MICROSCOPIC COLITIS

COLLAGENOUS AND LYMPHOCYTIC COLITIS

Andreas Münch

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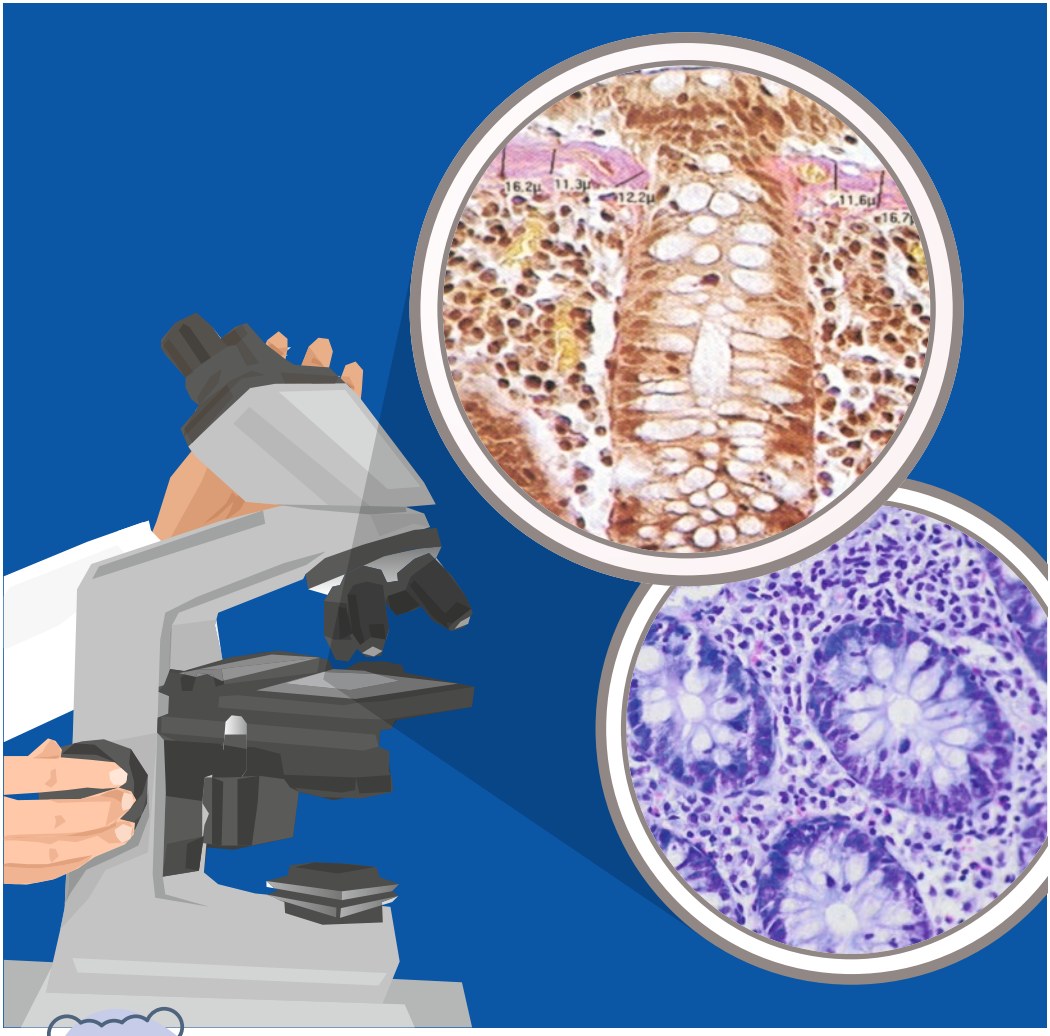

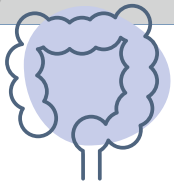

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1 History

Collagenous colitis (CC) was first described in 1976 by Lindström and colleagues as a distinct entity in a patient presenting with watery diarrhea. In 1980, Read et al. introduced the term "microscopic colitis" (MC) to describe 27 patients with chronic diarrhea. In the same year, Lazenby and colleagues demonstrated that the most distinctive histological feature of MC was a marked increase in intraepithelial lymphocytes (IELs), leading them to propose that the condition be renamed "lymphocytic colitis". In 1989, Sylwestrowicz and colleagues coined the term "watery diarrhea–colitis syndrome," reflecting the predominant clinical manifestation shared by both disorders. As increasing numbers of cases were reported, two independent research groups proposed in 1993 that "microscopic colitis" be used as an umbrella term encompassing the two histological subtypes, collagenous colitis and lymphocytic colitis (Figure 1).

A Scandinavian group reported more than 500 cases of microscopic colitis in 1996, and since then, our understanding of the disease has expanded considerably. Pharmacological treatment was initially based largely on empirical experience. However, in 1999, Fine and colleagues published the first controlled clinical trial in collagenous colitis, followed by several randomized controlled trials (RCTs) investigating budesonide. These studies ultimately contributed to the first Cochrane systematic review and meta-analysis by Chande et al. in 2003. In the years to follow, oral budesonide became the first drug approved for the disorder to treat collagenous colitis. Additional controlled studies and meta-analyses on the use of budesonide for the treatment of collagenous and lymphocytic colitis have since confirmed the superior therapeutic benefit of this drug.

Since then, an increasing number of studies have further advanced our understanding of the epidemiology, pathogenesis, diagnosis, and treatment of microscopic colitis. In 2013, Magro and colleagues published the European consensus on the histopathological diagnosis of inflammatory bowel disease, which recognized microscopic colitis and its variants as part of the spectrum of inflammatory bowel diseases.

The publication of these new data, together with the recent treatment recommendations from the European Microscopic Colitis Group (EMCG), provided the impetus for revising this booklet.

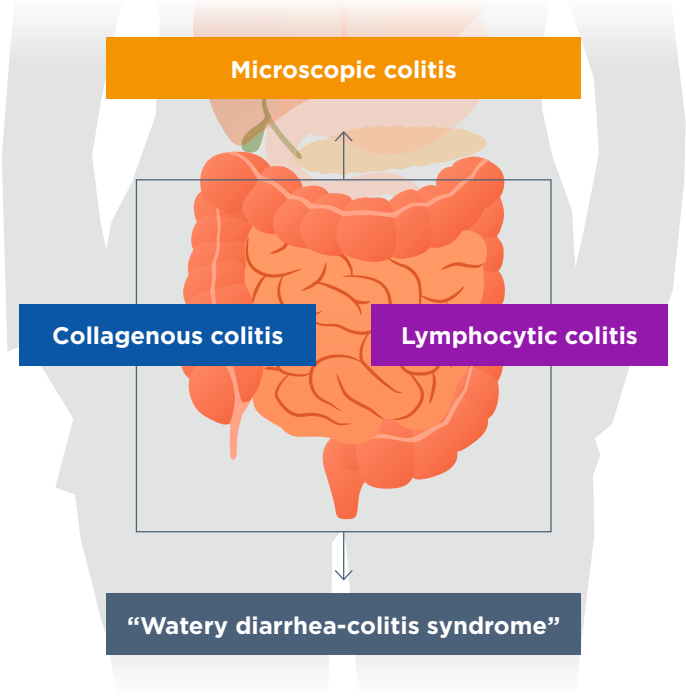


Figure 1: Microscopic colitis is the umbrella term encompassing the two histological subtypes, collagenous colitis and lymphocytic colitis.

2 Epidemiology

Sex ratio

Epidemiological studies to date have shown a clear predominance of women among collagenous colitis patients (female-to-male ratio of 3-5:1). This phenomenon is slightly less pronounced for lymphocytic colitis, with a female-to-male sex ratio of 2-3:1 (see Figure 2) [3–5].

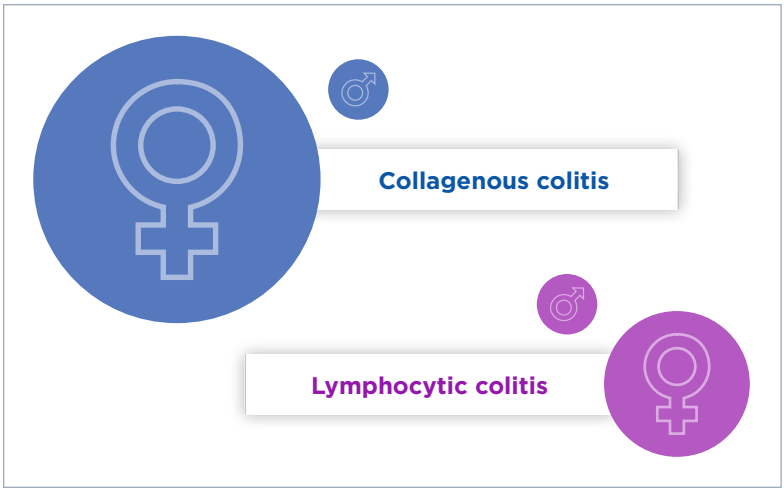


Figure 2: Female sex is a major epidemiologic risk factor for microscopic colitis. Female predominance is strongest in collagenous colitis and less pronounced in lymphocytic colitis [3–5].

Age

A meta-analysis revealed a clear age pattern in the incidence of microscopic colitis, with patients' median age greater than 60 years old (collagenous colitis: 64.9 [95% confidence interval (CI): 57.03–72.78] years old; lymphocytic colitis: 62.2 [95% CI: 54.0–70.4] years old [4]. However, up to 25% of patients diagnosed with collagenous colitis were younger than 45 years [6].

Incidence and prevalence

Epidemiological studies have documented an increasing incidence of microscopic colitis, especially in western, industrialized countries [7]. This increase is likely due both improvements in diagnosis

and increased endoscopic activity, as well as a real increase in the number of actual cases.

An overall pooled incidence rate of 11.4 (95% CI: 9.2–13.6, I^2 = 99.72%) cases of microscopic colitis per 100,000 person-years were calculated based on studies providing population-based data. Several studies from North America and Europe reported variations in incidence rates over a 10-year time period in the same region. They showed an increasing incidence in the early years, which has since reached a plateau. The pooled incidence rate per 100,000 person-years were 4.9 (95% CI: 4.2–5.7) for collagenous colitis and 5.0 (95% CI: 4.0–6.1) for lymphocytic colitis, respectively. Geographic variations in the incidence of microscopic colitis have been reported; however, the limited number of studies from Southern Europe compared to Northern Europe and the lack of direct comparative studies from different countries for the same period does hinder firm conclusions on this matter [1].

Five population-based studies have assessed the prevalence of microscopic colitis and provided a wide range from 47,5 to 219 cases per 100,000 persons. These studies were pooled to provide an overall microscopic colitis prevalence of 119.4 (95% CI: 72.9–165.9) cases per 100,000 persons. For collagenous colitis, the pooled prevalence was estimated to be 50.1 (95% CI: 13.69–76.5), whereas the estimated pooled prevalence of lymphocytic colitis was 61.7 (95% CI: 48.2–75.3) per 100,000 persons.

A meta-analysis of studies examining patients with chronic diarrhea has shown that the frequency of microscopic colitis is approximately 12.8% (95% CI: 10–16) [1].

Childhood microscopic colitis

Childhood onset of microscopic colitis is rare, and hence patient data in this age group is scarce. A study by El-Matary et al. described cases in 11 adolescent patients (mean age: 11.2 years old) [8]. However, it must be noted that only five of these children had lymphocytic colitis, while the other six were diagnosed with either non-specific colitis or eosinophilic colitis [8].

Microscopic colitis vs. inflammatory bowel disease (IBD)

Microscopic colitis belongs to the spectrum of inflammatory bowel diseases (IBD), an umbrella term that mainly includes ulcerative colitis and Crohn's disease. These conditions are characterized by

chronic inflammation of the gastrointestinal tract, leading to various digestive symptoms.

It is possible to directly compare the incidence of microscopic colitis with that of IBD for several European countries. During the period from 1980 to 2013, the incidence of Crohn's disease increased from 5.2 to 9.1 per 100,000 residents, while the incidence of ulcerative colitis rose from 10.7 to 18.6 [9]. By comparison, the Danish Pathology Register conducted a nationwide cohort study which showed that the overall incidence of microscopic colitis increased significantly in Denmark from 2.3 cases per 100,000 persons in 2001 to 24.3 cases per 100,000 persons in 2016. The highest observed incidence of microscopic colitis was 32.3 per 100,000 persons in 2011 [10].

In Northern France (EPIMAD register), the annual standardized incidence was 7.4 per 100,000 residents for Crohn's disease and 4.9 for ulcerative colitis, compared with 7.9 per 100,000 residents for microscopic colitis [11]. This data suggests that the incidence of microscopic colitis is comparable to, or may have even over-taken that of classical IBD.

3 Etiology and pathogenesis

The pathogenesis of microscopic colitis remains incompletely understood. The disease appears to be caused by multiple factors, including genetic and immunological factors, luminal agents, as well as mucosal aberrations (Figure 3). Explorative studies at the genetic and transcriptional levels have shed more light on the pathobiology of microscopic colitis and have demonstrated that collagenous colitis and lymphocytic colitis differ on a molecular level [2]. Medications and smoking appear to play a triggering role [12–15].

Genetics

A genome-wide association study meta-analysis, which included 1498 collagenous colitis and 373 lymphocytic colitis patients, highlighted HLA genes as predisposing factors for collagenous colitis, with HLA-DRB1*03:01 and the ancestral 8.1 haplo-type being dominant [2]. This study also showed partial genetic overlap of collagenous colitis with celiac disease and Crohn's disease as well as ulcerative colitis, based on enrichment of concordant genetic risk effects at immune-related loci. However, lymphocytic colitis lacks these genetic associations suggesting that collagenous colitis and lymphocytic colitis have different underlying pathophysiological mechanisms [2].

Genetic susceptibility may contribute to collagenous colitis pathogenesis. While associations with MMP-9 polymorphisms support a role for extracellular matrix remodeling, the evidence for TNF-α involvement is less compelling [16].

Immunology and autoimmunity

Histopathological examination of biopsy samples reveals extensive lymphocyte infiltration into microscopic colitis mucosa, which is accompanied by an inflammatory infiltrate – mainly lymphocytes and plasma cells with few eosinophils and neutrophils – in the lamina propria. Regulatory T cells appear to be unchanged in collagenous colitis mucosa, while a subset of non-suppressive FoxP3+ effector T helper (Th) cells is increased [17].

There is evidence that both the innate and adaptive immune system are involved in the pathogenesis of microscopic colitis; however, the exact role of each is not known [17]. Biopsy cytokine and immune cell analyses have suggested a mixed Th1/T cytotoxic (Tc)1 and Th17/Tc17 phenotype and cytotoxic T lymphocyte pro-

file in microscopic colitis [18]. However, since attempts to correlate mRNA expression with protein cytokine levels have consistently failed, the Th1/Tc1–Th17/Tc17 immune response in microscopic colitis remains unclear [19].

The fact that autoantibodies such as anti-nuclear antibodies (ANA), anti-Saccharomyces cerevisiae antibodies (ASCA), and thyroid peroxidase (TPO) antibodies are more prevalent in collagenous colitis and lymphocytic colitis than in controls has led to the hypothesis that microscopic colitis might have an autoimmune etiology [20]. Adding to that, concomitant autoimmune disorders have been reported in microscopic colitis. Among them, the strongest association was found with celiac disease, followed by Crohn's disease and ulcerative colitis, as well as autoimmune thyroid disease [21]. Despite the lack of genetic association of lymphocytic colitis with HLA genes, its association with celiac disease is similar to that of collagenous colitis, reaching up to 6% of all cases [22].

Despite these findings, there is no direct evidence that autoimmunity plays a key role in the pathogenesis of microscopic colitis, and to date, no biomarker has been identified to establish the diagnosis.

Influence of medications

Published study data support the hypothesis of an association between microscopic colitis and the use of non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and selective serotonin reuptake inhibitors (SSRIs). One case-control study with 5751 microscopic colitis patients demonstrated that these patients took PPIs, NSAIDs, statins, or SSRIs more frequently than the equivalent control groups [12].

An elevated risk of microscopic colitis has been described for NSAID and PPI use [13]. One epidemiological meta-analysis has reported that the risk of developing microscopic colitis is associated with the use of PPIs (OR = 2.8; 95% CI: 1.73–4.17) and SSRIs (OR = 2.4; 95% CI: 1.64–3.53) [4].

In addition, a case-control study analyzing a British database with more than 1200 patients between 1992 and 2013, found that the duration of PPI therapy (4–12 months) also appears to play a role. In this study, the greatest risk of developing microscopic colitis (5-fold higher) was observed with concurrent use of NSAIDs and PPIs [14].

A prospective case series of 8 patients with lansoprazole-associated microscopic colitis reported that discontinuation of PPI

therapy resulted in resolution of microscopic colitis without the need for further treatment [23]. However, this might not reflect a general class effect of PPI drugs [14].

NSAIDs can increase the permeability of the intestinal mucosa and may allow luminal agents to leak into the body. A study in 1992 reported higher use of NSAIDs among 31 patients with collagenous colitis versus 31 control patients with irritable bowel syndrome or diverticular disease. In particular, the onset of collagenous colitis was significantly higher among patients taking NSAIDs for longer than 6 months [24].

According to the EMCG recommendations, if the onset of symptoms coincides with the start of a new treatment, the latter should be discontinued [1].

Influence of smoking

Studies on the smoking habits of patients with microscopic colitis reported smoking to be a risk factor for developing microscopic colitis [1]. The disease also has an earlier age of onset in smokers

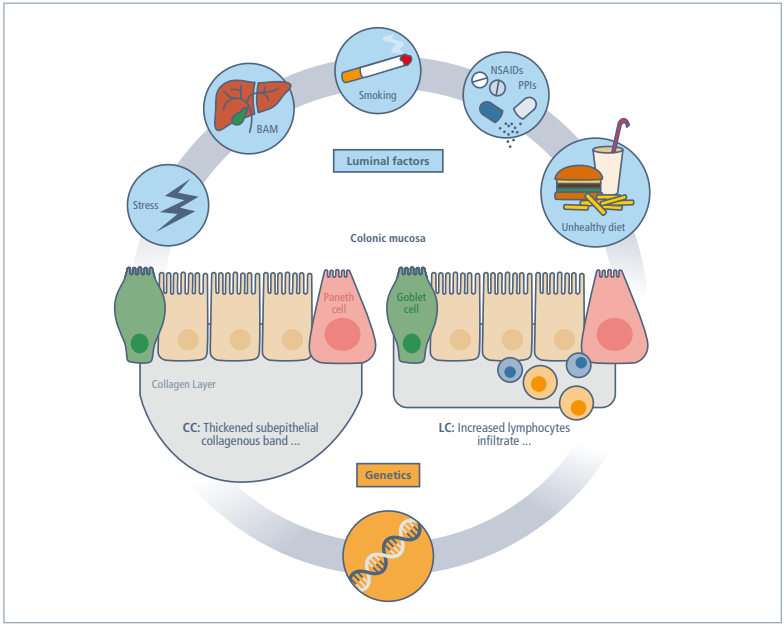


Figure 3: Genetics and luminal factors in microscopic colitis. BAM: bile acid malabsorption, CC: collagenous colitis; LC: lymphocytic colitis. Modified from [25].

than non-smokers. One study confirmed the association between smoking and microscopic colitis [15]. Adding to this, according to a recent meta-analysis, both smokers and even ex-smokers are at a significantly higher risk of developing microscopic colitis [26].

In one case-control study [27] with 116 patients, the percentage of smokers was (significantly) higher among patients with collagenous colitis, at 37%, versus a control group (17.0%; $p < 0.001$). The percentage of smokers was particularly high among patients between the ages of 16 and 34, at 75% vs. 15%. The age of initial disease onset was 42 years old for smokers versus 56 years old for non-smokers ($p < 0.003$). One possible explanation for this phenomenon is the greater permeability of the intestinal mucosa under the influence of nicotine. A post-hoc analysis by Münch and colleagues could show that smoking exacerbated the clinical symptoms of collagenous colitis and was associated with an increased number of watery stools; furthermore, smoking reduced the probability of achieving clinical remission [28].

Collagen synthesis and degradation

Data on collagen metabolism in the intestinal mucosa in patients with collagenous colitis indicates a normal architecture and extracellular matrix outside of the collagen band and no increase in type VI collagen mRNA levels [29]. Together with the reduction in levels of matrix metalloproteinase-1 and the increase in tissue inhibitor metalloproteinase-1 [30], these findings suggest diminished degradation of collagen. In contrast, no evidence for increased collagen synthesis was found [29].

Mechanism of diarrhea

Several models have been proposed to explain the pathology of chronic diarrhea in collagenous colitis, based on the small number of experimental studies available. Defective transport mechanisms together with the increased thickness of the collagen band lower the absorption of sodium and chloride ions. In addition, active chloride secretion may also play a role [31]. This explanation is consistent with observations that the epithelial sodium channel is inhibited in the sigmoid colon of patients with lymphocytic colitis [32] and that the concentrations of fecal sodium and chloride concentrations are elevated in patients with microscopic colitis [33].

Recent studies have investigated the expression of aquaporins (water channels) in mucosal samples from patients with collagenous colitis. The results of these studies suggest that dysregulated transcellular water transport, specifically a loss of aquaporin 8 in

intestinal epithelia, is a causative mechanism in chronic diarrhea which can be termed “malabsorptive”. This model is compatible with the current paradigm of secondary fluid loss due to altered osmoregulation in the gut, and may explain the massive, rapid changes in stool frequency and consistency [34].

Fecal stream diversion/microbiome

Microscopic colitis patients very rarely require surgery. However, among those who do, fecal stream diversion via ileostomy has been observed to resolve colonic inflammation. Moreover, inflammation recurs once intestinal continuity is restored [35]. These observations reinforce the theory that luminal factors trigger the inflammation occurring in microscopic colitis. Similar to IBD, collagenous colitis displays an abnormal epithelial translocation of bacteria that could be responsible of triggering collagenous colitis inflammation [36].

In recent years, the potential role of the microbiome in the development, progression, and treatment of IBD has been the focus of a great deal of research. Human studies have shown that there are differences in the gut microbiota between IBD patients and healthy controls, which is also the case for microscopic colitis.

Microscopic colitis is characterized by intestinal dysbiosis and its profile is shared with other IBD forms [37].

However, whether dysbiosis is causative or consequential to the inflammation remains unknown. At taxonomic levels, a decreased concentration of the epithelial-protective Akkermansia muciniphila bacteria and the Clostridia-related, butyrate-producing Ruminococcaceae bacteria family have been reported in microscopic colitis [38].

Another study has shown that treatment with budesonide can alter the microbiome in microscopic colitis patients such that the microbiome composition approaches that of healthy controls [39]. Furthermore, several case reports have demonstrated that fecal microbiota transplantation can be effective against microscopic colitis [40]. In 2020, in a pilot study of nine patients with collagenous colitis, three repeated fecal microbiota transplantations (FMTs) resulted in clinical remission (< 3 stools whereof < 1 watery stool per day) in three of the nine patients after 8 weeks and significantly improved several symptom-related and quality-of-life measures, although no significant reduction in watery stool frequency was observed overall [41].

4 Diagnosis

Endoscopy

Endoscopy is a proven method for diagnosing microscopic colitis. It also allows biopsies to be taken from multiple sites of gut mucosa with normal appearance, even in patients with unremarkable endoscopic findings. According to the European guidelines for microscopic colitis, collection of two biopsies each from the left and right colon is sufficient for confirmation of a diagnosis [1].

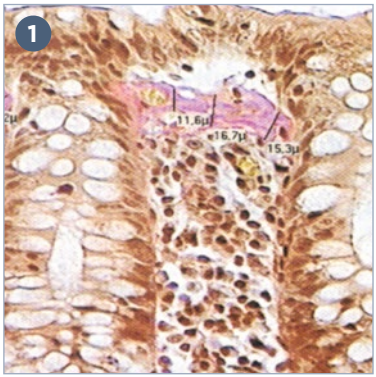
Numerous studies have shown that microscopic colitis can be diagnosed in more than 10% of patients with watery diarrhea lasting longer than 4 weeks and normal endoscopy findings [42].

Because the mucosa typically appears normal by endoscopy, the characteristic histological features of microscopic colitis represent the definitive diagnostic criteria. Subtle, non-specific mucosal changes such as edema or mucosal erythema have been described [43]. In one study, 37% of collagenous colitis patients exhibited subtle mucosal features such as erythema, edema, or irregular vascular patterns [5].

Histology

The main histological feature of collagenous colitis is a thickened subepithelial collagen band ≥ 10 µm (normal: 2–7 µm). An additional diagnostic criterion is inflammatory infiltrates in the lamina propria consisting of lymphocytes and plasma cells (Figure 4).

The main histological feature of lymphocytic colitis is increased intraepithelial T lymphocytes in the surface epithelia of the colonic mucosa. The definitive criterion is the detection of > 20 intraepithelial lymphocytes per 100 epithelial cells. The surface epithelia appear flattened and narrow. In contrast to collagenous colitis, the collagen band is not thickened in the subepithelial stroma (Figure 4a). Intraobserver and interobserver agreement in histological evaluation of microscopic colitis is high [44].



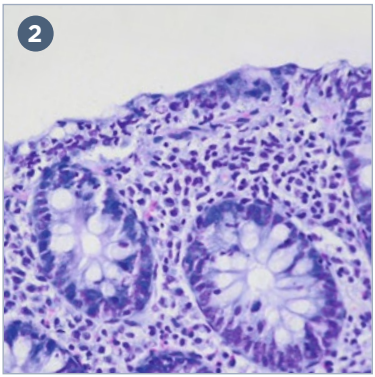


Figure 4a:

1 **Collagenous colitis:**
ssubepithelial collagen deposition'
≥ 10 µm (normal: 2–7 µm)

2 **Lymphocytic colitis:**
elevated counts of intraepithelial lymphocytes (CD3+) > 20/100 epithelial cells (normal: 3–5/100)

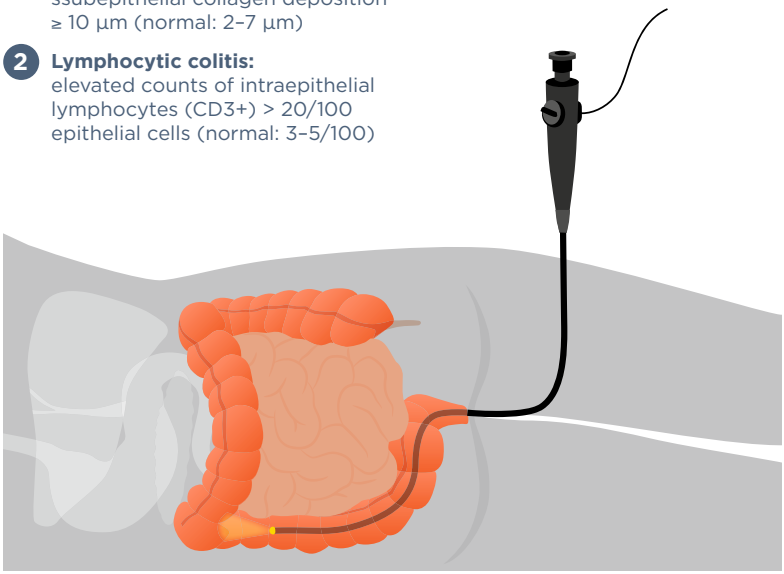


Figure 4b: Colonoscopy with removal of tissue samples from different segments of the colon with a minimum requirement of two samples each from the left and right colon.

Incomplete microscopic colitis

Several variants of microscopic colitis have been described under different names. Most recently, "incomplete microscopic colitis" has been the most common term used to describe patients who exhibit clear clinical features of microscopic colitis, mainly chronic, watery diarrhea, but do not meet the morphological criteria for lymphocytic colitis or collagenous colitis. Histological findings include an increased number of intraepithelial lymphocytes (> 5 and < 20) per 100 epithelial cells (incomplete lymphocytic colitis) or abnormal thickening of the subepithelial collagen band (> 5 and < 10 μm) (incomplete collagenous colitis) in conjunction with increased inflammatory infiltrates in the lamina propria [45].

One study has shown that intraobserver and interobserver agreement is high regarding the ability to discriminate between microscopic colitis/incomplete microscopic colitis and non-microscopic colitis, but lower for the ability to discriminate between incomplete microscopic colitis and collagenous colitis or lymphocytic colitis [44].

More studies are needed to evaluate this concept. However, this may eventually result in the need to revise the histological criteria for the subtypes of microscopic colitis and to reach a new consensus.

Objective markers/calprotectin

In general, microscopic colitis patients show no signs of laboratory abnormalities, e.g. electrolyte loss. X-ray of the bowel has no role in the diagnostic procedures for microscopic colitis.

Concerning calprotectin, small studies have demonstrated that fecal calprotectin was slightly higher in those with microscopic colitis as compared to patients without an organic cause of diarrhea and irritable bowel syndrome (IBS); however, the predictive value was low due to a large overlap [46, 47]. The UEG-EMCG recommendations state that fecal calprotectin is not useful for excluding or monitoring microscopic colitis and to date, there is no biomarker for microscopic colitis [1].

5 Clinical presentation

Symptoms

Chronic diarrhea, mainly watery, is the main characteristic symptom of microscopic colitis that is observed in nearly all patients. Patients with microscopic colitis also frequently report nocturnal diarrhea, weight loss, abdominal pain, and bowel urgency/-incontinence. The classic symptoms were observed at baseline in a European prospective incident cohort study (Table 1). Blood or mucus in the stool are very rarely observed in microscopic colitis. It has been shown that health-related quality of life (HRQoL) was impaired in patients with collagenous colitis compared with the general population. Disease activity is the most important factor associated with impairment of HRQoL, which is normalized in patients in remission [48]. The symptom of weight loss must be qualified by the observation that many patients alter their dietary habits in order to reduce their stool frequency. Bohr and colleagues have shown that fasting leads to a significant reduction in stool weight. They also reported a trend of lower fecal sodium concentration [49]. This explains why patients who initiate fasting on their own initiative report clinical improvement but may also experience weight loss [6].

Symptoms and stool frequency	
One-week defecation diary and self-reported combined Number of daily stools[1] Number of daily watery stools[1]	 3.7 ± 2.7 2.1 ± 2.8
Urgency	82% [78–86%]*
Fecal incontinence	39% [33–44%]*
Nightly defecation	45% [40–51%]*
Abdominal pain	48% [44–54%]*
	*95% CI

Table 1: Systems and stool frequency at baseline of a European prospective incident cohort study [50].

[1] One-week-defecation-diary and self-reported combined

Associated disorders and differential diagnoses

Celiac disease

Celiac disease appears to be closely associated with microscopic colitis [51]. A large, prospective study reported a 3.3% incidence of celiac disease among patients with microscopic colitis versus 0.4% among controls [52]. A study in a pathology registry with 3456 microscopic colitis patients who had undergone both upper endoscopy and colonoscopy with biopsy demonstrated that the presence of celiac disease is greater among patients with microscopic colitis than among the general population [53]. However, in many of these retrospective cohort studies, celiac disease was primarily diagnosed using biochemical tests and not by histology. According to Liu and colleagues, microscopic colitis is not associated with gluten uptake [54]. A recent nationwide population-based matched cohort study confirmed the strong association of microscopic colitis with celiac disease with an increased risk of future and previous microscopic colitis in celiac disease patients. This finding further underscores the need to consider the concomitance of these diagnoses in cases in which gastrointestinal symptoms persist or recur despite a gluten-free diet or conventional microscopic colitis treatment [22]. Based on the data available, the European Microscopic Colitis Group (EMCG) recommends testing all microscopic colitis patients for celiac disease [1].

Differentiation from Crohn's disease and ulcerative colitis

IBD primarily afflicts younger patients at an equal sex ratio; in contrast, microscopic colitis patients are typically over the age of 50 and approximately 70% are female [4, 9]. Diarrhea is typically watery in microscopic colitis, whereas Crohn's disease and ulcerative colitis are characterized by primarily soft stools with blood and mucus. While patients with microscopic colitis may have low body weight, their general health status is usually unaffected or only mildly impacted. Whereas IBD usually presents with typical changes to the intestinal mucosa (aphthous ulcers, bleeding), microscopic colitis patients usually have no endoscopic abnormalities.

Instead, the diagnosis must be made and/or confirmed by histology (to differentiate it from irritable bowel syndrome) [1]. Case reports have described an overlap between Crohn's disease or ulcerative colitis and microscopic colitis and basic science findings indicate genetic, immunological, and microbiome similarities between microscopic colitis and IBD [19].

Differentiation from irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that includes subtypes such as IBS-D (diarrhea-predominant), IBS-C (constipation-predominant) and IBS-M (mixed type). Reported IBS prevalence rates vary broadly (1.1%–45.0%) with national differences and methodological differences between the different studies; on behalf of the ROME Foundation, Sperber et al conducted a survey in 2021 interviewing 73076 adults from 26 countries and found a prevalence of 4.1% (3.9%–4.2%) of whom approximately 29% have IBS-D [55].

Since patients with microscopic colitis often experience abdominal pain, about one-third to one-half of these patients would also meet the symptom criteria for IBS [56, 57]. Furthermore, it has been observed that 7% of patients who meet the diagnostic criteria for IBS-D actually have microscopic colitis [57]. Because there is limited awareness of microscopic colitis, especially among primary care physicians – where the majority of IBS cases are diagnosed – there is a high risk that microscopic colitis patients will be misdiagnosed with IBS-D.

Patients with microscopic colitis typically have a different clinical history than patients with IBS (Table 2) and risk factors differ (Table 3), underscoring the importance of collecting a thorough medical history [57].

Characteristic features of microscopic colitis are advanced age (> 50 years old) and watery/soft diarrhea potentially causing fecal urgency and fecal incontinence. Patients may experience nocturnal stools, and weight loss is common. In contrast, IBS most frequently afflicts younger patients (< 50 years old) and is accompanied by stools of various consistency the frequency of which can change daily. In contrast to microscopic colitis, IBS is frequently associated with bloating/flatulence and incomplete bowel evacuation [56, 57]. Nonetheless, the most pragmatic approach is to refer patients with chronic (> 4 weeks), primarily watery diarrhea for a colonoscopy with biopsy to detect microscopic colitis, regardless of age or sex. Histological examination of colon biopsies remains the only procedure that can establish a diagnosis of microscopic colitis [1].

Clinical factors	IBS	Microscopic colitis
Stool consistency	Soft – variable – solid	Watery/soft
Stool frequency	Can vary from day to day	High and rather constant
Nocturnal diarrhea	Rare	Possible
Sensation of incomplete bowel evacuation	Common	Uncommon
Weight loss	Rare	Common
Fecal incontinence	Common	More common
Bloating/flatulence	Common	Rare
Pain	Mandatory	Possible

Table 2: Differences in the clinical history between patients with IBS and with microscopic colitis. Based on [56–58] and author's own clinical experience.

Risk factors	IBS	Microscopic colitis
Age at diagnosis	Mainly < 50 years	Mainly > 50 years
Smoking	No	Yes
Response to loperamide	Strong	Weak
Association with other autoimmune diseases	No	Yes
Association with other functional gastro-intestinal disorders		Weak
Strong		No
Weak	Common	Uncommon
Association with other pain syndromes	Yes	No
Psychological comorbidity	Common	Uncommon

Table 3: Risk factors for irritable bowel syndrome (IBS) and microscopic colitis that could be used to distinguish between the two diseases. Based on [57], [58] and author's own clinical experience.

6 Treatment

Response criteria

The goal of treating microscopic colitis is to achieve clinical remission, thereby leading to improvements in health-related quality of life (HRQoL). At present, no biomarkers are available to measure disease activity, and histological evaluation of both remission and relapse is not standardized. Furthermore, no correlation has been established between clinical disease activity and histological markers, which is why histological monitoring of patients with microscopic colitis is not recommended [1].

To date, there are no formally validated methods for measuring disease activity. In one population-based study, patients with an average of < 3 stools/day and < 1 watery stool/day reported no impact or little impact on HRQoL in a one-week survey and were therefore defined as being in remission. In contrast, patients with either ≥ 3 stools/day or ≥ 1 watery stool/day reported a major impact on HRQoL and were therefore defined as having active disease. This definition of disease activity is often referred to as "Hjortswang criteria" (Table 4).

	Stools per day		Watery stools per day
Clinical remission	< 3	**AND**	< 1
Clinical activity	≥ 3	**OR**	≥ 1

Table 4: Clinical criteria for disease activity of microscopic colitis [48].

These criteria have proven to be simple to apply and useful for patient care in multiple randomized controlled trials and in clinical practice.

Pharmacological basis of treatment with budesonide

Table 5 illustrates the difference between regimens of the locally acting, second-generation budesonide versus standard systemic corticosteroids (e.g. prednisolone). Prednisolone is rapidly absorbed after oral administration, enters the systemic circulation, and exerts glucocorticoid receptor mediated effects throughout the body. In contrast, oral budesonide formulations have been

specifically designed to achieve targeted drug delivery within the gastrointestinal tract while minimizing systemic exposure.

Most budesonide formulations release the active substance in a pH-dependent manner from the terminal ileum onwards, allowing delivery to the affected intestinal segments. Owing to its high affinity for the glucocorticoid receptor, budesonide can exert potent local anti-inflammatory effects within the intestinal mucosa. After absorption, budesonide is transported via the portal circulation to the liver, where more than 90% of the drug undergoes first-pass metabolism [59]. As a result, only a small proportion (around 10%) [60, 61] reaches the systemic circulation, associated with to a lower risk of systemic corticosteroid adverse effects compared with conventional systemic steroids such as prednisolone [60] and no clinically meaningful difference in adverse events and tolerability compared to placebo for short term treatment [59].

The concept of targeted intestinal drug delivery has been successfully established with oral mesalazine formulations for ulcerative colitis and has similarly been applied to budesonide. In microscopic colitis, pH-dependent delivery enables high local concentrations of budesonide at the site of inflammation, where its strong receptor affinity contributes to effective anti-inflammatory activity.

	Prednisolone	Budesonide
Systemically bioavailable	~80%	10%
First-pass metabolism	0–30%*	90%

First-pass metabolism: 90% of budesonide is inactivated in the liver before reaching the body

Table 5: Systemic vs. topical steroid therapy of microscopic colitis. *True first pass effects may be masked by reverse metabolism between prednisone and prednisolone [60–62].

A study investigated in 2006, the effects of budesonide on bile acid absorption by ^{75}Se-labeled homocholic acid-taurine testing in 15 patients with collagenous colitis [63]. Following 8 weeks of budesonide therapy, patients experienced a major increase in bile acid absorption from 23 ± 9.9% to 40 ± 14.7%.

These results suggest that budesonide might also exert its effects via an interaction with bile acid metabolism in a manner that increases bile acid absorption.

As mentioned above, the diarrheal mechanism in microscopic colitis is believed to be a down-regulation of aquaporin 8 in the large bowel resulting in malabsorption of water. Experimental data suggest that steroid drugs directly and rapidly increase aquaporin levels in intestinal epithelial cells, which may restore intestinal water homeostasis and thereby improve bowel frequency and consistency irrespective of additional anti-inflammatory steroid effects [34].

Induction therapy with budesonide

Budesonide for collagenous colitis

The clinical effects of budesonide at a daily dose of 9 mg on watery diarrhea were generally positive in four pilot studies [64–67].

Since these studies, four placebo-controlled studies [68–71] and two meta-analyses [72, 73] have been published in the past years on the effectiveness of oral budesonide (daily dose: 9 mg for 6–8 weeks) for the treatment of collagenous colitis. In these

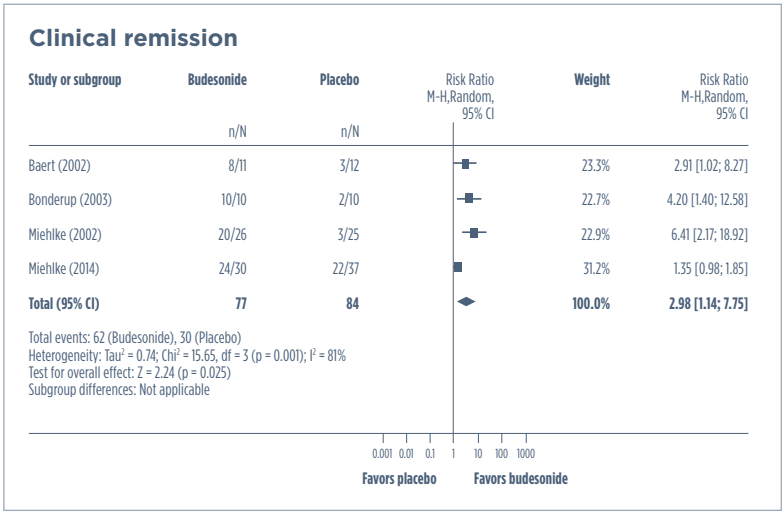


Figure 5a: Meta-analysis: budesonide vs. placebo for induction therapy of collagenous colitis [73].

studies, budesonide was significantly superior to placebo regarding clinical and histological response.

According to the meta-analysis by Kafil and colleagues [73], three of the four individual studies on the induction of clinical and histological remission of collagenous colitis demonstrate a clear benefit of budesonide versus placebo [74] (Figures 5a + b).

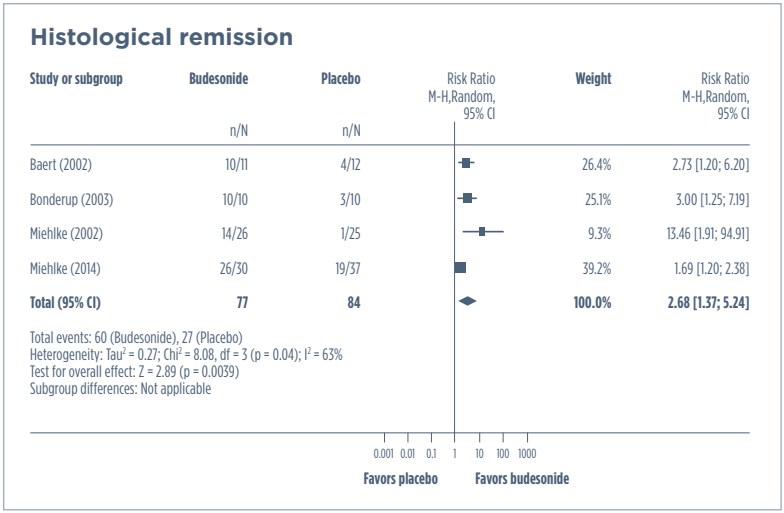


Figure 5b: Meta-analysis: budesonide vs. placebo for induction therapy of collagenous colitis [73].

A placebo-controlled multicenter study compared the effects of 9 mg budesonide daily (n = 30) versus 3 g mesalazine (n = 25) or placebo (n = 37). Clinical remission following 8 weeks of therapy was defined as ≤ 3 stools/day and < 1 watery stool/day in accordance with Hjortswang criteria. Using these criteria, 80% of patients achieved clinical remission with budesonide versus 37.8% of patients receiving placebo and 44% receiving mesalazine. Budesonide was significantly superior to both placebo (p = 0.006) and mesalazine (p = 0.0035). A fully successful treatment outcome was observed already within the first 14 days after the start of treatment with budesonide (average of 7 days with budesonide versus 21 days with placebo). The rate of adverse effects was comparable in all three arms of the study [71].

Others have also reported significant improvement in quality of life after treatment with budesonide versus placebo [75].

Because of its established clinical effectiveness, budesonide is considered the standard therapy for the induction of remission in collagenous colitis [1].

Budesonide for lymphocytic colitis

Placebo-controlled studies on lymphocytic colitis have compared the effects of 9 mg budesonide versus placebo for induction therapy [76–78].

Response was significantly higher with budesonide ($p < 0.01$) with a reported NNT of 3 [74]. Clinical remission was achieved by 86% of patients in the budesonide arm versus 48% in the placebo arm ($p = 0.01$). The NNT was reported to be 3. Histological remission was observed for 73% of patients with budesonide and 31% with placebo ($p = 0.03$). The NNT was also 3 [74, 77].

The most recent study compared budesonide at a dosage of 9 mg daily versus 3 g mesalazine and placebo for 8 weeks. In this study, budesonide was significantly superior to placebo in both clinical remission (79% vs. 42%; $p = 0.01$) and histological remission (69% vs. 21%; $p = 0.008$). No significant difference was

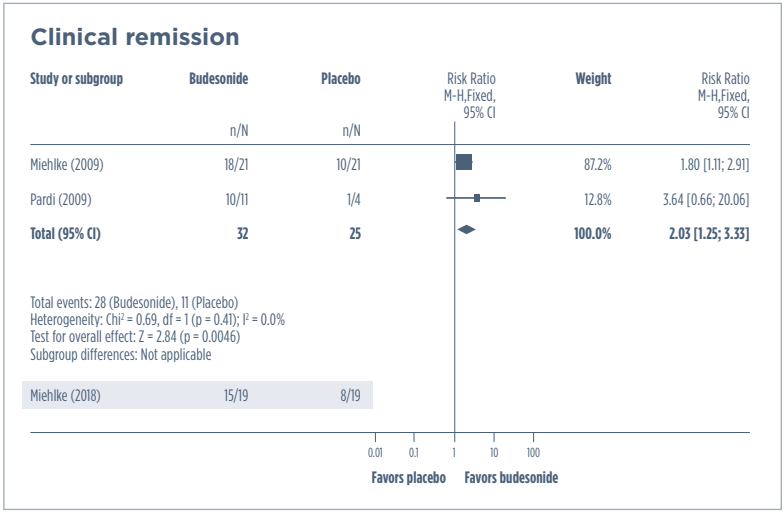


Figure 6a: Budesonide vs. placebo for induction therapy of lymphocytic colitis [74, 76].

observed between mesalazine and placebo regarding clinical remission (63% vs. 42%; p = 0.09), and mesalazine was also significantlyinferior to budesonide in histological remission (68% vs. 26%; p = 0.02) [76].

Due to its proven clinical effectiveness, budesonide is considered to be the standard treatment for the induction of remission in lymphocytic colitis [1].

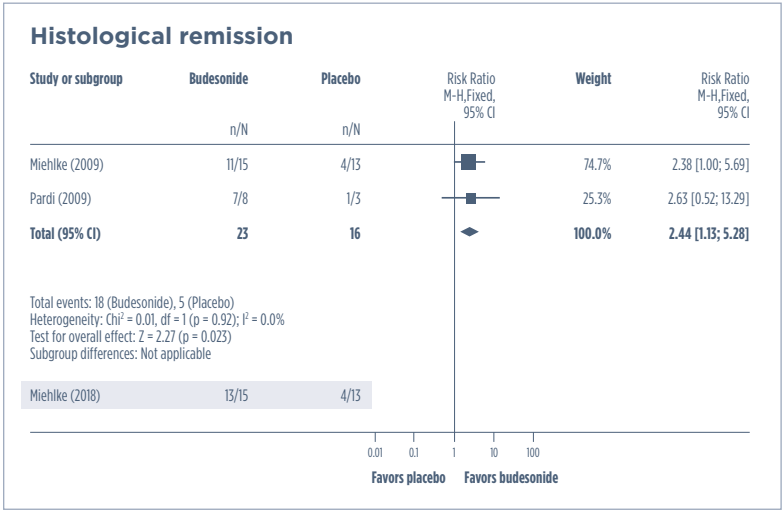


Figure 6b: Budesonide vs. placebo for induction therapy of lymphocytic colitis [74, 76].

Maintenance therapy with budesonide

Budesonide for collagenous colitis

In an analysis of 123 subjects in four randomized controlled trials who achieved clinical remission after short-term therapy with 9 mg budesonide per day, an overall relapse rate of 61% was calculated. Time to relapse was shorter in patients with a baseline stool frequency of > 5 per day. However, budesonide delayed the time to relapse from 56 to 207 days (p = 0.005). This high relapse rate points to the need for therapy to maintain remission [79].

The initial research on maintenance therapy for collagenous colitis centered around budesonide, including two studies [80, 81] and a meta-analysis [73]. Given its demonstrated positive effects,

budesonide is supported by high level evidence for treatment [80, 81]. An initial randomized, placebo-controlled trial with 48 subjects demonstrated the positive benefit of budesonide versus placebo for the maintenance of remission in collagenous colitis. Clinical remission was first induced in an open-label phase with 9 mg budesonide. Patients were then randomized into two groups (n = 23 each). Patients in the investigational drug group received 6 mg budesonide per day. The relapse rate after 24 weeks was significantly lower in the budesonide group at 26% compared with the placebo group at 65% ($p = 0.022$) [81].

A second randomized, placebo-controlled trial with 42 collagenous colitis patients utilized the same design. Following induction of remission with 9 mg budesonide daily for 8 weeks, subjects who responded were randomized.

The relapse rate was 4/17 (23%) after 24 weeks of treatment in the budesonide group and 15/17 (88%) in the placebo group. This difference was highly significant ($p < 0.001$). However, patient follow-up for another 24 weeks without treatment revealed a relevant increase in the relapse rate among the group previously treated with budesonide, meaning that a significant difference could no longer be observed after 48 weeks of follow-up [80].

Accordingly, a meta-analysis demonstrated the relevant benefit of budesonide therapy versus placebo for maintenance of clinical (Figure 7a) and histological remission (Figure 7b) in patients with collagenous colitis [73].

A prospective, placebo-controlled study investigated the effects of a lower-dose maintenance therapy following initial induction of remission with 9 mg for 12 months. The rate of clinical remission during the initial phase was 84.5% while the median time to remission was 10.5 days [82].

The 1-year remission rate was much higher in the budesonide group at 61.4% (27/44 patients) versus 16.7% (8/48 patients) in the placebo group. This study also used the Hjortswang criteria to define remission [48]. Budesonide was administered at alternating daily doses of 6 mg and 3 mg (mean dose 4.5 mg/day).

Currently, there is no data on maintenance therapy of lymphocytic colitis. However, as collagenous colitis and lymphocytic colitis have the same clinical symptoms and results in induction therapy, budesonide is also used for and recommended by the European Guideline in for maintenance in lymphocytic colitis [1].

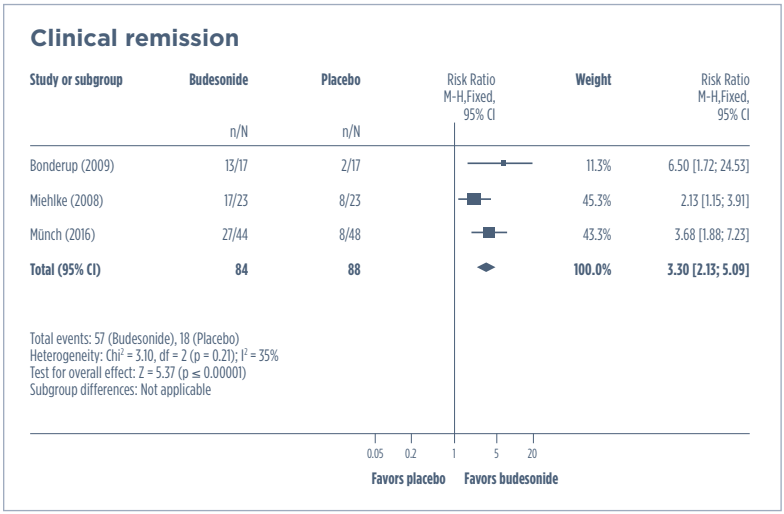


Figure 7a: Meta-analysis: budesonide vs. placebo for maintenance therapy of collagenous colitis [73].

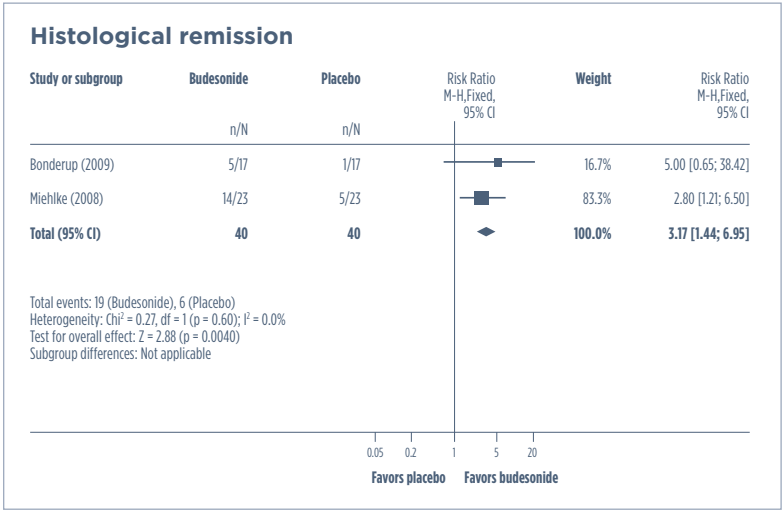


Figure 7b: Meta-analysis: budesonide vs. placebo for maintenance therapy of collagenous colitis [73].

Advanced therapies

Advanced therapies become a reasonable option when patients do not respond to or do not tolerate budesonide, both of which are rare occurrences. According to clinical trials, patients with microscopic colitis achieve clinical remission within 4 weeks of induction therapy with 9 mg budesonide and can maintain this remission using ≤ 6 mg budesonide. The Hjortswang criteria for disease activity are a useful tool for defining non-response or intolerance to budesonide, as shown in Table 6.

To date, no randomized controlled trials have been conducted on treatment using immunomodulators or biologics.

Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) have shown limited efficacy in small case series [83].

Three systematic reviews on biologic therapy in microscopic colitis have been published [84–86]. The pooled analysis of 14 studies (n = 164 patients) showed a remission rate for induction therapy of 63.5%, 57.8%, and 39.3% for vedolizumab, infliximab, and adalimumab, respectively. For maintenance, remission rates were 65.9%, 45.3%, and 32.5%. The rates of therapy limiting biologic-related adverse events were 12.2%, 32.9%, and 23.0%, respectively. In a separate article, tumor necrosis factor (TNF) inhibitors (infliximab and adalimumab) demonstrated a response rate of 73% with a remission rate of 44%. The response rate for vedolizumab was similar; 73% response with a remission rate of 56% [85]. A large retrospective European series analyzed 142 patients with microscopic colitis who were treated with advanced therapies following budesonide failure or tolerance: Anti–TNF agents were commonly used as first-line options, Vedolizumab and Ustekinumab were often given as second- or third-line therapies.

Although induction results were encouraging, discontinuation rates remained substantial (between 55% and 64% for monoclonal antibodies and 24% for JAKi), primarily due to primary non-response (45.9%), secondary loss-of-response (28.7%), or adverse events/intolerance (18.0%). JAK inhibitors showed a higher remission rate (81.0%) and superior drug durability compared with other advanced agents at the end of induction, but should be handled with care, especially in elderly patients, due to their associated safety warnings [87].

Thus, these therapies should only be initiated on a case-by-case evaluation based on patients' age and comorbidities. A comprehensive risk-benefit assessment must be performed in order to avoid serious adverse effects, and regular follow-up is crucial.

Non-response:
Clinical activity* despite 4 weeks of treatment with 9 mg budesonide
Refractory/loss of response:
Clinical activity despite budesonide 3–6 mg maintenance therapy
Intolerance:
Unacceptable, dose-independent adverse effects caused by budesonide.

* According to Hjortswang criteria (see Table 4)

Table 6: Indications for advanced therapy in microscopic colitis.

The European Microscopic Colitis Group (EMCG) recommends treating selected patients with microscopic colitis who do not respond to budesonide with anti-TNF drugs, vedolizumab or other biologics in order to induce and maintain clinical remission. However, the EMCG does not recommend the use of methotrexate in patients with microscopic colitis due to its lack of efficacy [1]. Nonetheless, these treatments may be justifiable for severe cases – which are often younger patients – since the disease greatly impairs their quality of life and ability to work. Generally speaking, when it comes to advanced therapy in microscopic colitis, it is recommended to treat them like IBD patients.

Surgery should be considered as a last resort for microscopic colitis patients who are refractory to all pharmacological options. Individual case reports have described positive outcomes using ileostomy, subtotal colectomy, or ileal pouch-anal anastomosis (IPAA). However, clinical experience has shown that patients frequently have a robust stoma with major fluid loss which requires hospitalization [35].

Other investigated therapies

Historically, treatment recommendations for microscopic colitis were based primarily on anecdotal case reports and personal experience. Several different drugs were proposed based on these sources, drugs which either address the symptoms (e.g. loperamide, cholestyramine) or which exert anti-inflammatory effects (e.g. aminosalicylates, steroids, antibiotics).

Importantly, when assessing treatment studies, attention must be paid to the underlying definition of clinical remission in each study.

The evidence for the use of bismuth is insufficient and is based on a single open-label study [88]. Mesalazine conferred no benefit over placebo or budesonide in a placebo-controlled study [71, 76].

Although little data is available on treatment with bile acid sequestrants like cholestyramine, this approach may be advisable for microscopic colitis, especially for those with concomitant bile acid malabsorption [89, 90].

A small study with 12 subjects reported limited effects of prednisolone, which is why the use of systemic steroids cannot be recommended [1, 91].

The effects of 400 mg *Boswellia serrata* extract (frankincense) 3 times daily versus placebo were investigated in a 6-week, randomized, placebo-controlled study with 31 collagenous colitis patients. The remission rates were 63.6% in the treatment group and 26.7% in the placebo group ($p = 0.04$, per protocol [30]; $p = 0.25$, intention-to-treat [ITT]). No effects on histology or quality of life were observed with frankincense treatment. Hence, the effectiveness of *Boswellia serrata* extract should be classified as low [92]. In contrast, no effects were observed in a placebo-controlled study for the combination of *Lactobacillus* and *Bifidobacterium* [93]. One pilot study investigated the effects of *Escherichia coli* Nissle 1917 on the frequency and consistency of stool in 14 patients with collagenous colitis.

Treatment lasted at least 4 weeks for all but 2 patients. The results revealed clear clinical response after oral administration of *E. coli* Nissle 1917, with a ≥ 50% reduction in stool frequency in 9 of 14 patients (64%). After 4–18 weeks of treatment, stool frequency decreased significantly ($p = 0.034$) from 7.6 ± 4.8 per day to 3.7 ± 5.8 per day. The results of this pilot study suggest there may be a therapeutic benefit of *E. coli* Nissle 1917 for the treatment of collagenous colitis [94]. There is no robust data on dietary recommendations at present.

Outlook and Prognosis

Microscopic colitis is a chronic, albeit benign, disease. However, this assumption is based primarily on retrospective studies with selective cohorts and incomplete follow-up as well as on patients' self-reported response, but not on systematic stool diaries [1].

Concerning the course of disease, prospective data has been published from the European microscopic colitis registry which evaluates one-year follow-up data as well as patient diaries an

questionnaires pertaining to quality of life. This study shows that only a minority of microscopic colitis patients experience a mild symptomatic course with spontaneous clinical improvement.

A larger share of patients suffers from chronic, active or recurring disease with persistent symptoms in the first year after diagnosis, which is associated with great impairment in their quality of life. All subtypes of microscopic colitis have similar courses [14].

In two large, nationwide cohorts of patients with microscopic colitis, patients' mortality risk was significantly higher than that of the general population. However, this increased mortality appears to be associated with the higher burden of comorbidities within this population [95, 96].

One meta-analysis of five case-control studies reported that microscopic colitis was associated with a lower risk of colorectal cancer or adenoma, and hence a special surveillance colonoscopy program is not recommended [1].

Conclusions

Microscopic colitis is a common cause of chronic watery diarrhea, especially in older adults, that impacts quality of life and daily functioning. A review of the literature demonstrates that budesonide is the drug which has been most investigated in randomized, placebo-controlled clinical trials for the treat-ment of collagenous colitis and lymphocytic colitis. These trials have shown both high efficacy and a very favorable safety profile. Accordingly, budesonide was named as the standard therapy for both induction and maintenance of remission of microscopic colitis by the consensus recommendation of a European expert committee (Figure 8) [1].

For patients who do not tolerate budesonide or who experience loss of response to budesonide, biologics may be used empirically to establish clinical remission and improve quality of life [2].

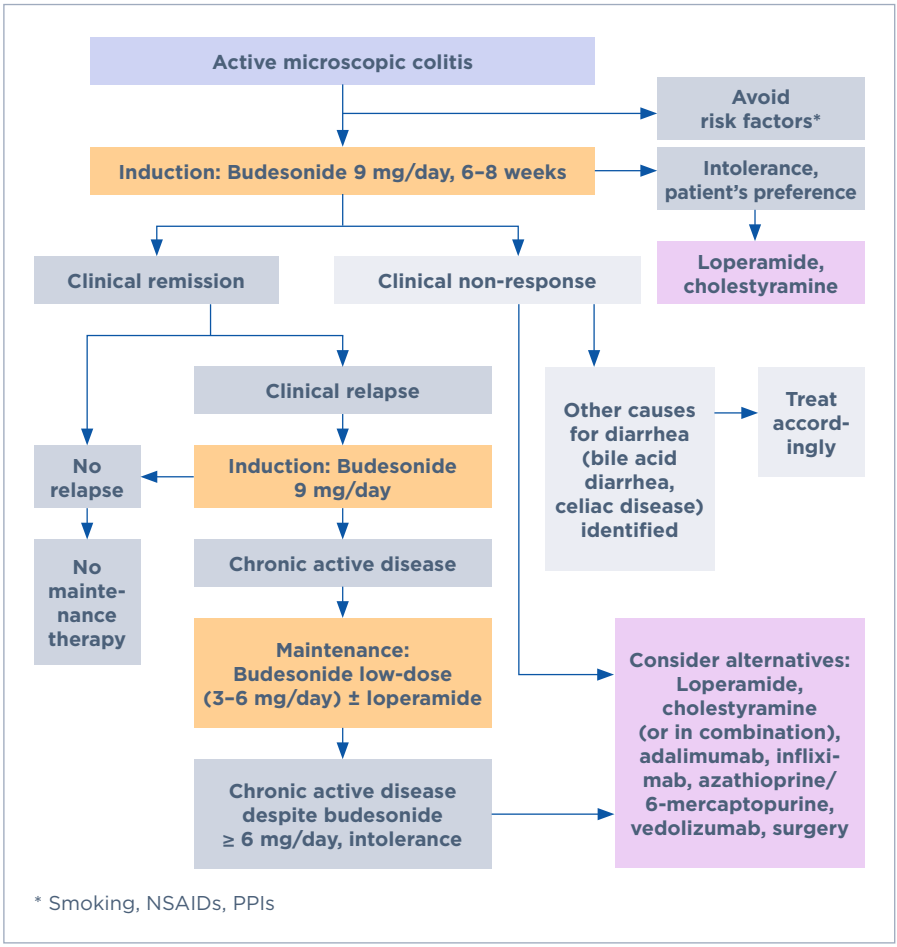


Figure 8: EMCG treatment algorithm. Modified from [1].

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8 Quiz

Your knowledge about MC:

Have you been able to refresh your medical expertise on MC with the help of this brochure? Test your knowledge!

This QR code (Microsoft Form) will take you to 10 questions. Only 1 answer out of 5 possible is correct.

Good luck!

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