Microscopic Colitis – Collagenous Colitis and Lymphocytic Colitis

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1 History

Collagenous colitis was first described in two separate publications in 1976 by Lindström and by Freeman and colleagues (Lindström 1976, Freeman et al. 1976), while **lymphocytic colitis** was first described by Read and colleagues in 1980 (Read et al. 1980). These two disorders are consolidated under the umbrella term of microscopic colitis. In 1989, Sylwestrowicz and colleagues coined the term "watery diarrhea-colitis syndrome", which reflects the primary clinical symptom of both of these disorders (fig. 1).

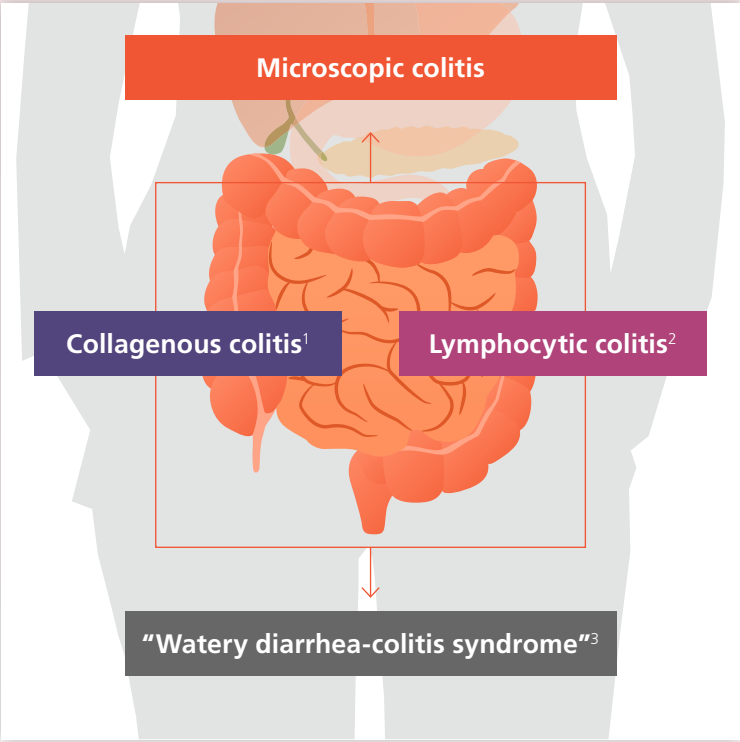


Fig. 1: Definition of microscopic colitis. **1** Lindström 1976, Freeman et al. 1976; **2** Read et al. 1980; **3** Sylwestrowicz et al. 1989

Our understanding of these disorders, and especially of collagenous colitis, have increased immensely in the three decades since they were first described. This is reflected by the quantum leap in publications on this topic:

1988 Small bowel involvement was first demonstrated in 1988 (Eckstein et al.).

1990 According to a report by Lindström (1991), 268 cases were published by 1990.

1996 The Scandinavian group led by Bohr reported more than 500 cases published in the literature by 1996.

1999 The first controlled study of pharmacological treatment was published in 1999 by Fine and colleagues. Previously, pharmacological treatment had been empiric.

2003 Chande and colleagues published the first meta-analysis in 2003 (Cochrane analysis).

2005 In 2005, oral budesonide became the first drug approved for the disorder anywhere in the world when it was approved in Great Britain 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.

Publication of the results of new studies on microscopic colitis as well as the recent publication of treatment recommendations by the **European Microscopic Colitis Group** (EMCG; Miehlke et al. 2021) were the inspiration for the revision of this booklet.

2 Epidemiology

Sex ratio

All epidemiological studies to date have shown a clear predominance of women among collagenous colitis patients (female:male = 4.75:1). This phenomenon is slightly less pronounced for lymphocytic colitis, with a female:male sex ratio of 2.4:1.

Age

A meta-analysis by Tong and colleagues (Tong et al. 2015) 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% CI: 57.03–72.78] years old; lymphocytic colitis: 62.2 [95% CI: 54.0–70.4] years old).

Incidence and prevalence

Retrospective data from longitudinal analyses from Olmsted County (Minnesota, USA) and Örebro (Sweden) have revealed that the number of cases of lymphocytic and collagenous colitis are increasing (Pardi et al. 2007, Wickbom et al. 2013). This increase is likely due to both improvements in diagnosis as well as a real increase in the number of actual cases.

According to epidemiological studies, the incidence of microscopic colitis is increasing in Western, industrialized countries. However, incidence rates appear to vary greatly from country to country. In comparison, more epidemiological studies have been performed in Northern Europe than in Southern Europe.

Tong et al. (2015) performed a meta-analysis comprising 19 epidemiological studies from 1995–2014. This meta-analysis reported an incidence rate of 4.14 (95% CI: 2.89–5.4) per 100,000 person-years for collagenous colitis and 4.85 (95% CI: 3.45–6.25) for lymphocytic colitis. It also reported that the female predominance is more pronounced for collagenous colitis, with a sex ratio of 3.5, than for lymphocytic colitis at 1.92.

An analysis of the Danish Pathology Register between 2002 and 2011 revealed 7,777 patients with microscopic colitis (Bonderup et al. 2015). Of these patients, 61% had collagenous colitis and 39% had lymphocytic colitis. The annual incidence rate of newly diagnosed cases of collagenous colitis rose from 2.9 per 10^5 residents to 14.9 per 10^5 residents. The annual incidence of newly diagnosed cases of lymphocytic colitis rose from 1.7 per 10^5 residents to 9.8 per 10^5 residents over the observation period. The incidence of microscopic colitis was reported to be 24.7 per 10^5 residents in 2011. However, the authors acknowledge that the increase in newly diagnosed cases may be in part attributable to increased endoscopic activity.

Childhood microscopic colitis

Childhood onset of microscopic colitis is very rare, and hence there is nearly no data on patients in this age group. A study by El-Matary et al. (2010) described cases in 11 adolescent patients (mean age: 11.2 years old). However, it must be noted that only 5 of these children had lymphocytic colitis, while the other 6 were diagnosed with either non-specific colitis or eosinophilic colitis.

Microscopic colitis vs. inflammatory bowel disease (IBD)

It is possible to directly compare the incidence of microscopic colitis with that of IBD (ulcerative colitis and Crohn's disease) for several European countries. The Danish Pathology Register conducted a nationwide cohort study of patients in Denmark with a documented diagnosis between 2001 and 2016. 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 (Lophaven et al. 2017). In contrast, 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 (Weimers et al. 2020).

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 (Fumery et al. 2017).

This data suggests that the incidence of microscopic colitis is equivalent to or has even overtaken 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 factors, luminal agents, as well as immunological factors. Medications and smoking appear to play a triggering function (Green et al. 2019).

Several different factors have been suggested to contribute to the pathogenesis of the disease (fig. 2). There appears to be a genetic predisposition to the disorder (possible HLA determination), since an association has been observed between microscopic colitis and HLA-DQ (Ohlsson 2015). In addition, patients have been shown to have a high prevalence of polymorphisms in tumor necrosis factor-α and metalloproteinase-9 genes. The immune reactions in microscopic colitis appear to be mediated by TH1/TH17 and by cytotoxic T lymphocytes (Pisani et al. 2016). More recent studies have reported elevated levels of anti-Yersinia antibodies in patients with collagenous colitis, indicating prior infection. The immune response also appears to be attenuated in these patients, with several markers of inflammation (TGF-β, VEGF) being reported as abnormally elevated.

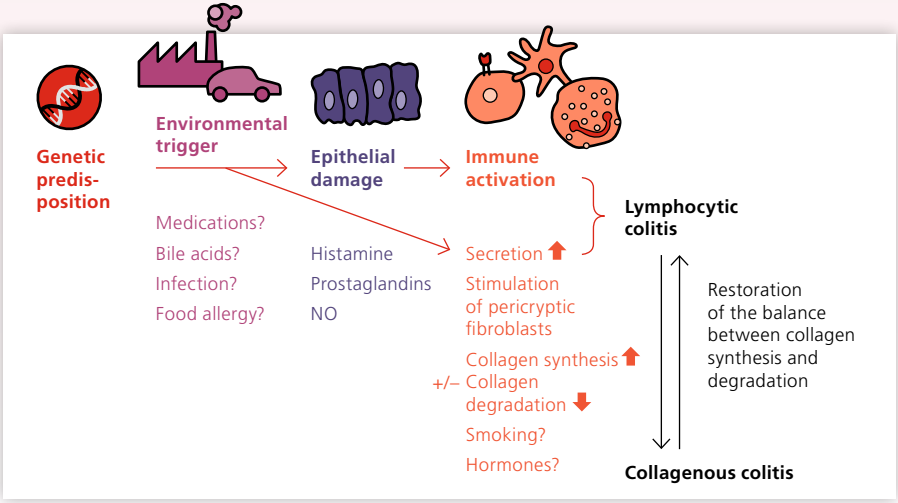


Fig. 2: Possible pathophysiological mechanisms of microscopic colitis

Influence of medications

Published study data supports 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 5,751 microscopic colitis patients demonstrated that these patients took PPIs, NSAIDs, statins, or SSRIs more frequently than the equivalent control groups (Bonderup et al. 2014). An elevated risk of microscopic colitis has been described for NSAID and PPI use (Masclee et al. 2015).

According to one epidemiological meta-analysis (Tong et al. 2015), 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). According to a case-control study that analyzed a British database with more than 1,200 patients between 1992 and 2013, 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 (Verhaegh et al. 2016).

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 (Capurso et al. 2011). However, this might not reflect a general effect of PPI-class drugs (Verhaegh et al. 2016).

NSAIDs increase the permeability of the intestinal mucosa and may allow luminal agents to leak into the body. A study by Riddell and colleagues (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.

According to the EMCG recommendations, all medications for which a temporal association between the start of treatment and the onset of symptoms has been observed should be discontinued (Miehlke et al. 2021).

Influence of smoking

Studies on the smoking habits of patients with microscopic colitis have clearly shown smoking to be a risk factor for developing microscopic colitis. The disease also has an earlier age onset in smokers than non-smokers. A study by Wickbom et al. (2017) confirmed the association between smoking and microscopic colitis.

According to a recent meta-analysis, both smokers and even ex-smokers are at a significantly higher risk of developing microscopic colitis (Jaruvongvanich et al. 2019).

In one case-control study (Vigren et al. 2011) 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. Smoking exacerbates the clinical symptoms of collagenous colitis and is associated with an increased number of watery stools. Furthermore, a post-hoc analysis by Münch and colleagues (2016a) could show that smoking reduces the probability of achieving clinical remission.

Collagen synthesis and degradation

The data available on collagen metabolism in the intestinal mucosa in patients with collagenous colitis has revealed a normal architecture and extracellular matrix outside of the collagen band and no increase in levels of type VI collagen mRNA (Aigner et al. 1997). Together with the reduction in levels of matrix metalloproteinase-1 and increase in tissue inhibitor metalloproteinase-1 (Günther et al. 1999), these findings suggest diminished degradation of collagen. In contrast, no evidence was found for increased collagen synthesis.

Mechanism of diarrhea

Several models have been proposed to explain the pathology of chronic diarrhea in collagenous colitis, which are based on the small number of experimental studies available. First, defective transport mechanisms together with the thickness of the collagen band lower the absorption of sodium and chloride ions. Second, the active secretion of chloride ions may also play a role (Bürgel et al. 2002). This explanation is in line with observations that the epithelial sodium channel is inhibited in the sigmoid colon of patients with lymphocytic colitis (Barmeyer et al. 2016) and that the concentrations of fecal sodium and chloride are elevated in patients with microscopic colitis (Protic et al. 2005).

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.

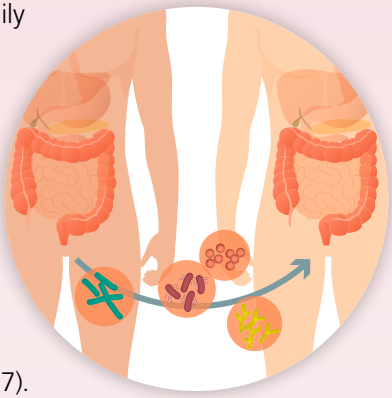
Fecal stream diversion/microbiome

Microscopic colitis patients very rarely require surgery, but in those who do it has been observed that fecal stream diversion by ileostomy leads to resolution of inflammation in the colon. Moreover, inflammation recurs once intestinal continuity is restored (Järnerot et al. 1995). These observations bolster the theory that a luminal factor triggers the inflammation occurring in microscopic colitis.

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 indeed 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 (Morgan et al. 2020) and is associated with higher counts of specific bacte-

rial strains such as the pro-inflammatory family Desulfovibrionales (Millien et al. 2019).

Another study has shown that treatment with budesonide can alter the composition of the microbiome in microscopic colitis patients such that the microbial composition approaches that of healthy controls (Krogsgaard et al. 2019). Furthermore, several case reports have demonstrated that fecal microbiota transplantation is effective against microscopic colitis (Günaltay et al. 2017, Fasullo et al. 2017). However, no clinical studies have been performed on this intervention to date.



4 Diagnosis

Endoscopy

Endoscopy is a proven method for diagnosing microscopic colitis in patients with watery diarrhea lasting longer than 4 weeks. It also allows biopsies to be taken from multiple sites of normal gut mucosa, even in patients with unsuspicious endoscopic findings. Numerous studies have shown that more than 10% of patients with watery diarrhea lasting longer than 4 weeks and normal endoscopy findings can be diagnosed with microscopic colitis (Marshall et al. 1995). 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 (Miehlke et al. 2021).

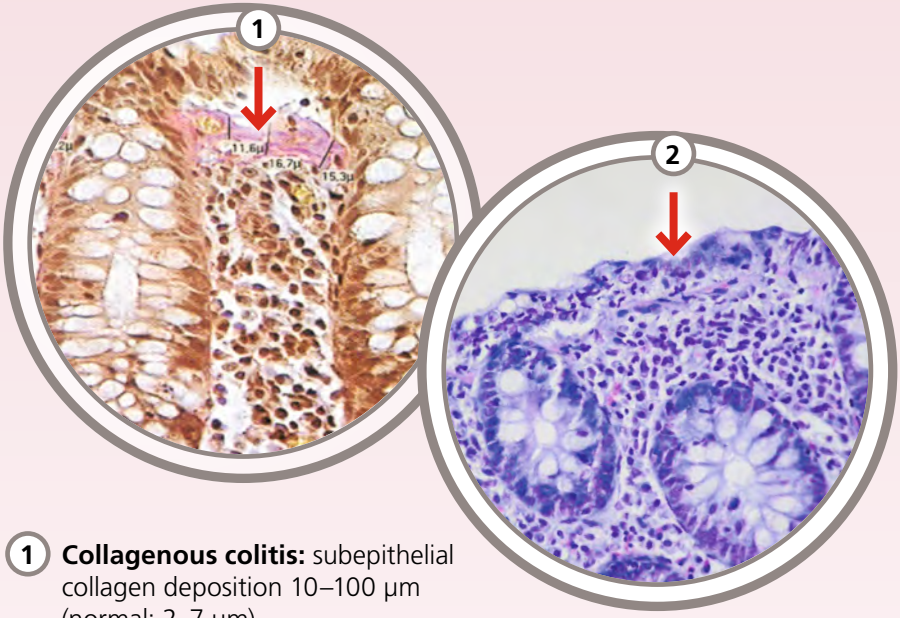
Because the mucosa typically appears normal by endoscopy, the characteristic histological features of microscopic colitis represent the definitive diagnostic criteria. Subtle, non-specific mucosal changes such as edema or mucosal erythema have been described (Pardi 2017). In a study by Mellander et al. (2016), 37% of collagenous colitis patients exhibited subtle mucosal features such as erythema, edema, or irregular vascular patterns.

Histology

The main histological feature of collagenous colitis is a thickened subepithelial collagen band ≥ 10 µm (normal: 2–7 µm). An additional diagnostic criteria is inflammatory infiltrates in the lamina propria consisting of lymphocytes and plasma cells (fig. 3).

The main histological feature of lymphocytic colitis is increased intraepithelial T lymphocytes in the surface epithelia of the colonic mucosa. The definitive criteria is the detection of > 20 intraepithelial lymphocytes per 100 epithelial cells. The surface epithelia are flattened and narrow. In contrast to collagenous colitis, the collagen band is not thickened in the subepithelial stroma (fig. 3).

Intraobserver and interobserver agreement is high in histological evaluation of microscopic colitis (Kanstrup Fiehn et al. 2013).



1 **Collagenous colitis:** subepithelial collagen deposition 10–100 µm (normal: 2–7 µm)

2 **Lymphocytic colitis:** elevated counts of intraepithelial lymphocytes (CD8+) > 20/100 epithelial cells (normal: 3–5/100)

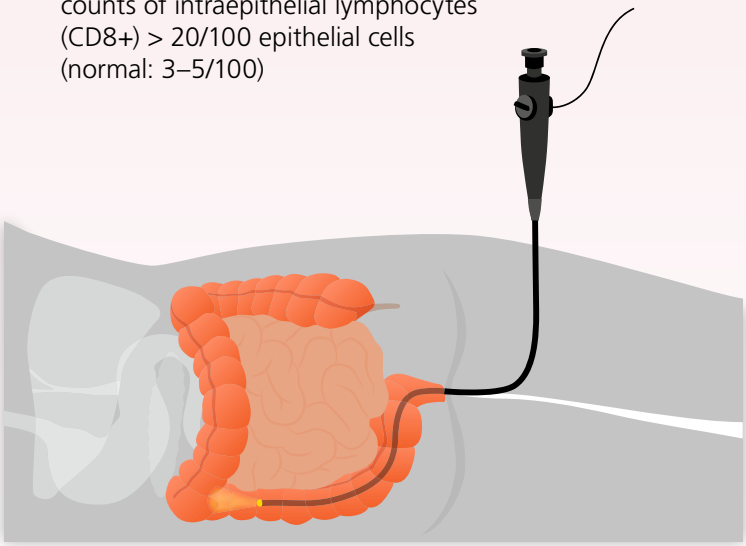


Fig. 3: Colonoscopy with removal of tissue samples from different segments of the colon with a minimum requirement of two samples each from the left and right colon

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 but do not meet the morphological criteria for lymphocytic colitis or collagenous colitis. The histological findings are an increased number of < 20 intraepithelial lymphocytes per 100 epithelial cells (incomplete lymphocytic colitis) or abnormal thickening of the subepithelial collagen band, i.e. < 10 µm (incomplete collagenous colitis) in conjunction with increased inflammatory infiltrates in the lamina propria (Langner et al. 2015).

One study has shown that intraobserver and interobserver agreement is high with regard to 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 (Kanstrup Fiehn et al. 2013).

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.

5 Clinical presentation

Symptoms

Watery diarrhea 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 fecal urgency (fig. 4). Blood or mucus in the stool are very rarely observed in microscopic colitis.

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. This explains why patients who initiate fasting on their own initiative report clinical improvement but may also experience weight loss (Bohr et al. 1996).

Using a population of 494 patients with microscopic colitis, Madisch and colleagues demonstrated that patients with collagenous colitis experienced symptoms for a mean of 37 months prior to diagnosis versus 23 months for patients with lymphocytic colitis (Madisch et al. 2014).

Kane and colleagues developed a scoring system which revealed that the factors of age over 50, female sex, PPI or NSAID use, weight loss, and the absence of abdominal pain were significantly associated with a diagnosis of microscopic colitis (Kane et al. 2015).

Symptom	Collagenous colitis (%)			Lymphocytic colitis (%)		
Watery diarrhea	55	92	85	43	88	78.5
Abdominal pain	28	48	22	30	52	26.5
Weight loss	38	59	49	33	48	48
Nocturnal diarrhea	28	57	64	18	39	60.8
Fecal urgency	23	74	–	21	67	–

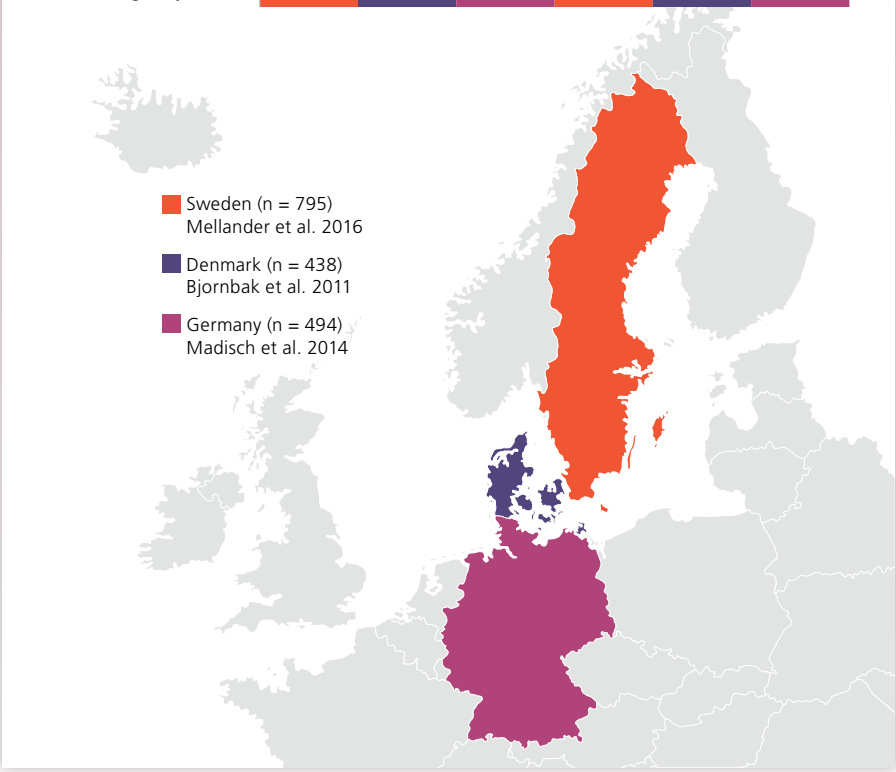


Fig. 4: Symptoms of microscopic colitis

Associated disorders and differential diagnoses

Celiac disease

Celiac disease appears to be closely associated with microscopic colitis (Stewart et al. 2011). A large, prospective study reported a 3.3% incidence of celiac disease among patients with microscopic colitis versus 0.4% among controls (Green et al. 2019). A study in a pathology registry with 3,456 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 (Sonnenberg et al. 2018). 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 (Liu et al. 2019). Based on the data available, the **European Microscopic Colitis Group (EMCG)** urgently recommends testing all microscopic colitis patients for celiac disease.

Differentiation from Crohn's disease and ulcerative colitis

Inflammatory bowel disease (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. 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 have no endoscopic abnormalities. Instead, the diagnosis must be made and/or confirmed by histology (to differentiate it from irritable bowel syndrome). Case reports have described an overlap between Crohn's disease or ulcerative colitis and microscopic colitis.

Differentiation from irritable bowel syndrome

Irritable bowel syndrome is estimated to have a prevalence of about 7% of the general population in North America and Europe (Sperber et al. 2017), of whom approximately 35% have IBS-D. 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 irritable bowel syndrome (Abboud et al. 2013, Guagnozzi et al. 2016). Furthermore, it has been observed that 7% of patients who meet the diagnostic criteria for IBS-D actually have microscopic colitis (Guagnozzi et al. 2016).

Because there is generally little awareness for microscopic colitis, especially among primary care physicians – where the majority of irritable bowel syndrome 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 irritable bowel syndrome (table 1), underscoring the importance of collecting a thorough history.

Characteristic features of microscopic colitis are advanced age (> 50 years old) and watery/soft diarrhea, which may lead to fecal urgency and fecal incontinence. Patients may experience nocturnal stools, and weight loss is common.

In contrast, irritable bowel syndrome most frequently afflicts younger patients (< 50 years old) and is accompanied by stools of various consistency whose frequency can change on a daily basis. In contrast to microscopic colitis, irritable bowel syndrome is frequently associated with bloating/flatulence and incomplete bowel evacuation.

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 confirm a diagnosis of microscopic colitis.

Clinical factors	Irritable bowel syndrome	Microscopic colitis
Initial onset	Often before age 50	Often after age 50
Stool consistency	Soft – variable – solid	Watery/soft
Stool frequency	Can vary from day to day	High and rather constant
Nocturnal diarrhea	Very unlikely	Possible
Sensation of incomplete bowel evacuation	Common	No
Weight loss	Rare	Common
Fecal incontinence	Rare	Common
Bloating/flatulence	Common	Rare
Concurrent autoimmune diseases	Rare	Common

Table 1: Differences in the clinical history between patients with irritable bowel syndrome and with microscopic colitis

6 Treatment

Historical

Treatment recommendations for microscopic colitis were historically based primarily on anecdotal case reports and personal experience. Several different drugs were proposed based on these data sources, drugs which either address the symptoms (e.g. loperamide, cholestyramine) or which exert anti-inflammatory effects (e.g. aminosalicylates, steroids, antibiotics). 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 not sufficient and is based on a study published as an abstract (Fine et al. 1999). Mesalazine conferred no benefit over placebo or budesonide in a placebo-controlled study (Miehlke et al. 2014, Miehlke et al. 2018).

Although little data is available on treatment with cholestyramine, this approach may be advisable for patients with abnormal bile acid uptake (Pardi et al. 2002, Jobse et al. 2009). In contrast, no effects were observed in a placebo-controlled study for the combination of *Lactobacillus* and *Bifidobacterium* (Wildt et al. 2006). A small study with 12 subjects reported limited effects of prednisolone (Munck et al. 2003).

Madisch and colleagues compared the effects of 400 mg *Boswellia serrata* extract (frankincense) 3 x daily versus placebo 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 [PP]; $p = 0.25$, 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 (Madisch et al. 2007).

One pilot study investigated the effects of *Escherichia coli* Nissle 1917 on the frequency and consistency of stool in 14 patients with collagenous colitis (Tromm et al. 2004). 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.

There is no robust data on dietary recommendations at present.

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 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 (Miehlke et al. 2021).

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" (Hjortswang et al. 2009; fig. 5).

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

Fig. 5: Clinical criteria for disease activity of microscopic colitis (Hjortswang et al. 2009)

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

Pharmacological basis of treatment with budesonide

Figure 6 illustrates the difference between the regimens of topical budesonide versus standard systemic corticosteroids (e.g. prednisolone). Whereas prednisolone rapidly enters the bloodstream following oral administration and exerts its pharmacodynamic receptor-mediated effects throughout the entire body, orally administered budesonide is delivered to the ileum owing to its galenic. Thanks to its long dwelling time on the mucosa and its high receptor affinity, this drug is highly suitable for achieving local effects in the intestinal mucosa. Budesonide is then transported to the liver via the portal vein. Due to its high first-pass metabolism, over 90% of the active substance is inactivated in the liver and only a small portion is released into the bloodstream. This results in a much lower rate of undesirable systemic steroid side effects than with prednisolone.

Because oral budesonide is rapidly absorbed from the gastrointestinal tract and is partially metabolized in the mucosa, oral formulations have been developed which allow controlled, targeted delivery of the active substance to the affected segments of the intestine. The release profile of budesonide was developed analo-

	Prednisolone	Budesonide
Systemically bioavailable	**80%**	10%
First-pass metabolism	20%	**90%**

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

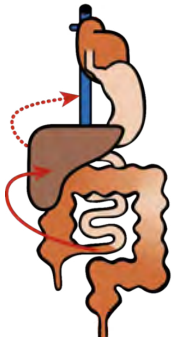


Fig. 6: Systemic vs. topical steroid therapy of microscopic colitis

gously to topical treatment of ulcerative colitis with oral mesalazine and is achieved using small pellets coated with Eudragit.

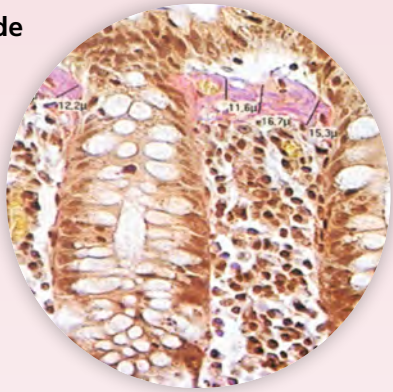
In 2006, Bajor and colleagues investigated the effects of budesonide on bile acid absorption by ^{75}Se-labeled homocholic acid-taurine testing in 15 patients with collagenous colitis. Following 8 weeks of budesonide therapy, patients experienced a major increase in bile acid absorption from 23 ± 9.9% to 40 ± 14.7%. These results suggest that budesonide may exert its effects via an interaction with bile acid metabolism in a manner that increases bile acid absorption.

In a study with 6 subjects, Griga et al. (2004) could show that budesonide treatment leads to reduced expression of vascular endothelial growth factor (VEGF) in the epithelia and the lamina propria.

The rationale for the use of budesonide delivered in a pH-dependent manner for the treatment of microscopic colitis is the high bioavailability of the steroid at the site of lymphocytic infiltration and thickened collagen band.

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 five pilot studies (Bohr 1998, Delarive et al. 1998, Janetschek and Böckmann 1998, Lanyi et al. 1999, Tromm et al. 1999).

Since these studies, four placebo-controlled studies and two meta-analyses 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 studies, budesonide was signifi-

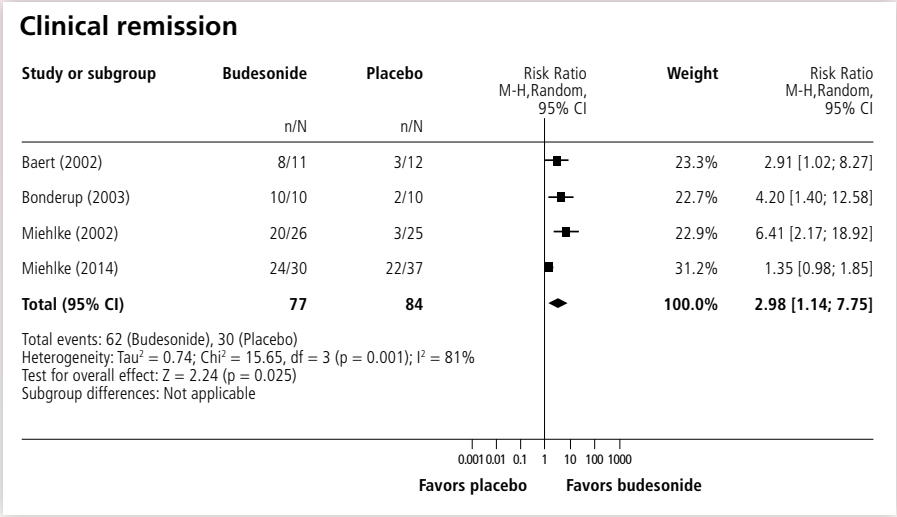


Fig. 7a: Meta-analysis: budesonide vs. placebo for induction therapy of collagenous colitis (Kafil et al. 2017, Cochrane)

cantly superior to placebo with regard to clinical and histological response. Due to its high local bioavailability and high receptor binding affinity, budesonide appears to be a very promising candidate for treating collagenous colitis.

According to the meta-analysis by Kafil et al. (2017), 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. The pooled odds ratio (OR) is 12.32 (Chande et al. 2005), illustrating the highly significant benefit (fig. 7a + b).

The number of patients with collagenous colitis who need to be treated in order to induce remission in one patient (number needed to treat = NNT) is reported as 1.58, which is a highly favorable ratio (Feyen et al. 2004).

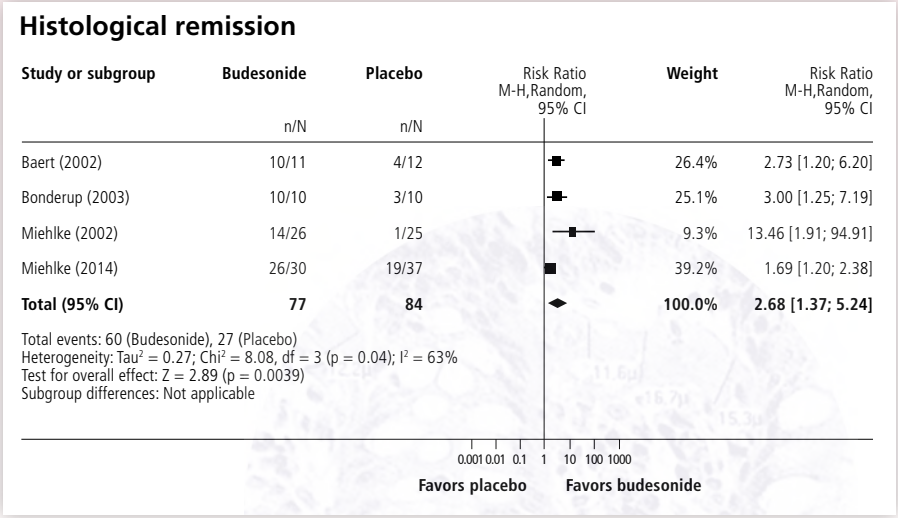


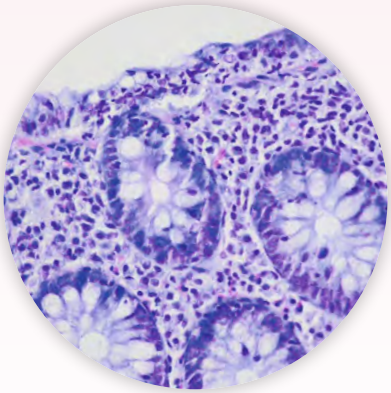
Fig. 7b: Meta-analysis: budesonide vs. placebo for induction therapy of collagenous colitis (Kafil et al. 2017, Cochrane)

A placebo-controlled multicenter study by Miehlke and colleagues compared the effects of 9 mg budesonide daily (n = 30) versus 3 g mesalazine (n = 25) or placebo (n = 37) (Miehlke et al. 2014). 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.

Madisch et al. (2005) also reported significant improvement in quality of life after treatment with budesonide versus placebo.

Budesonide for lymphocytic colitis

Placebo-controlled studies on lymphocytic colitis have compared the effects of 9 mg budesonide versus placebo for induction therapy (Pardi et al. 2009, Miehlke et al. 2009, Miehlke et al. 2018). Response was significantly higher with budesonide ($p < 0.01$). An NNT of 3 has been reported (Chande et al. 2017). Mesalazine is not significantly more effective than placebo (Miehlke et al. 2018; fig. 8a + b).



Clinical remission was achieved by 86% of patients in the budesonide arm versus 48% in the placebo arm ($p = 0.01$; Miehlke et al. 2009). 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 (Chande et al. 2017).

It is important to note the relatively high response rate to placebo in this study.

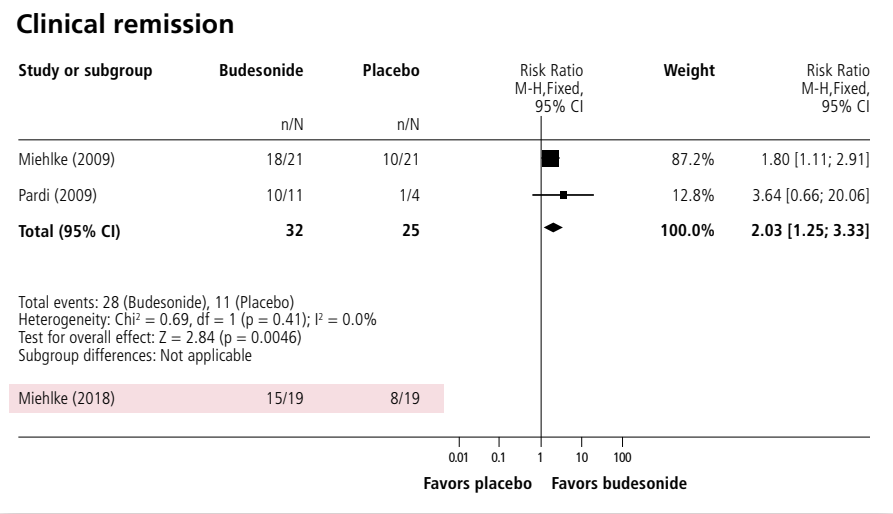


Fig. 8a: Budesonide vs. placebo for induction therapy of lymphocytic colitis (Chande et al. 2017, Cochrane, Miehlke et al. 2018)

The most recent study compared budesonide at a dosage of 9 mg daily versus 3 g mesalazine and placebo for 8 weeks (Miehlke et al. 2018). 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 observed between mesalazine and placebo with regard to clinical remission (63% vs. 42%; p = 0.09), and mesalazine was also significantly inferior to budesonide in histological remission (68% vs. 26%; p = 0.02).

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

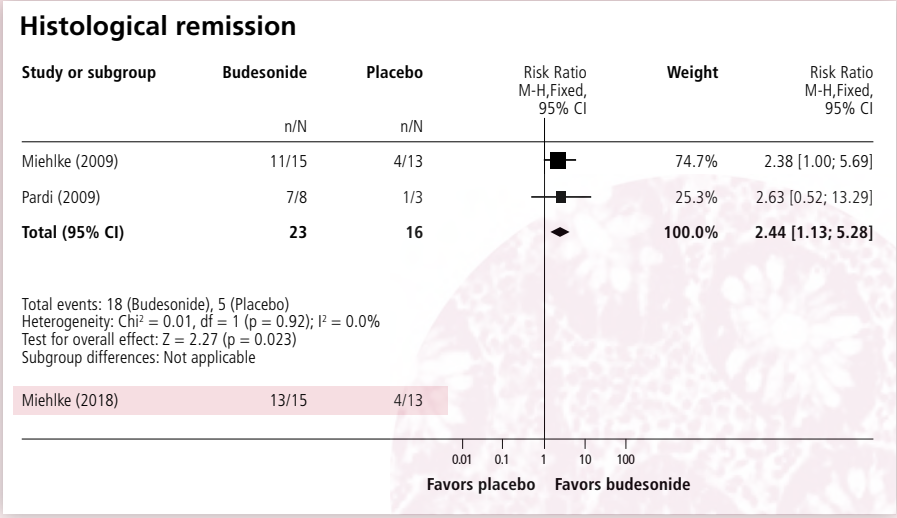


Fig. 8b: Budesonide vs. placebo for induction therapy of lymphocytic colitis (Chande et al. 2017, Cochrane, Miehlke et al. 2018)

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, Miehlke and colleagues (2013) calculated an overall relapse rate of 61%. The 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 persistence of relapse points to the need for therapy to maintain remission.

The only studies to date on maintenance therapy of collagenous colitis focused on budesonide: two studies (Miehlke et al. 2008, Bonderup et al. 2009) and one meta-analysis (Kafil et al. 2017). Due to its proven positive effect, there is thus level 1a evidence for the treatment with budesonide.

In an initial randomized, placebo-controlled trial with 48 subjects, Miehlke et al. (2008) demonstrated the positive benefit of bude-

sonide versus placebo for the maintenance of remission in collagenous colitis. In this study, 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% ($p = 0.022$).

A second randomized, placebo-controlled trial with 42 collagenous colitis patients utilized the same design (Bonderup et al. 2009). 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.

Accordingly, the meta-analysis by Kafil et al. (2017) demonstrates the relevant benefit of budesonide therapy versus placebo for the maintenance of clinical (fig. 9a) and histological remission (fig. 9b) in patients with collagenous colitis.

A prospective, placebo-controlled study by Münch and colleagues investigated the effects of low-dose maintenance therapy with 4.5 mg budesonide per day following initial induction of remission with 9 mg for 12 months (Münch et al. 2016). The rate of clinical remission during the initial phase was 84.5% while the median time to remission was 10.5 days.

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 (Hjortswang et al. 2009). Budesonide was administered at alternating daily doses of 6 mg and 3 mg (mean dose 4.5 mg/day).

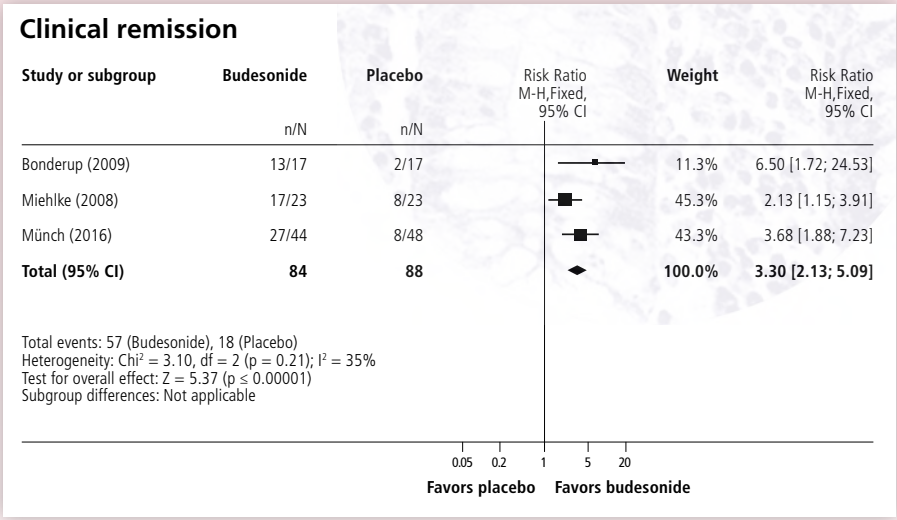


Fig. 9a: Meta-analysis: budesonide vs. placebo for maintenance therapy of collagenous colitis (Kafil et al. 2017, Cochrane)

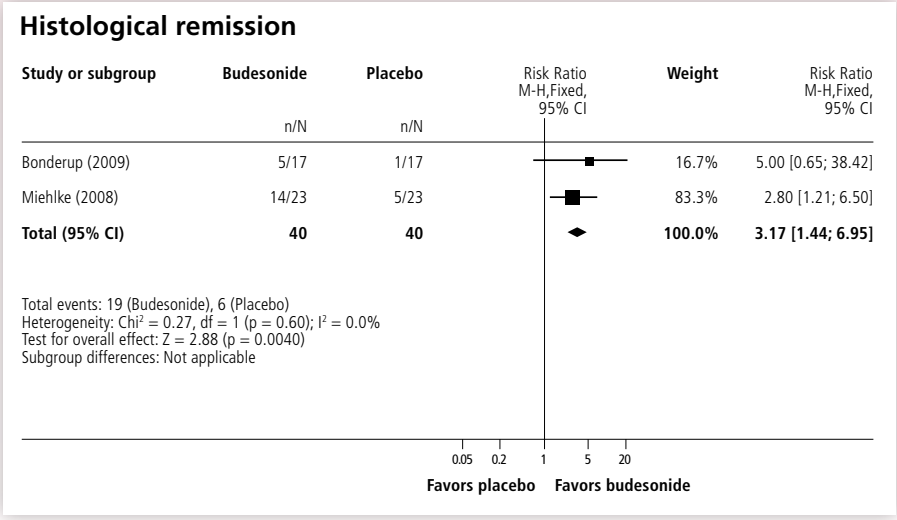


Fig. 9b: Meta-analysis: budesonide vs. placebo for maintenance therapy of collagenous colitis (Kafil et al. 2017, Cochrane)

Budesonide for lymphocytic colitis

There is currently no data on maintenance therapy of lymphocytic colitis.

Experimental therapies

Experimental 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 figure 10.

To date, no randomized controlled trials have been conducted on treatment using immunomodulators or biologics. The available data is very limited and is derived from a small number of case series using thiopurines, methotrexate, anti-TNF drugs, and vedolizumab.

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 to budesonide:

Clinical activity* despite 4 weeks of treatment with 9 mg budesonide (induction therapy) or 12 weeks of treatment with 6 mg budesonide (maintenance therapy).

Intolerance to budesonide:

Unacceptable, dose-independent adverse effects caused by budesonide.

* According to Hjortswang criteria (see fig. 5)

Fig. 10: Definition of non-response or intolerance to budesonide

The **European Microscopic Colitis Group (EMCG)** recommends treating selected patients with microscopic colitis who do not respond to budesonide with thiopurines, anti-TNF drugs, or vedolizumab 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 (Miehlke et al. 2021). 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.

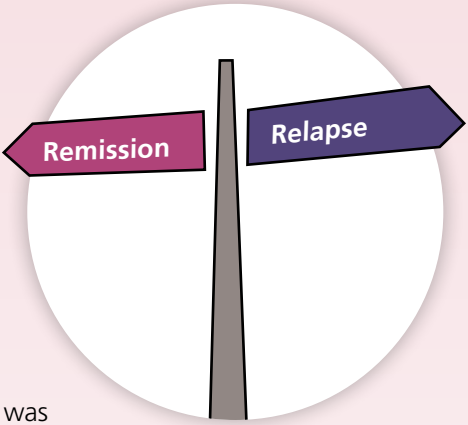
Surgery should be considered as a last resort for microscopic colitis patients who are refractory to all pharmacological options. Individual case reports have described positive outcomes using ileostomy, subtotal colectomy, or ileal pouch-anal anastomosis (IPAA). However, clinical experience has shown that patients frequently have a robust stoma with major fluid loss which requires hospitalization (Järnerot et al. 1995).

Outcome/prognosis

Microscopic colitis is considered to be 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.

In terms of the outcomes of microscopic colitis, in one cohort of 130 patients relapse of symptoms was reported in 28% of patients occurring at a median of 4 years after diagnosis (Loreau et al. 2019).

Nonetheless, prospective data has recently been published from the European microscopic colitis registry which evaluates one-year follow-up data as well as patient diaries and 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 suffer 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.



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 (Andersen et al. 2020, Khalili et al. 2020).

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 (Miehlke et al. 2021).

Conclusions

A review of the literature demonstrates that budesonide is the only drug which has been adequately investigated in randomized, placebo-controlled clinical trials for the treatment 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 (fig. 11; Miehlke et al. 2021). This treatment algorithm also proposes a harmonized treatment regimen for both forms of microscopic colitis, with budesonide being described as the only evidence-based treatment option. The long-term adverse effects of budesonide must always be taken into consideration (Reilev et al. 2020).

If patients do not tolerate budesonide or no response to budesonide is observed, other drugs may be used on an empiric basis taking account of disease activity. However, treatment with NSAIDs should be discontinued in all cases.

According to recent studies, patients with microscopic colitis should be strongly encouraged to cease nicotine use.

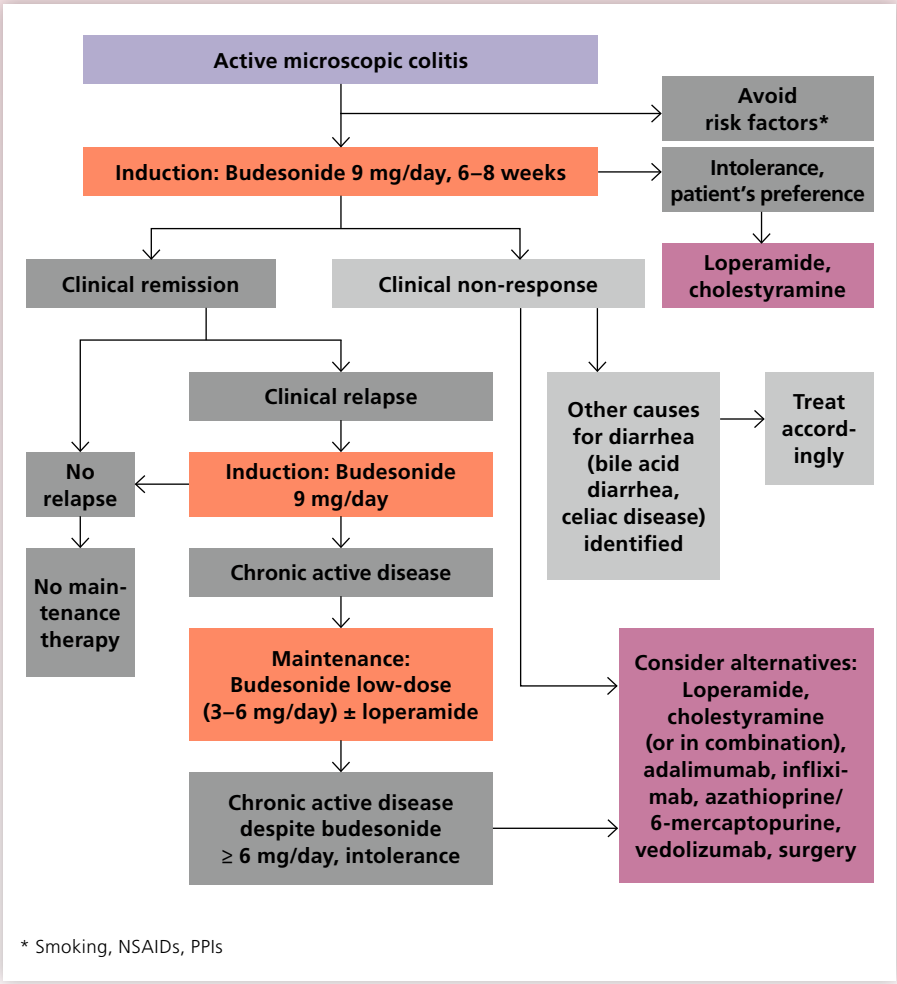


Fig. 11: EMCG treatment algorithm
Modified from Miehlke et al. (2021): European guidelines on microscopic colitis: United European Gastroenterology (UEG) and European Microscopic Colitis Group (EMCG) statements and recommendations [https://journals.sagepub.com/doi/10.1177/2050640620951905], licensed under CC BY[https://creativecommons.org/licenses/by/4.0/]

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