



Ask the Experts: UPDATES IN ULCERATIVE COLITIS

KEY STRATEGIES FOR EARLY RECOGNITION

2009 VOLUME 1, ISSUE 1



Sunanda V. Kane MD, MSPH

Associate Professor of Medicine
Miles and Shirley Fiterman Division of
Gastroenterology and Hepatology
Mayo Clinic College of Medicine
Rochester, Minnesota

Dr Kane received a medical degree from Rush Medical College in Chicago, Illinois. She completed a fellowship in gastroenterology at the University of Chicago and earned a master of science, biostatistics, and epidemiology degree from the University of Illinois. Dr Kane's areas of interest include gender-specific issues in gastroenterology and medication adherence.

Dr Kane is Chair of the Women's Committee of the American College of Gastroenterology and a past president of WE CARE in IBD, an organization dedicated to advancing the role of women in the field of inflammatory bowel disease.



Richard H. Davis Jr, PA-C

Senior Physician Assistant
Division of Gastroenterology,
Hepatology, and Nutrition
University of Florida College of Medicine
Gainesville, Florida

Mr Davis received a bachelor's degree in biology from St. Louis University in Missouri, a bachelor of science in medicine from the University of Florida, and graduate training in physiology at Kent State University in Ohio and the University of Virginia in Charlottesville. He is certified by the National Commission on Certification of Physician Assistants. Mr Davis is a fellow of the American Academy of Physician Assistants, Florida Academy of Physician Assistants, and the American Gastroenterological Association.



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.

Mr Davis Jr: honorarium: Procter & Gamble.
Dr Kane: consultant: Abbott Laboratories, Centocor Inc., Elan Corporation, Procter & Gamble, Shire Pharmaceuticals Inc., UCB; research: Elan Corporation, Procter & Gamble, Shire Pharmaceuticals Inc.

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 practice with practical strategies for recognizing the signs and symptoms of ulcerative colitis (UC) in patients who present with changes in bowel habits.

Learning Objectives

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

1. Recognize the clues in a patient history that signal the possibility of UC.
2. Utilize physical findings, laboratory tests, and endoscopy studies to establish a diagnosis of UC.
3. Differentiate patients with UC from patients with Crohn's disease.

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 hours 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 May 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 activity is supported by an independent 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: May 15, 2009
Expiration date: May 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 for questions regarding this activity.
©2009 Practicing Clinicians Exchange
SHPCE52308-1

INSIDE THIS ISSUE

Etiology of Ulcerative Colitis	2
Characteristic Features of Ulcerative Colitis	3
Ulcerative Colitis vs Crohn's Disease	5
Case Study Discussion	6

Ulcerative colitis (UC), an idiopathic chronic inflammatory disease of the colon, is estimated to affect >600,000 Americans.^{1,2} UC has an annual incidence of 10.4 to 12.0 cases per 100,000 persons in the United States and a prevalence of 238 per 100,000 adults.¹⁻³ Regional differences in UC prevalence have been noted in the United States, with prevalence being lower in the South than in the Northeast, Midwest, or West.³

Clinicians may underestimate the devastating impact UC can have on patients' health-related quality of life. The UC: New Observations on Remission Management and Lifestyle (NORMAL) surveys found disparities between patients' and clinicians'

perceptions of the real-life burden of UC. Clinicians tended to underestimate the disruptive impact of UC symptoms on patients' daily activities and the extent of patients' coping and to overestimate disease control. While 62% of surveyed patients with UC said that their disease made it difficult for them to lead normal lives, gastroenterologists surveyed estimated that only 36% of patients were so affected, suggesting suboptimal clinician-patient communication.⁴

As effective treatments are available for UC (see *Treatment of Ulcerative Colitis*, page 3), early diagnosis and optimal disease management are essential to helping patients lead normal lives. Barriers to early diagnosis include patient delay in presenting due to embarrassment or clinician delay in referral for

endoscopic evaluation. Also, presenting symptoms may vary, depending on the extent of the disease, and overlap with those of other inflammatory bowel disorders, such as Crohn's disease.

This issue of *PCE Ask the Experts: Updates in Ulcerative Colitis* is the first of 3 continuing education newsletters on UC. Here, the focus is on diagnostic strategies. Subsequent issues will highlight treatment strategies and adherence issues.

Etiology

Genetic, immune system, and environmental factors have been implicated in the development of UC.^{5,6} One way to clarify the genetic contribution to a disease is by studying twins. Concordance rates would approach 100% in monozygotic twins and 50% in dizygotic twins if a disease were entirely due to genetics but would be similar in both types of twins if a disease were caused only by extrinsic or acquired factors.⁵ For UC, various twin studies have found concordance rates of about 16% (ranging from 14%-19%) in monozygotic twins and 4% (ranging from 0%-7%) in dizygotic twins.⁷ In addition, UC has been consistently associated with the major histocompatibility complex

TABLE 1. Differential Diagnosis of Ulcerative Colitis

Disease	Clinical Features	Histologic Features
UC	Chronic bloody diarrhea with urgency and tenesmus	Mucosal inflammation with crypt abscesses/distortion
Crohn's disease	Frank bleeding less common than in UC; perianal lesions	Focal inflammation; submucosal involvement; granulomas; goblet cell preservation; transmural inflammation; fissuring
Infectious colitis	Sudden onset; pain; pathogens present in stool	Crypt architecture usually normal; edema; superficial neutrophil infiltrate; crypt abscesses
IBS	Abdominal pain or discomfort in association with altered bowel habits, occurring over a period ≥3 months	Colonic imaging/biopsy usually not indicated; however, if performed, results are normal
Ischemic colitis	Sudden onset; pain and vascular disease often present; affects older patients	Mucosal necrosis; ballooning of capillaries; red blood cell congestion; hemosiderin and fibrosis (chronic disease)
Pseudomembranous colitis	Suggested by recent antibiotic use; chronic diarrhea— <i>Clostridium difficile</i> toxin may be detectable in stool	Similar to acute ischemic colitis but may show "summit" lesions of fibrinopurulent exudate

IBS = irritable bowel syndrome.

From Kornbluth A, et al.¹⁰; Kefalides PT, et al.¹¹; and Langan RC, et al.¹²

TREATMENT OF ULCERATIVE COLITIS

(MHC) locus human leukocyte antigen (HLA) class II alleles. Other genes, the interleukin (IL)-1 family of genes and the multidrug resistance gene *MDRI*, also have been implicated as potential genetic susceptibility factors for the development of UC. Extraintestinal manifestations in UC have been associated with genetic susceptibility; in particular, the development of ankylosing spondylitis in patients with UC is associated with the HLA-B27 phenotype.⁶

Because UC involves chronic inflammation of the colon, inflammatory mediators are thought to be involved in its development. Increased natural killer cell activity and IL-13 may be associated with UC, consistent with a T helper cell-2 (Th-2) response model postulated for UC.⁸

Several environmental factors impact the risk for the development of UC, including diet, atypical mycobacterial infections, cigarette smoking, and appendectomy.^{1,5,6} Of these factors, the latter 2 are the strongest predictors, both having been shown to have a protective effect against the development of UC. Smoking reduces the risk of UC by 40%.⁹ The risk in ex-smokers is increased 1.7 times compared with that in nonsmokers.⁹ Moreover, ex-smokers develop more severe and extensive disease.⁶ Appendectomy, particularly at a younger age, reduces the risk of developing UC and is associated with a less severe clinical course.⁶

Despite these advances in our understanding of the genetic, immunologic, and environmental factors that contribute to the development of UC, a diagnostic marker for UC has yet to be identified. At present, the diagnosis of UC is based on clinical, endoscopic, and histologic criteria.

Characteristic Features

UC is characterized by chronic, diffuse, contiguous mucosal inflammation of the colon. It usually begins in the rectum and progresses proximally. It may be limited to the rectum and sigmoid colon (proctosigmoiditis), the descending colon (left-sided colitis), or the entire colon (pancolitis).¹⁰⁻¹² Among adult patients with UC, 55% present with only rectal involvement (proctitis), 30% with left-sided colitis, and 15% with pancolitis.¹³

Rectal bleeding or bloody diarrhea, tenesmus, and rectal urgency are the hallmark symptoms of UC⁵; however, symptoms at presentation may differ depending on the extent of disease. In patients with proctitis, symptoms may include rectal bleeding, tenesmus, painful straining, urgency, and fecal incontinence or constipation. With more proximal involvement, bloody diarrhea, frequency, and nocturnal bowel movements appear. Patients with

Treatment of UC is a 2-staged process. Stage 1 aims to induce remission and resolve all inflammatory symptoms. Stage 2 aims to maintain remission.¹⁰⁻¹² Treatment in stage 1 is based on the severity of the symptoms and the extent of colonic involvement. The agents used fall into 2 categories: anti-inflammatory and immunomodulatory.

AGENTS USED IN THE TREATMENT OF PATIENTS WITH UC

Anti-inflammatory

5-ASA compounds

– Sulfasalazine

– Olsalazine

– Balsalazide

– Mesalamine

Immunomodulatory

6-MP

Azathioprine

Methotrexate

Cyclosporine

Infliximab

Corticosteroids

5-ASA = 5-aminosalicylic acid compounds; 6-MP = 6-mercaptopurine.

From Kornbluth A, et al.¹⁰; Kefalides PT, et al.¹¹; and Langan RC, et al.¹²

more proximal involvement of the colon may also have lower abdominal pain, and patients with severe disease may experience nausea, vomiting, and weight loss.⁵

UC has a heterogeneous clinical course, oscillating between periods of exacerbation lasting for days, weeks, or months and periods of remission lasting for months, years, or decades.⁵ In the Inflammatory Bowel South-Eastern Norway (IBSEN) study, a prospective, population-based, 5-year follow-up study of 454 patients with UC, the most frequent clinical course was a decrease in symptoms, observed in 59% of the patients. A relapse-free course was seen in 22% of the patients. The extent of colonic involvement was found to be unrelated to symptoms, relapse rate, and clinical course.¹⁴

Patient History

Any condition that produces chronic, intermittent diarrhea may be considered in the differential diagnosis of UC. To help rule out other causes of chronic diarrhea (Table 1), clinicians should obtain a complete patient history. A thorough medical

history should include any recent use of antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs), recent infection, any family history of colitis, and smoking history.¹⁰⁻¹²

A history of recent antibiotic use might suggest pseudomembranous colitis, while recent infections might point to infectious colitis. The possibility of NSAID-induced colitis also should not be overlooked.¹⁵⁻¹⁷ A family history of colitis, including a first- or second-degree relative with inflammatory bowel disease (IBD), should increase the suspicion of IBD in a patient presenting with bloody diarrhea. A knowledge of the patient's smoking history can impact treatment decisions because smoking cessation can affect the development and clinical course of UC.^{10,11}

Physical Examination

In patients presenting with UC, physical findings may be normal. However, pallor may be evident in patients with anemia due to blood loss. Weight loss, fever, and tachycardia may be present in patients with severe UC.¹¹ An abdominal examination may reveal generalized tenderness in the setting of active disease. In patients with mild UC, abdominal findings may be normal or bowel sounds may be increased. However, in patients with severe disease, abdominal distention and tympany may be present and bowel sounds may be decreased or absent.¹¹ In most cases, rectal and perianal examination findings are normal.

Extraintestinal manifestations of UC include osteoporosis,

oral ulcerations, large-joint arthritis, primary sclerosing cholangitis, skin lesions (erythema nodosum, pyoderma gangrenosum; Figure 1A, 1B), ocular inflammation (episcleritis, uveitis; Figure 1C, 1D), and thromboembolic events (pulmonary embolism, deep venous thrombosis).^{11,12,18,19} Thus, the physical examination should include an assessment of the skin, buccal and ocular systems, as well as the joints.

Diagnostic Testing

If UC is suspected, laboratory studies and endoscopic evaluation with biopsy are needed to confirm the diagnosis.

Laboratory evaluation. Laboratory testing should include a complete blood cell count (CBC) with differential, metabolic panel, measurement of systemic markers of inflammation (eg, erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), and stool tests. The CBC can reveal anemia consistent with chronic blood loss or suggest an infectious cause if the white blood cell count is elevated. Electrolyte abnormalities such as hypokalemia are consistent with persistent diarrhea.¹⁰⁻¹² Elevated ESR or CRP levels may support a diagnosis of IBD. Stool culture and testing for microbial pathogens, parasites, and *Clostridium difficile* toxin can exclude (or reveal) infectious causes of chronic diarrhea.¹² Test results positive for fecal lactoferrin or fecal calprotectin help to rule out noninflammatory causes of bowel disease such as IBS.^{20,21} Celiac testing may be appropriate in patients who present with upper abdominal pain and watery diarrhea with bleeding.²²

Various (auto)antibodies have been described in patients with UC (Table 2),²³ the most studied of which are the antineutrophil cytoplasmic antibodies with perinuclear staining (pANCA) and the anti-*Saccharomyces cerevisiae* antibodies (ASCA). pANCA are present in 60% to 70% of patients with UC.¹⁰ However, they have also been detected in up to 40% of patients with Crohn's disease.¹⁰ These latter patients typically present with clinical features resembling those of left-sided UC. ASCA are usually absent in UC; nonetheless, they have been detected in 10% to 15% of cases. ASCA are more common in patients with Crohn's disease, with a prevalence of 60% to 70%.²³ Because of the lack of sensitivity of these 2 antibodies, they are not diagnostically useful to differentiate between UC and Crohn's disease.²⁴

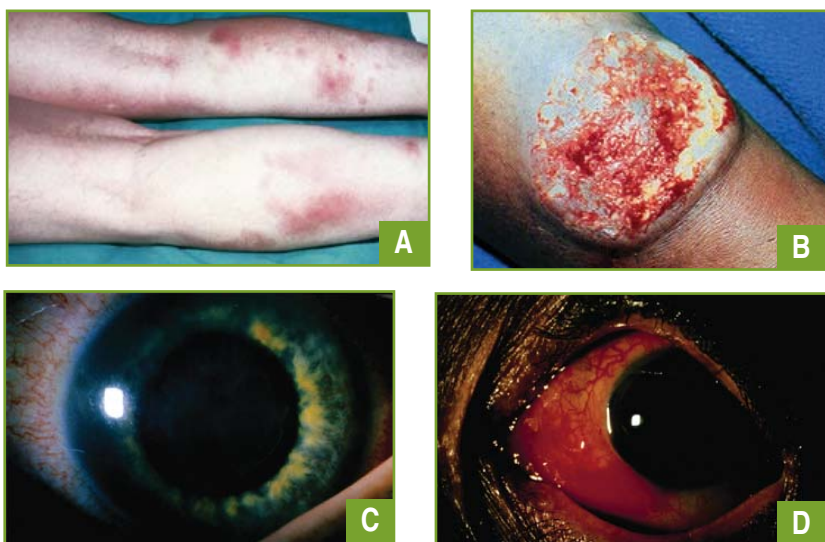


Figure 1. Extraintestinal manifestations are common in patients with UC. Two sites that may be affected are the skin and eye. Among the cutaneous manifestations, erythema nodosum (A) is the most common and pyoderma gangrenosum (B) is the most severe.¹⁸ Uveitis (C) occurs in 0.5%-3.0% of patients with UC; episcleritis (D) is less common in patients with UC than in patients with Crohn's disease.^{12,18} Photographs courtesy of Jean-Frederic Colombel, MD.

Table 2.
(Auto)antibodies
in Ulcerative Colitis

Antibody	Epitope
Colon extract	Unknown
Antigoblet cell antibodies	Unknown
ASCA	Mannan epitope of <i>S cerevisiae</i>
pANCA	Neutrophils
PAB	Pancreas
Anti-Omp(C)	Outer membrane porin

Anti-Omp(C) = antibody against outer membrane protein C of *Escherichia coli*;
PAB = pancreatic antibodies.
Adapted from Vermeire S, et al.²³

Table 3.
Comparison of
Ulcerative Colitis
and Crohn's Disease

Feature	UC	Crohn's Disease
Abdominal pain	Variable	Common
Depth of inflammation	Mucosal	Transmural
Diarrhea	Severe (including nocturnal episodes)	Less severe
Distribution	Diffuse, contiguous spread; always involves rectum; no involvement outside colon/rectum	Segmental, non-contiguous spread ("skip lesions"); rectal involvement less common; occurs in entire GI tract
Fistula and sinus tracts	Rare	Common

Langan RC, et al.¹² Reprinted with permission from 'Ulcerative Colitis: Diagnosis and Treatment,' November 1, 2007, *American Family Physician*. Copyright © 2007 American Academy of Family Physicians. All Rights Reserved.

Endoscopic evaluation: Endoscopic evaluation with biopsy is required for a definitive diagnosis of UC and is indicated when diarrhea is persistent, noninvasive test results do not reveal a pathogen, or inflammatory signs or symptoms are present.¹¹ The sensitivity of colonoscopy with biopsy for colonic pathology is 99% in patients with diarrhea.²⁵ The mucosal changes characteristic of UC seen on colonoscopy include loss of the typical vascular pattern, friability, exudates, ulcerations, and granularity in a continuous circumferential pattern.^{10,12} Flexible sigmoidoscopy is an alternative to colonoscopy, but it may miss lesions in the ascending and transverse colon in patients with Crohn's disease, in which lesion distribution is noncontiguous.¹²

Mucosal biopsies usually are performed during colonoscopy. The pathology in UC typically includes distortion of crypts, acute and chronic diffuse inflammatory infiltrate in the lamina propria, presence of neutrophils in the crypt epithelium, goblet cell depletion, crypt abscesses, and basilar lymphoid aggregates.^{10,11} Although these features are not specific for UC, the signs of chronic inflammation (eg, cryptitis and crypt abscesses) can help in differentiating UC from acute self-limited colitis (eg, infectious colitis, ischemic colitis, or NSAID-induced colitis).¹¹ However, crypt architectural distortion is a hallmark of chronic inflammation; differentiating acute UC from infectious colitis may be very difficult.

Ulcerative Colitis vs Crohn's Disease

Differentiating UC from Crohn's disease, especially in patients with early disease or pancolitis, is often difficult.^{11,12} Although UC and Crohn's disease share multiple features—gastrointestinal (GI) inflammation, waxing and waning severity, and unknown etiology—they differ in symptomatology, pathology, and GI tract distribution patterns.¹² Bloody diarrhea is generally characteristic of UC, while the diarrhea in Crohn's disease is usually nonbloody.^{10,12}

Perianal lesions tend to be more characteristic of Crohn's disease than UC. In one study of 170 patients with IBD, anal skin tags were found more often in patients with Crohn's disease (75.4%) than in patients with UC (24.6%).²⁶ The skin tags associated with Crohn's disease are often termed *elephant ears* and are generally flesh-colored, soft, and painless, while skin tags associated with healed ulcers, fissures, or hemorrhoids are more likely to be edematous, hard, and tender or painful.²⁶

Other characteristic features of UC and Crohn's disease are compared in Table 3.¹⁰⁻¹² However, some patients have features of both diseases, and the diagnosis remains "indeterminate" colitis.⁶

CASE: 26-YEAR-OLD WOMAN WITH CHANGES IN BOWEL HABITS

History and Presentation

A 26-year-old woman of Scotch-Irish ancestry presents with a 3-month history of an intermittent increase in bowel movement frequency, especially after meals. She notes some urgency at times and intermittent rectal bleeding, which she attributes to hemorrhoids. She has had no abdominal pain, other than mild cramps with bowel movements, and she denies weight loss and fevers. No other household members have had similar symptoms, but she does drink well water. She has moderately heavy menses and is currently using oral contraceptives. Other current medications include ibuprofen, 800 mg 3 times a day, for minor neck pain resulting from a recent automobile accident. She has a history of cigarette smoking but reports stopping 2 years ago.

Laboratory Findings

A recent CBC revealed a mild microcytic anemia.

- Hemoglobin: 11.4 g/dL
- Hematocrit: 32.4%
- Mean corpuscular volume: 78 μm^3
- Platelet count: $422 \times 10^3/\mu\text{L}$
- White blood cell count: 10,000/ μL

Additional laboratory tests ordered at presentation:

- Chemistry panel: within normal limits
- Stool testing: positive for fecal leukocytes

Physical Findings

- Head, eyes, ears, nose, and throat: pink conjunctiva
- Abdomen: normal to increased bowel sounds; no organomegaly to percussion; mild left lower quadrant tenderness to deep palpation but without palpable mass or fullness
- Perianal inspection: no external tags, no anal fissure

Differential Diagnosis

- >3 months of symptoms with change in bowel habits: possible IBS or IBD
- Scotch-Irish ancestry, microcytic anemia: possible celiac disease
- Rectal bleeding: possible hemorrhoidal disease
- Well water history: possible infectious pathogen (eg, coliforms, *Giardia*, cryptosporidia)
- Anemia could be explained by heavy menses

- Oral contraceptive use: possible bowel ischemia
- NSAID use: possible NSAID-induced colitis

Colonoscopy

- Endoscopic findings: rectal/distal sigmoid inflammation
- Biopsy results: mucosal inflammation, crypt abscesses, and architectural distortion

Discussion

Richard H. Davis Jr, PA-C, and Sunanda V. Kane, MD, discuss questions related to establishing a diagnosis in patients who present with chronic diarrhea.

What is the key to eliciting a good history?

Richard Davis: This patient was very uncomfortable talking about her bowel habits. I find this is true of many patients, especially women. Establishing a rapport with patients and demonstrating sensitivity to their complaints and concerns are important.

Sunanda Kane: The first thing I do is try to put patients at ease, saying, “This may be uncomfortable for you or may be embarrassing, but I’ve heard it all. This is what I do for a living. No question is embarrassing; nothing you can tell me is going to shock or surprise me.” I’ll also use the vernacular (eg, “Do you fart? Do you poop?”) to bring the tone down from a medical level so patients feel they can talk to me.

What laboratory tests should primary care clinicians order before referring patients for specialist consultation?

RD: At the University of Florida, I often see referrals from the student infirmary, young patients with a change in bowel habits and perhaps intermittent rectal bleeding, but not necessarily with classic symptoms of UC, and I’m asked whether this is IBS, UC, or Crohn’s disease. However, many times initial laboratory testing is not done by the referring clinician, who may not be sure what to order. In the case presented here, the patient was referred with the results of her CBC, but other blood and stool tests had not been ordered. Because this patient has well water as the source of her drinking water, I would have liked to have seen stool studies done earlier to rule out an infectious cause.

SK: I definitely like to see patients referred with the results of their CBC as well as testing for a marker of inflammation, either the ESR or the CRP level. The CRP level is much more sensitive for inflammation, but it’s so sensitive that if the patient has a cold that day, the CRP will be elevated. But either the CRP level or

the ESR should be measured. I also like to see stool studies done before the referral because if these tests show an infectious cause (eg, *C difficile* toxin, *Campylobacter*, or *Giardia* sp), endoscopy or x-ray films of the GI tract are not needed.

RD: I usually request fecal lactoferrin testing when I order stool studies because reference laboratories, used by many of our patients, may delay the analysis.

SK: Many clinicians test for fecal leukocytes. The problem is that the leukocyte count becomes inaccurate if the stool sample is too old. When ordering stool studies, I ask for measurement of fecal lactoferrin, as you do, or fecal calprotectin for assessment of intestinal inflammation.

RD: Ordering a chemistry panel is a good idea, too.

SK: Abnormal levels of electrolytes (eg, potassium, sodium, bicarbonate) signal that the patient is having a lot of diarrhea. High serum creatinine levels point to volume depletion.

When should testing for celiac disease be considered?

RD: The case patient's Scotch-Irish ancestry and microcytic anemia point to the possibility of celiac disease. However, her family history and symptoms are not consistent with celiac disease.

SK: Celiac disease can present in many different ways. However, patients with celiac disease usually will not have a significant amount of bleeding. They will be iron-deficient and may have the urgency and changes in bowel habits, but they will have upper GI tract symptoms rather than the lower GI tract symptoms. These patients will have watery diarrhea, bloating, gas, and symptom variability because of seasonal variations in their diet. They tend to feel better in the summertime, when they are eating more fresh fruits and vegetables.

Can UC be preceded by a sentinel infection?

RD: In Florida, especially northern Florida, which is fairly rural, many people drink well water. When a patient presents with changes in bowel habits, I always suspect an infectious cause, but only rarely do I find evidence of it. However, sometimes patients will report noticing changes in their bowel habits soon after experiencing an episode of gastroenteritis.

SK: Sometimes the infection can be the nidus that sets off the inflammatory cascade. Typically, the patient is someone who has had a bacterial or viral infection but never seems to recover. Sometimes a family is vacationing, and everyone comes down with traveler's diarrhea. They recover within 5 days, except for 1 of them. That's the person with IBD, and usually it's a woman. Women tend to have postinfectious IBD more often than men.

What clues help clinicians differentiate between UC and Crohn's disease?

SK: A family history positive for UC increases the likelihood of the diagnosis but certainly doesn't cinch it. Conversely, a negative family history wouldn't necessarily rule out a diagnosis of UC. The patient in the case presented here does not appear to have a family history of UC.

RD: I have seen patients who had been diagnosed with UC referred because they develop a fistula and the condition begins to look more like Crohn's disease. However, usually there are clues in the history that would make Crohn's a more likely diagnosis than UC and could lead to earlier recognition.

SK: Patients know their body best and what happens when their disease flares. I ask: "Have you been experiencing urgency, bleeding, and diarrhea but now are having pain and fevers? Is something different?" I also ask about smoking status. The patient who is a current smoker rather than a nonsmoker or former smoker is more likely to have Crohn's disease. I also ask, "Do you have a family history of Crohn's disease?" and explain that "the same disease tends to run in families. Even if, for all intents and purposes, your condition looks like UC initially, if 2 or 3 of your family members have Crohn's disease, Crohn's disease remains a possible diagnosis." Also, patients who have hemorrhoidal disease or perianal skin tags would be more likely to have Crohn's disease than UC.

RD: External skin tags resulting from inflammation may appear differently from external tags due to previous hemorrhoidal disease. Skin tags, often termed *elephant ears*, are associated with inflammatory disease.

SK: These are huge skin tags that are swollen and just very obvious.

RD: The position of anal fissures is also a clue. When I see a fissure in the anterior/posterior position, I think of it as a straightforward anal fissure, but if I see it off to the side, I think of IBD.

SK: If it's in the midline, it's a fissure. If it's in some other position, we have to think about inflammatory disease.

RD: Crohn's disease is often rectal sparing, while UC usually involves the rectum. But sometimes rectal involvement can be seen with Crohn's disease, too.

SK: Also, a patient with primary sclerosing cholangitis can have rectal sparing but still have UC. There's no strict rule for that at all.

Do radiologic studies have any value in patients with suspected UC?

SK: Not for patients with just diarrhea and bleeding but without pain, weight loss, or fevers. Imaging studies are not needed unless there is concern about a tumor or abscess or a stricture. A computed tomographic (CT) scan is nonspecific. It will show bowel wall

thickening, but it will not show whether the thickening is due to UC, infection, NSAID use, ischemia, or another cause.

RD: We use CT enterography, a new computerized visualization of images of the small intestine. It is more accurate for evaluating inflammation and strictures of the intestine in patients with Crohn's disease.

SK: We do as well. Crohn's disease is different. Patients have pain and weight loss, and we need to look for transmural disease or fibrostenotic disease.

When is colonoscopy warranted in patients who present with chronic diarrhea?

RD: Some primary care clinicians perform flexible sigmoidoscopy in their office and start treating inflammation before referring patients to a specialist. However, sigmoidoscopy may miss lesions in the transverse or ascending colon.

SK: When patients with signs of inflammatory disease on flexible sigmoidoscopy are referred to me, I perform a colonoscopy because I want to know how far their disease extends and what their terminal ileum looks like. If primary care clinicians do perform flexible sigmoidoscopy, they should use tap water enemas for bowel preparation. Sodium phosphate enemas can cause edema, and normal bowel can appear erythematous or edematous.

RD: I have had patients with a history of IBS and rectal bleeding attributed to hemorrhoidal disease referred because their symptoms have worsened. When we perform a colonoscopy, we find left-sided colitis or even more advanced disease.

SK: IBS is a diagnosis made by history, physical examination, and a few laboratory tests. Anytime the history includes bleeding, endoscopy is warranted. In the situation you describe, either UC was misdiagnosed as IBS, or if endoscopy had been performed and the findings were negative, except for hemorrhoids, something changed in the patient's history (eg, smoking cessation) since the earlier diagnosis. A patient can have IBS and then develop IBD.

When should acute colitis or toxic megacolon be suspected?

SK: Fortunately, such cases are rare. A patient with fulminant colitis could progress from well to ≥ 10 bowel movements in a 24-hour period, and then to fever, tachycardia, severe cramping and urgency, and even some nausea and vomiting within a few weeks of the onset of symptoms, and within 6 weeks might even require colectomy. I recently saw a patient with toxic megacolon. She was pregnant, and her clinician did not want to treat because of the pregnancy. The teaching point here is that women with UC need

to keep their disease controlled with medication so it won't flare during pregnancy.

CASE: 26-YEAR-OLD WOMAN WITH CHANGES IN BOWEL HABITS (continued)

Diagnosis

Physical, laboratory, and endoscopic findings are consistent with ulcerative proctitis.

Commentary

SK: This case illustrates some key points about the importance of taking a good history to better formulation of a specific differential diagnosis. The most common GI diagnosis in a primary care office is IBS, but because this patient has a history of anemia and rectal bleeding, further testing is absolutely warranted.

RD: The patient's Scotch-Irish ancestry and mild microcytic anemia make one think of possible celiac disease. Screening for celiac disease is best accomplished with a serologic test for tissue transglutaminase Ab IgA. Her history of well water usage accompanied by the finding that no other members of her household are ill decreases the likelihood of an infectious enteritis. However, stool studies for *Giardia* and enteric pathogens will rule out most infectious causes. Her history of heavy menses could explain her microcytic anemia, and her frequent use of NSAIDs might have exacerbated IBD or caused intestinal ulcers also. The chronicity of the patient's symptoms argues against an acute gastroenteritis.

The key to her history is the recent discontinuation of smoking, which frequently precedes the onset of UC. This case can be confusing at first, with many diagnoses possible, but a careful history and judicious testing can guide the clinician to the correct diagnosis of UC.

PCE TAKEAWAYS

- Taking a good history is key to diagnosing UC, with an attention to red flag symptoms of bleeding, pain, tenesmus, fever, and weight loss.
- Other noninflammatory etiologies need to be eliminated.
- Extraintestinal manifestations of UC should not be overlooked.
- Definitive diagnosis of UC is established by colonoscopy with biopsy.

References

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126:1504-1517.
2. 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.
3. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol*. 2007;5:1424-1429.
4. 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.
5. Thoreson R, Cullen JJ. Pathophysiology of inflammatory bowel disease: an overview. *Surg Clin North Am*. 2007;87:575-585.
6. Hanauer SB. Update on the etiology, pathogenesis and diagnosis of ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol*. 2004;1:26-31.
7. Halme L, Paavola-Sakki P, Turunen U, et al. Family and twin studies in inflammatory bowel disease. *World J Gastroenterol*. 2006;12:3668-3672.
8. Heller F, Fuss IJ, Nieuwenhuis EE, et al. Oxazolone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13-producing NK-T cells. *Immunity*. 2002;17:629-638.
9. Boyko EJ, Koepsell TD, Perera DR, Inui TS. Risk of ulcerative colitis among former and current cigarette smokers. *N Engl J Med*. 1987;316:707-710.
10. 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.
11. Kefalides PT, Hanauer SB. Ulcerative colitis: diagnosis and management. *Hospital Physician*. 2002;53-63. Available at: http://www.turner-white.com/pdf/hp_jun02_colitis.pdf. Accessed January 14, 2009.
12. Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD. Ulcerative colitis: diagnosis and treatment. *Am Fam Physician*. 2007;76:1323-1330.
13. Ghosh S, Shand A, Ferguson A. Ulcerative colitis. *BMJ*. 2000;320:1119-1123.
14. Henriksen M, Jahnsen J, Lygren I, et al; IBSEN Study Group. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). *Inflamm Bowel Dis*. 2006;12:543-550.
15. Davies NM. Toxicity of nonsteroidal anti-inflammatory drugs in the large intestine. *Dis Colon Rectum*. 1995;38:1311-1321.
16. Katsinelos P, Christodoulou K, Pilpilidis I, et al. Colopathy associated with the systemic use of nonsteroidal antiinflammatory medications. An underestimated entity. *Hepatogastroenterology*. 2002;49:345-348.
17. Tanner AR, Raghunath AS. Colonic inflammation and nonsteroidal anti-inflammatory drug administration. An assessment of the frequency of the problem. *Digestion*. 1988;41:116-120.
18. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol*. 2006;12:4819-4831.
19. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al; for the American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
20. Dai J, Liu WZ, Zhao YP, et al. Relationship between fecal lactoferrin and inflammatory bowel disease. *Scand J Gastroenterol*. 2007;42:1440-1444.
21. Gaya DR, Mackenzie JF. Faecal calprotectin: a bright future for assessing disease activity in Crohn's disease. *QJM*. 2002;95:557-558.
22. Presutti RJ, Cangemi JR, Cassidy HD, Hill DA. Celiac disease. *Am Fam Physician*. 2007;76:1795-1802.
23. Vermeire S, Vermeulen N, Van Assche G, et al. (Auto)antibodies in inflammatory bowel diseases. *Gastroenterol Clin North Am*. 2008;37:429-438.
24. 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.
25. Fine KD, Seidel RH, Do K. The prevalence, anatomic distribution, and diagnosis of colonic causes of chronic diarrhea. *Gastrointest Endosc*. 2000;51:318-326.
26. Bonheur JL, Braunstein J, Korelitz BI, Panagopoulos G. Anal skin tags in inflammatory bowel disease: new observations and a clinical review. *Inflamm Bowel Dis*. 2008;14:1236-1239.