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RESEARCH ARTICLE

DIAGNOSTIC ALGORITHM AND TREATMENT FOR MICROSCOPIC COLITIS: A REVIEW.

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Abstract

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Diagnostic algorithm and treatment for Microscopic Colitis: A Review

Abstract: Microscopic colitis is an inflammatory bowel disorder characterized by chronic non-bloody watery diarrhea in patients with a macroscopically normal or near-normal colonic mucosa, affecting elderly population. The diagnosis depends on specific histological findings of the colonic mucosa. The prevalence of microscopic colitis in recent population-based studies is found in ~10–15% of patients with chronic watery diarrhoea. It is a benign condition that has been shown to severely impact health-related quality of life. The etiology and pathophysiology are still unknown. There is a growing hypothesis of an immune-mediated cause, supported by the close association of microscopic colitis with celiac disease, thyroid disease and others autoimmunity disorders. A meta-analysis of 6 randomized clinical trials showed clear benefit of budesonide in inducing clinical response and maintenance remission.

Summary: At the present time, colonoscopy with multiple biopsies and histological analysis is the most important part of the diagnosis. However, there is a growing need for less-invasive procedures that can point out the diagnosis. A number of treatments are available for microscopic colitis, but only budesonide is well studied and effective for induction and maintenance treatment. This review focuses on the potential diagnostic tools and treatment algorithms of patients with microscopic colitis.

Introduction:-

Microscopic colitis (MC) is a chronic inflammatory bowel disorder characterized by watery, non-bloody diarrhea with a (near to) normal macroscopic appearance of the colonic mucosa by endoscopy though with typical histological inflammatory changes (Langner et al. 2015)(Magro et al. 2013). MC has emerged as a common cause of chronic watery non-bloody diarrhea, particularly in elderly females (Langner et al. 2015). The prevalence of MC in

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recent population-based studies is found in ~10–15% of patients with chronic watery diarrhea undergoing endoscopy with multiply biopsy (Rasmussen et al. 2016)(Bonderup et al. 2015)(Gentile et al. 2014). MC is a benign condition that has been shown to severely impact health-related quality of life (HRQOL), with baseline HRQOL being lower than that of patients with ulcerative colitis, anal fissures, chronic constipation and faecal incontinence (Nyhlin et al. 2014)(Cotter et al. 2016). The natural history of MC varies considerably (Ingle 2014)(Villanacci et al. 2016). Many cases are self-limiting, with symptoms lasting a few weeks or months and resolution of diarrhea in up to 50% of patients receiving steroid treatment (Ingle 2014)(Villanacci et al. 2016). Unlike other inflammatory bowel diseases (IBD), there is no evidence that the persistence of histological inflammation predicts long-term negative outcomes such as colorectal cancer or need for surgery (Nguyen et al. 2016)(Pardi, Tremaine, and Carrasco-Labra 2016).

Two histological subtypes have been described: Collagenous colitis (CC) and Lymphocytic colitis (LC) (Rasmussen et al. 2016)(Langner et al. 2015)(Miehlke S, Munch A 2012). The clinical symptoms and clinical findings do not differ between MC subgroups (Rasmussen et al. 2016). LC is defined by an increased number of surface intraepithelial lymphocytes (Langner et al. 2015). The key histological feature for CC is defined by a thickened collagen band underneath the surface epithelium (Langner et al. 2015). Incomplete and variant forms showing less characteristic features and they also have been reported under different names (Langner et al. 2015). It is also raising suspicions that the two conditions are two histological manifestations of the same entity, possibly representing different manifestations during the disease course or different stages of disease development (Langner et al. 2015). Presently, these entities are considered variants of the same condition (Cotter and Pardi 2017).

For many authors, MC is an inflammatory disease of the intestine and thus it is regarded as being a new member of the group of IBD (Chetty and Govender 2012). The etiology of MC is unknown, and studies to solve disease pathogenesis are still in their beginning (Park 2015)(Bouma and Münch 2015). The pathophysiology of MC is still unknown, but there is strong evidence that MC is frequently associated with the use of certain medications and certain systemic disorders (such as autoimmune diseases) (Storr 2013). It is consider that MC is a multifactorial disease, probably secondary to an abnormal immune reaction that appears in predisposed individuals, triggered by different luminal factors (infections, drugs, autoimmunity and/or bile acids), with subsequent epithelial barrier dysfunction in the colonic mucosa (Guagnozzi and Lucendo 2015)(Tysk et al. 2014)(Stoynov et al. 1989). The potential pathophysiological mechanism by which the alteration of the mucosal immune response generates the dominant symptom of the disease (diarrhea) is still under investigation, with several data showing that the diarrhea in MC patients could have an inflammatory origin (Guagnozzi and Lucendo 2015). Recent studies have revealed that MC is an immune-mediated disorder, with a prominent contribution from the adaptive immune system and cytotoxic responses (Pisani et al. 2016). Another supporting hypothesis of an immune-mediated cause of MC is the close association of MC with celiac disease, thyroid disease, rheumatoid arthritis, Sjogren's syndrome and Raynaud's syndrome (Vigren et al. 2013) (Kanıtez et al. 2016). In some study reports, celiac disease has been reported to be associated with LC between 4% to 31% of patients with celiac disease and also exhibit histopathological changes typical of LC (Guagnozzi et al. 2015)(Dewar 2012)(El-Salhy 2013).

A variety of drugs have been associated with MC and are supposed to induce MC (Table 1) (Langner et al. 2015). The increased use of medications, especially in older people, and this might explain the reported increased incidence of MC worldwide (Langner et al. 2015). Nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), statins, topiramate, venotonic agents and histamine antagonists have been associated with MC (Verhaegh et al. 2016)(Guagnozzi et al. 2015). In fact, the underlying mechanisms remain unclear (Verhaegh et al. 2016)(Guagnozzi et al. 2015). Current exposure to NSAIDs, PPIs or SSRIs and prolonged use for 4–12 months increased the risk of developing MC (Verhaegh et al. 2016)(Guagnozzi et al. 2015). Genetic factors or the involvement of miRNAs have been suggested, but they remain largely controversial (Pisani et al. 2016). Research has also explored genetic associations, with a recent genome-wide association study finding several loci that were associated with CC, including some that have been associated with IBD (Giulia et al. 2014). The genetic associations are poorly understood, and we are still far from being able to outline a possibly complex genetic risk profile for the diagnosis of MC (Pisani et al. 2016). Bile acid malabsorption (BAM) can coexists with MC, leading to more frequent bowel movements and looser stool consistency (Miehlke S, Munch A 2012)(Rasmussen and Munck 2012). A systemic analysis and some small retrospective case series that have found BAM to be presented in up to 60 % of patients with LC and in up to 44 % of those with CC, supporting the notion that BAM might have a key role in the development of the MC (Ingle 2014)(Rasmussen and Munck 2012)(Guagnozzi and Lucendo 2015).

It is important to emphasize that the aim of this review is to focus on the diagnostic tools that should improve our clinical practice and treatment algorithm of a patients with microscopic colitis.

Diagnosis:-

MC is fundamentally underdiagnosed disease, because of a lack of awareness of the disease among those professionals involved in diagnosing of chronic diarrhoea (Fernández-Bañares et al. 2016). The diagnosis of MC and assessment should begin from the onset of clinical symptoms (chronic or intermittent relapsing watery, non-bloody diarrhea) (Macaigne et al. 2014)(Okamoto et al. 2016)(Ingle 2014). If such a symptom appears in a woman over the age of 50, diagnosis of MC should be highly suspected (Macaigne et al. 2014)(Okamoto et al. 2016)(Ingle 2014). Also, if there is a newly started drug or a concomitant autoimmune disease will support the possible diagnosis of MC (Macaigne et al. 2014)(Okamoto et al. 2016)(Ingle 2014). Diagnosis of MC depends on a proper medical history, with the exclusion of other diseases, background disease, drug consumption history, normal radiological, normal or almost normal endoscopic findings and endoscopic biopsies with histopathological findings consistent with MC (Macaigne et al. 2014)(Okamoto et al. 2016)(Ingle 2014). MC shares certain common clinical manifestations with functional bowel disorders, especially diarrhoea-dominant irritable bowel syndrome (IBS-D) and functional diarrhea (Guagnozzi, Arias, and Lucendo 2016). From a systematic review and meta-analysis on the diagnostic overlap between functional bowel disorders and MC shows that there is a significant overlap of symptoms between MC and IBS-D (Guagnozzi et al. 2016). This data suggests that ruling out a diagnosis of MC by means of colonoscopy and adequate mucosal biopsies should always be considered, especially in patients with IBS-D (Guagnozzi et al. 2016). The differential diagnosis of MC is very large and mainly includes infectious colitis, resolving acute infectious colitis, post-dysenteric IBS, drug-induced changes, particularly those related to the intake of non-steroidal inflammatory drugs, but the classic IBD and celiac disease also have to be ruled out (Langner et al. 2015)(Guagnozzi et al. 2016)(Jauregui-Amezaga, Vermeire, and Geboes 2016). Usually colonoscopy cannot be avoided in patients with chronic diarrhea, but the ability to identify a subset of patients at higher risk of MC has the potential to reduce the number of patients in whom biopsies are taken and recent scoring systems have been proposed to identify lower risk patients (Cotter et al. 2016)(Kane et al. 2015). Series of clinical studies have shown that those patients with MC are more than 50 years of age, report weight loss, have a duration of diarrhea < 12 months, have recently taken a new drug, and have a coexisting autoimmune disease(s) (Macaigne et al. 2014)(Cotter et al. 2016)(Kane et al. 2015). From present literature it has to be assumed that there is an emerging need to identify a non-invasive diagnostic tool that can predict the presence of active MC and distinguish MC from other functional and organic causes of watery diarrhea (Cotter et al. 2016)(Pisani et al. 2017)(Macaigne et al. 2014). Such a diagnostic tool would furthermore serve to better assess the real need for colonoscopy and histological evaluation (Pisani et al. 2017)(Macaigne et al. 2014)(Kane et al. 2015). As a matter of fact, this non-invasive test should be rapid, inexpensive, standardized, reproducible, and accurate in reflecting the predominant lymphocytic activity in the large bowel of patients suffering from MC (Pisani et al. 2017).

2.1 Laboratory tests

Despite frequent diarrhoea, laboratory tests are usually normal or disclose unspecific abnormalities (Fischer et al. 2015)(Pisani et al. 2017). Until this moment, no reliable serum marker has been identified in MC (Pisani et al. 2017). The common serological inflammatory marker, such as C-Reactive Protein is usually normal or only slightly elevated in MC (Roth, Gustafsson, and Ohlsson 2013). However, the prevalence of antinuclear antibodies, anti-*Saccharomyces cerevisiae* IgG antibodies, anti-thyroid peroxidase, anti-perinuclear neutrophil cytoplasmic antibodies and anti-glutamic acid decarboxylase was significantly higher compared to controls (Roth et al. 2013)(Jauregui-Amezaga et al. 2016)(Tysk et al. 2014)(Pisani et al. 2017). Unfortunately, these antibodies do not have the potential to be used as a serological marker of MC, because they possess very low specificity and sensitivity (Roth et al. 2013)(Pisani et al. 2017).

2.2 Fecal markers

No pathological microorganisms are generally found in microbiological stool analyses in patients with MC (Tysk et al. 2014). In MC imaging with radiology is usually normal (Tysk et al. 2014). The quantification of inflammatory parameters in stool is considered specific for intestinal inflammation, and there have been several attempts to identify a fecal biomarker of inflammation in MC to aid the pre-diagnostic screening and subsequent monitoring of MC (Miehlke S, Munch A 2012). Fecal biomarkers evaluated in MC include a heterogeneous group of substances or proteins that either leak from or are generated by the inflamed mucosa in the gut (Miehlke S, Munch A 2012). The fecal markers can be good supportive tools for the diagnosis of MC (Fernández-Bañares et al. 2016). The neutrophil-derived proteins calprotectin and myeloperoxidase (MPO) detected in feces have emerged as markers of intestinal

inflammation in patients with ulcerative colitis and Crohn's disease, and their elevated levels correlate with disease activity (Miehlke S, Munch A 2012)(Wagner et al. 2016)(von Arnim et al. 2016). On the other hand, despite being primarily expressed by inflammatory cells, such as neutrophilic granulocytes, these biomarkers do not reflect the lymphocytic mucosal infiltration and their diagnostic accuracy is usually low in patients with MC (Pisani et al. 2017).

Finding a sensitive and sufficiently specific biomarkers in the feces of patients affected with MC hold promise in the diagnostic flowchart of MC (Pisani et al. 2017). Fecal biomarkers are easy to collect, easy for testing and may be a screening tool before performing more invasive examinations, such as colonoscopy (Pisani et al. 2017). In addition, to be sensitive and specific, fecal biomarkers in MC have to outline the most prominent histologic and biochemical feature of these diseases, which is the presence of an abundant intraepithelial lymphocytic infiltrate (Pisani et al. 2017). As a matter of fact, at the present time, such markers do not exist, leaving the need for more research projects (Pisani et al. 2017). Most of the data in the literature is related to neutrophil granulocyte proteins (Pisani et al. 2017). Neutrophils can release a multiplicity of toxic oxygen radicals and a variety of granular and soluble proteins (Pisani et al. 2017). Neutrophils play an important defensive role against bacteria (Pisani et al. 2017). Nevertheless, they are also believed to cause mucosal tissue injury, leading to the development of several inflammatory conditions of the bowel, including MC (Pisani et al. 2017). MPO is a peroxidase enzyme with bactericidal activity that is unique to polymorphonuclear leukocytes, monocytes and macrophages (Miehlke S, Munch A 2012). However, MPO is also a marker of neutrophil activation and was elevated in eight of the MC patients but no statistical difference was detected compared to normal subjects (Wagner et al. 2016).

2.2.1 Fecal Calprotectin

Calprotectin, also known as S100A8/S100A9 complex, is a calcium-binding protein with antibacterial, anti-proliferative and immunomodulating effects (Donato et al. 2013). It constitutes two-third of the cytosolic proteins stored into neutrophilic granulocytes (Donato et al. 2013). In large cohorts fecal calprotectin (FC) was significantly increased compared to healthy controls and decreased significantly when remission was induced in MC (Wagner et al. 2011)(Miehlke S, Munch A 2012). However, FC may be useful to discriminate between MC and IBS or active MC from inactive MC (von Arnim et al. 2016). In this prospective study performed by von Arnim et al., patients with active MC (both CC and LC) had significantly higher FC concentrations as compared to patients with IBS if analyzed by ELISA (von Arnim et al. 2016). Researchers also found a significant difference in FC concentrations when comparing active and quiescent MC in respect to IBS (von Arnim et al. 2016). A further potential use of FC is to measure/monitor the outcome of the treatment of MC patients under Budesonide therapy (von Arnim et al. 2016). Furthermore, their data suggest that FC could become part of the clinical workup to determine which patients with chronic diarrhea should undergo biopsies for histological assessment of active MC (von Arnim et al. 2016). In conclusion, using a conservative cut-off level of FC (100 µg) the estimated sensitivity for MC was 64% and the specificity 90% (Miehlke S, Munch A 2012)(von Arnim et al. 2016). But up to 39% of MC patients with active disease have normal fecal samples, and excretion of inflammatory markers in fecal samples is not a uniform characteristic, seriously hampering the sensitivity (Miehlke S, Munch A 2012)(von Arnim et al. 2016). This will limit the use of FC as a pre-diagnostic screening test in patients with potential MC (Miehlke S, Munch A 2012)(von Arnim et al. 2016).

Fecal eosinophil-derived proteins:-

In one study is demonstrated that the mucosal inflammation in active CC is characterized by eosinophil activation in addition to the lymphocytic infiltration of the epithelium and the lamina propria (Wagner et al. 2010). The eosinophil is regarded as a potent proinflammatory cell with the ability to release cytotoxic proteins such as eosinophil protein X (EPX) and eosinophil cationic protein (ECP), both detectable in blood and feces (Wagner et al. 2016). In a pilot study of 12 patients with active CC, fecal EPX and fecal ECP were positive in 67% and 92%, respectively, and both markers decreased after budesonide treatment (Wagner et al. 2011). Given this information, eosinophil markers of inflammation seem to be the most promising tool to detect patients with active CC (Wagner et al. 2016). In very recent study, Wagner et al. tested the diagnostic performance of fecal ECP and EPX, together with FC and fecal MPO, in a cohort of 67 patients referred to colonoscopy due to chronic non-bloody diarrhea (Wagner et al. 2016). The results demonstrate that elevated fecal EPX and fecal ECP can predict a diagnostic outcome of CC in patients with chronic non-bloody diarrhea (Wagner et al. 2016). This specific setting is very important, since it summarize the clinical scenario where the availability of MC biomarkers could represent a step forward in clinical practice (Pisani et al. 2017). According to endoscopy and pathology reports (available for 63 out of 67 patients), 46 patients were affected with IBS, 2 with UC, 2 with Crohn's disease, 2 with LC, and 9 with CC (Wagner et al.

2016)(Pisani et al. 2017). Notably, fecal ECP and EPX were significantly higher in CC patients and when all the four tested fecal markers (ECP, EPX, FC, and MPO) were negative, the chances of getting a normal histological description were 92% (Wagner et al. 2016)(Pisani et al. 2017). Additionally, in the same study, serum levels of ECP and EPX were also measured, without finding any differences between the different study groups (Wagner et al. 2016)(Pisani et al. 2017). Therefore, it is possible to use the EPX and ECP as diagnostic markers for CC (Wagner et al. 2016). In contrast, the mucosal inflammation in LC is dominated by an infiltration of lymphocytes (Wagner et al. 2016). In line with this, fecal EPX and fecal ECP levels did not predict a diagnosis of LC in their study (Wagner et al. 2016). This finding should, however, be interpreted with caution because of the small number of patients with LC (n-4) (Wagner et al. 2016). Also interesting in this study is that only three out of 13 patients with MC displayed elevated levels of FC (Wagner et al. 2016). It should be noted that FC is not unique to the neutrophil (Wagner et al. 2016). Fecal eosinophil-derived proteins may be able to distinguish collagenous from lymphocytic colitis or other causes of diarrhea, but these studies are small and further work is necessary to validate the role of fecal markers of inflammation in the diagnosis and monitoring of MC (Wagner et al. 2016).

Other markers:-

Other markers such as chromogranin A, chromogranin B, or secretoneurin are suggested to be a candidate fecal marker for CC (Wagner et al. 2013). A research group reported increased levels of fecal neuropeptides, suggesting involvement of the enteric nervous system in the pathogenesis of CC (Wagner et al. 2013). Levels of chromogranin A, chromogranin B, and secretoneurin were increased in 12 patients with CC compared both to controls and patients with ulcerative colitis or Crohn's disease (Wagner et al. 2013). During budesonide therapy, levels of secretoneurin rapidly declined (Wagner et al. 2013). These early data require further study and confirmation in bigger patient cohorts before they may be applied as potential biomarkers in MC (Wagner et al. 2013). Chromogranin A is therefore considered to be a general marker for all endocrine cells (El-Salhy 2013). Colonic chromogranin A-positive cell density being proposed as a diagnostic marker for LC (El-Salhy et al. 2012) . The use of the chromogranin A-positive cell density as a marker for the diagnosis of LC has a high sensitivity (97 and 100%, in the right and left colon, respectively) and specificity (98 and 94%, in the right and left colon, respectively) (El-Salhy et al. 2012). El-Salhy et al. hypothesized that in MC there may be a hyperactivation/hypertrophy of colonic neuroendocrine cells, and consequently, in their study, the authors demonstrated by immunohistochemistry an overabundance of Chromogranin A (CgA)+ cells interspersed among epithelial cells in LC (no data are provided for CC) (El-Salhy et al. 2012)(Pisani et al. 2017).

From pathophysiological perspective, these findings indicate that activation of both eosinophilic, neutrophilic leucocytes and macrophages might play a role in pathophysiology in patients with MC (Miehlke S, Munch A 2012). In conclusion, studies researching fecal markers in MC are small and the potential role of fecal markers as a pre-diagnostic screening or monitoring in patients with known MC deserves further study (Miehlke S, Munch A 2012).

1. Endoscopic findings

Upon endoscopic evaluation, the mucosa is normal in the vast majority of cases, but may occasionally show subtle changes, such as oedema and erythema (Langner et al. 2015). Endoscopic appearance of the colon of MC patients may vary between patients, and may not always appear as a macroscopically normal mucosa (Mellander et al. 2016)(Okamoto et al. 2016). The advances in diagnostic endoscopy have suggested that several MC-related mucosal lesions may exist, and should be considered as a supportive finding in the diagnostic process of MC (Mellander et al. 2016)(Okamoto et al. 2016).

Characteristic endoscopic findings that have been observed in MC patients are as follows (Okamoto et al. 2016)(Nguyen et al. 2016):

- Hypervascularity
- Indistinct vascular pattern
- Linear ulcers/scars
- Cat scratch sign
- Patchy erythema
- Mucosal fragility
- Granular mucosa
- Crack-like appearance (Okamoto et al. 2016) (Nguyen et al. 2016)

A warning about these finding is that they may also appear in non-MC cases, and therefore the disease sensitivity is not guaranteed (Okamoto et al. 2016). When using advanced endoscopic imaging techniques such as narrow band imaging (NBI) or Fujinon Intelligence Color Enhancement (FICE) may further reveal MC-related or MC-specific endoscopic findings (Okamoto et al. 2016). There are limited data on the use of indigo carmine to identify endoscopic changes in MC (Bickston 2015). Vital staining in this situation may allow targeted biopsies (Bickston 2015). There are also reports of real-time diagnosis using confocal microscopy (Bickston 2015). This modality holds promise, but the current costs of fixed and disposable components make it more of a research tool at this point (Bickston 2015). In one study was investigated the endoscopic features of MC with high-definition (HD+) endoscopy plus i-scan (Grassia et al. 2017). The research team found in 6 patients with MC mosaic pattern/celiac-like mucosa in 2/2 of the CC and 2/4 of the LC (Grassia et al. 2017). Dwindling or deranged vascular pattern and blotchy erythema were visible in 2/2 of CC and 2/4 of LC (Grassia et al. 2017). Friability or exudative bleeding and scars or "cat-scratch" appearance of the mucosa were present in 1/2 and 1/4 of CC and LC respectively (Grassia et al. 2017). Furthermore, due to the frequent patchy distribution of such lesions, HD+ endoscopy plus i-scan may help to guide targeted biopsies thus reducing the false negative rate (Grassia et al. 2017). The importance of endoscopic survey in the diagnosis of MC is also emphasized in taking biopsies from each part of the colonic segment (Fernández-Bañares et al. 2016). It is highly recommended to take at least two biopsies per segment, to assure a high likelihood of detecting any present MC-specific pathological findings (Fernández-Bañares et al. 2016). However, tangential sectioning of the biopsy specimen can mimic a thickened collagen band, and finally a slightly increased subepithelial collagen band can be found in hyperplastic polyps (Bouma and Münch 2015).

2. ***Histopathology***

The pathologic evaluation of the biopsy specimens is the most important part of the diagnosis of MC (Okamoto et al. 2016). Whether a patient may be diagnosed as CC or LC completely depends on the existence of the specific pathological findings in the biopsy specimens (Okamoto et al. 2016).

Lymphocytic colitis:-

The characteristic finding on biopsy in lymphocytic colitis is intraepithelial lymphocytosis, defined as >20 intraepithelial lymphocytes (IEL) per 100 surface epithelial cells, with little or no crypt architectural distortion has been adopted in the European Consensus on the Histopathology of Inflammatory Bowel Disease (ECCO-ESP) (Magro et al. 2013)(Langner et al. 2015).

Langner et al. proposed a key histological features of lymphocytic colitis (Langner et al. 2015)*:*

- An increased number of surface intraepithelial lymphocytes (>20 per 100 epithelial cells).
- Mild surface epithelial injury (vacuolization, flattening, and mucin depletion)
- Increased (and homogeneously distributed) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
- No or little crypt architectural distortion
- Thickening (<10 μm) of the subepithelial collagen band may be present
- Focal inflammatory bowel disease-like changes (cryptitis and Paneth cell metaplasia) possible
- Technical note: H&E-stained slides are generally sufficient to make the diagnosis; CD3 immunostaining may highlight intraepithelial lymphocytes, but is not needed routinely (Langner et al. 2015).

In borderline cases or in cases of uncertainty, it is highly recommended by European Microscopic Colitis Group (EMCG) to perform CD3 staining in order to determine the precise number of IELs and to confirm the diagnosis (A. Münch et al. 2012).

Collagenous colitis:-

The key histological feature of collagenous colitis is a broad, thickened collagen band under the surface epithelium (Chetty and Govender 2012)(Langner et al. 2015). The band does not usually extend around the crypts, and is most evident between the crypts immediately beneath the surface epithelial cells (Chetty and Govender 2012)(Langner et al. 2015). According to the ECCO-ESP, the thickness of the collagen band should exceed 10 μm (normal <3 μm) in well-oriented biopsies, i.e. biopsies cut perpendicularly to the mucosal surface (Magro et al. 2013).

Langner et al. proposed a key histological features of collagenous colitis (Langner et al. 2015)*:*

- Thickening (>10 μm) of the subepithelial collagen band (most prominent in the right colon; rectosigmoid may be normal)

- ❖ Marked surface epithelial injury (flattening, detachment)
- ❖ Increased (and homogeneously distributed) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
- ❖ No or little crypt architectural distortion
- ❖ An increased number of surface intraepithelial lymphocytes (<20 per 100 epithelial cells) may be present
- ❖ Focal inflammatory bowel disease-like changes (cryptitis and Paneth cell metaplasia) possible
- ❖ Technical note: H&E-stained slides are generally sufficient to make the diagnosis; collagen stains or tenascin immunostaining may highlight the thickened collagen band, but are not needed routinely (Langner et al. 2015).

In borderline cases, additional collagen-specific stains should be used for better visualization (Goldner, van Gieson, Masson-Trichrome) or immunohistochemistry with antibodies directed against tenascin may be helpful (Langner et al. 2015). A direct relationship between the thickness of the collagen band and the clinical symptoms does not seem to exist (Langner et al. 2015)(Stoinov et al. 1997).

MCi:-

Recently the term incomplete microscopic colitis (MCi) was introduced, for patients with diarrhea and an increase of cellular infiltrates that do not fulfill the histological criteria of CC or LC (Storr 2013). In these cases with MCi patients, an increase in the number of IELs is observed, but <20/100 epithelial cells in superficial epithelium (incomplete LC) and abnormal thickening of the subepithelial collagen band <10 μm (incomplete CC) (Münch and Langner 2015). Some patients meeting these criteria have been shown to respond to treatment for MC suggesting that these definitions are appropriate, but more research is required to ascertain if these broadened definitions should be accepted (Pisani et al. 2017).

3. Diagnostic criteria and Algorithm:-

5.1 It is of big importance to obtain precise and complete clinical information regarding the drugs that may cause symptoms of diarrhea or cause inflammatory changes, since several drugs (e.g., PPI, NSAIDs) may cause histological features of MC, and both the clinical and histological pictures may reverse following drug withdrawal (Villanacci et al. 2016).

5.2 Sampling of the colonic mucosa, with at the very least two biopsies from any segment of the colon including the terminal ileum, and correctly oriented samples (on acetate cellulose filters if possible) is needed for a correct histological evaluation, to avoid sampling bias due to too few biopsies and distortion of the fixed samples that may impair a precise evaluation by the pathologist (Villanacci et al. 2016).

5.3 Diagnosed should be made on the basis of strict histological criteria (Villanacci et al. 2016). Therefore, it is important to use CD3 to count IELs in the superficial epithelium for LC and the trichrome stain to evaluate the collagen band for CC (Villanacci et al. 2016). It is worth noting that this band may be intermittently present in the colon (Villanacci et al. 2016).

5.4 Apart from the variant forms displaying precise morphological characteristics, such as pseudomembranous collagenous colitis and cryptic lymphocytic colitis, authors suggest avoiding terms such as MCi and "undefined" microscopic colitis (UMC) in daily practice, because these terms are misleading and contradictory, with the result that other conditions such as infective, ischemic, pseudomembranous colitis, segmental colitis related to diverticular disease, and inflammatory bowel diseases may be underdiagnosed (Villanacci et al. 2016).

Villanacci et al. purposed that "simplification" is the better way to face actual problems, especially in a complex field such as that of endoscopic histological diagnosis, in order to avoid delays or errors in diagnosis and frequent, often unsuccessful revisions of the biopsy samples (Villanacci et al. 2016).

4. Treatment:-

The first step in managing patients with MC is to look for factors that might be exacerbating diarrhea, such as consumption of dairy products in a patient with lactose intolerance or excessive use of artificial sweeteners (Pardi et al. 2016). It is required to make a review of the patient's medication list, including over-the-counter products, to identify drugs or other substances that might cause MC or worsen diarrhea (Table 1) (Pardi et al. 2016). As the pathogenesis of the disease remains unclear, the goal of treatment in MC is to achieve clinical remission, that is <3 stools a day or <1 watery stool a day with subsequent improve quality of life (Jauregui-Amezaga et al. 2016). Currently, there are no evidences to consider histological remission as an aim in the treatment of MC (Jauregui-Amezaga et al. 2016). Before starting medical treatment, the discontinuation of those drugs that could induce MC should be proposed (Jauregui-Amezaga et al. 2016).

The goals of treatment are the same as any chronic inflammatory systemic disease: induction of remission, and once achieved, maintenance of remission (be it with expectant management or formal pharmacotherapy) (Cotter and Pardi 2017). There are several treatment options available for patients with MC (Figure 1) (Nguyen et al. 2016). However, budesonide is the only option that has been well studied in controlled clinical trials and is currently recommended by the American Gastroenterological Association (AGA) as first-line therapy (Nguyen et al. 2016)(Cotter and Pardi 2017). In this context a microscopic colitis disease activity (MCDAI) scoring index has been developed recently with the aim of standardizing outcome measures in future clinical trials and hopefully leading to higher quality pharmacotherapy evidence in MC management (Cotter et al. 2016).

Budesonide remains the first-line therapy, significantly improving symptoms and HRQoL (O'Toole 2016)(Nguyen et al. 2016). It is a locally active corticosteroid that undergoes first-pass metabolism in the liver with subsequent low systemic exposure (O'Toole 2016)(Nguyen et al. 2016). A systematic review and meta-analysis on the use of corticosteroids for short- and long-term treatment of MC in adults showed that budesonide was significantly more effective than placebo in short-term clinical response (risk ratio [RR]: 3.07; 95% CI: 2.06–4.57) and long-term clinical response (RR: 3.22; 95% CI: 1.05–9.89) (Stewart, Seow, and Storr 2011). Patients treated with budesonide of 9 mg daily were more than twice as likely to achieve clinical remission over an average of 7 to 13 days (clinical response in 6 to 8 weeks) when compared with no treatment (Stewart et al. 2011)(Nguyen et al. 2016). Cessation of budesonide can be considered after 8 weeks of therapy (Stewart et al. 2011)(Nguyen et al. 2016). One-third of patients will remain symptom-free thereafter and not require maintenance therapy, which alleviate long term cost issues with the drug (Stewart et al. 2011)(Nguyen et al. 2016). Oral Budesonide 9 mg/day for 6–8 weeks induces remission in 77%–100% of patients with CC (Münch et al. 2016). According to data from another randomized controlled trial (RCT) in patients with active CC who were randomly assigned to oral budesonide 9 mg, oral mesalazine 3 g or placebo for 8 weeks showed that oral budesonide was effective and safe for short-term treatment of CC and superior to mesalazine and placebo (Miehlke et al. 2014). If symptoms persist or recur, budesonide 9 mg can be used for 12 weeks and then adjusted accordingly (O'Toole 2016)(Miehlke et al. 2014). However, budesonide therapy was shown to improve histological scores, stool consistency and abdominal pain (O'Toole 2016)(Miehlke et al. 2014). There were no differences in adverse effects noted between treatment groups in this RCT (O'Toole 2016)(Miehlke et al. 2014). Despite differences in the clinical characteristics, response rates to available treatments appeared to be similar in both LC and CC (Colussi et al. 2015).

After withdrawal of budesonide, between 61% and 88% of patients experience clinical relapse (Münch et al. 2016). A low dose of oral budesonide (4.5 mg/day) given as maintenance therapy was also effective for maintaining clinical remission over a 12-month period in 61.4% of the patients with CC in an RCT, but 82.1% of patients who received budesonide during the 12 months relapsed during the treatment-free follow-up (Münch et al. 2016). There was a high-relapse rate after discontinuation 82.1% (23/28 patients) (Münch et al. 2016). Low-dose budesonide over 1 year resulted in few suspected adverse drug reactions (7/44 patients), all of which were non-serious (Münch et al. 2016). Risk factors associated with relapse included high-stool frequency at baseline and a long duration of diarrhea (O'Toole 2016). AGA recommends, for patients with recurrence of symptoms following discontinuation of induction therapy for MC, budesonide for maintenance of clinical remission (Nguyen et al. 2016). A lower dose of budesonide (3 mg daily alternating with 6 mg daily) over 12 months showed similar efficacy in maintaining clinical response (Nguyen et al. 2016). Although the systemic bioavailability of budesonide is low, prolonged use may predispose to bone loss (Nguyen et al. 2016). Maintained long term on budesonide should be assessed for steroid-related side effects, such as hypertension, hyperglycemia, metabolic bone disease (osteoporosis) and prevention and screening should be considered (Nguyen et al. 2016)(Pardi 2017).

Mesalazine is a bowel-specific anti-inflammatory agent, structurally related to the salicylates, that is active in IBD (Jauregui-Amezaga et al. 2016). In patients with symptomatic MC in whom budesonide therapy is not feasible, the AGA suggests treatment with mesalazine over no treatment for the induction of clinical remission (Nguyen et al. 2016). Because of the uncertain balance between benefits and potential harms, mesalazine is recommended conditionally as a potential second-line therapy that can be used under select circumstances (Nguyen et al. 2016). Moderate-quality evidence from a single RCT suggests that mesalazine therapy is associated with a lower likelihood of achieving clinical response when compared with no treatment (Nguyen et al. 2016).

The use of prednisone in the management of CC is limited given inferior efficacy and increased side effect profile compared to budesonide (O'Toole 2016). Compared to budesonide, prednisone is associated with a lower response rate, more side effects, and a higher risk of relapse when therapy is withdrawn (O'Toole 2016). Gentile et al.

compared clinical outcomes in 80 patients with MC (40 CC, 40 LC) treated with corticosteroids and budesonide (Gentile et al. 2013). Significantly higher rates of clinical response were observed in the budesonide treatment group (82.5% vs 52.9%; odds ratio, 4.18; 95% confidence interval (CI), 1.3–13.5) with lower rates of recurrence after treatment discontinuation (Gentile et al. 2013). The AGA offers a conditional recommendation for the use of systemic corticosteroids because of the uncertain balance between clinical benefit and potential harm (Nguyen et al. 2016).

Bismuth subsalicylate displays anti-inflammatory action due to salicylic acid and also acts as an antacid and a mild antibiotic (O'Toole 2016). A retrospective study found that most patients treated with this bismuth responded (53% complete response, 28% partial response), and that a dose of three tablets (262 mg each) three times per day appeared to be more effective than lower doses (Gentile et al. 2015). This study also suggested that bismuth might be most effective in patients with milder degrees of diarrhea (Gentile et al. 2015). Although based on these limited data, the use of bismuth appears to be effective and well tolerated (Bouma and Münch 2015). The use of bismuth in Western Europe is limited because it is not regularly available (Bouma and Münch 2015). For these reasons, the AGA has conditionally recommended bismuth salicylate as a second-line alternative treatment that may be appropriate for select patients who have contraindications to corticosteroids or for whom cost is a determining factor (Nguyen et al. 2016).

Cholestyramine, a bile acid sequestrant which binds bile in the gastrointestinal tract to prevent its reabsorption, has also been widely used for the treatment of MC, and it is considered an effective treatment in patients with MC and concomitant bile acid malabsorption (BAM) (Ung et al. 2000). Rates of BAM and the effect of bile acid sequestration were studied in 28 patients with CC, 12 (44%) had evidence of BAM (Ung et al. 2000). Eleven out of these 12 patients (92%) reported improvement in diarrhea within one week when treated with bile acid binding agents (cholestyramine 4 g 2-3 times per day, or colestipol 5g 2-3 times per day if the patients could not tolerate the smell or taste of cholestyramine) (Ung et al. 2000). Cholestyramine can be useful in patients with MC, regardless of whether there is concomitant BAM or not (Fernández-Bañares et al. 2016).

Loperamide is an opioid receptor agonist that decreases the activity of the myenteric plexus, allowing for more water to be absorbed out of the fecal matter and decreasing colonic mass movements (Jauregui-Amezaga et al. 2016)(Colussi et al. 2015). Although no RCTs have been performed to test its efficacy, several studies have shown clinical improvement with loperamide, but none reported sustained clinical remission (Jauregui-Amezaga et al. 2016)(Colussi et al. 2015). There are no RCT comparing efficacy of anti-diarrheals against placebo or other medical therapy for MC (Park 2015). Some authors think that anti-diarrheals may be used alone in mild MC or in conjunction with other therapies in moderate to severe MC to reduce frequency of diarrhea (Park 2015).

A prospective study with large cohort, with a long follow-up on the impact of dietary factors and lifestyle factors shows that, no association could be found between intake of protein, carbohydrates, different types of fat, fibre or zinc and occurrence of MC (Larsson et al. 2016). A diet quality index based on adherence to dietary recommendations failed to reveal any differences between cases and non-cases (Larsson et al. 2016). Additionally, there are no controlled data to advocate the use of antibiotics, but metronidazole or erythromycin have previously been used (O'Toole 2016). In patients with symptomatic MC, the AGA suggests against treatment with Boswellia serrata over no treatment for the induction of clinical remission (Nguyen et al. 2016). In patients with symptomatic MC, the AGA suggests against treatment with probiotics over no treatment for the induction of clinical remission (Nguyen et al. 2016). Low-quality evidence from a small randomized trial comparing a probiotic (Lactobacillus acidophilus, Bifidobacterium animalis, and lactis strains) with no treatment showed uncertain benefit with respect to clinical remission, histological response and quality of life due (Nguyen et al. 2016)(Jauregui-Amezaga et al. 2016).

Azathioprine and 6-mercaptopurine are immunosuppressive agents commonly used in IBD, both for their steroid-sparing effect and to maintain remission (Jauregui-Amezaga et al. 2016). They are an option of treatment in those patients with severe symptoms of MC who are refractory or intolerant to budesonide (Jauregui-Amezaga et al. 2016). Non-response to short term budesonide treatment can be found in 20% of cases (Jauregui-Amezaga et al. 2016). In the small number of patients with persistent symptoms despite budesonide and anti-diarrheal agents, immunomodulator therapy may be considered (A. Münch et al. 2012). Several published case reports have shown efficacy, but not enough RCT has been performed (Jauregui-Amezaga et al. 2016). This study showed 41% overall response rate to thiopurines (azathioprine or 6-mercaptopurine) in patients who were steroid dependent or failed other medical therapy, such as loperamide, cholestyramine, budesonide, mesalasine and methotrexate (A. Münch,

Fernandez-Banares, and Munck 2013). A retrospective series, demonstrated an overall response rate to thiopurines of 41% (19 of 46), but azathioprine was poorly tolerated accompanied by a high frequency of side effects, leading to treatment cessation (A. Münch et al. 2013). Also, short-term treatment with subcutaneous methotrexate (15 mg subcutaneously weekly for 6 weeks; dose was increased to 25 mg for a further 6 weeks if symptoms were unresponsive to the first 6-week treatment) had no clinical effect in CC patients intolerant or refractory to budesonide in a prospective case series (A. Münch et al. 2013).

There are no randomized trials studying the role of biologics in the management of MC, but recent case reports have suggested a role for anti-TNFα therapies (infliximab and adalimumab) in MC refractory to budesonide and the authors recommends considering biological therapy before colectomy (Park 2015)(O'Toole 2016)(Andreas Münch, Ignatova, and Ström 2012). In this case series, five of 372 MC patients (1.3%; 95% CI, 0.6 to 3.1) presented with severe symptoms refractory to standard medical therapies, including immunomodulators, received infliximab and showed clinical improvement (Esteve et al. 2011). From them 4 received infliximab therapy (Esteve et al. 2011). The response was excellent after one dose experiencing a 60–90% decrease in bowel movements (Esteve et al. 2011). Three patients were switched to adalimumab (2 allergic reactions and 1 early loss of response to infliximab) (Esteve et al. 2011). Long-term clinical remission (more than 1 year) was achieved in three cases (2 with adalimumab and 1 with infliximab) (Esteve et al. 2011). Münch et al. described three patients with collagenous colitis (CC) who developed side effects or were refractory to both budesonide and methotrexate and were given adalimumab (ADA) as a third-line treatment (Andreas Münch et al. 2012). ADA seems effective in budesonide and methotrexate refractory CC and can be administered to selected patients to achieve clinical remission, improve quality of life and possibly avoid colectomy (Andreas Münch et al. 2012). Further studies for induction and maintenance treatment should be conducted to confirm efficacy and examine safety issues, even in long term (Andreas Münch et al. 2012). There is also demonstrated a recent case-report of a patient with treatment-refractory lymphocytic colitis and diagnosed with ankylosing spondylitis, that is successfully use adalimumab injections which significantly improved patient's stool frequency, stool consistency and quality of life (Anderson and Makins 2016). The indication for surgical intervention is currently limited given the improved pharmacological treatment options (Bouma and Münch 2015). On the other hand, there are case reports of patients successfully undergoing colectomy or diverting ileostomy for refractory and severe MC (Park 2015). Considering advances in medical therapy the indication for surgery is limited (O'Toole 2016).

Conclusion:-

Microscopic colitis is relatively common cause of chronic watery (non-bloody) diarrhoea, particularly in the female elderly population. The diagnosis is based on clinical symptoms and requires colon biopsies from many segments. There is growing need to create awareness among general practitioner, gastroenterologist, pathologist and other medical doctors to refer the patient with chronic diarrhea for a colonoscopy. It is essential for gastroenterologist and endoscopist to obtain adequate biopsies at pancolonoscopy, although the colonic mucosa is normal, and pathologist to recognize features of MC. Great number of patients are still neglected or even misdiagnosed with IBS. As far as newly identified markers hold some potential, so far, none of the tested markers present sufficient accuracy for use in clinical practice, appearing as more useful to study MC pathogenic mechanisms, rather than to predict disease activity. The ideal biomarker for MC should correspond with lymphocyte collection in the mucosal layer, the collagenous band and also distinguishing MC from either healthy subjects or other forms of IBD. At the present time MC is considered as a worldwide condition, as common as IBD. Future research should focus on a better understanding of the underlying pathophysiological and immunological mechanisms, as well as the finding of biomarkers that reflect disease activity. There is also a need for further randomized placebo-controlled studies, especially with immunomodulators and anti-TNF drugs, in order to provide better long-term therapeutic strategies and better clinical management of the patients with microscopic colitis.

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Table 1:- List of medications

Medication (class)	Likelihood*
Proton pump inhibitors	High
Aspirin	High
NSAIDs ^	High

SSRIs	High
H2 receptor antagonists	High
Acarbose	High
Ticlopidine	High
Carbamazepine	Intermediate
Lisinopril	Intermediate
Flutamide	Intermediate
Statins	Intermediate
Levodopa/benserazide	Intermediate
Venotonic agents	Intermediate
Angiotensin II Receptor Blockers	Intermediate

Adapted from Aliment Pharmacol Ther 2005;22:277–84
^NSAIDs non-steroidal anti-inflammatory
drugs, SSRIs selective serotonin reuptake
inhibitors
*Likelihood refers to the strength of data

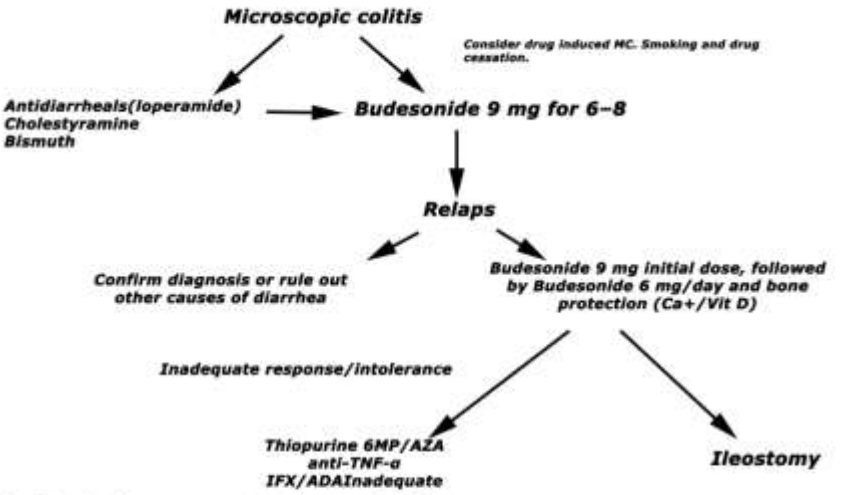

Figure 1. Curent algorithm for the management of microscopic colitis.
Notes: Adapted from Oxford University Press. Munch A, Aust D, Bohr J, et al. Microscopic colitis: current status, present and future challenges: statements of the European Microscopic Colitis Group. Journal of Crohn's and Colitis. 2012;6(9):932–945. Copyright © Oxford University Press
Abbreviations: 6MP, 6 mercaptopurine; ADA, adalimumab; AZA, azathioprine; IFX, infliximab; TNF, tumour necrosis factor; Vit D, vitamin D.

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