THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2002 by Am. Coll. of Gastroenterology
Published by Elsevier Science Inc.

Vol. 97, No. 4, 2002
ISSN 0002-9270/02/$22.00
PII S0002-9270(02)03951-5

## CLINICAL REVIEWS

# Microscopic Colitis: A Review

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## ABSTRACT

Microscopic colitis is a relatively common cause of chronic watery diarrhea, often accompanied by abdominal pain and weight loss. The colonic mucosa appears normal grossly, and the diagnosis is made when there is an intraepithelial lymphocytosis and a mixed inflammatory infiltrate in the lamina propria. The two main subtypes, collagenous and lymphocytic colitis, are similar clinically and histologically, distinguished by the presence or absence of a thickened subepithelial collagen band. Many potential pathophysiological mechanisms have been described, although none have been conclusively proved. There is a paucity of randomized treatment trials in these patients, although a rational approach to therapy often leads to satisfactory control of symptoms. (Am J Gastroenterol 2002;97:794–802. © 2002 by Am. Coll. of Gastroenterology)

## BACKGROUND

The term *microscopic colitis* was originally used in 1980 to describe patients with chronic watery diarrhea and normal findings on sigmoidoscopy and barium enema but who had microscopic inflammation on colon biopsies (1). The authors believed that the "mild inflammatory reaction" was an incidental finding (1). Collagenous colitis, first described in 1976, is a closely related condition with similar clinical and histological features, but with the additional finding of a thickened subepithelial collagen band (2). It is unclear whether these two conditions represent separate diseases or rather are different phenotypes of the same disease. Rereview of the histology from some of the early cases of "microscopic colitis" showed that many of the patients actually had collagenous colitis (3, 4). There are numerous reports of patients in whom one diagnosis was changed to the other over time (3, 5–9) or in whom there was a "mixed" histological picture (10–12), although this latter observation may simply represent the patchy distribution of collagen in some patients with collagenous colitis (13). Because the colonic mucosa in collagenous colitis appears normal or nearly normal endoscopically, it can also be considered a form of microscopic colitis. Thus, the current nomenclature has *microscopic colitis* as an umbrella term with two major subsets: collagenous colitis, with a thickened subepithelial collagen band, and lymphocytic colitis, without collagen thickening (4, 14).

## EPIDEMIOLOGY

Microscopic colitis accounts for 4–13% of patients investigated for chronic diarrhea (15–19). In Europe, collagenous colitis has a yearly incidence of 0.6–2.3/100,000 and a prevalence of 10–15.7/100,000, and lymphocytic colitis has an incidence of 3.1/100,000 and a prevalence of 14.4/100,000 (19–21). The incidence of collagenous colitis and lymphocytic colitis in elderly females may be as high as 15/100,000 (20) and 20/100,000 (19), respectively. No epidemiological data exist from North America.

In tertiary referral centers, the number of cases of lymphocytic colitis is similar to that of collagenous colitis (15) (D. S. Pardi, unpublished data). A female predominance has been described, particularly for collagenous colitis, with female to male ratios as high as 20:1 (8, 22–25). However, a review of all published cases of lymphocytic and collagenous colitis through 1994 showed no significant gender difference for either disease (26). Microscopic colitis typically presents in the 6th to 7th decades (11, 23–26), although a wide age range has been reported, including pediatric cases (27–31). There are reports of familial occurrence of microscopic colitis (32) and also of microscopic colitis and inflammatory bowel disease (IBD) (32–37), but no studies have been performed to determine whether these are chance associations or whether a true familial predisposition exists.

No association between microscopic colitis and colon cancer has been discovered (38), but long term studies are needed to confirm this observation. Several cases of lung cancer have been reported in patients with collagenous colitis (24, 38, 39), perhaps related to cigarette smoking, which is more common in collagenous than lymphocytic colitis (11, 40).

## CLINICAL FEATURES

Microscopic colitis is characterized by chronic or intermittent watery diarrhea, which can include nocturnal stools. The diarrhea can range from relatively mild and self-limited to severe and medically refractory, requiring surgery. Quality of life is affected in proportion to the degree of diarrhea and incontinence (41). Many patients will have abdominal pain or weight loss. The weight loss is typically mild but can exceed 40 lb in rare cases (5, 24, 42). Dehydration is unusual. Fecal leukocytes may be present (43), and mild

steatorrhea (42, 44) and a protein-losing enteropathy (45) have been reported. Significant fever, vomiting, or hematochezia should raise the possibility of an alternate diagnosis.

Arthralgias and various autoimmune conditions (*e.g.,* thyroid dysfunction, rheumatoid arthritis) are often seen in patients with microscopic colitis (8, 23, 24, 26, 42). In addition, an elevated erythrocyte sedimentation rate (9, 33, 34, 44) and a positive antinuclear antibody or other autoimmune markers (5, 8, 32, 44, 46) are seen in some patients. Endoscopic and radiological evaluation of the colon typically demonstrates normal findings or mild nonspecific changes such as erythema or edema (6, 24). Colonic ulceration is uncommon and, when seen, is likely related to use of nonsteroidal anti-inflammatory drugs (NSAIDs) (L. J. Burgart, unpublished data).

Of particular interest is the apparent association between microscopic colitis and celiac sprue. Among patients with definite celiac sprue, approximately one third have histological changes in the colonic mucosa consistent with microscopic colitis (47, 48). Thus, microscopic colitis is common in patients with celiac disease, and this diagnosis should be considered in patients who have continued diarrhea despite a gluten-free diet (49, 50).

The prevalence of small bowel spruelike changes in patients with microscopic colitis ranges from 2% to 40% (5, 8, 10, 24, 26, 33, 46, 51), although studies with the largest cohorts report the lowest rates (2–8%) (24, 26). Collagenous sprue (10, 52, 53) and collagenous gastroduodenitis (54) have also been described in microscopic colitis. Antigliadin and antiendomysial antibodies are found in 5–17% and 2–4% of patients with microscopic colitis, respectively (46, 51). These results do not significantly differ from those of controls (12% and 0%), and the titers in microscopic colitis are lower than those in celiac patients (51). Finally, as discussed below, human leukocyte antigen (HLA) typing in microscopic colitis was very similar to that seen in celiac sprue in one study (51) but not others. All of these data suggest that celiac sprue is not common in patients with microscopic colitis. However, it would be reasonable to consider screening antibody tests in patients with microscopic colitis as part of their initial evaluation. Furthermore, the association with celiac sprue should be reconsidered in treatment-refractory microscopic colitis patients. In this group, small bowel biopsies would be appropriate to more definitively assess for sprue.

The natural history of microscopic colitis is variable. Complete symptomatic remission after 3–4 yr of follow-up ranges from 60% to 93% in lymphocytic colitis (41, 55) and 2–92% in collagenous colitis (24, 55). Baert *et al.* (11) reported remission in 59% of lymphocytic colitis and 34% of collagenous colitis patients after 6 months of follow-up, with a further 25% and 40%, respectively, showing "significant improvement." Finally, Goff *et al.* (23) reported spontaneous remission in 15% and treatment-induced remission in 48% of patients with collagenous colitis after 3.5 yr of follow-up. Of the remaining 37% with ongoing disease, only 60% (22% of the entire cohort) required prolonged therapy. Spontaneous remission may be more likely in those with a shorter duration of diarrhea (55).

Several instances of patients with microscopic colitis later developing IBD have been reported (35, 56, 57), as well as patients with established IBD developing collagenous colitis (24, 57). Whether these few cases represent a true association between microscopic colitis and IBD or merely reflect chance associations or misdiagnoses remains unclear. The natural history of microscopic colitis may include an initial episode of active colitis (58), leading to some potential for misdiagnosis. If there is a risk of developing overt IBD in patients with microscopic colitis, it appears to be small.

## HISTOPATHOLOGY

The most distinctive histological feature of microscopic colitis is an intraepithelial lymphocytosis (Fig. 1), which is more striking in the surface epithelium than in the crypts (13). Patients with lymphocytic colitis have more than 10 lymphocytes for every 100 epithelial cells (often $>20$), whereas normals typically have fewer than five (11, 13). In addition, there is a mixed inflammatory infiltrate in the lamina propria (Fig. 1) with lymphocytes and plasma cells predominating over eosinophils and neutrophils (13, 22, 34, 59). It is important to note that neutrophils, though not dominating the histological picture, are seen in microscopic colitis. Even the presence of focal active cryptitis does not rule out microscopic colitis if other histological and clinical features support the diagnosis. One recent report (60) noted active cryptitis in 41% of patients with lymphocytic colitis and 29% with collagenous colitis. Some authors have mentioned the presence of mast cells in the inflammatory infiltrate (43, 61, 62) or embedded within the collagen band (63), although others showed no difference in the numbers of mast cells relative to controls (64). These inflammatory changes are often accompanied by focal or diffuse surface epithelial damage (loss of Goblet cells and atrophic, cuboidal, or thinned epithelial cells with degenerative features such as cytoplasmic vacuoles, nuclear irregularity, pyknosis, and karyorrhexis) (13, 34). Detachment of the epithelium may also be seen, despite the normal appearance of the mucosa grossly.

In collagenous colitis, the subepithelial collagen band is abnormally thickened (Fig. 2), ranging from 7 to 80 $\mu$m *versus* 5–7 $\mu$m in normals (11, 22, 34, 62). However, there are qualitative as well as quantitative differences in the collagen band, including entrapped red blood cells and inflammatory cells, and a ragged inferior edge, so that simply measuring the degree of thickening is neither adequate nor necessary for the diagnosis of collagenous colitis (59). The basement membrane appears to be normal (63, 64), although the abnormal collagen band may be intimately associated with it (62, 64).

The reliability of left-sided colon biopsies (*i.e.,* flexible

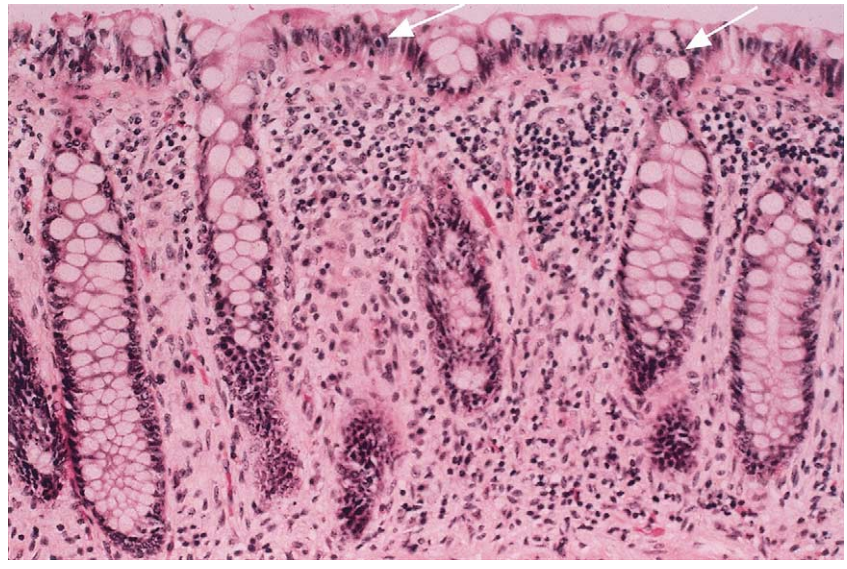

**Figure 1.** Lymphocytic colitis. Note the intraepithelial lymphocytosis (arrows) and mixed inflammatory infiltrate in the lamina propria. In distinction to ulcerative colitis or Crohn's colitis, the crypt architecture is normal. Hematoxylin and eosin, ×100.

sigmoidoscopy) for making the diagnosis of microscopic colitis is somewhat controversial. Some studies have suggested that collagen thickening (34) and intraepithelial lymphocytosis (65) become less evident from the cecum to the rectum, and that rectosigmoid biopsies can miss the diagnosis in 11–40% (7, 16, 23). Others report that the transverse colon provides the most diagnostic biopsies (66). Still others report that sigmoid biopsies are very reliable, missing 0–5% (26, 43, 67). Despite these mixed results, it is generally accepted that biopsies from the descending colon should be reasonably accurate and that flexible sigmoidoscopy is sufficient to make the diagnosis of microscopic colitis in most cases. If left-sided colon biopsies are nondiagnostic and clinical suspicion remains high, a colonoscopy with proximal biopsies can be considered.

The histological findings of microscopic colitis are not specific. Lymphocytic colitis–like changes have been described in subjects without diarrhea (41, 68), in HIV-positive men with chronic watery diarrhea (69), and in Crohn's disease (70). Changes suggesting collagenous colitis have been described in patients with *Clostridium difficile* infection, Crohn's disease, colon cancer, carcinoid diarrhea, jejunoileal bypass, hyperplastic polyps, and constipation and in "normal" subjects without diarrhea (23, 34, 39, 63, 70–75), although the collagen band tends to be less extensive and less pronounced in these settings (75). Another potential

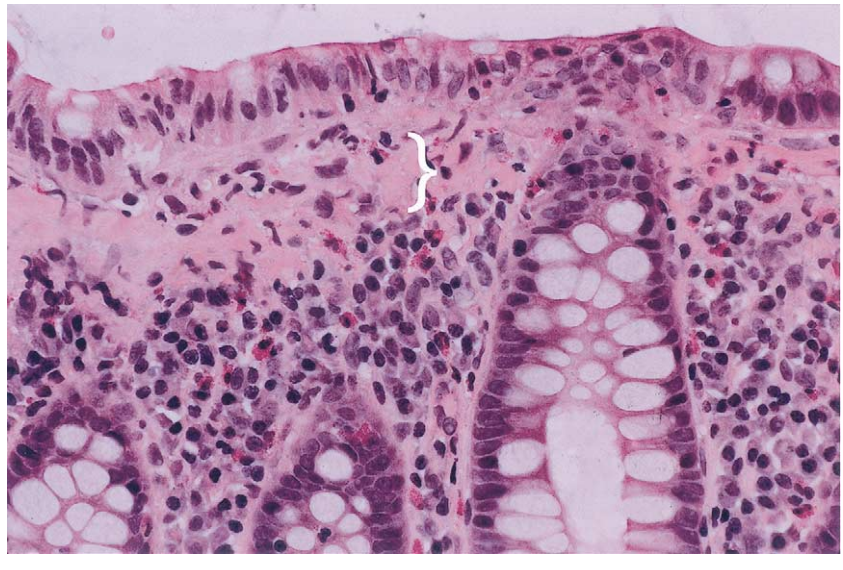

**Figure 2.** Collagenous colitis. In addition to the inflammatory infiltrate, note the thickened subepithelial collagen band (bracket). Hematoxylin and eosin, ×400.

diagnostic pitfall is tangential sectioning, which can cause a normal basement membrane to seem thickened, leading to a false diagnosis of collagenous colitis (59). The absence of entrapped blood cells and the absence of an inflammatory component should help avoid a false positive diagnosis.

## PATHOPHYSIOLOGY

Data on the pathophysiology of microscopic colitis typically come from small studies that often give conflicting results. Several hypotheses have been raised, ranging from immune dysregulation/autoimmunity to drug effect to infection. It may be that the clinicopathological term *microscopic colitis* encompasses several different diseases with similar histological endpoints.

### *HLA Associations*

One study of HLA haplotypes showed an increase in A1 and DRW53 in lymphocytic colitis and a decrease in DQ2 in collagenous colitis (8). However, this same group later reported increased A1 and decreased A3 in lymphocytic colitis and no HLA associations in collagenous colitis (76). Fine and colleagues (51) showed an increase in DQ2 and DQ1,3 in lymphocytic colitis and collagenous colitis, similar to the pattern seen in celiac sprue. Others have found no HLA associations (5). Abnormal HLA DR expression on colonic epithelial cells has been described, suggesting that major histocompatibility complex–restricted immune activation could be involved (65, 77). Given the discrepant findings, however, it is difficult to draw conclusions about HLA associations in microscopic colitis.

### *Abnormal Reaction to Luminal Antigen*

This mechanism is suggested by several lines of evidence. First, lymphocytic colitis is seen in patients with celiac sprue, and lymphocytic colitis–like changes can be induced in patients with sprue by a gluten enema (78). Second, symptoms and histological changes of microscopic colitis resolve with a diverting ileostomy (12, 79, 80). Finally, a lymphocytic colitis–like disorder in dogs resolves with a hypoallergenic diet (81). Characterization of the lymphocytic response has not been definitive, and has not provided any clues as to the nature of the offending antigen (10, 65, 77, 82).

### *Autoimmunity/Hormonal Influence*

If microscopic colitis represents an abnormal reaction to a luminal antigen, there might be an autoimmune element to the response. The association with various autoimmune conditions and markers supports an autoimmune process (5, 8, 32, 44, 46, 83, 84). Associated conditions include thyroid disease, diabetes, sprue, rheumatoid arthritis, and a variety of others. Furthermore, like other autoimmune diseases, microscopic colitis appears to be more common in females. The female predominance and the report of disease resolution with pregnancy (24) raise the possibility of hormonal influence, but there are no supporting data for such a mechanism.

### *Abnormalities in Fluid Homeostasis*

Several small studies have demonstrated abnormal fluid and electrolyte absorption or secretion in microscopic colitis (44, 85–88), whereas others have reported normal absorption (33). Elevations in luminal nitric oxide levels, plasma nitrate/nitrite levels (89), and inducible nitric oxide synthase (90) have been described in collagenous colitis. Others have shown that $N^G$-monomethyl-L-arginine, an inhibitor of nitric oxide synthase, decreases secretion (91), further suggesting a role for nitric oxide. Increased intraluminal and mucosal prostaglandin levels (75, 87, 92) have been demonstrated in microscopic colitis, and one patient with increased mast cells responded to a histamine-1 blocker (61). These reports suggest other possible mediators of secretion.

### *Bile Acid Malabsorption*

Several series have investigated the possibility of bile acid malabsorption (BAM) in microscopic colitis. This hypothesis is plausible, because patients with known BAM (*e.g.*, ileal resection) develop diarrhea. Furthermore, infusion of bile acids into the animal colon induces epithelial damage and colitis (93, 94). Ileal villous atrophy, inflammation, and collagen deposition have been described in microscopic colitis, suggesting a possible mechanism for BAM (26, 95–97). However, reports using a bile acid breath test showed little or no evidence for BAM in a small number of patients with microscopic colitis (22, 33, 44). Others have used a direct test of BAM (selenium homocholyltaurine retention) and found malabsorption in 12–67% (24, 98–100). Those with abnormal selenium homocholyltaurine tests often respond to cholestyramine, but up to 67% of those with normal tests also respond (98), casting some doubt on the validity of this test or the importance of demonstrating BAM for directing therapy.

### *Infection*

Microscopic colitis shares many features with "Brainerd diarrhea," an acute watery diarrhea associated with mucosal lymphocytosis without crypt distortion, epithelial destruction, or collagen deposition that can last for years (101, 102). Epidemiological evidence suggests an infectious etiology for Brainerd diarrhea. These similarities with Brainerd diarrhea raise the possibility of an infectious etiology for microscopic colitis as well. This is supported by the finding of acute inflammation on biopsy or a history suggesting an acute infection in many patients with microscopic colitis (3, 9, 24, 33). Moreover, HLA B27/B2 microglobulin transgenic mice develop a lymphocytic colitis–like process, but only if exposed to colonic bacteria (103). Finally, a subset of microscopic colitis patients does respond to antibiotic therapy (24, 26, 104). However, no causative organism has been identified for either Brainerd diarrhea or microscopic colitis, and the limited number of reported family clusters argues against a contagious organism.

### *Medication Side Effect*

An association between microscopic colitis and the use of NSAIDs has been suggested by some studies (23, 105, 106) but not by others (11, 12). Patients with microscopic colitis often have arthralgias, and thus NSAID use may simply be a marker for arthralgias. On the other hand, NSAIDs can cause colonic inflammation and exacerbate IBD (107). Furthermore, some patients with microscopic colitis improve with discontinuation of NSAIDs (23, 105, 106). Therefore, NSAID use should be discouraged in these patients.

Several other drugs have been implicated as possible causes of microscopic colitis, including histamine-2 receptor blockers (108, 109), carbamazepine (31), simvastatin (110), ticlopidine (11), flutamide (11), and others (77). However, the number of cases is small, and a chance association cannot be excluded.

### *Abnormal Collagen Metabolism*

Collagen typing has shown that the thickened subepithelial band is composed primarily of type VI collagen (83, 111). However, others have reported the presence of types I and III collagen and procollagen III and the absence of type IV collagen in collagenous colitis, although normal controls had the exact opposite findings (61). Finally, others have shown the presence of types I, III, *and* VI collagen (112). The presence of type III collagen would suggest a reparative process or "scar" in response to chronic inflammation, whereas type VI suggests a primary abnormality of collagen synthesis (113). Transmission electron microscopy has shown "the usual appearance of granulation tissue" (34), supporting the former hypothesis. There is no evidence of increased fibroblast growth factor levels relative to controls (114), and the absence of an increase in messenger RNA for collagen suggests that the abnormal collagen accumulation is due to decreased degradation rather than increased synthesis (111).

### *Dysfunction of the Pericryptal Fibroblast Sheath*

Pericryptal fibroblasts are responsible for the normal production and deposition of collagen in the basement membrane and are involved in the maintenance of normal structure and function of the colonic mucosa (62, 74, 115). In collagenous colitis, the sheath is separated from the epithelium, and the fibroblasts are activated with increased synthetic activity (62, 115). In addition, these cells assume the characteristics of myofibroblasts, the proliferating cells often encountered in granulation tissue (64, 115). An increase in the number and complexity of myofibroblasts (62, 116), sometimes "entrapped" within the collagen layer (12, 64, 74), has been described. It has been hypothesized that, as these altered pericryptal fibroblasts migrate up the crypt and mature, they produce excessive collagen, which is deposited under the basement membrane giving the histological appearance of a subepithelial collagen band (115, 117).

It is likely that any abnormality of the fibroblast sheath is a secondary phenomenon, as it would not explain the inflammatory infiltrate and is not present in lymphocytic colitis. Furthermore, the severity of diarrhea in collagenous colitis is proportional to the degree of inflammation, and not to the thickness of the collagen band (42, 118). Finally, changes in the pericryptal fibroblast structure and function identical to that seen in collagenous colitis were also found in the chronic "fibrotic stage" of ulcerative colitis (62).

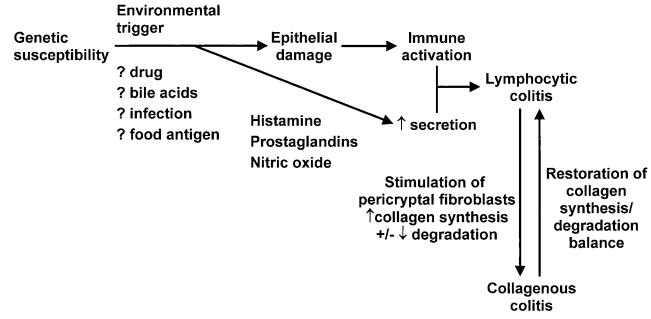


**Figure 3.** Possible pathophysiological mechanisms in microscopic colitis.

The various potential pathophysiological mechanisms discussed here are outlined in Figure 3. However, given the small number of patients studied in many of these reports, as well as the often contradictory findings, it is difficult to draw firm conclusions regarding the underlying pathophysiology of lymphocytic or collagenous colitis.

## TREATMENT

NSAIDs and agents that might exacerbate diarrhea (*e.g.*, caffeine, alcohol, dairy products) should be discontinued. Nonspecific antidiarrheal therapy, such as loperamide or diphenoxylate/atropine can be very effective and well tolerated (22, 24, 104), and is often the first therapy prescribed. If these agents are unsuccessful, bismuth subsalicylate at a dose of two or three tablets (262 mg each) three or four times a day (119, 120) is beneficial in many patients. Fine and colleagues reported that most patients treated with bismuth had complete resolution of diarrhea; however, other investigators (104) have reported that most patients experience only a partial response.

If diarrhea does not respond to bismuth, the next therapeutic intervention is usually mesalamine or sulfasalazine. These drugs were reported to be successful in a majority of patients in one review (26), but two large retrospective studies (24, 104) have reported benefit in fewer than half of the patients treated. Cholestyramine may be more effective (24, 104), although many do not tolerate the medication because of its texture.

Patients refractory to mesalamine or sulfasalazine may respond to corticosteroids (24, 104), but before embarking on corticosteroid therapy, the diagnosis should be re-evaluated and alternative diagnoses, such as coexistent celiac sprue or hyperthyroidism, should be excluded. Budesonide is a synthetic steroid with low systemic bioavailability and

**Table 1.** Medications Used to Treat Microscopic Colitis

| Medication | Dose |
|---|---|
| Loperamide | 2–16 mg/day |
| Diphenoxylate/atropine | 1–8 tabs/day |
| Cholestyramine | 4 g 1–4 times a day |
| Bismuth subsalicylate | 2–3 tabs *t.i.d.* to *q.i.d.* |
| Steroids (*e.g.*, prednisone) | 10–60 mg/day |
| Sulfasalazine | 2–4 g/day |
| Asacol | 2.4–4.8 g/day |
| Pentasa | 2–4 g/day |
| Azathioprine | 2–2.5 mg/kg/day |
| 6-Mercaptopurine | 1–1.5 mg/kg/day |

less risk of steroid side effects that has been used with some success in microscopic colitis (121, 122). Anecdotal experience suggests that the relapse rate after steroid discontinuation is high, and that many patients who require steroids become steroid dependent. For steroid refractory or steroid dependent patients, immune modifiers such as azathioprine or 6-mercaptopurine can be used, although side effects are frequent and may be treatment limiting in some patients (104, 123).

Other treatments reported to be of potential benefit include octreotide (104, 124) and other immune modifiers such as methotrexate or cyclosporin (24, 104). Rarely, surgery is necessary. This may include an ileostomy with or without a colectomy (12, 79, 104, 123) or an ileal pouch anal anastomosis (80, 125). Antibiotics may be beneficial in some patients, although diarrhea tends to recur when the antibiotic is stopped (23). The doses of medications used to treat microscopic colitis are outlined in Table 1, and response rates from two large cohorts are listed in Table 2. A treatment algorithm is presented in Figure 4.

## CLINICAL COURSE

Most patients with microscopic colitis have chronic watery diarrhea, although the course can be waxing and waning, and spontaneous resolution has been reported. Most patients will respond to the treatment algorithm suggested above, but it is not clear how long to continue therapy. For example, patients treated with bismuth subsalicylate for 8 wk have entered remissions lasting more than 2 yr (119). Thus, when an agent is found to control the diarrhea, it should be continued for 8–12 wk, after which an attempt at tapering can be considered. For those patients with recurrent symptoms, longer maintenance therapy can be used.

**Table 2.** Response to Therapy in Microscopic Colitis

| | Pardi *et al.* (104), Lymphocytic Colitis (N = 188) | Bohr *et al.* (24), Collagenous Colitis (N = 163) |
|---|---|---|
| Antidiarrheals | 72 | 71 |
| Bismuth | 69 | |
| Sulfasalazine | 36 | 34 |
| Mesalamine | 41 | 50 |
| All 5-ASAs | 37 | 35 |
| Cholestyramine | 59 | 59 |
| Steroids | 70 | 82 |
| AZA/6-MP | 28 | |

Data are percentages and include complete and partial responders. Response rates represent clinical experience and are not the result of controlled trials. Therefore, the results for different drugs are not directly comparable. ASAs = aminosalicylates; AZA = azathioprine; 6-MP = 6-mercaptopurine.

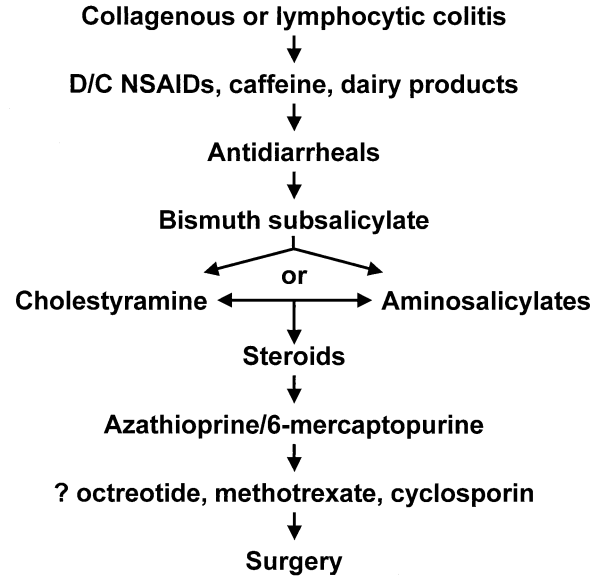


**Figure 4.** A treatment algorithm for microscopic colitis. D/C = discontinue.

## SUMMARY

Microscopic colitis is a relatively common cause of chronic diarrhea. Colonic biopsies are required to make the diagnosis, and should be performed in all patients undergoing flexible sigmoidoscopy or colonoscopy for unexplained diarrhea. The two subtypes, collagenous and lymphocytic colitis, are similar histologically and clinically, and may represent variants of the same disease. Although there are few controlled treatment trials, the approach outlined here often gives satisfactory control of diarrhea in these patients.

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*Received June 11, 2001; accepted Oct. 12, 2001.*

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