UNIVERSIDADE BEIRA INTERIOR

Microscopic colitis: a clinical review

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Dissertação para obtenção do Grau de Mestre em

Medicina

(mestrado integrado)

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janeiro de 2025

Declaração de Integridade

Eu, Jani Alexandra Saldanha Pombo Lang, que abaixo assino, estudante com o número de inscrição 43343 do Mestrado Integrado em Medicina da Faculdade Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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Universidade da Beira Interior, Covilhã 6 / 1 / 2025

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Agradecimentos

A realização desta tese marca o fim de um ciclo que jamais seria possível sem o apoio e o carinho das pessoas mais importantes da minha vida.

Primeiramente, gostaria de agradecer ao meu orientador, Dr. Pedro Marcos, pela sua disponibilidade ao longo da realização deste trabalho.

Quero expressar a minha mais profunda gratidão à minha família, sobretudo aos meus pais, que foram o meu alicerce em todos os momentos. À minha mãe, que além de ser o meu porto seguro, é também a minha melhor amiga, o meu exemplo e a minha inspiração, dedico um agradecimento especial. A tua força, paciência e amor incondicional foram e sempre serão o meu maior incentivo.

Aos meus amigos, que estiveram ao meu lado em todas as etapas desta caminhada, o meu mais sincero obrigado. Vocês foram a minha rede de apoio nos momentos difíceis e os responsáveis por tantos momentos de alegria e motivação. Um agradecimento especial à Beatriz, à Guida, às Anas, à Kika, ao Kiko e à Catarina, por estarem sempre presentes, por me ouvirem e por tornarem o percurso na Covilhã mais leve e cheio de memórias inesquecíveis. Por me fazerem entender que o que torna um sítio bom também são as pessoas.

Obrigada também aos que me apoiaram desde Bragança, em especial à Mafalda e à Daniela.

Ao Zé, que nunca deixou de acreditar em mim. A tua confiança no meu potencial e a tua capacidade de me motivar a ser melhor foram fundamentais.

A todos vocês, deixo o meu mais profundo agradecimento. Esta conquista também é vossa.

Abstract

Introduction: Microscopic colitis (MC) is a growing inflammatory bowel disease (IBD) that significantly impacts patients' quality of life but remains underrecognized. Therefore, we proposed conducting a clinical review to summarize the available data regarding this condition.

Methods: Review the published literature in PubMed. Systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case-control studies, expert reviews, and guidelines were prioritized for analysis.

Results: MC is characterized by chronic, watery, non-bloody diarrhea. Diagnosis involves ileocolonoscopy with biopsies from both the right and left colon. Collagenous colitis is identified by a collagen band thickness of 10 micrometers (μm) or more, while lymphocytic colitis has at least 20 intraepithelial lymphocytes (IEL) per 100 epithelial cells and a collagen band thickness of less than 10 μm. Both types show increased inflammatory infiltrate in the lamina propria. Incomplete MC includes cases with 10 to 20 IELs per 100 epithelial cells and a collagen band thickness between 5 and 10 μm. Treatment for MC typically involves avoiding triggers and taking budesonide, 9 mg daily for 6 to 8 weeks, with regular follow-up care needed for patients.

Conclusions: Significant progress has been made in understanding MC. This review summarizes the current knowledge and provides a clear overview of the management of this condition.

Keywords

Microscopic colitis; Collagenous colitis; Lymphocytic colitis; Inflammatory bowel disease; Colitis.

Resumo

Introdução: A colite microscópica (CM) é uma doença inflamatória intestinal (DII) cada vez mais prevalente e que impacta significativamente a qualidade de vida dos doentes, mas frequentemente esquecida. Esta revisão tem como objetivo resumir os dados disponíveis sobre a abordagem da CM.

Métodos: Revisão da literatura publicada na PubMed. Revisões sistemáticas, meta-análises, ensaios clínicos randomizados, estudos de coorte, estudos caso-controlo, revisões por *experts* e guidelines foram preferidas para análise.

Resultados: A CM é caracterizada por diarreia crónica, aquosa e não sanguinolenta. O seu diagnóstico envolve a realização de uma colonoscopia total com ileoscopia e biópsias do cólon direito e esquerdo. A colite colagenosa é identificada por uma espessura da banda de colagénio superior ou igual a 10 micrómetros (μm), enquanto a colite linfocítica apresenta pelo menos 20 linfócitos intraepiteliais (LIE) por cada 100 células epiteliais e uma espessura da banda de colagénio inferior a 10 μm. Ambos os tipos apresentam um aumento do infiltrado inflamatório na lâmina própria. A CM incompleta inclui casos com 10 a 20 LIEs por 100 células epiteliais e uma espessura da banda de colagénio entre 5 e 10 μm. O tratamento da CM envolve evitar fatores desencadeantes e tomar budesonida 9 mg por dia durante 6 a 8 semanas, sendo necessário um seguimento regular dos doentes.

Conclusões: Têm sido feitos progressos significativos na compreensão da CM. Esta revisão resume os conhecimentos atuais e fornece uma visão geral sobre a abordagem desta doença.

Palavras-chave

Colite microscópica; Colite colagenosa; Colite linfocítica; Doença inflamatória intestinal; Colite.

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Abbreviations List

ANAs	Antinuclear Antibodies
CC	Collagenous Colitis
H&E	Haematoxylin and eosin
HLA	Human Leukocyte Antigen
HRQL	Health-related Quality of Life
IBD	Inflammatory Bowel Disease
IELs	Intraepithelial Lymphocytes
IFNγ	Interferon Gamma
IL	Interleukin
LC	Lymphocytic Colitis
MC	Microscopic Colitis
MCi	Incomplete Microscopic Colitis
NSAIDs	Non-steroid anti-inflammatory drug
OR	Odds Ratio
TNF	Tumour necrosis factor

1. Introduction

Chronic diarrhea is a common issue encountered in both primary care and hospital settings. It is defined as the passage of loose or liquid stools, an urgent need to evacuate, or an increased frequency of stools that lasts for more than four weeks. It is estimated that more than 5% of the population suffers from chronic diarrhea (1). The causes can vary significantly, so it is crucial to perform a thorough medical history review and physical examination when evaluating these patients (2).

Microscopic colitis (MC) is an emerging cause of chronic diarrhea, recognized as an inflammatory bowel disease (IBD) that significantly affects patients' health-related quality of life (HRQL) (3). This condition is characterized by chronic, watery, non-bloody diarrhea and the absence of endoscopic changes in the colon and rectum. Typical histological findings in biopsies enable diagnosis and differentiation between the two main subtypes: collagenous colitis (CC) and lymphocytic colitis (LC). It is important to note that incomplete forms may also occur (3). Due to the limited guidelines for this condition and its under-recognition, we proposed conducting a brief review of the clinical manifestations, diagnosis, and management of MC. To gather references for this review, we searched MEDLINE via PubMed using the following query: (microscopic[Title] OR collagenous[Title] OR lymphocytic[Title]) AND colitis[Title]. Systematic reviews, meta-analyses, randomized controlled trials, cohort studies, case-control studies, expert reviews, and clinical guidelines were prioritized for analysis.

2. Epidemiology

The overall incidence rate of MC is around 11.4 cases per 100,000 person-years. When considering CC or LC specifically, the incidence ranges from 0.6 to 16 cases per 100,000 person-years for both conditions (3).

This disease exhibits geographic variations, with the highest prevalence in northern Europe (3). The true incidence of MC has sharply increased in recent decades. Studies indicate that MC is now almost as common as classic IBD. This increase may be due to the rise in multiple colonic biopsies performed during routine colonoscopies for chronic diarrhea, and it could also be linked to greater exposure to specific disease-related risk factors (3). The highest occurrence of MC typically happens around age 60 and is significantly more prevalent in women, with a female-to-male ratio as high as 9:1 (4). However, up to 25% of patients diagnosed with CC are under 45 years old, and there have even been a few reported cases in children (5,6).

3. Etiopathogenesis

The development of MC is a complex process influenced by various factors. Although the exact mechanisms remain unclear, research has identified key pathways that contribute to its onset and progression, which are described below.

3.1. Genetic predisposition

Genetic predisposition may play a role in the development of MC, as evidenced by familial clustering and its association with specific human leukocyte antigen (HLA) haplotypes (5,6). Studies on HLA have shown a connection between MC and the HLA-DQ2 or DQ 1/3 haplotypes. Additionally, individuals with MC have a higher frequency of the HLA-DR3DQ2 haplotype and are more likely to carry the tumor necrosis factor (TNF) 2 allele compared to control subjects (7,8). This genetic predisposition may impact the immune response in the colonic mucosa, making individuals more susceptible to inflammation. This may also explain the observed variation in geographic distribution among families affected by MC. In contrast to Crohn's disease, no functional polymorphism has been detected in the NOD2/CARD15 gene concerning MC (6,8).

3.2. Immune response

Lines of evidence regarding the pathogenesis of MC indicate that both CC and LC are immune-mediated conditions primarily involving the adaptive immune system and cytotoxic responses. Studies have shown an increase in intraepithelial lymphocytes (IELs) and thickening of the subepithelial collagen layer, with the latter observed only in CC (9). A prominent hypothesis is that MC results from a chronic inflammatory response to self-antigens, suggesting an autoimmune origin. The prevalence of MC is higher in females, like other autoimmune diseases. Additionally, antinuclear antibodies (ANAs) have been identified as markers of autoimmunity in MC (10). There is an association between MC and various autoimmune diseases, including autoimmune thyroiditis, rheumatoid arthritis, type 1 diabetes, disorders of the connective tissue, and celiac disease (7). It is known that individuals with MC have a 6.1 times higher odds ratio (OR) of developing celiac disease compared to those without MC (11).

MC is characterized by the infiltration of oligoclonal CD8+ lymphocytes in the colonic epithelium, along with cytotoxic T cells and T helper cells in the lamina propria (4). In active disease, there is an increase in Ki67+ staining, indicating heightened cell proliferation related to inflammation (4). Both CC and LC also show upregulation of chemokines and interleukins (IL), such as IL-6, IL-23, IL-17a, IL-21, and IL-22, compared

to controls (11). TNF and interferon-γ (IFNγ) increase epithelial barrier permeability, highlighting innate immunity's role. Additionally, IL-37 activity is found to be reduced in patients with MC and ulcerative colitis, suggesting decreased production of anti-inflammatory cytokines (12).

3.3. Environmental factors

Research has demonstrated that smokers typically develop MC approximately ten years earlier than non-smokers (7). Both current and former smokers face increased risk, with current smokers exhibiting a greater likelihood (with an OR of around 3 for developing MC compared to non-smokers and former smokers) (13). Former smoking is also linked to an increased risk of MC, with an OR of 1.6 (3).

When it comes to medication, the criteria for identifying a high likelihood of drug-induced diarrhea include the timing of diarrhea onset to drug exposure, improvement of symptoms after stopping the medication, and recurrence of symptoms upon re-exposure to the drug (8). Research has established a connection between certain medications and the risk of MC. Notable findings include: non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, which has an OR of 2.84 and an overall OR of 1.79; selective serotonin reuptake inhibitors have an OR of 2.34; beta-blockers have an OR of 2.0; statins show an OR of 1.12; proton pump inhibitors (PPIs) have varying OR, with lansoprazole having an OR of 9.57 and omeprazole with an OR of 2.49. Other medications and their respective OR are as follows: benzodiazepines - OR of 1.04; angiotensin-converting enzyme inhibitors - OR of 1.52; histamine H2 antagonists - OR of 1.31. These findings highlight the potential association between these medications and an increased risk of MC (14).

3.4. Gut microbiota

Dysbiosis may contribute to the development of MC (13). Changes in gut bacteria can increase the permeability of the intestinal barrier, allowing luminal antigens to trigger an inflammatory process in genetically susceptible individuals (6). A significant decrease in *Akkermansia* species was observed in MC patients compared to healthy controls. This bacterium thickens the colonic mucin layer, and its reduction exposes the epithelium to harmful components in the fecal stream (5). Fecal analysis revealed an altered microbial composition, with fewer members of the *Ruminococcaceae* family in patients with CC, similar to findings in IBD (15).

3.5. Bile acid malabsorption

Bile acid malabsorption, which can occur secondary to ileal resections, is relatively common in patients with MC, with a prevalence of about 44% in both CC and LC (8). When bile acids are not reabsorbed in the small intestine, they can reach the colon, leading to secretory diarrhea by stimulating colonic epithelial cells. This process contributes to mucosal injury, inflammation, collagen deposits, and villous atrophy, worsening the symptoms of MC and may act as a potential trigger for its development (6).

4. Clinical manifestations

The clinical presentations of LC and CC are pretty similar, making it impossible to distinguish between the two based on clinical observations. However, some reports suggest that symptoms in LC may be milder and more likely to resolve compared to those in CC (8). Both conditions result in chronic or recurrent watery, non-bloody diarrhea, which is reported by 84-100% of patients (3). Additionally, common accompanying symptoms include fecal urgency (55%), nocturnal stools (35%), and fecal incontinence (26%) (3,7). Less commonly reported symptoms vary in frequency across studies and include abdominal pain, weight loss, and bloating (3,7). Findings from several studies indicate an average of 6 to 7 bowel movements per day. In one-third of cases, the onset of diarrhea is acute, and it persists for at least 6 months before a diagnosis is made in 43% of patients (3). The onset of the disease can be sudden in 40% of cases, mimicking an enteric infection (5,16). The clinical course of MC is generally chronic, though some patients may experience a single episode and achieve remission after removing the trigger and/or receiving proper treatment (8). Anxiety and depression have also been reported in patients with MC, probably due to the relevant impact of symptoms on their HRQL (12). The presence of associated autoimmune diseases has been documented in over 30–50% of cases (6). Severe dehydration and the presence of mucus or blood in the stool are rare (8).

5. Differential diagnosis

The differential diagnosis of MC includes various other causes of chronic diarrhea. These may include irritable bowel syndrome, celiac disease, bile acid malabsorption, lactase deficiency, ulcerative colitis, Crohn's disease, colorectal neoplasia, dietary factors (such as excessive consumption of artificial sweeteners, caffeine, or alcohol), and infections, among other less common causes (3,5,6). Typically, these conditions can be distinguished from MC through patient history, laboratory evaluations, imaging studies, and both upper and lower digestive endoscopy with biopsies.

6. Diagnosis

To diagnose MC, ileocolonoscopy should be performed with biopsies (3). It is recommended to obtain two biopsies from the right colon (ascending and transverse colon) and, in a separate container, two biopsies from the left colon (descending and sigmoid colon) (17). Biopsies taken from the rectum have the highest rates of false negative results and are therefore not recommended (4).

The histopathologic criteria of CC, applying to hematoxylin and eosin (H&E) stained slides, are a thickened subepithelial collagenous band ≥10 μm combined with an increased inflammatory infiltrate in the lamina propria (3,18). The band may contain entrapped capillaries, red blood cells, and inflammatory cells. Focal damage of the surface epithelium, including detachment from the basement membrane, flattening, and mucin depletion, as well as an increased number of IELs is seen (3,19). This should be combined with an inflammatory infiltrate in lamina propria of mild to moderate degree, dominated by plasma cells and lymphocytes, but also includes eosinophils, mast cells, and, more rarely, neutrophils (3,19). Occasionally, Paneth cell metaplasia and cryptitis can be seen. The biopsies should be orientated vertically since tangential sectioning can simulate a thickened collagenous band (3).

Also applying to H&E-stained slides, the histopathologic criteria of LC are an increased number of IELs ≥20 per 100 surface epithelial cells combined with an increased inflammatory infiltrate in the lamina propria and a not significantly thickened collagenous band (<10 μm) (3,5,18). IELs counting should be performed in the surface epithelium, and areas in close relation to lymphoid aggregates in the lamina propria should be avoided. Focal and mild damage of the surface epithelium, including flattening, mucin depletion and vacuolization is seen, although not as prominently as in CC (3,19). This should be combined with an inflammatory infiltrate in lamina propria of a mild to moderate degree, dominated by plasma cells and lymphocytes, but might also include fewer eosinophils and neutrophils. Occasionally, cryptitis or Paneth cells metaplasia is seen (3).

In most cases, studying the biopsies with H&E and other conventional stains suffices to establish a diagnosis of MC (6). When conventional techniques prove insufficient in cases of doubt, 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).

Recently, a new concept of MC, paucicellular or incomplete MC (MCi), has been proposed for those with clinical manifestations of MC but whose histologic findings are equivocal or do not fulfill the criteria of CC and LC. MCi refers to atypical cases showing IELs between 10 to 20 per 100 epithelial cells and a normal collagenous band or with a

thickened subepithelial collagenous band ›5µm but ‹10µm (3,20). In these cases, the lamina propria has mild lymphoplasmacytic infiltrates, usually limited to the superficial half of the mucosa. The epithelial injury in classic MCi is generally less prominent or even absent (3,16).

The differential diagnosis should be thoroughly assessed through a comprehensive medical history, along with serological, stool, and endoscopic examinations. Testing for bile acid diarrhea is not typically part of the standard diagnostic process for patients with MC. However, this condition should be considered as a possible differential diagnosis, and an empirical treatment may be tried. Additionally, all patients with MC should be screened for celiac disease (3). Currently, the measurement of fecal calprotectin has not been shown to be effective in diagnosing or monitoring patients with MC, but it can be utilized (3,6).

7. Treatment

Although there are histological criteria to distinguish between MC subtypes, the clinical significance of the MC subtypes appears minimal, as treatment recommendations for CC, LC, and MCi are the same (20). Treatment focuses primarily on the severity of symptoms and their impact on the patient's HRQL (21). Eliminating potential risk factors or exacerbating medications may improve or even resolve diarrhea in mild cases of MC. If drugs that can trigger MC cannot be stopped, consider switching to a similar drug with lower risks (3,5,22). However, most patients will still need specific treatment (3).

Anti-diarrheal medications such as diphenoxylate, cholestyramine (a bile acid sequestrant), and loperamide have shown to be clinically effective for mild cases and can be used. However, budesonide is the only treatment that has been extensively studied in controlled trials (5,22).

Budesonide is a second-generation corticosteroid that works locally by binding to glucocorticoid receptors at the site of inflammation. It is recommended as the first-line induction treatment for symptomatic patients, with a typical daily dose of 9 mg for 6 to 8 weeks. This treatment is favored over no intervention at all. Due to its extensive first-pass metabolism (90%) in the small intestine and liver, the drug produces two metabolites - 6β-hydroxy budesonide and 16α-hydroxy prednisolone - with less than 1% systemic activity, resulting in minimal systemic effects (3,5,22–24). Short-term treatment can cause a mild, temporary drop in cortisol levels, but this is usually clinically irrelevant at standard dosages (25). Budesonide is designed to dissolve at a pH greater than 6.4 - this formulation allows for selective absorption of budesonide primarily in the distal ileum and colon (25). When treating symptomatic MC with budesonide, the clinical remission rate, along with histological improvement, is approximately 81%, compared to just 36% in placebo groups (20,23). If patients achieve remission without experiencing a relapse, maintenance therapy is not necessary. Patients who do not experience an early relapse after stopping treatment tend to remain in clinical remission for an extended period and do not require further treatment (8). However, relapse occurs in 60-80% of patients after discontinuing budesonide, typically within the first two weeks. In these cases, remission can often be achieved by reinitiating treatment at a lower dosage (20).

When maintenance therapy is needed, in patients who suffer two or more relapses, studies showed that treatment with 3 mg of budesonide daily or every several days is effective in maintaining long-term clinical remission in up to 80% of patients; however, up to 20% of patients require a 6mg dose (5,26). Maintenance therapy for 12 months has not been associated with an increased risk of opportunistic infections and reduces the risk of relapse during treatment, but the risk remains high once the drug is withdrawn (25).

Patients maintained long-term on budesonide should be assessed for steroid-related side effects, such as hypertension, hyperglycemia, and metabolic bone disease. However, the risk for these adverse events appears to be low (5).

Despite all this evidence, some patients are intolerant, dependent, or refractory to budesonide, and managing their treatment can be challenging, with limited data on the best second-line options (27). Regarding patients for whom treatment with budesonide is not feasible, the European and American guidelines are inconsistent with each other: the first one supports that neither mesalazine nor bismuth subsalicylate is recommended in these patients (3); however, the American Gastroenterological Association suggests treatment with mesalazine, prednisolone (or prednisone), or bismuth salicylate over no treatment for the induction of clinical remission (24). It is important to always account for patient intolerance and preferences in choosing therapies. Treatment with thiopurines, anti-TNF drugs, or vedolizumab can also be equated, but methotrexate or antibiotics are not reliable options (3).

When MC occurs alongside bile acid diarrhea, bile acid binders such as cholestyramine can be beneficial. The starting dose is typically 4 g/day, which can be adjusted based on clinical response, ranging from 2 to 12 g/day (3,28).

Surgery should be considered as a last resort for patients who do not respond to all alternative treatments and for whom alternative diagnoses have been definitively ruled out (3). Diverting ileostomy, either with or without colectomy, as well as ileal pouch-anal anastomosis, can lead to both clinical and histopathological remission. Once bowel continuity is restored, recurrence is nearly inevitable (21,27).

The primary objective of medical therapy is to achieve clinical remission and improve the patient's HRQL. The Hjortswang criteria can also be used to define clinical remission in patients with established MC (8,11). Patients who meet these criteria report no or only mild effects on their HRQL. According to these criteria, clinical remission is characterized by having fewer than three stools per day and/or no watery stools. In contrast, active disease is defined as having three or more stools per day and/or one or more watery stools per day (3,11).

Typically, LC has a milder clinical course than CC, but treatment should not be based on patient age or MC subtype (29). Patients with MCi show similar treatment responses to either CC or LC (6,20). Spontaneous remission without treatment occurs in about 15% of patients. Among those receiving treatment, only 60% of patients who achieve drug-induced remission remain asymptomatic after one year without targeted therapy (21,29).

Despite known pharmacological and lifestyle risk factors, no proactive screening and preventive measures are recommended at this time (11).

After starting treatment, the response should be assessed within 6 to 12 weeks (3). Long-term follow-up typically includes periodic checks every 6-12 months. Key tests include C-reactive protein (CRP) and routine blood tests like hemogram. Fecal calprotectin can also be used. A colonoscopy with biopsies should be performed if symptoms persist or if there is a relapse. It can also be conducted during clinical remission to confirm histological remission. The frequency of follow-up visits depends on the treatment used and varies based on the severity of the disease and the individual's response to treatment (3).

8. Conclusion

MC is a chronic inflammatory colon condition characterized by watery, non-bloody diarrhea. It often affects middle-aged and older adults, particularly women. This condition is a significant and often underrecognized clinical entity, affecting 10-15% of patients with chronic diarrhea (22). Over the past few decades, substantial progress has been made in understanding MC, leading to comprehensive clinical guidelines that have improved patient outcomes (3,24). Despite recent advancements, further investigation is still needed in managing MC due to gaps in understanding its pathogenesis, which complicates preventive measures. Diagnosis currently relies on ileocolonoscopy with biopsy - a procedure that may be contraindicated or not performed early enough in patients with chronic diarrhea, leading to delayed or missed diagnoses. Furthermore, there are limited long-term treatment options available. While avoiding triggers and taking budesonide can be effective for managing symptoms, relapse rates are high once the treatment is discontinued, and patients may become dependent on long-term use. For those who do not respond to budesonide, there are few established alternative treatments. There is also a lack of coherent information regarding the management of patients with multiple comorbidities.

Given these challenges, creating a cohesive and accurate review like this one could be very helpful in raising awareness about MC. Physicians and medical students should stress the importance of considering MC in patients with chronic diarrhea, particularly when other common causes have been ruled out. A summary flowchart outlining the management of MC is provided in Figure 1.

Future research should advance our understanding of MC's etiology, potentially through genetic and immunological studies. Developing non-invasive diagnostic markers or imaging techniques could facilitate earlier detection of MC and improve patient follow-up. Finally, expanding treatment options to incorporate more targeted therapies should be a priority, as this could lead to better patient outcomes while minimizing the risk of adverse effects.

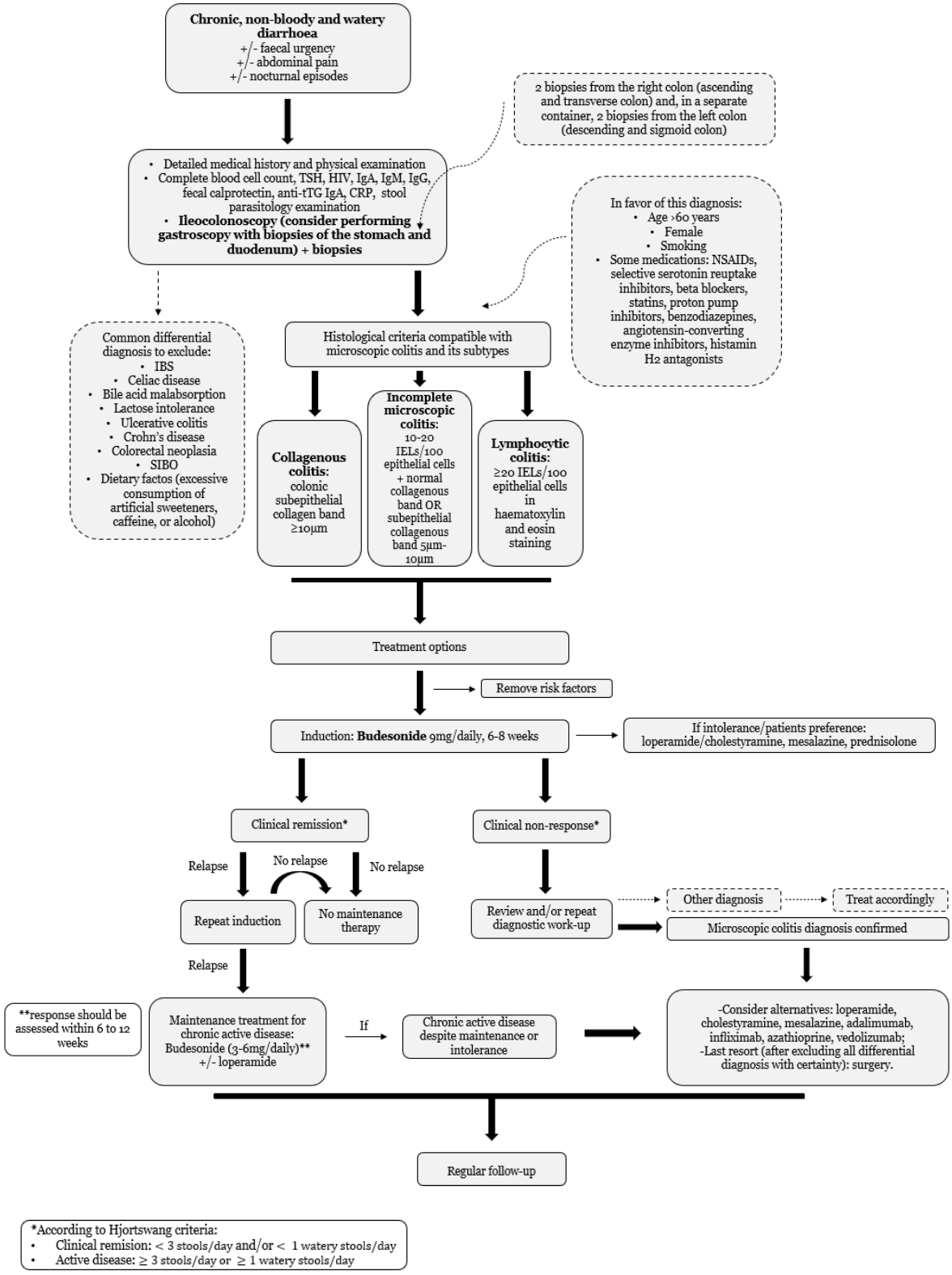

Figure 1. Summary approach to patients with microscopic colitis.

Anti-tTG IgA, anti-tissue transglutaminase antibody. CRP, C-reactive protein. HIV, human immunodeficiency virus. IBS, irritable bowel syndrome. NSAIDs, non-steroid anti-inflammatory drugs. SIBO, small intestinal bacterial overgrowth. TSH, thyroid-stimulating hormone.

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