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Microscopic Colitis: A Key Differential Diagnosis in Chronic Watery Diarrhea

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ABSTRACT

INTRODUCTION

Microscopic colitis (MC) is an often-overlooked inflammatory disorder of the colon. It presents with persistent, non-bloody, watery diarrhea. The characteristic of the condition is a lack of visible endoscopic abnormalities. It includes two main histological forms: collagenous colitis and lymphocytic colitis. While it mostly affects older individuals, MC is often missed in clinical practice, resulting in prolonged symptoms and excessive diagnostic procedures.

AIM OF THE STUDY

This review aims to present current knowledge of microscopic colitis. We summarize its key symptoms, clinical manifestations, diagnostic methods, and available therapies. The goal of this study is to understand this disease better and demonstrate why early detection and accurate diagnosis are important.

MATERIALS AND METHODS

A structured literature search was performed in PubMed and Google Scholar to identify relevant studies on MC. We focused on diagnostic methods and therapy possibilities. The search included relevant keywords and Medical Subject Headings (MeSH). Supplementary articles were included through manual review of the reference lists from key publications.

CONCLUSION

Microscopic colitis can be treated. Unfortunately, it is often underdiagnosed as a cause of chronic diarrhea in adults. Once you identify it quickly and confirm the disorder with histological samples, you can initiate effective treatment, usually with budesonide. Early recognition can minimize unnecessary, often expensive, testing and patient suffering. Ongoing follow-up may be necessary in cases with frequent relapse.

KEYWORDS:

Microscopic colitis; lymphocytic colitis; collagenous colitis; colonoscopy; diarrhea

INTRODUCTION

Microscopic colitis (MC) is a comparatively recent clinical condition, initially described in 1976 as a chronic inflammatory bowel disease and a notable cause of persistent, non-bloody watery diarrhea. It affects especially older individuals. In the years since its identification, MC has gained recognition as a common but often overlooked diagnosis. The disease is associated with significant patient burden and increased healthcare utilization. The condition can significantly affect the quality of life. Patients suffer from fatigue, sleep disturbances, and social limitations. To reduce patients' distress, early recognition and proper histological assessment of multiple colonic biopsies are essential for accurate diagnosis and timely initiation of effective treatment [1,2,3].

Microscopic colitis usually appears as chronic, watery diarrhea. There are also other symptoms of the disorder, like abdominal discomfort, fecal urgency, nocturnal episodes, and sometimes fecal incontinence. Even though those symptoms can be severe, colonoscopy often reveals macroscopically normal mucosa, underscoring the need for histopathological examination of multiple mucosal biopsies to establish a diagnosis. Histologically, the disease is divided into two primary subtypes: collagenous colitis and lymphocytic colitis. In addition, incomplete or atypical variants with less-defined microscopic features have been described [3,4,5].

While previously regarded as a rare condition, microscopic colitis is now acknowledged as a prevalent cause of chronic diarrhea in high-income countries. Its pathogenesis is thought to involve an abnormal immune reaction to changes in the intestinal environment. There is increasing evidence pointing to a genetic predisposition as a contributing factor [3,6].

The standard approach to treating microscopic colitis focuses on symptom relief and mucosal healing. Budesonide is the first-line therapy. Additionally, physicians should discontinue treating patients with suspected causative medications and implement dietary modifications. The immunosuppressive or biologic agents should be initiated once budesonide fails to respond. Although most patients experience favorable outcomes with appropriate treatment, relapses are common. In chronic or recurrent cases, therapy may need to be continued [7,8].

Current research aims to improve diagnostic accuracy, understand the immunogenetic mechanisms underlying the disease, and test new treatments in well-designed clinical trials. To improve the care of patients with microscopic colitis, we need a better understanding of how

the disease begins, how to recognize it early, and how to select the most effective treatment for each person. Continued work in these areas is needed. It will help reduce the burden of the disease and improve patients' quality of life. It will also guide future progress in clinical practice and support the development of new treatment options [3,9].

AIM OF THE STUDY

This review provides an up-to-date overview of microscopic colitis and describes its symptoms, diagnostic challenges, and recent treatment advances. It examines current data on the disease's prevalence, mechanisms, and treatment outcomes and highlights microscopic colitis as an essential but often overlooked cause of chronic diarrhea. The review also emphasizes the importance of early detection and the use of consistent, biopsy-based diagnostic methods to ensure timely and effective patient care.

MATERIALS AND METHODS

This review is based on a structured analysis of scientific literature from PubMed and Google Scholar. The search included publications up to August 2025 and covered microscopic colitis and its subtypes, collagenous and lymphocytic colitis. The review addresses clinical presentation, diagnostic criteria, disease mechanisms, and treatment options. Searched keywords and relevant Medical Subject Headings (MeSH) were: microscopic colitis, chronic diarrhea, collagenous colitis, lymphocytic colitis, and budesonide. Our review includes essential clinical guidelines, systematic reviews, and original research articles. Additional literature was identified through manual examination of reference lists from foundational studies.

Only English-language publications from peer-reviewed journals were included. Studies were selected for their relevance, methodological quality and clinical relevance. The aim was to synthesize the current evidence and provide a practical, clinician-oriented overview of microscopic colitis.

STATE OF KNOWLEDGE

Epidemiology and Demographics

Microscopic colitis is now widely acknowledged as a common cause of chronic, non-bloody diarrhea. It usually affects older patients. It is thought to occur about as often as the well-known

inflammatory bowel diseases: ulcerative colitis and Crohn's disease. Although MC was not diagnosed previously, mainly because endoscopic findings were not particularly remarkable, current data clearly indicate that MC is a frequent condition [10].

Tong et al. (2015) conducted an extensive systematic review and meta-analysis that included 25 studies. The authors found incidence rates of 4.14 cases per 100,000 person-years for collagenous colitis (CC) and 4.85 cases per 100,000 person-years for lymphocytic colitis (LC). The incidence increased with age, with median ages at diagnosis of 64.9 years for CC and 62.2 years for LC. The analysis also revealed a marked predominance among females, with incidence rate ratios of 3.05 for CC and 1.92 for LC—suggesting a potential role of hormonal or immune-related factors in disease vulnerability [11,12].

The same study also highlighted environmental and pharmacological contributors to microscopic colitis. In particular, it found a significant association between the condition and the use of proton pump inhibitors (PPIs) and selective serotonin reuptake inhibitors (SSRIs), with reported odds ratios of 2.68 and 2.41, respectively. These results lend support to the theory that both internal susceptibility and external exposures contribute to the development of the disease [11,13,14].

Overall, microscopic colitis primarily affects older women in developed countries. However, growing awareness and advancements in histological diagnostic techniques have likely contributed to increased detection rates across a broader range of patient populations [15,16,17].

Etiology and Risk Factors

The precise cause of microscopic colitis remains unclear. Still, it is thought to result from a complex interplay among genetic predisposition, immune dysfunction, environmental factors, and disturbances in the gut microbiota. While collagenous colitis and lymphocytic colitis share many pathogenic mechanisms, they may differ slightly in histological features and immune responses [18,19,20].

More and more studies suggest that genes play a role in the development of microscopic colitis. Both genome-wide association studies (GWAS) and targeted gene analyses have identified associations between MC and specific HLA haplotypes, many of which are also implicated in other autoimmune conditions. The frequent coexistence of MC with disorders such as celiac

disease, autoimmune thyroiditis, and rheumatoid arthritis further reinforces the role of immunogenetic susceptibility in its pathogenesis [21,22,23].

Environmental influences have also been linked to the development of microscopic colitis. Several widely used medications—such as proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and statins—have been associated with an elevated risk of disease onset. Proposed mechanisms include direct mucosal injury, increased intestinal permeability, and modulation of the local immune response. In some cases, discontinuing the suspected agent has been shown to result in clinical improvement [24].

Recent research has begun to examine the gut microbiome and its potential role in inflammation in microscopic colitis. Changes in the types and balance of gut bacteria—called dysbiosis—may trigger the immune system, especially in people who are genetically more sensitive. Even though the exact bacterial changes are not yet fully understood, this research shows that the innate immune system is vital for maintaining the gut lining and mucosa in a healthy, stable state [25,26].

In summary, MC is believed to arise from a multifaceted interplay of immune dysregulation, genetic predisposition, environmental triggers, and alterations in the gut microbiota. Recognizing and addressing modifiable risk factors—especially medication use—plays an important role in both accurate diagnosis and effective disease management.

Pathophysiology and Immunological Mechanisms

The defining features of microscopic colitis are evident on histopathology. Collagenous colitis is characterized by a markedly thickened subepithelial collagen layer—typically exceeding 10 μm—beneath the surface epithelium. In contrast, lymphocytic colitis is characterized by an elevated intraepithelial lymphocyte (IEL) count (> 20 per 100 epithelial cells), without significant collagen thickening. Both subtypes commonly exhibit lamina propria inflammation, with infiltration by lymphocytes, plasma cells, and, occasionally, eosinophils. Microscopic colitis not otherwise specified refers to a subgroup of patients who present with typical symptoms such as chronic diarrhea and increased cellular infiltrate, along with either a mildly abnormal collagen layer or elevated intraepithelial lymphocytes, but whose findings do not fully meet the criteria for collagenous or lymphocytic colitis [27,28].

Table 1. Histopathological Features of Microscopic Colitis	
Type of Microscopic Colitis	**Key Histological Features**
Collagenous colitis (CC)	Subepithelial collagen band >10 μm
Lymphocytic colitis (LC)	≥20 intraepithelial lymphocytes per 100 epithelial cells, usually without crypt distortion
Microscopic colitis not otherwise specified	Increased cellular infiltrate with either abnormal collagen layer or elevated intraepithelial lymphocytes, not fully meeting criteria for CC or LC

A central feature of immunopathology in microscopic colitis is an abnormal mucosal immune response. T lymphocytes actively mediate epithelial damage and disrupt intestinal barrier integrity. This is accompanied by elevated levels of pro-inflammatory cytokines—including TNF-α, IFN-γ, and IL-17—in the colonic mucosa, reflecting immune activation patterns similar to those observed in other autoimmune gastrointestinal disorders. These immune problems lead to chronic inflammation and impaired mucosal homeostasis [29,30].

There is more evidence that the involvement of the gut microbiota in the pathogenesis of microscopic colitis. Dysbiosis, an imbalance in the composition, diversity, or stability of intestinal bacterial populations, may act as a trigger or intensifier of mucosal immune responses in individuals with genetic susceptibility. Disruptions in microbial-host interactions probably contribute to compromised epithelial barrier function, persistent inflammation, and abnormal immune activity within the colonic mucosa. However, the specific bacterial profiles responsible have not yet been clearly identified [31,32].

In summary, MC is characterized by immune-driven epithelial disruption, with contributions from both the innate and adaptive immune systems. Advancing our understanding of its immunopathogenic mechanisms may pave the way for novel diagnostic biomarkers and targeted treatment strategies.

Clinical Presentation

Microscopic colitis usually appears with chronic, non-bloody, watery diarrhea that often continues for a long time and can seriously affect a person's daily life. The diarrhea is typically secretory, occurring multiple times a day and often continuing during the night. These nighttime episodes are an important clue, as they help distinguish microscopic colitis from functional gastrointestinal disorders [2,33].

Patients may also have abdominal cramping, urgency, bloating, and in some cases—especially in older adults—episodes of incontinence. When the disease persists or becomes more severe, additional symptoms such as weight loss, fatigue, and electrolyte disturbances may develop. Despite heavy symptoms, a standard colonoscopy often looks completely normal. This is why the diagnosis is frequently delayed unless tissue biopsies are taken [34].

The clinical presentation of microscopic colitis often overlaps with other gastrointestinal conditions, including celiac disease, bile acid diarrhea, and drug-induced colitis, which can make diagnosis more challenging. Notably, patients usually do not exhibit gross rectal bleeding, fever, or systemic symptoms—features that help differentiate microscopic colitis from classic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis [35].

Prompt identification of these clinical signs, along with the decision to collect multiple colonic biopsies despite a normal endoscopic appearance, is essential to achieve an accurate diagnosis and initiate appropriate treatment without delay [36].

Diagnostic Criteria

Diagnosing microscopic colitis involves both clinical suspicion and histological confirmation. Colonoscopy plays a central role, even though the colonic mucosa is usually normal on visual inspection. For this reason, it is essential to take multiple biopsies from different parts of the colon, especially from both the right and left sides. This approach increases the chance of finding the characteristic microscopic changes [12,37].

Histopathology is still the key method for diagnosing microscopic colitis. The biopsy samples must be evaluated using established criteria, such as a thickened subepithelial collagen band or an increased number of intraepithelial lymphocytes. In some cases, incomplete or unclear forms

show milder inflammatory changes, but the diagnosis can still be supported if these findings match the patient's symptoms [38].

Stool studies help rule out infectious etiologies, and blood tests may reveal nonspecific signs of inflammation. Several biomarkers have been proposed, but none are reliable enough to confirm microscopic colitis. Tests for related autoimmune conditions, such as celiac disease or thyroid disorders, may offer valuable clues. However, they cannot make the diagnosis on their own [39].

Making the diagnosis on time depends a lot on clinical awareness, especially in older patients who have ongoing watery diarrhea but a normal-looking colonoscopy. It is essential to recognize this diagnostic challenge, avoid missing cases, and ensure that treatment can start without delay [28].

Treatment Strategies

The primary goals in managing microscopic colitis are to relieve symptoms, achieve histological healing, and reduce the risk of recurrence. Treatment should be individualized based on the severity of the condition, the specific subtype, coexisting medical conditions, and the patient's overall tolerance to treatment. Clinical guidelines and accumulating evidence from randomized controlled trials and observational studies guide therapeutic decision-making [40].

Budesonide is the preferred first-line therapy for both collagenous and lymphocytic colitis due to its strong local anti-inflammatory effects and minimal systemic absorption, which result from extensive first-pass hepatic metabolism. Multiple clinical trials have confirmed its effectiveness in both inducing remission and maintaining long-term symptom control [41].

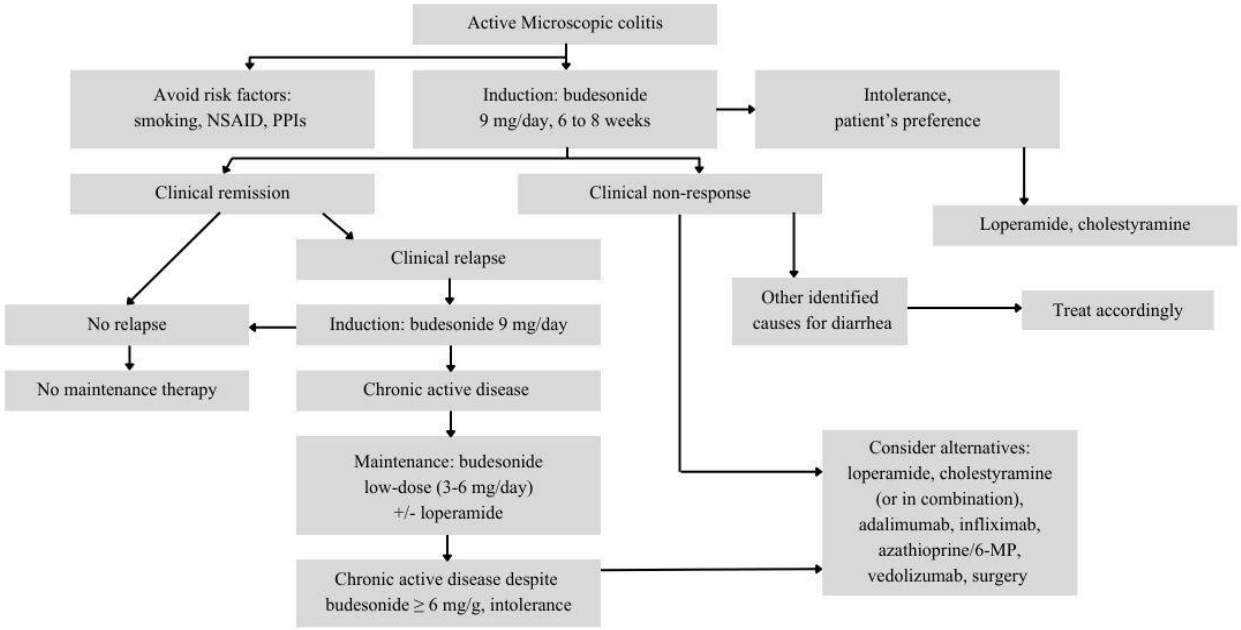

Figure 1. Clinical management pathway for microscopic colitis [42]. Abbreviations: NSAID, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; 6-MP, 6-mercaptopurine

Disease Course and Prognosis

Microscopic colitis usually follows a relatively mild course, although flare-ups are common. Most patients improve with budesonide, but their symptoms often return once the medication is stopped. For some people, the condition becomes long-lasting or requires continued treatment because they depend on budesonide to stay well. Even so, with proper management, most patients achieve good long-term outcomes. Follow-up endoscopy is not routinely necessary unless new or concerning symptoms emerge. It is essential to monitor patients who are receiving extended corticosteroid therapy. Using corticosteroids may lead to adverse effects, such as adrenal suppression or reduced bone density.

Although the condition is usually manageable, some patients may experience fluctuations in symptoms over time, which can affect daily functioning and overall well-being. Physicians should review medications that may worsen diarrhea, address dietary triggers, and ensure adequate hydration—these measures can help improve symptom control. Regular medical follow-up also plays an important role, as it allows clinicians to assess treatment response, adjust therapy when needed, and provide ongoing guidance to help patients maintain a stable quality of life [42].

CONCLUSIONS

Microscopic colitis is now recognized as a common cause of long-lasting, non-bloody diarrhea, especially in older patients. Unfortunately, it is still often missed. Even though the colon usually looks normal on endoscopy, untreated disease can significantly reduce quality of life. Proper diagnosis depends on careful clinical evaluation and microscopic examination of colon biopsy samples. That is why greater awareness among clinicians is needed.

Treatment for microscopic colitis has improved significantly, and budesonide is now widely considered the primary and most effective therapy. Most patients feel better with the first course of treatment, but relapses are common, and some people may need long-term maintenance therapy or second-line treatments. Even so, the overall prognosis is good, and patients usually do very well when the condition is treated correctly.

Ongoing efforts are essential to enhance early detection, establish consistent long-term management strategies, and develop new treatments for patients with refractory disease. A collaborative, multidisciplinary approach that prioritizes individual patient needs is vital for achieving the best possible outcomes in this frequently underdiagnosed condition.

DISCLOSURE

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