

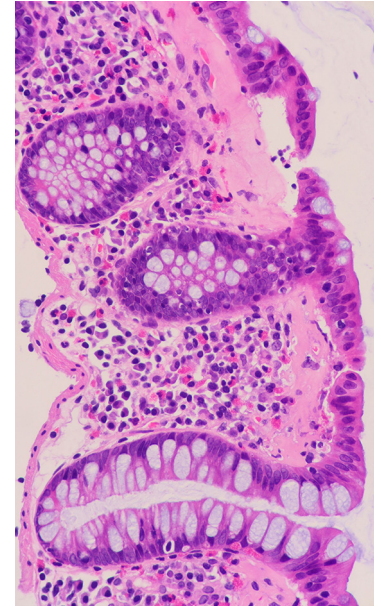
Mistakes in microscopic colitis and how to avoid them

Andreas Münch

Microscopic colitis is an inflammatory bowel disease (IBD) that leads to chronic, watery diarrhoea. First believed to be rare, microscopic colitis has received more attention in recent decades, resulting in increasing incidence rates that exceed those of classic IBD in some countries. Hopefully, it is common practice nowadays to refer patients with chronic diarrhoea for a colonoscopy with biopsy samples taken, as this is the only way to diagnose microscopic colitis. Histology results distinguish between the subtypes of microscopic colitis — lymphocytic colitis, collagenous colitis and the more recently introduced incomplete microscopic colitis.

The cardinal symptom of watery diarrhoea eventually results in severe urgency and faecal incontinence. Furthermore, many patients experience abdominal pain that can be misinterpreted as diarrhoea-predominant irritable bowel syndrome (IBS-D), resulting in inadequate treatment. Microscopic colitis is a benign condition but it can severely impact quality of life. Fortunately, there is effective treatment with budesonide, a locally active steroid, and thiopurines or biologics can be tried for budesonide-refractory disease.

The mistakes discussed here are derived from observations of the accepted view of microscopic colitis, but also reflect the many misconceptions I've encountered during lectures given throughout Europe. There is still a lack of awareness and knowledge when it comes to microscopic colitis compared with the other IBDs and avoiding these mistakes will alleviate unnecessary suffering and improve patient care. Recently, UEG and the European Microscopic Colitis Group (EMCG) have published clinical guidelines to improve the diagnosis and treatment of microscopic colitis.¹ The statements and recommendations, evidence based or expert-group consensus, are used as the backbone for tackling these mistakes and are backed up by my own clinical experience.



Mistake 1 Believing that microscopic colitis is a rare disease

Microscopic colitis was initially considered a rare disease. In the past two decades, however, increasing awareness of microscopic colitis means that it is now known to be a common IBD, even though it is often still considered rare. An overall pooled incidence rate of 11.4 cases per 100,000 person-years (95% CI: 9.2–13.6, I² = 99.72%) was calculated based on studies providing population-based data¹ and, in some European countries, the incidence rate has surpassed that of the classic IBDs (i.e. ulcerative colitis and Crohn's disease).²

The incidence of microscopic colitis is higher in the elderly. A previous meta-analysis showed that the median patients' age at the time of diagnosis was over 60 years old (collagenous colitis: 64.9 [CI: 57.03–72.78 years]; lymphocytic colitis: 62.2 [CI: 54.0–70.4 years]).¹ However, up to 25% of patients diagnosed with collagenous colitis were younger than 45 years old and cases of microscopic colitis have even been described in children.³

Microscopic colitis should be suspected in all patients with chronic diarrhoea, especially when it is watery (Bristol Stool scale, type 7).

The frequency of microscopic colitis in patients with chronic or intermittent watery diarrhoea and a macroscopically normal (or near normal) colon has been evaluated in several studies.¹ Based on studies of moderate or high quality and with a sample size of 100 patients, the pooled overall frequency of microscopic colitis was estimated to be 12.8% (95% CI: 9.9–15.9, I² = 93.6%).¹

Mistake 2 Misdiagnosing microscopic colitis as IBS-D

Besides diarrhoea, patients with microscopic colitis can present with abdominal pain, even when they are in clinical remission, which can lead to it being misdiagnosed as IBS-D. In a meta-analysis, 44% of patients with microscopic colitis fulfilled the IBS criteria, and this was more pronounced for lymphocytic colitis than for collagenous colitis.⁴ Other meta-analyses have shown that underlying microscopic colitis was diagnosed in 9% (95% CI: 4.5–14.9%) of patients who exhibited diarrhoea-predominant functional disorders.⁵ Because of the strong overlap of these conditions, it is not surprising that microscopic colitis can be mistaken for IBS-D, especially in a setting where a general

practitioner has to judge patients' symptoms.

However, with a thorough patient history, it is possible to distinguish between the diseases in many cases. It is helpful if the patient completes a stool diary over at least one week and describes the stool frequency and consistency. The main difference between these diseases is that microscopic colitis leads to watery diarrhoea (Bristol Stool scale, type 7) in nearly 80% of the cases and the stool frequency per day/week does not vary to the same degree as for IBS-D. Other differentials are given in table 1.

Mistake 3 Using faecal calprotectin to exclude or monitor microscopic colitis

Testing for faecal calprotectin, which can indicate active inflammation in the bowel, has become a common tool for diagnosing and monitoring classic IBD. In microscopic colitis, studies with small patient numbers have demonstrated that the faecal calprotectin concentration was slightly, albeit significantly, higher compared with patients without an organic cause of diarrhoea and patients with IBS. However, the predictive value was low and there was overlap between the results of patients with active and quiescent

© 2021 Münch.

Cite this article as: Münch A. Mistakes in microscopic colitis and how to avoid them. *UEG Education* 2021; 21: 10–13.

Andreas Münch is a senior consultant gastroenterologist in the Department of Health, Medicine, and Caring Sciences at

Linköping University, Linköping, Sweden, and President of the European Microscopic Colitis Group (EMCG).

Images: Lisa Culton/shutterstock.com

Correspondence to: andreas.munch@regionostergotland.se

Conflicts of interest: AM has received consulting fees from

Ferring, Vifor, Falk Pharma and Tillotts; lecture fees from Ferring, Vifor, Janssen and Tillotts, and has received an unrestricted grant from Ferring and Tillotts.

Published online: March 12, 2021.

Clinical history variable	Irritable bowel syndrome	Microscopic colitis
First occurrence of disease	Usually before 50 years of age	Usually after 50 years of age
Stool consistency	Soft, variable or hard	Watery/soft
Stool frequency	Can vary from day to day	High and more consistent
Nocturnal diarrhoea	Very unlikely	Possible
Feeling of incomplete bowel evacuation	Common	No
Feeling of fullness/bloating	Common	Rare
Accompanying autoimmune disease	Rare	Common

Table 1 | Differences in clinical history between patients with irritable bowel syndrome and those with microscopic colitis.

disease and even with normal controls.

In one study from Wildt et al., 50% of patients with active microscopic colitis had a calprotectin level below 100 mg/kg, and this level is used as the cut-off for colonoscopy referral in some countries.⁶ Reliance on this cut-off should therefore be avoided to prevent patients with microscopic colitis missing out on a diagnosis. Calprotectin is mainly released by neutrophils and these white blood cells are not involved in microscopic colitis to a great extent, which explains why faecal calprotectin levels might not reflect the degree of inflammation in these patients.

Mistake 4 Thinking that stool frequency is more important than consistency

The classic definition of chronic diarrhoea is ≥ 3 defecations/day for a duration of ≥ 4 weeks.⁷ Although stool frequency is easy to assess, it might not be the factor that has the greatest impact on a patient’s quality of life. The major symptom of microscopic colitis is watery diarrhoea, so defining diarrhoea in terms of stool consistency could have theoretical advantages. This is because stool form correlates better with other symptoms of microscopic colitis, like urgency and faecal incontinence, which are likely to have a bigger impact on a patient’s quality of life.

In one cross-sectional study, the aim was to evaluate the influence of bowel symptoms on the subjective experience of quality of life of patients with microscopic colitis and to suggest definitions for clinical activity. The results of this study are the Hjortswang criteria,⁸ which define clinical remission as a mean of < 3 stools/day and a mean of < 1 watery stool/day over a week of symptom registration, and clinical activity to be

a mean of ≥ 3 stools/day or a mean of ≥ 1 watery stool/day over a week (table 2). New with these criteria is the understanding that stool consistency might influence a patient’s quality of life more negatively than stool frequency and therefore that it is justifiable to treat patients who have just one watery stool daily.

Mistake 5 Failing to offer regular follow-ups to patients with microscopic colitis

According to some retrospective cohort studies, you could get the impression that most patients with microscopic colitis are in a state of long-lasting clinical remission so regular follow-ups are unnecessary. However, these studies often have major limitations and use varying criteria to assess disease course.

A more recent, prospective, one-year observation of patients in the EMCG registry (the PRO-MC collaboration) has shown that only a minority of patients with microscopic colitis follow a quiescent disease course with spontaneous clinical improvement. The majority suffer a chronic active or relapsing disease course during the first year after diagnosis, with persisting symptoms accompanied by a significantly impaired quality of life.⁹

In my experience, many patients are reluctant or embarrassed to talk about their bowel habits and do not seek help. It can be quite astonishing to discover how patients with microscopic colitis have adapted to live with their symptoms or live in a state of isolation and neglect. As doctors, we have to address these problems, inform patients about the clinical activity criteria for microscopic colitis as given in table 2 and encourage them to make contact if they have symptoms, whilst noting

	Stools per day	And	Watery stools per day
Clinical remission	< 3		< 1
Clinical activity	≥ 3	Or	≥ 1

Table 2 | The mean average number of stools or watery stools per day according to clinical remission or activity during one week of symptom registration.

that the endoscopic and histological follow-ups or screening programs that are used for colon cancer are not recommended.¹

Mistake 6 Believing that microscopic colitis is mainly drug induced

My impression is that there is a widespread opinion that microscopic colitis is often drug induced and some believe there is even causality. Many drugs have been suspected to induce microscopic colitis, but only the chronic or frequent use of proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors (SSRIs) is associated with an increased risk of microscopic colitis.¹ However, this association does not imply a causal relationship. The data derive mainly from retrospective case-control studies and different criteria for ‘drug exposure’ were applied or different reference populations were considered.¹ Moreover, the studies lack information on the evolution of clinical symptoms after drug exposure, withdrawal or rechallenge, which hinders the assessment of causality. It is therefore more reasonable to claim that these drugs are merely triggers of inflammation in predisposed individuals.

The EMCG suggests considering the withdrawal of any drugs for which there is a suspected chronological relationship between drug introduction and the onset of diarrhoea, especially in those cases where a patient has been continuously exposed to a drug for 4–12 months.¹ Symptoms should resolve within 1–2 weeks of drug withdrawal. To rechallenge a patient with the same drug to establish causality is often not feasible in clinical practice but, in 10 different cases, switching to another PPI did not result in the recurrence of diarrhoea, which contradicts the presumption of a class effect for PPIs.¹

Mistake 7 Neglecting patients with incomplete microscopic colitis

Incomplete microscopic colitis is a new term that is used to describe patients who have chronic, watery diarrhoea and histological findings that are not normal, but who fall short of fulfilling the classic criteria for microscopic colitis.¹⁰ Patients should have active disease according to the Hjortswang criteria⁸ and an established histological diagnosis of incomplete microscopic colitis defined as: an increased lymphoplasmacellular infiltrate in the lamina propria; a thickened subepithelial collagenous band, $> 5 \mu\text{m}$ and $< 10 \mu\text{m}$; and/or abnormal intraepithelial lymphocytes, > 5 and < 20 per 100 epithelial cells. To date, incomplete microscopic colitis is not yet established globally and has previously gone under many different names (e.g. paucicellular microscopic colitis).

The incidence rates of these incomplete cases is not known, but if patients are neglected they will not receive any diagnosis (or will receive the misdiagnosis of IBS-D) and thereby will not receive adequate treatment. The first randomised, controlled trial in patients with incomplete microscopic colitis that compared the efficacy of budesonide (9 mg) once daily versus a placebo for 8 weeks has recently been completed. The results demonstrate that budesonide decreases the frequency of loose/watery stools significantly compared with placebo. Furthermore, budesonide is safe and improves quality of life during an 8-week course.¹¹

Mistake 8 Not explaining the side effects of steroid treatments to patients and differentiating between budesonide and prednisolone

Steroids, which decrease inflammation and reduce the activity of the immune system, are used to treat microscopic colitis/IBD, and the two most commonly prescribed are budesonide and prednisolone. It is common knowledge that steroids can give side effects, especially with long-term treatment, so it is important that doctors give patients the correct information about these drugs and the differences between them.

Budesonide is a synthetic, locally acting glucocorticosteroid (glucocorticoid) with 90% first-pass metabolism in the liver after oral administration, whereas prednisolone is a systemic steroid that leads to more side effects. Budesonide is rapidly absorbed and metabolised by cytochrome P450 3A to produce metabolites with a lower glucocorticoid activity. The high receptor-binding affinity of budesonide makes it a glucocorticoid with strong topical effects in the gastrointestinal tract, and its reduced systemic availability is associated with a clear reduction in steroid-specific side effects. This, in combination with its improved safety profile, render it an alternative therapeutic option to conventional glucocorticoids with an improved benefit-risk ratio for the management of IBDs such as microscopic colitis. So far, randomised control trials of budesonide in patients with microscopic colitis, as induction or maintenance therapy, have shown a beneficial safety profile and no serious adverse events. Budesonide is therefore the first-choice treatment for patients with microscopic colitis and recommended in the European guidelines.¹

Mistake 9 Not trying rescue therapies for budesonide-refractory microscopic colitis

Very rarely, microscopic colitis becomes budesonide refractory, which is defined as continuous active disease despite treatment

with 9 mg budesonide for induction therapy or 6 mg budesonide for maintenance therapy. Even if there is a lack of long-term observations (over years) of the use of 6–9 mg budesonide to treat microscopic colitis, it can be considered in terms of individual patients; however, monitoring of specific side effects should be mandatory (e.g. development of diabetes, osteoporosis). According to the sparse literature in this field, it seems that patients with budesonide-refractory microscopic colitis are, on average, younger compared with the usual microscopic colitis population, which is important to acknowledge with respect to comorbidity and the risk of side effects when considering alternative immunomodulatory treatments. These patients have an immensely deteriorated quality of life and are often unable to have a social life and are housebound.

Despite the fact that the evidence for advanced treatment in microscopic colitis is limited, the EMCG recommends treatment with thiopurines, anti-tumour necrosis factor (TNF) drugs or vedolizumab in selected patients who have microscopic colitis that fails to respond when budesonide is used to induce and maintain clinical remission. Anti-TNF drugs might have the advantage of working faster, but the risk of side effects might be higher compared with vedolizumab. Use of the immunosuppressant methotrexate is not recommended in patients with microscopic colitis.¹

When initiating biological therapy in patients with microscopic colitis, the same routines and precautions should be followed as for classic IBD. There should be a special focus on comorbidities and contraindications, especially in elderly patients, who could have an increased risk of severe side effects. Decisions should therefore be made on an individual basis. Loss of response to one biologic can occur and switching to a second, of the same or another class, might be necessary. In my own experience, anti-TNF therapies are most effective but, for maintenance treatment, higher doses are frequently required or the time intervals between doses have to be shortened in order for patients to remain in clinical remission.¹² More clinical trial are definitely needed in this field, but so far, I recommend not giving up on patients who have budesonide-refractory microscopic colitis and to test biological treatment if appropriate.

Mistake 10 Failing to take microscopic colitis seriously

Microscopic colitis is certainly a benign disease in the sense that there is no increased risk of colon cancer or other serious complications. Patients with microscopic colitis have no alarming symptoms like rectal bleeding, intense abdominal pain or fistulas that trigger immediate action, and further laboratory or radiological examinations

are not helpful in diagnosing or monitoring the disease. Due to the lack of objective findings, microscopic colitis can therefore be perceived as being ‘invisible’ and not worthy of being taken seriously.

Patients express that they have to cope with disbelief from healthcare providers and relatives, which often leads to frustration and disappointment because they are not being taken seriously. Studies on quality of life with qualitative, semi-structured interviews have revealed that having microscopic colitis can be a disabling life experience and can impact every aspect of a patient’s life.¹³ Patients describe a disease-related worry that relates to urgency and faecal incontinence, which can remain even when they are in clinical remission because the sudden onset of microscopic colitis makes it unpredictable. Therefore, patients develop different strategies to adapt, cope and regain their previous performance level. As healthcare providers, it is important to take this illness seriously, because we know these patients have an impaired quality of life.¹⁴

References

- Miehlke S, Guagnozzi D, Zabana Y, et al. European guidelines on microscopic colitis: United European Gastroenterology (UEG) and European Microscopic Colitis Group (EMCG) statements and recommendations. *United European Gastroenterol J* Epub ahead of print 20 Aug 2020. DOI: 10.1177/2050640620951905.
- Weimers P, Ankersen DV, Lophaven S, et al. Incidence and prevalence of microscopic colitis between 2001 and 2016: A Danish nationwide cohort study. *J Crohns Colitis* 2020; 14: 1717–1723.
- Windon AL, Almazan E, Oliva-Hemker M, et al. Lymphocytic and collagenous colitis in children and adolescents: Comprehensive clinicopathologic analysis with long-term follow-up. *Hum Pathol* 2020; 106: 13–22.
- Guagnozzi D, Arias A and Lucendo AJ. Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders. *Aliment Pharmacol Ther* 2016; 43: 851–862.
- Kamp EJ, Kane JS and Ford AC. Irritable bowel syndrome and microscopic colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2016; 14: 659–668.
- Wildt S, Nordgaard-Lassen I, Bendtsen F, et al. Metabolic and inflammatory faecal markers in collagenous colitis. *Eur J Gastroenterol Hepatol* 2007; 19: 567–574.
- Fine KD and Schiller LR. AGA technical review on the education and management of chronic diarrhoea. *Gastroenterology* 1999; 116: 1464–1486.
- Hjortswang H, Tysk C, Bohr J, et al. Defining clinical criteria for clinical remission and disease activity in collagenous colitis. *Inflamm Bowel Dis* 2009; 15: 1875–1881.
- Verhaegh BPM, Münch A, Guagnozzi D, et al. Course of disease in patients with microscopic colitis — a European prospective incident cohort study. *J Crohns Colitis* Epub ahead of print 12 Jan 2021. DOI: 10.1093/ecco-jcc/jjab007.
- Langner C, Aust D, Ensari A, et al. Histology of microscopic colitis — review with a practical approach for pathologists. *Histopathology* 2015; 66: 613–626.
- Münch A, Mihalj E, Nagy F, et al. Budesonide as induction therapy for incomplete microscopic colitis: a randomized, placebo-controlled multicenter trial (paper submitted).

12. Daferera N, Hjortswang H, Ignatova S, et al. Single-centre experience with anti-tumour necrosis factor treatment in budesonide-refractory microscopic colitis patients. *United European Gastroenterol J* 2019; 7: 1234–1240.
13. Pihl Lesnovska K, Münch A and Hjortswang H. Microscopic colitis: struggling with an invisible, disabling disease. *J Clin Nurs* 2019; 28: 3408–3415.
14. Hjortswang H, Tysk C, Bohr J, et al. Health-related quality of life is impaired in active collagenous colitis. *Dig Liver Dis* 2011; 43: 102–109.

Your microscopic colitis briefing

UEG Week

- ‘Microscopic colitis — myth or truth?’ presentation in the ‘Endoscopy and imaging (Posters)’ session at UEG Week Virtual 2020 [<https://ueg.eu/library/microscopic-colitis-myth-or-truth/235444>].
- ‘European guideline on the management of microscopic colitis’ presentation in the ‘From guidelines to clinical practice: Diarrhoea and abdominal pain beyond IBD and IBS’ session at UEG Week Virtual 2020 [<https://ueg.eu/library/european-guideline-on-the-management-of-microscopic-colitis/234909>].
- ‘Topographical distribution of microscopic colitis, number of biopsies necessary for diagnosis, and importance of orientation of paraffin embedded biopsies’ presentation in the ‘IBS II’ session at UEG Week Virtual 2020 [<https://ueg.eu/library/topographical-distribution-of-microscopic-colitis-number-of-biopsies-necessary-for-diagnosis-and-importance-of-orientation-of-paraffin-embedded-biopsies/236262>].
- ‘Novel therapeutic approaches in microscopic colitis and *C. difficile*’ session at UEG Week 2019 [<https://ueg.eu/library/session/novel-therapeutic-approaches-in-microscopic-colitis-and-c-difficile/156/2589>].
- ‘Microscopic colitis: A neglected entity’ session at UEG Week 2018 [<https://ueg.eu/library/session/microscopic-colitis-a-neglected-entity/153/2019>].

Standards and Guidelines

- Fernández-Bañares F, Casanova MJ, Arguedas Y, et al. Current concepts on microscopic colitis: evidence-based statements and recommendations of the Spanish Microscopic Colitis Group. *Aliment Pharmacol Ther* 2016; 43: 400–426 [<https://ueg.eu/library/current-concepts-on-microscopic-colitis-evidence-based-statements-and-recommendations-of-the-spanish-microscopic-colitis-group/126265>].
- Langner C, Magro F, Driessen A, et al. The histopathological approach to inflammatory bowel disease: a practice guide. *Virchows Arch* 2014; 464: 511–527 [<https://ueg.eu/library/the-histopathological-approach-to-inflammatory-bowel-disease-a-practice-guide/128280>].
- Magro F, Langner C, Driessen A, et al. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013; 7: 827–851 [<https://ueg.eu/library/european-consensus-on-the-histopathology-of-inflammatory-bowel-disease/125499>].
- Münch A, Aust D, Bohr J, et al. Microscopic colitis: current status, present and future challenges: Statements of the European Microscopic Colitis Group. *J Crohns Colitis* 2012; 6: 932–945 [<https://doi.org/10.1016/j.crohns.2012.05.014>].
- Miehke S, Verhaegh B, Tontini GE, et al. Microscopic colitis: pathophysiology and clinical management. *Lancet Gastroenterol Hepatol* 2019; 4: 305–314. [[https://www.thelancet.com/journals/langas/article/PIIS2468-1253\(19\)30048-2/fulltext](https://www.thelancet.com/journals/langas/article/PIIS2468-1253(19)30048-2/fulltext)]