Ulcerative Proctitis

Charles B. Whitlow, M.D.¹

ABSTRACT

Ulcerative proctitis is an idiopathic mucosal inflammatory disease involving only the rectum and is therefore an anatomically limited form of ulcerative colitis. Diagnosis is made based on clinical presentation, endoscopic appearance, and histopathology. Additionally, other etiologies of proctitis are excluded. The course of the disease is variable ranging from complete resolution to easily maintained remission to frequent relapses or refractory disease. Extension of inflammatory changes involving the proximal colon occurs in some cases. Rectal 5-aminosalicylic acid (5-ASA) or steroids are the initial treatments of choice with oral 5-ASA, sulfasalazine, or steroids used for treatment failures or patients unable to tolerate rectally administered drugs. Immunomodulators like azathioprine and 6-mercaptopurine have been used successfully in small groups of patients who have not responded to 5-ASA or steroids. Oral or rectal 5-ASA products maintain remission but long-term steroid use should be avoided. Rare cases may require surgical therapy.

KEYWORDS: Proctitis, ulcerative proctitis, 5-ASA, hydrocortisone

Objectives: Upon completion of this article, the reader should be able to summarize the management of ulcerative proctitis.

The understanding that idiopathic inflammatory changes confined to the rectum (proctitis) or to the distal colon and rectum (proctosigmoiditis) are part of a spectrum of disease in ulcerative colitis (UC) has only been accepted since the second half of the last century. One piece of evidence that ulcerative proctitis is part of the same disease as UC is that proximal extension of disease occurs. Earlier data demonstrated roughly a 10% progression to involvement of the total colon—the majority of cases with proximal extension occurred in the first 2 years after initial diagnosis, and progression after 5 years was rare.¹ More recently, higher rates of proximal extension after diagnosis have been shown. Langholz and associates reported 5-, 10-, and 15-year probabilities for any progression of 27%, 41%, and 53% and 12% of patients eventually underwent colectomy.² Meucci and colleagues, in a multicentered study,

reported 5- and 10-year risks of progression proximal to the sigmoid of 8% and 30% respectively and a 10-year risk of extension proximal to the splenic flexure of 10%.³ Refractory ulcerative proctitis (more than three relapses per year, chronic disease activity on continuous medical therapy, or need for systemic steroid or immunosuppressants) was an independent predictor of proximal disease extension in this study.

Several Scandinavian reports have shown a recent increased incidence of ulcerative proctitis which accounts for 20 to 55% of patients with UC.³⁻⁵ In general the course of the disease is one of remission and exacerbation and spontaneous remission may occur, as was demonstrated by remission rates of 19 to 39% reported in placebo-treated patients in randomized trials.⁶⁻⁸ Unlike UC, the incidence of colorectal cancer in patients with proctitis or proctosigmoiditis is not increased.¹

Ulcerative Colitis; Editor in Chief, David E. Beck, M.D.; Guest Editor, Bruce G. Wolff, M.D. *Clinics in Colon and Rectal Surgery*, volume 17, number 1, 2004. Address for correspondence and reprint requests: Charles B. Whitlow, M.D., Department of Colon and Rectal Surgery, Ochsner Clinic Foundation, 1514 Jefferson Hwy., New Orleans, LA 70121. E-mail: cwhitlow@ochsner.org. ¹Department of Colon and Rectal Surgery, Ochsner Clinic Foundation, New Orleans, Louisiana. Copyright © 2004 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 1531-0043;p;2004;17,01,021,027,ftx,en;ccrs00157x.

DIAGNOSIS

The symptoms of ulcerative proctitis are those of a nonspecific proctitis and include tenesmus, lower abdominal pain, fecal urgency, and blood or mucous passage per rectum or mixed with stool. Systemic symptoms are uncommon. Other historical features consistent with idiopathic ulcerative proctitis are prior similar episodes, a family history of inflammatory bowel disease, and an indolent clinical course. Diagnosis is predominantly based on endoscopic findings which include: (1) involvement at the dentate line, confined to the rectum, a clear upper limit with the proximal mucosa appearing normal; (2) diffuse and uniform involvement; (3) granular, friable mucosa with blurring or absence of the normal vascular pattern; (4) contact or spontaneous bleeding. Histopathology shows nonspecific findings of acute mucosal inflammation, crypt abscesses, and decreased numbers of goblet cells.⁹ More specific findings are those of mucosal atrophy including short tubules with increased branching, muscularis mucosae thickening and Paneth cell metaplasia. Findings which suggest proctitis on contrast enemas are mucosal irregularity confined to the rectum and decreased rectal distention; however, radiographs and contrast enemas are not sensitive or specific in the evaluation of this disease.¹⁰ Laboratory testing may be useful in ruling out other causes of proctitis as discussed below. In addition, serum perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA) may aid in the diagnosis of idiopathic ulcerative proctitis and its differentiation from Crohn's disease or indeterminate proctocolitis.^{11,12}

While the diagnosis is frequently based on the presenting symptoms and endoscopic exam, the differential diagnosis for ulcerative proctitis must be considered. Patients with a prior diagnosis of inflammatory bowel disease who sustain a worsening of symptoms may have an additional etiology superimposed on their underlying disease. A systematic approach to establishing the correct diagnosis is vital in determining appropriate therapy and prognosis.

Crohn's disease may present with isolated rectal involvement and may be initially indistinguishable from ulcerative proctitis. Physical findings which are suggestive of Crohn's disease include edematous anal tags, perianal suppurative disease, anal fissures (especially in atypical locations), and anal stenosis. Endoscopically the distribution of the proctitis may be patchy with ulcerations, either linear or aphthoid. Langevin and colleagues reported on 13 patients who had an initial diagnosis of idiopathic UC and subsequently were diagnosed with Crohn's disease.¹⁰ When compared with patients with ulcerative proctitis whose diagnosis did not change over time, there were no epidemiologic, clinical, or histopathologic criteria which predicted an ultimate diagnosis of Crohn's disease.

A thorough history of sexual practices should be obtained because anoreceptive intercourse can lead to transmission of organisms causing proctitis. The most common of these organisms are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, and Herpes simplex virus (HSV).¹³ Identifying one of these pathogens as a cause for proctitis is made based on history and detection by appropriate laboratory methods: Gram stain (*N. gonorrhoeae*), culture (*N. gonorrhoeae*), tissue culture (*C. trachomatis*), viral culture (HSV), direct fluorescent antibody staining (*C. trachomatis*), serology (*T. pallidum*, HSV), dark-field microscopy (*T. pallidum*), biopsy (HSV). Proctoscopy is rarely diagnostic although mucopurulence from the anal crypts is suggestive of gonorrhea. Distal rectal and anal canal involvement is the typical pattern for venereal proctitis.

Historical features such as a travel history or similar symptoms present in close contacts suggest an infectious etiology. Most infectious organisms other than those listed above, whether sexually transmitted or not, result in a proctocolitis instead of an isolated proctitis. Diagnosis is by a combination of endoscopy and stool culture or exam for ova and parasites. Rectal biopsy detects *Entamoeba histolytica* trophozoites in some cases despite negative stool exams.

Pelvic irradiation may result in acute or chronic proctitis that is distinguished from idiopathic ulcerative proctitis based on history, the characteristic appearance of the proctitis, and biopsy. Endoscopically acute radiation proctitis appears as friable mucosa with edema and histopathology shows superficial mucosal changes—depleted epithelial mitotic rate, atrophy, acute inflammatory cells in the laminal propria.^{14,15} Findings on endoscopy which are suggestive of chronic radiation proctitis are telangiectasia, congested mucosa, ulceration, and stricture. Microvascular changes—intimal proliferation of arterioles, obliterative endarteritis, capillary ectasia—are typical histopathologic features of chronic radiation injury of the bowel wall.^{9,15}

Isolated proctitis from ischemia is rare but most commonly occurs after surgery involving the abdominal aorta. Arterial embolization and lymphoma of the rectum are additional etiologies of ischemic proctitis. Mucosal edema, cyanosis, ecchymosis, sloughing, and necrosis are seen on endoscopy depending on the severity of the disease. Mucosal edema and hemorrhage are seen on biopsies of the rectum in acute ischemic proctitis. Later in the course of this process regenerative changes (short, wide, irregularly spaced crypts) will be seen in mucosal biopsies.^{16,17}

Pseudomembranous proctocolitis is caused by proliferation of toxin-producing *Clostridium difficile* following antibiotic therapy. This process is easily distinguished from idiopathic proctitis by the presence of yellowish plaque-like pseudomembranes. The rectum may be spared but is almost never the only segment

affected. *C. difficile* toxin detected in stool in the appropriate clinical scenario establishes the diagnosis. Histopathology demonstrates inflammatory changes in the lamina propria and focal mucosal ulceration with eruption of purulent material and necrotic debris producing the so-called "volcano lesion."^{18,19}

TREATMENT

Until the last decade, the mainstay of treatment for ulcerative proctitis was topical hydrocortisone delivered by enema or foam. However, several studies have demonstrated the efficacy of rectally administered 5-aminosalicylic acid (5-ASA) preparations for proctitis and proctosigmoiditis, making them first-line treatment for these conditions. In a recent meta-analysis of treatments for left-sided UC and ulcerative proctitis, the authors concluded that topical 5-ASA preparations are more effective than oral 5-ASA preparations for distal UC and proctitis.⁴ They also found topical mesalamine to be superior to topical steroids in achieving remission. 5-ASA is available for rectal administration as a suppository or an enema. There is no 5-ASA rectal foam commercially available in the United States as of this writing. Suppositories effectively deliver 5-ASA to the rectal mucosa and in some instances to the sigmoid colon.^{20–22} The proximal extent of delivery of rectally administered foams and liquid enemas depends somewhat on the volume used. Preparations with volume of ≥ 60 mL reliably deliver medication to the descending colon. Another factor to consider in choosing a delivery form is that suppositories and foams are better tolerated by patients compared with enemas.

5-ASA

The efficacy of 5-ASA given by suppository for the treatment of ulcerative proctitis has been demonstrated by placebo-controlled randomized trials. Williams and associates compared the use of 500-mg 5-ASA suppositories t.i.d. to placebo and found a statistically significant difference in the disease activity index by 3 weeks with a complete remission rate of 78% at 6 weeks.²⁰ There were no side effects attributed to the 5-ASA suppositories. In a similar study, Campieri and colleagues found statistically significant differences in rates of remission or improvement, at 15 and 30 days, in patients treated with 500-gm 5-ASA suppositories t.i.d. compared with those given placebo.²³ Eighty-seven percent of patients in the 5-ASA arm had clinical remission or improvement at 1 month. Endoscopic and histological remission or improvement rates at 1 month were 78% and 65%, respectively. Again, there were no adverse events. In additional randomized trials, Campieri and group compared b.i.d. dosing to t.i.d. dosing for 5-ASA suppositories and found no difference in clinical, endoscopic, or histologic response rates at 4 weeks.⁷ Thus, the

current recommended dose for 5-ASA suppositories is b.i.d. for 1 month.

Additional studies have compared 5-ASA suppositories to oral preparations, enemas, and foams. In an investigator-blinded randomized trial, 400-mg 5-ASA suppositories given t.i.d. were compared with 800 mg of oral 5-ASA given t.i.d. for 1 month.²⁴ Patients who received suppositories had a statistically significant better response as measured by physician global assessment (83% reported "much improved"), disease activity index, and clinical (90%), endoscopic (72%) and histologic (62%) remission rates. Campieri and associates randomized a small group of patients (39) with distal UC extending no further than 20 cm to receive 1 month of 5-ASA as either a 1-g suppository b.i.d. or a daily 100-cc enema containing 2 g of 5-ASA.⁶ There was no difference in efficacy between the two preparations, but the suppositories were better tolerated. Several recent studies have demonstrated that a new 5-ASA foam is as effective as 5-ASA enemas and as well tolerated, but it is not yet available in the United States.^{25,26}

5-ASA suppositories have also been compared with rectally administered steroid foams and have similar or improved efficacy. Farup et al compared 5-ASA suppositories, 500 mg b.i.d., to hydrocortisone foam enemas, 178 mg b.i.d., in a randomized trial.²⁷ They found a statistically significant difference in the number of patients with complete response at 4 weeks in patients with proctitis treated with the suppositories versus those treated with steroid enemas. This difference was not demonstrated in patients whose disease extended above 15 cm from the anus. Lucidarme and associates compared 1-g slow-release 5-ASA suppositories given daily to 100-mg hydrocortisone foam enemas in a multicenter randomized trial.²⁸ They found no difference between the two treatments at 14 and 21 days in all parameters measured except that the percentage of patients with blood in their stool at 14 days was statistically lower in the suppository group. The slow-release 5-ASA suppositories have been shown to be as effective (and better tolerated) as twice-daily conventional 5-ASA suppositories.²⁹ They are not currently available in the United States.

As opposed to oral sulfasalazine, rectally administered topical 5-ASA preparations are well tolerated with low side-effect profiles and cessation of treatment secondary to side effects is infrequent. Because of the low systemic absorption of rectal 5-ASA, most of the adverse events reported are related to the mode of drug administration. Enemas and foams may cause bloating, difficulty with retention, and discomfort when used. Suppositories may cause perianal irritation and may be difficult to retain for some patients. Commercially available 5-ASA products in the United States are enemas (Rowasa, 4 g mesalamine/60 mL, Solvay) and suppositories (Canasa, 500 mg mesalamine, Axcan Scandipharma).

SULFASALAZINE

There is no commercially available sulfasalazine rectal preparation available in the United States. Oral sulfasalazine is inexpensive but poorly tolerated by many patients. Its role in the treatment of acute idiopathic ulcerative proctitis is in patients who are refractory to the topical 5-ASA and steroid agents or in maintenance after remission has been obtained. Side effects are not uncommon and fall into two groups. Dose-related side effects related to serum sulfapyridine levels include headache, nausea, vomiting, and abdominal discomfort. Hypersensitivity-type symptoms are not dose related and include fever, aplastic anemia, pancreatitis, nephrotoxicity, hepatitis, agranulocytosis, autoimmune hemolysis, and decreases in sperm counts.^{30,31}

STEROIDS

Steroids administered rectally as a foam or enema have been shown to be effective treatment for ulcerative proctitis, although as detailed above they are not as effective as 5-ASA preparations. Commercially available rectal corticosteroids in this country are hydrocortisone enemas (Colocort, 100 mg hydrocortisone/60 mL, Paddock Laboratories) and foam (Cortifoam, 10% hydrocortisone acetate, Schwarz Pharma). More recently budesonide, delivered as an enema or foam, has been studied but is not available in this form in the United States. Budesonide is a glucocorticosteroid which has less impact on the hypothalamic-pituitary-adrenal axis.³² Dose range studies have shown that the minimum effective dose of budesonide as an enema is 2 mg per day. No study to date has shown increased efficacy at higher doses and Lindgren and colleagues reported a statistically significant higher rate of adrenal impairment in patients who received 4 mg/day as opposed to 2 mg/day (32% versus 5%). A recent randomized trial compared hydrocortisone foam (100 mg) with budesonide foam (2 mg) used for 8 weeks and showed similar efficacy (remission rates of 51% and 55%, respectively) and safety between them.³³ Adrenal suppression occurred in 3% of patients treated with budesonide and none of the patients treated with hydrocortisone. In keeping with their belief that the role of rectal steroids is as second-line therapy, the authors examined patients who had failed treatment with rectal mesalamine. They reported a 52% response rate to budesonide and 37% to hydrocortisone (not statistically significant). Prednisolone and beclomethasone are other glucocorticoids that have been studied as enemas in the treatment of proctitis.³⁴

Refractory Disease

Although limited data exist to support its use, patients who do not respond to rectal 5-ASA or steroids as single agents can be treated with a combination of the two. Mulder et al found patients treated with beclomethasone

dipropionate and 5-ASA enemas had superior results after 4 weeks of treatment compared with patients who used single-agent therapy.³⁵ Other rectal steroids and other schedules have not been studied when combined with 5-ASA.

Oral 5-ASA and oral steroid (prednisone) agents have both been used to treat patients with proctitis who fail to improve with rectal 5-ASA or rectal steroids. While rectal 5-ASA has shown efficacy similar to or better than oral 5-ASA, one study has demonstrated that the two given in combination is superior to either given alone.³⁶ It should be noted that this study looked at patients with disease extending up to 50 cm from the anal verge and 43% had proctosigmoiditis. Results were not reported based on anatomic distribution of disease, so it is unclear if patients whose disease is confined to the rectum receive the same benefit from combined oral/rectal treatment. Oral steroids were the treatment of choice for ulcerative proctitis when it was first described. The long-term complications and effects on the hypothalamic-pituitary-adrenal axis associated with their use gave rise to the development of the topical formulations previously described. However, oral steroids remain a useful agent for short-term control of proctitis refractory to other treatment. The initial dose is 40 to 60 mg daily which tapers after treatment for 7 to 10 days if adequate response has been obtained. The daily dose is then reduced by 10 mg each week until it becomes a dose of 20 mg each day, at which time it is reduced by 5 mg per week until zero.³⁷ Table 1 is an algorithm for the treatment of ulcerative proctitis.

Cyclosporine enemas have been effective in small uncontrolled trials of patients with refractory active ulcerative proctitis. However, in the only randomized trial of cyclosporine enemas (350 mg/day) for patients with left-sided UC, there was no difference in disease activity after 1 month of treatment compared with placebo controls.³⁸ Sucralfate enemas have also been studied in a randomized trial of patients with ulcerative proctitis and are less effective at achieving clinical, endoscopic, or histologic remission than hydrocortisone enemas.³⁹

The use of oral immunosuppressants like cyclosporine and methotrexate in idiopathic proctitis is not well defined. Because of their toxicities and the lack of clinical experience in the treatment of ulcerative proctitis, cyclosporine and methotrexate are poor choices for

Table 1 Treatment Algorithm for Ulcerative Proctitis

Step 1 – Rectal 5-ASA

Step 2 – Rectal Steroid ± rectal 5-ASA

Step 3 – Oral 5-ASA ± rectal 5-ASA ± rectal steroid

Step 4 – Oral steroid ± Step 3

Once remission is attained—Rectal, oral or combined 5-ASA at minimum dose and interval required to maintain remission

treatment in this limited disease that fortunately responds to safer therapy in most patients. Other immunomodulators such as azathioprine and 6-mercaptopurine (6-MP) have proven beneficial in patients with refractory or steroid-dependent proctitis in studies with small numbers of patients. Love and colleagues reported on 27 patients with intractable proctosigmoiditis who were treated with 25 to 150 mg/day of 6-MP.⁴⁰ Complete or moderate improvement was seen in 63% of patients and in 68% of patients steroids could be discontinued. Reversible neutropenia was seen in 15% of patients. The same group reported the long-term results of 105 patients with refractory UC (10 with proctosigmoiditis).⁴¹ Only 11% were considered treatment failures. Approximately one third of patients developed a relapse while on 6-MP and in 88% of those remission was restored. Eighty-seven percent of patients who stopped their 6-MP relapsed, emphasizing the need for long-term treatment. Infliximab (monoclonal antibody to tumor necrosis α) has not been studied in patients with ulcerative proctitis. Two recent studies have reported on its use in patients with refractory or steroid-dependent UC.^{2,42} One study showed no benefit compared with placebo.⁴³

Surgery is rarely indicated for proctitis. However, patients with disease refractory to the treatments listed above, especially those with proximal extension, may require colectomy. Acceptable surgical options are restorative proctocolectomy or proctocolectomy with end or continent ileostomy. In select situations, a diverting colostomy may be the best option.

Maintenance

Oral 5-ASA, 5-ASA suppositories and enemas are all effective in maintaining remission in patients with ulcerative proctitis. No trials have directly compared the effectiveness of suppositories versus enemas for maintenance. While most reports have not found a dose response for rectal 5-ASA, D'Albasio et al reported a 1-year remission rate of 90% versus 68% for 500-mg ASA suppositories given b.i.d. versus daily, respectively.⁴⁴ Daily dosing is not always required as was shown by Marteau et al, who found 1-g slow-release 5-ASA suppositories are effective at preventing relapse when given three times per week.⁴⁵ Rectal 5-ASA is as effective as oral 5-ASA in maintenance of remission, although one randomized trial demonstrated higher 1-year remission rates in patients treated with combined oral/rectal therapy compared with oral therapy alone (61% vs 31%).⁴⁶

Patients who present with their first episode and respond completely and rapidly to rectal 5-ASA are treated for 1 month and then may be tried with no maintenance treatment. Infrequent exacerbations, which respond in a similar manner, do not require maintenance

therapy. Those who require longer treatment, steroids, or combined steroids and 5-ASA, are switched to 5-ASA suppositories alone and the dose gradually tapered to 500 mg every 1 to 3 days. Patients who relapse on this regimen are placed on a maintenance schedule of 500-mg 5-ASA suppositories b.i.d. Some patients may prefer oral therapy and are treated with 5-ASA (mesalamine) 1.2 to 2.4 g/day or sulfasalazine 2 gm/day. Combination oral and rectal treatment may be required to maintain remission. Long-term treatment may be necessary but my preference is to periodically attempt to reduce the dose or frequency of maintenance therapy to determine the minimum dosing required to maintain remission. Prolonged use of oral or rectal glucocorticoids should be avoided in patients with ulcerative proctitis.

CONCLUSION

Ulcerative proctitis is an idiopathic inflammation of the mucosa of the rectum. The diagnosis is made based upon characteristic clinical history, endoscopy, histopathology and exclusion of known etiologies of proctitis. The clinical course of the disease is highly variable. Some patients will experience rapid remission with little or no further disease, others will have frequent exacerbations requiring additional medical management, and still others will have difficult-to-control disease. The extent of disease is also variable with some remaining confined to the rectum while others demonstrate proximal colonic involvement.

Rectal 5-ASA (suppositories, enemas) and rectal steroids (enemas, foams) are effective treatment for ulcerative proctitis. Rectal 5-ASA has demonstrated increased efficacy compared with rectal steroids and oral 5-ASA and is therefore the first-line treatment. Patients who fail to respond to rectal 5-ASA are treated with rectal steroids alone or in combination with rectal 5-ASA. Those who fail this treatment or who do not tolerate rectal preparations are treated with oral 5-ASA or sulfasalazine alone or in combination with the rectally administered agents above. Patients with severe disease or who fail oral 5-ASA are given oral steroids. Long-term treatment with steroids should be avoided. Immunomodulators such as azathioprine and 6-MP have successfully treated patients with steroid-refractory proctitis, but the experience with these drugs is small and recurrence of symptoms is to be expected once they are discontinued. Maintenance of remission may require long-term oral or rectal 5-ASA or both.

REFERENCES

1. Farmer RG. Evolution of the concept of proctosigmoiditis. *Med Clin North Am* 1990;74:91-102
2. Langholz E, Munkholm P, Davidsen M, Nielson OH, Binder V. Changes in extent of ulcerative colitis: a study on the course

- and prognostic factors. *Scand J Gastroenterol* 1996;31:260-266
3. Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. *Am J Gastroenterol* 2000;95:469-473
 4. Russell MG, Dorant E, Volovics A, et al. High incidence of inflammatory bowel disease in The Netherlands: results of a prospective study. The South Limbourg IBD Study Group. *Dis Colon Rectum* 1998;41:33-40
 5. Stewenius J, Adnerhill I, Ekelund G, et al. Ulcerative colitis and indeterminate colitis in the city of Malmö, Sweden. A 25-year incidence study. *Scand J Gastroenterol* 1995;30:38-43
 6. Campieri M, Gionchetti P, Belluzzi A, et al. 5-aminosalicylic acid as enemas or suppositories in distal ulcerative colitis? *J Clin Gastroenterol* 1988;10:406-409
 7. Campieri M, De Franchis R, Bianchi Porro G, et al. Mesalazine (5-aminosalicylic acid) suppositories in the treatment of ulcerative proctitis or distal proctosigmoiditis. A randomized controlled trial. *Scand J Gastroenterol* 1990;25:663-668
 8. Sutherland LR, Martin F, Greer S, et al. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987;92:1894-1898
 9. Marshall JB, Butt JH. Proctitis: approach to diagnosis, causes, and treatment. *J Clin Gastroenterol* 1982;4:431-444
 10. Langevin S, Menard DB, Haddad H, et al. Idiopathic ulcerative proctitis may be the initial manifestation of Crohn's disease. *J Clin Gastroenterol* 1992;15:199-204
 11. Quinton JF, Sendid B, Reumaux D, et al. Anti-*Saccharomyces cerevisiae* mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1998;42:788-791
 12. Peeters M, Joossens S, Vermeire S, et al. Diagnostic value of anti-*Saccharomyces cerevisiae* and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. *Am J Gastroenterol* 2001;96:730-734
 13. Rampalo AM. Diagnosis and treatment of sexually acquired proctitis and proctocolitis: an update. *Clin Infect Dis* 1999;28(suppl 1):S84-S90
 14. Tagkalidis PP, Tjandra JJ. Chronic radiation proctitis. *ANZ J Surg* 2001;71:230-237
 15. Haboubi NY, Schofield PF, Rowland PL. The light and electron microscopic features of early and late phase radiation-induced proctitis. *Am J Gastroenterol* 1988;83:1140-1144
 16. Nelson RL, Briley S, Schuler JJ, Abcarian H. Acute ischemic proctitis. Report of six cases. *Dis Colon Rectum* 1992;35:375-380
 17. Dawson MA, Schaefer JW. The clinical course of reversible ischemic colitis. Observations on the progression of sigmoidoscopic and histological changes. *Gastroenterology* 1971;60:577-580
 18. Hurley BW, Nguyen CC. The spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea. *Arch Intern Med* 2002;162:2177-2184
 19. Kyne L, Farrell RJ, Kelly CP. *Clostridium difficile*. *Gastroenterol Clin North Am* 2001;30:753-777
 20. Williams CN, Haber G, Aquino JA. Double-blind placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using 99-m-Tc-labeled 5-ASA suppositories. *Dig Dis Sci* 1987;32:71S-75S
 21. Jay M, Beihn RM, Digenis GA, et al. Disposition of radiolabeled suppositories in humans. *J Pharm Pharmacol* 1985;37:266-268
 22. Brown J, Haines S, Wilding IR. Colonic spread of three rectally administered mesalazine (Pentasa) dosage forms in healthy volunteers as assessed by gamma scintigraphy. *Aliment Pharmacol Ther* 1997;11:685-691
 23. Campieri M, Gionchetti P, Belluzzi A, et al. Topical treatment with 5-aminosalicylic acid in distal ulcerative colitis by using a new suppository preparation. A double-blind placebo-controlled trial. *Int J Colorectal Dis* 1990;5:79-81
 24. Gionchetti P, Rizzello F, Venturi A, et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. *Dis Colon Rectum* 1998;41:93-97
 25. Malchow H, Gertz B. A new mesalazine foam enema (Clavarsol Foam) compared with a standard liquid enema in patients with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:415-423
 26. Ardiazzone S, Doldo P, Ranzi T, et al. Mesalazine foam (Salofalk foam) in the treatment of active distal ulcerative colitis. A comparative trial versus Salofalk enema. The SAF-3 study group. *Ital J Gastroenterol Hepatol* 1999;31:677-684
 27. Farup PG, Hovde O, Halvorsen FA, et al. Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis. A comparison of the efficacy and practicality of two topical treatment regimens. *Scand J Gastroenterol* 1995;30:164-170
 28. Lucidarme D, Marteau P, Foucault M, Vautrin B, Filoche B. Efficacy and tolerance of mesalazine suppositories versus hydrocortisone foam in proctitis. *Aliment Pharmacol Ther* 1997;11:335-340
 29. Marteau P, Florent C. Comparative, open, randomized trial of the efficacy and tolerance of slow-release 5-ASA suppositories once daily versus conventional 5-ASA suppositories twice daily in the treatment of active cryptogenic proctitis. *Am J Gastroenterol* 2000;95:166-170
 30. Das KM, Eastwood MA, McManus JP, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 1973;289:491-495
 31. Allgayer H. Sulfasalazine and 5-ASA compounds. *Gastroenterol Clin North Am* 1992;21:643-658
 32. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide Enema Study Group. *Gastroenterology* 1998;115:525-532
 33. Bar-Meir S, Fidler HH, Fasczyk M, et al. Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. *Dis Colon Rectum* 2003;46:929-936
 34. van der Heide H, van den Brandt-Gradel V, Tytgat GN, et al. Comparison of beclomethasone dipropionate and prednisolone 21-phosphate enemas in the treatment of ulcerative proctitis. *J Clin Gastroenterol* 1988;10:169-172
 35. Mulder CJ, Fockens P, Meijer JW, et al. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol* 1996;8:549-553
 36. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalazine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;92:1867-1871
 37. Bitton A. Medical management of ulcerative proctitis, proctosigmoiditis, and left-sided colitis. *Semin Gastrointest Dis* 2001;12:263-274

38. Sandborn WJ, Tremaine WJ, Schroeder KW, et al. A placebo-controlled trial of cyclosporine enemas for mildly to moderately active left-sided ulcerative colitis. *Gastroenterology* 1994;106:1429–1435
39. Ardizzone S, Pettillo M, Antonacci CM, Bianchi Porro G. Sucralfate and hydrocortisone enemas in the treatment of active ulcerative proctitis—a randomized single-blind comparative study. *Aliment Pharmacol Ther* 1996;10:957–960
40. Love MA, Rubin PH, Chapman ML, Present DH. 6-mercaptopurine is effective in intractable proctosigmoiditis. *Gastroenterology* 1995;100:A832
41. George J, Present DH, Pou R, Godian C, Rubin PH. The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996;91:1711–1714
42. Gornet JM, Couve S, Hassani Z, et al. Infliximab for refractory ulcerative colitis or indeterminate colitis: an open-label multicentre study. *Aliment Pharmacol Ther* 2003;18: 175–181
43. Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid-resistant ulcerative colitis: a randomized controlled trial. *Gut* 2003;52:998–1002
44. d'Albasio G, Paoluzi P, Campieri M, et al. Maintenance treatment of ulcerative proctitis with mesalazine suppositories: a double-blind placebo-controlled trial. The Italian IBD Study Group. *Am J Gastroenterol* 1998;93: 799–803
45. Marteau P, Crand J, Foucault M, Rambaud J-C. Use of mesalazine slow-release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomized double-blind placebo-controlled multicentre study. *Gut* 1998; 42:195–199
46. D'Albasio G, Pacini F, Camarri E, et al. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. *Am J Gastroenterol* 1997;92:1143–1147