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MODERN APPROACHES TO RECOGNITION AND MANAGEMENT OF MICROSCOPIC COLITIS

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Microscopic colitis is an inflammatory bowel disease characterized by chronic diarrhea with specific microscopic changes in the absence of macroscopic (endoscopic) and radiological changes in the large intestine. Microscopic colitis is a fairly common disease, so physicians should be familiar with its clinical features and treatment strategies, as the disease deserves the same attention as classical inflammatory bowel disease. The article reviews the current understanding of microscopic colitis, the epidemiology of the disease, risk factors, clinical presentation, diagnostic criteria, and treatment strategies according to the European guidelines of the United European Gastroenterology Society and the European Microscopic Colitis Group 2021 with the overall goal of raising awareness and improving the rational treatment of microscopic colitis in clinical practice.

Key words: microscopic colitis, lymphocytic colitis, collagenous colitis, chronic diarrhea, inflammatory bowel disease, rheumatoid arthritis, irritable bowel syndrome, budesonide.

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СУЧАСНІ ПІДХОДИ ДО РОЗПІЗНАВАННЯ ТА МЕНЕДЖМЕНТУ МІКРОСКОПІЧНОГО КОЛІТУ

Мікроскопічний коліт – це запальне захворювання кишечника, що характеризується хронічною діареєю з наявністю специфічних мікроскопічних змін за відсутності макроскопічних (ендоскопічних) та радіологічних змін у товстому кишечнику. Мікроскопічний коліт є досить поширеним захворюванням, тому лікарі повинні бути знайомі з його клінічними особливостями та стратегіями лікування, оскільки захворювання заслуговує такої ж уваги, як і класичні запальні захворювання кишечника. В статі розглянуто сучасні уявлення про мікроскопічний коліт, епідеміологію захворювання, фактори ризику, клінічну картину, критерії діагностики і тактики лікування відповідно до європейських рекомендацій Об'єднаного товариства європейських гастроентерологів та Європейської групи з вивчення мікроскопічного коліту 2021 р. з загальною метою підвищення обізнаності та покращення раціонального лікування мікроскопічного коліту в клінічній практиці.

Ключові слова: мікроскопічний коліт, лімфоцитарний коліт, колагенозний коліт, хронічна діарея, запальні захворювання кишечнику, ревматоїдний артрит, синдром подразненого кишечнику, будесонід.

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Microscopic colitis (MC) is a relatively new concept in gastroenterology, first described in 1976 by Swedish scientists Hugo Linder and Michael Boyan. They were the first to pay attention to a group of patients with chronic watery diarrhea, in whom endoscopic examination of the colon did not reveal visible changes in the mucous membrane. Despite the normal endoscopic picture, biopsies showed characteristic microscopic changes, which became the basis for defining a new disease - microscopic colitis. In their work, the researchers drew attention to specific changes in the mucous membrane that could not be detected without a microscope, which explains the name of the disease. These changes included chronic inflammation in the intestinal mucosa, thickening of the collagen layer, or an increased number of lymphocytes. The description by Hugo Linder and Michael Boyan was an important discovery in gastroenterology, as previously the cause of chronic diarrhea in patients without visible pathology often could not be explained. The disease initially did not arouse much interest among the medical community because it was difficult to diagnose. Still, this discovery helped develop new diagnostic approaches and shed light on patients who had previously failed a proper diagnosis. Later, other researchers continued the work of Hugo Linder and Michael Boyan, expanding knowledge about different forms of microscopic colitis, which improved approaches to treating the disease.

In 2010, the European Microscopic Colitis Group (EMCG) was founded in Stockholm, bringing together European researchers and clinicians from 14 countries involved in the study of microscopic colitis. Since its foundation, EMCG experts have been updating the current understanding of microscopic colitis, including the definition and the epidemiology of microscopic colitis, risk factors for the disease, pathophysiological mechanisms, diagnostic criteria, and principles of pharmacotherapy from the standpoint

of evidence-based medicine, based on the results of randomized controlled clinical trials, systematic reviews, and meta-analyses. In 2012, the European Microscopic Colitis Group (EMCG) released its first recommendations for the diagnosis and treatment of microscopic colitis. In 2013, microscopic colitis was included in the European Consensus on the Histopathology of Inflammatory Bowel Disease, published on behalf of the European Society of Pathology and the European Crohn's and Colitis Organization.

Given the updated data on the clinical management of microscopic colitis, the EMCG, together with the United European Gastroenterology (UEG), identified the need to develop updated clinical guidelines for the management of microscopic colitis to raise clinicians' awareness of microscopic colitis and provide them with advice on routine clinical care of patients. This work resulted in a revision of previous clinical practice guidelines, which was published in collaboration with the UEG in 2021. These guidelines provide information on the epidemiology and risk factors of microscopic colitis, as well as evidence-based statements and recommendations on diagnostic criteria and treatment options, including oral budesonide, bile acid binders, immunomodulators, and biologics. Recommendations for the clinical management of microscopic colitis are based on evidence, expert opinion, and best clinical practice [20].

The purpose of the study was to analyze diagnostic and treatment options for microscopic colitis by analyzing Ukrainian and foreign literary sources.

Materials and methods. The analysis of Ukrainian and foreign literary sources was carried out. Only full-text versions were used. Also, the electronic database of medical and biological publications Pubmed and Web of Science was used. The search depth was 5 years. This review includes mostly randomized controlled trials and articles covering the latest European Microscopic Colitis Group (EMCG) and United European Gastroenterology (UEG) guidelines. After analysis, the references of the selected publications were also searched. The articles were selected by reviewing their titles and abstracts as well as from the bibliography of the selected articles. Keywords used to search for relevant articles included “microscopic colitis”, “lymphocytic colitis”, “collagenous colitis”, “chronic diarrhea”, “inflammatory bowel disease”, “rheumatoid arthritis”, “irritable bowel syndrome”, “budesonide”.

Results of the study and their discussion. Microscopic colitis is a chronic inflammatory bowel disease of unknown etiology characterized by chronic watery diarrhea without blood impurities, the absence of macroscopic signs of colon damage, and the presence of specific pathomorphologic changes. Since the symptoms of microscopic colitis are nonspecific and the diagnosis requires histological examination, the disease is often either diagnosed late or not diagnosed at all [9].

Microscopic colitis is classified as a nonspecific inflammatory bowel disease, but the “classic” forms of inflammatory bowel disease (Crohn's disease, ulcerative colitis) differ from microscopic colitis because they cause macroscopic inflammation that is visible endoscopically.

Now, there are two subtypes of microscopic colitis: collagenous colitis (CC) and lymphocytic colitis (LC); incomplete variants of CC and LC are also distinguished separately, which are similar in clinical but differ in histological criteria.

In clinical practice, microscopic colitis is observed much more often than before, especially among older patients. In recent years, the incidence has been increasing due to the increased use of diagnostic methods such as colonoscopy with biopsy. A meta-analysis found a global pooled incidence of microscopic colitis of 4.9 (95 % CI 4.2–5.7) cases per 100,000 person-years for collagenous colitis and 5.0 (95 % CI 4.0–6.1) cases per 100,000 person-years for lymphocytic colitis [23]. Incidence estimates come primarily from North America and Europe, with significant variation in incidence between regions. Epidemiological studies have shown that in some countries, the incidence of microscopic colitis exceeds the incidence of Crohn's disease and ulcerative colitis among the elderly. Women, especially older women, are more likely to develop this disease than men. According to a large meta-analysis, MC is 9 times more likely to develop in female patients [23].

The causes of microscopic colitis are not fully understood, but researchers suggest it is a multifactorial disease, including genetic, immunological, and environmental factors. The disease occurs due to an abnormal immune response to stimuli that do not normally cause an inflammatory reaction.

Possible triggers include infections, medications (especially NSAIDs, and proton pump inhibitors), fatty acid malabsorption, and intestinal microflora disorders [33].

The association between bile acid absorption disorders and microscopic colitis remains poorly understood and is explained by the complex physiology and metabolism of bile acids in the intestinal tract [29]. In addition, the metabolism of primary bile acids into secondary bile acids depends on the bacteria present in the colon, and changes in the bacterial flora can affect the composition of bile acids.

There is evidence of a genetic predisposition to microscopic colitis, and some patients have associations with other autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, celiac disease, and thyroiditis. This suggests that certain genetic changes may play an important role in the pathogenesis of microscopic colitis [8, 32].

Smoking was defined as an important risk factor for microscopic colitis by the epidemiological studies, just as it was for rheumatoid arthritis. Thus, the results of a meta-analysis by V. Jaruvongvanich and co-authors (2019), which summarized the results of 7 studies, showed that active smokers have a significantly higher risk of developing microscopic colitis than those who have never smoked [12].

In microscopic colitis, there is an increase in the number of inflammatory cells in the colon mucosa, in particular lymphocytes and plasma cells. This indicates the immune system's involvement in the disease's development. Research suggests that immune responses may be directed against food antigens or microorganisms in the intestine, leading to chronic inflammation, but to date, there is no direct evidence that autoimmunity may be a key pathogenic element in the development of microscopic colitis, although some evidence suggests that it may be partially involved. No useful clinical marker of the disease has been identified so far [17].

There is evidence that the risk of microscopic colitis is significantly associated with the use of proton pump inhibitors [2], especially when used for a long time, selective serotonin reuptake inhibitors, and NSAIDs that are often used in the treatment of systemic diseases such as rheumatoid arthritis. The mechanisms of the disease occurrence and progression have not yet been elucidated, and these drugs may be just the triggers, rather than the cause of inflammation in individuals predisposed to developing colitis.

The bacterial flora in the colon is an important factor that directly or indirectly interacts with the colon epithelium, and thus its alteration may contribute to the pathogenesis of microscopic colitis. Although microscopic colitis is considered a noninfectious colitis, recent studies have demonstrated changes in the intestinal bacterial composition [15, 21]. It was found that the microbiota in patients with microscopic colitis is much less diverse and compositionally different from the microflora of a healthy control group due to a decrease in the number of Clostridiales and an increase in the growth of Prevotella [11]. Also, the analysis of the microbiota composition revealed a higher proportion of Haemophilus Parainfluenzae, Veillonella Parvula, and other Veillonella species in patients with microscopic colitis than in healthy individuals and a lower number of Alistipes Putredinis. This may be an important finding because of the protective anti-inflammatory effect of Alistipes species [26, 29].

Although the pathogenesis of microscopic colitis is still poorly understood, it is likely to result from an imbalance in the immune response, including epithelial dysfunction, collagen metabolism, and secretory diarrhea, in combination with the risk factors mentioned above in genetically predisposed individuals. The genetic component is important too, and recent studies support the role of HLA class I and II-related mechanisms and have identified potential non-HLA alleles associated with the pathogenesis of collagenous colitis [10].

Most authors believe that the following processes prevail in the development of secretory diarrhea in microscopic colitis:

– Reduced active sodium absorption;
– Inhibited metabolism of chlorides and bicarbonates;
– Increased electrogenic chloride secretion with subsequent passive sodium and water transport;
– Reduced passive permeability of the colon mucosa [25].

The precise mechanism of diarrhea remains unclear due to unknown etiologic factors that have yet to be discovered. Different mechanisms may cause diarrhea during the disease, depending on whether the pericryptic absorption sites are blocked by collagen deposits or infiltration of inflammatory cells [26].

The main symptom of microscopic colitis is watery diarrhea without blood (including at night), which can last for months or even years. The frequency of stools can reach 10 times a day. The presence of the urge to defecate, fecal incontinence, and weight loss are typical for microscopic colitis. Cases of systemic manifestations associated with microscopic colitis, such as arthralgia, and other joint syndrome symptoms indicate the possible involvement of systemic inflammation and the need for a differential diagnosis with rheumatoid arthritis [33].

Additional symptoms may include bloating, abdominal pain, and a feeling of constant fatigue. As the symptoms are usually nonspecific, many patients meet the diagnostic criteria for various other conditions such as irritable bowel syndrome, functional diarrhea, celiac disease, bile acid diarrhea, lactose absorption disorders, and excessive bacterial growth in the small intestine [23].

Thus, it is estimated that about 40 % of these patients are diagnosed with irritable bowel syndrome with diarrhea. The prevalence of microscopic colitis in those who meet the diagnostic criteria for irritable bowel syndrome with diarrhea is almost 10 %. Therefore, in the management of patients with symptoms of chronic diarrhea and abdominal pain, it is important to make a differential diagnosis between these two diseases due to the similar symptoms of both diseases [1].

Patients with microscopic colitis have a clinical history that is usually different from that of patients with irritable bowel syndrome. For example, microscopic colitis, unlike irritable bowel syndrome, is most

common in the elderly (>50 years), is accompanied by chronic watery diarrhea, and may be associated with fecal incontinence. At the same time, nocturnal defecation and weight loss are the main complaints of patients. Concomitant autoimmune diseases, such as rheumatoid arthritis, thyroid disease, diabetes mellitus, and celiac disease, are often noted in patients with microscopic colitis. In turn, irritable bowel syndrome is characterized by the predominant involvement of young people (<50 years). Their stool has different consistency, and fecal incontinence and nighttime defecation are rare [15]. Also, the diagnosis of irritable bowel syndrome is often associated with a feeling of fullness/bloating in the abdomen and incomplete bowel evacuation. In most cases, a thorough history can distinguish the diagnosis of irritable bowel syndrome from microscopic colitis, but the most pragmatic approach to diagnosis is to refer patients for colonoscopy with biopsy, which is the gold standard for the diagnosis of microscopic colitis [1, 16].

Despite the presence of a large number of clinical manifestations, the course of microscopic colitis is usually benign, with a mortality and colorectal cancer risk similar to the general population [4]. However, chronic diarrhea in combination with other possible symptoms, such as pain, urgency to defecate, fecal incontinence, nocturnal defecation, fatigue, arthralgia, joint syndrome, myalgia, and weight loss, significantly impair the quality of life of patients with MC [20].

At the initial visit, the diagnosis of microscopic colitis can be suspected if the patient has the following symptoms:

– intermittent/persistent, as well as nighttime watery diarrhea for several weeks (bowel movements ≥3 per day) without blood;

– the patient's age is usually >60 years;

– female gender;

– complaints of fecal incontinence;

– smoking status or history of smoking;

– concomitant treatment with NSAIDs, PPIs, SSRIs, histamine H2 receptor blockers, and statins;

– concomitant autoimmune pathology (rheumatoid arthritis, gluten enteropathy, psoriasis, Sjögren's syndrome, Raynaud's syndrome) [33].

You should always pay special attention to whether patients have “warning signs”. According to the American Gastroenterological Association (AGA), warning signs include weight loss, anemia and hypoalbuminemia, persistent blood in the stool, changes in stool patterns, nighttime pain or diarrhea, and a first-degree relative with inflammatory bowel disease or colorectal cancer [28].

A history of recent travel, recent antibiotics (risk of Clostridium Difficile infection), medications, dietary changes, and previous surgeries are common. Patients with underlying autoimmune diseases, such as rheumatoid arthritis, diabetes mellitus, thyroid disease, iron deficiency anemia, and infertility should be suspected of having not only celiac disease but also MC [7, 22]. Laboratory tests recommended for the initial examination include a fecal examination for Clostridioides Difficile and a routine fecal culture (Salmonella, Shigella, Campylobacter, Yersinia, Escherichia Coli). Fecal examination for eggs and parasites (three samples) should also be performed, especially if patients have risk factors, such as recent travel to endemic areas. A complete blood count, electrolytes, and albumin should be performed, as patients with microscopic colitis may have mild anemia and, in rare cases, protein-losing enteropathy [28].

The diagnosis of microscopic colitis is based on a combination of clinical data and histologic examination [30]. The results of routine laboratory tests and radiological examinations of the small and large intestines do not show clinically significant abnormalities, in particular, patients with microscopic colitis have normal levels of fecal calprotectin, which is a marker of inflammatory bowel disease. This is because inflammation in microscopic colitis is mainly caused by lymphocytes, not neutrophils, which produce fecal calprotectin [3].

Since the disease does not cause visible changes in the colon mucosa during endoscopic examination, a biopsy is the only reliable method to confirm the diagnosis [30]. The diagnosis of microscopic colitis is based on a complete colonoscopy with a histopathologic evaluation of several random biopsies obtained from the entire colon, despite the endoscopic absence of any macroscopic abnormalities. In a recent systematic review aimed at determining the optimal sites and minimum number of colon biopsies required for the diagnosis of microscopic colitis from published studies, it was concluded that a total of six biopsies (three from the ascending colon and three from the descending colon) should be obtained [18, 31]. This allows to detect the presence of a thickened collagen layer (collagenous colitis) or an increased number of lymphocytes (lymphocytic colitis) [15].

The histological examination of collagenous colitis reveals a thickened subepithelial collagen layer that is more than 10 micrometers thick, in combination with an increase in inflammatory infiltrate in the mucosal lamina propria. In lymphocytic colitis, there is an increased number of intraepithelial lymphocytes in the epithelial layer (>20 intraepithelial lymphocytes/100 epithelial cells) in combination with an increase

in the inflammatory infiltrate in the mucosal lamina propria and the absence of a pronounced thickening of the subepithelial collagen lining (<10 microns). The inflammatory infiltrate in the lamina propria can be represented not only by lymphocytes and plasma cells, but also by eosinophils, smooth muscle cells, and neutrophils [16].

Separately, the working group proposes to define incomplete variants of MC, which include patients with convincing clinical signs of the disease, but with an incomplete histopathological picture that does not meet the morphological criteria for CC or LC. Incomplete CC is characterized by thickening of the subepithelial collagenous lining (>5 μm but< 10 μm). Incomplete LC is characterized by an increased number of intraepithelial lymphocytes (>10 intraepithelial lymphocytes/100 epithelial cells, but <20 intraepithelial lymphocytes/100 epithelial cells) and the absence of a pronounced thickening of the subepithelial collagenous lining. In both cases, there is a slight increase in the inflammatory infiltrate in the mucosal lamina propria [6] (Fig. 1).

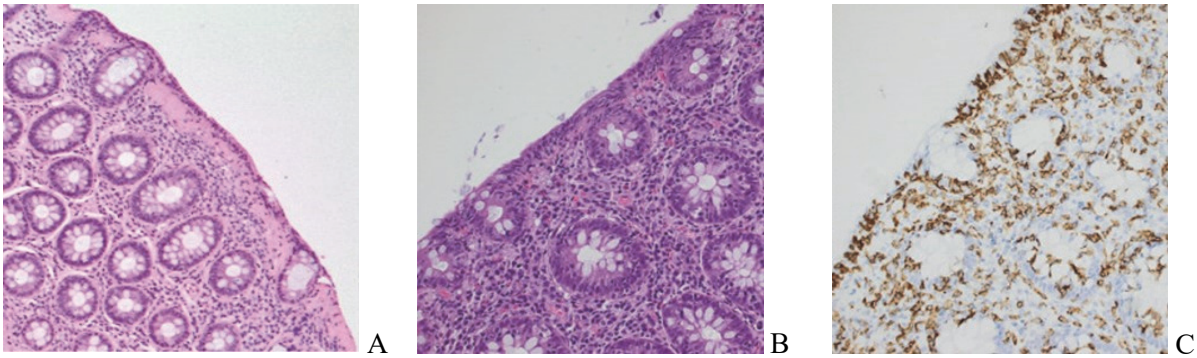

Fig. 1. Histological findings of microscopic colitis [6]. (A) Typical colonic biopsy from a patient with collagenous colitis with a subepithelial collagenous band of more than 10 μM. The surface epithelium is flattened, mucin is depleted, and a mixed inflammatory infiltrate is present in the lamina propria. H&E ×20. (B) Typical colonic biopsy from a patient with lymphocytic colitis with 20 or more intraepithelial lymphocytes per 100 surface epithelial cells. A mixed inflammatory infiltrate is present in the lamina propria. H&E ×20. (C) Lymphocytic colitis, immunohistochemistry stain for CD3 high-lighting lymphocytic infiltration of the epithelium. H&E ×20.

The key goal of microscopic colitis treatment is to induce clinical remission and improve or normalize the patient's quality of life. In the absence of official criteria for MC activity, the working group recommends that MC activity and clinical remission be assessed according to the criteria for diarrhea activity and remission (Hjortsvang score): clinical remission is considered to be achieved when the frequency of bowel movements is <3 times per day or ≥1 watery diarrhea per day for one week [6]. It is not known whether histologic remission is an important goal, so repeat biopsies are not recommended in patients who respond clinically [16].

The first stage of treatment for MC should be aimed at eliminating known risk factors, namely smoking and the use of certain medications (proton pump inhibitors, NSAIDs, selective serotonin reuptake inhibitors, and H2-histamine receptor antagonists). Although discontinuation of the offending drug leads to improvement in most cases, there is no clear evidence yet on how this can predictably change the course of the disease. Dietary restrictions can help reduce the symptoms of diarrhea. It is recommended to exclude caffeine, lactose, and fatty foods from the diet, as these foods can aggravate the disease [13].

At the current stage, the glucocorticosteroid budesonide remains the only drug with proven efficacy and safety in the treatment of MC. According to the 2021 UEG/EMCG clinical guidelines, budesonide is a 1st-line therapy for all patients with microscopic colitis, indicated for both induction and maintenance of remission of microscopic colitis (for collagenous colitis, the level of evidence is medium, the degree of recommendation is strong; for lymphocytic colitis, the level of evidence is low, the degree of recommendation is strong). This recommendation is based on the results of previous studies. Thus, the results of a meta-analysis conducted in 2017, which included 4 randomized placebo-controlled trials with a total of 161 participants with collagenous colitis, showed that 81 % (62/77) of patients receiving budesonide at a dose of 9 mg/day achieved a clinical response compared to 36 % (30/84) of patients who received placebo [19, 26]. The results of another study demonstrated that budesonide is an effective strategy for the treatment of lymphocytic colitis, including the maintenance of remission. Clinical remission was observed in 84 % (43/51) of patients treated with budesonide and 43 % (19/44) of patients in the placebo group [20]. According to the latest meta-analysis by S. Sebastian and colleagues (2019), which summarized the results of 9 randomized controlled trials, budesonide therapy helped to achieve remission induction in patients with microscopic colitis (95 %) and its maintenance (95 %) [23].

Budesonide is a safe drug indicated for induction and maintenance of remission of microscopic colitis. Budesonide is not associated with an increased risk of serious side effects in patients with

microscopic colitis [19]. Literature data do not report an increased risk of osteoporotic fractures in patients with microscopic colitis treated with budesonide, although long-term therapy may be associated with decreased bone mineralization [20].

In addition to budesonide, a wide range of drugs are used in clinical practice to treat patients with MC. However, today the place of these drugs in the treatment of MC is ambiguous due to the lack of a substantial evidence base based on the results of randomized placebo-controlled trials. Thus, the use of mesalazine, a subsalicylate for the treatment of MC is not recommended due to insufficient data [20].

The bile acid sequesterer Cholestyramine (a bile acid binding resin used for diarrhea due to bile acid absorption disorders) may be useful, especially in a significant number of patients with microscopic colitis and concomitant bile acid absorption disorders [20, 21].

In addition, antidiarrheal drugs are often prescribed for the treatment of diarrhea in MC, in particular loperamide hydrochloride, whose mechanism of action is to suppress peristalsis by binding to opiate receptors in the intestinal wall. As a result, the release of acetylcholine and prostaglandin dynes is inhibited, thus reducing propulsive peristalsis and increasing the time of passage of the contents through the digestive tract, as well as the ability of the intestinal wall to absorb fluids. Retrospective studies have shown the efficacy of loperamide hydrochloride at a dosage of 2-16 mg/day, but sustained clinical remission is rare with its use. According to the 2021 UEG/EMCG guidelines, there is insufficient evidence to recommend the use of loperamide hydrochloride in the treatment of MC. However, given the efficacy of the drug in the treatment of chronic diarrhea, experts recommend the use of loperamide hydrochloride in mild MC [20].

According to the UEG/EMCG guidelines, azathioprine/infliximab/adalimumab/vedolizumab is recommended for certain groups of patients who are resistant to budesonide therapy to induce and maintain remission of MC (second-line therapy). Prednisolone, methotrexate, antibiotics, and probiotics are not recommended for use in patients with MC due to insufficient evidence of their efficacy [5, 20].

The algorithm of MC therapy is shown in Fig. 2.

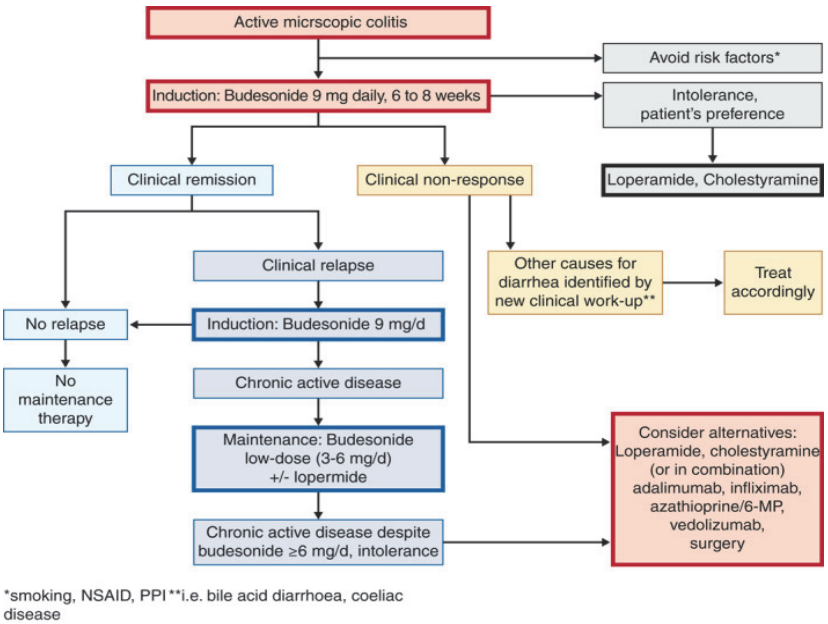

Fig. 2. Therapeutic algorithm for microscopic colitis in clinical practice [19].

Surgical intervention can be considered in some patients with MC as a last option if all medical treatments fail [20].

All patients with microscopic colitis after successful induction therapy should be offered regular follow-up until symptoms resolve and at least every 12 months thereafter to maintain control of the chronic disorder and to ensure easy access to treatment in a specialized outpatient clinic in the event of a flare-up. If patients require long-term maintenance therapy with budesonide to control the disease, supplementation with calcium and vitamin D is recommended, and these individuals should be monitored for osteoporosis. Moreover, proper selection of patients for colonoscopy is important to reduce health care costs, as this procedure can be overused if performed on patients with well-established microscopic colitis who do not experience significant changes in their symptoms [23].

Even though microscopic colitis is increasingly recognized as a common cause of diarrhea, especially among the elderly, it is necessary to continue to raise awareness among healthcare professionals. To this end, the latest EMCG/UEG guidelines containing evidence-based statements on the main aspects of the clinical management of microscopic colitis were reviewed. The main goal and potential of these guidelines is to increase awareness of a probably under-recognized medical condition and to improve care and patient outcomes. Widespread dissemination of these guidelines is necessary to promote widespread use and implementation in clinical practice. Several unmet needs have been identified, including understanding the natural history and pathophysiological mechanisms of the disease, finding reliable non-invasive biomarkers, validated tools to assess disease activity, and new therapies. These gaps should be addressed through high-quality basic research and well-designed clinical trials.

Therefore, the presence of chronic diarrheal syndrome ("watery diarrhea") in older people in the absence of classical markers of intestinal inflammation should attract special attention of the clinician and direct his efforts to a thorough examination of the patient (colonoscopy with biopsy of 6 separate sites in the absence of macroscopic changes in the intestinal mucosa) to establish the correct diagnosis.

Conclusions

1. Microscopic colitis is a fairly common, but underdiagnosed disease in the elderly.

2. The early diagnosis of microscopic colitis leads to better stratification of patients and the subsequent early prescription of effective treatment.

3. Better awareness about microscopic colitis, further clinical trials, and observations should improve the management of patients with intestinal diseases.

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CURRENT VIEWS ON THE IMPACT OF SODIUM NITRITE AND PONCEAU 4R FOOD ADDITIVES ON THE RETINA AND THE WHOLE BODY

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This article examines the effects of the food additives sodium nitrite and Ponceau 4R on the retina. Both are widely used in the food industry to improve the taste, color, and shelf life of foods. However, their use has raised concerns among scientists and healthcare professionals about potential adverse health effects, particularly on the eyes. Sodium nitrite and its derivatives may cause oxidative stress and inflammation in the retina, which may lead to degenerative changes and vision loss. Although some studies suggest a neuroprotective effect of sodium nitrite, more research is needed to confirm these findings. Ponceau 4R may cause oxidative stress and inflammation in the retina, which may lead to damage to retinal pigment epithelial cells. This could potentially lead to vision loss and other eye problems.

Key words: retina, rats, sodium nitrite, Ponceau 4R, oxidative stress.

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СУЧАСНІ ПОГЛЯДИ НА ВПЛИВ ХАРЧОВИХ ДОБАВОК НІТРИТУ НАТРІЮ ТА ПОНСО 4R НА СІТКІВКУ ОКА ТА ОРГАНІЗМ В ЦІЛОМУ

У статті розглянуто вплив харчових добавок нітриту натрію та Понсо 4R на сітківку ока. Обидві ці добавки широко використовуються в харчовій промисловості для поліпшення смакових якостей, кольору та тривалості зберігання продуктів. Проте їх використання викликає занепокоєння серед науковців та медичних працівників через потенційні негативні наслідки для здоров'я, зокрема для органів зору. Нітрит натрію та його похідні можуть спричиняти окислювальний стрес та запалення в сітківці ока, що може призвести до дегенеративних змін і погіршення зору. Хоча деякі дослідження показують нейропротекторний ефект нітриту натрію, необхідні додаткові дослідження для підтвердження цих даних. Понсо 4R може викликати окислювальний стрес і запалення в сітківці, що може призвести до пошкодження клітин пігментного епітелію сітківки. Це потенційно може спричинити погіршення зору та інші проблеми з очима.

Ключові слова: сітківка, щури, нітрит натрію, Понсо 4R, оксидативний стрес.

The study is a fragment of the research "Restructuring of the organs of the immune, respiratory and excretory systems under the effect of various exogenous factors (monosodium glutamate, sodium nitrite, ethanol, methacrylate)", state registration No. 0121U108234.

Food additives can be of two types: natural and synthetic ones [3]. Natural additives are derived from such food products as fruits, seaweed and minerals. For instance, agar-agar (E 406) and carrageenan (E 407) are obtained from seaweed, while pectin (E 440) is derived from fruits. Synthetic additives can be classified into two groups: synthesized substances that are also naturally present in food, such as ascorbic acid (E 300) and artificial substances that have no natural counterparts, such as butylated hydroxyanisole (E 320). Additionally, there are unauthorized and unapproved food additives that have not undergone the necessary testing. The use of certain additives may be permitted in one country but prohibited in another [5, 8, 17].