Erratum: Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee

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In the Conflict of Interest section of the article, the Financial Support subsection should have stated that "No support was provided for this work." The publisher regrets any confusion this misstatement may have caused.

The corrected Potential Competing Interests subsection for Dr Kornbluth is as follows:
"Asher Kornbluth is a consultant for Salix Pharmaceutical, Shire Pharmaceutical, Proctor and Gamble Pharmaceutical, Centocor, and Prometheus Laboratory and has received research support from Salix Pharmaceutical, Procter and Gamble Pharmaceuticals, and Centocor Inc. He is also on the Speaker's Bureau of Salix Pharmaceutical, Shire Pharmaceutical, Proctor and Gamble Pharmaceutical, Centocor, Prometheus, and Axcan Pharmaceutical."

Also in the Conflict of Interest section, Dr Sacher's Potential Competing Interests statement was not included. It is as follows:
"David Sachar serves as expert witness for the plaintiffs in litigation claiming that isotretinoin was a cause of their inflammatory bowel disease. He has no other conflicts of interest to report."

CME

Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee

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Guidelines for clinical practice are aimed to indicate preferred approaches to medical problems as established by scientifically valid research. Double-blind placebo controlled studies are preferable, but compassionate-use reports and expert review articles are used in a thorough review of the literature conducted through Medline with the National Library of Medicine. When only data that will not withstand objective scrutiny are available, a recommendation is identified as a consensus of experts. Guidelines are applicable to all physicians who address the subject regardless of specialty training or interests and are aimed to indicate the preferable but not necessarily the only acceptable approach to a specific problem. Guidelines are intended to be flexible and must be distinguished from standards of care, which are inflexible and rarely violated. Given the wide range of specifics in any health-care problem, the physician must always choose the course best suited to the individual patient and the variables in existence at the moment of decision. Guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the board of trustees. Each has been intensely reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision analysis. The recommendations of each guideline are therefore considered valid at the time of composition based on the data available. New developments in medical research and practice pertinent to each guideline will be reviewed at a time established and indicated at publication to assure continued validity. The recommendations made are based on the level of evidence found. Grade A recommendations imply that there is consistent level 1 evidence (randomized controlled trials), grade B indicates that the evidence would be level 2 or 3, which are cohort studies or case–control studies. Grade C recommendations are based on level 4 studies, meaning case series or poor-quality cohort studies, and grade D recommendations are based on level 5 evidence, meaning expert opinion.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95% of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to treatment changes or intercurrent illnesses (1,2). UC affects approximately 500,000 individuals in the United States with an incidence of 8–12 per 100,000 population per year; the incidence has remained relatively constant over the last five decades (3–8).

The disease accounts for a quarter million physician visits annually, 30,000 hospitalizations, and loss of over a million workdays per year (9). The direct medical costs alone exceed four billion dollars annually, comprising estimated hospital costs of over US$960 million (10,11) and drug costs of $680 million (11).

RECOMMENDATIONS FOR DIAGNOSIS AND ASSESSMENT

In a patient presenting with persistent bloody diarrhea, rectal urgency, or tenesmus, stool examinations and sigmoidoscopy or colonoscopy and biopsy should be performed to confirm the presence of colitis and to exclude the presence of infectious and noninfectious etiologies. Characteristic endoscopic and histologic findings with negative evaluation for infectious causes will suggest the diagnosis of UC.

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The diagnosis of UC is suspected on clinical grounds and supported by the appropriate findings on proctosigmoidoscopy or colonoscopy, biopsy, and by negative stool examination for infectious causes (12). Inquiries should be made regarding factors that may potentially exacerbate symptoms of UC; e.g., smoking cessation or nonsteroidal anti-inflammatory drug use or possibly isotretinoin (13–16). Infections can also produce clinical findings indistinguishable from idiopathic UC, so microbiologic studies for bacterial infection (including specific assays for *Escherichia coli* 0157:H7) and parasitic infestation, as well as serologic testing for ameba when clinical suspicion is high, should be performed in each new patient (17), and should be considered in patients in remission or with mild stable symptoms who unexpectedly develop a severe or atypical exacerbation (18,19). Similarly, patients who have recently been admitted to hospital or treated with antibiotics should have stools examined for *Clostridium difficile*, although antibiotic-associated diarrhea may be present even with a negative assay for *C. difficile* toxin. The incidence of *C. difficile* is increasing in UC (20–23), and in inflammatory bowel disease (IBD) patients it is associated with a more severe course, greater length of hospital stay, higher financial costs, greater likelihood of colectomy, and increased mortality (22,24). Multiple stool assays may be required for diagnosis because of frequent false-negative results (22,24,25).

Proctosigmoidoscopy or colonoscopy will reveal the mucosal changes characteristic of UC, consisting of loss of the typical vascular pattern, granularity, friability, and ulceration (26–28). These changes typically involve the distal rectum, both endoscopically and histologically (29) and proceed proximally in a symmetric, continuous, and circumferential pattern to involve all or part of the colon. However, isolated patchy cecal inflammation is often seen in UC patients with otherwise only distal disease (30). These endoscopic features may not present in a typical manner in UC patients who have already received treatment, in which case-selective healing may have resulted in skip areas and rectal sparing. Because none of these endoscopic findings is specific for UC, histologic findings obtained from biopsies may be helpful in the differential diagnosis (31). Imaging of the small bowel may also be helpful when the diagnosis of Crohn's disease (CD) is being considered (32,33).

In the patient with acute onset of bloody diarrhea, the mucosal biopsy may help distinguish UC from infectious colitis. In UC, more commonly than in infectious colitis, the mucosa shows separation, distortion, and atrophy of crypts; chronic inflammatory cells in the lamina propria; preferential homing of neutrophils to the crypt epithelium; increased number of lymphocytes and plasma cells at the crypt bases; "shortfall" of crypts not reaching to the muscularis mucosae; and basal lymphoid aggregates (12,34–36). Villous mucosal architecture and Paneth cell metaplasia on rectal biopsy are other features favoring the diagnosis of UC (37). Crypt abscesses, on the other hand, are a nonspecific indication of inflammation and do not indicate a particular diagnosis (38). However, a large, bulging, cystic dilation with a small "necklace" of flat or cuboidal cells around the crypt abscess is more common in infectious, or acute self-limited colitis, than it is in UC (12). CD may be suggested by certain histologic findings such as noncaseating granulomas or microscopic focality, but their absence does not rule out the diagnosis. Furthermore, even in UC or in acute self-limited colitis, muciphage (or "cryptolytic") granulomas may form in response to ruptured crypts and are therefore not pathognomonic for CD (37). "Backwash ileitis" may occur in UC and appears as mild ileal inflammation endoscopically; it is almost always associated with cecal inflammation and has characteristic histologic findings of mild villous atrophy and only scattered crypt abscesses (39).

Other histologic findings that may suggest an infectious etiology include caseating or confluent granulomas in tuberculosis (TB) (or less commonly in schistosomiasis, syphilis, and *Chlamydia trachomatis*), trophozoites in amebiasis, pseudomembranes in *C. difficile* colitis (although in UC, most cases of *C. difficile* infection occur in the absence of pseudomembranes) (22), ova in schistosomiasis, and viral inclusions in herpetic or cytomegaloviral colitis, although the latter appears almost exclusively in immunocompromised patients (see "Recommendations for management of severe colitis"). In the appropriate clinical settings, sigmoidoscopy or colonoscopy and biopsy may also distinguish the various noninfectious colitides from UC. These conditions include ischemia, radiation, collagenous and microscopic colitis, drug-induced colitis, and the solitary rectal ulcer syndrome (38,40,41). Segmental colitis associated with diverticulosis, which usually presents with painless hematochezia in patients older than 60, is distinguished from UC by its segmental location in an area of divericula, typically in the sigmoid colon and with rectal sparing (42–44).

Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been identified in 60–70% of UC patients, but are also found in up to 40% of patients with CD. These pANCA-positive CD patients typically have a clinical phenotype resembling left-sided UC, so pANCA detection alone is of little value in distinguishing between UC and Crohn's colitis (45). However, reactivity to CBir 1, an anti-flagellin antibody, is preferentially present in pANCA-positive CD patients as compared with pANCA-positive UC patients, 44% vs. 4%, respectively (46). A meta-analysis of 60 studies analyzing performance characteristics of pANCA and anti-saccharomyces cerevisiae antibodies in 3,841 UC patients and 4,019 CD patients found a specificity of 89% pANCA for UC, but a sensitivity of only 59%. For patients with CD, a positive anti-saccharomyces cerevisiae antibodies with a negative ANCA had a specificity of 93% for CD, but again with a sensitivity of only 55% (47). The low sensitivity of pANCA for the diagnosis of UC prevents it from serving as a useful diagnostic tool. However, their specificities may make these assays useful in the occasional patient in whom no other clinical or pathologic features allow a differential diagnosis between UC and Crohn's colitis (48,49). Although this distinction is not always crucial, it may have important consequences in terms of counseling, prognosis, and the choice of medical and surgical therapies (50).

APPROACH TO MANAGEMENT

Goals of treatment are induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk.

After the diagnosis of UC is confirmed, the anatomic extent is assessed endoscopically. The key question to be addressed at this point is whether the inflammation is "distal" (i.e., limited to below the descending colon and hence within reach of topical therapy) or extends proximal to the descending colon, requiring systemic medication. Therefore, a delineation of the proximal margin of inflammation, if not achieved on initial evaluation, is desirable at some point once the patient's condition permits. From a practical standpoint, the endoscopic extent and clinical severity of an acute attack determine the approach to therapy. Importantly, a flare-up during which distal disease extends proximally is often a severe episode with the need for early aggressive therapy (51). Although therapeutic decisions are rarely based on histologic severity of inflammation, histology may well be taken into account when planning a surveillance regimen (see below). Based on clinical and endoscopic findings, the severity and extent of the disease are characterized. Severity may be classified as mild, moderate, severe, or fulminant (52,53). Patients with mild disease have less than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate. Moderate disease is characterized by more than four stools daily but with minimal signs of toxicity. Severe disease is manifested by more than six bloody stools daily, and evidence of toxicity as showed by fever, tachycardia, anemia, or an elevated erythrocyte sedimentation rate (52). Patients with fulminant disease may have more than 10 bowel movement daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement, and colonic dilation on abdominal plain films (53). Although this classification of mild, moderate, and severe disease is based on the original Truelove–Witts criteria of 1,955 (52), more recent clinical trials, especially with ambulatory patients, have relied more frequently on composite scores based on the number of loose or soft stools, frequency of rectal bleeding, sigmoidoscopic appearance, and a physician global assessment. These scores are variably termed the Mayo Clinic index, Sutherland index, or the UC Disease Activity Index (54,55). Despite the widespread adoption of these indices in clinical trials, they do not take into account symptoms of abdominal pain, nocturnal bowel movements, urgency, or the dreadful fear of episodes of incontinence, which are often the patients' greatest concerns. Furthermore, in assessing patients' own perception of clinical response, the sigmoidoscopic score may not yield additional information beyond the patients' simple reports of stool frequency and rectal bleeding (56,57). As a practical therapeutic end point, endoscopic demonstration of mucosal healing is not usually necessary for a patient who achieves clinical remission. Conversely, long-term mucosal healing may reduce the risk of dysplasia (58,59) and perhaps predicts a better long-term outcome (60,61). In addition to the evaluation of colitis extent and activity, a global assessment of the patient should include attention to general health concerns, and quality of life issues that may be influenced by colitis activity as well as by extraintestinal manifestations (EIMs) of the disease. Some EIMs are associated with the colitis disease activity, and include the ocular complications of episcleritis, scleritis, and uveitis (which may require urgent consultation), peripheral arthropathies of small and large joints, and dermatologic findings of erythema nodosum and pyoderma gangrenosum. Other EIMs present with a course independent of the colitis activity and include the axial arthropathies, sacroilitis and ankylosing spondylitis, and the chief hepatic EIM associated with UC, primary sclerosing cholangitis (PSC). Although recognition of these EIMs is usually apparent, their management will often require consultation with the appropriate specialist.

Routine vaccination status should be reviewed (62). In patients on immunosuppresants, live vaccines are contraindicated, so if these are required they should be administered at the time of UC diagnosis. However, patients on immunosuppressant drugs can and should be vaccinated routinely for influenza and pneumococcal infection, and for tetanus and meningococcus in the appropriate settings (63–65). Patients being started on infliximab should be screened for hepatitis B before initiating infliximab therapy (63).

Referral-based series (66,67) have found an increase in abnormal Pap smears in women with IBD, whereas a population-based series found increased risk only in those patients on corticosteroids and immunosuppressants (68). IBD patients have been reported to undergo routine Pap smear testing with suboptimal frequency (69) and should be advised to adhere to guidelines for cervical dysplasia screening (70). Furthermore, current guidelines recommend consideration of administering the human papilloma virus vaccine to all females between the ages of 9 and 26 (71).

Concerns regarding quality of life should be addressed: impairment of function at school, work, or in personal relationships; social and emotional support; financial resources; and adequacy of patient education regarding their disease (13). Anxiety and major depression are more prevalent in patients with IBD than in the general population, and these conditions are more pronounced in patients with greater ongoing disease activity (72,73). Besides providing indication for specific therapies, these psychiatric diagnoses may also predict the likelihood for medication noncompliance, a frequent contributing factor to poorer clinical outcomes and greater health-care costs (74–76).

RECOMMENDATIONS FOR MANAGEMENT OF MILD–MODERATE DISTAL COLITIS

Patients with mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids (Evidence A). Topical mesalamine agents are superior to topical steroids or oral aminosalicylates (Evidence A). The combination of oral and topical aminosalicylates is more effective than either alone (Evidence A). In patients refractory to oral aminosalicylates or topical corticosteroids, mesalamine enemas or suppositories may still be effective (Evidence A). The unusual patient who is refractory to all of the above agents in maximal doses, or who

is systemically ill, may require treatment with oral prednisone in doses up to 40–60 mg per day, or infliximab with an induction regimen of 5 mg/kg at weeks 0, 2, and 6, although the latter two agents have not been studied specifically in patients with distal disease (Evidence C).

The therapeutic plan in these cases is determined largely by the patient's preferences, because both oral and topical therapies are effective. However, a meta-analysis of controlled trials indicates that topical mesalamine is superior to oral aminosalicylates alone in achieving clinical improvement in patients with mild–moderate distal colitis (77–79). Oral therapy with the aminosalicylates (sulfasalazine, olsalazine, mesalamine, or balsalazide) is beneficial in achieving and maintaining remission (1,80–84). Effective doses of sulfasalazine range between 4 and 6 g a day in four divided doses (85,86); for mesalamine 2 and 4.8 g per day in three divided doses (54,87); for balsalazide 6.75 g per day in three divided doses (82,88,89); and for olsalazine 1.5–3 g per day in two divided doses (90–93), although efficacy of olsalazine in active UC is not conclusively established, perhaps in part because of a confounding dose-related diarrhea. A newer mesalamine formulated with a multimatrix formulation allows comparable efficacy with once daily dosing in doses of 2.4–4.8 g per day (94,95). These drugs generally exert their effect within 2–4 weeks (80) and are effective in 40–80% patients (77,80). Intolerance to the sulfapyridine moiety of sulfasalazine is fairly common and may result in nausea, vomiting, dyspepsia, anorexia, and headache. More severe but less common adverse effects include allergic reactions, pancreatitis, hepatotoxicity, drug-induced connective tissue disease, bone marrow suppression, interstitial nephritis, and hemolytic anemia or megaloblastic anemia. Abnormal sperm counts, motility, and morphology are also related to the sulfapyridine moiety of sulfasalazine and are not seen with the mesalamine preparations. Approximately 80% of patients intolerant to sulfasalazine are able to tolerate olsalazine, mesalamine, and balsalazide (80,92,96–98). However, several of the allergic reactions previously thought to be due to the sulfa moiety have occasionally been seen with newer aminosalicylates as well (80).

The occurrence of nephrotoxicity with either sulfasalazine or any of the mesalamine compounds is rare. In a review of 30 series in which serum creatinine or creatinine clearance was measured regularly in 2,671 patients for 3,070 years of follow-up, the mean annual nephrotoxicity rate per patient-year was 0.26% (99). Nephrotoxicity usually presents as interstitial nephritis; it occurs most frequently during the first year of treatment, but can occur unpredictably with a delayed presentation. There is no clear relationship between dose and the risk of nephrotoxicity, raising the possibility that this reaction might be idiosyncratic (100). In addition, patients with active IBD may develop an increase in microalbuminuria in the presence of active disease (101). Furthermore in an epidemiologic study of over 20,000 IBD patients from the UK, there was not an increased incidence of nephrotoxicity in IBD patients taking mesalamine compounds, compared with IBD patients without mesalamine use (102). It is recommended that serum creatinine should be measured before initiating treatment with mesalamine or its prodrugs, and periodically while on treatment. Although it may be reasonable to monitor serum creatinine at 3–6 months intervals during the first year of mesalamine treatment, and then annually thereafter, at present the optimal monitoring schedule of serum creatinine in patients treated with mesalamine remains to be determined, as there is no evidence currently to suggest that the frequency of testing improves patient outcomes (99).

An alternative to oral aminosalicylates is topical therapy with either mesalamine suppositories or enemas, or hydrocortisone foam or enemas. Mesalamine suppositories in a dose of 500 mg twice daily or 1,000 mg once daily are effective in the treatment of proctitis (103), and maintenance of remission (104), whereas mesalamine enemas in doses of 1–4 g may be able to reach as proximal as the splenic flexure and are effective in inducing (105,106) and maintaining (107–109) remission in distal colitis. Topical corticosteroids, available in the United States as a 100 mg hydrocortisone enema, or as a 10% hydrocortisone foam, are effective in acute therapy of distal colitis (110–112) but have not proven effective in maintaining remission (77). Foam is often better tolerated by patients who have difficulty retaining enemas. Mesalamine enemas in a dose of 4 g have been more successful than corticosteroid enemas in inducing remission in two double-blind controlled studies (113–115). One-gram mesalamine enemas may prove as effective as the standard 4 g formulation for induction of remission in patients with left-sided colitis (77). Budesonide, a second-generation corticosteroid that undergoes first-pass hepatic metabolism, has also been evaluated; the optimal budesonide enema dose, 2 mg, not yet available in the United States, seems to be at least as effective as the standard hydrocortisone preparation with fewer side effects (116,117). Advantages of topical therapy include a generally quicker response time and a less frequent dosing schedule than oral therapy, as well as less systemic absorption. The choice of topical vehicle is also guided by patient preference as well as by the proximal extent of disease. Suppositories have been showed to reach approximately 10 cm, hydrocortisone foam to approximately 15–20 cm, and enemas as far as the splenic flexure (118–122), although of course in individual patients the actual proximal extent of distribution may vary.

Some patients may achieve maximum benefit from combination of oral and topical therapy; a combination of oral mesalamine 2.4 and 4 g per day mesalamine enema was more effective in achieving clinical improvement, as well as an earlier response, than either agent alone (123).

RECOMMENDATIONS FOR MAINTENANCE OF REMISSION IN DISTAL DISEASE

Mesalamine suppositories are effective in the maintenance of remission in patients with proctitis, whereas mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night (Evidence A). Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission; the combination of oral and topical mesalamine is more effective than either one alone (Evidence A). Topical corticosteroids including budesonide, however, have not proven effective for maintaining remission in distal colitis

(Evidence A). When all of these measures fail to maintain remission in distal disease, thiopurines (6-mercaptopurine (6-MP) or azathioprine) and infliximab (Evidence A), but not corticosteroids, may prove effective (Evidence B).

Mesalamine suppositories in doses of 500 mg daily or twice daily are effective in maintaining remission with an apparent dose–response relationship; only 10% of patients treated with 500 mg twice daily relapsed at 1 year, compared with a relapse rate of 36% with once daily dosing (124,125). Mesalamine enemas in doses of 2–4 g maintained remission when administered daily (78% effective), every other day (72% effective), or even as infrequently as every third day (65% effective) (77,78). Sulfasalazine in a dose of 2 g per day, olsalazine 1 g per day, Eudragit-S-coated mesalamine 3.2 g per day, balsalazide 3–6 g per day (126,127) , and granulated extended release mesalamine capsules 1.5 g per day (128) were all effective in maintaining remission in distal disease. The combination of oral mesalamine 1.6 g per day and mesalamine enema 4 g twice weekly was more effective than the oral mesalamine alone (129). Topical corticosteroids, whether hydrocortisone or budesonide, have not proven effective for maintaining remission in distal colitis (77,78,130).

The indications for the use of thiopurines and infliximab are identical to those described in the section on maintenance in extensive colitis although they have not been studied in trials limited to patients with distal disease (79).

RECOMMENDATIONS FOR MANAGEMENT OF MILD–MODERATE EXTENSIVE COLITIS: ACTIVE DISEASE

Patients with mild to moderate extensive colitis should begin therapy with oral sulfasalazine in daily doses titrated up to 4–6 g per day, or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-aminosalicylate acid (5-ASA) moiety (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates in combination with topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement (Evidence B). 6-MP and azathioprine are effective for patients who do not respond to oral steroids, and continue to have moderate disease, and are not so acutely ill as to require intravenous therapy (Evidence A). Infliximab is an effective treatment for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine, or who are intolerant of these medications. The infliximab induction dose is 5 mg/kg intravenously at weeks 0, 2, and 6 weeks (Evidence A). Infliximab is contraindicated in patients with active infection, untreated latent TB, preexisting demyelinating disorder or optic neuritis, moderate to severe congestive heart failure, or current or recent malignancies.

Aminosalicylates

When inflammation extends proximal to the reach of topical therapy (i.e., descending colon), oral therapy is required, either solely or in combination with topical therapy. For clinically mild to moderate but anatomically extensive disease, the first-line therapy traditionally has been sulfasalazine. Responses are dose related, with up to 80% of patients who receive daily doses of 4–6 g manifesting complete clinical remission or significant clinical improvement within 4 weeks (85,86) and approximately half achieving sigmoidoscopic remission (85). However, the benefits of greater efficacy with the higher dose are somewhat offset by an increase in side effects. The strongest advantage of sulfasalazine compared with the "newer" aminosalicylates is its considerably lower cost. However, the most recent Cochrane Systematic Review found a trend in favor of a slight benefit for the newer 5-ASA preparations over sulfasalazine in the induction of global/clinical and endoscopic improvement including remission, when equivalent amounts of the active 5-ASA moiety were compared. There was a modest dose–response relationship of mesalamine when compared to placebo; the trend was significant in terms of global/clinical improvement or remission. This trend was only marginally significant when the rate of complete global/clinical remission was evaluated (80).

If these higher doses of sulfasalazine are not well tolerated, or if there is concern regarding potential sulfonamide toxicity, then one of the other nonsulfonamide 5-ASA-containing compounds should be used at doses of at least 2 g per day, titrating up to 4.8 g per day of the active 5-ASA moiety (54).

The "newer" aminosalicylates—balsalazide (82,88,89), olsalazine (90–93), Eudragit-S-coated, pH-dependent mesalamine (54,87), ethylcellulose-coated mesalamine (131), and multimatrix-release mesalamine (83,132)—are all superior to placebo and equivalent to sulfasalazine in acute therapy (80). As with sulfasalazine, therapeutic benefit requires a threshold dose, with daily doses less than 2 g being ineffective (54,80,87,133). Two dose-ranging studies of Eudragit-S-coated pH-dependent release mesalamine show a dose–response relationship, comparing 2.4 g daily with 4.8 g daily, with a greater clinical response to the higher dose seen in patients with moderate but not mild disease. No differences were seen, however, in complete remission rates between the two dosages (134,135). Similarly, there were no significant differences in clinical responses or remissions in patients with mild or moderate disease when treated with multimatrix-mesalamine with 2.4 g daily compared to 4.8 g daily (83,132). The combination of oral mesalamine and topical mesalamine was more successful than oral mesalamine alone in achieving clinical remission at 8 (but not 4) weeks (136).

Nicotine

A Cochrane systematic review of transdermal nicotine in active UC identified five relevant studies (137). Nicotine was more effective than placebo in achieving remission and improvement. However, comparative trials to mesalamine did not show any clinical advantage for nicotine. At present therefore, the place of nicotine in the therapy of UC remains limited.

Corticosteroids

Oral prednisone shows a dose–response effect between 20 and 60 mg per day (52,138,139), with 60 mg per day modestly more effective than 40 mg per day but at the expense of greater side effects (139). No randomized trials have studied steroid taper

schedules; most recommendations (140) have advised 40–60 mg per day until significant clinical improvement occurs and then a dose taper of 5–10 mg weekly until a daily dose of 20 mg is reached. At this point tapering generally proceeds at 2.5 mg per week. The frequency and severity of steroid toxicity are substantial and may involve many metabolic activities in virtually every organ system. These adverse effects include cushingoid features, emotional and psychiatric disturbances, infections, glaucoma, and cataracts. Annual ophthalmologic examinations for patients on chronic steroids are recommended (140). Additional steroid-induced complications include gastroduodenal mucosal injury, skin striae, impaired wound healing, and metabolic bone disease. The latter can present insidiously with osteopenia and osteoporosis, or with the more dramatic bone fracture or unpredictable osteonecrosis. When osteonecrosis occurs, it is almost always after high cumulative doses of steroids. This complication is not prevented by calcium and vitamin D supplementation and is not detected by dual energy X-ray absorptiometry scanning. The diagnosis is generally not suspected until a patient complains of specific joint pain, and it is then established by magnetic resonance imaging. The distribution of affected joints in IBD is similar to other conditions associated with osteonecrosis, with the hips being the most frequently involved (141).

Steroid-induced metabolic disturbances include hyperglycemia, sodium and fluid retention, hypokalemia, metabolic alkalosis, hyperlipidemia, and accelerated atherogenesis. Patients on chronic steroids are at risk of adrenal insufficiency if steroids are discontinued or tapered too rapidly, and therefore require steroid replacement at periods of increased stress, such as surgery (142).

Dual-energy X-ray absorptiometry bone testing should be considered in IBD patients with risk factors for osteoporosis such as smoking, low body mass, sedentary lifestyle, hypogonadism, family history, and nutritional deficiencies (143,144). IBD patients at greatest risk for fracture are over age 60 and all these subjects should be considered for dual-energy X-ray absorptiometry testing. Patients using corticosteroids beyond 3 months consecutively or who are recurrent users should likewise be considered for dual-energy X-ray absorptiometry testing and even prevention with bisphosphonate therapy (143,145,146). Prospective implementation of these guidelines in IBD patients identified 44% of IBD patients with osteopenia and 12% with osteoporosis (147). Calcium supplementation 1,000–1,500 mg per day and vitamin D 800 U per day should be considered as well as estrogen replacement in the postmenopausal woman (148). In non-IBD populations, controlled trials have shown efficacy for alendronate (149), risedronate (150), etidronate (151), and teriparatide (152) in the prevention of glucocorticoid-induced osteoporosis. In IBD patients, clodronate (not yet available in the United States) has shown efficacy in preventing glucocorticoid-induced bone loss (153).

Modifiable risk factors, such as cigarette smoking, alcohol use, and a sedentary lifestyle, should be addressed. It is advisable to prescribe a bisphosphonate for IBD patients at a *T* score below −2.5. For patients on long-term corticosteroids, or with other important risk factors such as previous fractures, it may be reasonable to prescribe a bisphosphonate at *T* scores below −1.0 (146). However, referral to a specialist should be considered in view of the multiple variables to be assessed in patients with different risk factors, the choices of treatments available, and their potential adverse effects.

The use of steroids in IBD increases the risk of opportunistic infections about threefold: the risk is dose related and more common in those over the age of 50 (154). The risk for opportunistic infections is synergistically increased when steroids are used concomitantly with either the thiopurines or infliximab (154).

Infliximab

Infliximab, an intravenously administered monoclonal antibody to tumor necrosis factor-α, is effective in inducing response and remission and improving quality of life in patients with moderate to severe UC. The two largest randomized controlled trials of infliximab in UC, ACT 1 and ACT 2, studied 728 patients. In ACT 1, patients were enrolled if they had failed corticosteroids and/or thiopurines within the previous18 months; whereas in ACT 2, patients could be enrolled if they had failed aminosalicylates without having failed previous corticosteroids and/or thiopurines (155).

Doses of 5 vs. 10 mg/kg vs. placebo were studied for induction (and maintenance, see below) of response and remission, and were infused at weeks 0, 2, and 6 and then every 8 weeks through week 46 in ACT 1, and through week 22 in ACT 2. Both infliximab doses were more effective than placebo in inducing and maintaining response and remission. There was no difference in efficacy between the two doses. All of the patients in these trials were outpatients (for results of infliximab in severe UC, see below). Patients who fail to respond after the initial two doses are very unlikely to respond to a third dose. For patients who initially respond, but then begin to lose their response after a number of infusions, increasing the dose to 10 mg/kg, or shortening the interval between doses, may improve the likelihood of success (although this strategy was not studied in a controlled manner in the ACT 1 and 2 studies). Patients who do not respond to a dose as high as 10 mg/kg as often as every 4 weeks should not be continued on the drug (156).

At present it is unknown whether the concomitant administration of a thiopurine enhances the efficacy of infliximab in UC. In CD, for which infliximab was approved by the US Food and Drug Administration 8 years earlier than for UC, concomitant use of thiopurines reduced the formation of antibodies to infliximab. In CD, regular dosing at 8-week (or shorter) intervals, as opposed to episodic dosing does, reduces the incidence of antibodies to infliximab, and has been associated with higher likelihood of response (157), and a lower incidence of infusion reactions (157,158).

The infliximab infusion is administered over a 2 h period in a monitored setting, with personnel trained to treat severe infusion reactions (see next paragraph). Besides infusion reactions, the most common or troubling adverse effects of infliximab include autoimmunity and increased risks of infection, lymphoma, and possibly other malignancies; these concerns are described in more detail below. Other rare but serious adverse effects of infliximab include hepatotoxicity, development or exacerbation of multiple sclerosis or optic neuritis, and worsening of congestive heart failure in patients with preexisting cardiac disease (159).

Infusion reactions

As described above, the incidence of infusion reactions is decreased by regular 8-week dosing intervals and concomitant immunosuppressive treatment. In the ACT 1 and 2 studies, these reactions occurred in approximately 10% of patients, and were more frequent in patients with antibodies to infliximab (155). Even though adverse reactions to infliximab after a treatment hiatus are the exception rather than the rule, premedication with a corticosteroid and an antihistamine may still be prudent. Similarly, patients with previous mild–moderate infusion reactions should be premedicated with corticosteroids and an antihistamine (160). Most infusion reactions are mild–moderate and consist of flushing, headaches, dizziness, chest pain, cough, dyspnea, fevers, chills, and pruritus. For mild–moderate infusion reactions, slowing the infusion rate, or temporarily halting the infusion often relieves the reaction. Delayed hypersensitivity-like or serum sickness-like reactions occur in 1–2% of patients with CD (161,162), most commonly in patients who have had a long hiatus between infusions. The clinical presentations may include myalgias, arthralgias, fevers, or rashes similar to the symptoms of a serum sickness-like disorder. These symptoms generally respond to a brief course of corticosteroids. Autoantibodies may occur in response to infliximab use. In the ACT 1 and 2 studies, antinuclear antibodies and anti-double-stranded DNA antibodies occurred in approximately 30% and 10% patients, respectively. Fortunately, the development of a lupus-like illness occurs in fewer than 1% of patients (163).

Infections

Infliximab increases the risk of infection of intracellular pathogens, most notably TB (164–167). Furthermore, extrapulmonary involvement may occur in more than 50% of cases, and disseminated disease in approximately one-third of patients. A detailed history should be taken with attention to potential risk factors for TB, and a careful physical examination for any evidence of pulmonary or extrapulmonary evidence of TB. Patients should be screened for latent TB with a skin test of standard purified protein derivative, and chest radiograph. Interpretation of the purified protein derivative may be confounded either because of previous vaccination with BCG or because many patients may have anergy due to concomitant immunosuppressive treatment. In these patients, especially those at high risk of latent TB, testing with QuantiFERON (Cellestis International, Melbourne, Victoria, Australia), a more sensitive and specific TB assay, should be considered (156). Patients with evidence of latent TB should be treated according to the recommendations of the American Thoracic Society (168,169).

Patients treated with infliximab are also at increased risk for other opportunistic infections that require macrophages for intracellular killing. Serious infection occurred in approximately 3% of infliximab-treated patients in the ACT 1 and 2 trials. Additional information regarding risk of infection is available from the Therapy, Resource, Evaluation, and Assessment Tool registry, an ongoing observational infliximab safety registry in patients with CD, which contains approximately 6,000 patients with 16,000 years of patient follow-up, half of whom are treated with infliximab, and compared with an uncontrolled group treated without infliximab (170). Multivariate analysis of this registry indicates that increased rate of serious infection was not associated with infliximab use, but was associated with steroid use, narcotic use, and more severe disease activity. However, a meta-analysis of randomized controlled trials of antitumor necrosis factor treatment in rheumatoid arthritis found a twofold increased risk of serious infection, compared with rheumatoid arthritis patients treated with placebo (171). Furthermore, a case–control series from the Mayo Clinic found that IBD patients treated with infliximab had a significantly increased risk for opportunistic infections, especially when used in conjunction with either steroids or thiopurines or both (154). Similarly, analysis of post-marketing adverse event reported to the Food and Drug Administration indicated that serious infections occurred three times more often than expected (167,172–174). Use of infliximab is also associated with reactivation of hepatitis B infection, so screening for hepatitis B should be undertaken before initiation with infliximab therapy (175) and vaccination should be considered in those patients at risk for hepatitis B infection (63).

The risk of malignancy in IBD patients treated with tumor necrosis factor-inhibitors remains unclear. An analysis of the Therapy, Resource, Evaluation, and Assessment Tool registry has not found an increased risk of malignancy, though the mean follow-up to date is only 2 years (170). However, multiple analyses indicate an increased risk of lymphoma (176). In rheumatoid arthritis, a meta-analysis found 10 patients with lymphoma in 3,500 infliximab-treated patients, compared to none in 1,500 control patients (171). Review of the Food and Drug Administration adverse event registry found that lymphomas were reported seven times more likely than would have been expected (172). Furthermore, a cluster of cases of a rare, particularly aggressive lymphoma, hepatosplenic T-cell lymphoma, has been reported in CD patients treated with concomitant azathioprine and infliximab (177–179). This particular lymphoma has only rarely been reported and some cases were associated with azathioprine monotherapy (180). It usually presents in younger male patients and has an almost universally fatal outcome.

Patients with decompensated heart failure should not be treated with infliximab because of the risk of further decline in cardiac function (181,182). Rare reports of the development of optic neuritis and multiple sclerosis have led to the recommendation that infliximab is relatively contraindicated in patients with a history of these disorders (156).

Thiopurines

Randomized controlled trials with a relatively small number of enrolled patients (183,184) as well as uncontrolled trials (185,186) of azathioprine in doses up to 1.5–2.5 mg/kg per day have shown its effectiveness in patients who do not respond to, or cannot be weaned from steroids (187). Their primary benefit is in the steroid-sparing effect, rather than as an agent to be used as monotherapy to induce remission. Its use in this setting is somewhat limited by its slow onset of action; up to 3–6 months of treatment may be necessary to appreciate an optimal effect (188,189). However, its

long-term use results in steroid sparing (190), fewer admissions to hospital, and fewer operations (191). In a prospective 2-year trial, the addition of olsalazine did not enhance the efficacy of azathioprine (192).

Azathioprine and 6-MP toxicities include bone marrow suppression, particularly leukopenia, which is usually dose dependent. Leukopenia most often occurs within the first weeks to months of use, so complete blood counts should be measured more frequently during this period, though late bone marrow suppression may occur (193). The risk of opportunistic infections is increased approximately threefold, and there is a further synergistic risk when thiopurines are used concomitantly with either steroids or infliximab (154). There is a greater tendency for serious infections in patients with lower absolute lymphocyte counts or leukopenia (154). The frequency of liver abnormalities varies between 2% and 17% of patients and depends largely on the definitions of liver abnormalities reported (194). The liver test abnormalities are usually reversible and generally occur soon after the initiation of thiopurine treatment. Although the thiopurine metabolite 6-methylmercaptopurine (6-MMP) has been associated with elevated transaminases (195), the sensitivity and specificity of 6-MMP for hepatotoxicity are poor (196). Allergic reactions occur in approximately 2–5% of patients and usually present as some combination of fever, rash, myalgias, or arthralgias. Pancreatitis occurs as a hypersensitivity reaction in approximately 2% of patients (197), and will invariably reoccur if treatment with the alternative thiopurine is attempted. Conversely, patients with gastrointestinal intolerance to azathioprine not related to pancreatitis may tolerate 6-MP (198,199). Long-term use of thiopurines has not been associated with increased risk of solid tumors (200–202).

6-Mercaptopurine, after it is generated from its prodrug, azathioprine, is metabolized by thiopurine methyltransferase (TPMT), an enzyme that exhibits variation as a result of a genetic polymorphism of its alleles and that can be measured by commercial laboratories. Approximately 0.3% (1 in 300) of the general population has low to absent enzyme activity, 11% have intermediate, and 89% have normal to high levels of activity (203). However, only about a quarter of cases of leukopenia in practice are associated with one of these genetic polymorphisms (204). Although TPMT testing cannot substitute for complete blood count monitoring in patients being started on thiopurines, TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. Because the phenotype assay reports a quantitative level of the TPMT enzyme activity, it is preferred to the genotype assay. A TPMT assay is therefore recommended by many authorities before initiating thiopurine therapy, to identify the rare patient who is at risk of developing severe myelotoxicity (140).

A meta-analysis of the association between levels of the thiopurine metabolite 6-thioguanine nucleotide (6-TGN) and clinical remission rates (mostly in patients with CD) strongly suggested that higher levels of 6-TGN are associated with clinical remission rates (205). In addition, a retrospective study found that a subset of patients with 6-TGN levels of less than 235 pmol per 8×10^8 erythrocytes but with high 6-MMP levels may remain refractory to dose escalations of 6-MP/AZA, as they may preferentially metabolize 6-MP/AZA to 6-MMP and thus achieve suboptimal 6-TGN levels (206). Given the conflicting data, the retrospective nature of these studies, and the limited positive and negative predictive values for these particular uses, the utility of measuring metabolite levels needs prospective controlled evaluation before their routine use can be recommended as providing much incremental benefit to the traditional routine of monitoring the complete blood count, liver tests, and clinical response. However, these metabolite markers can be of value in assessing whether a patient is noncompliant or preferentially metabolizes the drug to 6-MMP instead of 6-TGN (206). Leukopenia was observed in only 8% of responders, indicating that it is not a necessary condition for effective dosing (195), though it may still be useful as an indication that maximal dosage has been achieved before abandoning the drug as a failure.

Methotrexate has not been proven to be effective in UC when administered in a weekly dose of 12.5 mg per day (207); neither higher doses nor administration by a parenteral route has been studied in controlled trials.

RECOMMENDATIONS FOR MILD–MODERATE EXTENSIVE COLITIS: MAINTENANCE OF REMISSION

Once the acute attack is controlled, a maintenance regimen is usually required, especially in patients with extensive or relapsing disease. Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses (Evidence A). Patients should not be treated chronically with steroids. Azathioprine or 6-MP may be useful as steroid-sparing agents for steroid-dependent patients and for maintenance of remission not adequately sustained by aminosalicylates, and occasionally for patients who are steroid dependent but not acutely ill (Evidence A). Infliximab is effective in maintaining improvement and remission in the patients responding to the infliximab induction regimen (Evidence A).

Sulfasalazine reduces relapse rates in UC in a dose-related manner, with benefits showed at 2–4 g per day (85,208,209). Although the 4 g per day regimen is the most effective in preventing relapse, up to one quarter of patients cannot tolerate the side effects at this dose, which limits its overall utility (208). The newer aminosalicylate preparations—including olsalazine (210,211), mesalamine (212–218), balsalazide (98) , granulated extended release mesalamine capsules (128) , and multimatrix-mesalamine (though the latter has not yet been studied in a placebo-controlled trial) (95,219) have relapse-prevention properties virtually the same as, but not greater than, those of equivalent doses of sulfasalazine (80,220). Because of the well-documented efficacy of sulfasalazine in the prevention of relapse, most (212,214–218,221–225) but not all (226) 5-ASA relapse-prevention trials have used sulfasalazine as the control. As with sulfasalazine, most (225,227,228) but not all (229,230) comparison studies of mesalamine have shown increased efficacy with higher doses up to 4 g per day of 5-ASA. However, unlike sulfasalazine, larger doses of 5-ASA in the newer preparations are generally well tolerated, lending these analogues an advantage over sulfasalazine for the prevention of relapse. However, the cost

of sulfasalazine, especially when considered for long-term use, is considerably lower. Although the maximum length of remission-maintenance benefit has not been established, most experts recommend permanent maintenance; however, the patient with a mild first episode, or with very infrequent mild relapses that are easily controlled, may opt for being followed without long-term medical maintenance therapy.

The immunomodulators, azathioprine and 6-MP, have been studied for the prevention of relapse prevention. Azathioprine has been found effective in maintaining remission in controlled and uncontrolled drug withdrawal studies (231,232) and in a meta-analysis of seven placebo-controlled maintenance trials (233). Retrospective studies have shown the value of 6-MP and azathioprine in maintaining long-term remission (200,234), and it is generally well tolerated during long-term use (197,200,201,234). As with induction of remission in UC, there have been no studies comparing 6-MP with azathioprine. A systematic review (235) and meta-analysis (236) concluded that azathioprine is a modestly effective (236) maintenance therapy for patients who have failed or cannot tolerate mesalamine or sulfasalazine, and for patients who require repeated courses of steroids and this benefit should be considered in the context of the potential for adverse events from the thiopurines (235). Similarly, uncontrolled retrospective data from 105 patients treated with continued long-term 6-MP (234), from 351 patients treated with long-term azathioprine (200) in the United States, and from 298 patients treated with azathioprine in multiple centers in Europe (186) appear to confirm the efficacy of these agents continued long-term in maintaining remissions of UC (237).

The risk–benefit ratio of indefinite azathioprine or 6-MP use for the maintenance of remission, especially when compared with colectomy, is not known. However, experience with the thiopurines over the last four decades indicates that there is not an increased risk of the development of solid tumors (as discussed above) (201) or overall mortality (200,238). Conversely, a recent meta-analysis of six cohort studies calculated a fourfold increased risk of lymphoma among IBD patients treated with thiopurines, but it remains unclear whether this risk was due to the medications themselves or due to the underlying disease (176,180,239).

In the double-blind, placebo-controlled ACT 1 and ACT 2 studies (155), infliximab administered every 8 weeks was effective in maintaining response and remission at week 30 (53% and 32%, respectively), and week 54 (45% and 42%, respectively) in those patients with an initial response or remission at week 8 (after three infusions of 5 or 10 mg/kg at weeks 0, 2, and 6). There was no benefit to initial treatment with the higher dose. Although not studied in a controlled manner in these trials, some patients with an initial response to 5 mg/kg in whom the benefit is attenuated after multiple doses may benefit from dose escalation, or shortening dosing intervals, or both. Similar response and remission rates were seen whether patients had been steroid refractory or steroid naive. However, the success rate in maintaining a steroid-free remission at week 54 was only 21%. These studies did not prospectively address whether concomitant thiopurine therapy would influence clinical success rates.

RECOMMENDATIONS FOR MANAGEMENT OF SEVERE COLITIS

The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab 5 mg/kg if urgent hospitalization is not necessary (Evidence A). The patient who presents with toxicity should be admitted to hospital for a course of intravenous steroids (Evidence C). Failure to show significant improvement within 3–5 days is an indication for either colectomy (Evidence B) or treatment with intravenous cyclosporine (CSA; Evidence A) in the patient with severe colitis. Long-term remission in these patients is significantly enhanced with the addition of maintenance 6-MP (Evidence B). Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting (Evidence A).

Infliximab 5 mg/kg is indicated for the patient who may not require immediate hospitalization but who continues to have severe symptoms despite optimal doses of oral steroids (40–60 mg daily of prednisone), oral aminosalicylates (4–6 g sulfasalazine, 4.8 g mesalamine or 6.75 g balsalazide), and topical medications (155). The mainstay of therapy for those patients requiring hospitalization at this point is an intravenous steroid in a daily dose equivalent to 300 mg hydrocortisone or 60 mg methylprednisolone if the patient has received steroids in the previous month. There is no benefit to treatment with a much higher daily dose of steroids, which exposes the patient to a higher potential rate of side effects (240).

In the absence of any proven infection, controlled trials of antibiotics have showed no therapeutic benefit from the use of oral vancomycin (241), intravenous metronidazole (242), or ciprofloxacin (243), when added to intravenous steroids. However, protocols outlining treatment regimens for severe colitis generally include broad-spectrum antibiotics for patients with signs of toxicity, or with worsening symptoms despite maximal medical therapy (244–246).

Controlled studies of the impact of total parenteral nutrition show no benefit from this maneuver as a primary therapy for UC (247,248). In fact, it may even be detrimental by depriving the colonic enterocytes of the short-chain fatty acids vital to their metabolism and repair (249). However, total parenteral nutrition may be useful as a nutritional adjunct in patients with significant nutritional depletion (250).

There are no studies to show that an oral aminosalicylate is of clinical benefit in this setting, so it is generally withheld if the patient is nil per os, but it may be continued if the patient is eating and has been tolerating this drug. Likewise, no controlled studies have confirmed any incremental benefit of topical medications in this setting, but they are still often prescribed if they can be retained and tolerated. Because the failure rate of medical therapy with intravenous steroids in patients admitted to hospital for severe colitis is approximately 20–40% (251), these patients should be followed closely in conjunction with a surgeon experienced in the management of patients with IBD.

Superimposed infection with enteric pathogens and *C. difficile* should be ruled out. The incidence of *C. difficile* in hospitalized patients with UC is rising dramatically. This infection results in higher costs, longer length of stay, and increased morbidity and mortality (20–22,24,252), and it is more refractory to treatment in patients on immunosuppressive drugs (253). A recent prospective study of hospitalized patients (without IBD) showed a high failure rate with metronidazole treatment for *C. difficile* in patients who had been recently treated with cephalosporins, in those who were positive for *C. difficile* on admission, and in those transferred from another hospital. In such cases, therefore, vancomycin should be considered as the preferred initial antibiotic (254).

Cytomegalovirus superinfection may also occur in the setting of severe colitis and should therefore be considered in any patient who is not responding to maximal immunosuppressive therapy. Cytomegalovirus superinfection can be diagnosed with sigmoidoscopic biopsy and viral culture; treatment with gancyclovir may lead to clinical improvement (255,256). The frequency with which cytomegalovirus has been reported in the setting of severe colitis depends in large part on the sensitivity of the method chosen to detect cytomegalovirus (19,257–259).

Patients may present with a megacolon with or without toxicity. The absolute dimension to define a "megacolon" has been variably defined and may be considered as total or segmental nonobstructive dilation to ≥6 cm. Hypokalemia or hypomagnesemia, which can exacerbate dilation, should be aggressively corrected (260,261). In patients with either toxic signs (fever, leukocytosis, or worsening symptoms) or megacolon, medications with anticholinergic or narcotic properties should be avoided for possibility of worsening colonic atony or dilatation, as increased colonic and small intestinal gas is a predictor of a poor outcome to medical therapy (262–265).

Enhanced vigilance must be maintained for an additional, potentially lethal complication; namely, venous thromboembolism, which occurs approximately twice as frequently in hospitalized UC patients compared with hospitalized controls. Although heparin no longer warrants consideration as primary therapy for UC (266), it has an important role in prophylaxis against thromboembolism in patients admitted to hospital with severe colitis (267). For the patient with a series of thrombotic or embolic events during a course of severe colitis, emergent colectomy may be lifesaving in preventing additional, potentially fatal thrombi.

Patients with severe colitis who do not improve significantly after 3–5 days (268,269) of maximal medical therapy are unlikely to benefit from prolongation of this medical treatment (246,270) and should either be referred for surgery (see below) or considered for treatment with intravenous CSA or perhaps infliximab. In one placebo-controlled double-blind trial, 82% of patients with steroid-refractory severe colitis treated with intravenous CSA with a dose of 4 mg/kg per day experienced improvement and were able to avoid colectomy in the acute stage (271). These results in the acute phase are consistent with multiple open-label series (272–274). Additional randomized controlled trials showed similar efficacy with an intravenous CSA dose of 2 mg/kg per day (275) , and CSA 2 mg/kg per day was as effective as hydrocortisone intravenously (276). Predictive factors for failure to respond to CSA include persistent fevers, tachycardia, elevated C-reactive protein, hypoalbuminemia, and deep colonic ulcerations (277,278).

Patients with fulminant colitis are treated similarly but decisions regarding surgery vs. CSA or infliximab should be taken within a few days of initiating intravenous steroid therapy (279). No randomized controlled trials have been performed studying the addition of azathioprine or 6-MP to CSA. Retrospective series with long-term follow-up of up to 14 years (274,280) indicate a significantly higher long-term success rate when azathioprine or 6-MP was used during the oral CSA phase (272,275,276,280,281) although the ideal dose or time to add 6-MP or azathioprine has not been studied. However, even in those patients in whom CSA is effective in combination with a thiopurine, the long-term success rate in avoiding relapse and colectomy is substantially lower in those patients who had already been treated (ineffectively) before initiating cyclosporin use. In the largest series to date, 83% of 113 patients had an initial response to CSA and avoided colectomy during the hospital stay. However, during continued follow-up, 54% of the initial patients initially responding to CSA required a future colectomy with the mean time to colectomy at 5 years. The rate of colectomy in those already on azathioprine compared with those starting azathioprine concurrently with CSA was 59% vs. 31%, respectively. Life-table analysis showed that although only 33% of patients required colectomy at 1 year, 88% required colectomy at 7 years (274).

Significant toxicity may occur with CSA use in UC. Severe adverse events include nephrotoxicity, infection, and seizures (particularly in patients with associated hypocholesterolemia or hypomagnesemia). More common but less severe side effects include paresthesias, hypertension, hypertrichosis, headache, abnormal liver function tests, hyperkalemia, and gingival hyperplasia (282). During intervals of triple immunosuppression with steroids, CSA, and a thiopurine, many experts treat patients with prophylaxis against *Pneumocystis jiroveci* (*carinii*), such as trimethoprim/sulfamethoxazole or dapsone. Most authors have found that CSA does not increase the rate of postoperative complications in patients undergoing proctocolectomy (281,283), in contrast to the preoperative use of corticosteroids in patients with IBD that substantially increases the risk of postoperative infections (284).

Tacrolimus, like CSA, is a calcineurin inhibitor, and has been studied in a single randomized controlled trial (285) as well as in several open-label series (286–288). In a 2-week placebo-controlled trial in moderate–severe UC, patients treated with tacrolimus doses targeted to trough levels of 5–15 ng/ml were more likely than placebo-treated patients to achieve clinical response, though not remission (285). However, at present the available data for tacrolimus are insufficient to guide optimal dosing, duration of acute and maintenance treatment, or follow-up intervals. Furthermore, the need for concomitant thiopurine therapy and benefits in achieving long-term, steroid-free remission and avoiding colectomy are not well defined for tacrolimus (289).

There are limited controlled trial data regarding the role of infliximab in patients with severe or fulminant UC refractory to intravenous steroids. In one double-blind series of 45 patients,

patients with either fulminant colitis at day 3, or severe colitis at days 6–8, despite continued intravenous steroids, were randomized to either a single dose of infliximab 5 mg/kg or placebo (290). At day 90, 29% of infliximab-treated patients had undergone colectomy, compared to 67% of placebo-treated patients. In patients with fulminant colitis, 47% of infliximab-treated patients underwent colectomy, compared to 69% of placebo-treated patients. In a smaller randomized controlled trial of patients failing intravenous steroids, four of eight patients treated with infliximab responded clinically 2 weeks after a single dose of infliximab, whereas none of three placebo-treated patients responded (291). Comparable results were achieved in open-label series (292) in the short term but at 5 years approximately half of infliximab-treated patients required colectomy (293–295).

There are no controlled or uncontrolled trials directly comparing CSA to infliximab in patients with severe steroid-refractory UC. However, in a series of 19 patients who failed one therapy, and were then treated with the alternative drug within 30 days, only approximately 30% of patients had avoided colectomy and remained in a steroid-free remission at 12 months; 2 patients developed septicemia, and 1 died during the 30-day interval of receiving both the drugs (296). There is conflicting evidence as to whether infliximab increases the risk of postoperative complications. Most (297–300), but not all (301) series found no increased risk of postoperative complications after infliximab treatment: in the latter series, although there was no increased risk of overall surgical morbidity in patients treated with perioperative infliximab, a multivariate analysis found that these patients did have a higher incidence of postoperative infectious complications albeit without correction for concomitant medications or immediate preoperative duration or severity of the attack (301).

Patients with fulminant colitis or toxic megacolon should be treated as above; in addition they should be kept nil per os, have a small bowel decompression tube if a small bowel ileus is present, and instructed to rotate frequently into the prone or knee-elbow (302 position to aid in evacuation of bowel gas. Broad-spectrum antibiotics are usually used empirically in these patients. The duration of medical treatment of megacolon is controversial; some experts advocate surgery within 72 h if no significant improvement is noted (303,304), whereas others take a more watchful stance if no toxic symptoms are present (302). All agree, however, that any clinical, laboratory, or radiologic deterioration on medical therapy mandates immediate colectomy.

RECOMMENDATIONS FOR SURGERY

Absolute indications for surgery are exsanguinating hemorrhage, perforation, and documented or strongly suspected carcinoma (Evidence C). Other indications for surgery are severe colitis with or without toxic megacolon unresponsive to conventional maximal medical therapy, and less severe but medically intractable symptoms or intolerable medication side effects (Evidence C).

There are no prospective randomized trials comparing medical treatment to surgery for any indication in UC, but three situations are absolute indications for surgery because continued medical therapy is doomed to failure and potentially fatal: exsanguinating hemorrhage, frank perforation, and documented or strongly suspected carcinoma; i.e., high-grade dysplasia (HGD) or perhaps low-grade dysplasia (LGD) in flat mucosa (see section "Recommendations for Cancer Surveillance").

Massive hemorrhage in UC is due to diffuse mucosal ulceration. If the hemorrhage is exsanguinating or even persisting despite maximal medical therapy (see above), it is an indication for emergency surgery. Subtotal colectomy with preservation of the rectum for a future restorative procedure is recommended in this situation (305–307) so long as the small risk of further hemorrhage is appreciated and appropriately monitored. Another indication for emergency surgery is severe colitis or toxic megacolon unresponsive to maximal intravenous medical therapy (see above). It is essential to recognize, however, that perforation can occur without being preceded by megacolon.

Although the clinical scenarios described above provide absolute indications for surgery, the most common indication is persistence of chronic refractory symptoms despite maximal medical therapy, resulting in physical debility, psychosocial dysfunction, or intolerable medication side effects.

Only rarely is surgery necessary to control the EIMs of UC (308,309). Previously, patients with severe progressive pyoderma gangrenosum, in whom the pyoderma activity paralleled the activity of the colitis, required surgery (310); however, infliximab (311–313) has been found effective in healing pyoderma gangrenosum, and should therefore be tried before resorting to surgery for this indication. By contrast, the course of PSC is independent of the activity of the colitis and is not affected by colectomy (314–317).

Whatever the indication for surgery, patients should be informed of the different options available. These include a total proctocolectomy with permanent ileostomy, or the ileal pouch-anal anastomosis (IPAA) procedure. The patient should be aware of the risks and benefits of these operations within different clinical settings.The option of a total proctocolectomy with a continent ileostomy (Koch pouch) is rarely used because of the frequency of pouch outlet obstruction over time. A subtotal colectomy with an ileorectal anastomosis is rarely advisable as it leaves the potential for disease recurrence and/or cancer risk in the retained rectal segment. IPAA has become the most commonly performed operation for UC, and is performed in 1, 2, or 3 stages, depending on the patient's clinical status at the time of surgery and the judgment and experience of the surgeon. In general, most series report an improvement in quality of life compared to the patients' preoperative status (318). Nevertheless, there is increasing recognition of the potential complications following IPAA (319). Besides pouchitis (see below), which may occur in up to 50% of patients during long-term follow-up, a variety of surgical complications may ensue (320). A meta-analysis of 17 series of nearly 1,500 patients undergoing IPAA found that when this surgery was performed without a diverting ileostomy, functional outcomes were similar to those of surgery with proximal diversion but there was an increased risk of anastomotic leak. Notably, 30% of these patients undergoing IPAA required reoperation for postoperative complications including anastomotic leak, pelvic sepsis/abscess, anastomotic stricture, and

bowel obstruction; the time intervals during which reoperations for complications were performed were not specified (321). A large database analysis of privately insured UC patients undergoing IPAA found a 20% rate of postoperative complications resulting in an unexpected reoperation. The most frequent early complications (defined as within 30 days of surgery) were abscess (12%), sepsis (8%), and fistula (4%). An additional 11% of IPAA patients required reoperation for complications of abscess and stricture, respectively, between 30 and 180 days after surgery (322). An additional sobering observation was that a 10-year (1995–2005) survey of 7,100 patients undergoing surgery for UC found a mortality and morbidity of 2% and 31%, respectively. Furthermore, there were higher mortality rates in hospitals with low-volume experience with IBD patients (323). For patients undergoing colectomy, mortality in hospitals performing low volumes of colectomies was increased twofold compared with high-volume hospitals. Increased mortality was also found in patients who were admitted emergently, aged over 60 years, or insured by Medicaid (324).

In addition to the risks described above, patients should be counseled regarding the effects of the IPAA on fertility and sexual function. A meta-analysis of eight series found a threefold increase in infertility in women after IPAA, compared with women with UC treated medically (though there was no control for the extent of disease severity in patients treated medically) (325). Fecundity among women with UC before surgery is comparable to a control population of women without UC, but is only 20% of fecundity rates of controls after IPAA (326). Approximately 20% of women will have dyspareunia or fecal incontinence during intercourse during a 3-year follow-up after IPAA (320). A meta-analysis of 43 observational studies found a 4% risk of sexual dysfunction in men postoperatively (320). However, most men note improvement in overall sexual quality of life after IPAA, likely due to improvement in general health (327).

RECOMMENDATIONS FOR THE MANAGEMENT OF POUCHITIS

Patients who develop typical symptoms and signs of pouchitis after the IPAA should be treated with a short course of antibiotics (Evidence A). Controlled trial studies show efficacy for metronidazole in a dose of 400 mg three times daily, or 20 mg/kg daily, or ciprofloxacin 500 mg twice daily (Evidence A). Other etiologies mimicking pouchitis include irritable pouch syndrome, cuffitis, CD of the pouch, and postoperative complications such as anastomotic leak or stricture. Inadequate evidence exists to recommend routine surveillance of the pouch for dysplasia or adenocarcinoma (Evidence C).

Patients who undergo the IPAA procedure may develop an idiopathic inflammation termed "pouchitis," which typically presents with variable symptoms of increased stool frequency, rectal bleeding, abdominal cramping, rectal urgency, tenesmus, incontinence, fevers, and the appearance of EIMs (328,329). The diagnosis is suggested based on clinical symptoms but needs to be confirmed with the characteristic endoscopic and histologic features (330,331). Symptoms do not always correlate with endoscopic and histologic findings (332). Demonstrating the diagnosis with pouchoscopy as opposed to empiric treatment with metronidazole may be the more cost-effective strategy (333). Pouchitis occurs in up to 60% of patients after a mean follow-up of 40 months (334,335) and occurs more frequently in patients with PSC, preoperative EIMs (336–338), and in patients who had never smoked (339). Chronic pouchitis may be more likely to occur in those patients with early postoperative anastomotic complications (340).

Only rarely does refractory or recurrent pouchitis occur because of the missed diagnosis of CD (341), which may occur more commonly in patients with a family history of CD or preoperative anti-saccharomyces cerevisiae antibody seropositivity (342). CD of the pouch should be suspected if a *de novo* fistula develops 6–12 months after ileostomy takedown in the absence of postoperative leak, abscess, or sepsis. Endoscopically, CD of the pouch shows ulcers and/or strictures in the afferent limb or in other areas of the small bowel, in the absence of nonsteroidal anti-inflammatory drug use. In CD of the pouch, pelvic magnetic resonance imaging may reveal sinus tracts, fistulae, and leaks and abscesses outside the cuff (343). Pouch excision, or revision in expert hands (344), is required as a result of intractable pouch complications in fewer than 5% of patients in most series.

Some patients with episodes of increased stool frequency and cramping, but with normal endoscopic and histologic findings in the pouch may be experiencing "irritable pouch" symptoms and may respond to anticholinergics, antidepressants, and antidiarrheals (343,345). Other patients may have inflammation limited to a short cuff of retained rectal mucosa ("cuffitis") and may respond to topical hydrocortisone or mesalamine (346). *C. difficile* infection should be considered in cases of recurrent or refractory pouchitis, as it may occur in as many as 20% of these patients, who may then benefit from eradication of *C. difficile*. In patients using chronic nonsteroidal anti-inflammatory drugs, chronic pouchitis may resolve on cessation of the nonsteroidal anti-inflammatory drugs (343).

Controlled drug trials for the treatment of pouchitis are very limited (329,347–350). Metronidazole in a dose of 400 mg three times daily (349) or 20 mg/kg per day (347) is effective in the treatment of chronic active pouchitis; in clinical practice, metronidazole in a dose of 250 mg three times daily is often used (329,349). Controlled trials showed at least similar efficacy with ciprofloxacin 500 mg twice daily (347), or with budesonide enema 2 g daily (not available in the United States) (350). Many uncontrolled trials show similar results with metronidazole and other antibiotics (334,351,352) as well as with oral and topical mesalamine and steroids. An oral probiotic formulation VSL-3 (containing lactobacilli, bifidobacteria, and *Streptococcus salivarius*) was effective in the prevention of pouchitis for up to 1 year after surgery (353) and in the prevention of pouchitis relapse (354), although benefit has not been as consistently seen in open-label use in other centers (355).

The development of dysplasia or adenocarcinoma in pouches is very infrequent (356,357). Risk factors for dysplasia include long duration of UC before proctocolectomy, chronic pouchitis, PSC, and dysplasia or adenocarcinoma in the colectomy specimen (356,358,359).

In a surveillance program of 106 high-risk patients, only 1 patient had multifocal LGD, and no adenocarcinoma was found (356). Nonetheless, adenocarcinoma remains a risk after IPAA as the duration of follow-up increases. A recent review of 26 cases of adenocarcinoma developing after IPAA found that carcinoma can occur after either mucosectomy or stapled anastomosis, even in patients without dysplasia or cancer before colectomy, as well as in patients whose preoperative dysplasia was not located in or near the rectum (360).

RECOMMENDATIONS FOR CANCER SURVEILLANCE

After 8–10 years of colitis, annual or biannual surveillance colonoscopy with multiple biopsies at regular intervals should be performed (Evidence B). The finding of HGD in flat mucosa, confirmed by expert pathologists' review, is an indication for colectomy, whereas the finding of LGD in flat mucosa may also be an indication for colectomy to prevent progression to a higher grade of neoplasia (Evidence B).

Patients with UC are at increased risk for colorectal cancer (CRC); the degree of risk is related to the duration and anatomic extent of colitis and also to the degree of microscopic inflammation over time (58,59,361–368). After 10 years of universal disease, the cancer risk has been widely reported in the range of 0.5–1% per year (361,363–367). However, a recent nation-wide population-based analysis from the Netherlands found that 20% of all UC-related cancers were detected before 8 years of disease had elapsed (369). Even patients with left-sided colitis reach similar levels of cumulative cancer risk after 3–4 decades of disease (361,363,370,371); patients with proctitis or proctosigmoiditis do not appear to be at increased cancer risk. Although some data suggest a later onset of cancer risk in left-sided than in more extensive colitis (361), this evidence is not sufficiently strong to justify different guidelines for surveillance in the two groups (372).

Compared with noncolitis-associated CRC, colitis-associated cancers are more often multiple, broadly infiltrating, anaplastic, and uniformly distributed throughout the colon, and seem to arise from flat mucosa instead of following the usual adenoma–cancer sequence (363). However, lesions that may previously have been interpreted as "flat" may now may be more readily visible with newer, widely available colonoscopes with improved optics, or with the use of chromoendoscopy (described below). Furthermore, colitis-associated CRC often occurs in a much younger patient population than does CRC in the general population (361,363–367,369,371,372).

Determination of anatomic extent in assessing cancer risk has historically been based on macroscopic rather than histologic inflammation. On the other hand, both macroscopic and microscopic healing may occur, but once extensive colitis is documented, the cancer risk should be assumed to correlate with the greatest previously determined extent. Furthermore, areas of microscopic inflammation, without history of macroscopic inflammation may also harbor the risk of neoplasia proximal to known macroscopic disease (58,367,373).

Most groups have found that patients with PSC complicating UC have an increased risk of CRC (362,374–377). Whether this observation reflects a true biologic phenomenon or a statistical artifact of longer than appreciated colitis duration, it is prudent to start colonoscopic surveillance as soon as the coexisting diagnoses of UC and PSC are established. In addition, ursodeoxycholic acid in daily divided doses of 13–15 mg/kg should be considered, because a prospective randomized, placebo-controlled trial found that this strategy significantly reduced the risk for developing colorectal neoplasia in these patients (378). UC patients with a family history of CRC have a fivefold risk of cancer compared with matched controls (379).

However, the risk of CRC and dysplasia may be reduced with the use of mesalamine. A meta-analysis of six case–control (58,380–384) and three cohort studies (385–387) that included 334 cases of CRC and 140 cases of dysplasia among 1,932 patients suggested a chemopreventive effect of mesalamine with a 50% risk reduction of CRC and dysplasia (388). Additional series reported since this meta-analysis (362,389) have not shown the same chemopreventive effect of mesalamine. However comparison of the different series is confounded by failure to control consistently for risk factors including disease duration, family history of CRC, presence of PSC, patient adherence, daily and cumulative mesalamine dose, and degree and duration of colonic inflammation.

The degree of histologic inflammation is an important variable to consider and control risk reduction of dysplasia and CRC in UC. In a case–control series from a surveillance database of 600 patients, Rutter *et al.* (58) found in a univariate analysis that both increased microscopic and macroscopic inflammation increased CRC and dysplasia risk, whereas in a multivariate analysis microscopic inflammation increased CRC and dysplasia risk fivefold. Similarly, a cohort study from a surveillance database of 400 patients found that an increase in microscopic inflammation increased the risk of CRC threefold (59). Several studies have shown that most dysplasia is visible at colonoscopy: in approximately three quarters of cases of confirmed dysplasia, the endoscopist had noted an abnormality during the procedure (390–392). Endoscopic features that have been predictive of greater likelihood of presence of dysplasia include the presence of pseudopolyps (393,394) and colonic strictures (393,395,396). Although pseudopolyps *per se* are not premalignant, they indicate a higher degree of previous colonic inflammation. In the presence of countless pseudopolyps, which are too numerous to biopsy or which obscure substantial areas of mucosa, an adequate surveillance examination may be impossible. Patients should be informed of the reduced reliability of colonoscopic surveillance in this situation.

In an effort to increase the sensitivity of detecting dysplasia colonoscopically, several enhanced colonoscopic surveillance techniques have been studied. These methods aim to increase the recognition of nearly flat, or minimally raised lesions and their associated mucosal pit patterns using mucosal dye spraying with either carmine indigo or methylene blue (397). Some series have used additional imaging technologies not widely available, including confocal laser microscopy (398) and magnification colonoscopy

(399,400). These series have reported detection rates of dysplasia 1.5- to 5-fold greater than standard white light colonoscopy by endoscopists trained in the use of these techniques (399–401). Two series using chromoendoscopy with standard white light microscopy, without magnification, also showed a higher yield per biopsy and per patient in detecting dysplasia (402,403). However, the natural history of dysplastic lesions found by chromoendoscopy and not seen with routine white light colonoscopy is unknown. At present, therefore, the recommendation to routinely use chromoendoscopy-enhanced surveillance in low-risk patients awaits additional information regarding longer-term follow-up. Given the increased yield of chromoendoscopy, it may be of value in follow-up of the "higher-risk" patient (i.e., patients with indefinite or known dysplasia not proceeding to colectomy), and to ensure adequacy of previous resection of polypoid or minimally raised lesions. In any event, appropriate use of chromoendoscopy will require adequate training in the techniques of endoscopic staining and interpretation of mucosal pit patterns.

Simply stated, the goals of any cancer surveillance program in UC are to prevent cancer and to save lives. There are no randomized prospective studies comparing different surveillance protocols or, for that matter, even surveillance vs. no surveillance. Nonetheless, at present, the best practical recommendation for patients who are candidates for surgery, based on review of dysplasia surveillance series, calls for annual or biannual colonoscopy. A recent Cochrane analysis concluded that for patients undergoing surveillance, cancers tend to be detected at an earlier stage and hence have a better prognosis. However, lead-time bias could contribute substantially to this apparent benefit. In addition, there appears to be indirect evidence that surveillance is likely to be effective in reducing the risk of death from IBD-associated CRC and that it may be acceptably cost-effective (404).

Examination every second year as opposed to annually would reduce costs, particularly in patients with longer disease duration, but at the expense of reducing likelihood of early cancer detection (405), as in some (365,406), but not all (367) series annual hazard rates increased with longer disease duration. Whatever schedule might be theoretically most advisable, being both frankly informative and programmatically flexible with patients is important in gaining adherence. The cost of such a surveillance program for each successful detection of precancer or cancer compares favorably with the cost of population-wide screening by flexible sigmoidoscopy for all subjects at average risk for CRC (407–409) as well as with the cost of other widely accepted screening programs such as mammography (410) and Pap smears (411). Patients with long-standing UC may also be offered the option of a prophylactic total proctocolectomy, but patients in remission rarely opt for this approach.

The standardization of "high-grade" and "low-grade" dysplasia published by the Inflammatory Bowel Disease—Dysplasia Morphology Group (IBD-DMG) has been widely adopted and has served to make the diagnosis of dysplasia more stringent and more consistent (412). When colon cancer is identified, the need for surgery is obvious; similarly, the colonoscopic biopsy diagnosis of dysplasia in flat mucosa is often indicative of a concurrent or future cancer. Such findings are an absolute indication for colectomy in patients with HGD (413,414), and should prompt consideration of colectomy in patients with LGD as well. LGD in a mass lesion (415) that does not resemble a typical sporadic adenoma and cannot be resected endoscopically (see below), or a stricture that is symptomatic or not passable during colonoscopy (393,395,396), especially in long-standing disease, is often indicative of coexistent colon cancer; hence, colectomy is advisable. LGD in flat mucosa (i.e., when no raised lesion is visible endoscopically) may also be an indication for colectomy, as the 5-year predictive value of LGD for either cancer or HGD has been reported as high as 54% (416–418). In fact, a meta-analysis of 20 surveillance series found that among patients with LGD who underwent colectomy within 6 months, 26% of patients had a concurrent cancer, and an additional 12% of patients were found to have HGD. Furthermore, the detection of LGD on surveillance was associated with a 9-fold risk of developing cancer and a 12-fold risk of developing any advanced lesion (cancer or HGD) over a mean of 5.2 years (419). Patients not undergoing colectomy should be counseled regarding these risks, and undergo surveillance at a more frequent surveillance schedule.

A number of series have addressed an approach to management of patients with long-standing UC who are found to have a polypoid or adenomatous mass within a colitic area (420–425). If the lesion is resected in its entirety by colonoscopic polypectomy and if no dysplasia is found in the adjacent flat mucosa or anywhere else in the colon, long-term follow-up has not found an increased risk of cancer in these cases, suggesting that vigilant follow-up surveillance colonoscopy may suffice (420–425). Polyps with a plaque or carpet-like morphology that could not be endoscopically resected in their entirety were excluded from these studies; such cases should be referred for surgery. From a practical perspective, therefore, it matters little whether a mass lesion is called an adenoma-like mass, or a dysplasia-associated lesion or mass; the important issue is to determine whether the lesion is completely resectable endoscopically and the rest of the colon is free of dysplasia.

Guidelines for the patient found to have LGD or HGD are discussed above. It is essential to obtain corroborating pathologic review to confirm the unequivocal distinction between definite neoplastic dysplasia and regenerative atypia due to inflammation and repair (426). However, attempts to repeatedly show dysplasia on subsequent examinations before recommending colectomy should not be undertaken without the awareness of the high risk of concomitant or subsequent advanced neoplasia by both patient and physician. Conversely, the patient whose biopsies are interpreted as "indefinite" for dysplasia should have the slides reviewed by an expert gastrointestinal pathologist and should undergo repeat surveillance colonoscopy at a briefer interval (412), because these patients may have an elevated risk of subsequent progression to definite dysplasia (389).

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