*Annals of Gastroenterology* (2011) **24,** 253-262

# Recent advances in diagnosis and treatment of microscopic colitis

**Curt Tysk [a], Anna Wickbom [a], Nils Nyhlin [a], Sune Eriksson[b], Johan Bohr [a]**
Örebro University Hospital, Örebro, Sweden

**Abstract**

Microscopic colitis, comprising collagenous colitis and lymphocytic colitis, is a common cause of chronic diarrhea. It is characterized clinically by chronic watery diarrhea and a macroscopically normal colonic mucosa where diagnostic histopathological features are seen on microscopic examination. The annual incidence of each disorder is 4-6/100,000 inhabitants, with a peak incidence in individuals 60-70 years old and a noticeable female predominance in collagenous colitis. The etiology is unknown. Chronic diarrhea, abdominal pain, weight loss, fatigue, and fecal incontinence are common symptoms that impair the health-related quality of life of the patient. There is an association with other autoimmune disorders, such as celiac disease, thyroid disorders, diabetes mellitus, and arthritis. Budesonide is the best-documented treatment, both short-term and long-term. Recurrence of symptoms is common after withdrawal of successful budesonide therapy, and the optimal long-term treatment strategy needs further study. The long-term prognosis is good, and the risk of complications including colon cancer is low. We review the epidemiology, clinical features, diagnosis and treatment of microscopic colitis.

**Keywords** *Microscopic colitis, collagenous colitis, lymphocytic colitis, chronic diarrhea, budesonide*

*Ann Gastroenterol 2011; 24 (4): 253-262*

## Introduction

Chronic diarrhea, reported by 4-5% of individuals of a Western population, is a common cause for consulting a physician in general practice or in internal medicine and for referral to a gastroenterologist [1]. Microscopic colitis (MC), previously regarded as rare, and certainly overlooked, now has emerged as a common cause of chronic diarrhea, especially in elderly females. The condition is characterized clinically by chronic watery diarrhea and a macroscopically normal or almost normal colonic mucosa, where microscopic examination of mucosal biopsies reveals characteristic histopathological changes [2]. MC comprises two entities: collagenous colitis (CC) and lymphocytic colitis (LC), which have indistinguishable clinical presentations but are separated by histopathological characteristics. This review will present recent advances in the epidemiology, clinical features, diagnosis, and management of MC.

[a]Department of Medicine, Division of Gastroenterology, Örebro University Hospital and School of Health and Medical Sciences, Örebro University, Örebro, Sweden (Curt Tysk, Anna Wickbom, Nils Nyhlin, Johan Bohr); [b]Department of Laboratory Medicine, Division of Pathology, Örebro University Hospital, Örebro, Sweden (Sune Eriksson)

Funding: Örebro County Research Committee, Örebro University Hospital Research Foundation and the Swedish Society of Medicine (Bengt Ihre Foundation, grants 21142-2008, 22100-2009, 98031-2010) supported our studies of microscopic colitis.

Conflict of Interest: None

Correspondence to: Professor Curt Tysk, Department of Medicine, Division of Gastroenterology, Örebro University Hospital, SE-701 85 Örebro, Sweden. Tel +46 19 6021000; fax +46 19 6021774. curt.tysk@orebroll.se

Received 5 September 2011; accepted 11 September 2011

## Epidemiology

CC and LC, first described in 1976 [3] and in 1989 [4], respectively, have mostly been reported from European or North American centers, but the disease is found worldwide [5-11]. Currently, epidemiological data have been reported from five different regions (Table 1) [5,6,12-17]. The difference between data from Spain and those reported from Northern Europe and North America may suggest that there is a North–South difference in the incidence of MC. Long-term epidemiological data from Sweden and the United States since the 1980s show rising incidences, which seem to have levelled off during the last study periods in the Swedish study. Whether the increasing incidence figures are an artefact reflecting an increased awareness and improved diagnosis of the condition, or in fact represent a true rise, is at present unknown. MC may be diagnosed in 10-20% of cases investigated for chronic watery

**Table 1** Annual incidence/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 [13] | 0.8 | |
| Örebro, Sweden 1989-1993 [13] | 2.7 | |
| Örebro, Sweden 1993-1995 [5] | 3.7 | 3.1 |
| Örebro, Sweden 1996-1998 [5] | 6.1 | 5.7 |
| Örebro, Sweden 1999-2003 [15] | 4.7 | 5.1 |
| Örebro, Sweden 2004-2008 [15] | 5.8 | 4.5 |
| Terassa, Spain 1993-1997 [14] | 1.1 | 3.1 |
| Terassa, Spain 2004-2008 [17] | 2.6 | 2.2 |
| Iceland 1995-1999 [12] | 5.2 | 4.0 |
| Olmsted County, Minnesota, USA 1985-1997 [6] | 1.6 | 2.7 |
| Olmsted County, Minnesota, USA 1998-2001 [6] | 7.1 | 12.6 |
| Calgary, Canada 2002-2004 [16] | 4.6 | 5.4 |

diarrhea [5]. In 2001, the prevalence of microscopic colitis in Olmsted County, Minnesota, USA was 103/100,000 inhabitants; 39.3/100,000 for collagenous colitis and 63.7/100000 for lymphocytic colitis.

CC mainly affects middle-aged women, with a peak incidence around 65 years of age (Fig. 1) [6,18]. However, the disease can occur in all ages, including children [19]. In LC the peak incidence is in the same age group as CC, but the female predominance is less pronounced (Fig. 1) [20].

## Clinical presentation

The clinical symptoms of CC and LC are similar and the diseases cannot be differentiated on clinical grounds. Both disorders cause chronic or recurrent non-bloody, watery diarrhea, often associated with nocturnal diarrhea, diffuse abdominal pain, and weight loss, which may be substantial [18,20,21]. Although some patients may suffer from severe diarrhea, serious dehydration is rare. Fatigue, nausea, and

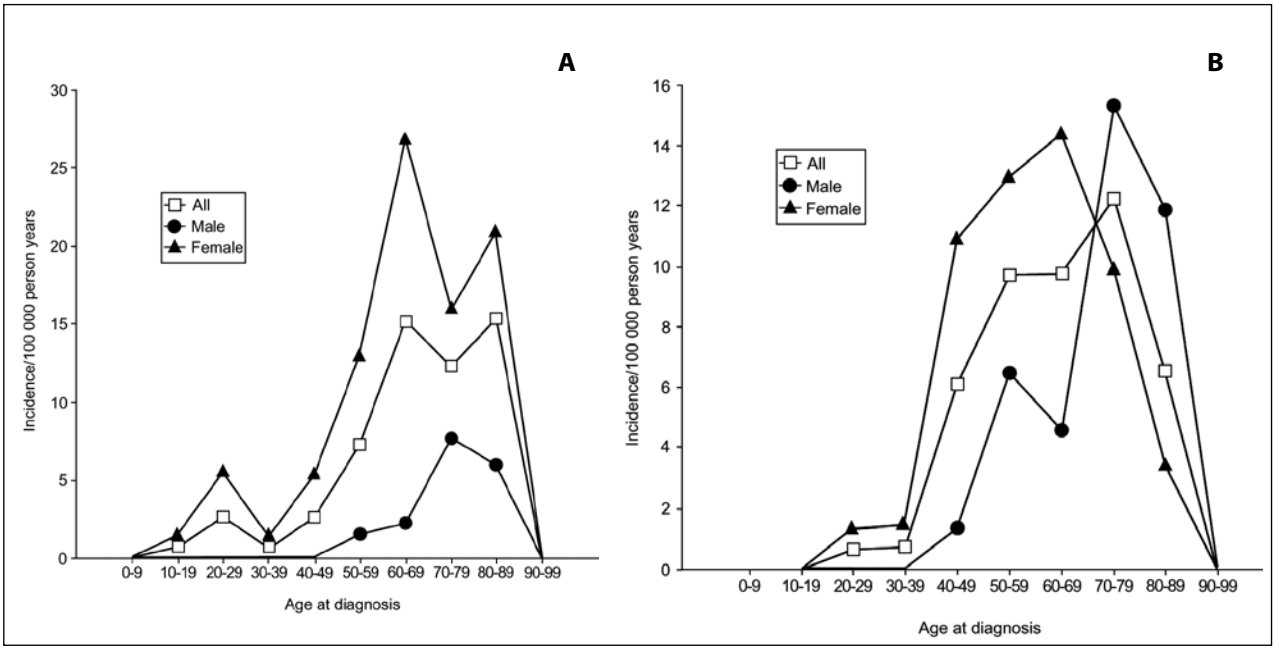


**Figure 1** Age- and sex-specific incidence of (A) collagenous colitis and (B) lymphocytic colitis. Reprinted with permission from *Gut* 2004;53:346-50

fecal incontinence are other associated symptoms, and the disease may significantly impair quality of life of the affected patient [22-24].

The onset of disease can be sudden, mimicking infectious diarrhea [18,20]. The clinical course is often chronic, relapsing, and benign. Severe complications are rare, although there are reports of colonic perforations, spontaneous or after a colonoscopy, in CC [25-27]. No increased risk of colorectal cancer is reported in CC or LC [28-30]. However, an increased risk of lung cancer was reported in women with CC [28] probably related to smoking, which is more common among patients compared to controls [31,32].

Some patients have mild symptoms that may be misinterpreted as irritable bowel syndrome [33]. Morphologic findings of MC have been reported even in constipated or asymptomatic patients [34]. The natural history of the condition in these patients is unknown.

Patients with MC often have concomitant autoimmune diseases [18,20,21]. The most common are thyroid disorders, celiac disease, diabetes mellitus, and rheumatoid arthritis. The occurrence of such associations, reported in up to 40-50% of patients, is variable depending on the study, and differences between LC and CC with respect to associated conditions have been described [18,20,21,35]**.** Bile acid malabsorption can often coexist with MC, leading to worsening of symptoms [36]. An interchange between ulcerative colitis or Crohn's disease and MC has been reported occasionally [37,38]. Whether this is merely a chance association of two fairly common disorders occurring in the same individual or due to common genetic predisposition or shared immunologic pathways remains unknown thus far.

## Etiology and pathogenesis of mucosal inflammation

The cause of microscopic colitis is multifactorial and largely unknown. CC and LC are presently considered to represent specific mucosal responses to various noxious luminal agents, in predisposed individuals. As CC and LC have many clinical similarities and share histopathological features, except for the subepithelial collagen layer found in CC, it has been discussed whether LC and CC are in fact the same disease seen in different stages of development. Conversion of LC to CC or the opposite has been reported, but occurs infrequently. However, in clinical practice the management is not determined by histological type.

Data on the mucosal inflammation in MC are increasing but still limited. In the epithelium mainly CD8+ T-lymphocytes are found that carry the α/β form of the T-cell receptor, and in the lamina propria there are largely CD4+ T-lymphocytes [39]. CD25+FOXP3+ T reg cells are a common feature in the lamina propria of both CC and LC patients [40]. By means of segmental colorectal perfusion technique, increased luminal levels of eosinophilic cationic protein (ECP), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) were found in CC [41-43]. Likewise, Wagner et al found an increased number of activated eosinophils in the colonic mucosa in CC, which became normal after budesonide treatment [44]. By immunohistochemistry technique, others verified increased mucosal levels of VEGF that were not affected following therapy with budesonide [45]. A study of cytokines in MC found a $T_H1$ mucosal cytokine profile with IFNγ, TNFα, and IL-15 as the predominantly upregulated cytokines [46]. Using Ussing chamber technology, increased transcellular and paracellular mucosal permeability were found in patients with CC that persisted after treatment with budesonide [47,48]. The excess subepithelial collagen in CC may be due to an imbalance of collagen turnover. An increased collagen synthesis is supported by findings of an increase in the number or the activity of myofibroblasts [49]. Among degrading enzymes, matrix-metalloproteinases (MMPs) have a central role that is regulated by tissue endogenous inhibitors of metalloproteinases (TIMPs) [50]. Impaired collagen degradation in CC was supported by findings of restricted MMP-1 RNA expression and increased TIMP expression [51].

### Genetics

It is uncertain whether there is a genetic predisposition to MC. Familial cases have been reported, but it is unclear whether these reflect shared familial traits or random associations [52-55]. HLA-studies have earlier shown an association between MC and HLA-DQ2 or DQ1,3, and recently an association was reported between MC and HLA-DR3-DQ2 haplotype, and with TNF2 allele carriage, irrespective of presence of concomitant celiac disease [56,57]. Variants of MMP-9 gene associated with CC have been reported [58]. No association with NOD2/CARD15 polymorphisms and susceptibility to CC has been found [59].

### Luminal factor

Mucosal inflammation with an increased number of intraepithelial T-lymphocytes has suggested that MC may be caused by an immunological response to a luminal agent in predisposed individuals. This theory is supported by the observation that diversion of the fecal stream by an ileostomy normalized or reduced the characteristic histopathologic changes in CC [60]. After closure of the ileostomy, recurrence of symptoms and histopathologic changes occurred.

### Drug-induced MC

There are several reports of drug-induced MC and a strong likelihood of association has been found with acarbose, aspirin, Cyclo3 Fort, non-steroidal anti-inflammatory drugs, lansoprazole, ranitidine, sertraline, and ticlopidine [61]. Assessment of concomitant drug use in patients with MC is therefore important to identify and consider withdrawal of drugs that might cause or worsen the condition.

### Infection

An infectious cause has been suspected, especially in patients with a sudden onset of disease. An association with MC and *Campylobacter jejuni, Yersinia enterocolitica* or *Clostridium difficile* has been reported occasionally [62-65]. LC shares many features with "Brainerd diarrhea", which refers to outbreaks of acute watery diarrhea with long duration, first reported among 122 residents of Brainerd, Minnesota [66]. Colonic biopsies of these patients show epithelial lymphocytosis similar to LC, but not crypt distortion or epithelial destruction [67]. Investigations of several outbreaks of "Brainerd diarrhea" have established an incubation period of 10-30 days and median duration of illness of 16 months [68]. Although an infectious agent is thought to be the cause of "Brainerd diarrhea", no microorganism has as yet been identified. Furthermore, a seasonal pattern of onset of LC [20,69] may support an infectious cause. However, in most cases of MC with a sudden onset, stool cultures remain negative.

### Bile acids

Bile acid malabsorption can coexist with MC, leading to worsening of symptoms. Concurrent bile acid malabsorption was found in 27-44% of patients with CC and in 9-60% of patients with LC [36,70,71]. These observations are the rationale for recommendations of bile acid binding treatment in MC. The treatment is especially effective in patients with concomitant bile acid malabsorption, but improvement has also been shown in patients without bile acid malabsorption.

### Autoimmunity

The association with other autoimmune diseases such as thyroid disease, celiac disease, diabetes mellitus, or arthritis has suggested an autoimmune process. However, no specific autoantibody or marker has been identified.

### Nitric oxide

Colonic nitric oxide (NO) production is greatly increased in active MC, caused by an upregulation of inducible nitric oxide synthase (iNOS) in the colonic epithelium [72-75]. A major transcriptional inducer of iNOS gene expression is the transcription nuclear factor κB (NFκB). In active CC colonic mucosal NFκB was found activated in epithelial cells, but not in lamina propria macrophages, in contrast to ulcerative colitis [76]. The levels of NO correlate to clinical and histological disease activity [73]. It has been suggested that NO is involved in the pathophysiology of diarrhea in CC, as infusion in the colon of $N^G$-monomethyl-L-arginine, an inhibitor of NOS, reduced colonic net secretion by 70%, and the addition of L-arginine, a precursor in NO synthesis, increased colonic net secretion by 50% [74]. Further support for NO being involved in the pathogenesis of CC comes from therapy studies. Treatment with budesonide, in contrast to placebo, resulted in a significant reduction in iNOS mRNA that correlated with clinical and histopathological improvement [77].

### Secretory or osmotic diarrhea

The exact mechanism of diarrhea in MC is not fully clarified. In CC, diarrhea has been regarded as secretory, caused by reduced net absorption of $Na^+$ and $Cl^-$ ions due to epithelial cell lesions, and the thickened collagenous layer as a co-factor causing a diffusion barrier, and by an additional active chloride secretion [78]. Fasting, on the other hand, seems to reduce diarrhea, which would indicate an osmotic component in some patients, as well [79].

## Diagnosis

The diagnosis of MC relies solely on findings of typical microscopic changes in colonic mucosal biopsies [80]. In CC a thickening of the subepithelial collagen layer is seen, together with a chronic mononuclear inflammation in the lamina propria, and epithelial cell damage with occasionally increased number of intraepithelial lymphocytes (Fig. 2). The thickened subepithelial collagen layer in CC is ≥10μm on well-orientated sections, in contrast to a normal basal membrane of <3μm. The thickening of the collagen layer may be variable and is most prominent in the ascending or transverse colon, and may be absent in biopsies from the sigmoid colon or rectum, emphasizing the importance of obtaining biopsies from the proximal colon when diagnosing CC [81]. Generally, the histopathologic changes are restricted to the large bowel, but a thickened collagen layer has infrequently been found in the stomach, duodenum, or terminal ileum. In addition to conventional histological staining, the use of tenascin immunostaining has been suggested in uncertain cases of CC (Fig. 3) [49,82].

The diagnostic features of LC (Fig. 2) are an increased number of intraepithelial lymphocytes (≥20/100 surface epithelial cells) in conjunction with surface epithelial cell damage and an infiltration of lymphocytes and plasma cells in the lamina propria, but the collagen layer is normal, in contrast to CC [80]. In uncertain cases, immunostaining of CD3+ T-lymphocytes facilitates the assessment of intraepithelial lymphocyte count (Fig. 4).

Barium enema and colonoscopy are usually normal, although subtle mucosal changes can be seen, such as edema, erythema, and abnormal vascular pattern [18,20]. Tears of colonic mucosa have occasionally been seen during colonoscopy, which might be a sign of increased risk of colonic perforation during the procedure [27,83-85]. In the future, the use of confocal laser microscopy may enable *in vivo* diagnosis of MC [86-88].

Laboratory tests are non-diagnostic and only non-specific

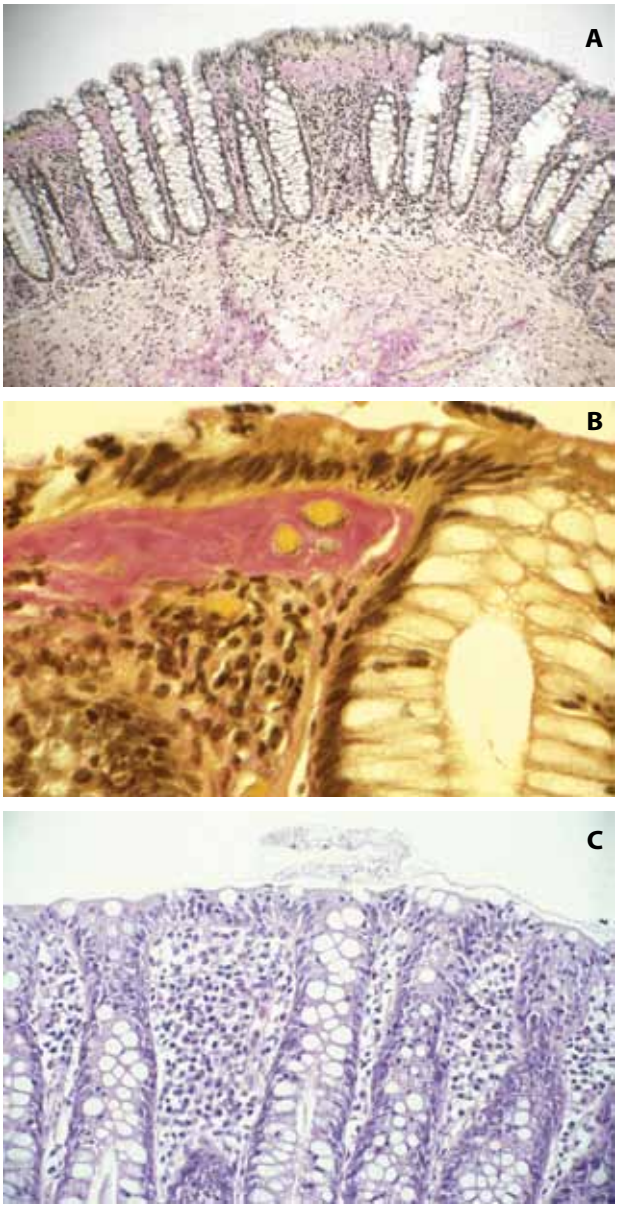


**Figure 2** Biopsy from colon showing (A, B) typical findings of collagenous colitis - increased subepithelial collagen layer, inflammation of lamina propria, and epithelial cell damage with intraepithelial lymphocytes; (C) typical findings of lymphocytic colitis - epithelial cell damage with intraepithelial lymphocytes, inflammation in the lamina propria but no increased collagen layer

abnormalities, such as moderately elevated C-reactive protein, ESR, or mild anemia are found. Stool tests generally reveal no pathological microorganisms. The diagnostic accuracy of fecal calprotectin and lactoferrin is low [89]. In a small pilot study, fecal eosinophil markers such as eosinophil cationic protein (F-ECP) and eosinophil protein X (F-EPX) were positive in 92% and 67%, respectively, of 12 patients with active CC, and a rapid fall of both markers was seen after budesonide treatment [90].

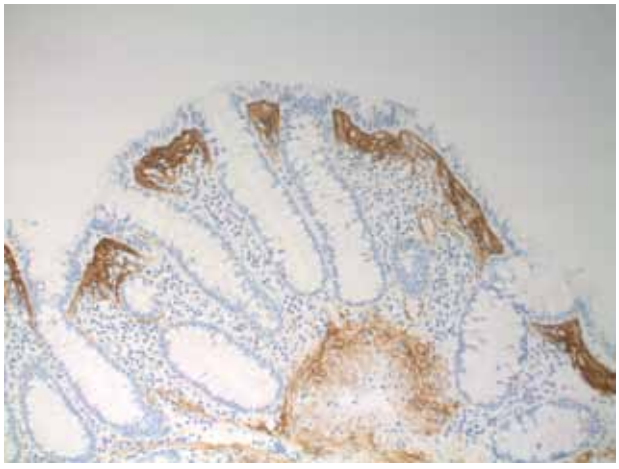

**Figure 3** Tenascin immunostaining in collagenous colitis

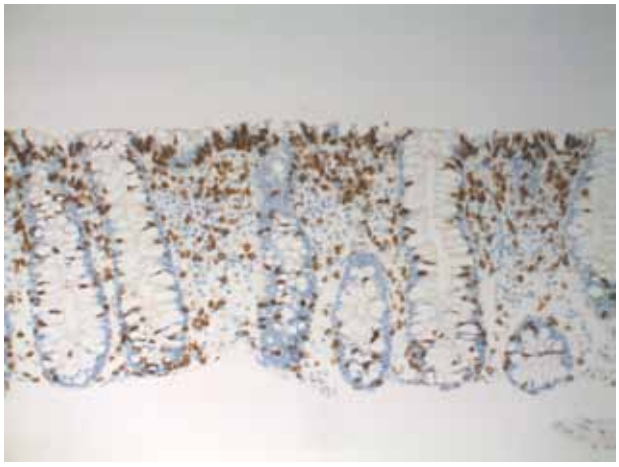

**Figure 4** Immunostaining of CD3+ T-lymphocytes in lymphocytic colitis

### "Atypical" microscopic colitis

In addition to CC and LC, other rare subtypes of MC have been described, including microscopic colitis with giant cells [91,92], paucicellular lymphocytic colitis [93], cryptal lymphocytic colitis [94], pseudomembranous collagenous colitis [95], microscopic colitis with granulomatous inflammation [96], and microscopic colitis not otherwise specified [80]. The clinical features of these conditions are similar to classical MC, but histopathologic appearance differs. Further studies are required to address the relationship and clinical significance of these "atypical" types of MC [40,97].

## Therapy

No curative therapy currently exists for MC. The primary

goals of medical therapy are to achieve and maintain remission of symptoms, and to improve the patient's quality of life. Whether histological remission is an essential objective is currently unknown. A careful assessment of concomitant drug use and dietary factors such as excess use of caffeine, alcohol, and dairy products that might worsen the condition is important. Concomitant bile acid malabsorption or celiac disease should be considered.

### Antidiarrheals

Although loperamide or cholestyramine have not been formally studied in randomized placebo-controlled trials, they are generally recommended as the first step of treatment in the patient with mild symptoms. Clinical experience suggests a symptomatic benefit in a proportion of patients, mainly in those with mild symptoms. However, sustained clinical remission is rarely achieved and an impact on colonic inflammation is unlikely.

### Budesonide

Budesonide is the best-documented treatment and significantly improves the clinical symptoms and the patient's quality of life. Three short-term, randomized controlled trials in CC have consistently shown that budesonide 9 mg daily for 6-8 weeks is superior to placebo (Table 2) [98-100]. About 80% of patients responded to budesonide and had a decrease in the number of loose stools after 2-4 weeks of therapy. In a Cochrane meta-analysis, the pooled odds ratio for clinical response with budesonide compared to placebo was 12.32 (95% CI 5.53-27.46) and number needed to treat was two patients [101]. In a placebo-controlled trial including 41 patients, budesonide treatment was effective also in LC [102]. After 6 weeks of treatment, 18 of 21 patients (86%; 95% CI 65-96%) in the budesonide group achieved a clinical response compared to 8 of 20 patients (40%; 95% CI 22-61%) in the placebo group, yielding an odds ratio of 9.00 (95% CI 1.98-40.93; P = 0.004) [103]. The number needed to treat to achieve a clinical response in LC with budesonide was 3 patients.

The relapse rate is high after cessation of successful short-term budesonide therapy in CC, and 61-80% of treated patients will have an early recurrence of symptoms [98-100]. In clinical practice tapering doses of budesonide to 3-6 mg/day have been used as maintenance therapy and may well control clinical symptoms. The evidence for such a strategy in CC now exists, and two studies have proven that maintenance therapy with budesonide 6 mg/day for six months is well tolerated and superior to placebo [104,105]. A total of 80 patients, who had responded to open-label budesonide, were randomized to budesonide 6 mg daily or placebo for 6 months. Clinical response was maintained in 33/40 (83%) patients who received budesonide compared to 11/40 (28%) patients who received placebo (P=0.0002). Pooled odds ratio for maintenance of clinical response with budesonide compared to placebo, was 8.40 (95% CI 2.73-25.81) with a number needed to treat of 2 patients. Histological response was seen in 48% of patients who received budesonide compared to 15% of patients who received placebo (P = 0.002) [101]. However, six-month maintenance therapy did not alter the subsequent disease course, as the relapse risk after withdrawal of 24-week maintenance

**Table 2** Data from four randomized, placebo-controlled trials of oral budesonide in collagenous colitis and lymphocytic colitis

| Collagenous colitis | | | | | |
|---|---|---|---|---|---|
| Author Year | Number of cases | Dosage | Clinical response budesonide vs placebo | Histologic response budesonide vs placebo | Adverse events |
| Baert et al 2002 [98] | 28 | 9 mg/day Budenofalk 8 weeks | Improvement: 8/14 *vs* 3/14 (P=0.05) | Reduction in lamina propria inflammation in 9/13 *vs* 4/12. (P<0.001) No difference in collagen layer | Mild. No difference between treatment groups |
| Miehlke et al 2002 [100] | 45 | 9 mg/day Entocort 6 weeks | Remission: 15/23 *vs* 0/22 (P<0.0001) | Improvement in 17/23 *vs* 5/22 (P<0.01) No difference in collagen layer | Mild 38% *vs* 12% P =0.052 |
| Bonderup et al 2003 [99] | 20 | 9 mg/day Entocort 8 weeks | Response: 10/10 *vs* 2/10 (P<0.001) | Reduction in overall inflammation (P<0.01) and of collagen layer in sigmoid colon (P<0.02) | None |
| Lymphocytic colitis | | | | | |
| Miehlke et al 2007 [102] | 41 | 9 mg/day Budenofalk 6 weeks | Remission: 18/21 *vs* 8/20 (P=0.004) | Response in 11/15 *vs* 4/12 (P = 0.04) | Mild. No difference between treatment groups |

treatment was similar to that observed after 6-week induction therapy, and the median time to relapse was equal in the two groups (39 days versus 38 days) [104].

#### Prednisolone

Other oral corticosteroids, such as prednisolone, are associated with more frequent side effects, and the efficacy seems inferior to budesonide, although no formal comparative studies are available [106].

#### Bismuth subsalicylate

Bismuth subsalicylate has been shown effective in a small, placebo-controlled study including 9 patients with CC and 5 with LC [107]. This drug is not available in a number of countries because of concerns regarding drug toxicity.

#### Aminosalicylates

Sulfasalazine or mesalazine have been extensively used in MC, but not strictly evaluated in randomized, placebo-controlled trials. In a recent trial, 64 patients with MC were randomized to mesalazine 2.4 g/day or mesalazine 2.4 g/day + cholestyramine 4 g/day for 6 months. A high remission rate was seen in both treatment arms, and 85% of patients with LC and 91% of patients with CC were in remission at the study's end. Combined therapy was superior in CC and induced an earlier clinical response in both diseases [108]. The benefit of mesalazine with or without cholestyramine needs to be confirmed in a placebo-controlled trial.

#### Antibiotics, probiotics, Boswellia serrata

Antibiotics such as metronidazole or erythromycin have been used, but not in a controlled fashion. Probiotic treatment shows uncertain results and needs further evaluation [109]. Boswellia serrata extract has been tried in a placebo-controlled trial, showing a nonsignificant trend in favor of active treatment [110].

#### Immunosuppressive therapy

In patients with unresponsive or steroid-resistant disease, immunosuppressive therapy may be considered, although the evidence is virtually absent. An open study with azathioprine gave partial or complete remission in eight of nine patients with MC [111]. There are conflicting data on the efficacy of methotrexate. Riddell et al reported that of 19 patients with CC treated with methotrexate orally, a good response, generally within 2-3 weeks of treatment, was seen in 14 patients, and a partial response in 2 patients. The dose of methotrexate ranged from 5-25 mg/week and was in median 7.5-10 mg/week [112]. Divergent data were reported in nine patients with CC refractory to budesonide treatment. After 12-week treatment with subcutaneous methotrexate 15-25 mg/week, no patient improved [113]. Determining the best therapeutic alternative for patients who are intolerant or fail therapy with budesonide is thus an important goal for future clinical trials.

#### Surgery

Surgical therapy may be considered for patients with severe, unresponsive MC. Both split ileostomy and subtotal colectomy have been performed and reported successful [60,114]. The indication for surgical therapy today is limited, considering the improvement in medical therapy.

## Prognosis

The long-term prognosis of MC is generally good [115-117]. In a follow-up study of CC, 63% of patients had a lasting remission after 3.5 years [115,116]. In another cohort study all 25 patients were improved 47 months after diagnosis, and only 29% of them required ongoing medication [115,116]. After a mean follow-up time of 6.4 years, others reported that about half the patients with MC had no diarrhea and only a minority had diarrhea more than once a week [117]. However, others reported that abdominal pain may persist even after diarrheal symptoms have disappeared [32]. A benign course was reported in 27 cases with LC, with resolution of diarrhea and normalization of histology in over 80% of patients within 38 months [118]. Others reported that 63% of patients with LC had a single attack with a median duration from onset of symptoms to remission of 6 months [20].

## Conclusions

- Microscopic colitis is a fairly common cause of chronic watery diarrhea, especially in elderly women.
- The correct diagnosis depends on the awareness of the condition by the clinician (referring the patient with chronic diarrhea to colonoscopy), by the endoscopist (obtaining mucosal biopsies, even though the colonic mucosa is endoscopically normal), and by the pathologist (recognizing the histopathological features of MC).
- Budesonide is an effective treatment, both short- and long-term, and improves the patient's symptoms and quality of life.
- The relapse risk after discontinuation of therapy is high, and the optimal long-term management needs further study.
- The long-term prognosis is good and the risk of complications, including colonic cancer, is low.

## References


1. Thomas PD, Forbes A, Green J, et al. Guidelines for the investigation of chronic diarrhoea, 2nd edition. *Gut* 2003;**52 (Suppl 5)**:v1-v15.
2. Pardi DS, Kelly CP. Microscopic colitis. *Gastroenterology* 2011;**140**:1155-1165.
3. Lindström CG. 'Collagenous colitis' with watery diarrhoea--a new entity? *Pathol Eur* 1976;**11**:87-89.
4. Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. *Hum Pathol* 1989;**20**:18-28.
5. Olesen M, Eriksson S, Bohr J, Jarnerot G, Tysk C. Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Orebro, Sweden, 1993-1998. *Gut* 2004;**53**:346-350.
6. Pardi DS, Loftus EV, Jr., Smyrk TC, et al. The epidemiology of microscopic colitis: a population based study in Olmsted County, Minnesota. *Gut* 2007;**56**:504-508.
7. Rubio-Tapia A, Martinez-Salgado J, Garcia-Leiva J, Martinez-Benitez B, Uribe M. Microscopic colitides: a single center experience in Mexico. *Int J Colorectal Dis* 2007;**22**:1031-1036.
8. Fekih M, Ben Hriz F, Sassi A, Matri S, Filali A, Boubaker J. [Microscopic colitis. A 20 cases series]. *Tunis Med* 2006;**84**:403-406.
9. Tagkalidis P, Bhathal P, Gibson P. Microscopic colitis. *J Gastroenterol Hepatol* 2002;**17**:236-248.
10. Garg PK, Singh J, Dhali GK, Mathur M, Sharma MP. Microscopic colitis is a cause of large bowel diarrhea in Northern India. *J Clin Gastroenterol* 1996;**22**:11-15.
11. Park YS, Baek DH, Kim WH, et al. Clinical characteristics of microscopic colitis in Korea: prospective multicenter study by KASID. *Gut Liver* 2011;**5**:181-186.
12. Agnarsdottir M, Gunnlaugsson O, Orvar KB, et al. Collagenous and lymphocytic colitis in Iceland. *Dig Dis Sci* 2002;**47**:1122-1128.
13. Bohr J, Tysk C, Eriksson S, Järnerot G. Collagenous colitis in Orebro, Sweden, an epidemiological study 1984- 1993. *Gut* 1995;**37**:394-397.
14. Fernandez-Banares F, Salas A, Forne M, Esteve M, Espinos J, Viver JM. Incidence of collagenous and lymphocytic colitis: a 5-year population- based study. *Am J Gastroenterol* 1999;**94**:418-423.
15. Wickbom A, Nyhlin N, Eriksson S, Bohr J, Tysk C. Collagenous colitis and lymphocytic colitis in Örebro, Sweden 1999-2004; a continuous epidemiological study. *Gut* 2006;**55(suppl V)**:A111.
16. Williams JJ, Kaplan GG, Makhija S, et al. Microscopic colitis-defining incidence rates and risk factors: a population-based study. *Clin Gastroenterol Hepatol* 2008;**6**:35-40.
17. Fernandez-Banares F, Salas A, Esteve M, et al. Evolution of the incidence of collagenous colitis and lymphocytic colitis in Terrassa, Spain: a population-based study. *Inflamm Bowel Dis* 2011;**17**:1015-1020.
18. Bohr J, Tysk C, Eriksson S, Abrahamsson H, Järnerot G. Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients. *Gut* 1996;**39**:846-851.
19. Benchimol EI, Kirsch R, Viero S, Griffiths AM. Collagenous colitis and eosinophilic gastritis in a 4-year old girl: a case report and review of the literature. *Acta Paediatr* 2007;**96**:1365-1367.
20. Olesen M, Eriksson S, Bohr J, Jarnerot G, Tysk C. Lymphocytic colitis: a retrospective clinical study of 199 Swedish patients. *Gut* 2004;**53**:536-541.
21. Pardi DS, Ramnath VR, Loftus EV, Jr., Tremaine WJ, Sandborn WJ. Lymphocytic colitis: clinical features, treatment, and outcomes. *Am J Gastroenterol* 2002;**97**:2829-2833.
22. Madisch A, Heymer P, Voss C, et al. Oral budesonide therapy improves quality of life in patients with collagenous colitis. *Int J Colorectal Dis* 2005;**20**:312-316.
23. 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.
24. 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.
25. Allende DS, Taylor SL, Bronner MP. Colonic perforation as a complication of collagenous colitis in a series of 12 patients. *Am J Gastroenterol* 2008;**103**:2598-2604.
26. Bohr J, Larsson LG, Eriksson S, Jarnerot G, Tysk C. Colonic perforation in collagenous colitis: an unusual complication. *Eur J Gastroenterol Hepatol* 2005;**17**:121-124.
27. Sherman A, Ackert JJ, Rajapaksa R, West AB, Oweity T. Fractured colon: an endoscopically distinctive lesion associated with colonic perforation following colonoscopy in patients with collagenous colitis. *J Clin Gastroenterol* 2004;**38**:341-345.
28. Chan JL, Tersmette AC, Offerhaus GJ, Gruber SB, Bayless TM, Giardiello FM. Cancer risk in collagenous colitis. *Inflamm Bowel Dis* 1999;**5**:40-43.
29. Yen EF, Pokhrel B, Bianchi LK, et al. Decreased colorectal cancer and adenoma risk in patients with microscopic colitis. *Dig Dis Sci* 2011 (in press)
30. Kao KT, Pedraza BA, McClune AC, et al. Microscopic colitis: a large retrospective analysis from a health maintenance organization experience. *World J Gastroenterol* 2009;**15**:3122-3127.
31. Vigren L, Sjöberg K, Benoni C, et al. Is smoking a risk factor for collagenous colitis? *Scand J Gastroenterol* 2011;**46**:1334-1339
32. Nyhlin N, Wickbom A, Montgomery S, Tysk C, Bohr J. Symptom burden in collagenous and lymphocytic colitis compared to a matched control group. *Gut* 2009;**58 (suppl II)**:A309.
33. Limsui D, Pardi DS, Camilleri M, et al. Symptomatic overlap between irritable bowel syndrome and microscopic colitis. *Inflamm Bowel Dis* 2007;**13**:175-181.
34. Barta Z, Mekkel G, Csipo I, et al. Microscopic colitis: a retrospective study of clinical presentation in 53 patients. *World J Gastroenterol* 2005;**11**:1351-1355.
35. Koskela RM, Niemela SE, Karttunen TJ, Lehtola JK. Clinical characteristics of collagenous and lymphocytic colitis. *Scand J Gastroenterol* 2004;**39**:837-845.
36. Ung KA, Gillberg R, Kilander A, Abrahamsson H. Role of bile acids and bile acid binding agents in patients with collagenous colitis. *Gut* 2000;**46**:170-175.
37. Aqel B, Bishop M, Krishna M, Cangemi J. Collagenous colitis evolving into ulcerative colitis: a case report and review of the literature. *Dig Dis Sci* 2003;**48**:2323-2327.
38. Pokorny CS, Kneale KL, Henderson CJ. Progression of collagenous colitis to ulcerative colitis. *J Clin Gastroenterol* 2001;**32**:435-438.
39. Mosnier JF, Larvol L, Barge J, et al. Lymphocytic and collagenous colitis: an immunohistochemical study. *Am J Gastroenterol* 1996;**91**:709-713.
40. Fernandez-Banares F, Casalots J, Salas A, et al. Paucicellular lymphocytic colitis: is it a minor form of lymphocytic colitis? A clinical pathological and immunological study. *Am J Gastroenterol* 2009;**104**:1189-1198.
41. Taha Y, Carlson M, Thorn M, Loof L, Raab Y. Evidence of local eosinophil activation and altered mucosal permeability in collagenous colitis. *Dig Dis Sci* 2001;**46**:888-897.
42. Taha Y, Raab Y, Larsson A, et al. Mucosal secretion and expression of basic fibroblast growth factor in patients with collagenous colitis. *Am J Gastroenterol* 2003;**98**:2011-2017.
43. Taha Y, Raab Y, Larsson A, et al. Vascular endothelial growth factor (VEGF)--a possible mediator of inflammation and mucosal permeability in patients with collagenous colitis. *Dig Dis Sci* 2004;**49**:109-115.
44. Wagner M, Lampinen M, Sangfelt P, Agnarsdottir M, Carlson M.

Budesonide treatment of patients with collagenous colitis restores normal eosinophil and T-cell activity in the colon. *Inflamm Bowel Dis* 2010;**16**:1118-1126.
45. Griga T, Tromm A, Schmiegel W, Pfisterer O, Muller KM, Brasch F. Collagenous colitis: implications for the role of vascular endothelial growth factor in repair mechanisms. *Eur J Gastroenterol Hepatol* 2004;**16**:397-402.
46. Tagkalidis PP, Gibson PR, Bhathal PS. Microscopic colitis demonstrates a T helper cell type 1 mucosal cytokine profile. *J Clin Pathol* 2007;**60**:382-387.
47. Münch A, Söderholm JD, Wallon C, Öst A, Olaison G, Ström M. Dynamics of mucosal permeability and inflammation in collagenous colitis before, during, and after loop ileostomy. *Gut* 2005;**54**:1126-1128.
48. Münch A, Söderholm JD, Öst Å, Ström M. Increased transmucosal uptake of E. coli K12 in collagenous colitis persists after budesonide treatment. *Am J Gastroenterol* 2009;**104**:679-685.
49. Salas A, Fernandez-Banares F, Casalots J, et al. Subepithelial myofibroblasts and tenascin expression in microscopic colitis. *Histopathology* 2003;**43**:48-54.
50. Medina C, Radomski MW. Role of matrix metalloproteinases in intestinal inflammation. *J Pharmacol Exp Ther* 2006;**318**:933-938.
51. Gunther U, Schuppan D, Bauer M, et al. Fibrogenesis and fibrolysis in collagenous colitis. Patterns of procollagen types I and IV, matrix-metalloproteinase-1 and -13, and TIMP-1 gene expression. *Am J Pathol* 1999;**155**:493-503.
52. Freeman HJ. Familial occurrence of lymphocytic colitis. *Can J Gastroenterol* 2001;**15**:757-760.
53. Järnerot G, Hertervig E, Grännö C, et al. Familial occurrence of microscopic colitis: a report on five families. *Scand J Gastroenterol* 2001;**36**:959-962.
54. Abdo AA, Zetler PJ, Halparin LS. Familial microscopic colitis. *Can J Gastroenterol* 2001;**15**:341-343.
55. van Tilburg AJ, Lam HG, Seldenrijk CA, et al. Familial occurrence of collagenous colitis. A report of two families. *J Clin Gastroenterol* 1990;**12**:279-285.
56. Fine KD, Do K, Schulte K, et al. High prevalence of celiac sprue-like HLA-DQ genes and enteropathy in patients with the microscopic colitis syndrome. *Am J Gastroenterol* 2000;**95**:1974-1982.
57. Koskela RM, Karttunen TJ, Niemela SE, Lehtola JK, Ilonen J, Karttunen RA. Human leucocyte antigen and TNFalpha polymorphism association in microscopic colitis. *Eur J Gastroenterol Hepatol* 2008;**20**:276-282.
58. Madisch A, Hellmig S, Schreiber S, Bethke B, Stolte M, Miehlke S. Allelic variation of the matrix metalloproteinase-9 gene is associated with collagenous colitis. *Inflamm Bowel Dis* 2011 (in press) 59. Madisch A, Hellmig S, Schreiber S, Bethke B, Stolte M, Miehlke S. NOD2/CARD15 gene polymorphisms are not associated with collagenous colitis. *Int J Colorectal Dis* 2007;**22**:425-428.
60. Järnerot G, Tysk C, Bohr J, Eriksson S. Collagenous colitis and fecal stream diversion. *Gastroenterology* 1995;**109**:449-455.
61. Beaugerie L, Pardi DS. Review article: drug-induced microscopic colitis - proposal for a scoring system and review of the literature. *Aliment Pharmacol Ther* 2005;**22**:277-284.
62. Erim T, Alazmi WM, O'Loughlin CJ, Barkin JS. Collagenous colitis associated with Clostridium difficile: a cause effect? *Dig Dis Sci* 2003;**48**:1374-1375.
63. Perk G, Ackerman Z, Cohen P, Eliakim R. Lymphocytic colitis: a clue to an infectious trigger. *Scand J Gastroenterol* 1999;**34**:110-112.
64. Bohr J, Nordfelth R, Järnerot G, Tysk C. Yersinia species in collagenous colitis: a serologic study. *Scand J Gastroenterol* 2002;**37**:711-714.
65. Makinen M, Niemela S, Lehtola J, Karttunen TJ. Collagenous colitis and Yersinia enterocolitica infection. *Dig Dis Sci* 1998;**43**:1341-1346.
66. Osterholm MT, MacDonald KL, White KE, et al. An outbreak of a newly recognized chronic diarrhea syndrome associated with raw milk consumption. *JAMA* 1986;**256**:484-490.
67. Bryant DA, Mintz ED, Puhr ND, Griffin PM, Petras RE. Colonic epithelial lymphocytosis associated with an epidemic of chronic diarrhea. *Am J Surg Pathol* 1996;**20**:1102-1109.
68. Mintz E. A riddle wrapped in a mystery inside an enigma: Brainerd diarrhoea turns 20. *Lancet* 2003;**362**:2037-2038.
69. LaSala PR, Chodosh AB, Vecchio JA, Schned LM, Blaszyk H. Seasonal pattern of onset in lymphocytic colitis. *J Clin Gastroenterol* 2005;**39**:891-893.
70. Fernandez-Banares F, Esteve M, Salas A, et al. Bile acid malabsorption in microscopic colitis and in previously unexplained functional chronic diarrhea. *Dig Dis Sci* 2001;**46**:2231-2238.
71. Ung KA, Kilander A, Willen R, Abrahamsson H. Role of bile acids in lymphocytic colitis. *Hepatogastroenterology* 2002;**49**:432-437.
72. Lundberg JON, Herulf M, Olesen M, et al. Increased nitric oxide production in collagenous and lymphocytic colitis. *Eur J Clin Invest* 1997;**27**:869-871.
73. Olesen M, Middelveld R, Bohr J, et al. Luminal nitric oxide and epithelial expression of inducible and endothelial nitric oxide synthase in collagenous and lymphocytic colitis. *Scand J Gastroenterol* 2003;**38**:66-72.
74. Perner A, Andresen L, Normark M, et al. Expression of nitric oxide synthases and effects of L-arginine and L- NMMA on nitric oxide production and fluid transport in collagenous colitis. *Gut* 2001;**49**:387-394.
75. Perner A, Nordgaard I, Matzen P, Rask-Madsen J. Colonic production of nitric oxide gas in ulcerative colitis, collagenous colitis and uninflamed bowel. *Scand J Gastroenterol* 2002;**37**:183-188.
76. Andresen L, Jorgensen VL, Perner A, Hansen A, Eugen-Olsen J, Rask-Madsen J. Activation of nuclear factor kappaB in colonic mucosa from patients with collagenous and ulcerative colitis. *Gut* 2005;**54**:503-509.
77. Bonderup OK, Hansen JB, Madsen P, Vestergaard V, Fallingborg J, Teglbjaerg PS. Budesonide treatment and expression of inducible nitric oxide synthase mRNA in colonic mucosa in collagenous colitis. *Eur J Gastroenterol Hepatol* 2006;**18**:1095-1099.
78. Burgel N, Bojarski C, Mankertz J, Zeitz M, Fromm M, Schulzke JD. Mechanisms of diarrhea in collagenous colitis. *Gastroenterology* 2002;**123**:433-443.
79. Bohr J, Järnerot G, Tysk C, Jones I, Eriksson S. Effect of fasting on diarrhoea in collagenous colitis. *Digestion* 2002;**65**:30-34.
80. Warren BF, Edwards CM, Travis SP. 'Microscopic colitis': classification and terminology. *Histopathology* 2002;**40**:374-376.
81. Tanaka M, Mazzoleni G, Riddell RH. Distribution of collagenous colitis: utility of flexible sigmoidoscopy. *Gut* 1992;**33**:65-70.
82. Muller S, Neureiter D, Stolte M, et al. Tenascin: a sensitive and specific diagnostic marker of minimal collagenous colitis. *Virchows Arch* 2001;**438**:435-441.
83. Cruz-Correa M, Milligan F, Giardiello FM, et al. Collagenous colitis with mucosal tears on endoscopic insufflation: a unique presentation. *Gut* 2002;**51**:600.
84. Wickbom A, Lindqvist M, Bohr J, et al. Colonic mucosal tears in collagenous colitis. *Scand J Gastroenterol* 2006;**41**:726-729.
85. Smith RR, Ragput A. Mucosal tears on endoscopic insufflation resulting in perforation: an interesting presentation of collagenous colitis. *J Am Coll Surg* 2007;**205**:725.
86. Kiesslich R, Hoffman A, Goetz M, et al. In vivo diagnosis of collagenous colitis by confocal endomicroscopy. *Gut* 2006;**55**:591-592.
87. Meining A, Schwendy S, Becker V, Schmid RM, Prinz C. In vivo histopathology of lymphocytic colitis. *Gastrointest Endosc* 2007;**66**:398-399.

88. Zambelli A, Villanacci V, Buscarini E, Bassotti G, Albarello L. Collagenous colitis: a case series with confocal laser microscopy and histology correlation. *Endoscopy* 2008;**40**:606-608.
89. Wildt S, Nordgaard-Lassen I, Bendtsen F, Rumessen JJ. Metabolic and inflammatory faecal markers in collagenous colitis. *Eur J Gastroenterol Hepatol* 2007;**19**:567-574.
90. Wagner M, Peterson CG, Stolt I, et al. Fecal eosinophil cationic protein as a marker of active disease and treatment outcome in collagenous colitis: a pilot study. *Scand J Gastroenterol* 2011;**46**:849-854.
91. Libbrecht L, Croes R, Ectors N, Staels F, Geboes K. Microscopic colitis with giant cells. *Histopathology* 2002;**40**:335-338.
92. Sandmeier D, Bouzourene H. Microscopic colitis with giant cells: a rare new histopathologic subtype? *Int J Surg Pathol* 2004;**12**:45-48.
93. Goldstein NS, Bhanot P. Paucicellular and asymptomatic lymphocytic colitis: expanding the clinicopathologic spectrum of lymphocytic colitis. *Am J Clin Pathol* 2004;**122**:405-411.
94. Rubio CA, Lindholm J. Cryptal lymphocytic coloproctitis: a new phenotype of lymphocytic colitis? *J Clin Pathol* 2002;**55**:138-140.
95. Yuan S, Reyes V, Bronner MP. Pseudomembranous collagenous colitis. *Am J Surg Pathol* 2003;**27**:1375-1379.
96. Saurine TJ, Brewer JM, Eckstein RP. Microscopic colitis with granulomatous inflammation. *Histopathology* 2004;**45**:82-86.
97. Chang F, Deere H, Vu C. Atypical forms of microscopic colitis: morphological features and review of the literature. *Adv Anat Pathol* 2005;**12**:203-211.
98. Baert F, Schmit A, D'Haens G, et al. Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 2002;**122**:20-25.
99. Bonderup OK, Hansen JB, Birket-Smith L, Vestergaard V, Teglbjaerg PS, Fallingborg J. Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut* 2003;**52**:248-251.
100. Miehlke S, Heymer P, Bethke B, et al. Budesonide treatment for collagenous colitis: a randomized, double- blind, placebo-controlled, multicenter trial. *Gastroenterology* 2002;**123**:978-984.
101. Chande N, McDonald JW, Macdonald JK. Interventions for treating collagenous colitis. *Cochrane Database Syst Rev* 2008:CD003575.
102. Miehlke S, Madisch A, Karimi D, et al. Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. *Gastroenterology* 2009;**136**:2092-2100.
103. Chande N, McDonald JW, Macdonald JK. Interventions for treating lymphocytic colitis. *Cochrane Database Syst Rev* 2008:CD006096.
104. Bonderup OK, Hansen JB, Teglbjaerg PS, Christensen LA, Fallingborg JF. Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gut* 2009;**58**:68-72.
105. Miehlke S, Madisch A, Bethke B, et al. Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2008;**135**:1510-1516.
106. Munck LK, Kjeldsen J, Philipsen E, Fischer Hansen B. Incomplete remission with short-term prednisolone treatment in collagenous colitis: a randomized study. *Scand J Gastroenterol* 2003;**38**:606-610.
107. Fine KD, Ogunji F, Lee E, Lafon G, Tanzi M. Randomized, double blind, placebo-controlled trial of bismuth subsalicylate for microscopic colitis. *Gastroenterology* 1999;**116**:A880.
108. Calabrese C, Fabbri A, Areni A, Zahlane D, Scialpi C, Di Febo G. Mesalazine with or without cholestyramine in the treatment of microscopic colitis: randomized controlled trial. *J Gastroenterol Hepatol* 2007;**22**:809-814.
109. Wildt S, Munck LK, Vinter-Jensen L, et al. Probiotic treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial with Lactobacillus acidophilus and Bifidobacterium animalis subsp. Lactis. *Inflamm Bowel Dis* 2006;**12**:395-401.
110. Madisch A, Miehlke S, Eichele O, et al. Boswellia serrata extract for the treatment of collagenous colitis. A double-blind, randomized, placebo-controlled, multicenter trial. *Int J Colorectal Dis* 2007;**22**:1445-1451.
111. Laing AW, Pardi DS, Loftus EV, Jr., et al. Microscopic colitis is not associated with cholecystectomy or appendectomy. *Inflamm Bowel Dis* 2006;**12**:708-711.
112. Riddell J, Hillman L, Chiragakis L, Clarke A. Collagenous colitis: oral low-dose methotrexate for patients with difficult symptoms: long-term outcomes. *J Gastroenterol Hepatol* 2007;**22**:1589-1593.
113. Münch A, Bohr J, Vigren L, Tysk C, Ström M. Methotrexate in budesonide refractory collagenous colitis. *Gut* 2011;**60(suppl III)**:P1451.
114. Varghese L, Galandiuk S, Tremaine WJ, Burgart LJ. Lymphocytic colitis treated with proctocolectomy and ileal J-pouch-anal anastomosis: report of a case. *Dis Colon Rectum* 2002;**45**:123-126.
115. Bonner GF, Petras RE, Cheong DM, Grewal ID, Breno S, Ruderman WB. Short- and long-term follow-up of treatment for lymphocytic and collagenous colitis. *Inflamm Bowel Dis* 2000;**6**:85-91.
116. Goff JS, Barnett JL, Pelke T, Appelman HD. Collagenous colitis: histopathology and clinical course. *Am J Gastroenterol* 1997;**92**:57-60.
117. Sveinsson OA, Orvar KB, Birgisson S, Agnarsdottir M, Jonasson JG. Clinical features of microscopic colitis in a nation-wide follow-up study in Iceland. *Scand J Gastroenterol* 2008;**43**:955-960.
118. Mullhaupt B, Guller U, Anabitarte M, Guller R, Fried M. Lymphocytic colitis: clinical presentation and long term course. *Gut* 1998;**43**:629-633.