# Microscopic colitis: an update

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## Abstract

Microscopic colitis (MC) is an inflammatory pathology of the bowel diagnosed predominantly in older patients. MC is a cause of chronic watery, non-bloody diarrhea, that affects the older patients, mostly women, and leads to impaired health-related quality of life. The diagnosis and treatment can be often difficult. There are three main histological subtypes: collagenous colitis, lymphocytic colitis and incomplete microscopic colitis. Because of the variable nature of this pathology, the therapeutic options should be individualized for every patient. MC has a variable course, varying from occasional symptoms to recurrent or progressive symptoms. A literature search was performed on the main databases. Data on microscopic colitis was collected and presented. This comprehensive review aims to raise awareness of this pathology while providing the latest data regarding current recommendations. General practitioners and gastroenterologists should always take microscopic colitis into consideration when diagnosing a patient with chronic diarrhea.

**Keywords:** microscopic colitis, inflammatory bowel disease, diarrhea, collagenous colitis, lymphocytic colitis

Increasingly considered an inflammatory bowel disease, MC is a cause of chronic watery, non-bloody diarrhea diagnosed predominantly in older patients and has three major histological subtypes: collagenous colitis (CC), lymphocytic colitis (LC) and incomplete microscopic colitis [1]. The latest epidemiological data show that the incidence and prevalence of MC are greater than those of Crohn's disease and ulcerative colitis in some areas [2]. The most common symptom of MC is chronic, non-bloody, watery diarrhea. Other symptoms may include fecal urgency, nocturnal stools, abdominal pain, arthralgias, weight loss or fecal incontinence. The severity of these symptoms is variable. Sometimes, these symptoms can be misinterpreted as diarrhea-predominant irritable bowel syndrome, leading to inadequate treatment. It is estimated that the frequency of MC in patients with chronic watery diarrhea is 12.8% [1]. Although it is considered benign, since MC is not associated with an increase in mortality, unlike other inflammatory bowel diseases, it can lead to a deeply impaired health-related quality of life (HR-QoL). Endoscopically, macroscopic changes are inconsistent or absent, so histology is always required for the diagnosis of MC. CC is characterized by a thickened collagen band under the surface epithelium, while LC is defined by substantially intraepithelial lymphocytosis and increased cellularity in the lamina propria. Incomplete MC have both findings but in lower degrees [1]. Some patients achieve spontaneous remission. With the current treatment options, some patients require budesonide for induction of clinical response, others may require low-dose budesonide as maintenance therapy. In some cases, immunomodulators or biological agents may be required. Surgical treatment is used as a last resort.

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## Epidemiology

The latest data indicate that the overall incidence rate of MC is 11.4 (95% Confidence Interval (C.I.) 9.2-13.6) per 100,000 person-years. The pooled incidence for CC and LC are 4.9 (95% C.I.: 4.2-5.7) and 5.0 (95% C.I.: 4.0-6.1) cases per 100,000 persons-years, respectively [1]. In Europe, the reported incidence of Crohn's disease varies from 0.5 to 10.6 cases per 100,000 person-years and for ulcerative colitis (UC) the numbers are between 0.9 and 24.3 per 100,000 person-years [3]. The overall prevalence of MC is estimated to be 119 (95% C.I.: 73-166) per 100,000 persons, with an overall prevalence for CC and LC of 50.1 and 61.7 per 100,000, respectively. There are geographic variations in the incidence and prevalence of MC. Its rising incidence until the early 2000s has reached a plateau [1,4]. To this date, the highest incidence is described in Denmark, 16.4 CC cases per 100,000 persons-years and 11.5 LC per 100,000 persons-years [5]. Almost similar rates were described in a cohort in Olmsted County, Minnesota [6]. The median patients' age is 65 years old (95% C.I. 57.03-72.78) [1]. Approximately 25% of patients with MC were diagnosed before the age of 45 years [7]. It has also been described in children [8].

## Risk factors

The risk of developing MC is greater in women, especially in collagenous as compared with lymphocytic colitis [1,2]. Other risk factors for MC include current smoking (history of smoking is also associated with an attenuated risk), a history of autoimmune disease, including diabetes mellitus, rheumatoid arthritis, a history of celiac sprue, celiac disease (O.R.: 50-70), nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, selective serotonin reuptake inhibitors; proton pump inhibitors (PPIs), especially lansoprazole; and drugs with various other mechanisms of action, including statins, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [9-12]. Microscopic colitis has also been linked with duloxetine, a serotonin and norepinephrine reuptake inhibitor antidepressant [13].

Beaugerie and Pardie assessed in 2005 the level of probability with which different medications can trigger MC [14]. This is displayed in table I.

Patients exposed to PPIs have significantly higher probability of MC. Numerous studies imply odds ratios varying from 3.37 (95% CI 2.77-4.09) to 7.3 (95% CI: 4.5-12.1), although a cause-effect relationship between the dose of PPIs and the risk of developing MC has not yet been demonstrated [15,16]. The other drug class consistently linked with are the NSAIDs, with ORs varying between 1.86 (95% CI 1.39-2.49) to 5.6 (95% CI 1.2-27.0) [15,16]. It has also been suggested that the concurrent use of PPIs and NSAIDs, frequently prescribed in combination, increases the risk of MC fivefold [15].

It should be noted that these medications linked with MC are not considered a direct cause. The current recommendations suggest the withdrawal of any drug that is suspected to have a chronological relation to the onset of diarrhea.

## Pathogenesis

To this date, there are a number of studies regarding the genetic alterations in MC. It has been confirmed that there are single nucleotide polymorphisms on the MHC 8.1 haplotype, indicating an immune component to the pathogenesis of MC [17]. The MCH 8.1 haplotype, also called 'ancestral haplotype', contains blocks of conserved genomic sequences derived from a common ancestor. These individuals have an altered cytokine profile, increased TNF- α production and higher titers of autoantibodies. These adaptations are thought to be beneficial in response to infections, but may cause autoimmune diseases as a long-term side effect [17,18].

The interleukin (IL)-6-174 gene polymorphism has a possible association with MC. This polymorphism may be linked with excess IL-6 production, evoking a proinflammatory bias in the mucosal cytokines milieus [19].

**Table I.** Drugs linked with MC [14].

| High likelihood to trigger MC | Intermediate likelihood to trigger MC | Low likelihood to trigger MC |
|---|---|---|
| Acarbose | Carbamazepine | Cimetidine |
| Aspirin and NSAIDs | Celecoxib | Gold salts |
| Clozapine | Duloxetine | Piascledine |
| Entocapone | Fluvastatin | Pembrolizumab |
| Flavonoids | Flutamide | Topiramat |
| Lansoprazole | Oxetorone | Biphosphonates |
| Omeprazole | Levodopa+benseracide | β-Blockers |
| Esomepazole | Simvastatin | ACE inhibitors |
| Setrtaline | Carbidopa + Levodopa + Entocapone | |
| Ticlopidine | | |

One of the largest genetic studies of CC to this date identified three HLA alleles (HLA-B*08:01, HLA-DRB1*03:01, and HLA-DQB1*02:01) that are associated with increased CC risk. The gene HLA-DRB1*04:01 was associated with a protective effect [20]. These genes are part of the HLA 8.1 ancestral haplotype. They are commonly found in Caucasians and include several alleles that are linked with autoimmune diseases [21]. In a case series, four pediatric patients that were diagnosed with LC were found to have a CTLA4 or STAT3 mutations. These mutations were previously reported in association with inflammatory bowel disease and are linked with increased apoptosis [22].

One of the mechanisms linked with the pathogenesis of CC is abnormal collagen metabolism, which causes the thickened collagen band. In situ hybridization showed that there was increased expression of transforming growth factor (TGF) beta-1 in patients with CC compared to controls. The increased expression of TFG beta-1 has been linked with increased deposits of collagen in tissues [23].

A dysregulated immune response to luminal antigens in predisposed individuals is considered to be the cause of MC, similar to Crohn's disease or ulcerative colitis. The adaptive immune system and the cytotoxic responses are believed to be altered in patients with MC. Because the granulocyte infiltration is absent in patients with MC, this fact shows that there is a minor involvement of innate immunity [24].

It has also been demonstrated that the patients with LC and CC present a mixed Th17/Tc17 and Th1/Tc1 mucosal cytokine profile [25]. IL-37 was shown to have a decreased activity in patients with MC and ulcerative colitis, proving that the anti-inflammatory cytokine production is reduced [26].

The watery diarrhea is the result of a multi-factorial process that includes reduced expression of colonocyte aquaporins, sodium malabsorption caused by the upregulation of epithelial sodium channels and increased flux of molecules caused by downregulation of epithelial junctions [27].

## Clinical presentation, diagnosis

MC is characterized by chronic, non-bloody, watery diarrhea and should be considered when a middle-aged patient presents with this symptom. It has also been reported in children [8]. One study found that 25% of the patients with MC were under 45 years [28]. Female-to-male incidence rate ratios are 3.0 for CC and 1.9 for LC [2]. Other symptoms include fecal urgency, incontinence, nocturnal episodes or weight loss due to fluid loss. Extraintestinal manifestations include arthralgias and fatigue. Anxiety and depression have been reported in patients with MC.

The onset is sudden in up to 42% of patients; 65-89% of patients have intermittent episodes of diarrhea [28,29]. These symptoms lead to a significantly impaired quality of life. The symptoms are displayed in table II.

The differential diagnostic plays a special role when diagnosing MC. A carefully taken history should include recent antibiotic exposure, recent travels, concomitant or family history of autoimmune diseases.

**Tabel II.** Symptoms of MC [30].

| Symptoms | Percentage (%) |
|---|---|
| Chronic, non-bloody, watery diarrhea | 100 |
| Fecal urgency | 70 |
| Abdominal pain | 50 |
| Nocturnal episodes | 50 |
| Incontinence | 40 |

Because macroscopically no colonoscopic changes are pathognomonic when dealing with MC, the differential diagnosis with irritable bowel syndrome (IBS) and functional diarrhea is the most important, which as well show no macroscopic alterations on lower endoscopy. Patients with IBS are diagnosed using the ROME IV criteria. The histological exam is diagnostic. Other pathologies that should be considered include infections (C. Difficile) and inflammatory bowel diseases. Physical examination findings are nonspecific in patients with MC [1].

Some studies suggested the use of fecal calprotectin to monitor disease activity [31]. At this moment there is a moderate level of confidence statement that recommends not to use fecal calprotectin to exclude or monitor MC [1]. Other fecal biomarkers including fecal eosinophil protein, eosinophil cationic protein and fecal lactoferrin demonstrated inconstant values when assessed in patients with MC [32]. More studies are needed in order to use the biomarkers in diagnosing or monitoring MC.

At the moment, the Hjortswang criteria are used to monitor disease activity and clinical remission (see table III). These criteria state that the patients in clinical remission have a mean of <3 stools per day and a mean of <1 watery stool during a one-week registration. Active disease is diagnosed in patients that have one of these two metrics elevated [1].

**Table III.** Hjortswang's criteria.

| | Stools per day | | Watery stools per day |
|---|---|---|---|
| Clinical remission | <3 | AND / OR | <1 |
| Active disease | >=3 | | >=1 |

MC Disease Activity index (MCDAI) was proposed to quantify the symptoms and to measure the quality of life in these patients. The index takes into consideration the number of unformed daily stools, presence of nocturnal stools, abdominal pain, weight loss, fecal urgency and fecal incontinence [33]. Neither the Hjoortswang criteria nor the MCDAI are currently validated by the Food And

Drug Administration [1].

Since a biopsy is required to assess MC, colonoscopy is the procedure of choice and is generally safe in these patients [1]. The endoscopic appearance is non-specific. In most patients there are no macroscopic changes. Visible changes reported include linear ulcerations, mucosal lacerations, erythema, edema and surface textural alterations [1]. There are also case reports that indicate the presence of pseudomembranes in patients with MC, which resolved after the treatment with budesonide was initiated [34].

There are histopathological criteria when describing both CC and LC.

CC is diagnosed in patients that present a thickened subepithelial collagenous band ≥10μm combined with an inflammatory infiltrate in the lamina propria. Sometimes, crypts may be present in the biopsy specimens. The band is most visible between the crypts [1,30].

The criteria for LC are an increased number of intraepithelial lymphocytes (IEL) ≥20 per 100 surface epithelial cells. Inflammatory infiltrate may be present, but what is most important, when present, is that the collagenous band should not be thickened significantly (≤10 μm) [1,30].

Not otherwise specified (NOS) or incomplete MC include a subgroup of patients with diarrhea that do not present the histopathological criteria for either CC or LC. Patients with incomplete CC present a subepithelial collagenous band measuring between 5 to 10 μm, while patients with incomplete LC have a number of IEL varying between 10 to 20 per 100 surface epithelial cells [1,30].

Celiac disease is more common in patients with MC. One study found that the risk of MC in patients with celiac disease is 70 times higher compared with the general population. The patients diagnosed with both pathologies were older and had more severe villous atrophy [35]. Current recommendations state that patients with MC should be screened for celiac disease [1]. Table IV displays the differential diagnosis of MC.

**Table IV.** Differential diagnosis of MC [30].

| Differential diagnosis of MC |
|---|
| Celiac disease |
| Crohn's disease |
| Irritable bowel syndrome |
| Ulcerative colitis |
| Infectious colitis |
| Laxative abuse |
| Ischemic colitis |
| Bile acide malabsorption |
| Bacterial overgrowth syndrome |
| Giardiasis |
| Hyperthyroidism and thyreotoxicosis |

## Treatment

The main goal of the treatment is achieving clinical remission described by the Hjortswang criteria. Achieving clinical remission significantly increases HR-QoL. The current treatments include general measures, antidiarrhea medication, oral glucocorticoids, immunomodulators, biologic agents, and surgery as a last resort.

General measures include smoking cessation, avoidance of nonsteroidal anti-inflammatory drugs. Each medication associated with the debut of MC should be discontinued, if possible [30].

The main purpose of the antidiarrheal treatment is to decrease the frequency of nocturnal episodes. Loperamide is the agent of choice [36].

Budesonide is a potent glucocorticoid with a broad anti-inflammatory spectrum and high affinity to intracellular glucocorticoid receptors [37]. When budesonide is orally administrated, its effects are most frequently only local, systemic exposure being minimum due to its extensive first-pass metabolism [37]. The current recommendations state that budesonide should be used for inducing clinical remission in patients with MC [38]. Budesonide was shown to induce clinical remission of CC in 88% of patients, compared to patients treated with placebo, of which only 32% achieved remission [39]. The remission was also seen in 84% of patients with LC that were treated with budesonide, compared with 43% in those treated with placebo. It also induces a histological response. One study found that the histological response was noticed in 78% of patients treated with budesonide compared with the response of 32% of the patients treated with placebo [40]. Most patients achieved remission in 6-8 weeks, with 9 mg of budesonide administrated daily. It is also recommended in maintaining remission of both LC and CC, it has a low-risk of systemic adverse effects and it does not increase the risk of bone fractures in prolonged use.

Alternatives to the standard treatment are currently being studied. Beclometasone dipropionate is a topically acting corticosteroid which has the same safety profile as budesonide while being also cheaper [41]. One study showed that after 8 weeks of 10 mg beclometasone daily, 70% of patients were in remission and 77% responded [42]. Further studies are needed to establish beclometasone as a standard treatment in patients with MC and to assess the most appropriate regime.

Mesalazine was considered at one point the standard treatment in patients with MC. Studies showed that its remission rates are consistently lower than those of budesonide. One study that compared the remission rates of budesonide and mesalazine showed that 80% of patients treated with budesonide achieved remission compared to only 44% in patients treated with mesalazine [43].

Patients that present bile acid diarrhea despite budesonide are treated with loperamide and cholestyramine [1]. Cholestyramine is a bile-acid binder that can treat diarrhea in patients with simultaneous bile acid malabsorption [1,44].

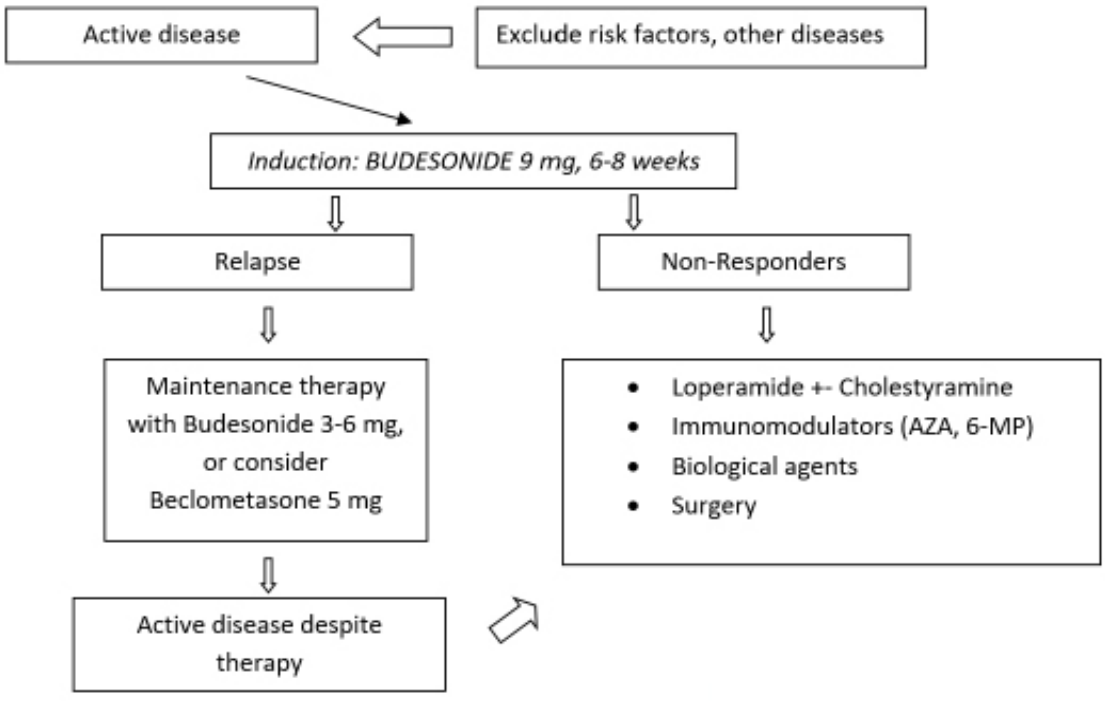


**Figure 1.** Treatment algorithm for microscopic colitis [1].

The role of probiotics was assessed by one study due to the potential pathogenic role of the gut microflora in the development of MC. Lactobacillus acidophilus LA-5 and Bifidobacterium animalis subsp. lactis BB-12 (AB-Cap-10) were not superior to placebo in this study [45]. Further studies are needed to assess the role of probiotics in patients with MC.

Immunomodulators and biological agents are used in selected patients that are non-responders or intolerant to glucocorticoids. In one study, azathioprine induced long-term clinical remission in 28% of patients. The biggest downside of this treatment is that it is not well-tolerated. In the same study, the patients that could not tolerate azathioprine were switched to 6-mercaptopurine. Clinical remission was achieved in 46% of them [46]. The use of methotrexate is not recommendable in treating MC [1,47]. Patients who fail to respond to the standard treatment can benefit from the use of biological agents. Anti Tumor Necrosis Factor agents, including infliximab and adalimumab, and vedolizumab are the agents to be considered in selected patients [1,48,49].

In patients that do not achieve remission despite medical treatment, surgery can be considered. An ileostomy is the procedure of choice, but a total colectomy can also be taken into consideration [1,30]. Figure 1 displays the algorithm of the management of MC.

## Conclusions

Microscopic colitis is increasingly recognized as a common cause of chronic, watery diarrhea and should be taken into consideration by every general practitioner, gastroenterologist or pathologist when making a differential diagnostic, given certain clinical features. It is divided into collagenous colitis, lymphocytic colitis and incomplete microscopic colitis based on the histological findings. The incidence and prevalence rates are comparable to those of well-established inflammatory bowel diseases.

While the pathogenesis is multifactorial, abnormal collagen metabolism or a dysregulated immune response can trigger the symptoms in predisposed individuals. The older age, female sex and use of high-risk medications can give a hint when diagnosing. Patients with active disease present more than 3 stools daily or more than 1 watery stool every day. Since no biomarker or endoscopic aspect is currently pathognomonic for microscopic colitis, only the histological exam is diagnostic. Patients should be screened for celiac disease.

Budesonide is currently the standard treatment in microscopic colitis. Non-responders or frequent-relapsers can be treated with immunomodulators or biological agents. Surgery can be used as a last resort.

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