic adverse effects—including infections, glucose intolerance, osteoporosis, psychiatric disturbances, and dependence, it is recommended that they not be used for prolonged treatment (>2–3 months).<sup>8,22</sup> Corticosteroids do not have a role in maintenance of remission.

Corticosteroids are available in oral, parenteral, and rectal (suppositories, foams, enemas) formulations. As first-line therapy, the oral formulations (eg, prednisolone) are reserved for moderate-to-severe disease while the parenteral formulations are used in patients hospitalized with severe or fulminant disease.<sup>8,22</sup> Parenteral corticosteroids also are used as second-line therapy for UC unresponsive to 7 to 14 days of high-dose oral corticosteroids.<sup>22</sup> If a response is achieved with oral corticosteroids, a gradual tapering of the dose over the next 8 weeks is recommended.<sup>8</sup> Most patients who respond to parenteral steroids do so within 5 days, but treatment usually is continued for 7 to 10 days.<sup>12</sup> Rectally administered corticosteroids are less effective than rectal 5-ASA formulations in distal disease and are reserved for patients whose disease fails to respond to rectal 5-ASA therapy or who are intolerant of it.<sup>8</sup>

Given the serious adverse effects of systemic corticosteroids, the efficacy of nonsystemic steroids, such as budesonide, is being investigated for the treatment of UC.<sup>12</sup> Nonsystemic steroids have extensive first-pass metabolism and minimal toxicity. Budesonide may have limited effect in UC as orally ingested budesonide is released in the distal ileum and proximal colon, but it has been shown to have equal efficacy to prednisolone in left-sided or extensive colitis.<sup>23</sup>

According to the findings of a population-based cohort study, the immediate outcomes for patients with UC treated with corticosteroid therapy are favorable: 54% achieve complete remission and 30%, partial remission.<sup>21</sup> After 1 year, 49% of UC patients achieve a prolonged response, but 22% develop corticosteroid-dependence and 29% require colectomy.<sup>21</sup>

**Thiopurines:** Azathioprine (AZA) and 6-mercaptopurine (6-MP) are chemically related immunomodulators. The American Gastroenterological Association recommends either AZA or 6-MP for treatment of chronic active corticosteroid-dependent UC, with the goal of reducing or, preferably, eliminating corticosteroid use.<sup>22</sup> These drugs also may be effective as a substitute for 5-ASA in maintaining remission, but data supporting this use are inconsistent. AZA and 6-MP have limited to no utility in inducing remission because the onset of full activity is believed to be slow

(about 3 months).<sup>22</sup> Toxicities associated with AZA and 6-MP include bone marrow suppression (particularly leukopenia), hepatotoxicity, and allergic reactions (including fever, rash, myalgias, and pancreatitis).<sup>1,12</sup>

**Cyclosporine:** This agent is reserved for severe UC refractory to parenteral corticosteroids.<sup>1,22</sup> Following induction of remission or a response with parenteral cyclosporine, continuation of therapy with oral cyclosporine for 3 to 6 months typically is required, followed by maintenance of remission with AZA or 6-MP.<sup>8,22</sup> Cyclosporine is not recommended for maintenance therapy because it is associated with severe adverse effects, such as nephrotoxicity, infection, and seizures.<sup>1</sup>

**Infliximab:** This tumor necrosis factor- $\alpha$  inhibitor is reserved for moderate-to-severe UC after inadequate response to therapy with 5-ASA, corticosteroids, or thiopurines or intolerance to or contraindications for such therapy.<sup>22</sup> For induction of remission as well as minimization of immunogenicity, 3 doses scheduled at 0, 2, and 6 weeks are recommended. If remission is not induced after 3 doses, infliximab therapy should be discontinued. In patients who respond to the induction regimen, infliximab should

be continued as maintenance therapy with infusions every 8 weeks.<sup>22</sup> Adverse effects include infusion reactions and opportunistic infections.<sup>12</sup> Patients should be screened for active or latent tuberculosis before infliximab therapy is initiated and should be monitored closely for signs and symptoms of infection during and after treatment with infliximab.

### Evolving Treatment Goals

The treatment algorithm for UC is based on a “step-up” approach in which therapies with the least toxicity are utilized early and subsequent therapies are added because of lack of response or toxicity (Figure 1).<sup>9,24</sup> However, future treatment goals for UC may include sustained clinical remission, prevention of colorectal dysplasia and cancer, and maintenance of a normal gastrointestinal physiology (Table 3).<sup>25</sup> Thus, the treatment of UC is likely to shift away from treatment based on the control of symptoms and toward treatment aimed at the achievement of endoscopic healing and improved outcomes.<sup>25</sup>

Evidence indicates that 5-ASA therapy may confer a protective effect against CRC in patients with UC. Data pooled from

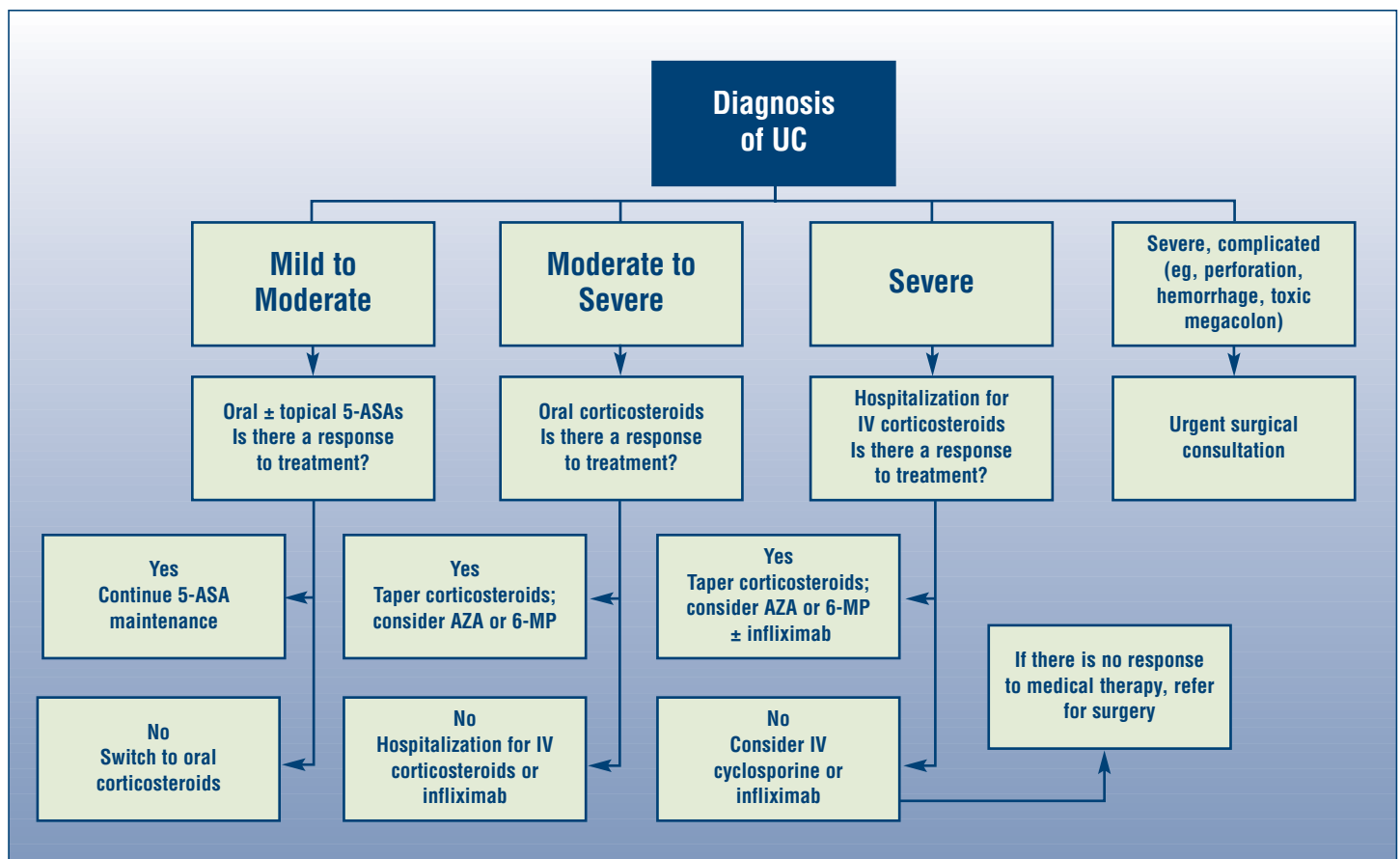


Figure 1. Treatment algorithm for ulcerative colitis. Adapted from Panaccione R, et al<sup>9</sup>; Langan RC, et al.<sup>24</sup>

**Table 3. Evolving Treatment Goals for UC**

**Historic Goals**

Induce and maintain clinical response  
Induce and maintain clinical remission

**Current Evolution of Goals**

Steroid-free remission  
Induce and maintain endoscopic healing  
Reduce hospitalization  
Reduce surgery

**Potential Future Goals**

Primary prevention of colorectal dysplasia and cancer  
Maintain normal gastrointestinal physiology  
Reduce risk of serious infection and cancer

Adapted from Sandborn WJ.<sup>25</sup>

**Table 4. Risk Factors for CRC in Patients With UC**

Extent and duration of UC

Presence of primary sclerosing cholangitis

Young age at disease onset

History of pseudopolyps

Family history of CRC

Severity of bowel inflammation

Kornbluth A, et al<sup>1</sup>; Lakatos PL, et al<sup>30</sup>; Velayos FA, et al<sup>31</sup>; Loftus EV Jr<sup>32</sup>; Eaden A, et al.<sup>33</sup>

9 case control and cohort studies found a reduced risk of CRC (odds ratio [OR]: 0.51; 95% confidence interval [CI]: 0.37-0.69), but not a reduced risk of colorectal dysplasia (OR: 1.18; 95% CI: 0.41-3.43) in 5-ASA users.<sup>26</sup> Regular use and a dose of at least 1.2 g of mesalamine equivalents per day contributed to the reduced risk of CRC, suggesting a dose effect as well as maintenance therapy with 5-ASA as being chemopreventive.<sup>26</sup>

Because the multicenter double-blind placebo-controlled Active Ulcerative Colitis Trials, ACT1 and ACT2, showed that

patients treated with infliximab were less likely to have mucosal damage than patients given placebo,<sup>27</sup> there is growing interest in the possibility of administering biologic therapy earlier in the disease course. Expected benefits of such an early intervention include induction of rapid remission in a steroid-free environment with mucosal healing and sustained remission with fewer complications and a reduced need for surgical interventions.<sup>9,28</sup> However, the effect of infliximab on colorectal dysplasia and CRC has not been determined.<sup>25</sup>

Thus, mesalamine is likely to remain the first-line therapy for UC. More data are needed to determine whether the preferred second-line therapy will evolve to be infliximab or combination therapy with AZA and infliximab or corticosteroids.<sup>25</sup> Several new agents for treating UC also are in development.

**Colon Cancer Screening Recommendations**

Patients with UC have an increased risk of CRC. The risk increases with both the duration and extent of disease.<sup>1</sup> According to the American Cancer Society (ACS) screening guidelines, CRC risk begins to be significant 8 years after onset of pancolitis or 12 to 15 years after the onset of left-sided colitis.<sup>29</sup> In patients with extensive disease, the annual risk of CRC is 0.5% to 1.0% after 10 years of disease.<sup>1</sup> In addition to the risk factors discussed previously, several other risk factors for CRC have been identified in patients with UC (Table 4).<sup>1,30-33</sup> In particular, patients with UC who have a family history of CRC have a 5-fold risk versus matched controls.<sup>1</sup>

The pathology as well as the pathophysiology of some colitis-induced CRC is distinct from that of noncolitis-induced CRC. Colitis-induced CRC more often presents at multiple locations uniformly distributed throughout the colon and are broadly infiltrating and anaplastic compared with noncolitis-induced CRC. Pathophysiologically, some colitis-induced CRC arises from the flat mucosa as opposed to the adenoma-cancer sequence seen in noncolitis-induced CRC.<sup>1</sup> More recent work has demonstrated that many neoplastic lesions in UC are visible with optical or dye-sprayed chromoendoscopy colonoscopy, suggesting that the previous belief that dysplasia in UC is “invisible” or flat is not true for most patients.<sup>34,35</sup>

To prevent or reduce the risk of CRC in patients with UC, the ACS recommends beginning colonoscopic surveillance after 8 years of symptoms.<sup>29</sup> This should include multiple biopsies for dysplasia at regular intervals throughout the colon as well as targeted biopsies for raised lesions. Thereafter, colonoscopy with biopsies for dysplasia should be performed every 1 to 2 years.<sup>1,29</sup> Chromoendoscopy is more effective at identification of dysplasia in UC, but it has not been standardized or clarified for standard of care.<sup>36</sup>

## CASE: 23-YEAR-OLD WOMAN WITH BLOODY DIARRHEA AND ABDOMINAL CRAMPING

### History and Presentation

A 23-year-old woman presents with bloody diarrhea (6 episodes per day) and mild, bilateral lower abdominal cramping. Her other current complaints include fatigue and mild arthralgia. Her bowel frequency has increased during the past 6 weeks. She has a history of alternating episodes of diarrhea with cramping and painful constipation that are associated with times of stress as well as a history of occasional postprandial diarrhea and cramping that was diagnosed as irritable bowel syndrome (IBS). She denies nocturnal stools, fevers, and night sweats. She reports a family history of “bowel problems,” but no CRC. Her current medications include oral contraceptives and sumatriptan as needed for migraine. She denies use of nonsteroidal anti-inflammatory drugs (NSAIDs), isotretinoin, or antibiotics for recent infections. She is a nonsmoker.

### Discussion

*Beth-Ann Norton, MS, RN, CS, ANP, and David T. Rubin, MD, FACP, AGAF, discuss questions related to inducing and maintaining clinical remission in patients with UC.*

### What in this patient’s history and presentation suggests the possibility of UC instead of her usual stress-related IBS?

**Beth-Ann Norton:** The bleeding is a signal. No one should have blood in the stool, particularly not a 23-year-old adult who is too young to be troubled by hemorrhoids. In addition, changes in her bowel habits have persisted for several months, pointing to the possibility of a chronic problem. When patients present with increased urgency, I like to know whether they also are having problems associated with extraintestinal manifestations, such as canker sores, red or sore eyes, or any joint aches. Usually, patients will complain about some arthralgias even when they present early in the course of the disease. I also want to know whether they have fevers or night sweats, have lost weight without trying, or are fatigued. This patient is complaining of fatigue and arthralgia.

**David Rubin:** I agree. The presence of such signs and symptoms suggests a systemic inflammatory process. It is also important to ask, “How many times do you go to the bathroom?” not “How many bowel movements do you have?” Patients who have an inflamed rectum have false alarms, where they feel like everything

that goes into their rectum is sending them to the bathroom, whether it is just a little blood or mucus or even gas. I often ask whether they can distinguish between gas and stool and about incontinence. Losing the ability to distinguish between these things is a sensitive sign that their rectum is inflamed.

**BN:** I also would be concerned if patients report having to get up in the middle of the night or at 4:00 AM instead of their usual 6:00 AM or 7:00 AM.

**DR:** Absolutely, nocturnal symptoms are a big red flag. Patients who have an irritable bowel might have increased frequency during the day, especially if their condition is severe. But increased frequency, urgency, and nocturnal symptoms make me immediately think about an inflammatory or infectious process. This patient denies nocturnal symptoms, however.

**BN:** She also denies having a family history of IBD, which would be another red flag, but not everyone with IBD has a positive family history. Smoking history is a clue here. This patient is a nonsmoker. Current smokers are more likely to have Crohn’s disease and nonsmokers or exsmokers to have UC. She denies using isotretinoin or NSAIDs. I ask patients about their history with these drugs because they may increase the risk for developing IBD, especially UC.

**DR:** She also reports not having used antibiotics. It is important to ask about this. People may completely forget that 4 or 5 weeks ago or 2 months ago they were given a course of antibiotics for some infection. The antibiotics might have triggered the onset of IBD or another problem like *Clostridium difficile* colitis.

### Should treatment ever be initiated before the diagnosis of UC can be confirmed?

**BN:** It depends on the individual case. This patient’s history and presenting complaints are strongly suggestive of UC, and she is suffering quite a bit. I would try her on oral mesalamine. It is well tolerated, and it will not alter the course of her disease sufficiently within the next few days to confound the diagnostic pathology.

Whether she is feeling better when she returns for the endoscopic examination also will provide a clue about what may be going on.

**DR:** I often start treatment if I suspect inflammatory colitis, and frankly, I often do it even if I think the problem might be infectious colitis. The 5-ASA agents as a class are extremely safe. They are the first-line therapy for UC but also have an anti-inflammatory role for other conditions. It is reasonable to initiate treatment while waiting for the next step—laboratory and endoscopic findings.

## CASE: 23-YEAR-OLD WOMAN WITH BLOODY DIARRHEA AND ABDOMINAL CRAMPING (continued)

Because this patient's history and presenting complaints strongly suggest UC, empiric therapy with mesalamine was prescribed, and further evaluation with laboratory testing and colonoscopy was ordered.

### Initial Empiric Therapy

Delayed-release mesalamine orally 2.4 g/d

### Laboratory Findings

- Hemoglobin: 13 g/dL
- Hematocrit: 36.9%
- White blood cell count: 8200/ $\mu$ L
- Platelet count:  $475 \times 10^3/\mu$ L
- ESR: 36 mm/h
- Serum chemistries and liver function: within normal limits
- Stool testing: negative for *C difficile* toxin, ova and parasites, and enteric pathogens

### Colonoscopy

- Endoscopic findings: diffuse erythema and granularity with loss of distinct vascular markings from anal verge to the splenic flexure
- Biopsy result: chronic colitis with architectural distortion

### Diagnosis

*Findings are consistent with mild-to-moderate left-sided UC.*

### Treatment

Continuation of mesalamine orally 2.4 g/d

### Discussion (continued)

#### Do normal laboratory test results rule out a diagnosis of UC?

**DR:** Clinicians should not be reassured by laboratory results that are OK or minimally elevated. People with limited UC can have completely normal labs. It doesn't mean clinicians should stop the evaluation or write off the diagnosis as hemorrhoids or an irritable bowel. With the exception of the platelet count, which is slightly elevated, and the elevated ESR, this patient's laboratory test results are all within normal limits. She clearly needs endoscopic evaluation.

**BN:** If there is room in the schedule, I would do a flexible sigmoidoscopy on the spot. If patients are having frequent diarrhea, as this patient is, they would probably be pretty emptied out anyway.

If a flexible sigmoidoscopy cannot be performed that day, I usually try to schedule endoscopy for that same week.

**DR:** If it can be scheduled on the day the patient presents, starting with a sigmoidoscopy is always important, but referral to a gastroenterologist or another practice where a full examination can be done is critical because biopsies of the colon are necessary to confirm the diagnosis. In this patient, colonoscopy with biopsy confirmed left-sided UC. She should continue with the mesalamine therapy.

#### What is the best way to educate patients about the need for therapy for UC?

**BN:** I tell my patients the inflammation looks like fire up a wall; it starts low and works its way up in a confluent fashion. There are no "skip lesions" or patchiness, which is typical for Crohn's disease. I also tell people that we see the same type of sores in their colon that they sometimes see in their mouth—canker sores—as a way to help them visualize why they need medication.

**DR:** I like to explain to patients with UC that the inside of their colon looks like somebody took sandpaper to it or maybe like a skinned knee does—diffusely superficially inflamed. It gives them ways to visualize what's going on inside and helps them understand why we are going to treat it.

#### What are the therapeutic goals for UC?

**BN:** I ask my patients to understand that UC is a chronic illness requiring long-term use of medication. I tell them that their disease will flare again if they stop taking it. My goal is to (1) make them feel better and (2) get their colon to heal and avoid accelerating their risk for cancer.

**DR:** I do exactly the same thing. After being diagnosed with a chronic disease, patients often have some degree of disbelief—especially when they start to feel better after their first course of therapy. If the treatment successfully induces remission, they think, "Maybe this was just some fluke, and I'm going to be fine now." I emphasize, as you do, that step 1 is inducing remission. Getting back to our fire analogy, we want to put out the fire. We want to do it as quickly as we can, and we want to do it as safely as we can. 5-ASA therapy is the first-line treatment for induction of remission. I emphasize to patients that they should feel perfect. They should have formed stools, no blood, and no urgency; they should be sleeping through the night; they should be able to distinguish gas from liquid. When they get to that point, we have achieved clinical remission.

Step 2 is committing them to maintenance therapy. Often patients think that they are receiving long-term treatment to sup-

press chronically active disease. I explain to them that that is not the purpose of maintenance therapy for UC. Maintenance therapy for UC is for prevention of relapse. This is a different concept. If patients leave the office thinking they have to take the 2.4 g of mesalamine every day to suppress active disease, then when they miss a couple of days or don't refill their prescription on time, but still feel fine, they will mistakenly think they don't need medication. I try to emphasize the need to continue therapy and then to come up with a strategy that will help them stay on their medicine long term. Patients on long-term mesalamine therapy should have their renal function monitored once or twice a year because, although it is a rare complication, there is the risk of interstitial nephritis.

### When should rectal therapy—suppositories or enemas—be used?

**BN:** If the patient is starting to feel better on the oral therapy alone, but still complains about some urgency, I will add mesalamine suppositories or a mesalamine liquid enema. I tell patients that the rectum was the first part of the colon to become diseased and that it is also the last part to get well. I'll usually start with the suppository, and if the follow-up endoscopy shows the inflammation is still above the rectum, I will prescribe the enema for use at bedtime. It also depends on the patient's situation. For college students sharing living space, using suppositories generally is more feasible than using the enemas.

**DR:** My colleagues always say how much patients hate rectal therapy, but I have found that most people are willing to try it, if I explain to them what it's for, that it's not forever, and that it's the most effective way to get the medicine where it can do its job.

### If there is no response to 5-ASA therapy, what is the next step?

**BN:** If patients don't respond to combination oral and topical 5-ASA therapy, I would add a prednisone taper or change to treatment with a cortisone enema at nighttime.

**DR:** One of the important lessons about UC management is that the choice of maintenance therapy likely will be dictated by the agent that is most effective for induction. Another reason to appreciate 5-ASA therapy is that when it works for mild or moderate UC, it can also be used for maintenance. Patients who require corticosteroids often will need an immunosuppressive or immune-modulating therapy like AZA or 6-MP. What clinicians need to understand is long-term corticosteroid therapy is not an option. Any patient who needs more than 1 course of corticosteroids

Surgical management of UC is indicated in patients with life-threatening complications such as bleeding, perforation, or toxic megacolon; in patients with medically-refractory disease; and in patients with documented or suspected CRC.<sup>1</sup> Toxic megacolon is characterized by fever, tachycardia, leukocytosis, and abdominal tenderness and distention. It is associated with a high mortality rate when it occurs with perforations. The latter is the most fatal complication of toxic megacolon and contributes to mortality rates of 40% to 60%. In the absence of perforations, the mortality rate of toxic megacolon is 2% to 3%.<sup>37</sup>

Depending on the indication for surgery, surgical options may vary.<sup>1</sup> Total proctocolectomy is usually the preferred surgical procedure for exsanguinating hemorrhage or persistent hemorrhage (despite medical therapy at maximum doses) because of the risk (albeit small, in 12% of patients) of continued hemorrhage from the spared rectal region of a subtotal colectomy. In the case of perforations, the preferred surgical option is subtotal colectomy. It is important that patients be informed of the various surgical options and their risks and benefits prior to surgery.

teroids during the year should be evaluated for a different treatment strategy. When patients need immunosuppressive therapy, they need to be referred to a specialty clinic.

### If oral corticosteroids are not effective, what is the next treatment option?

**BN:** When oral corticosteroids fail, patients generally have to be hospitalized for intravenous corticosteroid therapy. Alternatively, if they can be treated safely as outpatients, infliximab is an option. Do you add 6-MP or AZA to infliximab, and after 6 months, discontinue infliximab? Or do you keep patients on infliximab alone? At my clinic, we tend to keep them on infliximab.

**DR:** Right, so do we. The next outpatient option after oral corticosteroids is infliximab. For some patients, we may consider cyclosporine.

### What should be done if medical therapy fails?

**DR:** When we exhaust our medical options, we have to go to surgery, and even in 2009, despite all the advances in care, about one quarter to one third of our patients will need surgery at some point (see *Surgical Management*). Surgery for UC is considered a curative

procedure, but it has implications because we want to restore some type of rectal delivery for patients by creating an ileoanal J-pouch anal anastomosis. However, some people develop inflammation of the pouch, called *pouchitis*, that requires additional treatment. Sometimes, despite our best efforts, we later find they actually had Crohn's disease. We give them a new rectum out of their small intestine, and Crohn's disease develops in it. That's a problem, but fortunately it's a rare problem.

**BN:** Right. And then we're back to immunosuppressive therapy to prevent these patients from losing their J-pouch.

**DR:** If we can get UC diagnosed early and treated effectively and then keep it in remission, we can try to avoid all these things.

### What do primary care clinicians need to know about cancer risk in UC?

**BN:** After 8 to 10 years of extensive UC, patients need to have surveillance colonoscopies yearly. Surveillance may mean multiple biopsies to check for precancerous changes, which often do not show up as polyps in patients with IBD.

**DR:** Right. This is really important. Patients who are doing well with their UC may not be seeing their gastroenterologist often. So, primary care providers need to know that patients with chronic inflammation of the colon are at increased risk for CRC. Although patients are fearful of this complication, the reality is that it is rare. The risk is probably 1% after 10 years of disease, and the risk might increase by about 0.5% every 2 years after that. But even though the risk is very low, we recommend that screening be started after about 8 to 10 years of their disease.

### Should patients with UC undergo bone density screening?

**BN:** My clinic is a tertiary care facility. Sometimes patients with UC who have been on prednisone more than once or twice are referred to us, and, at that point, we do start checking bone density. If patients had prolonged or multiple corticosteroid bursts throughout their UC history, they should be screened for osteopenia or osteoporosis.

**DR:** I totally agree with that.

**BN:** As an aside, it's also important to remember that Crohn's disease itself actively destroys bone. Patients with Crohn's disease don't need to have received corticosteroid therapy to be at risk for osteopenia or osteoporosis. They definitely need bone density screening.

## CASE: 23-YEAR-OLD WOMAN WITH BLOODY DIARRHEA AND ABDOMINAL CRAMPING (continued)

### Clinical Course

This patient's UC responded quickly to oral mesalamine therapy. By her 6-month follow-up, clinical remission had been achieved. Maintenance therapy at the same dosage (mesalamine orally 2.4 g/d) was prescribed. After 3 months, the patient reports having a recurrence of her symptoms.

### Management Options

- Addition of topical 5-ASA therapy
- Increase dosage of oral therapy
- Switch to corticosteroid therapy (if unresponsive to 5-ASA therapy)

### Discussion (continued)

#### How should this patient's recurrence be managed?

**BN:** The first thing I would ask is, "Have you stopped taking the medication?"

**DR:** Yes. First of all, I ask, "Did you actually stay on your medicine? You've been doing so well for so long." And she may say, "You know, I have to be honest with you. I ran out, and I stopped taking it about 3 weeks ago."

**BN:** Then I would ask her to go back on the medication as soon as possible. I would ask her to call me after 5 days on it and let me know how things are going. If she is not 50% better by the end of that 5-day period, I would add a mesalamine enema or, if privacy were an issue for her—if she were living in a dormitory or had a roommate, for example, I would prescribe a mesalamine suppository.

**DR:** People are likely to be nonadherent to their therapy, especially during the first year after being diagnosed with UC when they are beginning to feel better. Adding rectal therapy or going to a higher dose of 5-ASA might be helpful. For this woman, we have some room to move because she's on a daily dose of only 2.4 g mesalamine. Going up to 4.8 g/d would be reasonable.

**BN:** And we would want to avoid corticosteroids. Young women may not need much convincing about steroid avoidance because they don't like having a moon face and acne. Sometimes they listen when I say, "If you flare again, I may have to give you a steroid, either rectally or orally."

**DR:** If this patient were taking her 5-ASA therapy but started to have breakthrough, what would you do then?

**BN:** I would be a bit worried about that. I would try her on 5-ASA enemas. Sometimes, if people catch their flares early—if

they let the flare go only 2 or 3 days—and we give them enemas on top of their oral 5-ASA, many of these people can turn the flare around. If this patient's disease flare doesn't respond to the addition of topical therapy to her oral regimen, I would prescribe a corticosteroid enema at bedtime, which would require a tapering. If, within 1 or 2 weeks, the flare doesn't respond, I would be looking at oral corticosteroids for her.

**DR:** When the flare can't be controlled quickly, often we have to escalate therapy, and that requires an additional work-up and considerations regarding immunosuppressives, for example.

**BN:** Once patients get to the point where they need immunosuppressive medication, they really should be in the care of a gastroenterologist who has a lot of experience with IBD.

## Commentary

**DR:** This is a typical case that emphasizes the importance of early diagnosis of UC, its distinction from IBS, and patient education about the need for long-term maintenance therapy. It also emphasizes the importance of bone health and cancer prevention, both of which should be understood by the primary care clinician.

**BN:** I feel it is important to educate patients about IBD and the medications used to treat it. They need to understand that it is a chronic, relapsing, inflammatory illness that requires *maintenance* medication for them to stay well and avoid steroids. Surveillance for CRC is paramount in patients with long-term UC.

## PCE TAKEAWAYS

- 5-ASAs are the mainstay of therapy for mild-to-moderate UC for induction and maintenance of remission.
- Corticosteroids are first-line therapy for the induction of remission in moderate-to-severe disease and second-line therapy in 5-ASA refractory mild-to-moderate disease. They are not recommended as maintenance therapy and need to be tapered after induction of remission.
- Cyclosporine is used for the induction of remission in severe disease and in corticosteroid-refractory disease.
- Infliximab is recommended for the induction and maintenance of remission in moderate-to-severe disease, refractory to conventional therapies.
- Surgical management is reserved for patients with life-threatening complications or with medically-refractory disease.
- CRC screening is recommended after 8 years of disease and every 1 to 2 years thereafter.

## References

1. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2004;99:1371-1385.
2. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med*. 2008;50:1261-1272.
3. Janke KH, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11:272-286.
4. Bernklev T, Jahnsen J, Schulz T, et al. Course of disease, drug treatment and health-related quality of life in patients with inflammatory bowel disease 5 years after initial diagnosis. *Eur J Gastroenterol Hepatol*. 2005;17:1037-1045.
5. Rubin DT, Siegel CA, Kane SV, et al. Impact of ulcerative colitis from patients' and physicians' perspectives: results from the UC: NORMAL survey. *Inflamm Bowel Dis*. 2009;15:581-588.
6. Sachar DB. Ten common errors in the management of inflammatory bowel disease. *Inflamm Bowel Dis*. 2003;9:205-209.
7. Reddy SI, Friedman S, Telford JJ, Strate L, Ookubo R, Banks PA. Are patients with inflammatory bowel disease receiving optimal care? *Am J Gastroenterol*. 2005;100:1357-1361.
8. Carter MJ, Lobo AJ, Travis SP; IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2004;53(suppl 5):V1-V16.
9. Panaccione R, Rutgeerts P, Sandborn WJ, Feagan B, Schreiber S, Ghosh S. Review article: treatment algorithms to maximize remission and minimize corticosteroid dependence in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2008;28:674-688.
10. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *BMJ*. 1955;ii:1041-1048.
11. Walmsley RS, Ayres RCS, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut*. 1998;43:29-32.
12. Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: a review of medical therapy. *World J Gastroenterol*. 2008;14:354-377.
13. McCormack PL, Robinson DM, Perry CM. Delayed-release Multi Matrix System (MMX) mesalazine: in ulcerative colitis. *Drugs*. 2007;67:2635-2642.
14. Howell HR. Ulcerative colitis: achieving and maintaining remission. *US Pharm*. 2008;33:30-37.
15. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007;369:1641-1657.
16. Cohen RD. Review article: evolutionary advances in the delivery of aminosaliclates for the treatment of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;24:465-474.
17. Sandborn WJ. Treatment of ulcerative colitis with oral mesalazine: advances in drug formulation, efficacy expectations and dose response, compliance, and chemoprevention. *Rev Gastroenterol Disord*. 2006;6:97-105.
18. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2006;(2):CD000543.

19. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol*. 2005;100:2478-2485.
20. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;23:577-585.
21. Faubion WA, Loftus EV, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121:255-260.
22. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006;130:935-939.
23. Lofberg R, Danielsson A, Suhr O, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 1996;110:1713-1718.
24. Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD. Ulcerative colitis: diagnosis and treatment. *Am Fam Physician*. 2007;76:1323-1330.
25. Sandborn WJ. Current directions in IBD therapy: what goals are feasible with biological modifiers. *Gastroenterology*. 2008;135:1442-1447.
26. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2005;100:1345-1353.
27. 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.
28. Velayos FS, Sandborn WJ. Positioning biologic therapy for Crohn's disease and ulcerative colitis. *Curr Gastroenterol Rep*. 2007;9:521-527.
29. Smith RA, von Eschenbach AC, Wender R, et al.; ACS Prostate Cancer Advisory Committee, ACS Colorectal Cancer Advisory Committee, ACS Endometrial Cancer Advisory Committee. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001—testing for early lung cancer detection. *CA Cancer J Clin*. 2001;51:38-75.
30. Lakatos PL, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. *World J Gastroenterol*. 2008;14:3937-3947.
31. Velayos FS, Loftus EV Jr, Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology*. 2006;130:1941-1949.
32. Loftus EV Jr. Epidemiology and risk factors for colorectal dysplasia and cancer in ulcerative colitis. *Gastroenterol Clin North Am*. 2006;35:517-531.
33. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48:526-535.
34. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. *Gastrointest Endosc*. 2004;60:334-339.
35. Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? *Gastrointest Endosc*. 2007;65:998-1004.
36. Rubin DT. An updated approach to dysplasia in IBD. *J Gastrointest Surg*. 2008;12:2153-2156.
37. Kaiser AM, Beart Jr, RW. Surgical management of ulcerative colitis. *Swiss Med Wkly*. 2001;131:323-337.