

Systematic review: microscopic colitis

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SUMMARY

Background

Collagenous and lymphocytic colitis are fairly common causes of chronic non-bloody diarrhoea, especially in elderly female.

Aim

To present a systematic review of microscopic colitis.

Methods

A PubMed search using the MeSH terms microscopic colitis, collagenous colitis, lymphocytic colitis and chronic diarrhoea was performed.

Results

Annual incidence of each disorder is 4–6/100 000 inhabitants. The aetiology is unknown. Clinical characteristics are well described and there is an association with autoimmune diseases. Budesonide is the best-documented short-term treatment of collagenous colitis. In meta-analysis pooled odds ratio for clinical response after 6–8 weeks of treatment was 12.3 (95% CI: 5.5–27.5) in comparison with placebo. The evidence for bismuth subsalicylate is weaker and the effectiveness of other alternatives such as loperamide, cholestyramine, aminosalicylates, probiotics, or *Boswellia serrata* extract is unknown. Although unproven, in unresponsive severe disease azathioprine or methotrexate may be tried. No controlled trials have been carried out in lymphocytic colitis. The long-term prognosis of microscopic colitis is good, serious complications are rare and there is no increased mortality.

Conclusions

Clinical and epidemiological aspects of microscopic colitis are well described. Budesonide is the best-documented short-term therapy in collagenous colitis, but the optimal long-term strategy needs further study. Controlled treatment data of lymphocytic colitis are awaited for.

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INTRODUCTION

Chronic diarrhoea is a common reason for referral to a gastroenterologist. The prevalence of chronic diarrhoea in a western population varies depending on definitions and population differences and is reported in 4–5% of the general population and in 7–14% of an elderly population.¹ Microscopic colitis (MC), previously regarded rare, now has emerged as a common cause of chronic diarrhoea. The condition is characterized clinically by chronic non-bloody diarrhoea, a macroscopically normal or near-normal colonic mucosa, where microscopic examination of mucosal biopsies reveals diagnostic histopathological changes. Microscopic colitis mainly includes the two diseases collagenous colitis (CC) and lymphocytic colitis (LC). CC was first described in 1976 by Lindström² and LC in 1989 by Lazenby *et al.*³

This review will focus on epidemiology, clinical features and treatment of MC.

METHODS

Publications for this review were identified by searching PubMed using the following MeSH terms: microscopic colitis, collagenous colitis, lymphocytic colitis and chronic diarrhoea. Additional reports were found searching the reference list of pertinent articles. Other publications known by us were also reviewed and relevant abstracts presented at international gastroenterological conferences were included.

EPIDEMIOLOGY

Previously considered rare, MC now has evolved as a fairly common cause of chronic diarrhoea in the western world. The incidence of CC and LC each is close to the incidence of Crohn's disease and combined rates approach the incidence of ulcerative colitis.⁴ The diagnosis is made in 10–20% of cases investigated for chronic non-bloody diarrhoea.

Most cases have been reported from Europe and North America but there are a few case reports from Africa,⁵ Asia,⁶ South America⁷ and Australia.^{8–11} At present, epidemiological data have been presented from seven different regions (Table 1).^{4, 12–18} The figures from UK and France are lower than reported figures from the other European or North American regions. An epidemiological study in Sweden of the period 1993–1998 showed an annual incidence of 4.9/10⁵ in CC and of 4.4/10⁵ in LC.⁴ Similarly, a survey of all cases detected in Iceland between 1995 and 1999 revealed an annual incidence of 5.2/100 000 in CC and of 4.0/100 000 in LC.¹² Even higher figures in LC were reported from Olmsted County, US.¹⁶ Both in the Swedish and in the Olmsted studies rising incidence rates were found during the study periods. Whether this is an artefact, reflecting an increased awareness and improved diagnosis of the condition, or in fact represents a true rise of the incidence is at present unknown.

The typical CC patient is a middle-aged woman. The peak incidence is around 65 years of age and the female:male ratio is about 7:1 (Figure 1). However, the disease can occur in all ages, and a few children

Region/study period	Collagenous colitis	Lymphocytic colitis
Örebro, Sweden/1984–1988 ¹³	0.8	
Örebro, Sweden/1989–1993 ¹³	2.7	
Örebro, Sweden/1993–1995 ⁴	3.7	3.1
Örebro, Sweden/1996–1998 ⁴	6.1	5.7
Franche-Comté, France/1987–1992 ¹⁷	0.6	
Terrassa, Spain/1993–1997 ¹⁴	2.3	3.7
Iceland/1995–1999 ¹²	5.2	4.0
Olmsted County, USA/1985–1989 ¹⁶	0.3	0.5
Olmsted County, USA/1990–1993 ¹⁶	1.6	1.0
Olmsted County, USA/1994–1997 ¹⁶	3.9	6.4
Olmsted County, USA/1997–2001 ¹⁶	6.2	12.9
Lothian, UK/1998–2003 ¹⁸	0.8	
Tayside, UK/1999–2004 ¹⁵	1.1	0.6

Table 1. Annual incidence per 10⁵ inhabitants in population-based epidemiological studies of collagenous and lymphocytic colitis

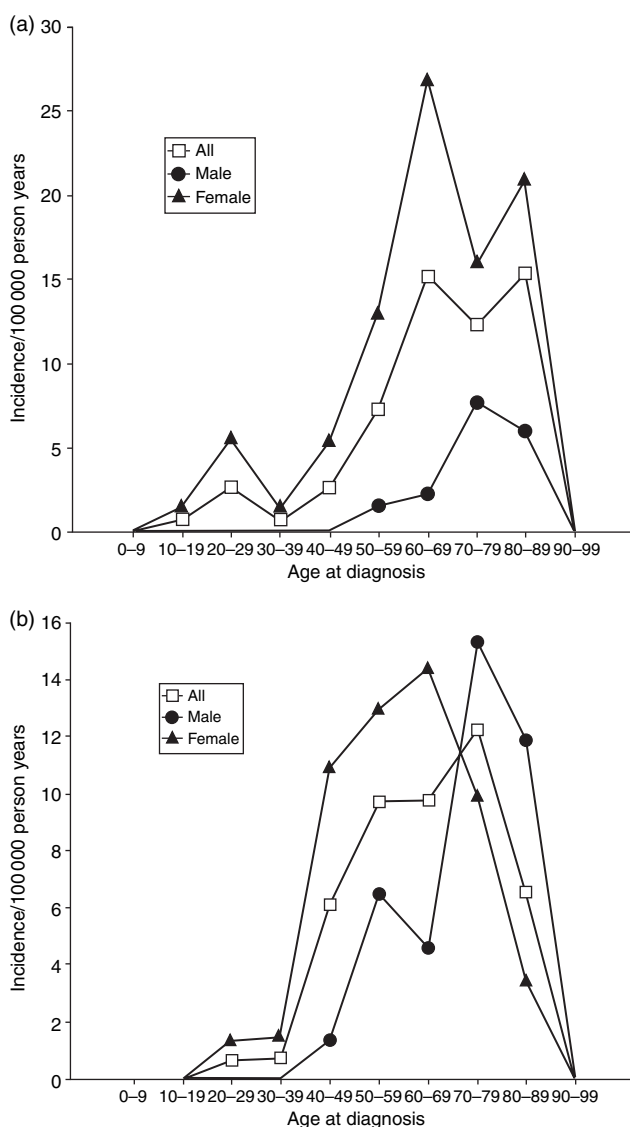


Figure 1. Age- and sex-specific incidence of (a) collagenous colitis and (b) lymphocytic colitis. Reprinted with permission from Olesen *et al.*⁴

with CC have been reported.^{19, 20} In LC, the female predominance is less pronounced with a female:male ratio of 2.4:1. The peak incidence is similar to CC around 60–65 years of age (Figure 1).

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 diarrhoea, often associated with nocturnal diarrhoea, abdominal pain and weight loss, which may

be substantial.^{21–23} Although some patients may suffer from severe diarrhoea, serious dehydration is rare. Fatigue, nausea and faecal incontinence are other associated symptoms and the disease may significantly impair quality of life of the affected patient.^{24, 25}

The onset of disease can be sudden mimicking infectious diarrhoea.^{21, 22} The clinical course is most often chronic relapsing and benign. Severe complications are rare although there are a few reports of colonic perforation in CC.^{26, 27} No increased risk of colorectal cancer is reported in CC.²⁸ Three cases with concomitant lymphoproliferative disorders and CC have been presented but further studies are required to assess if there is an increased risk.²⁹

Some patients may have mild symptoms that may be misinterpreted as irritable bowel syndrome. Morphological findings of LC have been reported even in constipated or asymptomatic patients.³⁰ The natural history of the condition in these patients is unknown.

Patients with MC often have concomitant autoimmune diseases.^{21–23} The most common are thyroid disorders, coeliac disease, diabetes mellitus, rheumatoid arthritis and asthma/allergy. The occurrence of such associations, reported in up to 40–50% of patients in some reports, is variable depending on the study, and differences between LC and CC with respect to associated conditions have been described.^{21–23, 31}

DIAGNOSIS

Microscopic assessment of colonic mucosal biopsies is currently the only means of verifying the diagnosis of MC. Only non-specific minor laboratory abnormalities are found. Stool tests reveal no pathological microorganisms. Barium enema and colonoscopy are usually normal, although subtle non-specific changes such as oedema, erythema or abnormal vascular pattern are seen in up to 30% of the cases.^{21, 22} Colonic mucosal tears are extraordinary endoscopic lesions reported hitherto only in a few patients, which possibly may be associated with an increased risk of colonic perforation during colonoscopy.^{32, 33}

HISTOPATHOLOGY

The diagnosis of the different subtypes of MC relies on specific microscopic changes seen in colonic mucosal biopsies.³⁴ In CC the most characteristic feature is a thickening of the subepithelial collagen layer (SCL) beneath the basal membrane (Figure 2). The collagen

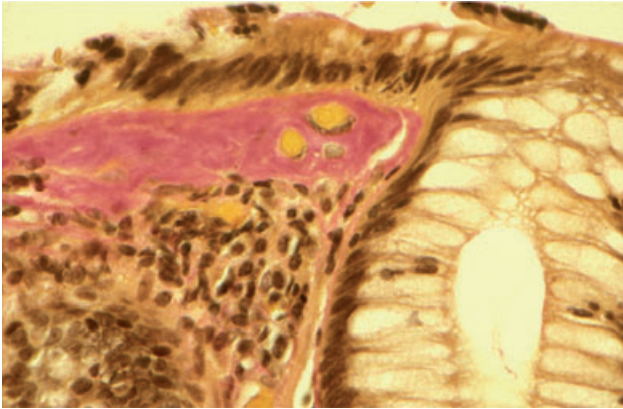


Figure 2. Biopsy from colon showing typical findings of collagenous colitis – increased subepithelial collagen layer, inflammation of lamina propria and epithelial lesions with intraepithelial lymphocytes.

layer is most prominent in proximal colon and may be absent in biopsies from sigmoid colon and rectum emphasizing the importance of obtaining biopsies from the proximal colon when diagnosing CC.³⁵ The thickened SCL in CC is $\geq 10 \mu\text{m}$ on well-orientated sections in contrast to the normal basal membrane of $0\text{--}3 \mu\text{m}$. The assessment of SCL must be carried out on sections perpendicular to the mucosa avoiding tangential sections that may give a false impression of a thickened collagen layer. In addition to the thickened collagen layer, there is a chronic inflammation in the lamina propria dominated by lymphocytes and plasma cells. Flattening, vacuolization and detachment of the surface epithelial cells are seen together with increased frequency of apoptotic bodies. Intraepithelial lymphocyte (IEL) infiltration may be seen although not as prominent as in LC. Generally, the histopathological changes in CC are restricted to the large bowel, but a thickened collagen layer has infrequently been reported in the stomach, duodenum or terminal ileum. Cryptitis or Paneth cell metaplasia may be seen and does not rule out a diagnosis of MC.³⁶

The diagnosis of LC relies on a characteristic increase of the number of IELs, which exceeds 20 IEL/100 surface epithelial cells compared with <5 IEL/100 surface epithelial cells in normal colonic mucosa (Figure 3). Surface epithelial cell lesions are seen as well as an infiltration with lymphocytes and plasma cells in the lamina propria. The SCL is normal in LC in contrast to CC.

In addition to CC and LC, other rare subtypes of MC have been described including MC with giant cells,^{37, 38} paucicellular LC,³⁹ cryptal LC,⁴⁰ pseudo-

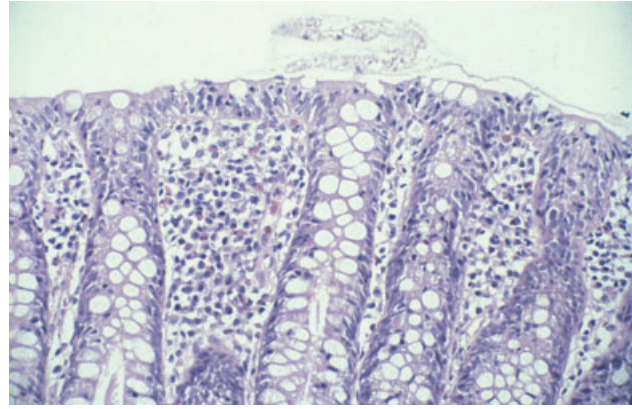


Figure 3. Biopsy from colon showing typical findings of lymphocytic colitis – epithelial lesions with intraepithelial lymphocytes and inflammation in the lamina propria.

membranous CC,⁴¹ MC with granulomatous inflammation¹¹ and MC not otherwise specified.³⁴ The clinical features of these conditions are similar to classical MC but the histopathological appearance differs. Further studies are required to address the relationship and clinical significance of these 'atypical' MC.⁴²

AETIOLOGY

The cause of the diseases is largely unknown and probably multifactorial. CC and LC are presently considered to represent specific mucosal responses in predisposed individuals to various noxious luminal agents.

Genetics

Data on genetic predisposition in MC are sparse. A small number of familial cases with CC, LC or with mixed diseases have been reported.^{43–46} Others found that 12% of patients with LC reported a family history of other bowel disorders such as inflammatory bowel disease, coeliac disease or CC.²² Whether these associations are due to genetics, environmental factors or chance cannot be assessed. Data on human leucocyte antigen (HLA) associations are not conclusive.⁴⁷

Luminal factor

The increased number of T lymphocytes in the epithelium 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 faecal stream by an

ileostomy normalized or reduced the characteristic histopathological changes in CC.⁴⁸ After closure of the ileostomy, recurrence of symptoms and histopathological changes occurred. The importance of a luminal factor is further supported by the observation that an elemental diet reduced diarrhoea in patients with MC.⁴⁹

Infection

A sudden onset of MC in a subset of patients and effect of various antibiotics support a possible infectious cause. LC shares many features with 'Brainerd diarrhea', which refers to outbreaks of acute watery diarrhoea with long duration, first reported among 122 residents of Brainerd, Minnesota.⁵⁰ Colonic biopsies of these patients show epithelial lymphocytosis similar to LC but not crypt distortion or epithelial destruction.⁵¹ Investigations of several outbreaks of 'Brainerd diarrhea' have established an incubation period of 10–30 days and median duration of illness of 16 months.⁵² Although an infectious agent is thought to be the cause of 'Brainerd diarrhea', no micro-organism has yet been identified.

Yersinia enterocolitica was found in three of six patients with CC prior to diagnosis and another study showed that antibodies to *Yersinia* species were more common in CC patients than in healthy controls.^{53, 54} An association with MC and *Campylobacter jejuni* and *Clostridium difficile* has also been reported.^{55, 56} A seasonal pattern of onset of LC has been suggested, which may further support an infectious origin.^{22, 57} However, in most cases of MC with a sudden onset, stool cultures remain negative.

Drugs

There are several reports on drug-induced MC, some of them anecdotal creating difficulties to assess causality. To address this issue, Beaugerie and Pardi suggested a scoring system, which was recently published in this Journal.⁵⁸ Applying strict criteria, 17 drugs were found associated with a high or intermediate probability of causality. A high likelihood of inducing MC was associated with acarbose, aspirin, Cyclo3 Fort, lansoprazole, non-steroidal anti-inflammatory drugs (NSAIDs), ranitidine, sertraline and ticlopidine. Carbamazepine, flutamide, lisinopril, modopar (levodopa and benserazide), oxetorone, paroxetine, simvastatin, tardyferon and vinburnine were associated with an intermediate likelihood of inducing MC. Assessment of concomitant drug use in patients with MC is important

to identify and consider withdrawal of drugs that might cause or worsen the condition.

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.^{59–61} These observations are the rationale for recommendations on 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, coeliac 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.^{62–65} The levels of NO correlated with clinical and histological disease activity.⁶³ NO has been suggested to be involved in the pathophysiology of diarrhoea 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%.⁶⁴ A major transcriptional inducer of iNOS gene expression is the transcription factor nuclear factor κ B (NF κ B). In active CC colonic mucosal NF κ B was found activated in epithelial cells but not in lamina propria macrophages in contrast to ulcerative colitis.⁶⁶

Secretory or osmotic diarrhoea

The precise mechanism of diarrhoea in MC is not fully clarified. In CC, diarrhoea 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.⁶⁷ Fasting on the other hand, seems to reduce diarrhoea, which would indicate an osmotic component in some patients as well.⁶⁸

RELATIONSHIP BETWEEN COLLAGENOUS COLITIS – LYMPHOCYTIC COLITIS – ULCERATIVE COLITIS – CROHN'S DISEASE?

As CC and LC have similar clinical expression and similar histopathological features except for the SCL in CC, it has been discussed whether LC and CC are the same disease in different stages of development or rather two different but related conditions. Conversion of LC to CC or the opposite has been reported. However, conversion is seen infrequently and this fact together with the observed difference in sex ratio makes it more likely to consider CC and LC as two separate but related entities.

An interchange between ulcerative colitis or Crohn's disease and MC has been reported in a few patients.^{9, 69} Whether this merely is a chance association of two fairly common disorders occurring in the same individual or due to common genetic predisposition or shared immunological pathways remains unknown thus far.

TREATMENT

Recommendations on treatment of MC were earlier based mainly on retrospective and uncontrolled data. As no variable could predict the response to medical therapy, the strategy generally was a 'step-up' treatment according to clinical response and outcome. Seven randomized placebo-controlled trials have now been published in CC on budesonide,^{70–72} bismuth subsalicylate,⁷³ prednisolone,⁷⁴ *Boswellia serrata* extract⁷⁵ and probiotics.⁷⁶ Controlled data on the treatment of LC are still absent.

A careful assessment of concomitant drug use and dietary factors such as excess caffeine, alcohol and dairy products that might worsen the condition is important. Similarly, concomitant bile acid malabsorption or coeliac disease should be considered. In the patient with mild symptoms, loperamide or cholestyramine can be recommended as the first step of treatment, the latter preferably in the patient with proven bile acid malabsorption.

Budesonide

Budesonide is currently the best-documented treatment in CC and significantly improves the patient's clinical symptoms^{70–72} and quality of life.²⁴ A total of 93 patients with CC were enrolled in three short-term trials of budesonide 9 mg daily for 6–8 weeks. The efficacy of

budesonide was superior to placebo in all trials (Table 2). In a Cochrane meta-analysis, pooled odds ratio was 12.3 (95% CI: 5.5–27.5) for clinical response with budesonide compared with placebo, and number needed-to-treat was two patients.⁷⁷ Most responders had a decrease in the number of loose stools after 2–4 weeks of therapy. Histological improvement was significant with budesonide in all three trials. A significant decrease of the lamina propria inflammation was seen, whereas a reduction in the thickness of the collagen layer was found only in one study. Of further interest is that in addition to anti-inflammatory effects, corticosteroids may also ameliorate bile acid absorption.⁷⁸

After cessation of successful short-term budesonide therapy, the relapse risk is high and occurs in 61–80% of treated patients.^{70–72} The median time to clinical relapse was only 2 (range: 1–104) weeks after cessation of treatment, and age <60 years was a significant risk factor for relapse.⁷⁹ Although unproven, tapering doses of budesonide to 3–6 mg/day may be used as maintenance therapy and has been reported effective in clinical practice.⁸⁰ The corticosteroid adverse effects of budesonide are less compared with prednisolone but must be considered during long-term treatment. Randomized placebo-controlled trials of budesonide as maintenance therapy are, however, currently in progress to address the long-term efficacy and safety.

Bismuth subsalicylate

The evidence for bismuth subsalicylate treatment in MC is weaker. A small trial (published in abstract form only) studied oral bismuth subsalicylate (nine 262 mg tablets daily in three divided doses) vs. placebo for 8 weeks in 14 patients with MC, of which nine had CC.⁷³ All patients on bismuth therapy improved clinically, and six of seven also displayed histological regression, whereas the improvement in the placebo group was marginal. Bismuth subsalicylate is not available in a number of countries for concerns regarding drug toxicity.

Prednisolone

Twelve patients with MC were enrolled in a trial comparing prednisolone 50 mg daily and placebo for 2 weeks.⁷⁴ A clinical response was seen in five of nine patients on active treatment compared with none on placebo. The small number of patients and the short study period limits the study.

Table 2. Data from randomized, placebo-controlled studies of budesonide in collagenous colitis

Author	Number of cases	Dosage of budesonide and duration of trial	Clinical response in budesonide vs. placebo treated cases	Histopathological response in budesonide vs. placebo-treated cases	Side-effects
Baert <i>et al.</i> ⁷⁰	28	9 mg/day for 8 weeks	8/14 vs. 3/14 ($P = 0.05$)	Reduction of lamina propria inflammation in 9/13 vs. 4/12 ($P < 0.001$). No difference in collagen layer	Mild. No difference between treatment groups
Miehlke <i>et al.</i> ⁷¹	45*	9 mg/day for 6 weeks	Remission: 20/23 vs. 3/22 ($P < 0.001$)	Improvement in 14/23 vs. 1/22 ($P < 0.001$). No difference in collagen layer	Mild. 38% vs. 12%, $P = 0.052$
Bonderup <i>et al.</i> ⁷²	20	9 mg/day for 8 weeks	10/10 vs. 2/10 ($P < 0.001$)	Reduction of overall inflammation ($P < 0.01$) and of collagen layer in sigmoid colon ($P < 0.02$)	None

* Per-protocol analysis, 51 patients were randomized but six were withdrawn early due to lack of efficacy or adverse events.

Boswellia serrata extract

Thirty-one patients with CC were for 6 weeks enrolled in a placebo-controlled, randomized trial of *B. serrata* extract, which has anti-inflammatory properties. Clinical remission was achieved in 58% of the *B. serrata* extract group compared with 31% in the placebo group.⁷⁵ Further studies are required to confirm these results.

Probiotics

A small, open-labelled study with the probiotic *Escherichia coli* Nissle 1917 in CC showed some promising results.⁸¹ However, in another small, placebo-controlled trial using *Lactobacillus acidophilus* and *Bifidobacterium animalis* subsp. *lactis* for 12 weeks no significant difference was found in comparison with placebo; a clinical response was seen in six of 21 patients randomized to probiotics compared with one of eight placebo-treated.⁷⁶

Sulfasalazine, 5-ASA, antibiotics

Sulfasalazine (sulphasalazine) and mesalazine have been extensively used in MC but never strictly evaluated in randomized-controlled trials. Retrospective assessment of sulfasalazine and mesalazine has reported

effect in 21–50% of the patients with CC or LC.^{21–23} Antibiotics such as metronidazole and erythromycin have been used but not in a controlled fashion.²¹

Immunosuppressive therapy

In patients with steroid-resistant disease immunosuppressive therapy may be considered although it must be pointed out that there are no supportive controlled data.^{82, 83} An open study with azathioprine gave partial or complete remission in eight of nine patients with MC.⁸² Low-dose methotrexate was effective in 10 of 11 patients with prednisolone refractory CC. The required median dose of methotrexate was 7.5 mg/week. The clinical response to the therapy was rapid and was seen within 3 weeks of treatment.⁸⁴

Surgery

If medical therapy fails and alternative diagnoses are ruled out, surgical therapy may be considered for patients with severe MC. Split ileostomy was conducted successfully in nine women with CC, whereas others have reported a successful outcome both in CC and LC after total or subtotal colectomy.^{48, 85–88} The proportion of patients that needs surgical therapy today is small considering the progress of medical therapy.

PROGNOSIS

The long-term prognosis of MC is generally good. In a follow-up study, 63% of the patients with CC had lasting remission after 3.5 years, and in another cohort study all 25 patients were improved 47 months after diagnosis and only 29% of them required ongoing medication.^{89, 90} A benign course was reported in 27 cases with LC with resolution of diarrhoea and normalization of histology in over 80% of the patients within 38 months.⁹¹ Others reported that 63% of the patients with LC had a single attack of disease with a median duration from onset of symptoms to remission of 6 months.²² Medical therapy, however, may fail and surgical therapy has been recommended in these single patients. However, the number of patients requiring surgery in the future will likely diminish considering that the understanding of the diseases and the medical therapy is advancing.

CONCLUSION

Collagenous colitis and LC are common causes of chronic diarrhoea especially in elderly women and have a significant impact on the patient's quality of life. The diagnosis depends on the awareness of the condition by the clinician, the endoscopist and the pathologist.

Although the colonic mucosa is normal endoscopically, mucosal biopsies must be obtained preferably from the proximal colon. Medical therapy is generally successful. Budesonide is the best-documented short-term treatment in CC. It is the drug of choice in the patient not responding to antidiarrhoeal drugs, cholestyramine, aminosalicylates or bismuth subsalicylate and may be the first-line treatment in the patient with severe symptoms. The evidence for bismuth subsalicylate is weaker and the effectiveness of the other therapeutic alternatives is unknown. Consequently, further studies are necessary to define the best long-term management of CC. In clinical experience a lower dose of budesonide, 3–6 mg/day, may well control the patient's symptoms long-term. Although unproven, azathioprine or methotrexate can alternatively be tried in the patient with steroid-refractory or steroid-dependent disease. No controlled treatment data are available in LC, but a strategy similar to CC can be proposed, until evidence-based recommendations can be made.

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