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SPECIAL ARTICLE

Microscopic colitis: Current status, present and future challenges

Statements of the European Microscopic Colitis Group

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Abstract

Microscopic colitis (MC) is an inflammatory bowel disease presenting with chronic, non-bloody watery diarrhoea and few or no endoscopic abnormalities. The histological examination reveals mainly two subtypes of MC, lymphocytic or collagenous colitis. Despite the fact that the incidence in MC has been rising over the last decades, research has been sparse and our knowledge about MC remains limited. Specialists in the field have initiated the European Microscopic Colitis Group (EMCG) with the primary goal to create awareness on MC. The EMCG is furthermore a forum with the intention to promote clinical and basic research. In this article statements and comments are given that all members of the EMCG have considered being of importance for a better understanding of MC. The paper focuses on the newest updates in epidemiology, symptoms and diagnostic criteria, pathophysiology and highlights some unsolved

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problems. Moreover, a new treatment algorithm is proposed on the basis of new evidence from well-designed, randomized control trials.

Contents

1. Introduction

Microscopic colitis (MC) is increasingly recognized as a common cause of chronic, non-bloody diarrhoea. Epidemiological studies have shown a rising incidence in the last decade. The diagnosis rests on specific histological findings in colonic biopsies from patients with chronic diarrhoea demonstrating either lymphocytic colitis (LC) or collagenous colitis (CC).

Proper diagnosis and regular follow-ups are important to differentiate these patients from those with irritable bowel syndrome (IBS), to provide relevant treatment, and to improve quality of life.

In comparison with the other inflammatory bowel diseases (IBD), our knowledge about MC remains limited. More research is needed to investigate the aetiology and pathophysiology of MC, but above all more clinical studies are needed to improve the handling of MC patients.

To address these apparent shortcomings, physicians dedicated to the understanding of MC met in September 2010 in Stockholm, Sweden to found the European Microscopic Colitis Group (EMCG). The primary objective of the EMCG is to create awareness on MC among patients, general practitioners, gastroenterologists, surgeons, and pathologists on all aspects of MC, and to eliminate misconceptions. Another aim is to promote collaboration among the EMCG members in clinical trials and basic science. In the long run this should result in the recommendation of evidence-based guidelines which can improve the care of MC patients.

Each topic in this article was initially written by 1–3 authors and discussed and revised at two meetings by all members of the EMCG. All members agreed on statements which are considered to be of importance for the understanding of MC. The statements are highlighted in the text and further explained and specified in comments. The paper focuses on the newest updates in epidemiology, symptoms and diagnostic criteria, pathophysiology, and treatment guidelines, and gives an overview of unsolved problems and future aspects. Since only limited knowledge is available regarding some of these topics, this document should be read as the best attempt to inform about clinical practice and knowledge in areas where rigorous evidence may not yet be available. However, we propose a new treatment algorithm on the basis of additional recent evidence from multiple well-designed, randomized controlled studies.

2. Epidemiology

2.1. MC is a common cause of chronic diarrhoea, especially in the elderly

Epidemiologic studies show that MC is almost as common as classic IBD (i.e. Crohn's disease and ulcerative colitis).[1–3] Epidemiologic data have now been reported from five different regions in Europe and North America. In recent years there have also been reports of cases and cohorts with MC from Africa, Asia, Latin America, and Australia, proving it to be a worldwide condition.[4–9] Microscopic colitis may be diagnosed in 10% of patients investigated for chronic non-bloody diarrhoea, and in 20% or more of such patients older than 70 years.[10,11] This observation is very important in the management of diarrhoea patients, but the disease must also be considered in younger patients, as 25% of MC patients are diagnosed before the age of 45 years.[12] MC has been reported in a few children below the age of 12, but is apparently a rare phenomenon in childhood.[13–15]

Table 1 Annual incidence per 100,000 inhabitants in population-based epidemiological studies of collagenous and lymphocytic colitis.

Region and study period	Collagenous colitis	Lymphocytic colitis
Örebro, Sweden 1984–1988[21]	0.8	
Örebro, Sweden 1989–1993[21]	2.7	
Örebro, Sweden 1993–1995[1]	3.7	3.1
Örebro, Sweden 1996–1998[1]	6.1	5.7
Örebro, Sweden 1999–2003[2]	4.7	5.1
Örebro, Sweden 2004–2008[2]	5.8	4.5
Terassa, Spain 1993–1997[22]	1.1	3.1
Terassa, Spain 2004–2008[19]	2.6	2.2
Iceland 1995–1999[16]	5.2	4.0
Olmsted County, Minnesota, USA 1985–1997[3]	1.6	2.7
Olmsted County, Minnesota, USA 1998–2001[3]	7.1	12.6
Calgary, Canada 2002–2004[23]	4.6	5.4
Calgary, Canada 2004–2008[18]	7.2	14.0
Zeeland, Denmark 2002–2010[17]	10.8	6.7

After a period of rising incidence figures, the data have been more divergent in recent studies. Incidence rates of 2.6/100,000 to 10.8/100,000 inhabitants have been reported for CC, and incidence rates of 2.2 to 14 per 100,000 inhabitants for LC.[1–3,16] To date, the highest incidence for MC was reported from USA,[3] Denmark[17] and Canada[18] while in more southern regions (e.g. Spain) the incidence seems to be lower (Table 1).[19] These reports indicate that MC is more frequent in the northern countries and follow a north–south gradient. However, a recent report from USA fails to support the notion of a north–south gradient regarding the incidence of MC in the USA.[20]

Patients with MC are typically elderly women, and the average age at diagnosis is approximately 65 years. The female predominance is very obvious in MC, but is less pronounced for LC than for CC. Recent prevalence estimates for MC are 103 cases per 100,000 persons (42 for CC and 69 for LC).[3]

2.2. Smoking is a risk factor for MC

Little is known about environmental risk factors in these diseases. However, smoking has been studied in three cohort studies. The first one revealed that smoking was significantly more frequent in CC than in controls and smokers developed their disease 10 years earlier than non-smokers,[24] results which were corroborated in a recent Spanish study.[25] In another study, more MC patients than controls were smokers; previous or current smoking yielded an OR of 2.4 (1.5–3.8) for CC ($p<0.001$) and 1.6 (1.0–2.5) for LC ($p<0.05$).[26,27]

3. Clinical features and health-related quality of life

3.1. Chronic non-bloody diarrhoea is the main clinical feature of MC

The main symptom of MC is chronic, non-bloody diarrhoea that may be accompanied by nocturnal diarrhoea, faecal incontinence and mild weight loss.[12,17,28] Abdominal pain is significantly more common in CC compared with a background population.[26] Serious dehydration and mucus or blood in the stool are rare. LC is clinically indistinguishable from CC. In two reports, however, it was found that symptoms in LC were milder and more likely to disappear than those in CC.[11,29,30]

3.2. The natural course of MC is largely unknown, but appears to differ between CC and LC

The onset of the disease is often insidious, but in about 40% of patients it is sudden.[12] In most cases, the clinical course is chronic relapsing and benign.[10,31–34] In earlier small follow-up studies of CC, a majority of patients, mostly without treatment, had lasting remission after 3–4 years,[35,36] which is in accordance with a more recent study from Iceland.[34] For LC a benign course was reported, with resolution of diarrhoea and normalization of histology in over 80% of patients. According to Olesen et al., in 63% of patients the clinical course is a single attack.[11]

On the other hand, prospective studies show high relapse rates up to 60% after cessation of budesonide.[37,38] Furthermore, in a number of patients the course can be complicated due to lack of response to medication. Surgery with a diverting ileostomy or colectomy is an option in patients with refractory and severe symptoms.[12,33,39,40]

3.3. MC is often associated with autoimmune diseases

Autoimmune disorders such as rheumatic disease, coeliac disease, thyroid disease, and diabetes were more often reported in patients than in controls, with an odds ratio of 11.0 (5.1–23.8) for CC patients ($p<0.001$).[26]

Autoimmune diseases have also been reported in LC patients. The odds ratio for LC patients of having one or more associated autoimmune diseases is 16.6 (6.4–43.1, $p<0.001$).[26]

3.4. MC-related complications are rare

Serious complications are uncommon, though there have been a few reports of patients with colonic perforation.[41–43] Perforation seems to be related to 'mucosal tears' that can be seen at colonoscopy.[44–48] Some authors have concluded that the risk for colorectal cancer is the same as in the general population,[49–51] while conversely a recent case–control study concluded that MC patients show a decreased risk.[52]

3.5. Health-related quality of life is significantly reduced in MC

The symptoms of CC may impair patients' health-related quality of life (HRQL).[53]

There is still no valid biomarker to define disease activity in CC. Clinical trials have used various different definitions for relapse or clinical response, making it difficult to compare results.[37,38,54–58] However, a definition of clinical remission has now been proposed, based on the finding of a natural "break-point" between high and low impact of bowel symptoms on HRQL in patients with CC.[59] In a survey of 116 patients with CC, stool frequency and consistency were found to give a clear cut-off to define remission. CC patients with a mean of <3 stools per day and a mean of <1 watery stool/day during a one-week symptom registration were defined as being in remission, since they had no or only mild impact on their HRQL. In contrast, CC patients with either ≥ 3 stools/day or ≥ 1 watery stool/day had a significant impact on their HRQL and were thus defined as having active disease (Table 2). Further prospective validation of this definition of disease activity in CC is needed, preferably in a prospective study where change in stool frequency or consistency over the defined "break-point" should result in a similar significant change in HRQL.

Table 2 Definition of clinical disease activity in collagenous colitis.

	Stools per day [a]		Watery stools per day [a]
Clinical remission	<3	AND	<1
Clinical activity	≥ 3	OR	≥ 1

[a] Mean during a one-week symptom registration.

4. Diagnostic criteria and spectrum of microscopic colitis

4.1. Colonoscopy with multiple colonic biopsies is the main diagnostic procedure to establish the diagnosis and to rule out other causes of diarrhoea

4.1.1. Bile acid diarrhoea, coeliac disease, and lactose malabsorption should be considered

The diagnosis of MC rests on characteristic pathological findings in biopsies from normal or oedematous colonic mucosa. Although the topographic distribution of MC remains controversial, rectal biopsies do not suffice.[60,61] Some studies demonstrate that biopsies from the right and transverse colon are necessary for the diagnosis of CC,[61,62] while others demonstrate that biopsies from the descending and sigmoid colon suffice for diagnosing MC.[17,63–65] However, colonoscopy should be preferred because it is essential to rule out malignant colonic disease. Diarrhoea caused by other diseases should be excluded; these diseases include bile acid diarrhoea, coeliac disease, and lactose malabsorption. Other imaging procedures are not recommended.

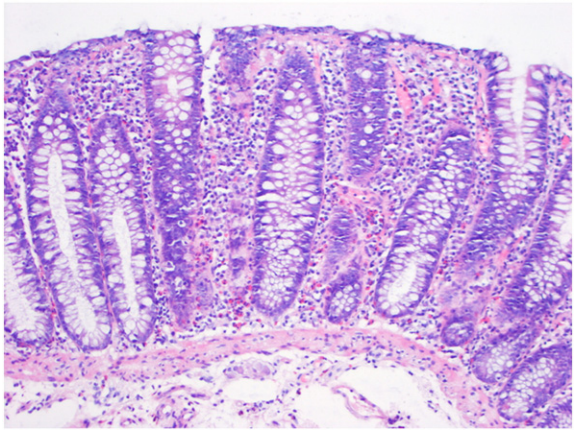

Figure 1 Biopsy from colon showing typical findings of lymphocytic colitis: inflammation of lamina propria, intraepithelial infiltration with lymphocytes and epithelial lesions.

4.1.2. Diagnosis of MC is based on clinical symptoms and histology

Histologically, MC is comprised of two well-defined entities: lymphocytic colitis (LC) and collagenous colitis (CC). As LC and CC share clinical similarities and histopathological features,[61,64,66,67] there has been some discussion of whether the two are in fact different stages of disease development.[68] However, conversion of LC to CC or vice versa is infrequent, and at present LC and CC are considered two separate but related entities.[69]

Chronic inflammation in the lamina propria is hard to define. In MC, the lamina propria shows increased numbers of plasma cells and lymphocytes with loss of the normal gradient (plasma cells around the crypt bases).[70] Eosinophil and neutrophil granulocytes may also be present in the lamina propria and sometimes within the epithelium.[71] Focally, active cryptitis with intraepithelial neutrophil granulocytes may be encountered.

Histological findings of MC are fairly inconsistent with repeat endoscopy.[17,61,72] It is possible that the inflammation in lamina propria is more important for the symptoms than the changes characterizing the MC subtypes.[66,72–74] This notion is supported by the lack of correlation between symptoms and either the thickness of the subepithelial collagenous layer or the number of intraepithelial lymphocytes (IELs).[72]

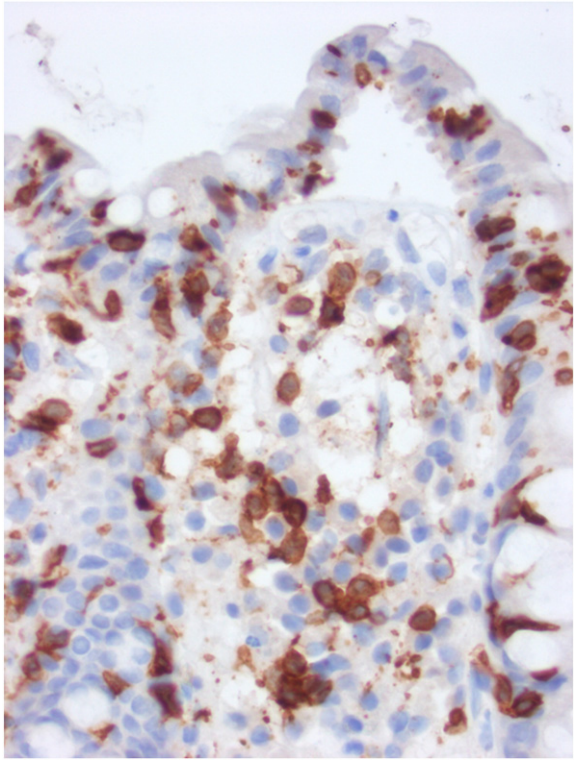

Figure 2 Lymphocytic colitis: note the increased numbers of intraepithelial lymphocytes and inflammatory infiltrate in the lamina propria after staining for CD3.

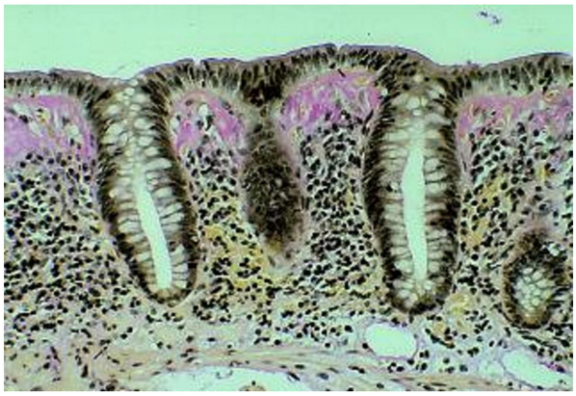

Figure 3 Histological features of collagenous colitis: an increased subepithelial collagenous layer (van Gieson staining), inflammation of lamina propria, intraepithelial infiltration with lymphocytes and epithelial lesions.

4.1.3. The key histological feature of LC is an increased proportion of surface intraepithelial lymphocytes (>20 IELs per 100 epithelial cells) (Fig. 1)

The general opinion in the literature is that >20 IELs per 100 epithelial cells are required to warrant a diagnosis of LC.[71,75–77] Epithelium overlying lymphoid follicles should not be evaluated. The number of IELs is greatest in the ascending and transverse colon and lowest in the rectosigmoid colon. IELs are T-lymphocytes, mostly cytotoxic CD8-positive T-lymphocytes. The epithelium itself can show regressive changes, with focal or diffuse flattening of the columnar cells, loss of mucin, decreased goblet cells, and signs of degeneration such as cytoplasmic vacuoles and pyknotic nuclei. The nuclei in the colonic crypts may be enlarged, with slightly increased mitoses. The crypts are normal in size, shape, and architecture. Very rarely, some epithelial multinucleated giant cells and collections of macrophages may be seen, as well as Paneth cell metaplasia distal to the transverse colon.[78] In borderline cases or in cases of uncertainty, it is highly recommended to perform CD3 staining (Fig. 2) in order to determine the precise number of IELs and to confirm the diagnosis.[78]

4.1.4. The key histological feature of CC is a broad subepithelial fibrous band>10 μm in thickness, immediately underneath the surface epithelium (Fig. 3)

Mucosal inflammation with slightly to moderately increased numbers of lymphocytes and plasma cells, admixed with mast cells and variable numbers of eosinophils and neutrophils is another hallmark of CC (Fig. 3).[71,76,77] The collagen band can contain entrapped capillaries, red blood cells, and inflammatory cells.[75] There is almost no extension of the thickened collagen table around the crypts. It is important to use only well-oriented biopsies for the analysis of subepithelial collagen, since tangential sectioning of tissue may mimic a thickened collagen table. The epithelium itself may show vacuolization and desquamation as well as increased IELs (though not as many as seen in LC).[79] Damaged epithelial cells appear flattened, mucin-depleted, and irregularly oriented. Focally, small strips of surface epithelium may lift off from their basement membrane.[80]

In cases of uncertainty, tenascin staining is recommended for better visualization and measurement of the collagen band thickness.[81]

4.1.5. Patients with chronic diarrhoea not fulfilling the histological CC/LC criteria may have incomplete MC (MCi) Fraser has suggested the term "MC not otherwise specified" (MCnos) for a subgroup of patients with diarrhoea, an increase in cellular infiltrate in the colonic lamina propria, and either an abnormal collagenous layer or IELs short of fulfilling the criteria for CC and LC.[82] Similarly, the term "paucicellular lymphocytic colitis" has been proposed for patients with typical clinical symptoms of MC and increased numbers of colonic IELs not fulfilling the diagnostic cut-off for LC.[74] Others have also reported such patients with clinical characteristics indistinguishable from LC and CC.[72,74,83] Uncontrolled data suggest that these patients respond to budesonide as well as patients with MC.[17] Prospective studies are needed to describe this possible third subgroup of MC and the effect of medical treatment.

5. Aetiology and pathophysiology

5.1. Familial occurrence of MC has been reported, but the role of genetic factors remains unclear

Familial microscopic colitis has been reported in small numbers.[84,85] Human leukocyte antigen (HLA) studies have demonstrated an association between MC and HLA-DQ2 or DQ1/3, as well as a higher frequency of HLA-DR3DQ2 haplotype and TNF2 allele carriage in MC compared with controls.[86–88] Furthermore, allelic variation of the matrix metalloproteinase-9 gene does appear to be associated with CC.[89] In contrast to Crohn's disease, functional polymorphism in the NOD2/CARD15 gene has not been detected.[90]

5.2. Epithelial barrier function is compromised in MC

In vitro experiments on colonic biopsies revealed a significant mucosal barrier dysfunction in CC patients in clinical remission, which was aggravated in active disease presenting with increased transmucosal uptake of non-pathogenic bacteria. The mucosal barrier dysfunction even persisted despite clinically effective short-term treatment with budesonide.[91] It is though uncertain if the underlying mucosal dysfunction is a primary or secondary phenomenon. On the other hand, the small bowel mucosa integrity seems intact, as assessed with urinary excretion after ingestion of ^{14}C-labelled mannitol and ^{99}mTc-labelled diethylenetriamine-pentaacetic acid.[92]

5.3. Mechanism of diarrhoea includes secretory and osmotic components

Bürgel et al. used an Ussing chamber technique to reveal the diarrhoeal mechanism in CC as being a reduced Na^+ and Cl^- absorption accompanied by a secretory component of active chloride secretion.[93] Analysis of faecal electrolytes also suggested a secretory mechanism.[94] The severity of diarrhoea seems to be best reflected by the intensity of inflammation in the lamina propria and is not correlated to the thickness of

Table 3 Factors and mediators involved in the pathophysiological mechanism of MC.

Factors	Mediators	References
Cellular	-Predominance of CD 8+ T lymphocytes carrying the α/β form.	101
	-Increased infiltration of functional active eosinophils.	102
	-Increased CD25+FOXP3+ lymphocytes.	74
Altered collagenous deposition	-Stains for collagen types III and VI, and particularly for tenascin.	81,103
	-Imbalance of fibrogenesis and fibrolysis due to restricted matrix metalloproteinase (MMP-1) RNA and increased tissue inhibitor of metalloproteinases (TIMP) expression.	103,104
	-Increased transforming growth factor-β_1 (TGF-β_1), which may be of pathophysiological importance in connective tissue remodelling.	105
	-Increased expression of connective tissue growth factor (CTFG) as a mediator of cellular collagen production.	106
	-Vascular endothelial growth factor (VEGF) might play a role in the accumulation of immature subepithelial matrix and intestinal inflammation.	107,108
	-Subepithelial myofibroblasts might be involved in the formation of the subepithelial collagen band.	81,109
Cytokines	-CC demonstrates a Th1 mucosal cytokine profile with interferon gamma (IFN γ) as the predominantly upregulated cytokine. Mucosal mRNA levels of interleukin (IL) 15 and tumour necrosis factor alpha (TNF-α) are increased.	110
	-Increased expression of iNOS correlates with luminal nitric oxide (NO) concentrations and clinical activity.	111
	-$NF_\kappa B$ is activated and recruited to the iNOS promoter in vivo via an IKKβ mediated pathway.	112
Faecal markers	-Eosinophil protein X, myeloperoxidase, and tryptase can be increased in CC.	113
	-Results for calprotectin are contradictory and it cannot be recommended as a diagnostic tool.	114

the collagenous band,[95] indicating that the diarrhoea is of inflammatory origin. The clinical observation that fasting can reduce diarrhoea indicates an osmotic component,[96] making it likely that the watery stools in MC are driven by a combination of osmotic and secretory components.

5.4. Bile acid diarrhoea is frequently seen in MC

By using selenium-labelled homocholic acid-taurine (SeHCAT), concurrent bile acid malabsorption (BAM) was shown to frequently exist in patients with CC (up to 44% of patients)[97,98] and LC.[17,97] It remains to be elucidated whether the association between BAM and MC is causal. No association was found between cholecystectomy and MC.[99] Uncontrolled data indicate that bile acid binding treatment is effective in MC, especially when BAD is concomitant, but does not result in significant changes in histopathology.[17,100]

5.5. A number of mucosal factors and mediators of intestinal inflammation have been described in MC, but none has reached clinical relevance

The cause of MC is unknown, but most likely involves a specific mucosal immune response to luminal factors in predisposed individuals. Numerous observational studies have looked at different mechanisms that may be involved in the development of the mucosal inflammation in MC, but the pathophysiological importance of these findings are uncertain (Table 3).

5.6. Drug-induced MC should be considered

Drug consumption has been suggested to act as an environmental risk factor implicated as causative or triggering agent of MC. Multiple drugs have been mentioned. For some of them causality is considered to be certain, for other only probable or possibly (Table 4). Criteria to define certainty (high likelihood of causality) are based on a compatible timing of the start of diarrhoea relative to drug exposure, improvement of the symptoms after stopping the medication (dechallenge), and recurrence of the symptoms on repeat exposure (rechallenge). Case–control studies have shown the association of drug usage with MC,[115–118] mainly for aspirin, NSAIDS, lansoprazole, omeprazole, and sertraline consumption. However, in these cases, a cause–effect relationship cannot be established. The only report based on data from prescription databases found no association with drug consumption.[119]

Drugs and their metabolites may affect the colon directly through their pharmacological actions or through idiosyncratic hypersensitivity reactions by the colonic mucosa. Drugs can also act indirectly on the colon by altering colonisation by gastrointestinal organisms. The rarity of an association between a drug and MC favours the existence of an idiosyncratic hypersensitivity reaction, i.e., it does not occur in most patients at any readily achieved dose of the drug and does not involve the known pharmacologic effects of the drug.

Most of the drugs suggested to be associated with MC are also well known to be associated with the development of chronic diarrhoea as an adverse event.[120] For example, in a study on diarrhoea and drug use in the elderly, the use of proton pump inhibitors, NSAIDs, and selective serotonin reuptake inhibitors were associated with the risk of developing diarrhoea.[121] In a study on MC, use of some drugs presumptively associated with MC did not show significant differences as compared to a chronic diarrhoea group.[116] Therefore, considering an association of a drug with MC should imply the improving or disappearing of the histological damage after dechallenge, and recurrence after rechallenge, and not only the effect on the diarrhoea symptom. However, rechallenge followed by clinical and histological relapse has been scarcely reported.[122–126]

Further studies on the impact of medication discontinuation on clinical symptoms and colonic histology will help advance the understanding of which is the true link between the drugs and the disease.

Table 4 Assessment of the level of likelihood that a specific drug can trigger MC: Review of the literature.[127]. [a]Modified from Beaugerie and Pardi.

High likelihood	Intermediate likelihood	Low likelihood
Acarbose[123]	Carbamazepine[11,128–131]	Cimetidine[132]
Aspirin and NSAIDs[118,133–136]	Celecoxib[137]	Gold salts[138]
Clozapine[139]	Duloxetine[140]	Piascledine[141]
Entocapone[142]	Fluvastatin[137]	
Flavonoid[124,137,143–147 b]	Flutamide[29,138]	
Lansoprazole[125,148–151]	Oxetorone[152,153]	
Omeprazole/Esomeprazole[126]	Madopar[154 c]	
Ranitidine[122]	Paroxetine[11]	
Sertraline[11,127,137]	Simvastatin[155]	
Ticlopidine[29,138,156–159]	Stalevo[160 c]	

[a] This paper used the 'French algorithm' to evaluate causality assessment of adverse drug reactions. This implies the evaluation of seven criteria belonging to two groups: chronological and semiological. Chronological criteria are: Time to onset, dechallenge, and rechallenge. Semiological criteria are: Search for non-drug related causes, evocative semiology of drug responsibility and/or risk factors for drug reaction, and specific validated laboratory test. A bibliographic score taking into account how often the adverse reaction has been reported was used to calculate the total likelihood score of causality.

[b] Venotonic drugs containing flavonoids (diosmin, rutin, or hesperidin).

[c] Anti-parkinsonian drugs, containing levodopa and benserazide (Madopar[R]) and carbidopa, levodopa and entocapone (Stalevo[R]).

6. Treatment

6.1. The choice of treatment in MC depends on severity of symptoms

Medical treatment of MC should take into account the severity of symptoms, their impact on the patient's quality of life, and the availability of outcome data from randomized clinical trials. The primary aim of medical therapy is to achieve clinical remission and improve the patient's quality of life.[59] In patients with recurrent disease, the maintenance of clinical remission may be desirable. It is currently not known whether histological remission is relevant for the rate of recurrence, and hence it is not clear whether it should be an important goal.

6.2. Budesonide is the only drug which has been proven effective in MC by randomized, placebo-controlled trials

The strongest evidence from clinical trials for the treatment of MC is currently available for budesonide.[161] Three randomized, placebo-controlled trials in collagenous colitis have proven budesonide at 9 mg per day to be effective for induction of clinical remission.[54–56] The majority of patients respond rapidly to budesonide, and experience a substantial improvement in quality of life.[58,162] A Cochrane meta-analysis revealed a pooled response rate of 81%, and a number-needed-to-treat of two patients.[163] After cessation of budesonide treatment, symptomatic relapse may occur in 60–80% of patients, most of whom respond to retreatment with budesonide.[37,55] Subsequently, two randomized placebo-controlled trials have shown that clinical remission and histological response can be maintained in the majority of patients with budesonide at 6 mg per day for 6 months,[38,164] with a pooled response rate of 83% and a number-needed-to-treat of 2 patients.[163]

A similarly high efficacy of budesonide at 9 mg per day in LC has been demonstrated by two randomized placebo-controlled trials.[165,166] A Cochrane meta-analysis revealed an odds ratio of 9 for clinical response and a number-needed-to-treat of 3 patients.[167] Both studies also demonstrated substantial improvement of colonic inflammation.

6.3. There are currently no evidence-based alternatives to budesonide

Antidiarrhoeals such as loperamide are frequently used in MC, but have never been formally tested in randomized placebo-controlled trials. Clinical experience suggests a symptomatic benefit in some patients.[11,12,159] However, sustained clinical remission is rarely achieved, and an impact on colonic inflammation is unlikely.

Prednisolone has been investigated in retrospective studies[11,12,159] and in one small randomized, placebo-controlled trial.[57] A clinical response was noted in 5 of 8 patients after 2 weeks of prednisolone compared to none of 3 patients with placebo.

Bismuth subsalicylate was tested in a small randomized placebo-controlled trial which has never been fully published.[168] Clinical and histological responses were noted in all 7 patients receiving bismuth subsalicylate and none of the 7 receiving placebo.

Mesalazine for the treatment of MC has mainly been reported in retrospective studies suggesting a therapeutic response in about half of patients.[11,12] At the time of writing, there has only been one prospective but uncontrolled trial on mesalazine, which showed a higher efficacy when administered over a period of 6 months.[169] Due to lack of control groups, the true value of mesalazine in MC remains inconclusive.

Retrospective studies suggest a benefit of cholestyramine in MC.[138,170,171] In a randomized study, 23 patients with CC and 41 with LC received mesalazine at 2.4 g per day alone or in combination with cholestyramine at 4 g per day for 6 months.[171] Remission was noted in 91% of patients with CC and 85% of patients with LC after 6 months; the combined treatment appeared to be slightly better.

The probiotics *Lactobacillus acidophilus* LA-5 and *Bifidobacterium animalis* subspp. *lactis* BB12 (AB-Cap-10) given for 12 weeks did not show any benefit over placebo with respect to clinical response, histological improvement, or quality of life in a randomized placebo-controlled study in 29 patients with CC.[172] *Boswellia serrata* extract given at a dose of 3×400 mg per day for 6 weeks failed to show a significant benefit over placebo in a randomized, placebo-controlled trial. Clinical response was noted in 7 of 16 patients given *B. serrata* extract (44%) compared to 4 of 15 given placebo (27%). Neither histology nor quality of life was improved by active treatment.[173] The probiotic *E. coli* strain Nissle 1917 was investigated in an open-label uncontrolled trial in 14 patients with CC, administered at different dosages for at least 4 weeks.[174] A reduction in stool frequency was observed in 64% of patients and an improvement of stool consistency in 50%.

Although the evidence is limited, immunosuppressive therapies might be considered in patients with severe symptoms who fail to respond to budesonide. In such cases, azathioprine or 6-mercaptopurine have been tried in dosages similar to those used for other inflammatory bowel disease.[40] The first reports suggest that anti-TNF therapy may be effective in refractory MC.[175,176]

Oral methotrexate has produced clinical response in budesonide-naïve CC patients,[177] but a recent report showed no efficacy of methotrexate (25 mg s.c.) in patients that were intolerant or refractory to budesonide.[178] However, these data remain limited and inconclusive, and treatment with immunosuppressants or biologicals must therefore be regarded as experimental.

Surgical intervention in microscopic colitis should be regarded as ultima ratio in patients refractory to any medical intervention. Both diverting ileostomy and subtotal colectomy have been performed successfully in individual cases.[39,179]

7. Summary: recommendations for the treatment of MC

Based on the currently available evidence, the EMCG members wish to propose a novel algorithm for the treatment of microscopic colitis (Fig. 4). According to this algorithm, patients with active MC should be primarily treated with

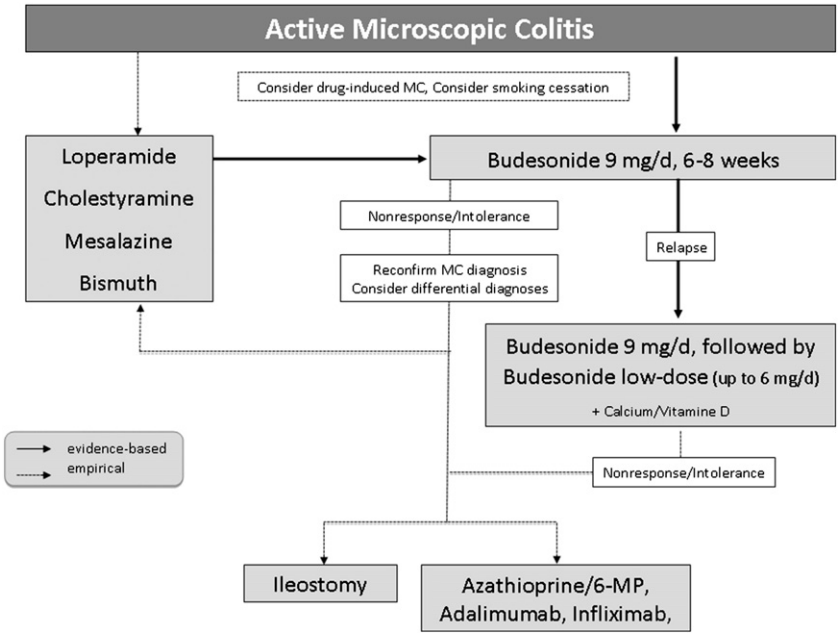

Figure 4 Treatment algorithm for active microscopic colitis.

short-term budesonide. Antidiarrhoeals and/or colestyramine may be considered in patients with only mild symptoms, however this recommendation is not evidenced-based. In case of relapse after budesonide withdrawal, budsonide can be used again either as intermittent or as low-dose continuous therapy. In patients who do not respond to budesonide, alternative drugs such as cholestyramine, aminosalicylates or bismuth can be considered if symptoms are only mild.

There is currently no evidence to recommend azathioprine/6-mercaptopurine or anti-TNF-α antibodies. However, there are case reports to suggest that AZT/6-MP or TNF-α blockers might be considered in individual cases. Surgical treatment should be regarded as the last resort in patients refractory to medical therapies.

8. Future aspects

It is important to create awareness of MC among general practitioners, gastroenterologists, surgeons, and pathologists, as MC is a fairly "new" and frequent disease and should always be considered in patients with chronic diarrhoea. Numerous patients are still overlooked or even misdiagnosed with IBS, and not referred to colonoscopy. Regular follow-ups with a gastroenterologist should be conducted in order to assess the disease course and discuss individual treatment options if necessary.

Future research should focus on a better understanding of the underlying pathophysiological and immunological aberrations, as well as the finding of biomarkers that reflect disease activity. The search for susceptibility genes in this condition could give us deeper insight into pathogenic processes such as the defective mucosal barrier. Furthermore, well designed studies should address the possibility of drug aetiology in this condition.

One major unresolved question is whether MC is one disease with different expressions, or several diseases. The diagnosis of MC rests on strict but arbitrary histopathological findings in colonic biopsies. Recent results indicate that the histological findings in the individual patient are inconsistent over time, as findings of MC interchange with chronic inflammation or incomplete signs of MC at prior or repeated endoscopy. The histological interchange between MC subtypes and the incomplete identification of all patients have led to the introduction of the term "incomplete MC" (MCi), which needs further evaluation, including placebo-controlled studies of the effect of budesonide treatment.

It is important to know which maintenance treatment is most effective and safe in MC patients with a chronic, active course. The 6 mg daily budesonide dose which has been used is probably too high for long-term treatment in most elderly people, and ongoing trials with lower doses are eagerly awaited (EudraCT No: 2007-001315-31).

A further challenge is MC patients that fail to respond to budesonide treatment. Although this subgroup of the MC population is small, these patients have a very poor quality of life and represent a real clinical challenge. Therefore, randomized, controlled studies should investigate the efficacy of immunosuppressive therapy, especially azathioprine/6-mercaptopurine and anti-TNF therapy in patients that are non-responders or intolerant to budesonide.

Conflict of interest

Aust D, Bonderup O, Hjortswang H, Munck LK and Ström M have declared no conflict of interest.

Bohr J: MSD, Tillotts Pharma AB, MEDA: honoraria.

Fernández Bañares F: lecture fees from Tillots Pharma; Research Funding from Falk Pharma.

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Miehlke S: Falk Pharma: research funding, honoraria.

Münch A: Falk Pharma: honoraria.

Tysk C: lecture fees from Tillotts Pharma, Falk Pharma, Ferring, MSD and Astra-Zeneca.
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Contributorship

The topics have been initially written by 1–3 authors with recognized experience in the specific field. In two additional meetings all members of the EMCG discussed the topics and agreed on statements. All authors have read and approved the final version which was put together by the corresponding author.

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