Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management

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INTRODUCTION

Microscopic colitis is a chronic inflammatory disease of the colon that is characterized by chronic, watery, non-bloody diarrhea. It typically occurs in middle-aged patients and has a female preponderance. The colon appears typically normal or almost normal on colonoscopy in patients with microscopic colitis. The diagnosis is established by biopsy of the colonic mucosa demonstrating characteristic histologic changes. Microscopic colitis, first described in 1980 [1], has two main histologic subtypes, lymphocytic colitis, more specifically defined in 1989 [2], and collagenous colitis.

This topic will review the clinical manifestations, diagnosis, and management of microscopic colitis. Our recommendations are largely consistent with the American Gastroenterological Association Institute guidelines on the management of microscopic colitis [3] and the European guidelines on microscopic colitis [4]. The clinical manifestations, diagnosis, and management of the classic inflammatory bowel disease including ulcerative colitis and Crohn disease are discussed in detail, separately. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults" and "Medical management of low-risk adult patients with mild to moderate ulcerative colitis" and "Management of the hospitalized adult patient with severe ulcerative colitis" and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults" and "Overview of the medical management of mild (low risk) Crohn disease in adults" and "Medical management of moderate to severe Crohn disease in adults".)

EPIDEMIOLOGY

Incidence and prevalence — The estimated incidence of collagenous colitis and lymphocytic colitis are 2.0 to 10.8 and 2.3 to 16 per 100,000 per year, respectively, with higher incidence in northern Europe and northern parts of North America [5-12]. The increasing incidence has reached a plateau [13,14]. The median age at diagnosis of microscopic colitis is approximately 65 years [15]. Approximately 25 percent of patients with microscopic colitis are diagnosed before the age of 45 years. Although microscopic colitis has been reported in children, it is rare [16-18]. Microscopic colitis has a higher incidence in women [6-10,19-32], in the range of 52 to 86 percent [4]. Female preponderance appears to be more pronounced in collagenous as compared with lymphocytic colitis (female-to-male incidence rate ratios, 3.0 and 1.9, respectively) [13].

Associated conditions — Microscopic colitis has also been associated with several other diseases with autoimmune background (eg, autoimmune thyroiditis, type 1 diabetes mellitus, and nonerosive, oligoarticular arthritis) [33-38]. In one report, concomitant autoimmune diseases were more common in patients with collagenous colitis as compared with lymphocytic colitis (53 versus 26 percent) [35]. Whether these associations reflect an autoimmune pathogenesis of microscopic colitis is unclear.

The HLA-DR3-DQ2 haplotype that predisposes to celiac disease is also associated with microscopic colitis [39,40]. Microscopic colitis demonstrates a T helper type 1 mucosal cytokine response pattern with upregulated interferon gamma and interleukin-15, tumor necrosis factor, and nitric oxide synthase, a pattern similar to that in celiac disease [41]. While patients with celiac disease have an increased risk of microscopic colitis, limited data suggest that the prevalence of celiac disease is relatively low among patients with microscopic colitis [42-51]. The prevalence of celiac disease-like changes in the small bowel of patients with microscopic colitis ranges from 2 to 9 percent. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children".)

In rare cases, concurrent microscopic colitis has been reported in patients with inflammatory bowel disease, especially with ulcerative colitis, or vice versa [52]. There are also case reports of concurrent lymphocytic and collagenous gastritis in patients with microscopic colitis [53]. (See "Endoscopic diagnosis of inflammatory bowel disease in adults", section on 'Differentiating ulcerative colitis from Crohn disease' and "Endoscopic diagnosis of inflammatory bowel disease in adults".)

ETIOLOGY AND RISK FACTORS

Medications — Nonsteroidal anti-inflammatory drugs (NSAIDs) have been implicated as being causative or triggering flares of microscopic colitis [54-57]. Several other drugs have also been implicated as potential causes of microscopic colitis, including proton pump inhibitors (PPIs), specifically lansoprazole, statins, selective serotonin reuptake inhibitors and other drugs, (eg, pembrolizumab) [58,59]. Concomitant use of PPIs and NSAIDs may increase the risk even further [60] (table 1). However, convincing pathophysiologic evidence is still lacking, and most of the drugs that have been associated with microscopic colitis are also known to be associated with the development of chronic diarrhea as a side effect [54,60-72].

Smoking — Smoking may play a role in the development of microscopic colitis and the clinical outcome [73-75]. In a case-control study that included 340 patients with microscopic colitis, cigarette smoking (past or present) was associated with a significantly increased risk of microscopic colitis (odds ratio 2.1, 95% CI 1.6-2.9) [76-80]. On average, smokers also develop microscopic colitis more than 10 years earlier than non-smokers [77,78].

PATHOPHYSIOLOGY

The pathogenesis of microscopic colitis is unclear; however, it is likely to be multifactorial, involving mucosal immune responses to luminal factors in a genetically predisposed individual [21-26]. Although lymphocytic and collagenous colitis have a similar inflammatory cell response, it is uncertain whether they are related colitides [19,20,30,81].

Pathogenesis of microscopic colitis

- **Genetic susceptibility** – It is unclear to what extent a genetic predisposition is associated with the development of microscopic colitis. However, familial cases have been described [27-29]. Interestingly, different members of the same family developed either lymphocytic or collagenous colitis, supporting a similar underlying pathophysiology. Studies have also demonstrated an association between microscopic colitis and HLA-DQ2 or DQ1,3, as well as a higher frequency of HLA-DR3DQ2 haplotype and tumor necrosis factor 2 allele carriage in microscopic colitis, as compared with controls [39,40,82].

- **Abnormal collagen metabolism** − Abnormal collagen metabolism may be responsible for the thick collagen band in collagenous colitis. The prominent subepithelial matrix deposition has been attributed to increased expression of the main fibrogenic genes, procollagen I and metalloproteinase inhibitor (TIMP-1), by myofibroblastic cells and

inadequate fibrinolysis [83-86]. Patients with collagenous colitis also have increased expression of transforming growth factor (TGF) beta-1, which has been associated with the accumulation of collagen in tissues [86]. TGF beta-1 and vascular endothelial growth factor may influence the balance of local fibrogenesis and fibrinolysis, leading to a net accumulation of immature subepithelial matrix [87,88]. The modification of collagen metabolism has also been explained by the expression of endogenous histamine, prostaglandins, and/or nitric oxide (NO). Increased transcriptional activity of nuclear factor kappa B causes upregulation of inducible NO synthase activity and, subsequently, increased production of NO in the colonic epithelium, which might be a direct cause of secretory diarrhea in patients with collagenous colitis [89].

- **Altered epithelial barrier function** − An alternative hypothesis is that a defect in epithelial barrier function and luminal factors may lead to an increased transmucosal permeability of antigens and bacteria, leading to immune dysregulation and intestinal inflammation seen in microscopic colitis [90].

  Synchronous collagenous and pseudomembranous colitis have also been described in some patients, suggesting a possible etiologic role for *C. difficile* [91-93]. Infection with *Yersinia* has also been suggested as an inciting event for collagenous colitis [94]. Furthermore, resolution of collagenous colitis has been described following treatment for *Helicobacter pylori*, but the association remains unclear [95]. A role for bacteria in the pathogenesis of this disorder is also supported by the observation that symptoms and histology can improve in patients with lymphocytic colitis after treatment with bismuth. However, this hypothesis is not supported by the finding that local immunosuppressive treatment with budesonide is very efficient in microscopic colitis.

Mechanism of diarrhea — Diarrhea in microscopic colitis is likely caused by mucosal inflammation [20,30,96]. The severity of diarrhea correlates with the inflammatory changes in the lamina propria and not with collagen band thickening. Colonic perfusion studies have demonstrated that secretory diarrhea in microscopic colitis results from decreased absorption of sodium chloride, accompanied by a component of active chloride secretion [20,97]. The subepithelial collagenous band plausibly may act as a diffusion barrier. Down-regulation of tight junction molecules, but not epithelial apoptosis, is a structural correlate of barrier dysfunction that contributes to diarrhea by a leak flux mechanism [97]. The observation that fasting can reduce stool volume in microscopic colitis suggests that the diarrhea in microscopic colitis also has an osmotic component [98].

Concurrent bile acid malabsorption frequently coexists in patients with collagenous colitis. The cause of bile acid malabsorption in patients with microscopic colitis is unclear since

morphologic alterations in the terminal ileum are usually absent [15,99].

CLINICAL MANIFESTATIONS

Clinical presentation — Microscopic colitis is characterized by chronic, non-bloody, watery diarrhea [15,19,21,100]. The onset of diarrhea is often insidious, but sudden onset was reported in approximately 40 percent of patients [15]. Patients with microscopic colitis usually have between four and nine watery stools per day, but in rare cases, bowel movements can exceed 15 or up to 2 liters per day [15,101]. Patients may have associated fecal urgency (70 percent), incontinence (40 percent), and nocturnal episodes (50 percent). Abdominal pain occurs in up to 50 percent of patients with active microscopic colitis (≥3 stools or ≥1 watery stool per day) [102,103]. Patients may have associated weight loss due to fluid loss or decreased oral intake. Extraintestinal symptoms, such as arthralgia, arthritis, or uveitis can occur. The quality of life is reduced [104]. (See 'Associated conditions' above.)

Collagenous colitis seems to be a more severe type of bowel inflammation and lymphocytic colitis tends to occur earlier in life [33].

Laboratory findings — Laboratory findings in microscopic colitis are generally nonspecific. Mild anemia, elevated erythrocyte sedimentation rate, and autoantibodies are found in approximately one-half of patients [15,36,105-107]. These autoantibodies include rheumatoid factor, antinuclear and antimitochondrial antibodies, antineutrophilic cytoplasmic antibodies, anti-*Saccharomyces cerevisiae* antibodies, and antithyroid peroxidase antibodies. In rare cases, patients may have a protein-losing enteropathy and associated hypoalbuminemia. (See "Protein-losing gastroenteropathy", section on 'Clinical features'.)

Increased levels of the inflammatory markers, eosinophil protein X, myeloperoxidase, and tryptase, have been detected in stool from patients with collagenous colitis [108]. Studies that have evaluated fecal calprotectin excretion as a marker of active microscopic colitis have been conflicting [109,110]. Additional studies are needed to validate these findings and to clarify the role of fecal markers in the diagnosis and management of microscopic colitis.

DIAGNOSTIC APPROACH

Diagnosis — Microscopic colitis should be suspected in patients with chronic diarrhea, particularly in middle-aged and older adults. The diagnosis of microscopic colitis is established by biopsy of the colonic mucosa demonstrating characteristic histologic changes. (See 'Endoscopy and biopsy' below.)

Evaluation — Evaluation of a patient with suspected microscopic colitis serves to exclude other causes of diarrhea and establish the diagnosis of microscopic colitis [111,112].

Laboratory studies — Stool studies should include stool *Clostridioides difficile* toxin, routine stool cultures (*Salmonella, Shigella, Campylobacter, Yersinia*), and specific testing for *Escherichia coli O157:H7*. Microscopy for ova and parasites (three samples) and a *Giardia* stool antigen test should also be performed, particularly if the patient has risk factors such as recent travel to endemic areas. We perform celiac serologies to exclude celiac sprue. In addition, a complete blood count, electrolytes, and albumin should be obtained as patients with microscopic colitis may have mild anemia and, in rare cases, a protein-losing enteropathy. The use of calprotectin to exclude or monitor microscopic colitis is not recommended [4,113,114]. (See 'Laboratory findings' above.)

Endoscopy and biopsy — Endoscopic evaluation of the colon with mucosal biopsies is necessary to establish the diagnosis of microscopic colitis [33].

- **Choice of procedure** – We perform colonoscopy with separate sampling at least of the right and left colon. Colonoscopy is generally safe in patients with microscopic colitis. Perforations have been reported in patients with significant collagen deposits ("fractured colon"), but are rare [115-117]. The rationale for performing colonoscopy rather than a more limited evaluation of the left colon with flexible sigmoidoscopy is that microscopic colitis can be patchy. In addition, the severity of histologic changes declines from the proximal to the distal colon. However, flexible sigmoidoscopy (rectum is not sufficient), will diagnose more than 90 percent of microscopic colitis [118-120].

  In small case series, chromoendoscopy using indigo carmine has been used to highlight mucosal alterations that correspond to the histological distribution of microscopic colitis [121]. However, larger studies are needed before routine use of chromoendoscopy can be recommended for the diagnosis of microscopic colitis. Confocal laser endomicroscopy is a promising endoscopic tool but its specific role in diagnosing microscopic colitis has to be determined [122].

- **Endoscopic findings** – The endoscopic appearance of the colon is typically normal. Macroscopic features can include slight edema, erythema, friability, exudative lesions, and scars [33,123]. However, there is significant inter-observer variability among endoscopists [124,125].

- **Histology** – The inflammatory cell response is similar in lymphocytic and collagenous colitis, consisting mainly of mononuclear infiltrates, with few neutrophils and eosinophils

in the lamina propria (picture 1). However, there are certain key histologic features that are used to diagnose collagenous and lymphocytic colitis (table 2).

- **Collagenous colitis** – Collagenous colitis is characterized by a colonic subepithelial collagen band ≥10 micrometers in diameter (image 1 and picture 2A-B) [20]. The band is most evident between the crypts. While assessing the thickness of the collagen band, it is important that biopsy specimens are well-oriented and cut perpendicular to the mucosal surface so that the collagen band does not falsely appear to be thickened.

- **Lymphocytic colitis** – Lymphocytic colitis is characterized by ≥20 intraepithelial lymphocytes (IEL) per 100 surface epithelial cells [19]. Crypt architecture is usually not distorted, but focal cryptitis may be present.

- **Incomplete microscopic colitis or microscopic colitis not otherwise specified (NOS) –** NOS has been used to describe a subgroup of patients with diarrhea, an increase in cellular infiltrate in the colonic lamina propria, and either an abnormal collagenous layer or IELs short of fulfilling the criteria for collagenous colitis and lymphocytic colitis [126]. However, it is unclear if this represents a separate subtype of microscopic colitis as these findings may be seen in a variety of conditions (eg, adjacent to an adenoma, in ischemic colitis, irritable bowel syndrome, and chronic trauma) [127].

Focal areas of histologic findings as typically associated with microscopic colitis have also been described in patients with established inflammatory bowel disease (IBD) [128-132]. However, endoscopic features of IBD are frequently present [128-132]. They may also precede the development of overt clinical and histopathologic evidence of IBD, particularly Crohn disease. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Endoscopy'.)

DIFFERENTIAL DIAGNOSIS

The main considerations in the differential diagnosis of microscopic colitis includes celiac disease, inflammatory bowel disease, and irritable bowel syndrome. These can be differentiated from microscopic colitis by history, laboratory evaluation, and endoscopy with biopsy. Other causes of chronic diarrhea are discussed in detail, separately. (See "Approach to the adult with chronic diarrhea in resource-abundant settings", section on 'Initial evaluation'.)

- **Celiac disease** – Patients with celiac disease may have similar symptoms of chronic diarrhea but can be distinguished from microscopic colitis by serologic testing and small

bowel biopsy. (See "Diagnosis of celiac disease in adults", section on 'Diagnostic approach'.)

- **Crohn disease** – Patchy colitis in patients with microscopic colitis can mimic Crohn disease. Characteristic features of Crohn disease such as the presence of perianal disease (fissures, fistulas), chronic transmural inflammation, and granulomas on biopsy are absent in microscopic colitis.

  It is important to note that focal areas of histologic findings as typically associated with microscopic colitis have also been described in patients with established inflammatory bowel disease (IBD) [128-132]. They may also precede the development of overt clinical and histopathologic evidence of IBD, particularly Crohn disease. However, endoscopic features of IBD are frequently present, providing a clue toward the diagnosis [128-132]. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Endoscopy'.)

- **Irritable bowel syndrome** – Patients with diarrhea-predominant irritable bowel syndrome (IBS) may present with chronic diarrhea similar to patients with microscopic colitis [133,134]. However, IBS is predominantly characterized by recurrent chronic abdominal pain. The abdominal pain in IBS is often related to defecation and is associated with a change in frequency or consistency (form) of the stools. (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults", section on 'Clinical manifestations'.)

INITIAL APPROACH

Pretreatment evaluation of disease activity — The primary goal of management in patients with microscopic colitis is to achieve clinical remission (<3 stools per day and no watery stool during a one-week period) and to improve the patient's quality of life. It is unclear if histologic remission is necessary [23]. Active disease is defined ≥3 stools daily or ≥1 watery stool daily [135].

General measures in all patients

Avoid culprit medications and smoking cessation — Patients should be advised to avoid nonsteroidal anti-inflammatory drugs and, if possible, discontinue medications associated with microscopic colitis (table 1) [136]. (See 'Etiology and risk factors' above.)

Antidiarrheals — For symptomatic management of diarrhea, we use the antidiarrheal agent, loperamide, particularly at night to decrease the frequency of nocturnal episodes [137].

Antidiarrheals may be used alone in patients with mild diarrhea (<3 stools daily and no watery stool daily) or in conjunction with other therapies, based on the severity of symptoms, but evidence-based studies are lacking.

Glucocorticoids for active disease

- Budesonide — In patients with active disease (≥3 stools daily or ≥1 watery stool daily) or diarrhea that persists despite the use of antidiarrheals, we recommend the addition of oral budesonide (9 mg daily for six to eight weeks). Budesonide is a locally active corticosteroid with extensive first-pass metabolism in the liver and low systemic exposure [4,138-141].

  Symptomatic improvement can be seen within a few days. However, complete resolution usually requires six to eight weeks or longer. We continue budesonide for at least eight weeks and then gradually taper budesonide in patients in clinical remission (<3 stools daily and no watery stools). We taper oral budesonide to 6 mg for two weeks, followed by 3 mg for another two weeks, and then discontinue therapy.

  In patients who are not in clinical remission at eight weeks, or if symptoms recur on tapering, the budesonide dose of 9 mg can be continued for 12 weeks or longer before tapering the dose.

  Randomized trials in patients with collagenous colitis suggest that budesonide is effective for short-term treatment of microscopic colitis and can improve quality of life [139,142-147]. A meta-analysis of eight randomized trials that included 248 patients randomized to glucocorticoids versus placebo found that short-term clinical response rates were significantly higher with budesonide, as compared with placebo (risk ratio 3.1, 95% CI 2.1-4.6) [148].

  Budesonide has also demonstrated efficacy in inducing clinical and histologic remission in patients with lymphocytic colitis [149]. In a meta-analysis of two randomized trials (only one of which was published) that included 57 patients with lymphocytic colitis assigned to budesonide or placebo, treatment with budesonide resulted in an improvement in diarrhea and microscopic inflammation as compared with placebo (88 versus 38 percent, and 78 versus 33 percent, respectively). In a subsequent randomized trial, 57 patients with active lymphocytic colitis were assigned to budesonide (9 mg daily), mesalazine (3 g daily), or placebo for eight weeks [138]. Clinical and histologic remission rates at week 8 were higher in patients treated with budesonide as compared with placebo (79 versus 42 percent and 68 versus 21 percent, respectively). However, there was no statistically significant difference in clinical remission rates between the mesalamine and placebo

groups (63 versus 42 percent). Rates of drug-related adverse events were not significantly different between the three groups. Of the 27 patients in clinical remission at the end of the eight weeks, seven (26 percent) had a relapse in the 16-week treatment free follow-up. Of note, the study excluded patients with suspected drug-induced lymphocytic colitis and those with mild symptoms. The placebo group had a higher proportion of smokers and a longer duration of symptoms as compared with the treatment groups, both of which may be a source of potential bias, however, these results are consistent with prior studies.

- Prednisone — We reserve the use of prednisone or prednisolone for the treatment of microscopic colitis in patients in whom budesonide therapy is not feasible. While indirect evidence suggests that prednisone should induce clinical remission, its efficacy has not been demonstrated. In addition, systemic glucocorticoids have a higher risk of adverse events. In a randomized clinical trial in which 12 patients with microscopic colitis were assigned to prednisone or placebo for two weeks, there was no difference in the clinical remission rates [150]. Prednisone lead to a reduction in colonic inflammation, but not in the thickness of the collagen band [16,151,152]. As compared with budesonide, prednisone is associated with a lower response rate (53 versus 83 percent), more side effects, and a higher risk of relapse when therapy is withdrawn [152,153].

SUBSEQUENT APPROACH

Mild persistent symptoms despite glucocorticoids

Cholestyramine — In patients with mild, persistent diarrhea despite budesonide, we use concomitant therapy with loperamide and cholestyramine (4 g four times per day). In patients with an improvement in diarrhea, we continue cholestyramine until the diarrhea resolves. Cholestyramine is a bile acid binding resin that is used to treat diarrhea that is due to concurrent bile acid malabsorption in patients with microscopic colitis [99]. In a randomized trial, 23 patients with collagenous colitis and 41 with lymphocytic colitis were assigned to mesalamine at 2.4 g per day alone or in combination with cholestyramine at 4 g per day for six months [154]. Clinical and histologic remission was observed in 91 percent of patients with collagenous colitis and 85 percent of patients with lymphocytic colitis. While the rates of clinical remission were slightly higher in patients with collagenous colitis who were treated with the combination of cholestyramine and mesalamine (100 versus 73 percent), this trial lacked blinding, and there was no placebo group. In addition, part of the measured effect may have been due to spontaneous improvement in microscopic colitis. Cholecystectomy is not associated with microscopic colitis [155]. (See 'Mechanism of diarrhea' above.)

Bismuth subsalicylate — In patients who fail to respond to a two-week trial of cholestyramine, we use bismuth subsalicylate (three 262 mg tablets three times daily) [99,156]. However, there are limited data to support bismuth subsalicylate, and its use is controversial [4]. In an open-label study, treatment with bismuth subsalicylate was associated with improvement in symptoms in 11 of 13 patients and resolution of colitis in nine [156]. These results were confirmed in a subsequent preliminary trial in which 14 patients were randomly assigned to receive bismuth subsalicylate (three 262 mg chewable tablets three times daily) or placebo for eight weeks [157]. As compared with placebo, treatment with bismuth was reportedly associated with a significant decrease in fecal frequency and weight, improvement in consistency, and improvement in colonic histology. However, the results of this study have not been published.

Non-responders or intolerance to glucocorticoids — Approximately 10 to 20 percent of patients treated with budesonide are nonresponders [144]. Other treatment approaches may also be required for patients whose symptoms do not respond to budesonide, and for patients who cannot tolerate budesonide, or corticosteroid therapy in general.

Exclude other etiologies in budesonide non-responders — Patients with an inadequate response to budesonide, cholestyramine, antidiarrheals, and/or bismuth should be re-evaluated for other causes of diarrhea (eg, celiac disease, hyperthyroidism, carcinoid syndrome, VIPoma, persistent NSAID use) [158,159]. (See "Diagnosis of celiac disease in adults", section on 'Diagnostic approach' and "Diagnosis of hyperthyroidism" and "Diagnosis of carcinoid syndrome and tumor localization" and "VIPoma: Clinical manifestations, diagnosis, and management" and "NSAIDs: Adverse effects on the distal small bowel and colon".)

Biologic agents and immunomodulators — In patients with refractory microscopic colitis, we use anti-tumor necrosis factor (TNF) therapy (eg, infliximab, adalimumab) or immunomodulators (eg, 6-mercaptopurine, azathioprine). Limited evidence from small case series and retrospective studies suggest that anti-TNF agents and immunomodulators can induce remission in patients with refractory microscopic colitis [160-164]. Biologic agents and immunomodulators including vedolizumab [165-169] could be considered in selected patients with severe symptoms refractory to budesonide. We do not use methotrexate for the treatment of microscopic colitis.

Surgery for treatment resistant disease — Surgery (ileostomy, colectomy) should be reserved for management of microscopic colitis that is refractory to medical therapy [170-173]. Ileostomy may be the procedure of choice in older patients with refractory disease [172].

Therapies lacking efficacy

- **Aminosalicylates** − Aminosalicylates including mesalamine appear to be ineffective in the treatment of collagenous colitis and lymphocytic colitis [174]. In a randomized trial in which 92 patients with active collagenous colitis were assigned to treatment with oral budesonide (9 mg daily), mesalamine (3 grams daily), or placebo for eight weeks, remission rates with mesalamine were comparable to placebo (32 and 38 percent, respectively) [15,147]. Maintenance treatment has not been studied.

  Similarly, in a randomized trial in which 57 patients with active lymphocytic colitis were assigned to treatment with budesonide, mesalamine (3 grams daily), or placebo for eight weeks, there was no significant difference in clinical and histologic remission rates between mesalamine and placebo.

- **Other** – Although a number of other agents (eg, octreotide, methotrexate, verapamil, probiotic *E. coli* strain Nissle, *Boswellia serrata* extract, and *Lactobacillus acidophilus* and Bifidobacterium subspecies) have been used to treat patients with microscopic colitis, they have not been consistently effective [139,140,175-179].

Relapse and maintenance therapy — Symptomatic relapse occurs in up to 80 percent of patients after cessation of initial budesonide treatment [142]. However, routine maintenance treatment with budesonide in all patients with microscopic colitis is controversial as long-term treatment may increase the risk of steroid-related side effects [153,180]. In patients with relapse following remission we use continuous maintenance therapy at the lowest dose that maintains clinical remission (no more than 6 mg per day then tapered to the lowest effective dose and continued for 6 to 12 months) [3,148,149]. Alternatively patients can either be retreated with intermittent courses (six to eight weeks) of budesonide. (See 'Glucocorticoids for active disease' above.)

Several randomized trials have demonstrated the efficacy of budesonide in maintenance of remission in collagenous colitis [181,182]. A pooled analysis included two maintenance budesonide trials with a six-week, open-label induction phase, followed by a six-month, double-blind maintenance phase with either budesonide (6 mg daily) or placebo, in patients with collagenous colitis [148]. In this analysis, long-term treatment with budesonide was significantly superior to placebo for maintenance of clinical response (risk ratio 3.2, 95% CI 1.1-9.9). However, relapse occurred in 46 to 80 percent of patients within six months of treatment cessation. In another trial, budesonide at a mean dose of 4.5 mg per day maintained clinical remission for at least one year in the majority of patients with collagenous colitis and preserved health-related quality of life [183].

Unlike patients with inflammatory bowel disease, the risk of osteoporosis is not increased in patients with microscopic colitis in the absence of glucocorticoid use. However, patients with active disease requiring long-standing glucocorticoid treatment may require supplementation of calcium and vitamin D [184]. (See "Prevention and treatment of glucocorticoid-induced osteoporosis", section on 'Calcium and vitamin D'.)

NATURAL HISTORY

Microscopic colitis has a chronic, intermittent course in most patients [15,185,186]. Diarrhea may resolve within weeks with or without treatment, but relapses are common (approximately 30 to 60 percent) [23,63,142,171]. Few prospective studies have examined the natural history of microscopic colitis in patients who received medical treatment. One of the largest such studies included 37 patients with collagenous and 44 patients with lymphocytic colitis who were followed prospectively after diagnosis for an average of 37 months [63]. Patients were treated with a variety of interventions, including withdrawal of implicated medications and the use of salicylates, cholestyramine, prednisone, and budesonide. These interventions were associated with long-term cessation of diarrhea in approximately 70 percent of patients, while 25 to 30 percent relapsed.

The long-term course of patients with lymphocytic colitis may be more favorable than with collagenous colitis [61,187]. A retrospective study compared the natural history of 96 patients with collagenous colitis and 80 patients with lymphocytic colitis [61]. Resolution or significant improvement occurred significantly more often in those with lymphocytic colitis, as compared with collagenous colitis (84 versus 74 percent).

Microscopic colitis has not been associated with an increased risk of colorectal cancer, and transformation between collagenous and lymphocytic colitis is rare [19,187].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Microscopic colitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Microscopic colitis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology and clinical presentation –** Microscopic colitis is a chronic inflammatory disease of the colon that is characterized by chronic, watery, non-bloody diarrhea. Based on the histologic features, microscopic colitis is divided into collagenous colitis, lymphocytic colitis, and incomplete microscopic colitis. Microscopic colitis has a female preponderance, with a mean age at diagnosis of 65 years. Patients typically present with insidious onset of chronic, non-bloody, watery diarrhea. Associated symptoms include fecal urgency (70 percent), abdominal pain (50 percent), fecal incontinence (40 percent), and nocturnal episodes (50 percent). (See 'Epidemiology' above and 'Clinical manifestations' above.)

- **Pathogenesis –** The pathogenesis of microscopic colitis is unclear, but it is likely to be multifactorial, involving mucosal immune responses to luminal factors in a genetically predisposed individual. Medications and smoking have been implicated as being causative or triggering flares of microscopic colitis (table 1). Diarrhea in microscopic colitis is likely caused by mucosal inflammation. However, concurrent bile acid malabsorption frequently coexists in patients with collagenous colitis. (See 'Pathophysiology' above and 'Etiology and risk factors' above.)

- **Diagnosis –** Microscopic colitis should be suspected in a patient with chronic diarrhea, particularly in middle-aged and older adults. Evaluation of a patient with suspected microscopic colitis should include stool cultures and a colonoscopy, with mucosal biopsy to establish the diagnosis of microscopic colitis and to exclude other inflammatory diseases. Collagenous colitis is classically characterized by colonic subepithelial collagen band >10

micrometers in thickness. Lymphocytic colitis is characterized by an intraepithelial lymphocytic infiltrate (≥20 lymphocytes per 100 epithelial cells). (See 'Diagnostic approach' above.)

- **Management**

  - **General measures for all patients** – Patients should be advised to avoid nonsteroidal anti-inflammatory drugs and, if possible, discontinue medications associated with microscopic colitis. Antidiarrheals may be used alone in patients with mild diarrhea or in conjunction with other therapies based on the severity of symptoms.

  - Budesonide **for patients with active disease** – For patients with microscopic colitis with active disease **(≥3 stools daily or ≥1 watery stool daily)**, we recommend budesonide (**Grade 1B**). We usually begin with 9 mg per day for six to eight weeks. If the patient is in clinical remission (<3 stools daily and no watery stools), we taper to 6 mg for two weeks, to 3 mg for another two weeks, and then discontinue therapy. If the symptoms are not controlled or if symptoms recur on tapering, the dose of 9 mg can be continued for 12 weeks or longer before tapering budesonide. (See 'Initial approach' above.)

  - **Patients who fail to respond to** budesonide – In patients who do not respond to budesonide, we suggest concomitant therapy with cholestyramine (**Grade 2C**). If the combination of budesonide and cholestyramine is not effective, we suggest a trial of bismuth subsalicylate (**Grade 2C**). We reserve the use of anti-tumor necrosis factor agents for microscopic colitis that is refractory to a combination of budesonide, antidiarrheals, cholestyramine and/or bismuth subsalicylate once other causes of diarrhea have been excluded. We reserve surgery for patients with microscopic colitis that is refractory to medical therapy. (See 'Non-responders or intolerance to glucocorticoids' above.)

  - **Maintenance therapy in selected patients** – Patients with recurrent symptoms after an initial response to budesonide can be retreated with budesonide as maintenance therapy at the lowest dose that maintains clinical remission. (See 'Relapse and maintenance therapy' above.)

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Topic 4071 Version 31.0

GRAPHICS

Assessment of the level of likelihood that a specific drug can trigger microscopic colitis

High likelihood	Intermediate likelihood	Low likelihood
Acarbose	Carbamazepine	Cimetidine
Aspirin and NSAIDs	Celecoxib	Gold salts
Clozapine	Duloxetine	Piascledine
Entocapone	Fluvastatin	
Flavonoid*	Flutamide	
Proton pump inhibitors	Oxetorone	
Sertraline	Madopar	
Ticlopidine	Paroxetine	
	Simvastatin	
	Stalevo¶	

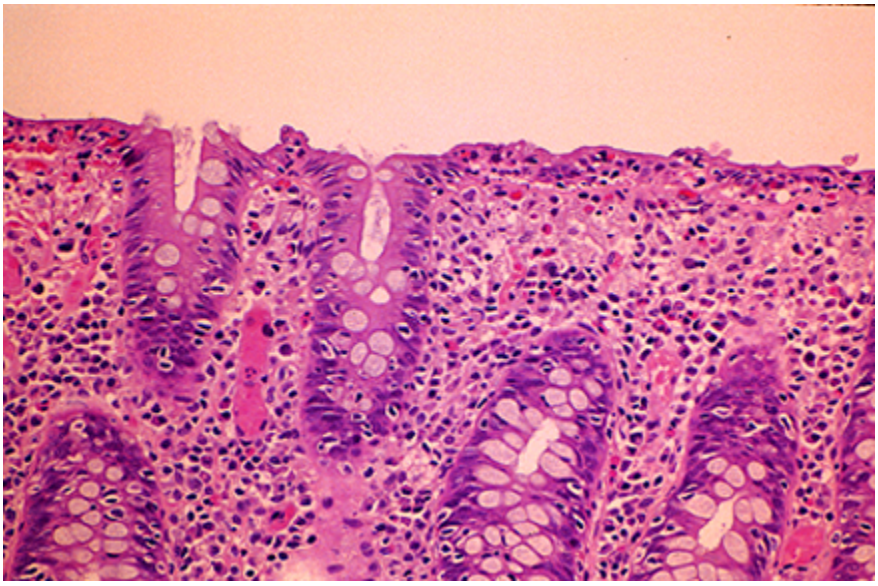
NSAIDs: nonsteroidal anti-inflammatory drugs.

* Venotonic drugs containing flavonoids (diosmin, rutin, or hesperidin).

¶ Anti-parkinsonian drugs, containing levodopa and benserazide (Madopar) and carbidopa, levodopa and entocapone (Stalevo).

Graphic 96937 Version 5.0

Lymphocytic colitis

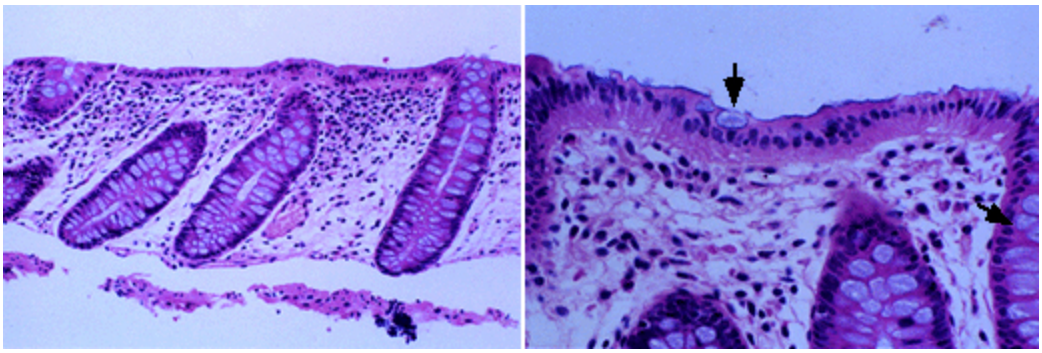


Medium power view of a colonic biopsy from a patient with lymphocytic colitis shows intraepithelial and lamina propria lymphocytic infiltrate.

Courtesy of Robert Odze, MD.

Graphic 54897 Version 1.0

Normal colon



Low (left) and high (right) power views of a biopsy of a normal colon. Low power reveals straight crypts and mild lamina propria mononuclear cell infiltration. High power shows the surface enterocytes with interspersed goblet cells (arrows).

Courtesy of Robert Odze, MD

Graphic 81083 Version 6.0

Histologic key features of different forms of microscopic colitis

	LC	CC	MCi or MCnos
IELs	>20 IELs	Normal to slightly increased	5-20 IELs
Subepithelial collagen layer	Normal to slightly thickened	>10 micrometers	5-10 micrometers
Surface epithelium damage	+	++	(+)
Lamina propria inflammation	++	++	+/++

LC: lymphocytic colitis; CC: collagenous colitis; MCi: microscopic colitis incomplete; MCnos: microscopic colitis not otherwise specified; IELs: intraepithelial lymphocytes.

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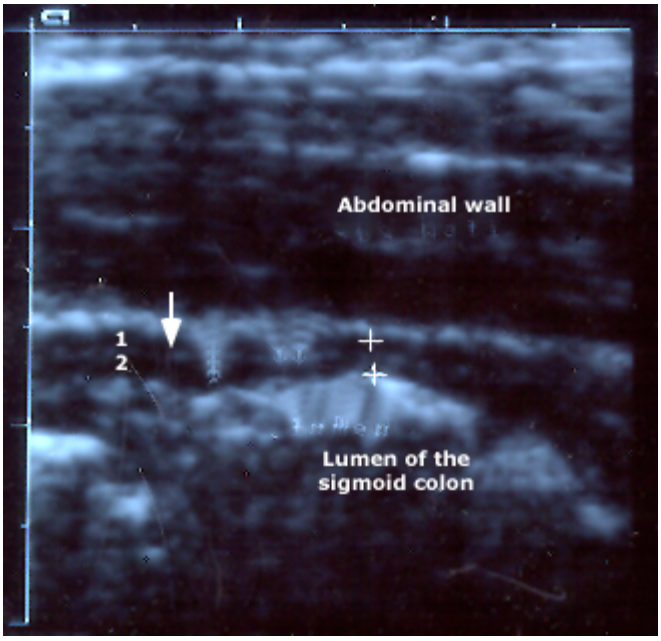
Collagenous colitis

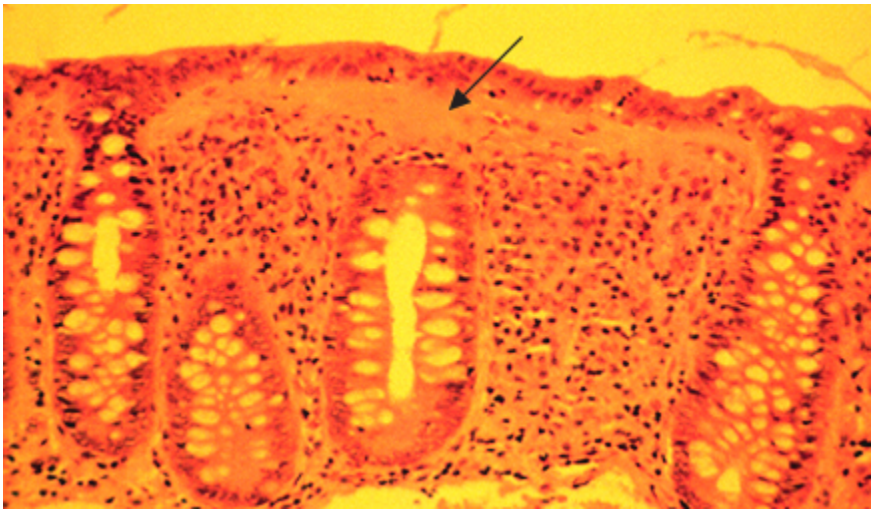


Ultrasound examination of the sigmoid colon in collagenous colitis. The sigmoid colon is normal size but the layers are more pronounced. 1 = lamina muscularis; arrow = submucosa; and 2 = mucosa. The distance between the crosses is 1.7 mm.

Courtesy of C F Dietrich, MD and Wolfgang F Caspary, MD.

Graphic 79824 Version 2.0

Collagenous colitis

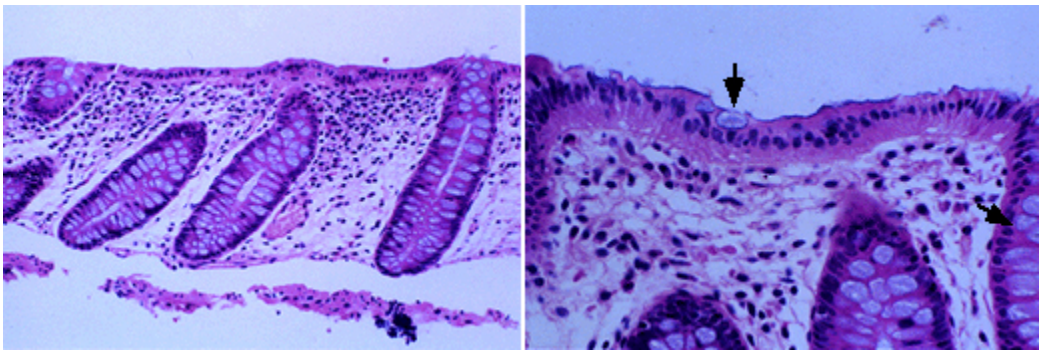


High power view of a colonic biopsy from a patient with collagenous colitis. There is a thickened subepithelial collagenous band (arrow) associated with increased mononuclear cell infiltration and epithelial degeneration.

Courtesy of Robert Odze, MD.

Graphic 60570 Version 1.0

Normal colon

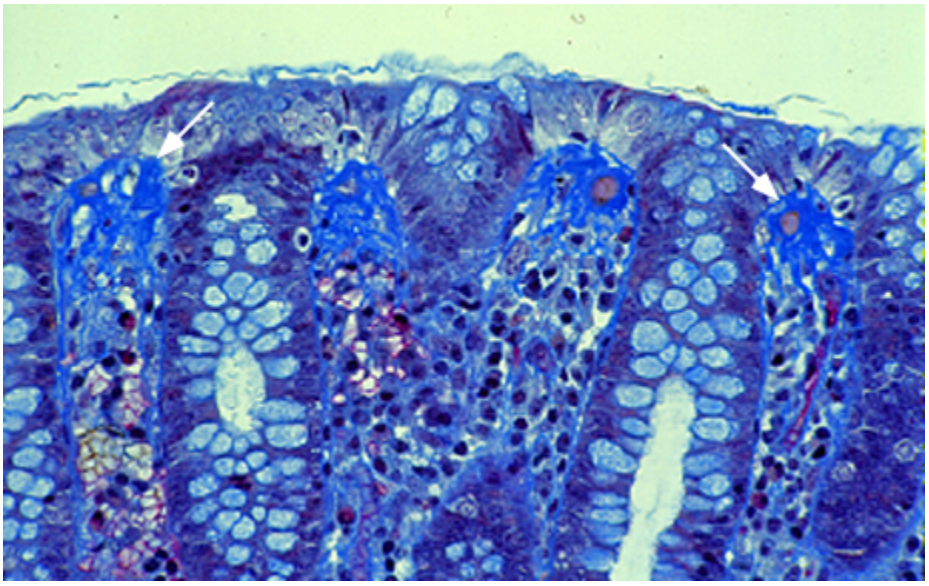


Low (left) and high (right) power views of a biopsy of a normal colon. Low power reveals straight crypts and mild lamina propria mononuclear cell infiltration. High power shows the surface enterocytes with interspersed goblet cells (arrows).

Courtesy of Robert Odze, MD

Graphic 81083 Version 6.0

Collagenous colitis

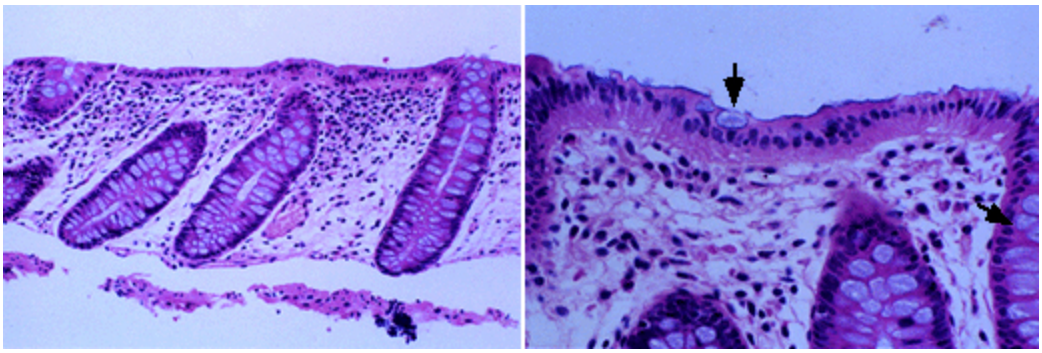


Light micrograph of a colonic biopsy from a patient with collagenous colitis. The characteristic change is thickened subepithelial collagenous band in the colonic mucosa that stains in bright blue (arrows).

Courtesy of Prof Dr G Herrmann, Frankfurt.

Graphic 74390 Version 1.0

Normal colon



Low (left) and high (right) power views of a biopsy of a normal colon. Low power reveals straight crypts and mild lamina propria mononuclear cell infiltration. High power shows the surface enterocytes with interspersed goblet cells (arrows).

Courtesy of Robert Odze, MD

Graphic 81083 Version 6.0

Contributor Disclosures

Christoph F Dietrich, MD, MBA No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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