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Current concepts on microscopic colitis: evidence-based statements and recommendations of the Spanish Microscopic Colitis Group

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SUMMARY

Background
Microscopic colitis (MC) is an underdiagnosed inflammatory bowel disease.

Aim
To develop an evidence-based clinical practice guide on MC current concepts.

Methods
Literature search was done on the Cochrane Library, EMBASE and MEDLINE electronic databases, which were consulted covering the period up until March 2015. Work groups were selected for each of the reviewed topics, with the purpose of drafting the initial statements and recommendations. They subsequently underwent a voting process based on the Delphi method. Each statement/recommendation was accompanied by the result of the vote the level of evidence, and discussion of the corresponding evidence. The grade of recommendation (GR) using the GRADE approach was established for diagnosis and treatment recommendations.

Results
Some key statements and recommendations are: advancing age increases the risk of developing MC, mainly in females. The symptoms of MC and IBS-D may be similar. If MC is suspected, colonoscopy taking biopsies is mandatory. Treatment with oral budesonide is recommended to induce clinical remission in patients with MC. Oral mesalazine is not recommended in patients with collagenous colitis for the induction of clinical remission. The use of anti-TNF-alpha drugs (infliximab, adalimumab) is recommended for the induction of remission in severe cases of MC that fail to respond to corticosteroids or immunomodulators, as an alternative to colectomy.

Conclusions
This is the first consensus paper on MC based on GRADE methodology. This initiative may help physicians involved in care of these patients in taking decisions based on evidence.

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INTRODUCTION

Microscopic colitis (MC) is an inflammatory bowel disease (IBD) that can greatly affect patient health-related quality of life (HRQoL). However, although specific and very effective treatment is available, MC is underdiagnosed fundamentally because of a lack of awareness of the disease among those professionals involved in diagnosing the condition. The diagnosis of MC involves motivated general practitioners, gastroenterologists, endoscopists and pathologists, being necessary a good relationship between them so that all patients with a compatible clinical picture are detected.

A number of literature reviews on MC have been published in recent years,[1–5] and in 2012 the European Microscopic Colitis Group (EMCG) established a series of recommendations related to different aspects of the disease, with a view to enhancing awareness of the disorder among the professionals involved.[6] Although these publications, and especially the aforementioned EMCG recommendations, are based on the available evidence, they only constitute more or less developed consensus documents. In this regard, in none of the reviews have the quality of the evidence and the weight of the statements and recommendations been established using methods specifically suited to the purpose. The use of GRADE (Grading of Recommendations Assessment, Development and Evaluation) technology has been recommended in recent years as a standard tool for the development of clinical practice guides.[7] The present guide is the first clinical practice guideline in MC developed using this methodology.

The statements and recommendations in the present consensus document are meant to be used by physicians and other health professionals involved in the management of MC. Epidemiological and aetiopathogenic aspects are reviewed, and the currently preferred approach to diagnosis and treatment of the disorder is defined. Whenever possible, the specific statements/recommendations were based on the available evidence, and when such evidence was either not available or was found to be inconsistent, the recommendations were established by consensus among the authors. This is a practical guide for clinicians rather than a review article, and those professionals who are interested can consult some of the excellent recently published reviews.[1–5]

METHODOLOGY

Participants in the consensus

The professionals belonging to the Spanish Microscopic Colitis Group (*Grupo Español de Colitis Microscópica*, GECM) were invited to participate. The invited experts were gastroenterologists and pathologists with expertise in scientific methodology and evidence-based medicine. A gastroenterologist (FF-B) acted as coordinator.

Literature searches

Priority was placed on the identification of systematic reviews and other documents offering a critical synthesis of the scientific literature. The Cochrane Database of Systematic Reviews (The Cochrane Library), EMBASE and MEDLINE (accessed via PubMed) electronic databases were consulted covering the period up until March 2015. In a second phase, a manual search was made of individual studies, randomised clinical trials and observational studies.

Classification of the scientific evidence and strength of the statements and recommendations

Data on epidemiology, aetiopathogenesis, and clinical manifestations were critically reviewed, and statements with their level of evidence (LE) were formulated. In contrast, classification of the scientific evidence and strength of the recommendations about diagnostic procedures and treatment was based on the GRADE system (http://www.gradeworkinggroup.org/). The GRADE is an explicit structured classification proposal that is being adopted on a generalised and worldwide basis to assess the accuracy of diagnostic procedures, or the efficacy of a treatment. One of the aims of the GRADE is to overcome the limitations of the previous instruments and consolidate a homogeneous system for all institutions that develop recommendations.[7]

Evaluation of the statements and recommendations by the consensus group

Work groups were selected composed of three to four professionals for each of the reviewed topics, with the purpose of drafting the initial statements and recommendations. The statements and recommendations subsequently underwent a voting process based on the Delphi method.[8] The participants decided whether they consid-

ered the statement/recommendation to be adequate, based on a 6-point Likert scale (1: strongly disagree; 2: quite disagree; 3: somewhat disagree; 4: somewhat agree; 5: quite agree; 6: strongly agree), and suggested changes or new ones.

After voting, the work groups revised the statement and recommendations according to the comments received, and a second vote was then held. The statements and recommendations resulting from the second vote were discussed and approved during a physical presence meeting. This meeting was held in Madrid in March 2015, and was moderated by the coordinator (FF-B). The statements and recommendations were reviewed, modified (where necessary) and voted again during the meeting. A statement/recommendation was approved if over 75% of the participants agreed with it (Likert score of 4–6).

Statements and recommendations

Each statement/recommendation is accompanied by the result of the vote (percentage agreement), the level of evidence (LE: high, moderate, low or very low), and discussion of the corresponding evidence. The GR (strong or weak) using the GRADE approach was only given for studies on the accuracy of diagnostic procedures, or which assessed the efficacy of a treatment, as mentioned above. A strong recommendation in favour means that the benefits clearly outweigh the risks, and that a great majority of well-informed people would make the same decision. A weak recommendation in favour means that a majority of well-informed people would make the same decision, although a substantial group would not make the recommendation, and the benefits and risks are balanced or uncertain. The same reasoning applies to recommendations against, whether strong or weak.

In establishing a recommendation, consideration was made not only of the level or quality of evidence but also of the balance between the potentials benefits and risks of the intervention, its applicability to the treated population, and its cost. The recommendations were classified into four grades: (i) recommended (implies strong and clear advice for the clinician): 'Do it'; (ii) suggested (advice for the clinician): 'Probably do it'; (iii) suggested against or not suggested (advice for the clinician): 'Probably don't do it' and (iv) recommended against or not recommended (implies strong and clear advice for the clinician): 'Don't do it'. This kind of classification is easy to understand and is flexible, since it can be applied to the different clinical scenarios.

Ethical aspects

The consensus was adjusted to the established ethical recommendations.[9]

STATEMENTS AND RECOMMENDATIONS

Tables 1 and 2 summarize the complete list of statements and recommendations of the Spanish Microscopic Colitis Group.

Concept and epidemiology

What is the accepted definition of microscopic colitis?

Statement 1:

Microscopic colitis (MC) is a generic term that includes two main presentations [collagenous colitis (CC) and lymphocytic colitis (LC)] and which describes a form of chronic and relapsing IBD characterised by the following triad of manifestations:

(i) Chronic or intermittent watery diarrhoea without blood.

(ii) A macroscopically normal or almost normal colonic mucosa as evaluated by colonoscopy.

(iii) Characteristic histopathological features.

***LE**: NA*; ***Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

There are data in the literature that support the different concepts used in the definition and which will be discussed in other parts of this guide, where the LE is assessed separately for each concept.

MC as a generic term: In 1993, two research groups (one in France and the other in the USA) suggested the use of MC as a generic term covering any type of colitis characterised by histological changes but without endoscopic or radiological alterations. Subsequently, it became a generic reference to the two main presentations, known as CC and LC,[10] which are clinically characterised by chronic watery diarrhoea without blood. In any case, some authors consider that CC and LC should be regarded as histological subtypes of one same disease – not as differentiated disease conditions.[11] This issue remains subject to controversy.[12]

Recurrent course and intermittent diarrhoea: Although there are few data on the clinical course of patients with MC, the disease is considered to be characterised by chronic or intermittent diarrhoea and recurrent symptoms.[10]

Macroscopically normal or almost normal colonic mucosa: Although the colonic mucosa is macroscopically normal in most patients, mild erythema and oedema

Table 1 | Statements on epidemiology, aetiopathogenesis and clinical manifestations

1. MC is a generic term that includes two main presentations (CC and LC) and which describes a form of chronic and relapsing inflammatory bowel disease characterised by the following triad of manifestations: (i)Chronic or intermittent watery diarrhoea without blood. (ii)A macroscopically normal or almost normal colon mucosa as evaluated by colonoscopy. (iii)Characteristic histopathological features.
2. MC is not infrequent in the elderly. Advancing age increases the risk of developing MC, mainly in females
3. Smoking (whether present or past) is a risk factor for the development of both CC and LC, and moreover favours early onset of the disease
4. Although diarrhoea is a common adverse effect of many drugs, several case–control studies have associated MC to the use of certain medicines. Although, this does not imply a causal relationship in all cases. A feasible cause–effect relationship has only been described for a few drugs and in individual cases
5. Healing of the mucosal lesions observed after faecal stream diversion suggests that luminal antigens are involved in the pathogenesis of MC
6. There is no evidence that autoimmunity is a key pathogenic element in MC, since many of the affected patients do not present autoantibodies
7. Specific features have been described, such as the cytokine profile, the expansion of certain lymphocyte populations and the absence of peripheral lymphocyte recruitment, that appear to point to the existence of immunological aspects specific of MC
8. The activation of pericryptic myofibroblasts and alterations in collagen depositing and reabsorption has been described in CC, although the pathogenic significance of these phenomena is not clear. These changes are not observed in LC
9. There are data supporting the existence of genetic factors in the pathogenesis of MC
10. Although different studies have suggested the existence of bile acid malabsorption in MC, there is no conclusive proof of its aetiopathogenic role
11. The mechanism underlying diarrhoea in MC is not fully clear, although the existing data suggest the participation of a mixed mechanism with components of secretory, osmotic and inflammatory diarrhoea
12. The guiding symptom in MC is chronic watery diarrhoea without blood
13. The symptoms of MC and IBS-D may be similar. If MC is suspected, colonoscopy taking biopsies is mandatory
14. Health-related quality of life in patients with MC can be affected, depending on the severity of the symptoms
15. The clinical evolution of MC is benign and intermittent in most cases. In general, LC is comparatively milder. Diarrhoea persists on a continuous basis in only 10–15% of the cases
16. The presence of certain autoimmune diseases is more common in patients with MC than in the general population

MC, microscopic colitis; CC, collagenous colitis; LC, lymphocytic colitis; IBS-D, irritable bowel syndrome with a predominance of diarrhoea.

may be observed. There have also been occasional descriptions of mucosal tearing or fracture and an altered vascular pattern, particularly in patients with CC.[13]

Characteristic histopathological alterations: The microscopic findings of MC differ between CC and LC, with characteristics specific of each form.[14]

Is microscopic colitis (collagenous colitis and lymphocytic colitis) a frequent disease?

Statement 2:

Microscopic colitis is not infrequent in elderly. Advancing age increases the risk of developing MC, mainly in females.

***LE**: Moderate; **Agreement**: 100%, votes: strongly agree (87%), quite agree (13%).*

Summary of the evidence

Ten population-based studies have been published on the incidence of CC and/or LC in five European countries (Sweden, Iceland, Denmark, The Netherlands and Spain) and in North America (USA and Canada).[15–25] Four of these studies have described the evolution of the incidence of the disease over several decades.[26–30] Table S1 describes the results of these studies and their quality.

The diagnostic criteria and the population considered being at risk – the entire population or only those over 18 years of age [19, 30] – differ slightly among these studies. As a result, they are not fully comparable. The incidence of CC in northern Europe and in North America ranges from 5.2 to 10.8 cases per 100 000 inhabitants and year, while in Spain the figure is <1–2.9 cases. Unfortunately, there are no other studies carried out in other southern European countries that might suggest the existence of North – South differences in incidence. The incidence of LC in northern Europe and in North America ranges from 4 to 19 cases per 100 000 inhabitants and year, while in Spain the figure is 2.3–16 cases.

Table 2 | Recommendations on diagnosis and treatment

1. Colonoscopy taking biopsies is essential in patients with chronic watery diarrhoea to establish a diagnosis of MC
2. It is advisable to obtain biopsies from each of the explored colonic segments (ascending, transverse and descending colon, and sigmoid colon) separately, specifying the location corresponding to each biopsy
3. At least two biopsies should be obtained from each explored segment
4. In most cases, studying the biopsies with haematoxylin and eosin (H&E) and other conventional stains suffices to establish a diagnosis of MC
5. The conventional techniques may prove insufficient in cases of doubt. In such cases immunohistochemical techniques can be used, with anti-CD3 antibodies to quantify the intraepithelial lymphocytes, or the use of tenascin to evaluate the subepithelial collagen band
6. To date, the determination of calprotectin in faeces has not been found to be useful in diagnosing or following-up on patients with MC
7. Treatment with oral budesonide is recommended to induce clinical remission in patients with CC
8. Treatment with oral budesonide is recommended to induce clinical remission in patients with LC
9. Oral budesonide is effective in maintaining remission in patients with CC who have previously responded to the drug.
10. Oral mesalazine is not recommended in patients with CC for the induction of clinical remission.
11. There is not enough evidence to recommend oral mesalazine for the induction of clinical remission in patients with LC
12. The use of loperamide is suggested in cases of mild MC, since it reduces the frequency of stools and the incontinence, thereby improving patient health-related quality of life
13. Cholestyramine can be useful in patients with MC, regardless of whether there is concomitant biliary acid malabsorption or not
14. Treatment with octreotide can be useful in selected cases of severe watery diarrhoea secondary to CC that fail to respond to conventional treatment
15. The use of anti-TNF-alpha drugs (infliximab, adalimumab) is recommended for the induction of remission in severe cases of MC that fail to respond to corticosteroids or immunomodulators, as an alternative to colectomy
16. Antibiotics are not recommended for the treatment of MC
17. The use of bismuth subsalicylate could be considered in patients with MC, as treatment for the induction of clinical remission
18. The use of probiotics for inducing clinical remission in MC is not recommended
19. In patients with MC who are corticosteroid-dependent or fail to respond to corticosteroids, azathioprine is suggested for the induction of clinical response
20. The use of methotrexate for inducing clinical remission in MC is not recommended

MC, microscopic colitis; CC, collagenous colitis; LC, lymphocytic colitis.

The studies with the highest incidence of LC[20, 21] might be affected by inclusion bias due to the inclusion of cases with a doubtful diagnosis ['probable cases' in the Canadian study, and cases that did not meet the diagnostic criteria regarding the intraepithelial lymphocyte (IEL) count with haematoxylin and eosin (H&E) staining, but which met the IEL count criterion with anti-CD3 labelling in the Spanish study]. The studies that have evaluated the evolution of the incidence of MC show a rising frequency over the last few decades for both CC and LC,[18, 19, 21, 25] which may be due not only to a genuine increase in incidence but also to greater knowledge of the disease and fewer cases that fail to be diagnosed.

Microscopic colitis is most often seen in elderly individuals, with an estimated mean age at the time of diagnosis of 61.1 ± 6.5 years[15, 17–30] (Table S3). In these studies, the peak incidence of MC corresponded to patients ≥70 years of age and even ≥80 years of age.[15, 18, 26–29] Advancing age increases the risk of developing both CC and LC, with no significant differences between the two forms in population-based studies,[15, 17–30] case–control and cohort studies,[41, 42] and systematic reviews.[11] A Canadian study recorded a significant increase in the risk of developing MC with advancing age: 30–59 years (RR 6.94; 95% CI: 5.38–8.97), ≥60 years (RR 22.45; 95% CI: 17.38–29.01), as compared to age group 0–29 years.[16] In any case, it must be taken into account that MC is not seen exclusively in elderly patients. It has been reported that 25% of the patients with CC were under 45 years of age at the time of the diagnosis.[26] Cases of CC have also been described in paediatric populations.[44–48] Three of the population-based epidemiological studies provide data referred to the incidence of CC and LC separately for males and females [15, 18, 25] (Table S4). The incidence of CC/LC was two to eight times higher in females than in males, with significant differences between the two sexes. No clear differences between CC and LC were noted. A study suggests that age exerts a stronger influence than sex in relation to the risk of CC (OR 8.3 for age ≥65 years and OR 2.8 for the female sex).[24]

Different studies have determined the frequency with which MC is diagnosed in patients with a history of chronic or intermittent watery diarrhoea without blood and presenting normal colonoscopic findings, in which other possible causes have been discarded. However, it must be taken into account that the available data come from different types of studies, and that only a minority has been obtained from population-based studies. Furthermore, the diagnostic protocols and diagnostic tests used before colonoscopy taking biopsies are not described in most of the studies. As a result, the different publications might not be comparable. However, it must be noted that cases of MC have been reported in practically all parts of the world. On considering only those studies with a sample size of ≥150 patients, the mean frequency of MC is seen to be 12.1 ± 6.2% (range 3.7–29.3%)[18, 20, 27–29, 31–40] (Table S5). Some studies have evaluated the frequency of MC with respect to patient age. In this regard, the frequency of MC in males over 70 years of age or in females over 50 years of age is about 20% in two studies, vs. 9.5% and 13.7% on considering all ages.[20, 28]

Does smoking increase the risk of microscopic colitis (collagenous colitis and lymphocytic colitis)?

Statement 3:

Smoking (whether present or past) is a risk factor for the development of both CC and LC, and moreover favours early onset of the disease.

***LE**: Moderate; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Current smoking as a risk factor for MC has been investigated in at least four cohort studies in Europe and the USA. The first of them,[24] involved a retrospective analysis of Swedish patients with CC only, and found the disease to be more common in smokers than in nonsmokers (OR 2.95; 95% CI: 2.01–4.32). These findings were subsequently corroborated by a Spanish prospective, multicentre cohort study,[49] for both CC (OR 2.4; 95% CI: 1.05–7.6) and LC (OR 3.8; 95% CI: 1.6–9.2), and by a retrospective study in the USA, which showed smoking to be significantly more common among patients with both variants of MC than in healthy controls.[50]

The risk of developing MC among smokers was particularly high in the younger subjects aged 16–44 years (OR 16.54; 95% CI: 4.46–61.37).[24] In this same respect, two studies have found active smokers to develop the disease 10 years earlier than nonsmokers.[24, 49] On the other hand, smoking was associated to more serious digestive manifestations, as well as to a greater risk of suffering IBS symptoms.[51]

The criteria used to define smoking were not consistent among the different studies. Two studies considered 'active smoking' as the consumption of seven or more cigarettes a week for at least 6 months,[49, 50] while the rest of the studies included as active smokers those patients who had smoked to any degree, whether regularly or sporadically.[24, 52]

The association of ex-smoker status (defined as smoking cessation at any time before the diagnosis of MC) to an increased risk of developing MC was also demonstrated in three studies,[24, 50, 52] although the risk was greater among the active smokers. However, no differences were observed in terms of clinical presentation, remission rates or type of MC between active smokers and ex-smokers.[53]

No studies have examined the effect of smoking cessation upon the clinical course of smokers with MC.

Is microscopic colitis (collagenous colitis and lymphocytic colitis) associated with the chronic use of drugs prescribed for other comorbidities?

Statement 4:

Although diarrhoea is a common adverse effect of many drugs, several case–control studies have associated MC to the use of certain drugs. This does not imply a causal relationship in all cases, however. A feasible cause-effect relationship has only been described for a few drugs and in individual cases.

***LE**: Low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Diarrhoea is a common adverse effect of drug treatments, having been reported for over 700 drug substances. No universally accepted methods are available for assessing cause–effect relationships in adverse drug reactions.[54] Consequently, such relationships are based on the feasibility criteria proposed by the World Health Organisation (WHO)[55] (Table S6). The existing information on the capacity of drugs to act as risk factors for MC has been derived from different sources:

Case series including a limited number of patients, which have been repeatedly documented since the 1990s,[56, 57] involving a number of drugs. However a definitive causal relationship (based on the time relationship between drug exposure and the symptoms, resolution of the clinical and disease findings after drug discontinuation, and relapse after challenge testing) has

only been demonstrated for a few drug substances – including acarbose,[58] nonsteroidal anti-inflammatory drugs (NSAIDs),[57] ranitidine,[59] omeprazole,[60] lansoprazole,[61] ticlopidine[62] and the venotonic product Cyclo 3 forte,[63] although in some cases patient evaluation after challenge was exclusively clinical.[57, 62]

Case–control studies demonstrating the association, but without being able to establish causal relationships, although they may suggest possible risk factors meriting further investigation (Table S7). The use of NSAIDs, including low-dose aspirin (<300 mg),[22, 49, 64, 65] and of proton pump inhibitors (PPIs) [66] has been associated to a increased risk of developing MC, in agreement with the drug imputability studies discussed above. In general, this last association was more intense and more frequently reported for CC than for LC,[22, 49, 64] as well as for more symptomatic forms of MC.[51] Exposure to antidepressants in the form of selective serotonin reuptake inhibitors (SSRIs), particularly sertraline, has been associated to an increased risk of MC in several studies.[49, 64, 65]

Although not on a universal basis, other studies have related MC to the use of statins,[49, 64, 65] beta-blockers,[22, 49, 59, 61, 65] and bisphosphonates.[65] However, no differences were found in the consumption of these drugs in a control group with chronic diarrhoea [65] – thus suggesting that these substances may be inducers of diarrhoea rather than of true MC.

The recent start of a new drug (<3 months), particularly PPIs or anti-parkinson agents, has been identified as a significant risk factor associated to MC.[65] In this sense, the induction or worsening of diarrhoea after drug exposure could be an indication for colonoscopy – thereby contributing to diagnose underlying MC, which would not be simply caused by the drug.

Drug prescription registry data: The two available case–control studies have yielded opposite results. While a large Danish national study including 5751 cases of CC or LC recorded a significant association with PPIs, statins, NSAIDs and SSRIs,[64] the other study conducted in Pennsylvania (USA) found no association between MC and the use of commonly related drug substances[67] – although the agreement between patient reported drug use and the information recorded in the database was generally poor.

In addition to the limitations regarding the definition of causal relationship, the different criteria used to define 'drug exposure' [ranging from at least one prescription in the last year,[64] or in the previous 6 months,[66] to continuous or frequent use (at least 3 days a week during 2 weeks or more)],[49, 65] the lack of systematic consideration of the mean drug exposure time before the diagnosis of MC, and the different reference populations used as controls, all constitute additional limitations for defining the nature of the relationship between drugs and MC.

Etiopathogenesis of microscopic colitis

The most widely accepted aetiopathogenic hypothesis at this time suggests an immune disorder, with chronic inflammation of the intestinal mucosa, triggered against host antigens by an unidentified initial stimulus (bacterial, chemical or of some other nature), in a genetically susceptible individual.[4]

Can intestinal luminal antigens determine the pathogenic response of microscopic colitis?

Statement 5:

Healing of the mucosal lesions observed after faecal stream diversion suggests that luminal antigens are involved in the pathogenesis of MC.

***LE**: Low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Several factors support the involvement of luminal antigens in the pathogenesis of MC. First, it has been seen that an ileostomy, with the consequent faecal stream diversion, results in histological healing of the disease.[68] Even after a Hartmann colon diversion procedure, the histological lesion is seen to persist in the proximal colon but disappears from the excluded distal colon.[69] In fact, it has been suggested that the use and effect of bile acid chelating agents is more dependent upon the clearance of associated toxins than on bile malabsorption as such.[70]

The search for a specific infectious agent has been based on the observation that some patients with MC respond to antibiotics – specifically metronidazole.[71] It has not been possible to identify an aetiopathogenic agent, however. The possible involvement of infectious agents such as *Yersinia* sp.,[72] *Clostridium difficile*,[73, 74] *Campylobacter jejuni*[74] and *Aeromonas hydrophyla*[69] has been suggested, exhibiting some similarity to post-infectious irritable bowel syndrome (IBS).[75]

A study has attempted to characterise the bacterial flora associated to the ascending colon mucosa in two patients with CC.[76] This study has shown the presence of an intestinal flora very similar to that seen in healthy individuals, and composed mainly of *Firmicutes* and *Bacteroides*. Of note is the observation that clones of *Bacteroides* represent up to 40%, while the existing studies in healthy

individuals show the proportion of these clones to be between 5% and 20%.[77, 78] The two patients studied showed an important presence of potentially pathogenic species of *Bacteroides* spp., and also of clones related to *C. clostridiforme* – although no clearly pathogenic agents as such were identified. It has been speculated that the detected strains are able to disgregate the mucosal layer and increase intestinal permeability – thereby facilitating onset of the altered immune response.

In vitro studies in colonic biopsy samples showed significant mucosal barrier dysfunction in patients with CC in clinical remission, which worsened in the active phases of the disease, with a greater transmucosal uptake of non-pathogenic bacteria. Although it is not clear whether increased mucosal permeability is a primary or secondary event in the pathogenesis of CC, it has been seen that the altered mucosal barrier function in CC persists despite effective clinical treatment with budesonide.[79]

Is an autoimmune response the key pathogenic factor in microscopic colitis?

Statement 6:

There is no evidence that autoimmunity is a key pathogenic element in MC, since many of the affected patients do not present autoantibodies.

***LE**: Very low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The origin of MC has been related to autoimmune conditions, because the disease responds to corticosteroid treatment and is associated to a high frequency of pleomorphisms of genes that encode for HLA and TNF-α, which pre-dispose to autoimmune disorders.[80] Furthermore, MC is more common in middle-aged women, who are more susceptible to autoimmune processes. Forty per cent of all patients with MC have other associated autoimmune diseases (see statement 16).[81, 82] Few studies have examined the prevalence of autoantibodies in MC. The levels corresponding to rheumatoid factor, anti-thyroglobulin antibodies, microsomal antigen and anti-transglutaminase antibodies have not been found to be increased in MC. Some studies have reported an increase in anti-nuclear antibodies (ANAs) and anti-*Saccharomyces cerevisiae* antibodies (ASCAs) in CC.[83] A recent study has observed an increased prevalence of ANA, p-ANCA, ASCA IgG, anti-GAD and anti-TPO antibodies in patients with MC vs. the general population,[84] but the difference is small and is moreover not observed in many of the patients. Likewise, there are no autoantibody differences between CC and LC. The increase in autoantibody titres may be due to the association of other autoimmune disorders and to the prevalence observed among middle-aged women. Thus, until prospective studies are carried out to clarify this issue, the current position is that autoimmunity does not seem to be a key aetiopathogenic element, although it may be partially involved in the disease.

Does innate and acquired immune dysregulation have characteristic features in microscopic colitis?

Statement 7:

Specific features have been described, such as the cytokine profile, the expansion of certain lymphocyte populations, and the absence of peripheral lymphocyte recruitment, that appear to point to the existence of immunological aspects specific of MC.

***LE**: Very low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Microscopic colitis is characterised by an exacerbated and dysregulated inflammatory response which recently has been found to be related to the intramucosal clonal expansion of CD3-positive lymphocytes in response to an intramucosal or luminal stimulus. The disease does not involve a great peripheral lymphocyte recruitment effect, as demonstrated by a decrease in T cell receptor excision circles (TRECs)[85] – this constituting a clearly differentiating feature with respect to other disorders such as ulcerative colitis and Crohn's disease, where TRECs are increased and a lymphocyte recruitment effect is indeed observed. It is therefore believed that 'anti-homing' drugs will not be useful in application to MC.

The studies suggest that the intestinal inflammation seen in MC is characterised by a predominant Th1 type response, with the expression fundamentally of interferon-gamma (IF-γ), IL-15 and TNF-α, and the production of inducible NOS (iNOS).[86, 87] A recent study has shown LC to be characterised by an increased expression of IF-γ, TNF-α and IL-8, thus suggesting the implication of innate immunity.[88] While IL-1b is elevated in Crohn's disease, it is significantly diminished in LC, and the regulatory interleukins (ILs) (IL-4, IL-12 and IL-10) experience no changes. It therefore seems that the aetiopathogenic cytokine profile is indeed different from that seen in ulcerative colitis and Crohn's disease. An increase has also been reported in the expression of prostaglandin receptor EP-4, which facilitates the action of prostaglandins that are increased in the course of the inflammatory process – although the effect of this receptor remains to be deter-

mined (both pro- and anti-inflammatory actions have been described following EP-4 activation, depending on the microenvironment and activation site).[88]

Cytokine IL-17 has recently been measured for the first time in MC,[89] and has been found to be significantly increased in the mucosa of affected patients. This cytokine is produced by T-17 cells, and regulates the anti-microbial processes in innate immune defence, as well as intestinal permeability. In this regard, IL-17 block has been suggested as a treatment option meriting future evaluation. Last, the study has compared CC and LC – no differences in terms of cytokine expression having been noted, although expression of the enzymes COX-2 and iNOS appears to be comparatively greater in CC.

Have extracellular matrix remodelling alterations been described in the pathogenesis of microscopic colitis?

Statement 8:

The activation of pericryptic myofibroblasts and alterations in collagen depositing and reabsorption has been described in CC, although the pathogenic significance of these phenomena is not clear. These changes are not observed in LC.

***LE**: Very low; **Agreement**: 100%, votes: strongly agree (77%), quite agree (23%).*

Summary of the evidence

Altered pericryptic fibroblast function has been suggested, with the facilitation of subepithelial collagen formation and accumulation. The studies have yielded contradictory results,[90, 91] with an increase in collagen VI (primary collagen alteration) vs. the accumulation of collagen I and III, representing attempted repair. There has also been reported increase in activated pericryptic myofibroblasts and in tenascin in CC, but not in LC.[92] These fibroblastic alterations have also been observed in the fibrotic forms of ulcerative colitis. In this regard, such alterations are considered to be a consequence of the process rather than a pathogenic element, and no clear association has been found between MC and pericryptal fibroblast dysfunction.

Are there well-defined genetic factors allowing the diagnosis or prediction of the risk of developing microscopic colitis?

Statement 9:

There are data supporting the existence of genetic factors in the pathogenesis of MC.

***LE**: Low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

There have been reports of families with cases of MC (both CC and LC),[93–98] exhibiting a highly varied geographic distribution (including countries such as Canada, the UK or Sweden, among others). There have also been descriptions of haplotypes of the major histocompatibility complex (HLA) that are more frequent in patients with MC. In this regard, an increase in HLA A1 has been described in patients with LC.[90] Other authors have found an association between MC and HLA-DQ2 or DQ1/3, and a greater frequency of haplotype HLA-DR3DQ2 and of allele TNF2 in these individuals.[80, 99, 100]

Other studied genes are the polymorphisms of NOD2/CARD15, which have not been seen to be related to CC[101]; an allelic variant of the gene encoding for matrix metalloproteinase 9, which is associated to CC[102]; and allele IL-6-174-DG, which is frequent in patients with MC.[103]

Is bile acid malabsorption related to the aetiopathogenesis of microscopic colitis?

Statement 10:

Although different studies have suggested the existence of BAM in MC, there is no conclusive proof of its aetiopathogenic role.

***LE**: Very low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The hypothesis that BAM exerts a decisive influence upon the development of diarrhoea or the histological lesions in patients with MC has not been fully confirmed, despite the existence of data suggesting its possible implication.

On the one hand, there are animal models of colitis induced by bile acid infusion in the colon.[104–106] On the other hand, it has been seen that BAM diagnosed using the tauroselcholic (selenium-75) acid technique (SeHCAT) is common (incidence about 44%) in both CC [104, 107] and LC.[104] Other authors have described morphological changes in the terminal ileum (villous atrophy, inflammation and collagen deposits) that can favour BAM at this level.[108] The BAM hypothesis is plausible, since certain patients with known BAM (e.g. secondary to ileal resection) develop diarrhoea, while other patients suffer diarrhoea following cholecystectomy.[109] However, no association has been found between cholecystectomy and MC.[110]

In noncontrolled studies, bile acid chelating agents have been shown to be effective in improving the symptoms of CC, although without significant improvement of the colon histological lesions.[111] Small series (n = 25 patients) have also shown budesonide to normalise the

SeHCAT test results and reduce bile acid production in patients with CC.[112]

Has the precise mechanism of diarrhoea in patients with microscopic colitis been established?

Statement 11:

The mechanism underlying diarrhoea in MC is not fully clear, although the existing data suggest the participation of a mixed mechanism with components of secretory, osmotic and inflammatory diarrhoea.

***LE**: Very low; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The precise mechanism of diarrhoea in patients with MC has not been established. The intervention of a mixed mechanism with components of secretory, osmotic and inflammatory diarrhoea has been suggested.

On the one hand, Breuer *et al.* described a triple mechanism of diarrhoea in CC:[105] (i) malabsorptive diarrhoea secondary to defective transporters and collagen bands; (ii) secretory diarrhoea due to rheogenic anion secretion and (iii) 'leakage flow' diarrhoea secondary to alteration of the epithelial barrier with the consequent passive flow of water and ions into the intestinal lumen. On the other hand, fasting has been shown to reduce diarrhoea, thus supporting the existence of an underlying osmotic component.[113] A significant inflammatory component is also believed to be involved in the origin of diarrhoea in these patients, since its severity is related to the intensity of inflammation in the *lamina propria* and not to the thickness of the collagen band.[114]

Regarding the presence of anorectal functional disorders in patients with MC as a possible cause of diarrhoea, it is interesting to note that manometric studies have not observed rectal hypersensitivity or anal function disturbances in CC with inflammatory activity. In fact, the rectal pressure threshold appears to be elevated in such patients compared with healthy controls.[115]

Clinical manifestations and associated diseases

Is there a guiding symptom in microscopic colitis?

Statement 12:

The guiding symptom in MC is chronic watery diarrhoea without blood.

***LE**: High; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The main symptom in MC is chronic recurrent or intermittent watery diarrhoea without blood. It can be associated with abdominal pain (in 50–70% of the cases), nocturnal diarrhoea (25–50%), abdominal bloating, defecation urge (70%), incontinence (40%) and discrete weight loss (in up to 50% of the cases).[3, 5, 116] In the case of significant weight loss, associated coeliac disease must be discarded. Fatigue is a common symptom observed in 50–60% of the patients. Mucus and blood is rare, in the same way as dehydration.

In some cases, the clinical manifestations have been present for months or even years before, a correct diagnosis is established. Onset of the disease is usually insidious, although acute manifestation is seen in up to 40% of the cases.[71] There is no specific symptom allowing distinction between CC and LC. The differences between the two variants are based on the histopathological features.

Can microscopic colitis be distinguished from irritable bowel syndrome with a predominance of diarrhoea (IBS-D) or functional diarrhoea based on the clinical manifestations?

Statement 13:

The symptoms of MC and IBS-D may be similar. If MC is suspected, colonoscopy taking biopsies is mandatory.

***LE**: Moderate; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

A differential diagnosis with IBS-D is required in patients presenting chronic watery diarrhoea without blood and with abdominal pain (more common in CC).[3, 5, 116] An orienting clue is the fact that nocturnal diarrhoea is rarely seen in IBS-D.

Previous retrospective studies have suggested an overlapping of clinical symptoms in MC, IBS-D and functional diarrhoea. A recent prospective study reported that 38–58% of the patients with MC met the criteria of IBS.[117]

Thus, the diagnosis cannot be based only on clinical criteria. In the case of a strong suspicion of MC (patient >50 years of age, nocturnal diarrhoea, recent start of drug treatment or presence of autoimmune disease),[43] or in the absence of adequate response to symptomatic treatment for IBS-D, colonoscopy must be performed taking biopsy samples.

Can microscopic colitis affect patient health-related quality of life?

Statement 14:

Health-related quality of life in patients with MC can be affected, depending on the severity of the symptoms.

***LE**: Moderate; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

There is no biological marker for defining clinical activity in MC. Clinical studies have proposed a number of definitions for disease flare-up or response, but it is difficult to establish comparisons among them.

The literature shows faecal consistency rather than the faecal frequency to be the determining factor underlying changes in HRQoL. The retrospective study published by Hjortswang *et al.* in patients with CC evaluated the faecal frequency and consistency with a view to establishing an optimum cut-off point for defining clinical remission, taking into account the possible existence of worsened HRQoL. The authors defined clinical remission in CC as an average of <3 faeces/day and an average of <1 liquid faeces/day in 1 week. Accordingly, those patients who do not meet these criteria, e.g. individuals with ≥3 faeces/day or ≥1 liquid deposition/day, present clinically active disease.[118]

A more recent study by the same authors has reported poorer HRQoL in CC vs. the general population. The study also concluded that active disease is associated to poorer HRQoL.[119] Clinical trials have shown budesonide to improve patient quality of life. The HRQoL in patients in clinical remission is similar to that found in the general population.[120] Similar findings have also been reported by Nyhlin *et al.*, who included patients with both CC and LC. Clinical activity was associated to worsen HRQoL, while no differences were observed between patients in remission vs. the controls. On the other hand, although the patients were in clinical remission according to the above mentioned definition, they presented persistent abdominal pain, fatigue and joint and muscle pain years after the diagnosis, and this also affected HRQoL.[5, 121]

How does microscopic colitis evolve from the clinical perspective?

***Statement 15**:*

The clinical evolution of MC is benign and intermittent in most cases. In general, LC is comparatively milder than CC. Diarrhoea persists on a continuous basis in only 10–15% of the cases.

***LE**: Moderate; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The studies conducted to date involve only limited follow-up or small sample sizes.[4, 122, 123] MC can manifest as a single symptomatic episode lasting a few months, as a persistent episode, or as alternating episodes of clinical activity and remission.[2] The spontaneous remission rates vary greatly.[4, 124–126] Over the long term, two recent studies (one conducted in Iceland and the other in Italy) indicate that most patients remain symptom-free or suffer only sporadic symptoms.[122, 127]

A placebo response rate of 12–20% and 48% has been reported in CC and LC, respectively, thus suggesting that LC has a milder course than CC and a greater tendency towards spontaneous remission.[128] According to two studies with an average follow-up of 3–4 years, CC shows high remission rates even without the need for specific maintenance treatment.[129, 130] In the case of LC, a benign course with resolution of the diarrhoea and normalisation of the histological characteristics have been described in 80% of the patients.[124] In one study, LC manifested as a single disease outbreak in 63% of the cases.[131]

Although the prospective, placebo-controlled studies in patients with CC report an 80% relapse rate after discontinuing treatment with budesonide, the evidence obtained from clinical practice studies suggests that only 30% of the patients continue to experience symptoms over the long term.[132–134] Prospective studies would be needed to confirm these results.

Although MC is a benign disorder, there have been reports of some uncommon clinical complications. Both spontaneous and post-colonoscopy colon perforations have been reported that might be related to the presence of mucosal tears seen at colonoscopy.[135–138] On the other hand, MC is not associated to an increased risk of colorectal cancer. These patients therefore do not need specific screening recommendations.[44, 139, 140]

Is microscopic colitis associated to autoimmune diseases?

***Statement 16**:*

The presence of certain autoimmune diseases is more common in patients with MC than in the general population.

***LE**: Moderate; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The associated presence of autoimmune diseases has been described in over 30–50% of all cases of MC.[5] A study has found autoimmune disorders to be more common in patients with MC than in controls, with OR 11 (95% CI: 5.1–23.8) for CC ($P < 0.001$) and OR 16.6

(95% CI: 6.4–43.1) for LC ($P < 0.001$).[3] Another recent study has reported that associated autoimmune disorders are an independent risk factor for MC, together with the use of certain drugs and smoking.[49]

Coeliac disease is the most common disorder, and is seen in 2–20% of the cases. In a recent study involving 116 patients with CC, coeliac disease was found to be the most frequent associated autoimmune disorder (13%), and in these cases, the digestive symptoms were seen to manifest earlier.[24] Another large population-based study also recorded a strong association between MC and concomitant coeliac disease, with rates about 50 times higher than expected in the general population, fundamentally in women between 40 and 60 years of age.[21] It is therefore important to take this possible association into account, particularly when a patient diagnosed with MC fails to respond to the prescribed treatment. On the other hand, in a large cohort of patients with coeliac disease, 4.3% were diagnosed with MC – this representing a 72-fold higher diagnostic rate than in individuals without coeliac disease.[141] Despite this association, however, there is a low percentage of serological coeliac disease markers in MC. In some studies, the incidence of anti-endomysial antibodies was 0–4%, and no patient proved positive for anti-transglutaminase antibodies.[71, 100] The serological study therefore does not seem to be useful, in view of its low sensitivity in diagnosing coeliac disease in patients with concomitant MC.[123]

Other associated autoimmune disorders are type 1 diabetes, autoimmune thyroiditis (observed in 10–20% of the cases), seropositive/seronegative rheumatoid arthritis (3%), Sjögren's syndrome, Raynaud syndrome, and psoriasis (2%).[142] Last, other studies have found that juvenile spondyloarthropathy or SAPHO syndrome [a variety of rheumatic disease associated to skin lesions (acne, pustulosis) and synovitis, hyperostosis and osteitis] might be associated to MC. However, little is known of the association of these disorders in the paediatric population.[143, 144]

On the other hand, there have been reports of MC progressing to IBD,[123, 145, 146] and vice versa.[71, 147] However, a recent large cohort study has concluded that there is no increased risk of developing IBD in MC.[41] It is important to note that there are histological changes typical of IBD, such as Paneth cell metaplasia and crypt architectural distortion, that occasionally can be seen in patients with MC in the absence of IBD.[148]

Diagnostic criteria

Is colonoscopy taking biopsies indicated in patients with chronic watery diarrhoea to diagnose MC?

Recommendation 1:

Colonoscopy taking biopsies is essential in patients with chronic watery diarrhoea to establish a diagnosis of MC.

***LE**: High; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Complete colonoscopic examination with ileal intubation forms part of the studies required in cases of chronic diarrhoea. Endoscopically, MC is characterised by a normal colonic mucosa or a mucosa with only nonspecific changes in the form of oedema and erythema. Taking biopsies is therefore the only way to establish the diagnosis. In fact, MC is the most frequent diagnosis in patients with chronic watery diarrhoea and normal colonoscopic findings when biopsies are collected.[20, 38, 149] Biopsies of normal colon mucosa in patients with chronic watery diarrhoea moreover can confirm the diagnosis of other forms of colitis such as Crohn's disease,[31] or certain forms of infectious colitis.[150]

The diagnostic yield of this procedure has been questioned, but the cost-effectiveness ratio of colon biopsies in the case of chronic watery diarrhoea is superior to that of other procedures such as duodenal biopsies in patients who have a relative with coeliac disease, diarrhoea or anaemia, or in screening for dysplasia in ulcerative colitis.[151] This yield depends on the prevalence of MC.[152]

There are aspects which have already been discussed in previous sections such as the fact that MC is much more frequent in women and in people over 65 years of age,[27, 34, 38, 149, 153] in the presence of coexisting autoimmune disorders or coeliac disease, or in situations of recently started treatments with certain drugs (NSAIDs, lansoprazole, sertraline, etc.), which may increase the diagnostic yield of biopsies.[20, 43, 149] A scoring system has recently been proposed for identifying patients with MC, affording a sensitivity of 90% and a specificity of 45%, with the inclusion of a patient age of over 50 years, the female sex, previous treatment with PPIs or NSAIDs, weight loss, and abdominal pain as variables.[154] This scoring system requires validation through prospective studies.

Last, chromoendoscopy with indigo carmine could make endoscopically detectable lesions more manifest. This in turn could help select patients for biopsy, although the existing information comes from a series

of only 13 patients. Further studies are therefore needed.[155]

The colon mucosa is not always normal in MC. Subtle or nonspecific mucosal changes have been described, such as oedema, erythema, a rough or nodular surface, an altered vascular pattern, red points or linear tears or scratches and pseudomembranes.[13, 31, 156]

Should biopsies of the different colon segments be obtained?

Recommendation 2:

It is advisable to obtain biopsies from each of the examined colonic segments (ascending, transverse and descending colon, and sigmoid colon) separately, specifying the location corresponding to each biopsy.

***LE**: Low; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Microscopic colitis affects the different colon segments with variable intensity,[31, 157] with the detection of a diffuse lymphoplasmacytic infiltrate in the *lamina propria*, but with a more irregular distribution of those characteristic findings that allow the diagnosis to be established.[31, 158] The optimum colon segments for biopsy, and their number, have not been clearly established,[159] although obtaining biopsies only of the rectum is not advisable, since they prove normal in 8% of the cases of LC and in 43% of the cases of CC.[27] A prospective study of 103 patients including 13 cases of MC (12 cases of LC and a single case of CC) has found that up to 23% of the cases would not have been diagnosed if biopsies of the ascending or transverse colon had not been obtained.[160] Another study involving 79 patients with CC and biopsies from the rectum, sigmoid and descending, transverse and ascending colon found taking biopsies from the ascending, transverse and descending colon to be the combination affording the greatest diagnostic rate (96%).[158] Notoriously, the collagen band was only detected in all five segments in 47% of the patients.

The histological findings allowing the diagnosis of MC are more often detected in the right colon.[27] In LC, IELs are more numerous in the ascending and transverse colon,[6] while in the case of CC, the collagen band is thicker in the proximal colon.[156, 158, 161] It must be taken into account that in the normal colon mucosa, the presence of inflammatory cells and lymphocytes is greater in the right colon than in the left colon.[162] It is therefore important for the pathologist to know the origin of the biopsies.[161, 163]

Furthermore, both forms of MC may overlap in one same patient. A patient with CC or LC may present histological changes suggestive of the other type of MC in another colon segment, as well as segments with criteria of incomplete MC (MCi). In 48% of the cases of CC, there may be >5 IELs per 100 epithelial cells, and in 24% of the cases of LC there may be a collagen band measuring 5–10 μm in thickness.[17] In the event of segments diagnosed with LC or MCi and of other segments diagnosed with CC, the final diagnosis is CC.

In sum, although MC is a diffuse disease, it is often not detected in some of the biopsies of some of the colon segments. The observed changes moreover tend to be more intense in the right colon, and there may be overlapping of both forms of the disease. These characteristics suggest that it is justified to obtain biopsies of the different segments of the colon examined separately, allowing the pathologist to recognise the origin of each biopsy.

How many biopsies should be obtained from each colonic segment?

Recommendation 3:

At least two biopsies should be obtained from each explored segment.

***LE**: Low; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The optimum number of biopsies has not been established, but the American Association of Gastroenterology recommends a minimum of eight biopsies from the entire colon.[159] At least two biopsies should be obtained from the transverse colon (if accessed), together with two biopsies from the descending colon and two from the sigmoid colon if sigmoidoscopy is performed. If a complete colonoscopic exploration is performed, at least two biopsies should be obtained from the ascending colon, with two from the transverse colon, two from the descending colon, and two from the sigmoid colon.[164] According to the published literature, the number of biopsies ranges from 2 to 4 per explored colon segment. Not only the normal mucosa should be biopsied but it is also advisable to obtain biopsies from the areas showing anomalies.[165]

Is it enough to examine the colonic mucosa biopsies with conventional stains?

Recommendation 4:

In most cases, studying the biopsies with H&E and other conventional stains suffices to establish a diagnosis of MC.

***LE**: Moderate; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Haematoxylin and eosin staining complemented by other conventional techniques such as the Masson trichromic stain or van Gieson stain (which is useful for evaluating the collagen band) allows the diagnosis of most cases of MC. The use of other techniques should be considered in those cases where the differentiation between CC and LC is not clear, or where incomplete forms may be involved. Congo red staining can be useful for the differential diagnosis of amyloidosis in the case of amorphous eosinophilic deposits in the walls of the submucosal vessels.

The histological findings of the biopsies from patients with MC using H&E staining have been described and used for the diagnosis in many studies.[17, 27, 34, 166] These findings are included in the recommendations of the EMCG and of the Working Group of Digestive Diseases of the European Society of Pathology [10, 161] (Table S8).

There is no agreement on how to measure the thickness of the collagen band in MC. A study of the differences in precision of three measurement methods (conventional histological assessment, micrometric scale and semiautomatic micrometry) found all three methods to produce errors (in 7.4%, 6% and 6% of the cases respectively).[167] In any case, the diagnosis of CC is based more on a global set of findings than on strict measurement of the collagen band.

The reliability of H&E staining in diagnosing MC has been demonstrated in two studies that measured intra- and inter-observer variability. One study analysed inter-observer variability in the diagnosis of MC based on biopsies from 90 patients (20 with CC, 20 with LC, 20 with IBD, and 30 normal subjects). Four pathologists specialised in gastroenterology classified the 90 H&E-stained biopsies as corresponding to CC, LC, chronic colitis, focal active colitis, normal mucosa or other conditions, on a blind and independent basis. Inter-observer agreement for the six disease categories proved acceptable (k = 0.68–0.78). Considering MC as a single group vs. colitis of other types, agreement was found to be very good (k = 0.80–0.95). Intra-observer agreement was also good for the 6 disease categories (k = 0.75–0.79), and even better on differentiating MC from the rest of the biopsies (k = 0.84–0.91).[168] In another study including H&E-stained biopsies from 125 patients diagnosed with CC, LC, MCi, nonspecific colitis/IBD and normal biopsies, inter-observer agreement among three pathologists with different degrees of experience was seen to be good (k = 0.81–0.89) in distinguishing MC (CC, LC and MCi) from nonspecific colitis/IBD and normal biopsies. There was less inter-observer agreement in differentiating among CC, LC and MCi (k = 0.60–0.75).[14]

The diagnosis of LC and particularly of MCi requires a solid clinical-pathological correlation (i.e. patients with chronic watery diarrhoea with normal colonoscopic findings – see above), for although their characterising signs are specific, they are not pathognomonic, and a risk of overdiagnosis therefore exists.[161–163] In the case of CC, the diagnosis is not only based on the presence of the collagen band, and must be accompanied by the rest of the characterising findings.[161]

When are immunohistochemical techniques recommended?

***Recommendation 5**:*

The conventional techniques may prove insufficient in cases of doubt. In such cases immunohistochemical techniques can be used, with anti-CD3 antibodies to quantify the IELs, or the use of tenascin to evaluate the subepithelial collagen band.

***LE**: Low; **GR:** Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Conventional staining might not suffice to establish a firm diagnosis, either because histological changes consistent with both CC and LC are detected, or because the diagnostic criteria of MC are not met [i.e. incomplete forms (MCi) may be involved]. The expression of markers such as CD25 and FOXP3 in MCi differs from that seen in CC and LC, and this might be useful in diagnostic terms.[169] However, further studies are needed to confirm this observation.

In the case of LC, immunohistochemical anti-CD3 staining may facilitate IEL counting.[161] Nevertheless, it must be taken into account that there is a risk of overdiagnosing MCi or LC if the origin of the biopsies is not considered, since under normal conditions the inflammatory infiltrate of the *lamina propria* is greater in the mucosa of the proximal colon than in the distal colon.[161, 162] Likewise, it must be taken into account that the optimum cut-off point in IEL count using anti-CD3 antibodies has not been established.

The selective accumulation of tenascin at subepithelial level facilitates the distinction between CC and LC vs. other types of colitis, and could allow the diagnosis of incipient cases. However, pathologist experience with these techniques is not very extensive, and no cut-off point has been established.[10, 161, 170] A retrospective

study including 35 cases of CC, 35 cases of LC, 28 cases of nonspecific inflammation, and 18 controls has suggested that tenascin can be useful in doubtful cases with a collagen band thickness within the limit of normal.[92]

Is the determination of calprotectin in faeces useful for the diagnosis or follow-up of MC?

Recommendation 6:

To date, the determination of calprotectin in faeces has not been found to be useful in diagnosing or following-up on patients with MC.

***LE**: Low; **GR**: Weak; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Different studies have examined the usefulness of faecal markers in screening for MC[149, 171–179] (Table S9). The most widely used marker is faecal calprotectin. However, the existing series involve a very limited number of patients, and the methods and cut-off points used differ. Furthermore, there are contradictory results. In effect, while some studies have found 60–75% of the patients with active CC to have elevated faecal calprotectin levels,[171, 175, 176, 178] another study has reported no differences between active CC and a control group with chronic watery diarrhoea.[149]

Other stool markers have offered promising results (Table S9). In this regard, it has been suggested that eosinophil cationic protein in faeces could offer better discrimination of clinical disease activity than faecal calprotectin.[176] Tryptase, eosinophil protein X and myeloperoxidase also could differentiate MC from IBS.[174]

Pharmacological treatment

What treatment is recommended for the induction of clinical remission in patients with collagenous colitis?

Recommendation 7:

Treatment with oral budesonide is recommended to induce clinical remission in patients with CC.

***LE**: High; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

A meta-analysis conducted in 2011 with the aim of assessing the efficacy of budesonide vs. placebo in the induction of clinical response among patients with MC included three randomised clinical trials in patients with CC.[180] The analysis of the subgroup of patients with CC showed budesonide to be more effective than placebo, since the percentage of patients with clinical response was significantly higher (76% with budesonide vs. 16% with placebo; RR 4.45; 95% CI: 2.36–8.39).

A new randomised clinical trial has recently been published, evaluating the efficacy of 9 mg of budesonide vs. placebo in patients with CC. Evaluation was made of clinical remission (≤3 liquid faeces a day) in week 8 of treatment. A total of 92 patients were included (25 administered mesalazine, 30 treated with budesonide and 30 administered placebos). At the end of 8 weeks of treatment, 80% of the patients in the budesonide group and 44% of those receiving mesalazine showed clinical remission ($P = 0.0035$), vs. 59.5% of those receiving placebo.[181]

The results of this study support the efficacy of budesonide in inducing symptom remission in patients with this disease. Figure 1 shows the updated meta-analysis which includes the four clinical trials that compare the efficacy of budesonide vs. placebo in inducing clinical response in patients with CC.[125, 126, 181, 182] As can be seen, budesonide was seen to be effective in reducing remission in 78% of the patients, while remission was observed in 26% of those administered placebo. The OR for this comparison was 3.06 (95% CI: 2.09–4.48). No serious adverse effects were reported in any of the four studies.

In sum, it is concluded that oral budesonide is the drug of choice for inducing clinical response in patients with CC.

What treatment is recommended for the induction of clinical remission in patients with lymphocytic colitis?

Recommendation 8:

Treatment with oral budesonide is recommended to induce clinical remission in patients with LC.

***LE**: Moderate; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

In the sub-analysis of patients with LC included in a previously published meta-analysis including two studies and with the principal aim of evaluating the clinical response of patients with MC to treatment with 9 mg/day of oral budesonide during 6–8 weeks, the subjects administered budesonide were seen to have a higher clinical response rate than those who received placebo. There were 32 patients in the active treatment group and 25 in the placebo group. The response rate in the budesonide group was 88% vs. 44% in the placebo group (RR 2.03; 95% CI: 1.25–3.33) (Figure 2).[180] The drug was well tolerated, and no serious adverse effects were reported in either of the two studies.

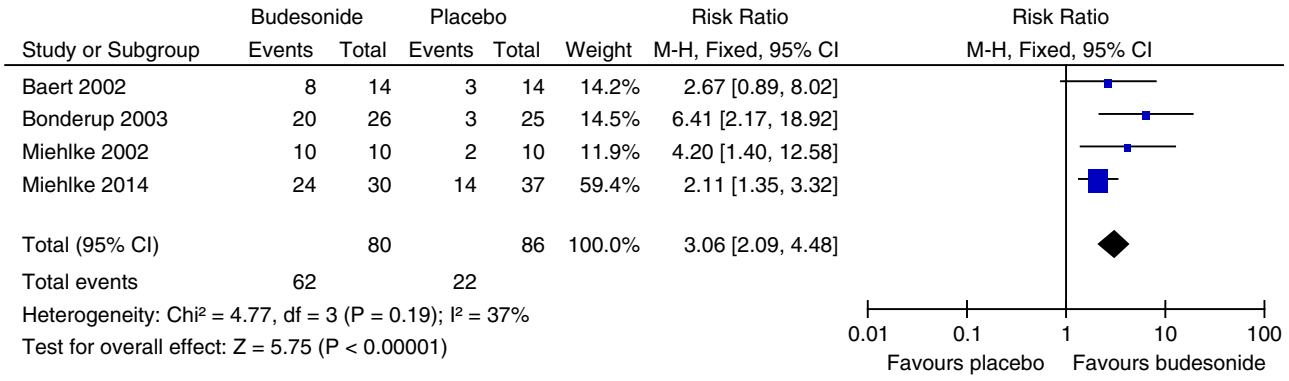

Figure 1 | Meta-analysis of trials comparing the efficacy of oral budesonide vs. placebo in inducing clinical response in patients with collagenous colitis.

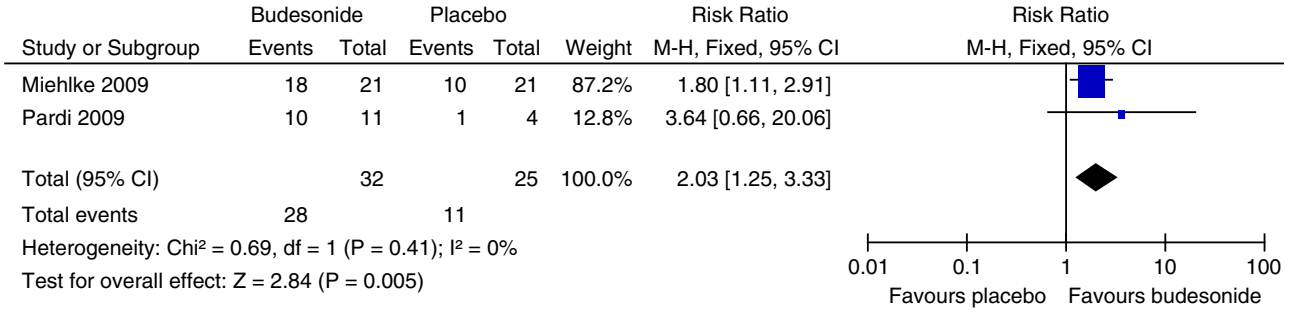

Figure 2 | Meta-analysis of trials that comparing the efficacy of oral budesonide vs. placebo in inducing clinical response in patients with lymphocytic colitis.

In sum, the available evidence supports the use of oral budesonide, compared with placebo, for inducing clinical response in patients with LC. Nevertheless, the existing experience is very limited, and further studies are therefore needed to confirm these promising results.

What treatment is most effective for maintaining clinical remission in patients with MC?

Recommendation 9:

Oral budesonide is effective in maintaining remission in patients with CC who have previously responded to the drug.

***LE**: Moderate; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

A meta-analysis published in 2011 evaluated the efficacy of long-term budesonide in the maintenance of clinical response among patients with CC.[180] Two randomised clinical trials published up until that time were included. Both studies included patients with CC who presented clinical disease activity (≥3 liquid faeces a day), and who in a first open-label phase received 9 mg/day of budesonide during 6 weeks.[134, 183] The patients found to be in clinical remission in week 6 (≤3 liquid faeces a day) were randomised to 6 mg/day of budesonide as maintenance therapy during 24 weeks, or placebo. In the first study, 48 patients were treated with 9 mg/day of budesonide during 6 weeks.[183] Ninety-six per cent of the patients achieved clinical remission in week 6, and these individuals were then randomised to 6 mg/day of budesonide as maintenance therapy, or placebo, during 24 weeks. At the end of the 24-week period, the patients treated with budesonide had a lower relapse rate compared with placebo (26% and 65% respectively; $P < 0.022$). The second study included 42 patients with active CC who were treated for 6 weeks with 9 mg/day of budesonide.[134] A total of 34 patients in clinical remission in week 6 were randomised to 6 mg/day of budesonide as maintenance therapy, or placebo, during 24 weeks. At the end of follow-up, 76% of the patients in the budesonide group and 12% of those administered placebo showed clinical remission ($P < 0.001$). After the 24 weeks of mainte-

nance therapy, the follow-up of both patient groups was extended for a further 24 weeks. After 48 weeks, the remission rate was 24% among the patients who received budesonide, vs. 12% in the placebo group. The mean time to clinical relapse after treatment discontinuation was 39 days for the patients who received budesonide (6 weeks of induction plus 24 weeks of maintenance treatment) and 38 days in the placebo group.

A very recent placebo-controlled clinical trial has evaluated the efficacy of 4.5 mg/day of budesonide in maintaining clinical remission in patients with CC.[184] The study included a total of 92 patients who had achieved remission after 8 weeks of therapy with 9 mg/day of budesonide. Of these 92 patients, 44 were randomised to maintenance treatment with budesonide at an average dose of 4.5 mg/day (the doses were 6 and 3 mg/day on alternating days) during 52 weeks, followed by discontinuation, while 48 received placebo. After discontinuation of budesonide, the patients were followed up on for 24 weeks. A total of 61.4% (27/44) of the patients in the budesonide group and 16.7% (8/48) of those in the placebo group maintained remission after 52 weeks of treatment ($P < 0.001$). After 24 weeks of follow-up without treatment, 82% of the patients who had received budesonide suffered relapse.

None of the three studies published to date recorded serious adverse effects, and budesonide was well tolerated in all of them.

No studies have examined the efficacy of maintenance treatment with budesonide in patients with LC.

Figure 3 shows the results of the meta-analysis of the three studies that compare the efficacy of budesonide vs. placebo in the maintenance of remission in patients with CC.

In sum, oral budesonide is effective in maintaining clinical remission in patients with CC. However, the clinical relapse rate after treatment discontinuation is very high.

Is mesalazine effective in the induction of clinical remission in patients with collagenous colitis?

Recommendation 10:

Oral mesalazine is not recommended in patients with CC for the induction of clinical remission.

***LE**: Moderate; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Although oral mesalazine is widely used for the treatment of MC, its efficacy information was based on observational studies and case series. A very recent randomised clinical trial has evaluated and compared the efficacy of 3 g/24 h of mesalazine and 9 mg/day of budesonide in the induction of clinical remission in patients with CC, vs. placebo.[181] Evaluation was made of clinical remission (≤3 liquid faeces a day) in week 8 of treatment. A total of 92 patients were included (25 administered mesalazine, 30 treated with budesonide, and 30 administered placebo). At the end of 8 weeks of treatment, 44% of the patients in the mesalazine group and 80% of those administered budesonide showed clinical remission ($P = 0.0035$), vs. 59.5% of those administered placebo.

Percentage clinical remission with mesalazine in this clinical trial was similar to that reported in other observational studies that have included relatively large patient samples.[185–187] However, in this latter (randomised) study, mesalazine was not superior to placebo – thus indicating that the drug is ineffective in inducing clinical remission in patients with CC.

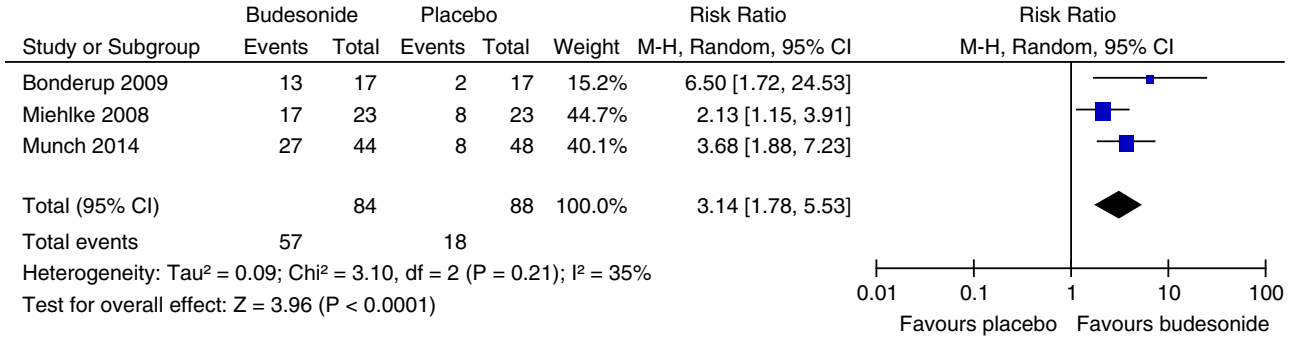

Figure 3 | Meta-analysis of trials comparing the efficacy of oral budesonide vs. placebo in the maintenance of clinical remission in patients with collagenous colitis.

In sum, it is concluded that oral mesalazine is ineffective in inducing clinical remission in patients with CC, and therefore should not be used.

Is mesalazine effective in the induction of clinical remission in patients with lymphocytic colitis?

Recommendation 11:

There is not enough evidence to recommend oral mesalazine for the induction of clinical remission in patients with LC.

***LE**: Low; **GR**: Weak; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Regarding LC, a randomised clinical trial (although without a placebo group) has compared the efficacy of treatment during 6 months with mesalazine in monotherapy vs. mesalazine with cholestyramine for the induction of clinical response in patients with active MC (41 subjects with LC and 23 with CC).[187] Eighty-five per cent of the patients with LC (18 administered mesalazine with cholestyramine and 17 treated with mesalazine alone, $P < 0.05$) and 91% of the patients with CC achieved clinical and histological disease remission after 6 months of therapy. However, the results of this study must be interpreted with caution, since as has been mentioned, no placebo group was included.

In an observational study including patients with active LC and CC treated with mesalazine, the percentage of responders was significantly greater in the LC group than in the CC group (86% vs. 42%, $P = 0.005$).[186]

In sum, there is not enough evidence to recommend oral mesalazine for the induction of clinical response in patients with LC, since no placebo-controlled clinical trials have evaluated the efficacy of the drug in the induction of clinical response in patients with this disease.

Is loperamide useful in the treatment of microscopic colitis?

Recommendation 12:

The use of loperamide is suggested in cases of mild MC, since it reduces the frequency of stools and the incontinence, thereby improving patient health-related quality of life.

***LE**: Low; **GR**: Weak; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Despite the widespread use of loperamide in patients with MC, no controlled studies have been made, and the information on its efficacy is based on published case series [71, 188] and retrospective reviews,[185, 189, 190] describing response rates of over 70%, with no serious adverse effects. In a retrospective review including 163 patients, loperamide was found to be effective in 49 of 63 individuals (71%), although high doses of up to 4 mg three times a day were needed, and treatment had to be discontinued in two cases (2.9%) because of adverse effects. Although the quality of the evidence is low, and it is unlikely that loperamide can act upon inflammation of the colonic mucosa, the use of this drug at a dose of 2–16 mg/day as an antidiarrhoeal agent may be useful in that it reduces the frequency of faeces and attenuates the effects of incontinence – thereby improving patient HRQoL.

Is cholestyramine useful in the treatment of microscopic colitis?

Recommendation 13:

Cholestyramine can be useful in patients with MC, regardless of whether there is concomitant BAM or not.

***LE**: Low; **GR**: Weak; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The possible implication of BAM in the pathogenesis of MC has been discussed under Recommendation 9 of the present guide. Cholestyramine could play a role in the management of MC not only because of its bile acid-binding capacity but also because the drug adheres to bacterial toxins, which have also been suggested to exert an effect particularly in the pathogenesis of CC.[185] Perhaps for this reason the studies that have evaluated the role of cholestyramine in the treatment of this disease have suggested its possible efficacy (20–66%) independently of whether there is concomitant BAM or not.[71, 107, 186]

In the only available controlled study, Calabrese *et al.* described a series of 64 patients with MC (41 with LC and 23 with CC) randomised to mesalazine or mesalazine with cholestyramine during 6 months (open-label design without a placebo group).[187] The clinical and histological response rates reached 85.36% in the patients with LC and 91.3% in those with CC. In the patients with CC, combination treatment (mesalazine with cholestyramine) was found to be significantly better than mesalazine alone. However, the study design does not allow the exclusion of bias, and moreover a recent randomised, double-blind trial has shown mesalazine to be ineffective in inducing clinical remission in patients with CC.[181]

Considering the high response rate without serious adverse effects, it is suggested that cholestyramine might be an alternative in the management of MC, particularly CC. Controlled studies involving large patient series are needed to further assess the hypothetical benefits of this treatment.

Is octreotide useful in the treatment of microscopic colitis?

***Recommendation 14**:*

Treatment with octreotide can be useful in selected cases of severe watery diarrhoea secondary to CC that fail to respond to conventional treatment.

***LE**: Very low; **GR**: Weak; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Octreotide is a synthetic somatostatin analogue that exerts an inhibitory effect upon all the hepatobiliopancreatic and digestive tube secretions, reducing the secretory volume in the small bowel and colon, and prolonging colonic transit. Based on these mechanisms, it has been suggested that octreotide might offer benefit in severe cases of secretory diarrhoea associated to MC. There is some experimental evidence that octreotide may in fact reduce mucosal damage in cases of experimental colitis.[191]

However, the only evidence of potential benefit from octreotide in MC comes from an anecdotal case description published in 1996.[192] This case suggests that the drug might play a role in severe watery diarrhoea associated to CC, and thus would deserve to be investigated in the context of well-designed studies.

Can anti-TNF-alpha drugs be regarded as rescue treatment in patients with microscopic colitis refractory to corticosteroids and immunomodulators?

***Recommendation 15**:*

The use of anti-TNF-alpha drugs (infliximab, adalimumab) is recommended for the induction of remission in severe cases of MC that fail to respond to corticosteroids and immunomodulators, as an alternative to colectomy.

***LE**: Low; **GR**: Strong; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

The prevalence of severe MC refractory to treatment with corticosteroids and/or immunomodulators is relatively low. The literature therefore does not contain many studies on the effects of anti-TNF-alpha therapy in application to this disease. The existing information is limited to four case series,[193–196] only one of which involved a prospective design, with no control group in any of them, and comprising a total of 10 reported cases: 6 patients with CC and four with LC. All the patients had severe clinical manifestations and were refractory to treatment with budesonide and immunomodulators. Six patients initially received infliximab (IFX) and three were treated with adalimumab (ADA), at the doses usually employed for inducing remission in IBD (5 mg/kg in weeks 0, 2 and 6 for IFX and 160, 80 and 40 mg in weeks 0, 2 and 4 for ADA). Four of the patients initially administered IFX required switching to ADA: two because of a loss of response and two because of hypersensitivity to the anti-TNF-alpha drug. One of the patients administered ADA showed poor tolerance (abdominal pain and vomiting) requiring treatment discontinuation. One of the patients who received ADA due to allergy to IFX failed to respond to the treatment and was referred to colectomy. Thus, clinical and histological disease remission, and measurable improvement of the HRQoL indexes, was achieved in 8 of the 10 patients treated with anti-TNF-alpha drugs. At least one of the studies showed the response to be sustained after 1 year of treatment.[193]

The few data available in the literature suggest that anti-TNF-alpha drugs could be an alternative to colectomy in patients with severe MC refractory to corticosteroid therapy. Well-designed prospective trials are needed to confirm the efficacy and safety of this type of treatment over the long term.

Are antibiotics useful in the treatment of microscopic colitis?

***Recommendation 16**:*

Antibiotics are not recommended for the treatment of MC.

***LE**: Low; **GR**: Strongly against; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

There are no controlled clinical studies in this regard. A large retrospective clinical review has been made,[71] pooling 163 patients with CC, in which the authors describe an overall antibiotic response rate of 60%. Forty-four patients received metronidazole, which proved effective in 24 cases (54%). It should be noted that 9% of the patients developed some kind of adverse effect. Erythromycin was administered to 15 patients,

with a clinical response in 10 cases (66%). Lastly, eight patients received penicillin G, with a response rate of 100%. The authors offered no information on concomitant treatments, the relapse rate after antibiotic discontinuation, or the dosing regimens used.

Another retrospective review,[131] evaluated 199 patients with LC. Metronidazole was administered to 23 patients, of which 14 showed clinical responses (61%), with a 9% incidence of adverse effects. Among the 14 responders, six relapsed 1 month after treatment discontinuation.

In sum, on considering the quality of the available scientific evidence, and the adverse effect rates, it is concluded that antibiotics cannot be recommended for the treatment of MC.

Is bismuth subsalicylate useful in the treatment of microscopic colitis?

Recommendation 17:

The use of bismuth subsalicylate could be considered in patients with MC, as treatment for the induction of clinical remission.

***LE**: Low; **GR**: Weak in favour; **Agreement**: 100%, votes: strongly agree (7%), quite agree (97%).*

Summary of the evidence

The available evidence on the use of bismuth subsalicylate for the induction of remission in patients with MC is scarce. Mention should be made of a double-blind clinical trial,[197] published in abstract format, which included nine patients with CC and five with LC, administered three 262 mg tablets three times a day during 8 weeks. No adverse effects were reported. Of the four patients with CC who received the treatment, a full 100% responded (100%; 95% CI: 38–100) vs. none of the patients administered placebo (0%; 95% CI: 0–49; $P = 0.03$). Of the three patients with LC who received bismuth subsalicylate, a full 100% responded (100%; 95% CI: 38–100) vs. none of the patients administered placebo (0%; 95% CI: 0–71; $P = 0.10$). From the histological perspective, two of the three patients who received the drug responded (67%; 95% CI: 20–94) vs. one of the patients administered placebo (50%; 95% CI: 9–91; $P = 0.71$).

It is therefore concluded that bismuth subsalicylate could offer benefit as second line treatment for MC, following failed treatment with budesonide. Caution must be exerted in elderly patients, where the drug safety profile is poorer. Bismuth subsalicylate is not marketed in Spain and in other European countries.

Are probiotics useful in the treatment of microscopic colitis?

Recommendation 18:

The use of probiotics for inducing clinical remission in MC is not recommended.

***LE**: Moderate; **GR**: Weak against; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

Regarding the use of probiotics in MC, a single randomised, double-blind and placebo-controlled trial has been carried out in patients with CC.[198] The treatment consisted of *Lactobacillus acidophilus* LA-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12 (AB-Cap-10) during 12 weeks. Twenty-one patients received the probiotic treatment and eight received placebo. Clinical response was determined in week 12 of treatment, defined as a decrease in at least 50% in the number of faeces. This decrease was recorded in 23% of the patients in the probiotic group and in 13% of those administered placebo. Statistical significance was not reached. There were no differences in the histopathological findings or in faecal consistency. It should be mentioned that the number of patients with CC that had to be included in the statistical analysis was 45.

Another open-label study administered *Escherichia coli* of the Nissle 1917 strain to 14 patients with CC.[199] A response was noted in 64% of the patients, with a 50% reduction in the frequency of bowel movements.

There are no clinical trials warranting probiotic use for inducing remission in patients with LC.

Is azathioprine useful for the induction of clinical remission in patients with microscopic colitis who are corticosteroid-dependent or fail to respond to corticosteroids?

Recommendation 19:

In patients with MC who are corticosteroid-dependent or fail to respond to corticosteroids, azathioprine is suggested for the induction of clinical response.

***LE:** Low; **GR**: Weak in favour; **Agreement:** 100%, votes: strongly agree (100%).*

Summary of the evidence

The effect of thiopurines upon CC has been evaluated in small patient series. One case series included nine patients who were corticosteroid-dependent or failed to respond to corticosteroids, and reported an 89% response rate allowing corticosteroid discontinuation.[200]

Another series described 6 corticosteroid-dependent patients.[201] Three of them responded and three suffered intolerance. Mention should be made of a retrospective case series including 46 patients with MC (32 with CC and 14 with LC) who were corticosteroid-dependent or did not tolerate corticosteroids.[202] In this study, 13 of the patients (28%) showed a long-term clinical response to azathioprine. Thirty-one patients experienced intolerance (67%), and in two cases the thiopurine drug proved ineffective (4%). Thirteen of the 31 patients that did not tolerate azathioprine were switched to mercaptopurine (6-MP), obtaining clinical remission in six cases (46%). The overall thiopurine response rate in this study was therefore 41%. The study reported the overall response rate without distinguishing between CC and LC.

On the basis of these results, it is concluded that azathioprine/6-MP may be effective in patients with MC who are corticosteroid-dependent or fail to respond to corticosteroids. The GR is weakly in favour, considering that thiopurines are drugs with a relevant incidence of adverse effects.

Is methotrexate useful for the induction of clinical remission in patients with microscopic colitis?

Recommendation 20:

The use of methotrexate for inducing clinical remission in MC is not recommended.

***LE**: Low; **GR**: Strong against; **Agreement**: 100%, votes: strongly agree (100%).*

Summary of the evidence

There is conflicting scientific evidence regarding the results of methotrexate as treatment for CC. Mention should be made of a retrospective series[203] in which 19 patients received methotrexate at a mean daily dose of 7.5–10 mg via the oral route. It is not possible to know whether these patients were receiving some other concomitant drugs, although they had received different treatments in the past. Of the 19 patients, 16 (84%) showed complete or partial clinical response. Colonoscopy with control biopsies was performed in 10 of the 19 patients. Of these, five showed regression of the histological changes, two only showed improvement and three experienced no changes.

In an open-label study,[204] nine patients with CC refractory to budesonide were administered methotrexate at a dose of 15 mg a week via the subcutaneous route, for a total of 6 weeks. In the absence of a response, the dose was increased to 25 mg a week for another 6 weeks. Of the nine patients included, five completed the treatment protocol and four suffered adverse effects. No patient achieved clinical remission.

No quality scientific evidence has been published on the use of methotrexate for treating LC. In view of the published data, it is concluded that methotrexate is not indicated for the induction of clinical response in patients with MC. The strength of the recommendation is moreover strong, taking into account that methotrexate is not free from adverse effects.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Population-based studies on the incidence and prevalence of collagenous colitis and lymphocytic colitis.

Table S2. Criteria for the 'ideal' incidence study.

Table S3. Population-based studies on collagenous and lymphocytic colitis in relation to mean age and analysis of age as a risk factor.

Table S4. Differences in the incidence of collagenous colitis and lymphocytic colitis between males and females: Results of the population-based epidemiological studies.

Table S5. Studies on the frequency of LC and CC in patients with a history of chronic or intermittent watery diarrhoea (only studies with a sample size of ≥150 patients).

Table S6. Causality criteria proposed by the World Health Organisation (WHO) to assess an adverse drug reaction.

Table S7. Observational case–control studies on the association of microscopic colitis to drug exposure.

Table S8. Key histological findings in collagenous colitis and lymphocytic colitis.[161]

Table S9. Faecal markers in microscopic colitis.

AUTHORSHIP

Guarantor of the article: FF-B.

Author contributions: FF-B was the coordinator of the study and written the final version of the article. FF-B, MJC, JPG were the responsible of the study conception and design. All authors contributed equally in the literature search, analysis and interpretation of information, writing and voting the recommendations.

All authors reviewed and accepted the final version of the article.

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