MICROSCOPIC COLITIS

Background: Poorly understood disease that is an autoimmune attack on the Colon. It can in some cases be early IBD or the result of an infection. It is sometimes thought of being two sides of the same coin. Lymphocytic Colitis, if untreated, may be a precursor to Collagenous Colitis. It is associated with celiac disease, autoimmune thyroiditis, type I diabetes, and nonerosive oligoarticular arthritis.

Incidence: 2-16 per 100,000 per year

Epidemiology: Median age is 65 years of age. It affects mostly females (52-86%). Pts with microscopic colitis have a higher risk of non-gallstone pancreatitis. Higher incidence in Northern Europeans.

Environmental factors: Associated with Smoking and Medications.

Presentation: Nonbloody chronic diarrhea. Insidious onset. 4-9 BM per day. (Up to 20+) Associated with nocturnal diarrhea and incontinence. Abdominal pain associated in 50%. Weight loss, arthralgias, arthritis or uveitis. Relapsing Remitting Course

Labs are generally nonspecific, Mild anemia, elevated ESR and autoantibodies can be seen (RF, ANA, AMA, ANCA, anti-Saccharomyces Cerevisiae and antithyroid peroxidase.) Can have an elevated calprotectin.

Diagnosis: DDX includes Infection, Celiac, IBD, IBS. On endoscopy, the colon is generally normal. Diagnosis is made with pathology.

Work-Up

Rule out infection

Colonoscopy with biopsies from Right and Left side (9 bites) It can have a patchy distribution.

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	++	++	+/++

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

Associated Drugs:

NSAIDs	PPIs
SSRIs	Statins
Immune Checkpoint Inhibitors	Hormone Therapy (Cont. & Menopausal)

MICROSCOPIC COLITIS

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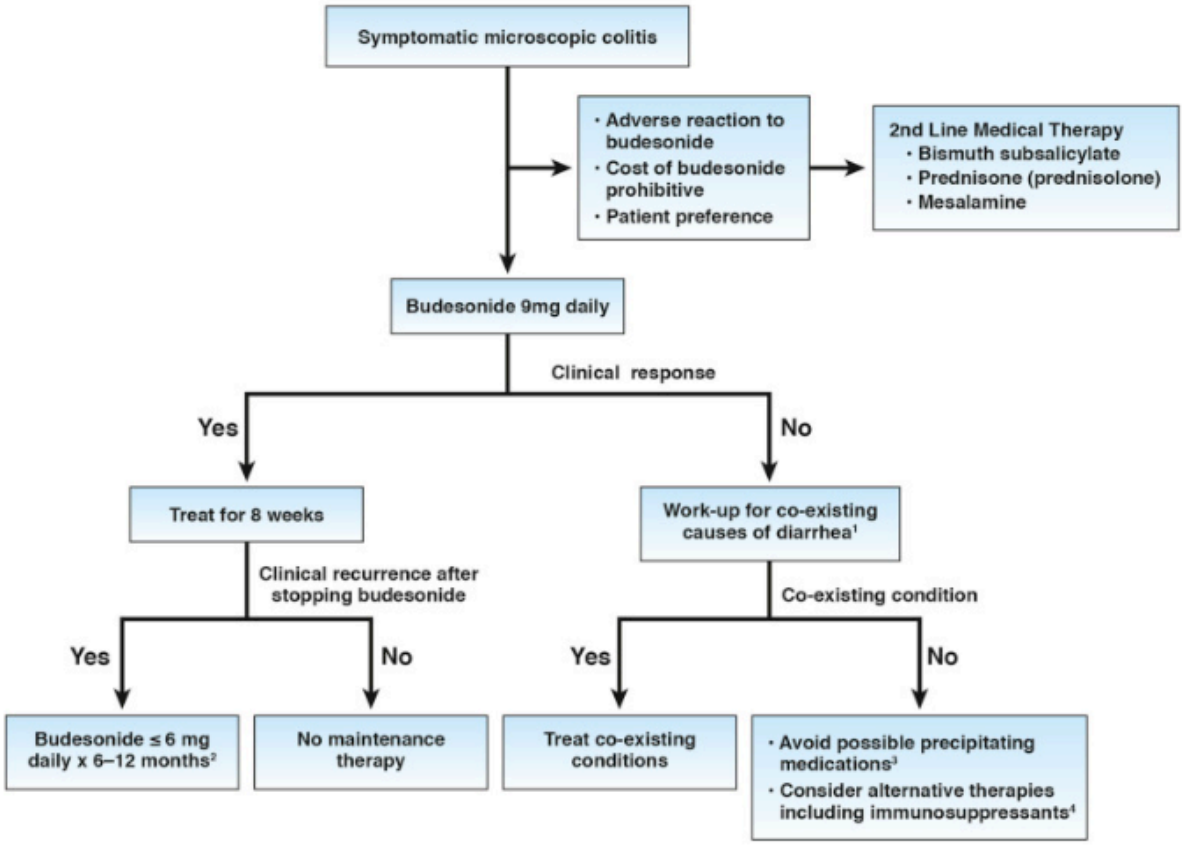
AGA Institute Guideline on the Management of Microscopic Colitis
Clinical Decision Support Tool



[1]Work-up should include but not be limited to evaluation for celiac disease, hyperthyroidism, irritable bowel syndrome.
[2]Maintenance dosing can be tapered to lowest effective dose which may range from 3 mg every other day to 6 mg daily.
[3]Potential precipitating medications include but are not limited to: NSAIDs, aspirin, PPI, SSRI, clozapine, and acarbose.
[4]Though direct evidence is very limited, case series suggest that azathioprine and anti-TNF agents may be effective in refractory microscopic colitis.

Lomotil
Bismuth Subsalicylate (3 tablets 3x per day)
Cholestyramine
TNF-Alpha Inhibitors
6-MP
Surgery
(MTX and Mesalamine didn't work in small studies.)

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AGA SECTION

American Gastroenterological Association Institute Guideline on the Medical Management of Microscopic Colitis

Geoffrey C. Nguyen,[1] Walter E. Smalley,[2] Santhi Swaroop Vege,[3] Alonso Carrasco-Labra,[4,5] and the Clinical Guidelines Committee

[1]Mount Sinai Hospital Centre for Inflammatory Bowel Disease, University of Toronto, Toronto, Ontario, Canada; [2]Division of Gastroenterology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; [3]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [4]McMaster University, Hamilton, Ontario, Canada; and [5]Evidence-Based Dentistry Unit, Faculty of Dentistry, Universidad de Chile, Santiago, Chile

This article has an accompanying continuing medical education activity on page e17. Learning Objective: Upon completion of this test, successful learners will be able to: (1) learn first-line treatment for the induction of remission in microscopic colitis; (2) identify the expected clinical benefits and adverse effects of induction therapy for microscopic colitis; (3) understand the indications for and dosing of maintenance therapy for microscopic colitis; (4) consider medications that may precipitate microscopic colitis especially in those who are refractory to medical therapy; and (5) become familiar with treatment strategies for microscopic colitis refractory to first-line therapy.

This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on the medical management of microscopic colitis. The guideline was developed by the AGA Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of clinical evidence from which these recommendations were formulated.[1]

Microscopic colitis is characterized by chronic watery diarrhea caused by inflammation in the colon and diagnosed by colonic biopsy. With a predilection for those 60 years of age or older, it comprises 2 subtypes, lymphocytic colitis and collagenous colitis; there is a female predominance in the latter. The reported prevalence of microscopic colitis ranges from 48 to 219 per 100,000.[1] Microscopic colitis is not associated with increased mortality, although symptoms can lead to impaired quality of life. Unlike other inflammatory colitides, there is no evidence that the persistence of histological inflammation portends long-term unfavorable outcomes such as colorectal cancer or need for surgery. Accordingly, the goal of medical therapy reflected in these recommendations is to relieve symptoms and improve quality of life while minimizing drug-related adverse effects. Because outcomes did not differ between lymphocytic colitis and collagenous colitis in the technical review, the recommendations in this guideline do not distinguish between subtypes of microscopic colitis.[1]

This guideline focuses on the medical treatment of microscopic colitis and does not specifically address its diagnosis, surgical management, or the appropriateness of screening for associated autoimmune disorders. Because microscopic colitis occurs in 7.5% of patients undergoing evaluation for chronic diarrhea, it would be prudent when assessing these patients with endoscopy to perform colonoscopy with biopsies of multiple segments of the colon. If for any reason flexible sigmoidoscopy is performed instead of colonoscopy, it is important to obtain biopsy specimens from the descending colon in addition to those from the rectosigmoid colon because biopsy specimens from the latter may not reveal the disease in some cases. Moreover, when patients with microscopic colitis have ongoing symptoms despite medical therapy, coexisting causes of chronic diarrhea such as celiac disease should be considered. The persistence of residual bowel symptoms may also reflect coexisting or postinflammatory functional bowel disorders. Patients with refractory symptoms should also avoid potential medication triggers such as nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and selective serotonin reuptake inhibitors.

The guideline was developed using a process outlined elsewhere.[2] Briefly, the AGA process for developing clinical practice guidelines incorporates best practices of guideline development as outlined by the Institute of Medicine.[3] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to prepare the background summary of evidence, develop the technical review, and assess the certainty of the evidence and grade the strength of the recommendations.[4] Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met in person on April 25, 2015, to discuss the quality of evidence (Table 1) and consider other factors relevant for the risk/benefit assessment of the recommendations. The guideline authors subsequently formulated the recommendations. Although quality of evidence was a cardinal factor in determining the strength of the recommendations (Table 2),

Abbreviations used in this paper: AGA, American Gastroenterological Association; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Most current article

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Table 1. GRADE Definitions of Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

the balance between benefit and harm, patients' values and preferences, and resource utilization was also taken into consideration.

Recommendation 1. In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over no treatment for the induction of clinical remission. *Strong recommendation, moderate quality of evidence.*

A meta-analysis of 6 randomized clinical trials showed clear benefit of budesonide in inducing clinical response, with 5 studies also showing histological response. Two studies also showed improvement in quality of life, although the difference did not reach statistical significance. Patients treated with 9 mg of budesonide daily were more than twice as likely to achieve clinical remission over an average of 7 to 13 days when compared with no treatment (relative risk, 2.52; 95% confidence interval, 1.45–4.4). The risk of serious adverse events is low with budesonide. Because of the highly favorable risk/benefit profile and convenience of once-daily dosing, budesonide should be considered first-line therapy for the treatment of microscopic colitis. However, because budesonide is expensive, alternative therapies may also be considered if cost is a determining factor. In general, it is not necessary to perform colonoscopy to assess histological response. However, for patients who have residual symptoms after treatment with budesonide, normal colonic biopsy specimens may be suggestive of coexisting irritable bowel syndrome or celiac disease. Cessation of budesonide can be considered after 8 weeks of therapy. One-third of patients will remain symptom-free thereafter and not require maintenance therapy, which mitigates long-term cost issues with the drug.

Recommendation 2. In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over mesalamine for the induction of clinical remission. *Strong recommendation, high quality of evidence.*

A high-quality clinical trial provided direct evidence that budesonide should be considered first-line therapy over mesalamine whenever possible. Patients with symptomatic microscopic colitis who were treated with budesonide 9 mg daily were nearly twice as likely as those treated with mesalamine 3 g daily to achieve clinical and histological remission, and there was no statistically significant difference in occurrence of adverse events.

Recommendation 3. In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with mesalamine over no treatment for the induction of clinical remission. *Conditional recommendation, moderate quality of evidence.*

Moderate-quality evidence from a single randomized clinical trial suggests that mesalamine therapy is associated with a lower likelihood of achieving clinical response when compared with no treatment (odds ratio, 0.74; 95% confidence interval, 0.44–1.24), although this was not statistically significant. Thus, due to serious imprecision, the benefit of mesalamine in achieving clinical remission is uncertain. Although not directly comparable, it should be noted that in 2 other clinical trials in which mesalamine was administered in the control arm, the clinical response rate was 84% and 87%, while in a third it was 44%. Because of the uncertain balance between benefits and potential harms, mesalamine is recommended conditionally as a potential second-line therapy that can be used under select circumstances. A trial of mesalamine may be appropriate for

Table 2. GRADE Definitions of Strength of Recommendation

	For the patient	For the clinician
Strong	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful in helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

patients who have a contraindication or had a poor response to budesonide or those who have a strong preference against using it. Because costs are similar between mesalamine and budesonide, it is not likely to be a determining factor.

Recommendation 4. In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with bismuth salicylate over no treatment for the induction of clinical remission. *Conditional recommendation, low quality of evidence.*

In a small randomized controlled trial of bismuth salicylate, all 7 patients in the intervention arm showed clinical response whereas none of the 7 patients in the control arm responded. Patients treated with bismuth salicylate had a 3-fold higher likelihood of achieving histological response, although this was not statistically significant. Due to serious imprecision, the clinical benefit from treatment was uncertain. Although there were no adverse events reported, it is unknown whether long-term treatment would be associated with salicylate or bismuth toxicity. Moreover, taking 8 to 9 bismuth salicylate tablets divided 3 times daily imposes a significant pill burden on an older patient population that frequently takes multiple medications. For these reasons, the AGA has conditionally recommended bismuth salicylate as a second-line alternative treatment that may be appropriate for select patients who have contraindications to corticosteroids or for whom cost is a determining factor.

Recommendation 5. In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with prednisolone (or prednisone) over no treatment for the induction of clinical remission. *Conditional recommendation, very low quality of evidence.*

A very small randomized clinical trial showed a 22% clinical response rate among 9 patients in the intervention arm, whereas none of the 3 patients in the control arm exhibited a response. Due to serious imprecision and risk of bias, the clinical benefit of systemic corticosteroids is uncertain. Despite the paucity of evidence, the panel considered that systemic prednisolone would likely reduce clinical symptoms given the indirect evidence of the effectiveness of budesonide. Although the quality of the evidence for safety data was also very low, extensive clinical experience with systemic corticosteroids for other conditions suggests that the risk of adverse events is significant. The AGA offers a conditional recommendation for the use of systemic corticosteroids because of the uncertain balance between clinical benefit and potential harm. Although in most cases it should not be used as first-line therapy, there may be circumstances in which it may be the preferred agent. Prednisolone may be considered in patients who have refractory symptoms after treatment with budesonide and when other coexisting etiologies such as celiac disease have been excluded. Moreover, because prednisolone is considerably less expensive than budesonide, it may be an alternative choice when the cost of the latter is prohibitive.

Recommendation 6. In patients with symptomatic microscopic colitis, the AGA suggests against combination therapy with cholestyramine and mesalamine over mesalamine alone for the induction of clinical remission. *Conditional recommendation, low quality of evidence.*

Low-quality evidence from a single randomized clinical trial failed to show incremental clinical benefit from the addition of cholestyramine to mesalamine therapy. In providing a conditional recommendation against combination therapy with cholestyramine and mesalamine, the AGA considered not only the uncertain balance between benefits and harms but also the feasibility of taking cholestyramine, which can interfere with the administration of other medications, especially in an older population in which polypharmacy is commonplace. The panel is not able to comment on the appropriateness of cholestyramine monotherapy in the absence of clinical trials that have evaluated that intervention.

Recommendation 7. In patients with symptomatic microscopic colitis, the AGA suggests against treatment with Boswellia serrata over no treatment for the induction of clinical remission. *Conditional recommendation, low quality of evidence*

In a single randomized controlled trial, 44% of 16 patients treated with Boswellia serrata improved clinically compared with 27% of 15 patients in the placebo arm, and there was no difference in quality of life between the 2 groups. Adverse events were more frequent. All outcomes were not statistically significant. In addition to the uncertainty of the balance between benefits and risks, the panel also had concerns regarding the feasibility of access to a standardized formulation of Boswellia serrata given the numerous products available. For these reasons, the AGA provides a conditional recommendation against its routine use for the treatment of microscopic colitis.

Recommendation 8. In patients with symptomatic microscopic colitis, the AGA suggests against treatment with probiotics over no treatment for the induction of clinical remission. *Conditional recommendation, low quality of evidence.*

Low-quality evidence from a small randomized trial comparing a probiotic (*Lactobacillus acidophilus, Bifidobacterium animalis,* and *lactis* strains) with no treatment showed uncertain benefit with respect to clinical remission, histological response, and quality of life due to serious

Table 3. Summary of Recommendations of the AGA Guideline on the Medical Management of Microscopic Colitis

Statement	Strength of recommendation	Quality of evidence
Recommendation 1. In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over no treatment for the induction of clinical remission.	Strong	Moderate
Recommendation 2. In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over mesalamine for the induction of clinical remission.	Strong	High
Recommendation 3. In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with mesalamine over no treatment for the induction of clinical remission.	Conditional	Moderate
Recommendation 4. In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with bismuth salicylate over no treatment for the induction of clinical remission.	Conditional	Low
Recommendation 5. In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with prednisolone (or prednisone) over no treatment for the induction of clinical remission.	Conditional	Very low
Recommendation 6. In patients with symptomatic microscopic colitis, the AGA suggests against combination therapy with cholestyramine and mesalamine over mesalamine alone for the induction of clinical remission.	Conditional	Low
Recommendation 7. In patients with symptomatic microscopic colitis, the AGA suggests against treatment with Boswellia serrata over no treatment for the induction of clinical remission.	Conditional	Low
Recommendation 8. In patients with symptomatic microscopic colitis, the AGA suggests against treatment with probiotics over no treatment for the induction of clinical remission.	Conditional	Low
Recommendation 9. For patients with recurrence of symptoms following discontinuation of induction therapy for microscopic colitis, the AGA recommends budesonide for maintenance of clinical remission.	Strong	Moderate

imprecision. Due to the uncertain balance between benefit and harm, the AGA provides a conditional recommendation against the use of probiotics. The panel acknowledges the uncertainty to which the findings from one trial of a specific probiotic formulation can be generalized to the panoply of probiotic products available.

Recommendation 9. For patients with recurrence of symptoms following discontinuation of induction therapy for microscopic colitis, the AGA recommends budesonide for maintenance of clinical remission. ***Strong recommendation, moderate quality of evidence.***

Moderate-quality evidence from 2 randomized clinical trials showed that maintenance therapy with budesonide 6 mg daily over 6 months resulted in a 66% lower relative risk of clinical relapse (relative risk, 0.34; 95% confidence interval, 0.19–0.6). This regimen also effectively maintained histological response and quality of life. A lower dose of budesonide (3 mg daily alternating with 6 mg daily) over 12 months showed similar efficacy in maintaining clinical response. The panel would like to emphasize that maintenance therapy should only be offered to patients with microscopic colitis who have had a clinical relapse after cessation of induction therapy. Up to one-third of patients may not require maintenance therapy. Although maintenance dosing of budesonide may start at 6 mg, in clinical practice, it is commonly tapered to the lowest effective dose. Cessation of maintenance therapy can be considered after 6 to 12 months. Although the systemic bioavailability of budesonide is low, prolonged use may predispose to bone loss. Thus, osteoporosis prevention and screening should be considered in patients who require maintenance therapy.

Summary

These actionable recommendations for the medical management of microscopic colitis (Table 3) were developed under the framework of the GRADE methodology and were consistent with the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines. This guideline is intended to reduce practice variation and promote high-value care. The weight of evidence supports the first-line use of budesonide for induction and, when appropriate, maintenance therapy. Because the technical review and guideline focused on treatments assessed in clinical trials, it did not address the full armamentarium of therapies currently used in practice. We would endorse clinical trials that more rigorously assess the effectiveness of lower-cost alternatives such as antidiarrheal agents

(eg, loperamide) and cholestyramine monotherapy with accompanying cost-effective analyses. The role of combination therapies has yet to fully explored. Due to the absence of clinical trial data, this guideline did not address medical treatment of corticosteroid-refractory microscopic colitis. Very limited evidence from case series, however, suggests that immunosuppressants such as azathioprine and anti–tumor necrosis factor agents may benefit these patients.[5–9] We encourage prospective clinical trials to further investigate these early findings.

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Reprint requests
Address requests for reprints to: Chair, Clinical Guidelines Committee, AGA National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: msiedler@gastro.org; telephone: (301) 941-2618.

Acknowledgments
The AGA Institute Clinical Guidelines Committee included Steven L. Flamm (Northwestern Feinberg School of Medicine, Chicago, IL), Lauren Gerson (California Pacific Medical Center, San Francisco, CA), Ikuo Hirano (Northwestern University School of Medicine, Chicago, IL), Joel H. Rubenstein (Veterans Affairs Center for Clinical Management Research, Ann Arbor, MI, and Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, MI), Siddharth Singh (Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN), Neil Stollman (University of California San Francisco, Northern California Gastroenterology Consultants, San Francisco, CA), Shahnaz Sultan (Minneapolis VA Health Care System, University of Minnesota, Minneapolis, MN), Sachin B. Wani (University of Colorado, Aurora, CO), David S. Weinberg (Department of Medicine, Fox Chase Cancer Center, Philadelphia, PA), and Yu-Xiao Yang (Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA).

Conflicts of interest
All guideline panel members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report.