Emerging Issues in Ulcerative Colitis and Proctitis

A Report from a Clinical Roundtable Discussion
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This publication is specifically designed for practicing gastroenterologists who wish to review and update their knowledge of the management of inflammatory bowel disease (IBD).

Educational Objectives
At the conclusion of this activity, participants should be able to:
1. Describe the different physiologic manifestations of ulcerative colitis, proctitis, and proctosigmoiditis.
2. Discuss the use of different formulations of oral and topical mesalamine in the treatment of these disease states.
3. Discuss therapy options for patients with mild-to-moderate disease that is refractory to mesalamine treatment.

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Daniel H. Present, MD: Dr. Present discloses the following. Grant/research support: Procter & Gamble, Crohn’s and Colitis Foundation of America, Otsuka, Centocor, Human Genome Sciences, Abbott Corp., Elan Pharma, Salix, Schering, Jacobus, Ocera. Consultant: NIH, Tech Lab, UCB, Inc, NPS. Speakers’ Bureau: Procter & Gamble, Prometheus, Salix, Shire (US), Elan Pharma, Axcan.


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Daniel H. Present, MD

Dr. Present received his undergraduate degree from Syracuse University and his medical degree from the State University of New York—Downstate Medical Center. He completed his postgraduate training at Mount Sinai School of Medicine, where he currently serves as Clinical Professor of Medicine. He is also an Attending Physician at The Mount Sinai Hospital. Dr. Present is a member of the American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG). Recent awards include Master of the ACG and the AGA’s Distinguished Clinician Award. Dr. Present has published more than 150 scientific articles and abstracts on inflammatory bowel disease and its treatment. He serves as a reviewer for the New England Journal of Medicine, Gastroenterology, American Journal of Gastroenterology, Gut, and Inflammatory Bowel Disease.

Gary R. Lichtenstein, MD

Dr. Lichtenstein received his medical degree from the Mt. Sinai School of Medicine in New York and completed residency at the Duke University Medical Center, Durham, NC. His fellowship was completed at the Hospital of the University of Pennsylvania in Philadelphia and he is currently Professor of Medicine at the University of Pennsylvania School of Medicine and the Director of the Center for Inflammatory Bowel Diseases at the Hospital of the University of Pennsylvania. His clinical interests focus on inflammatory bowel disease and his research interests include therapies for ulcerative colitis and Crohn’s disease. He has worked extensively in the area of refractory IBD and the role of immunosuppressant and biologic agents for the treatment of Crohn’s disease. He has taught and lectured extensively throughout the United States. Dr. Lichtenstein has many articles published in peer-reviewed journals on a wide variety of topics in inflammatory bowel disease.

Ellen J. Scherl, MD

Dr. Scherl earned her doctor of medicine degree from New York Medical College in Valhalla, New York. After graduating, she completed a residency in Internal Medicine at Beth Israel Medical Center and a fellowship in Gastroenterology at Mount Sinai Medical Center, both in New York. She is currently Director of the Inflammatory Bowel Disease Center and the Jill Roberts Associate Professor of Medicine at Weill Medical College of Cornell University/New York-Presbyterian Hospital in New York. Dr. Scherl’s current interests encompass investigational therapies for ulcerative colitis and Crohn’s disease. She is a Fellow of the American College of Physicians and is a member of the American College of Gastroenterology and the American Gastroenterological Association. An editorial reviewer for the Journal of Clinical Gastroenterology and Gastrointestinal Endoscopy, she is the co-author of “Crohn’s Disease of the Small Intestine” in Gastroenterology and Hepatology: The Comprehensive Visual Reference. Dr. Scherl is currently participating in several national multicenter trials focusing on both ulcerative colitis and Crohn’s disease.

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Ulcerative colitis is a chronic, often highly morbid inflammatory bowel disease of unknown origin. Proctitis, or inflammation of the rectum, is a classic hallmark of this disease. Inflammation limited to the rectum is termed ulcerative proctitis, but is classified as ulcerative colitis when the inflammation extends into the upper parts of the colon. There is a wide spectrum of disease severity, ranging from mild to severe inflammation (Figure 1). Clinically, ulcerative colitis is characterized by intermittent rectal bleeding, abdominal cramping and pain, and diarrhea. Patients often suffer from fatigue, weight loss, and loss of appetite and can experience adverse events outside of the colon, including arthritis, ocular inflammation, liver and biliary disease, osteoporosis, skin rashes, and anemia, all of which are exacerbated during the active phase of the disease.

Ulcerative colitis most commonly affects patients between the ages of 15 and 30 years. Its yearly incidence rate in North America is approximately 10–12 per 100,000, and its prevalence is approximately 200 per 100,000. The cause of ulcerative colitis is unknown, but may be related to an improperly regulated immune response to food, infectious agents, or commensal bacteria. In a long-term follow-up study conducted by investigators at the Cleveland Clinic between 1960 and 1983, almost half of all ulcerative colitis patients were described as having proctosigmoiditis, typically defined as inflammation of the rectosigmoid, or distal, colon (Figure 2). Pancolitis was reported in 37% of patients and left-sided colitis in 17%.

Treatment approaches for ulcerative colitis are determined by extent of colonic involvement and disease severity. The goal of treatment is to relieve symptoms and prevent future inflammatory flare-ups. A number of randomized studies have demonstrated the efficacy of aminosalicylate agents in the treatment of mild to moderate ulcerative colitis. These anti-inflammatory drugs have become the first-line treatment option for this disease. Sulfasalazine was the first aminosalicylate used to treat ulcerative colitis, but subsequent studies demonstrated that 5-aminosalicylate (5-ASA; mesalamine) was the active moiety of this molecule and has greater potency and fewer sulfonamide-associated side effects than its parent compound. A number of treatment options exist for patients who experience disease progression or are refractory to 5-ASA, including oral and systemic steroids, immunosuppressive drugs, and surgery (Figure 3).

Compliance with long-term maintenance therapy has proved problematic in ulcerative colitis patients, particularly when they are asymptomatic. Epidemiologic studies have revealed that between 40–60% of patients take less than 80% of their prescribed mesalazine dose in
the quiescent phase of their disease.\textsuperscript{13,14} This noncompliance is associated with increased risk of disease flare-up and possibly colorectal cancer.\textsuperscript{15-17} Reasons for discontinuing therapy are complex, but male sex, single status, full-time employment, and a three-times-daily dosing regimen have all been identified as independent predictors of noncompliance.\textsuperscript{13,14}

Mesalamine is available in a number of oral and topical formulations, including tablets, suppositories, and enemas. Rectal formulations of 5-ASA have proven especially effective for distal colitis because they can ensure drug delivery to the active site of disease at levels not achievable with oral agents.\textsuperscript{18,19} However, rectal formulations of 5-ASA are associated with leakage and bloating.\textsuperscript{20,21} In addition, retention of suppositories and enemas, critical for proper dosing, may be difficult in patients suffering from diarrhea. The rectal agents are especially unpopular among college students and young adults, the primary population for this disease.

The impact of higher mesalamine dose on treatment efficacy was evaluated by Hanauer and colleagues\textsuperscript{22} in two recently published phase III trials, ASCEND I and ASCEND II. In these studies, patients were randomized to receive oral mesalamine 2.4 g or 4.8 g daily, divided into three doses. Hanauer and colleagues reported that the 4.8 g/day dose was superior to the 2.4 g/day dose for treatment success, improvement in physician's global assessment (PGA) score and sigmoidoscopic improvement, but not in four other endpoints, including improvement in stool frequency and rectal bleeding. The benefits of higher-dose 5-ASA were observed in moderate-risk patients only; lower-risk patients did not appear to have a significant dose-related response.\textsuperscript{22}

Mesalamine remains the standard of care for patients with mild to moderate ulcerative colitis patients. Novel therapies in development for this debilitating inflammatory disorder include higher-dose formulations of 5-ASA that allow once-daily dosing and may increase patient compliance. The efficacy and long-term benefits of such agents, however, have not been established. The following roundtable discussion addresses many of the most topical issues of interest to the practicing clinician concerning the management of ulcerative colitis, including the strengths and weaknesses of oral and topical agents, maintenance of remission, combination regimens for induction and maintenance of remission, “top-down” therapeutic approaches, and management of progressive or refractory disease with novel therapies.

References

The following roundtable, moderated by Daniel Present, MD, was convened on June 20, 2006, at the Tribeca Grand Hotel in New York City to discuss the latest findings and share opinions on the approach to diagnosis and treatment of proctitis, proctosigmoiditis, and ulcerative colitis.

**Dr. Daniel Present** Is there a difference between proctitis and proctosigmoiditis? Do you make a distinction if the inflammation goes up beyond 12–15 centimeters?

**Dr. Gary Lichtenstein** I personally do. The problem is that the literature is murky in the area of defining disease extent. Is it 15 centimeters? Is it 20 centimeters where one defines proctosigmoiditis? If different studies are looked at over time, they vary as to what is considered proctitis or proctosigmoiditis. If inflammation goes up beyond 20–25 centimeters, then I’ll call it proctosigmoiditis. I would define proctitis at 15–20 centimeters at the most proximal extent. It is in making this distinction that we dictate medical therapy. I am more likely to use an enema, either alone or in combination with oral therapy, in patients with proctosigmoiditis. In patients that have proctitis alone, I use suppository therapy.

**Dr. Ellen Scherl** Proctitis to me is anything less than 15–20 centimeters. Whether it’s proctosigmoiditis or proctitis, though, I prescribe a combination of suppositories and enemas. It does not matter to me whether patients use the suppositories first, followed by the enemas, or the enemas first followed by the suppositories as a plug.

**DP** What is your treatment strategy for proctitis: initial treatment, maintenance, and long-term follow-up?

**GL** I initially treat proctitis with topical suppositories and continue treatment as long as the patient has the disease. The introduction of the 1,000 mg suppository has made induction easier for patients, allowing once-daily administration as opposed to 500 mg twice-daily. The morning dose is usually the hardest dose for patients who are taking suppositories twice a day because they place it in the rectum and then have to go to work. They worry about leakage and other problems. The 1,000 mg dose allows patients to use the suppository at night only.

**ES** I initially treat with topicals, once or twice daily for 3–4 months. After that time, I advise topicals twice weekly, indefinitely. Stephen Hanauer’s group showed...
that maintenance therapy with topical mesalamine as little as two times a week will maintain remission for up to 2 years (Figure 4). I also consider oral therapy during the maintenance phase if the patient refuses to continue using the topical agent. For follow-up, I do a colonoscopy and take multiple biopsies throughout the colon to ascertain whether or not there is microscopic disease in addition to proctitis. If microscopic disease is present, I will advise starting oral therapy. For maintenance of remission, however, it is critical that patients understand the importance of topical suppository therapy. My recommendation is to stay on it for life. Never change a winning strategy. If a patient is taking suppositories twice weekly, they should not stop.

**DP** It is well known that sustaining maintenance therapy is important. A study by Wendy Biddle and colleagues showed that relapse rates for ulcerative colitis are more than three times higher for patients taking placebo than for those taking mesalamine (Figure 5). How do you get a patient to stay on medication when they are asymptomatic?

**GL** They should be advised that they are much more likely to remain in remission and avoid active symptoms if they adhere to their maintenance therapy. It should also be emphasized that they will probably lessen their chances of getting cancer by maintaining therapy. That is the most effective approach, I think, because there is a cancer phobia amongst many patients.

**ES** What I tell them is that for induction of remission there is no making a deal. This is what they need to take if they want to get better. However, for maintenance of remission, the name of the game is “let’s make a deal.” I suggest that the patient take the induction medication and continue that dose for remission, but I will negotiate. I don’t really care if they go way down on their oral therapy or take the 5-ASA suppositories as infrequently as twice a week. But I tell them that the minute they flare they have got to increase dosing. I give my patients the control to modulate their own medicine. For the oral mesalamines, I don’t care if they take it once a day, but I insist they take something because that is what most of the studies recommend. I usually tell my patients about an experience I had with medical students who, when going through the charts of ulcerative colitis patients, were surprised by how many times patients flare. Some of these medical students have ulcerative colitis and what they know, that patients do not, is that the most common reason for a flare is to stop the medication. So they stay on their medicine. Sometimes relating that story to a young man or woman who is going off to college makes a big difference.

**DP** Which of the 5-ASAs is best for ulcerative colitis? The old azo bond agents or Pentasa, which has a 500 mg pill, or Asacol, which is working on an 800 mg pill (Figure 6). Which do you use and why?

**GL** Based on evidence from the meta-analysis by Lloyd Sutherland that looked at C. P. Willoughby’s trial and Fleig’s trial, if one could create a sulfasalazine without the adverse events, that would be the ideal agent. For patients who have responded to mesalamine but have discontinued therapy or have been on a lower dose, I’ll escalate dose or initiate therapy with the mesalamine to which they’ve responded in the past. Past response usually dictates future treatment. The new mesalamine SPD 476, a once-a-day oral agent with reasonably high delivery to the colon, may change the landscape of ulcerative colitis treatment.

**ES** I think that both effective dose and ease of delivery make the best medication. The meta-analyses were done in

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**Figure 5.** Distal ulcerative colitis: maintenance therapy.

**Figure 6.** Aminosalicylate adult dosing in inflammatory bowel disease: pill size.
the 80s and early 90s before we had some of the other azo-bonded 5-ASAs, so they’re really comparing sulfasalazine to true mesalamines. Remission rates with topical 5-ASA are approximately 60%. Oral 5-ASAs with comparable remission rates are the best oral agents, but they may not be as effective as topical agents, which allow high-dose delivery to the site of active disease. Remission rates with 4.8 g, for example, are only 35–40%. Again, topical 5-ASAs are 50–60% effective.

**DP** A number of studies suggest that oral agents bulk up in the upper colon and never reach the rectum. Do the 5-ASAs that we have available get to the rectum when administered orally? What is your opinion on the importance of topical medicines?

**GL** I think it’s very important to look at the numbers. At week 8, remission rates are 64% for patients taking oral 5-ASA (4 g) plus an enema, compared with a 43% remission rate for those on the oral agent alone. So the addition of the enema provides further benefit to 1 in 5 patients who would have not had benefit with oral therapy alone. That is an important concept.

**ES** And this is not looking at suppositories, which might actually add an additional percentage to the response or remission rate. Also, it is important to keep in mind that many of our patients suffer from irritable, inflamed colon; Rao and others have shown that this is a major problem. About 50% of our patients will have constipation due to distal irritability. The concept of adding suppositories and enemas needs to be looked at more aggressively. Some of our patients, even if you maximize the oral dose and you maximize the delivery system in terms of azo-bonded colonic delivery, still may not get the medications down to the distal rectum. If the option of topical medications is overlooked, some mileage may be lost in terms of therapeutic efficacy. With distal colitis of 20 cm, for example, Biddle and colleagues showed complete remission rates of 75% with topical mesalamines (4 g), getting it right to the site of active disease. Even in moderate ulcerative colitis, the inflamed rectal rectum is symptomatic for many patients and, based on the data, we should be adding topical mesalamines.

**DP** The study by Piodi and associates demonstrated that a combination of topical and oral mesalamine is superior to either agent alone. We now know that the mesalamine dose was low in this study. Do you think the combination regimen would remain superior if the dose of mesalamine were raised to 4.8 g per day?

**ES** The problem is that we don’t know whether these patients had mild or moderate distal colonic disease. With mild disease, it would not make a difference. In moderate disease, there may be a marginal difference in elevating the dose to 4.8 g with mesalamine. What is missing from the studies by Marteau and colleagues and Piodi and colleagues is an arm that looks at the enema alone.

**DP** What topical agent do you prefer to prescribe and why? Do you use steroids?

**GL** Rates of remission (endoscopic, histologic, and clinical) are twice as high in patients receiving both oral and topical mesalamines and show very little associated toxicity. Steroids, on the other hand, have much higher rates of adverse events. Approximately 30% of patients absorb topical corticosteroids and develop systemic side effects. It is well documented that osteonecrosis can occur with administration of topical corticosteroids. This is relatively rare, but it can occur. Given these safety issues, I would certainly advocate the use of topical mesalamine for someone who has an initial presentation with distal ulcerative colitis.

**ES** Agreed.

**DP** In the ASCEND trials, which compared two different doses of oral mesalamine (2.4 vs 4.8 g, three times daily), the higher dose worked better for patients with moderate disease (Figure 7). For patients with mild symptoms, both doses were effective. Based in part on these data, the Food and Drug Administration recommends mesalamine induction at 2.4 g divided over three doses daily. Do you agree with this recommendation? Is the dose of 5-ASAs important? Do you start at 2.4 g daily or higher in the management first of proctitis and then ulcerative colitis? What’s your standard of therapy?

**GL** The big questions is, is there a dose response as you suggest? I think there is. The studies that have not shown a clear-cut dose response have not been powered appropriately to examine this question. The ASCEND trial did not look at the 2.4 versus 4.8 g dose of mesalamine as a primary endpoint. The overall endpoint in the ASCEND trial was patient functional assessment. Did the patients feel that they had improved? And 4.8 g was effective. There were several parameters where there was benefit with 4.8 g versus 2.4 g. Experience in our clinic dictates that 4.8 g is more efficacious than 2.4 g. If the patient has more severe disease, a higher dose is often given as an initiation.
dose due to the perception that a rapid onset of action is important—a belief that has yet to be analyzed in an objective manner in any prospective trial.

**ES** If you use the azo-bonded agent sulfasalazine and start with 4 g, that releases, I believe, about 1.8 g of free 5-ASA to the colon. The azo bond of balsalazide (6.75 g) is broken to release 2.4 g in the colon. With mild disease I start with 2.4 g of mesalamine; if the colitis is moderate I, like most practitioners, start with 4.8 g. Likewise with controlled-release capsules of mesalamine, most gastroenterologists start with 4 g. If topicals are administered right away, and they should be, the enema will add between 2 and 3 g of topicalized 5-ASA and 1 g of mesalamine via rectal suppository. This is very important to the induction regimen.

**GL** We have a study that looked at 1, 2, and 4 g of topical 5-ASA. There was no difference in efficacy between these doses in nonrefractory patients with UC, which is an important distinction. These were not patients that had active symptoms on medication and continued; these were new-onset patients. If you look as well at the topical suppository studies, there has not been a dose response. Five-hundred gram mesalamine suppositories twice daily have comparable efficacy to the same dose three times daily, with no statistical difference. I think, in general, we perceive that topical therapy does not necessarily have the dose response that might be seen with oral therapy. The question is, what is the ceiling? Should we be going to 6 g or even higher doses? I think that perhaps we have not hit the plateau of the dose-response curve, though tolerability, cost, and other issues come into play. We realize that there is no safety difference between 2.4 g and 4.8 g daily of oral mesalamine, based on several studies in which these two doses have been compared. More, I believe, is better when mesalamines are given orally. However, this remains to be seen for topical formulations.

**ES** I think what you are indicating is that with moderate-to-severe disease, there may be a topical dose response that needs to be examined.

**DP** I think the main point is the absolute safety of these agents. If you’re not sure whether your patient is getting better or not, go up higher. These are perfectly safe drugs to use. There’s no downside to going up higher in terms of the management. Do you agree?

**GL** Yes, with both oral and topical 5-ASAs, intolerance that limits the patient’s abilities to take mesalamine occurs in approximately 4%, based on Sutherland and Macdonald’s meta-analysis.4

**DP** How do you define a patient as refractory to 5-ASA therapy?

**ES** First, review the medications. Is it really refractory disease or has it been undertreated? Topicals are used in distal proctitis. If a patient has not been on topical therapy for 4 months, to me that is not refractory. They have been undertreated. If the patient is not on maintenance, it’s also undertreatment. If the patient has proctosigmoiditis, then they will likely need suppositories plus enemas, again for the same 4-month induction with subsequent evaluation. If the patient still doesn’t respond, I would consider oral mesalamine as part of the strategy.

If the patient is optimized in terms of oral and topical agents, I would consider whether they also have an irritable bowel syndrome. Ten to 15 percent of the population has irritable bowel syndrome.1 I would also determine if the patient is lactose intolerant or if they have celiac disease and might examine the patient with the flexible sigmoidoscope to see if proctitis is present. If not, I would very quickly conclude that this is actually irritable bowel syndrome. If there is inflammation, I test for concurrent or intercurrent infections. With the emerging *Clostridium difficile* epidemic, I cannot emphasize how important it is to obtain repeat stool cultures and examine sigmoidoscopically to check for pseudomembranes. Other infections can also be documented. Sometimes the physician needs to look further. The patient may have Crohn’s disease with jejunitis or jejunoileitis. The entire colon needs to
be examined. In patients with refractory left-sided colitis, the diagnosis should always be challenged and Crohn’s ruled out.

Performing a biopsy is also critical. A patient cannot be labeled as refractory, with ulcerative proctitis or proctosigmoiditis, unless a biopsy has been performed to confirm that the disease is in fact inflammatory, not infectious. I recommend that the pathologist make sure that it is not a common variable immunodeficiency with absence of plasma cells.

**GL** Another thing to consider is intolerance to medication. Mesalamine intolerance is relatively rare, but it has been recorded and should be considered. Dysplasia can be present in patients and they become refractory or develop cancers.

It is also important to consider the time frame to gain benefit. Every trial in ulcerative colitis is 4–8 weeks in duration, so if the patient doesn’t start to see improvement within the first 2 days, this is not an indication that the medication is not effective. The patient needs to wait 1–2 weeks and see if there’s a trend. If they do not respond to escalation of therapy or if they experience escalation of symptoms, then other therapeutic interventions need to be considered.

Another rare possibility is pelvic floor dysfunction causing unrelated incontinence. This is something to consider with elderly patients. This is very uncommon, but in differential diagnosis it can fool patients and physicians.

**DP** What do you do if a flexible sigmoidoscopy shows colonic inflammation in a patient who has been taking topical mesalamine? Do you continue to prescribe the rectal agent?

**ES** I persist. The first thing to do is to review how the topical agent is being administered. If they’ve been taking mesalamine 1-g suppositories once daily or twice daily, I suggest that they go up to three times daily for 1 or 2 weeks. If the disease extends beyond 20 centimeters, I’ll suggest that they take two or three additional suppositories at night. Then I discuss other topical agents if this is mostly distal disease and their symptoms are of irritable, inflamed colon with tenesmus and urgency. I tell them to use hydrocortisone acetate suppositories and aerosol foam, followed by the mesalamine. If they have more distal disease, I recommend a hydrocortisone acetate rectal aerosol in the morning and a hydrocortisone retention enema at night with a mesalamine enema in between. Suppositories should be administered either before or after all of these.

**GL** I might add an oral agent at this point. It has been established that a combination of oral and topical agents is effective.\(^7\)\(^9\) The other question to be considered is, whether this truly is just proctitis? Often a patient with just proctitis is unable to retain the enema due to a decrease in rectal compliance. A suppository is certainly better in this case. It should also be considered how much proctosigmoiditis the patient may have and if they are being effectively treated higher up in the colon while missing the rectum.

It must also be considered whether the patient might be pseudorefractory: is something else present—C. difficile infection, giardia infection, lactose intolerance, the dietary chewing gum or candies, etc? If there is still no response, it may be time to consider an oral corticosteroid or perhaps go right to an immunomodulator. Using an immunomodulator in lieu of corticosteroids is really something that one might consider, realizing that most people who take a corticosteroid will flare within a year.\(^12\) Approximately 60% will continue to need another agent, and immune modulators are down the road for that population regardless.\(^12\)

**DP** In controlled trials, one of the primary endpoints is often endoscopic remission. How applicable is this to clinical practice? Do you verify endoscopic remission if you observe clinical remission in your patients?

**GL** If a patient calls me on the phone and says, “Dr. Lichtenstein, I’m doing great. I don’t need to see you because I’ve initiated therapy and I’m fine,” I don’t do an endoscopy to look and see the mucosa. I think most clinicians would advocate the same thing. By doing that sigmoidoscopy, one can “stir things up.” Symptomatically, we have patients feeling good, so we assume that they are okay.

**ES** If patients are doing well, don’t change a winning strategy. However, if they start negotiating to stop their topicals, then I suggest sigmoidoscopic examination with a tap-water enema or examine them without an enema at all. I take a biopsy and get a good look at the mucosa. If there is inflammation, I can make a more compelling case for maintenance of remission. But it is individualized. I think that if we are going to insist on endoscopic healing, maybe we should do a complete colonoscopy before and after, at least with a subset of patients.

**DP** Let’s turn to immunomodulatory therapy. I’d like to start with the simple question: does methotrexate work for ulcerative colitis or proctitis?

**GL** The problem with this question is that the correct study has not yet been done. We have the study by Oren and colleagues in steroid-dependent ulcerative colitis patients that examined 12.5 mg of methotrexate once weekly and
showed no benefit over placebo, either for induction or maintenance, but this study used oral agents. If you look at the initial study by Kozarek and colleagues, 5 of 7 patients with ulcerative colitis demonstrated response when methotrexate was administered subcutaneously or intramuscularly. We don’t know whether a higher dose (eg, 25 mg once a week) administered subcutaneously or intramuscularly would work in active ulcerative colitis.

**ES** Another caveat with Oren’s study is that 10–15% of patients were described as having “indeterminate colitis.” Some of those patients may have actually had ileitis or jejunitis. In that small subgroup of patients, methotrexate may be a more appropriate treatment.

**DP** The efficacy of azathioprine in the maintenance of remission in ulcerative colitis has been demonstrated in randomized trials. Do you use azathioprine or its metabolite, 6-MP, to treat distal proctitis or proctosigmoiditis? Is there an indication there? Most physicians consider them when patients are on steroids. Do you think about them before prescribing steroids?

**GL** For a patient with mild to moderate disease who cannot receive corticosteroids for some reason and is unresponsive to other agents like infliximab, I’d prescribe 6-mercaptopurine (6-MP) or azathioprine without using corticosteroids. However, given that we have population cohort studies from Olmstead County and others showing that approximately 40% of patients respond to corticosteroids after one year and do not need a subsequent course, I think corticosteroids are worth consideration for some patients. If they flare within a year, then I’ll use an immunomodulator. Azathioprine is my preferred choice. There is not a single study with 6-MP in ulcerative colitis, but it is perceived that 6-MP and azathioprine are equivalent for treatment of patients with UC.

**ES** I have been convinced that steroids are problematic in the treatment of ulcerative colitis because one third of patients on steroids alone will end up undergoing colectomy, and two thirds will be hospitalized. If I can avoid starting an ulcerative colitis patient on steroids, I will. The problem with ulcerative colitis is that there may not be the amount of time available that is the case with Crohn’s disease. Therefore, if the patient requires immediate response and they have moderate to severe disease, steroids are necessary. However, if they present with nonprogressing moderate ulcerative colitis, I advise bypassing the steroids and considering earlier interven-

**GL** The main concerns in a patient with this disease history are colectomy and cancer. The question is, if you wait and give 6-MP alone or azathioprine without the concurrent administration of infliximab, will you alter their risk of colectomy or cancer? The answer is, we don’t know. So I really have to look at the patient and say, is this a patient who’s going to be compliant, who’s going to get blood testing done? If he or she is not going to get blood tests, I certainly would prefer to use infliximab. At the time they get the infliximab infusion, you can draw a blood sample. We don’t have any evidence whatsoever that this is the appropriate course to take; it’s total conjecture. If the patient responds, I would consider azathioprine indefinitely as maintenance therapy.

**ES** My primary concern would be to verify the mesalamine failure. I would make sure that I’ve optimized both the oral and the topical medication. If time is not a factor, I would consider 6-MP and azathioprine, weight-based, and then at a lower dose for maintenance. If immediate results were necessary, I would use infliximab as a bridge to 6-MP and azathioprine.

**DP** Deficiencies in thiopurine-S-methyltransferase (TPMT), an enzyme critical for the metabolism of 6-MP, may result in excessive production of metabolites that can induce severe bone marrow toxicity. Do you get a TPMT level before you start azathioprine or 6-MP?

**GL** The question is one of whether the patient’s overall outcome is altered. This depends on the patient’s willingness to get a complete blood count test with differential every week or two during the initiation of therapy. If patients are very adherent and receive the necessary blood work, then there does not seem to be added benefit from TPMT testing. However, the FDA recommends TPMT-level testing based upon the severe myelosuppression and death that has occurred in individuals who have low TPMT enzyme activity. Based on that information, I do measure...
TPMT enzyme activity in all patients prior to initiation of therapy. If the patient does not follow up with their blood tests, I will still be able to effectively manage their care. I have seen two patients over the years who had severe pancytopenia and actually died in our ICU because they were not followed locally. These individuals were reported to the FDA and were found to have low enzyme activity. I have tested 3 or 4 patients over the last two years who have proved to have low enzyme activity and this finding certainly altered my treatment approach. I did not offer azathioprine or 6-MP to these patients. It is recommended that it be given at about one tenth the normal dose, if there is no other option to be considered; for example, 25 mg azathioprine every 3 days as the initiation dose.

In select patients I get TPMT levels, namely in older patients where I really want to make sure that I don’t overdose, and in patients where I want to start upfront weight-based dosing (2.5–3 mg/kg azathioprine or 1.5 mg of 6-MP). I want to make sure that their TPMT is either heterozygous or a true level, so that I know that I can decrease the dose. If there is time, I start with 50 mg of 6-MP or 100 mg azathioprine, and insist the patient comes in once a week for the first month for complete blood counts. This is also what doctors in the community are doing. Immunomodulators are readily available in the community. 6-MP is associated with high remission rates in patients with refractory ulcerative colitis. I think we have to advocate community physicians comfortably using TPMT monitoring.

How would you treat a patient with moderate to severe ulcerative colitis who has been hospitalized? Let’s assume they’ve received steroids, because most refractory patients have been put on steroids. Would you use infliximab, cyclosporine, or the anti-CD3 monoclonal antibody visilizumab?

Visilizumab would be my choice of treatment if it really turns out to be as effective as the initial pilot study has indicated. Visilizumab is an attractive alternative because it is a monotherapy and about two thirds of patients maintain remission after two years, off all other immunomodulators.

I vote for infliximab in this case. It’s easier to use with easy administration. We published very promising initial data with infliximab in a similar population three or four years ago, showing a response rate of over 66%.

Here’s a case study. A patient presents with classic proctosigmoiditis: on colonoscopic examination, disease extends for 35 centimeters. The mucosa looks perfectly normal all the way up the rest of the colon. But you do some sample biopsies and the pathologist reports it as mildly active or inactive ulcerative colitis. Your eye said that this was proctosigmoiditis. How do you treat this patient? Is there a long-term cancer risk? Do you think of this patient differently because there’s microscopic colitis through the rest of the colon?

We need a prospective dysplasia study to answer that question. The microscopic colitis would worry me. I am always concerned about proctosigmoiditis. If disease is present in 30–35 centimeters of a shortened colon where the cecum is at 60 centimeters, that’s half the length of the colon with proctosigmoiditis.

The data that we have associating ulcerative colitis with increased relative risk for colorectal cancer comes from a number of studies dating back to the 1970s and looking at radiology and colonoscopy, not microscopic data. Data from the classic study by Anders Ekbom and coworkers published in the New England Journal of Medicine in 1990, suggest that individuals with proctitis and left-sided colitis are 1.4–5.7 times more likely to be diagnosed with colon cancer than are control patients. Those with left-sided disease were shown to have a 5- to 7-fold increased risk for colon cancer and patients with extensive colitis had approximately 15 times the risk for colon cancer. Data from the Gillen group shows a similar risk profile for Crohn’s patients. These are not microscopic data. The study for microscopic data and the relative risk for colon cancer has yet to be done.

Unpublished data from our group showed robust responses to cyclosporine in patients with severe ulcerative colitis: an 80% response rate for patients on cyclosporine versus 0% for placebo. Similarly, Vincent and Bensousan saw a response rate of 81% for cyclosporine a similar patient population. So cyclosporine is a very effective drug. Why isn’t it being used more for severe colitis?

We (inflammatory bowel disease experts/researchers) are different than community practitioners given our experience with cyclo-
sporine, the clinician has to remember to provide antibiotic prophylaxis (sulfamethoxazole and trimethoprim), due to the increased risk of pneumocystis infection. The practice needs to be able to administer assays like high-performance liquid chromatography to measure cyclosporine levels at least twice weekly, with rapid turnaround. The physician has to supplement the patient with oral magnesium, check blood urea nitrogen and creatinine serum levels at least twice weekly, and adjust the cyclosporine dose if it is getting into the toxic range. It is a very complicated regimen requiring significant monitoring. In addition, Paul Rutgeerts’ most recent data show that even at a very experienced medical center, there is mortality associated with cyclosporine.26 These agents are associated with a 2.5% annual mortality rate, compared with a rate of about 1% per year for conventional agents.

ES This is why, despite the compelling numbers in terms of remission rates with cyclosporine in moderate to severe colitis, it is not widely used in the community. In a busy practice, it is difficult to initiate and follow through.

DP Do you advocate probiotics for ulcerative colitis and ulcerative proctitis?

ES Fergus Shanahan’s group recently did a study looking at patients who were weaned off steroids.27 They were put on various probiotic regimens and none were shown to help maintain remission. My assessment is that if you start the probiotic after you’ve introduced steroids, it’s probably too late. So if you have time, probiotics before steroids may be an option. I also think it would be interesting to look at the effect of steroids on the gut microecology. When we talk about steroids increasing infection, what does it do to the gut micro-ecology? Timing is critical with probiotics in the treatment of ulcerative colitis. Unfortunately, this has not been controlled in the trials.

GL In my experience, probiotics do not work for ulcerative colitis.

DP How would you design a study to treat ulcerative colitis from the top down, introducing more potent therapies at an earlier disease stage? What arms would you compare?

GL I’d make it a large study because it would change the management of disease if found to be effective. I would look at infliximab plus an immune modulator versus infliximab alone versus the bottom-up. The trial would be very expensive. The ACCENT 1 trial was very expensive and this trial would need to be larger in order to have the power to differentiate between arms. But that would be, I think, the end-all trial to really tell us the best way to treat this disease. I would make it a 2-year study at least; if possible, 3–4 years to look at follow-up. We could never do a study for colon cancer, but hospitalization, surgery, days lost from work, quality of life, all are important endpoints that could be evaluated. Endoscopy should be done somewhere in the middle to look at mucosal healing as a primary factor as well

ES The first thing I would want, though it would be very expensive, is a colonoscopy before and after any intervention with at least three biopsies from the right, transverse, and left colon, so that we can evaluate the role of microscopic disease in refractory left-sided colitis or proctosigmoiditis. I would evaluate moderate to severe UC (above 20 cms) treated with 3-dose induction therapy with infliximab and concomitant weight-based AZA/6-MP versus induction with corticosteroids and concomitant weight-based AZA/6-MP.

References
Emerging Issues in Ulcerative Colitis and Proctitis

CME Post-Test: Circle the correct answer for each question below.

1. Ulcerative colitis most commonly affects patients between the ages of ___ and ___ years.
   a. 25/35
   b. 15/30
   c. 20/30
   d. 20/40

2. In the study by Farmer and associates, ___% of patients presented with pancolitis as opposed to left-sided disease or proctitis.
   a. 30
   b. 33
   c. 37
   d. 40

3. According to Dr. Lichtenstein, in patients with proctitis whose disease state is advancing, 5-aminosalicylate (5-ASA) therapy should be initiated with ___.
   a. enemas
   b. suppositories
   c. oral therapy
   d. combination oral-enema therapy

4. Among UC patients receiving topical corticosteroids, approximately ___% develop systemic side effects.
   a. 25
   b. 30
   c. 35
   d. 40

5. According to Dr. Scherl, a patient with distal proctitis cannot be labeled “refractory” to topical 5-ASA medication unless they have been on treatment for at least ___ months with no response.
   a. 2
   b. 3
   c. 4
   d. 6

6. In the 1990 study by Ekbon and coworkers, patients with left-sided ulcerative colitis were shown to have a ___ times increased chance of developing colon cancer versus control patients.
   a. 1–2
   b. 2–4
   c. 3–5
   d. 5–7

7. In a study by Rutgeerts and associates, treatment with cyclosporine was associated with ___% mortality versus 1% for conventional agents.
   a. 2
   b. 2.5
   c. 4
   d. 5

8. In the study by Shanahan and associates, it was found that probiotics are effective in the treatment of UC patients who have previously received steroids.
   a. True
   b. False

9. Epidemiologic studies have shown that between ___% of UC patients take less than 80% of their prescribed maintenance medication.
   a. 20–30
   b. 20–40
   c. 40–50
   d. 40–60

10. Mild UC is generally characterized by no signs of toxicity and less than ___ stools per day.
    a. 4
    b. 6
    c. 7
    d. 8

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Please complete the CME post-test, the CME registration form, and this evaluation form and return to: CME Consultants, Inc., 94 Main St, Wakefield, RI 02879. Answers should be submitted no later than September 15, 2007. Please read the instructions below.

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Thank you for completing the evaluation form. Your evaluation of the activity and comments are important to us and will remain confidential.

Please answer the following questions by circling the number that best reflects your view. (Scale: 1 = poor; 2 = fair; 3 = satisfactory; 4 = good; 5 = excellent)

1. Please rate how effectively you are able to:
   a. Describe the different physiologic manifestations of ulcerative colitis, proctitis, and proctosigmoiditis. 1 2 3 4 5
   b. Discuss the use of different formulations of oral and topical mesalamine in the treatment of these disease states. 1 2 3 4 5
   c. Discuss therapy options for patients with mild-to-moderate disease that is refractory to mesalamine treatment. 1 2 3 4 5

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   a. The extent this program met your continuing professional development goals 1 2 3 4 5
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   d. The applicability/usefulness of the material to your practice Not in practice 1 2 3 4 5

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   Too basic  □  Appropriate  □  Too complex  □

4. Do you feel that the activity was objective, balanced, and free of commercial bias? Yes  No
   If no, why? ________________________________________________________________

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   ________________________________________________________________

6. Please list any speakers and/or topics you would like in future programs.

   ________________________________________________________________

7. Would a periodic review of this or related material be appropriate? Yes  No

8. We welcome your comments

   ________________________________________________________________