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PRACTICE GUIDELINES

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

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Guidelines for clinical practice are intended 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 utilized 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 without regard to the specialty training or interests and are intended 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 extensively reviewed and revised by the Committee, other experts in the field, physicians who will use them, and specialists in the science of decision of analysis. The recommendations of each guideline are therefore considered valid at the time of their production 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 the publication in order to assure continued validity.

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 the treatment changes or intercurrent illnesses (1, 2). UC affects approximately 250,000–500,000 individuals in the United States with an incidence of 2–7/100,000 population per year; the incidence has remained relatively constant over the last five decades (3, 4). The disease accounts for a quarter million physician visits annually, 20,000 hospitalizations, and loss of over a million work-loss days per year. The annual financial costs approach half a billion dollars annually and include hospital costs of $192 million, and drug costs of $138 million (4).

The quality of evidence on which a recommendation is based is as follows:

Grade A: Homogeneous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power.

Grade B: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta analysis.

Grade C: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

RECOMMENDATIONS FOR DIAGNOSIS AND ASSESSMENT

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

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. Inquiries should be made regarding factors known to exacerbate symptoms of UC, *e.g.*, recent or past smoking cessation or nonsteroidal drug use (5). Infectious etiologies of colitis can produce clinical

findings indistinguishable from idiopathic UC, so microbiologic studies for bacterial (including specific assays *for E. coli 0157:H7*) and parasitic infection, as well as serologic testing for amoeba when clinical suspicion is high, should be performed in each new patient, and should be considered in patients in remission or with mild stable symptoms who unexpectedly develop a severe exacerbation. Similarly, patients who have recently been hospitalized or treated with antibiotics should have stools examined for *Clostridium difficile*, although antibiotic-associated diarrhea may be present in the absence of *C. difficile* toxin.

Proctosigmoidoscopy or colonoscopy will reveal the mucosal changes characteristic of UC, consisting of loss of the typical vascular pattern, granularity, friability, and ulceration (6). These changes typically involve the distal rectum and proceed proximally in a symmetric, continuous, and circumferential pattern to involve all or part of the colon. However, isolated patchy cecal inflammation may be seen discontinuous from more distal inflammation in UC patients with otherwise only distal disease (7). Since none of these endoscopic findings is specific for UC, histologic findings obtained with biopsies may be helpful in the differential diagnosis. A small bowel radiograph series may also be helpful in the differential diagnosis when the diagnosis of Crohn's disease is being considered. In the patient with acute onset of bloody diarrhea, the mucosal biopsy may help in distinguishing UC from infectious colitis. In UC, more commonly than in infectious colitis, the mucosa demonstrates separation, distortion, and atrophy of crypts; acute and chronic inflammatory cells in the lamina propria, preferential homing of neutrophils to the crypt epithelium; increased number of plasma cells near the crypt bases; and basilar lymphoid aggregates (8–10). Villous mucosal architecture and Paneth cell metaplasia on rectal biopsy are other features favoring the diagnosis of UC (11). Crypt abscesses, on the other hand, are a nonspecific indication of inflammation and do not indicate a specific diagnosis (12).

Crohn's disease may be suggested by certain histologic findings such as noncaseating granulomas or microscopic focality, but their absence does not rule out the possibility of Crohn's disease. Furthermore, in acute self-limited colitis, muciphage granulomas, or intraepithelial granulomas in the presence of ruptured crypts, may be seen and are therefore not pathognomonic for Crohn's disease (11). Other histologic findings that may suggest an infectious etiology, include granulomas in tuberculosis (and even less commonly in *schistosomiasis*, *syphilis*, and *Chlamydia trachomatous*), amoebic trophozoites, pseudomembranes in *C. difficile* colitis, and viral inclusions in cytomegalovirus or herpetic colitis. In the appropriate clinical settings, sigmoidoscopy or colonoscopy and biopsy may also distinguish the various noninfectious colitides from UC. These include ischemia, radiation, collagenous and microscopic colitis, drug-induced colitis, and the solitary rectal ulcer syndrome (12).

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 Crohn's disease. These pANCA-positive Crohn's patients typically have a clinical phenotype resembling left-sided UC, so ANCA detection alone is of little value in distinguishing between UC and Crohn's colitis (13). In a cohort of patients already known to have IBD, the combination of a positive pANCA and a negative anti-*Saccharomyces cervisiae* antibody (ASCA) had a positive predictive value of 75%, while a negative ANCA and a positive ASCA had a positive predictive value of 86% for the diagnosis of Crohn's disease (14). While, pANCA and ASCA assays at this stage of knowledge are neither a first step nor a definitive step in differential diagnosis or clinical decision-making, they may be useful in the patient in whom all other clinical features do not allow a distinction between UC and Crohn's colitis. While this distinction is not always essential, it may have direct consequences in terms of counseling, prognosis, cancer risk, and medical and surgical therapies (15).

APPROACH TO MANAGEMENT

Goals of treatment are directed at inducing and then maintaining remission of symptoms and mucosal inflammation in order to provide an improved quality of life.

Once 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 splenic flexure and thus within reach of topical therapy) or "extensive" (*i.e.*, extending proximal to the splenic flexure, requiring systemic medication). Therefore, a delineation of the proximal margin of inflammation, if not achieved on initial evaluation, is desirable at some point in the management of the case once the patient's condition permits.

From a practical standpoint, the anatomic extent and clinical severity of an acute attack determine the approach to therapy. Therapeutic decisions rarely are based upon histologic severity of inflammation.

Based upon clinical and endoscopic findings the disease is characterized as to its severity and extent. Severity is defined as mild, moderate, severe, or fulminant (16, 17). 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 (ESR). 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 demonstrated by fever, tachycardia, anemia, or an elevated ESR (16). However, some patients even with the most severe colitis may not demonstrate an elevated ESR. Patients with fulminant disease have features which include more than 10 bowel movement daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement, and colonic dilation on abdominal plain films (17).

In addition to the evaluation of the colitis extent and activity, a global assessment of the patient should include attention to extraintestinal manifestations, general health

concerns, and quality of life issues. Patients should be asked whether they have noted symptoms of ocular, oral, joint or skin or mood changes, and laboratory evaluation for anemia and liver function test abnormalities should be performed. 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 (5).

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 are 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 (Evidence C).

The therapeutic plan here is largely determined by the patient's preference since either oral or topical therapy is effective; however, a metaanalysis of controlled trials indicates that topical mesalamine is superior to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis (18).

Oral therapy with the aminosalicylates, sulfasalazine, olsalazine, mesalamine, or balsalazide, is beneficial in achieving and maintaining remission (1, 19, 20, 25). Effective doses of sulfasalazine range between 4 and 6 g a day in four divided doses (21, 22); for mesalamine 2–4.8 g per day in three divided doses (23, 24), for balsalazide 6.75 g per day in three divided doses (25–27), and for olsalazine 1.5–3 g/d in divided doses (28–31), although efficacy of olsalazine in active UC is not conclusively established, perhaps in part because of a confounding dose-related diarrhea. These drugs generally act within 2–4 wk (11–20) and are effective in 40–80% of patients (18–20). 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, nephrotoxicity, 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 (32). Approximately 80% of the patients intolerant to sulfasalazine are able to tolerate olsalazine, mesalamine, and balsalazide (19, 31, 33–35). However, several of the allergic reactions previously thought to be due to the sulfa moiety have been seen with newer aminosalicylates as well (19).

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 a day are effective in the treatment of proctitis (36), and maintenance of remission (37), while mesalamine enemas in doses of 1–4 g are able to reach as proximal as the splenic flexure and are effective in inducing (38, 39) and maintaining remission in distal colitis (40–43). 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 (44–46) but have not proven effective in maintaining remission (18). Mesalamine enemas in a dose of 4 g have been more successful than corticosteroid enemas in inducing remission in two double-blind controlled studies (47–49). One-gram mesalamine enemas may prove as effective as the standard 4-g formulation for induction of remission in patients with left-sided colitis (18). 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 (50, 51).

Advantages of topical therapy include a generally quicker response time and a less frequent dosing schedule than oral therapy. The choice of topical vehicle is also guided by patient preference as well as by the proximal extent of disease: suppositories reaching approximately 10 cm, hydrocortisone foam reaching approximately 15–20 cm, and enemas reaching up to the splenic flexure (52–56), although in daily clinical practice the actual extent distribution may vary.

Some patients may achieve maximum benefit from the combination of oral and topical therapy; a combination of oral mesalamine 2.4 g/d and 4 g/d mesalamine enema was more effective in achieving clinical improvement, as well as an earlier response, than either agent alone (57).

RECOMMENDATIONS FOR MAINTENANCE OF REMISSION IN DISTAL DISEASE

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

Mesalamine suppositories in doses of 500 mg daily or twice a day are effective in maintaining remission with an apparent dose-response relationship; only 10% of patients treated with 500 mg twice a day relapsed at 1 yr, compared with a relapse rate of 36% with once daily dosing (58, 59). Mesalamine enemas in doses of 2–4 g maintained remission

when dosed daily (78% effective), every other day (72% effective), or even as infrequently as every third day (65% effective) (18). Sulfasalazine in a dose of 2 g/day, olsalazine 1 g/day, Eudragit-S coated mesalamine 3.2 g/day, and balsalazide 3–6 g/day (60, 61) were all effective in maintaining remission in distal disease. The combination of oral mesalamine 1.6 g/day and mesalamine enema 4 g enema twice weekly, was more effective than the oral mesalamine alone (62). Topical corticosteroids, whether hydrocortisone or budesonide, have not proven effective for maintaining remission in distal colitis (18, 63).

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-ASA moiety (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates with or without topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement (Evidence C). 6-Mercaptopurine (6-MP), or azathioprine are effective for patients who do not respond to oral prednisone but are not so acutely ill as to require intravenous therapy (Evidence C).

When the inflammation extends proximal to the reach of topical therapy (*i.e.*, mid-descending colon-splenic flexure) oral therapy is required, either solely or in combination with topical therapy (though this latter option has not been studied in randomized controlled trials). 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 wk (21, 22) and approximately half achieving sigmoidoscopic remission (21). However, the benefits of greater efficacy with the higher dose are offset by the increase in side effects. The advantages of sulfasalazine compared with the "newer" aminosalicylates are its longer track record and considerably lower cost. If these higher doses of sulfasalazine are not well tolerated, or if there is concern regarding potential toxicity then a 5-aminosalicylate containing compound should be used at doses of at least 2 g per day, titrating up to 4.8 g per day of the active 5-aminosalicylate moiety (24).

The "newer" aminosalicylates—balsalazide (25–27), olsalazine (28–31), Eudragit-S coated mesalamine (23, 24), and ethylcellulose-coated mesalamine (64)—are all superior to placebo and equivalent to sulfasalazine in acute therapy (19). As with sulfasalazine, therapeutic benefit is dose-related, with daily doses less than 2 g being ineffective (19, 23, 24, 65). Although controlled trials have not studied the combination of oral aminosalicylates with topical treatments, patients often note a more prompt resolution of rectal symptoms when a topical therapy is added.

Controlled trials have demonstrated that transdermal nicotine patches are effective in achieving clinical improvement (66) and clinical remission (67) in patients with mild-moderate UC, with a dose-response effect between 15 and 25 mg of nicotine daily, but their success rates are generally lower than with traditional aminosalicylate therapy. Benefit was more evident in ex-smokers than in those who had never smoked (66, 68) and was better tolerated in the ex-smokers (66). The most common adverse effects were skin irritation, dizziness, and nausea. Transdermal nicotine in a daily dose of 15 mg was not effective in maintenance of remission (69) and the long-term consequences of long-term transdermal usage are uncertain. At present, it is uncertain where nicotine fits into the therapeutic algorithm.

Oral prednisone demonstrates a dose-response effect between 20 and 60 mg per day (70–73), with 60 mg per day modestly more effective than 40 mg per day but at the expense of greater side effects (72). No randomized trials have studied steroid taper schedules; many authorities (20, 73) recommend 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/wk.

The frequency and severity of steroid toxicity are significant and may involve virtually every organ system and many metabolic activities. These include the appearance of cushingoid features, emotional and psychiatric disturbances, infections, glaucoma, cataracts, 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. Steroid-induced metabolic disturbances include hyperglycemia, sodium and fluid retention, hypokalemia, metabolic alkalosis, hyperlipidemia, and accelerated atherogenesis (32).

The National Institute of Health have recently published their consensus statement regarding the prevention, diagnosis, and therapy of osteoporosis: any patient who is treated with a daily dose of at least 5 mg of prednisone for more than 2 months should be considered for measurement of bone mass density (74). Prospective studies on successful osteoporosis-prevention strategies in steroid-treated UC patients are lacking (75, 76). However, the American College of Gastroenterology and American Gastroenterological Association have both recently published guidelines for the diagnosis and management of osteoporosis in IBD (77, 78). DXA bone testing should be considered in IBD patients with a number of risk factors for osteoporosis such as smoking, low body mass, sedentary lifestyle, hypogonadism, family history, and nutritional deficiencies. IBD patients at greatest risk for fracture are over age 60 and all these subjects should be considered for DXA testing. Patients using corticosteroids beyond 3 months consecutively or who are recurrent users should likewise be considered for DXA testing and even prevention with bisphosphonate therapy (77). 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 (77).

Calcium supplementation 1,000–1,500 mg/day and vitamin D 800 units/day should be considered as well as estrogen replacement in the postmenopausal woman (78). Controlled trials have demonstrated efficacy for alendronate (79), risedronate (80), and etidronate in the prevention of corticosteroid-induced osteoporosis (81) in non-IBD populations. Modifiable risk factors, such as cigarette smoking, alcohol use, and a sedentary lifestyle should be addressed. For the patient with significant bone loss, referral to a specialist should be considered.

Controlled (82, 83) and uncontrolled trials (84, 85) of azathioprine in doses up to 1.5–2.5 mg per kg per day have demonstrated its effectiveness in patients who do not respond to, or cannot be weaned from steroids. Uncontrolled series have also demonstrated its value in achieving remission in patients refractory to high doses of oral steroids (84, 86). In this capacity, its use in acute induction of remission is somewhat limited by its slow onset of action; up to 3–6 months of treatment may be necessary to appreciate an optimal effect (87).

Azathioprine and 6-MP toxicities include bone marrow suppression, particularly leukopenia, which is usually dose-dependent. Serious infections are infrequent and are usually, but not always, related to leukopenia and often occur with concomitant steroid use. Liver abnormalities occur in approximately 2% of patients and usually represent a reversible drug-induced hepatitis. 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 (88). Long-term use has not been associated with increased neoplasia risk (89, 90).

Some (91, 92) but not all (93, 94) recent retrospective data have suggested that measurement of azathioprine and 6-MP metabolites may be useful in dose adjustments since serum 6-thioguanine nucleotide (6-TGN) levels of greater than 235 pmol/8 $\times$ 10^8erythrocytes may be associated with a greater response rate than patients with lower 6-TGN levels. Hepatotoxicity, on the other hand, may correlate with the elevated levels of 6-methylmercaptopurine (6-MMP). A retrospective study (95) found that a subset of patients with 6TGN levels of less than 235 pmol/8 $\times$ 10^8erythrocytes may remain refractory to dose escalations of 6-MP/AZA since they may preferentially metabolize 6-MP/AZA to 6-MMP and maintain suboptimal 6TGN levels (95). 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 these tests need prospective controlled evaluation before their routine use can be recommended. However, these metabolite markers can be of value in assessing whether a patient is noncompliant with their immunomodulator therapy. Leukopenia was observed in only 8% of responders, indicating that it is not a necessary condition for effective dosing (91).

6-MP and its prodrug azathioprine are both metabolized by thiopurine methyltransferase (TPMT), an enzyme that exhibits variation as a result of a genetic polymorphism of its alleles and this enzyme can now be measured by commercial laboratories. Approximately 0.3% of the general population have low to absent enzyme activity, 11% have intermediate, and 89% have normal to high levels of activity (96). However, only about a quarter of cases of leukopenia in practice are associated with one of these genetic polymorphisms (97). Therefore, prospective studies of dose-optimization based on measurements of TPMT, 6-TG, or 6-MP levels to monitor clinical response are still needed before the routine use of these assays can be recommended as providing much incremental benefit to the traditional routine of monitoring the CBC, liver associated laboratory chemistry abnormalities, and clinical response.

As described below, azathioprine has been found effective in maintaining remission in a controlled drug withdrawal study (98), while retrospective studies have demonstrated the value of 6-MP in maintaining long-term remission (99, 100) and is generally well tolerated during the long-term use (88–90, 99).

Methotrexate has not been proven to be effective in UC when administered in a weekly dose of 12.5 mg/day (101); higher doses, or administration by a parenteral route has not been studied in controlled trials.

RECOMMENDATIONS FOR MILD-MODERATE EXTENSIVE COLITIS: MAINTENANCE OF REMISSION

A maintenance regimen is usually required when the acute attack is controlled, especially in patients with extensive, or relapsing disease. Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses (Evidence A). As a rule, 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-refractory but not acutely ill (Evidence C).

Sulfasalazine reduces relapse rates in UC in a dose-related fashion, with benefits demonstrated at 2–4 g per day (102–104). 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, thus limiting its overall utility (104). The newer aminosalicylate preparations—including olsalazine (105, 106), mesalamine (107–115), and balsalazide (116)—have relapse-prevention properties virtually the same as, but not greater than, those of equivalent doses of sulfasalazine (19, 117). Because of the well-documented efficacy of sulfasalazine in relapse-prevention, most (107, 108, 110, 111, 114, 119–124) but not all (115, 118), 5-ASA relapse-prevention trials have used sulfasalazine as the control. As with sulfasalazine, most (115, 124–127), if not all

(128, 129), comparison studies of mesalamine have demonstrated increased efficacy with higher doses up to 4 g per day of 5-ASA. However, unlike sulfasalazine, use of larger doses of 5-ASA in the newer preparations are generally well tolerated, lending these analogues an advantage over sulfasalazine for relapse-prevention. On the other hand, 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 relapse-prevention. (As with induction of remission in UC, there have been no studies comparing 6-MP with azathioprine.) In patients whose remission was achieved with azathioprine, continuation of active drug reduced the 12-month relapse rate to 36%, compared to 59% on placebo (98). Similarly, uncontrolled retrospective data from 105 patients treated with continued long-term 6-MP (99), and 351 patients treated with long-term azathioprine (100) appear to confirm the efficacy of these agents continued long-term in maintaining remissions of UC. The risk-benefit ratio of indefinite azathioprine or 6-MP use, especially when compared to colectomy, for the maintenance of remission, is not known, although a recent retrospective series of 621 IBD patients treated during a 30-yr interval indicated that azathioprine is generally well tolerated (89) and is not associated with an increased cancer risk (90) or mortality (100).

RECOMMENDATIONS FOR MANAGEMENT OF SEVERE COLITIS

The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications, or the patient who presents with toxicity, should be hospitalized for a course of intravenous steroids (Evidence C). Failure to demonstrate significant improvement within 7–10 days is an indication for either colectomy (Evidence C) or treatment with intravenous cyclosporine (Evidence A) in the patient with severe colitis. Long-term remission, in these patients is significantly enhanced with the addition of long-term maintenance 6-MP (Evidence C).

The patient who continues to have severe symptoms despite optimal doses of oral steroids (40–60 mg of prednisone daily), oral aminosalicylates (4–6 g of sulfasalazine, 4.8 g of mesalamine, or 6.75 g of balsalazide), and topical medications as tolerated, should be hospitalized for further treatment (130–137). Superimposed infection with enteric pathogens and *C. difficile* should be excluded. The mainstay of therapy at this point is an intravenous steroid in a daily dose equivalent to 300 mg of hydrocortisone or 60 mg of methylprednisolone if the patient has received steroids in the prior month, or perhaps intravenous ACTH if the patient has not recently received steroids, as has been suggested by some, but not all series (134–136). There is no benefit to treatment with a much higher daily dose of steroids and it exposes the patient to a higher potential rate of side effects (137). The clinical impression that continuous infusion is preferable to bolus therapy has not been subjected to a controlled trial. Controlled trials of antibiotics, however, have demonstrated no therapeutic benefit from the use of oral vancomycin (138), intravenous metronidazole (133), or ciprofloxacin (139), 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 (130–132).

There is a prevalent tendency to place patients with severe colitis almost routinely on total parenteral nutrition (TPN). Controlled studies on this subject, however, show no benefit from this maneuver (140, 141) as a primary therapy for UC, which may even be detrimental by depriving the colonic enterocytes of the short-chain fatty acids vital to their metabolism and repair (142). However, TPN may be useful as a nutritional adjunct in patients with significant nutritional depletion (143).

There are no studies to demonstrate that an oral aminosalicylate is of clinical benefit in this setting either, so it is generally withheld if the patient is NPO, 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. Since the failure rate of medical therapy in patients hospitalized for severe colitis is approximately 40% (144), these patients should be followed closely in conjunction with a surgeon experienced in the management of patients with inflammatory bowel disease.

Infrequently, cytomegalovirus superinfection may occur in the patient with severe colitis and this possibility should be considered in the patient who is not responding to maximal immunosuppressive therapy. CMV superinfection can be diagnosed with sigmoidoscopic biopsy and viral culture and treatment with gancyclovir may lead to clinical improvement (145, 146).

In patients with either toxic signs (fever, leukocytosis, or worsening symptoms) or megacolon, medications with anticholinergic or narcotic properties should be avoided for fear of worsening colonic atony or dilatation. Patients with severe colitis who do not improve significantly after 7–10 days of maximal medical therapy are unlikely to benefit from prolongation of this medical treatment (132, 134) and should either be referred for surgery (see below) or offered treatment with intravenous cyclosporine. In one placebo-controlled double-blind trial, 82% of patients with steroid-refractory severe colitis, treated with intravenous cyclosporine in a dose of 4 mg per kg per day improved and were able to avoid colectomy in the acute stage (147); another series demonstrated similar efficacy with an intravenous cyclosporine dose of 2 mg/kgday^{-1} (148). Patients with fulminant colitis are treated similarly but decisions regarding surgery *versus* cyclosporine should

be made within a few days of initiating intravenous steroid therapy.

No randomized controlled trials have been performed studying the addition of azathioprine or 6-MP to cyclosporine. Retrospective series with long-term follow-up of up to 5.5 yr (149) indicate a significantly higher long-term success rate when azathioprine or 6-MP were added during the oral cyclosporine phase (148–152), although the ideal dose or time to add 6-MP or azathioprine has not been studied. In the largest reported series the long-term success rate, defined as the avoidance of subsequent courses of intravenous steroids or colectomy, was 76% when 6-MP was added, *versus* 23% in patients in whom 6-MP was not added, during follow-up of 3.6 yr (150).

Significant toxicity may occur with cyclosporine 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 (153). Based on data from a small series, it has been suggested that cyclosporine does not increase the rate of postoperative complications in patients undergoing proctocolectomy (154) while the preoperative use of corticosteroids in patients with inflammatory bowel disease does substantially increase the risk of postoperative infections in patients undergoing elective bowel surgery (155).

Patients with fulminant colitis or toxic megacolon should be treated as above; in addition they should be kept NPO, have a small bowel decompression tube if a small bowel ileus is present, and instructed to rotate frequently into the prone or knee-elbow (156) position to aid in evacuation of the 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 (157) while others take a more watchful stance if no toxic symptoms are present (156). All agree, however, that any clinical, laboratory, or radiologic deterioration on medical therapy mandates immediate colectomy.

RECOMMENDATION 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 the patient with 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 since 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 or possibly low-grade dysplasia in flat mucosa (see in 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. If the patient's condition permits, total proctocolectomy may be the most reliable procedure since a small group (approximately 12%) of patients may have continued hemorrhage from the retained rectal segment if only a subtotal colectomy is performed (158, 159). On the other hand, subtotal colectomy with the preservation of the rectum for a future restorative procedure is an acceptable choice, so long as the small risks of further hemorrhage are appreciated and appropriately monitored.

Perforation, fortunately occurring in only 2–3% of hospitalized UC patients at tertiary referral centers (160), is the most dreaded and most lethal complication of toxic colonic dilation. In a univariate analysis, perforation had a more adverse impact on survival than any other single clinical variable (160). Moreover, it is essential to recognize that perforation can occur without being preceded by megacolon. The surgical procedure of choice in this setting is a subtotal colectomy with rectosigmoid mucous fistula or Hartmann's closure (160).

Other indications for surgery include the patient with severe colitis or toxic megacolon unresponsive to maximal intravenous medical therapy (see above). The patient with less severe but medically intractable symptoms, resulting in physical debility, psychosocial dysfunction, or intolerable steroid side effects, may also be best served by colectomy. However, uncontrolled series suggest that approximately 2/3 of these patients may achieve remission with the use of the immunosuppressive drugs azathioprine or 6-MP (85, 99).

Only rarely is surgery necessary to control the extraintestinal manifestations of UC (161). Likewise, patients with severe, progressive pyoderma gangrenosum, in whom the pyoderma activity parallels the activity of the colitis (162), or with hemolytic anemia refractory to steroids and splenectomy, may benefit from colectomy (163, 164). By contrast, the course of primary sclerosing cholangitis (PSC) is independent of the activity of the colitis and is not affected by colectomy (165).

Whatever the indication for surgery, patients should be informed of the different operations available (*i.e.*, total proctocolectomy with permanent ileostomy *vs* the ileoanal anastamosis procedure) and be aware of the risks and benefits of these operations within different clinical settings.

RECOMMENDATIONS FOR THE MANAGEMENT OF POUCHITIS

Patients who develop the typical symptoms of pouchitis after the ileoanal pouch anastomosis (IPAA) should be treated with a short course of antibiotics (Evidence A). Although controlled data are scarce, metronidazole in a dose of 250 mg

thrice a day or ciprofloxacin 500 mg twice a day are most commonly used (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 extraintestinal manifestations (166). The diagnosis can be made clinically and is associated with characteristic endoscopic and histologic features (167); symptoms do not always correlate with endoscopic and histologic findings (168). Demonstrating the diagnosis with pouchoscopy as opposed to empiric treatment with metronidazole may be a cost-effective strategy (169). Pouchitis occurs in up to 50% of patients after a mean follow-up of 40 months (170) and occurs more frequently in patients with PSC or other preoperative extraintestinal manifestations (171). Only rarely does refractory or recurrent pouchitis occur because of the missed diagnosis of Crohn's disease (172), and pouch excision is required 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. Other patients may have inflammation limited to a short cuff of retained rectal mucosa ("cuffitis") and may respond to topical hydrocortisone or mesalamine (173).

Controlled drug trials for the treatment of pouchitis are very limited (174, 175). Metronidazole 400 mg thrice a day was effective in the treatment of chronic active pouchitis (177), while other controlled trials demonstrated at least similar efficacy to metronidazole with ciprofloxacin 500 mg twice a day (175), or with budesonide enema 2 g daily (176). Numerous uncontrolled trials demonstrate similar efficacy with metronidazole as well as with other antibiotics (170, 178), as well as oral mesalamine, 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 yr following surgery) (179), and in the prevention of pouchitis relapse (180).

RECOMMENDATIONS FOR CANCER SURVEILLANCE

After 8–10 yr of colitis, annual or biannual surveillance colonoscopy with multiple biopsies at regular intervals should be performed (Evidence B). The finding of high-grade dysplasia in flat mucosa, confirmed by expert pathologists' review, is an indication for colectomy, while the finding of low-grade dysplasia 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; the degree of risk is related to the duration of disease and anatomic extent of colitis (181, 182). After 10 yr of universal disease, the cancer risk is in the range of 0.5–1% per year (181–185). Even patients with left-sided colitis reach similar levels of cumulative cancer-risk after 3–4 decades of disease (182, 186, 187); patients with proctitis or proctosigmoiditis are not at increased cancer risk. Although some data suggest a later onset of cancer risk in left-sided than in more extensive colitis (181), this evidence is not sufficiently strong to justify different guidelines for surveillance in the two groups. 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. Some (188, 189), but not all (190, 191) groups have found that patients with UC and PSC have an increased risk of colorectal cancer. 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 (190, 191). In a recent, prospective randomized, placebo-controlled trial, ursodeoxycholic acid in daily divided doses of 13–15 mg/kg, significantly reduced the risk for developing colorectal neoplasia in patients with UC and PSC (192).

UC patients with a family history of colorectal cancer have a five-fold risk of cancer compared with the matched controls-(193). On the other hand, population-based data suggest that there is a reduced relative cancer risk in patients who are taking at least 2 g/day of an aminosalicylate (194, 195), or who visit a physician at least twice a year (194). Similarly, a chemoprotective effect has been suggested in some (196, 197), but not all series (198), for sulfasalazine; an effect that may be confounded in part by its effect on folate metabolism (198).

Compared with noncolitis associated colorectal cancer, 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 (182, 187, 199). Furthermore, colitis-associated colorectal cancer often occurs in a much younger patient population than does colorectal cancer in the general population (182, 184).

Simply stated, the goals of any cancer surveillance program in UC are to prevent cancer and to save lives. There are no randomized studies comparing different surveillance protocols or, for that matter, even surveillance *versus* no surveillance. Nonetheless, at present, the best practical recommendation for patients who are surgical candidates, based upon review of dysplasia surveillance series calls for annual or biannual colonoscopy, avoiding periods of clinical relapse, with multiple biopsies at 10-cm intervals (200–202). Examination every second year would reduce the cost but at the expense of reducing likelihood of early cancer detection (200), especially in patients with longer disease duration since hazard rates increase with time (203, 204). Whatever schedule might be theoretically most advisable, being both frankly informative and programmatically flexible with patients is important to compliance. 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 colorectal cancer (201). Patients with longstanding 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 (205). When colon cancer is identified the need for surgery is obvious; similarly, the colonoscopic biopsy diagnosis of high- or low-grade dysplasia in flat mucosa is often indicative of a concurrent or future cancer and is an absolute indication for colectomy for patients with high-grade dysplasia (206, 207), and should prompt consideration of colectomy in patients with low-grade dysplasia as well.

The finding of low-grade dysplasia in a mass lesion (208) that does not resemble a typical sporadic adenoma (see below), or a stricture that is symptomatic, or is not passable during colonoscopy (209, 210) especially in longstanding disease, are likewise often seen in conjunction with colon cancer and colectomy is advisable. The findings of low-grade dysplasia in flat mucosa may also be an indication for colectomy since an analysis of 10 prospective series of dysplasia surveillance in 1,225 patients found cancer at colectomy immediately after colonoscopic biopsy evidence of low-grade dysplasia in 19% of patients (211), while the 5-yr predictive value of low-grade dysplasia for either cancer or high-grade dysplasia is as high as 54% (212–214).

How to manage the patient with longstanding UC, who is found to have a polypoid mass within a colitic area, that resembles a typical sporadic adenoma, *i.e.*, an adenoma-like mass (215)? Two recent series reported 72 such patients who had a polypoid mass resected in its entirety by colonoscopic polypectomy (216, 217) and who had no dysplasia in the adjacent flat mucosa. Although longer-term data are required, during a mean follow-up of 3.9 yr no dysplasia in flat mucosa or carcinoma was found, suggesting that vigilant follow-up surveillance colonoscopy may suffice for these patients. Polyps with a plaque or carpet-like morphology were excluded from these studies and should continue to be considered dysplasia associated with a lesion or mass (DALM) and requires surgery.

Guidelines for the patient found to have low-grade or high-grade dysplasia 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. However, attempts to repeatedly demonstrate dysplasia on subsequent examinations before recommending colectomy should not be undertaken without the awareness by both patient and physician of the high risk of concomitant or subsequent advanced neoplasia. On the other hand, 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 (205), since these patients may have an elevated risk of subsequent progression to definite dysplasia (218).

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