There continue to be evolutionary changes in the management of ulcerative colitis despite the fact that, aside from a variety of aminosalicylate formulations, no new therapies have been approved over the past few decades. Nevertheless, debates continue regarding the optimization of treatment with aminosalicylates and the short- and long-term benefits of immunomodulation in ulcerative colitis. This article focuses on the most recent clinical studies pertaining to the management of ulcerative colitis and explores both the advances and controversies pertaining to aminosalicylate therapy, corticosteroids, cyclosporine, and the purine antimetabolites. Novel therapeutic approaches—including preliminary experience with biological therapies directed at tumor necrosis factor and other cytokines, adhesion molecules, growth factors, and probiotics—will be reviewed. Recent data regarding potential chemoprevention in long-standing ulcerative colitis and management of postoperative complications and pouchitis will also be discussed.

Despite recent advances in the understanding of the genetics, immune and inflammatory mechanisms, and potential environmental triggers that contribute to ulcerative colitis, an exact etiopathogenesis remains elusive. In parallel to the basic underpinning of disease evolution and perpetuation and in contrast to the confirmed utility of biological (anti–tumor necrosis factor [TNF]) therapy for Crohn’s disease, advances in medical therapy for ulcerative colitis continue to be evolutionary rather than revolutionary. Nevertheless, a number of advances have either improved the efficacy or reduced the toxicity related to acute (inductive) and chronic (maintenance) therapy. At the same time, a number of controversies have come to light regarding the optimization of therapy with aminosalicylates, corticosteroids, immunomodulators, novel biologics, and probiotics. This review will focus on the most recent advances and current controversies in therapy for ulcerative colitis.

### Aminosalicylates

The aminosalicylates remain the mainstays of therapy for induction of remission in mild to moderately active ulcerative colitis and to prevent relapse of quiescent disease. The expansion of mesalamine formulations and delivery systems has exposed several gaps in the evidence base for the treatment of ulcerative colitis that require further elucidation. These include substantiating differences in pharmacokinetic profiles and systemic “load” of different formulations, discrimination between formulations for differing extents of disease, and clarification of the dose response for active and maintenance therapy.

The development of the azo-bond formulation, balsalazide, by using aminobenzoyl-β-alanine, an inert carrier devoid of the sulfa moiety, has created controversies regarding the pharmacokinetics and competitive advantages of different aminosalicylates for the treatment of ulcerative colitis. Recent trials have shown that balsalazide is comparable in efficacy to sulfasalazine and is better tolerated when equimolar concentrations of mesalamine are administered to patients with active ulcerative colitis. However, recent comparative trials with mesalamine have been more controversial in their interpretation. Unfortunately, lack of standardized evaluations of disease activity, differing definitions of improvement or remission, and exuberant reliance on secondary end points impair optimal interpretation of these trials. In a trial reported by Green et al., balsalazide 6.75 g/day was compared with a European pH-release mesalamine formulation of Asacol (Proctor and Gamble, Cincinnati, OH) 2.4 g/day in patients with active ulcerative colitis over 12 weeks. The authors reported a faster onset of action (not the primary end point) and improved tolerance in this study population, which included patients with moderate or even severe disease. Post hoc analysis also suggested that patients with left-sided disease might have responded better to balsalazide. Two additional trials have been performed comparing balsalazide 6.75 g/day with mesalamine 2.4 g/day. Both trials showed similar efficacy according to the primary end point of symptomatic remission at 8 weeks.
Secondary or post hoc analyses suggested a faster onset of action and improved responses for patients with left-sided disease. Although the authors suggested that there was less systemic absorption of mesalamine from balsalazide and considered pharmacokinetics as a rationale for (possible) improved efficacy in left-sided colitis, a recent meta-analysis of pharmacokinetic studies with all the mesalamine compounds showed greater similarities in systemic availability and renal excretion than differences between any of the agents.14

Direct comparison studies are necessary to determine whether patients with left-sided disease respond better to an azo-bond compound than to alternative delivery systems of mesalamine.7,9 Even in the trials described previously, there was a lack of consistency in primary end-point evaluations, with “remissions” defined as “no or mild symptoms, a sigmoidoscopy score of 0 or 1, and no use of rectal steroids”11; “normal stool frequency, no blood in stool for 48 hours, physician’s global assessment of “quiescent,” and a sigmoidoscopy score of normal or mild,”12; and “a patient functional assessment rating of normal or mild and absence of rectal bleeding.”13 In a recent critical systematic review focusing on evidence-based interpretation of the use of mesalamine in ulcerative colitis, the authors emphasized the requisite for well-defined primary end points, cautious interpretation of secondary end points when primary end points are not achieved, prespecification of statistical corrections for multiple secondary end points, and post hoc or posttrial analyses.10

In clinical trials with oral mesalamine compounds, both pH-dependent and time-release, patients with pancolitis and left-sided colitis responded similarly.15–17 However, a potential mechanism for azo-bond drug efficacy in left-sided disease is the increased small-bowel secretion that has been shown with olsalazine18 and, most recently, with sulfasalazine and balsalazide (E. Chang, personal communication, March 2004). This may also limit the upward dosing of azo-compounds in active disease because of increased loosening of stools, as has been shown with olsalazine at doses greater than 2 g/day (similar to balsalazide at 6 g/day). In any event, the issue of optimal therapy for left-sided disease with varied formulations of oral aminosalicylates is made less relevant by the well-defined superiority of topical (rectal) mesalamine in distal colitis.19

Another recent controversy regarding mesalamine pertains to the dose response for active and quiescent disease. While most clinicians in the U.S. have advocated a dose response up to 4.8 g/day in active disease, these recommendations have been based on trials with formulations of Pentasa15 (Shire Pharmaceuticals, Cincinnati, OH) and Asacol.16 However, a recent European trial failed to show superiority of a new oral mesalamine formulation at doses greater than 3 g/day.20 Controlled maintenance trials, to date, have not evaluated doses greater than 1.6 g of mesalamine daily to prevent relapse.21 Nevertheless, many clinicians believe that there will be a dose response at greater than 1.6 g of mesalamine to maintain remissions for patients with ulcerative colitis,22 particularly for patients who have required higher doses to achieve remission. Controlled trials to assess this postulate would be helpful to complete the evidence base for maintenance therapy with aminosalicylates in ulcerative colitis.2

Finally, no medication is likely to be effective if the patient is not adherent (compliant). Kane et al.24 have followed up on their previous studies25 to determine the effect of compliance on the clinical outcomes of maintenance therapy with mesalamine. They showed that patients who were nonadherent (more often unmarried men or patients taking numerous concomitant medications) had a 5-fold risk of relapsing compared with patients who took at least 80% of their prescribed dose. These findings have been supported by others, who have shown that nonadherence (present in approximately 40% of patients receiving maintenance therapy) is worse with more frequent dosing (3 times daily) or in patients with depression25 and that an educational program with self-directed therapy during chronic therapy can improve outcomes, as defined by physician visits and hospitalizations.26

**Corticosteroids**

Although corticosteroids remain the primary therapy for moderate to severe ulcerative colitis or for patients who have failed initial therapy with an aminosalicylate,22 there have been few recent developments regarding glucocorticoid therapy in this setting. The biological effects of corticosteroids are pluripotent and include both immunologic and anti-inflammatory properties, including the inhibitory effects on nuclear factor-κB and activating protein-1 regulation of proinflammatory cytokines27,28 and the downstream effects on leukocyte function and eicosanoid production.29 Recent efforts have also been undertaken to identify why some patients with ulcerative colitis are less responsive or lose their response to corticosteroids.30,31 Higher levels of glucocorticoid receptors32 and glucocorticoid receptor messenger RNA33 have been identified in patients with steroid-refractory ulcerative colitis. It has also been suggested that up-regulated production of pro-inflammatory
corticosteroid effects, much remains to be learned regarding the mechanisms of action and prediction of the response to steroids in ulcerative colitis.

It is reassuring to recognize that outside of tertiary centers, only approximately one third of patients require systemic steroid therapy. In a survey of the Olmsted county population, 54% of patients treated with systemic steroids went into complete remission, and only 16% of patients did not respond. However, after 1 year, only half of the patients remained in remission, and nearly one third of patients who required steroids progressed to the need for colectomy. These data are consistent with prior meta-analyses of therapeutic outcomes in ulcerative colitis that reported long-term remissions in only approximately 50% of patients who received parenteral steroids for severe ulcerative colitis. It remains to be determined whether high-dose pulse dexamethasone therapy will improve on conventional parenteral steroid regimens. Recent experience has also emphasized that patients who have required steroid therapy also have a relatively poor prognosis for maintenance therapy with standard-dose mesalamine.

Pharmacological development of novel glucocorticoids has been more difficult in ulcerative colitis, compared with Crohn’s disease, because of variations in colonic pH, transit time, and bacterial metabolism. Trials of enteric-coated budesonide have not been effective in the setting of distal colitis, although a recent trial of combination therapy with beclomethasone dipropionate 5 mg/day in conjunction with mesalamine did show an additive benefit, albeit with evidence of inhibition of the hypothalamic-pituitary-adrenal axis. Topical corticosteroid therapy has been relegated to a secondary role in distal ulcerative colitis because numerous trials have shown superiority of rectal mesalamine compared with either conventional or non-systemic steroids. Combination therapy with topical mesalamine and a corticosteroid may provide additive benefits.

Immunomodulators

The efficacy of cyclosporine in severe ulcerative colitis has been validated since the pioneering trials by Lichtiger and Present and Lichtiger et al. Parenteral cyclosporine in conjunction with steroids has been consistently effective in the approximately 40% of patients with severe ulcerative colitis who have failed corticosteroid therapy. Over the past several years, trials have also shown that parenteral cyclosporine is effective alone, without steroids. In the group of patients randomized to cyclosporine and maintained on azathioprine, the 1-year prognosis was superior to that of the steroid-treated group maintained on aminosalicylates (78% vs. 37% remissions), and this, again, calls into question the prognosis of patients maintained on aminosalicylates after steroid therapy. The Leuven group confirmed that 2 mg/kg dosing, compared with 4 mg/kg, was equally effective and safe in a randomized, controlled trial that has been substantiated in clinical practice. Although most cyclosporine therapy for ulcerative colitis has been administered parenterally, for severe disease, microemulsion formulations or tacrolimus may eventually become useful as an adjunctive therapy for steroid-refractory ulcerative colitis. Currently, although intravenous cyclosporine has become an acceptable therapy for severe, steroid-refractory ulcerative colitis, the oral agents have not been widely accepted because of their potential toxicity and requisite evaluation in a controlled setting. Meanwhile, it is reassuring that several series have not identified increased postoperative complications in patients who have failed cyclosporine and required colectomy.

There have been few new data regarding the utility of purine antimetabolites, azathioprine, and 6-mercaptopurine for ulcerative colitis. It is also intriguing that, despite their general acceptance for steroid-dependent ulcerative colitis, there remain limited evidence-based data to support the overall efficacy or to delineate a dose response in ulcerative colitis. The clinical trials from the 1970s provided equivocal results regarding the efficacy of azathioprine in ulcerative colitis, although steroid-sparing effects were suggested. The most convincing controlled trial to date evaluated the maintenance benefits of azathioprine for patients who had required azathioprine to achieve remission. The 12-month relapse rate was 36% for patients maintained on azathioprine, compared with 59% for patients randomized to placebo. In the latter trial, most patients had maintained aminosalicylate therapy, although a recent case series calls into question whether the addition of aminosalicylates is necessary. Uncontrolled experience has suggested a benefit from azathioprine or 6-mercaptopurine for ulcerative colitis. An area of consistency has been the general acceptance that a purine antimetabolite is useful to prolong remissions after in-
duction with cyclosporine. The benefits for refractory left-sided disease may not be as paramount as with more extensive disease, and it is, again, reassuring that immunomodulatory therapy with the purine analogues has not affected surgical outcomes or morbidity for patients who fail therapy.

Optimal dosing for the purine metabolites has not been established for ulcerative colitis, nor has the question of therapeutic monitoring in this setting been evaluated. Recently, a novel potential mechanism of action for azathioprine—induction of apoptosis of CD4+ T cells—has been proposed and warrants further investigation.

**Biological Agents**

The remarkable effect that infliximab has had on the treatment of Crohn’s disease has not yet been extrapolated to ulcerative colitis. To date, there are no biological agents approved for ulcerative colitis in the United States or abroad.

Infliximab has been evaluated in a few open-label and controlled clinical trials in ulcerative colitis, and, compared with the results in Crohn’s disease, the outcomes could best be described as ambiguous. In the first reported pilot trial, 4 of 8 patients with severe, steroid-refractory ulcerative colitis randomly assigned to receive a single dose of infliximab at 5, 10, or 20 mg/kg responded by week 2, versus none of the 3 placebo-treated patients. Subsequently, in an open-label series, Chey et al. reported a response in all 8 patients with refractory ulcerative colitis who received a single 5 mg/kg infusion of infliximab, and, in a subsequent report, the authors described the achievement of clinical remission and maintenance for more than 4 months in 14 of 16 patients (88%). In another positive open-label observation, 4 of 6 patients with severe, steroid-refractory ulcerative colitis were reported in a long-term remission (median follow-up, 5.5 months) after a single 5 mg/kg infliximab infusion. Similarly, Kohn et al. treated 13 patients with severe, steroid-refractory ulcerative colitis with a single infusion of infliximab 5 mg/kg, and of 10 with a clinical response, 9 patients were reported to have maintained clinical remission off corticosteroids at a mean of 10 months. In a separate uncontrolled experience from several separate practices, 27 patients with medically refractory active ulcerative colitis received either a single infusion or multiple infusions of infliximab. Of these, 44% were reported to have achieved remission and 22% partial response. Half of the responders experienced a relapse, 95% of whom responded to repeat infusions. However, in contrast to previous reports, steroid-refractory patients were less likely to respond to infliximab.

In contrast to these aforementioned positive and mostly uncontrolled studies, Actis et al. reported an initial response rate in 4 of 8 patients who received a single dose of infliximab, but a sustained response rate was maintained in only 2 patients after 7 months with combinations of azathioprine and repeated infliximab dosing. In another open-label study, although infliximab was able to induce a rapid response in 30 patients with ulcerative or “indeterminate” colitis refractory to conventional treatment, long-term results were less favorable, with frequent relapses, and one third of patients required a colectomy by 1 year. Finally, in the only published randomized, placebo-controlled trial, Probert et al. did not identify a difference in remission rates at 6 weeks in moderately severe steroid-resistant ulcerative colitis treated with 2 doses of infliximab 5 mg/kg or placebo at 0 and 2 weeks (39% vs. 30%; P = 0.76). Although this study was inadequately powered and a true clinical difference may have been missed (type II error), the disparity among published reports needs to be clarified and the efficacy of infliximab needs to be assessed with properly conducted placebo-controlled trials. Results of ongoing phase III trials will provide long-awaited answers.

CDP571, an immunoglobulin G4 humanized monoclonal antibody, has also been evaluated in a pilot study that enrolled 15 patients with mild to moderate ulcerative colitis. Although there was a modest but significant reduction in clinical activity by 1 week after a single infusion, the effects were short lived and failed to remain significant at 2 weeks.

Although some rationale remains for the treatment of ulcerative colitis with anti-TNF therapy—based on increased levels of TNF-α in the colonic mucosa; increased production of TNF-α by lamina propria mononuclear cells; high concentrations of TNF-α in stools, rectal dialysates, and urine; and beneficial effects of CDP571 in cotton-top tamarins—it remains to be determined whether these strategies will have similar effects on the human disease.

RDP58, a novel anti-inflammatory decapeptide, blocks TNF production at a posttranscriptional level and also inhibits the production of interferon (IFN)-γ, interleukin (IL)-2, and IL-12. RDP58 has been effective in murine and primate models of colitis, and in a phase II study, 127 patients with mild to moderate active ulcerative colitis were randomized to receive placebo or an oral solution of RDP58 at 100, 200, or 300 mg daily for 4 weeks. Clinical remission was reported in 72%, 70%, 29%, and 40% of patients in the 300, 200, and
colitis. After a single dose of intravenous basiliximab, a chimeric monoclonal antibody to IL-2R, has also assessed by endoscopic and histological scores. Clinical remission did not achieve mucosal healing, as were in remission after 8 weeks. However, all patients in 10 patients achieved a clinical response, of which 5

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Anti–leukocyte adhesion therapies are a novel approach to prevent egress of inflammatory cells into the tissues of patients with inflammatory bowel disease. To date, preliminary trials have been reported regarding monoclonal antibodies to the $\alpha_4\beta_7$ integrin (natalizumab)$^{95}$ and $\alpha_4\beta_1$ integrin (MLN-02)$^{96}$ for ulcerative colitis and an antisense compound inhibiting production of intercellular adhesion molecule-1 (ISIS 2302) for pouchitis.$^{97}$ The results are too preliminary to make ultimate predic-

Anti–Interleukin-2 Therapies

The pathogenic role of IL-2 in ulcerative colitis is inferred from the established efficacy of cyclosporine in severe ulcerative colitis, which inhibits IL-2 synthesis through inhibition of the calcineurin pathway. Recent approaches to the treatment of transplant rejection have targeted the IL-2 receptor (IL-2R) with the monoclonal antibodies daclizumab and basiliximab. Daclizumab, a recombinant humanized immunoglobulin G1 monoclonal antibody to IL-2R$\alpha$ (CD25), binds with high affinity. In an open-label, single-center pilot study, 2 infusions of daclizumab 1 mg/kg 4 weeks apart in 10 patients with refractory ulcerative colitis resulted in significant decreases in clinical activity scores after week 2 with a parallel decrease in C-reactive protein and significantly reduced CD25$^+$ cells in mucosal biopsy samples.$^{98}$ Eight of 10 patients achieved a clinical response, of which 5 were in remission after 8 weeks. However, all patients in clinical remission did not achieve mucosal healing, as assessed by endoscopic and histological scores. Basiliximab, a chimeric monoclonal antibody to IL-2R, has also been evaluated in a pilot open-label study in ulcerative colitis.$^{99}$ After a single dose of intravenous basiliximab 40 mg, 9 of 10 patients with steroid-resistant disease achieved a clinical remission by 8 weeks, with significant improvement in the clinical activity score as early as 1 week. Although 8 of the 9 responders relapsed after a median of 9 weeks, remissions were easily reestablished by increasing the steroid dose, adding azathioprine, or both. These trials suggest that, in addition to immuno-suppressive actions, anti–IL-2R antibodies may have steroid-sensitizing properties that could lead to improved efficacy when administered in combination with steroids. Unfortunately, retreatment with basiliximab is compromised by reports of hypersensitivity with repeated infu-

sions secondary to the development of human antichimeric antibodies. Ultimately, a role for “bridging” therapy for steroid-resistant patients to a maintenance immunomodulator may need to be compared with the efficacy and safety of cyclosporine in future trials.

Anti–CD3 Therapy

Visilizumab (HuM291), a humanized antibody with a mutated immunoglobulin G2 Fc region directed at the CD3$\varepsilon$ chain of the T-cell receptor complex, has been shown to selectively induce apoptosis in activated T cells.$^{100}$ Preliminary results of an ongoing phase I dose-escalation study recently described 7 patients with severe steroid-refractory ulcerative colitis who received 2 daily infusions of visilizumab 15 $\mu$g/kg.$^{101}$ Data presented for 5 patients described clinical and endoscopic remissions for all 5 patients that persisted for several months as steroids were tapered. Side effects included a transient decrease in T-lymphocyte counts and cytokine-release symptoms, although no infectious complications were seen in this small pilot study. Two patients had transient low-level Epstein–Barr virus (EBV) titers not associated with clinical symptoms. In trials with visilizumab for graft-versus-host disease, EBV reactivation and post-transplantation lymphoproliferative disease have been encountered that necessitated close monitoring of EBV DNA. Preemptive treatment with rituximab, based on increasing DNA titers, seems to prevent the complication of posttransplantation lymphoproliferative disease after visilizumab in patients with graft-versus-host disease.$^{102}$

The role of IFNs has been evaluated in ulcerative colitis, initially in 7 patients with chronic active hepatitis and quiescent colitis.$^{103}$ The absence of worsening symptoms led to a 6-month trial with subcutaneous IFN-\(\alpha\)-2a (3–9 MIU thrice weekly) in 28 inpatients who had a rapid response (within 2 weeks) and an eventual 82% remission rate within 6 months.$^{104}$ In a randomized study comparing 12 weeks of subcutaneous IFN-\(\alpha\)-2a with 30 days of prednisolone enemas in 32 patients with mild to moderate left-sided colitis, IFN-\(\alpha\)-2a treatment was as effective as steroid enemas,$^{105}$ and, most recently, the efficacy of pegylated IFN-\(\alpha\)-2b was recently evaluated in 60 patients with ulcerative colitis randomized to placebo, 0.5 $\mu$g/kg, or 1 $\mu$g/kg of subcutaneous pegy-
lated IFN-\(\alpha\)-2b once weekly for 12 weeks.$^{106}$ Clinical remission at week 12 was highest in the pegylated IFN 0.5 $\mu$g/kg group (58%) compared with placebo (40%), although the pegylated IFN 1 $\mu$g/kg was less well tolerated: 8 of 21 patients dropped out of the study because of adverse events.
IFN-β-1a has also been evaluated in a several trials. In 25 patients with steroid-refractory ulcerative colitis given 0.5 MIU of intravenous human natural IFN-β or subcutaneous injections of 1 MIU of recombinant IFN-β-1a, a remission rate of 88% was described, with a mean response time of 3 weeks. Although there was no difference in efficacy between the 2 forms of IFN-β, a subsequent study involving 97 steroid-refractory patients treated with placebo or subcutaneous recombinant IFN-β-1a at doses of 1 or 3 MIU 3 times per week for 8 weeks showed remission rates of 38%, 30%, and 56%, respectively. In the most recent placebo-controlled, dose-escalating study of subcutaneous recombinant IFN-β-1a at doses of 22, 44, or 88 μg 3 times a week, clinical response and remission were achieved in 50% and 30% in the IFN-β group, compared with 14% and 0% in the placebo group (P = 0.14 and P = 0.02, respectively).

Growth factors, including transforming growth factor-β, trefoil factors, epidermal growth factor (EGF), and keratinocyte growth factor (KGF), regulate the integrity of the colonic mucosa and maintain its barrier function. The potential use of these growth factors to heal and restore mucosal integrity has stimulated recent studies using KGF and EGF for the treatment of ulcerative colitis. KGF is a potent stimulator of intestinal epithelial cells, and in animal models, colitis has been improved with both recombinant human KGF-1 (fibroblast growth factor-7) and KGF-2 (repifermin; fibroblast growth factor-10). However, in a placebo-controlled trial that enrolled 88 patients with active ulcerative colitis who were randomized to receive intravenous repifermin 1 to 50 μg/kg or placebo for 5 consecutive days, there was no significant benefit, although the study did not rule out the possibility of higher dosing or longer treatment intervals. In contrast, EGF, a mitogenic peptide produced by salivary and duodenal Brunner’s glands that has been used topically for healing of skin wounds and systemically to treat necrotizing enterocolitis in neonates, was recently evaluated as an enema therapy in conjunction with mesalamine therapy in 24 patients with mild to moderately active ulcerative colitis. After 2 weeks, 10 of 12 patients who received EGF enemas (5 μg in 100 mL of an inert carrier) experienced remission, compared with 1 of 12 patients treated with placebo enemas. All 10 patients remained in remission at a 4-week assessment, and this decreased to 8 after 12 weeks. Despite these impressive results, additional confirmation is necessary, and potential benefits need to be balanced against the potential for up-regulation of protooncogene expression and the risk of malignant transformation with EGF therapy in ulcerative colitis or adenomatous polyps.

**Chemopreventive Strategies in Ulcerative Colitis**

Recent series have provided optimism regarding the potential for diminishing the risk of neoplasia in patients with ulcerative colitis. There has been increasing although, again, conflicting evidence regarding the potential for mesalamine compounds to reduce the development of dysplasia, cancer, or both in ulcerative colitis. There are numerous potential mechanisms by which mesalamine could affect the carcinogenesis sequence, including inhibition of cell growth; proliferation by inhibition of prostaglandins, lipoxygenases, nuclear factor-κB, and MAP kinases; activation of apoptosis; and inhibition of gene transcription by targeting the peroxisome proliferator-activated receptor-δ. There are also evolving data that ursodeoxycholic acid may provide chemoprotective benefits for patients with ulcerative colitis and primary sclerosing cholangitis. Large prospective studies would be helpful to elucidate the dose response and efficacy of the mesalamine compounds and ursodeoxycholic acid alone and in combination as chemopreventive agents in ulcerative colitis. Meanwhile, the data regarding the maintenance benefits of mesalamine are a compelling rationale to continue long-term treatment with additional hope, if not expectation, of chemoprevention, and supplementation with folic acid is also an inexpensive and risk-free recommendation, particularly for patients receiving sulfasalazine.

**Postcolectomy Management**

Proctocolectomy and ileo-anal pouch surgeries have become the standard approach to curative resections in young patients with ulcerative colitis. The cosmetic and quality-of-life benefits have been well described and confirmed. Now that these operative techniques have matured, the short- and long-term risks and failures have become well established and are acceptable within the gastroenterological and surgical communities. However, the recent description of reduced fecundity in women undergoing restorative proctocolectomies has been quite disturbing and requires further evaluation of risk factors and preventive measures to avoid this significant impediment to elective surgical interventions. Two additional postoperative complications deserve mention: pouchitis and the risk of neoplasia. Pouchitis has been a well-recognized complication of restorative proctocolectomy for ulcerative colitis. Although a re-
cent Cochrane analysis had difficulty identifying evidence-based support, the antibiotics metronidazole and ciprofloxacin have become, at least, empirical standards of treatment of acute\textsuperscript{125,126} and chronic\textsuperscript{127} pouchitis. Recent clinical trials have also shown a role for the probiotic formulation VSL\textsuperscript{#3}, in high doses, for primary prevention\textsuperscript{128} and maintenance of remission after antibiotic therapy.\textsuperscript{129,130} This formulation continues to be marketed over the Internet as a food supplement and has yet to be compared with other empirical approaches from the standpoints of safety and efficacy. Additional alternative therapeutic approaches to acute pouchitis have been the use of budesonide enemas\textsuperscript{131} or infliximab for patients who develop Crohn’s disease in or around the pouch.\textsuperscript{132}

### Summary

This review has attempted to update information regarding the current state of medical therapy for ulcerative colitis and its surgical complications. Considerable incremental progress is being made on all fronts. Nevertheless, aside from an expanding array of aminosalicylate formulations, no new therapy has been approved for the treatment of ulcerative colitis over the past several decades. There is consistent evidence for the role of cyclosporine in severe ulcerative colitis and expanding, if not definitive, evidence for purine antimetabolites. The most recent provocative data regarding EGF enemas are the first clinical evidence that epithelial restitution may have a therapeutic role; additional targeted immunosuppressive strategies are under investigation. The future is bright for expanding therapeutic potentials for ulcerative colitis with hopes that predictive factors will be identified that will allow better patient selection for individual agents as they enter into clinical investigation.

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Address requests for reprints to: Stephen B. Hanauer, M.D., Department of Medicine and Clinical Pharmacology, Section of Gastroenterology and Nutrition, University of Chicago, 5841 S. Maryland Avenue, MC 4076, Chicago, Illinois 60637. e-mail: shanauer@uchicago.edu; fax: (773) 702-2182.