

Microscopic enteritis: Bucharest consensus

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Author contributions: Rostami K and Becheanu G organised the Consensus Meeting and the authors agreed on consensus objectives; all authors completed the consensus questionnaire; Rostami K coordinated the study and consensus manuscript; Rostami K, Aldulaimi D and Materacki L wrote the first draft of manuscript; Holmes G, Johnson MW, Robert M, Srivastava A, Fléjou JF, Sanders DS, Volta U, Derakhshan MH, Going JJ, Bassotti G, Catassi C, Danciu M, Ghafarzadegan K, Ishaq S, Rostami-Nejad M, Peña AS, Marsh MN and Villanacci V revised critically the manuscript in numerous occasions and contributed in re-writing and approving the last draft.

Conflict-of-interest: Non declared on behalf of all authors.

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Received: October 19, 2014

Peer-review started: October 27, 2014

First decision: November 26, 2014

Revised: December 29, 2014

Accepted: January 21, 2015

Abstract

Microscopic enteritis (ME) is an inflammatory condition of the small bowel that leads to gastrointestinal symptoms, nutrient and micronutrient deficiency. It is characterised by microscopic or sub-microscopic abnormalities such as microvillus changes and enterocytic alterations in the absence of definite macroscopic changes using standard modern endoscopy. This work recognises a need to characterize disorders with microscopic and submicroscopic features, currently regarded as functional or non-specific entities, to obtain further understanding of their clinical relevance. The consensus working party reviewed statements about the aetiology, diagnosis and symptoms associated with ME and proposes an algorithm for its investigation and treatment. Following the 5th International Course in Digestive Pathology in Bucharest in November 2012, an international group of 21 interested pathologists and gastroenterologists formed a working party with a view to formulating a consensus statement on ME. A five-step agreement scale (from strong agreement to strong disagreement) was used to score 21 statements, independently. There was strong agreement on all statements about ME histology (95%-100%). Statements concerning diagnosis achieved 85% to 100% agreement. A statement on the management of ME elicited agreement from the lowest rate (60%) up to 100%. The remaining two categories showed general agreement between experts on clinical presentation (75%-95%) and pathogenesis (80%-90%) of ME. There was strong agreement on the histological definition of ME. Weaker agreement on management indicates a need for further investigations, better definitions and clinical trials to produce quality guidelines for management. This ME consensus is a step toward greater recognition of a significant entity affecting symptomatic patients previously labelled as non-specific or functional enteropathy.

Key words: Microscopic enteritis; Enteropathy; Gluten; Malabsorption; Non-celiac gluten; Bucharest consensus

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Core tip: This is a global consensus on the classification, etiology, diagnosis and multidisciplinary treatment of milder enteropathy. There is no such thing as non-specific. The consensus on microscopic enteritis (ME) brings an end to the era of the non-specificities and opens a new prospect in characterisations of milder enteropathies including submicroscopic small intestinal mucosal changes in patients presenting with unexplained malabsorption syndrome and other category of so called non-specific gastrointestinal disorders. Recognition of ME is the first step toward identifying the masked etiologies under

the out of date diagnoses like irritable bowel syndrome and other so called functional gut disorders. It proposes the algorithm for imposing specific targeted treatment according to the etiologies instead of symptomatic treatment aiming to prevent the long term comorbidities.

Rostami K, Aldulaimi D, Holmes G, Johnson MW, Robert M, Srivastava A, Fléjou JF, Sanders DS, Volta U, Derakhshan MH, Going JJ, Becheanu G, Catassi C, Danciu M, Materacki L, Ghafarzadegan K, Ishaq S, Rostami-Nejad M, Peña AS, Bassotti G, Marsh MN, Villanacci V. Microscopic enteritis: Bucharest consensus. *World J Gastroenterol* 2015; 21(9): 2593-2604 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i9/2593.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i9.2593>

INTRODUCTION

Microscopic inflammatory conditions affecting the gastrointestinal tract include eosinophilic/ and lymphocytic oesophagitis, gastritis or enteritis, lymphocytic and collagenous gastroenteritis^[1] and other autoimmune disorders^[2-5]. Microscopic enteritis (ME) is an emergent diagnostic category first described in 2009^[6]. Clinically, the condition may be associated with symptomatic malabsorption, or more subtle micronutrient deficiencies. At the histological level, villous structure is largely preserved, but the epithelium is variably infiltrated by small lymphocytes, and there may be increases in crypt depth (crypt hyperplasia). These mucosal abnormalities may extend to subtle microvillous changes at sub-microscopic level, an increase in plasma cells, eosinophils and other inflammatory cells is likely to be present in the lamina propria.

It is increasingly recognised that subtle abnormalities of small bowel mucosa may be associated with significant symptoms and malabsorption^[7-9]. Relevant aetiologies include coeliac disease^[10], non-coeliac gluten sensitivity with microscopic or sub-microscopic changes^[11], microvillous inclusion disease^[12], common variable immunodeficiency^[13], tufting enteropathy^[14], parasitic infestations or infections like *Helicobacter pylori* (*H. pylori*)^[15], drugs including non-steroidal anti-inflammatory agents (NSAIDs) and inflammatory bowel disease (IBD)^[16].

Malabsorption is multifactorial with several aetiologies. The concept of ME is an attempt to take the first steps in explaining how specific histological changes could potentially lead to malabsorption despite association with only submicroscopic abnormalities^[17,18]. The concept of ME has arisen from the mucosal changes associated with celiac disease, as originally described in detail by Marsh in 1992 (Marsh 0; Marsh I; Marsh II; and Marsh III)^[19]. Note that the original Marsh IV is no longer in use, as it was thought to represent lymphomatous destruction of the mucosa. However, following widespread adoption of this classification, certain laboratories began to question the validity of

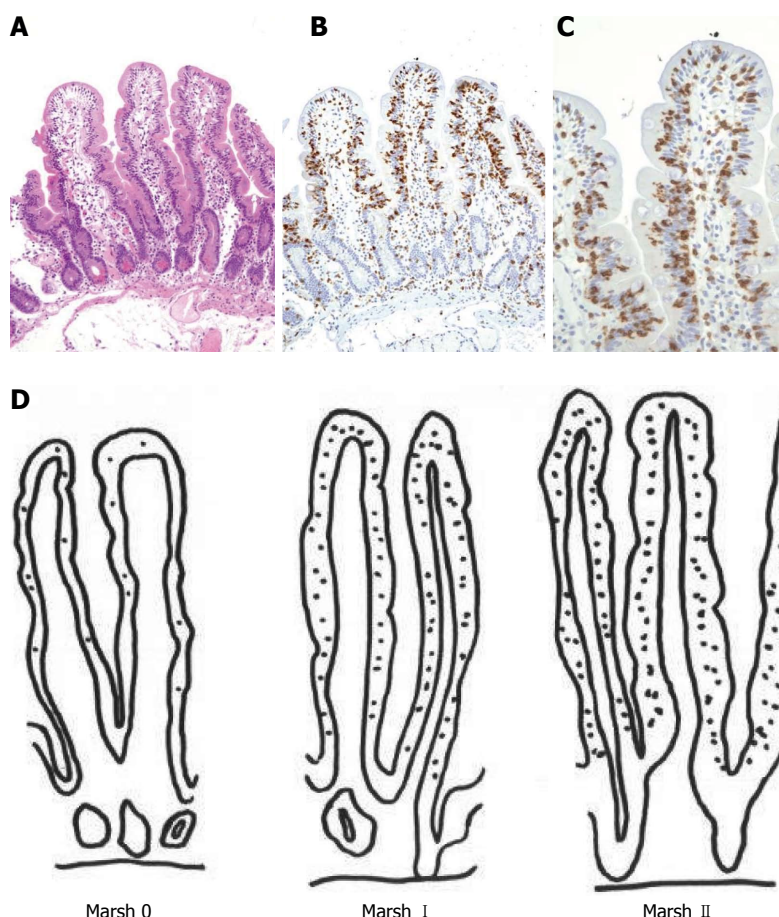


Figure 1 Legends for micrographs. A: Microscopic enteritis (ME), normal villi with pathological increase of T lymphocytes, HE $\times 10$; B: ME with immunohistochemistry for CD3 $\times 10$; C: ME; evident pathological number of T lymphocytes in the superficial epithelium of villi. CD3 immunohistochemistry $\times 40$; D: This diagram is representative of the phases of ME, in addition to the Marsh I ("infiltrated") and Marsh II ("infiltrated-hyperplastic") lesions, it is important to note that a histologically normal-appearing mucosa is a part of the ME spectrum, and that its underlying pathological connotations should therefore not be overlooked nor ignored.

the earlier Marsh categories, dismissing them as "non-specific", which was entirely inappropriate.

It has become clear that "non-specific" referred to multiple aetiological conditions, other than gluten related disorders, giving rise to identical, or similar, changes in the mucosa (Marsh 0, I, II). In other words, there is a differential diagnosis attached to Marsh 0-II categories which needs to be recognised. This collection of diseases, now referred to as ME, is the subject of this paper (Figure 1).

A contentious point in the histological characterisation of small bowel mucosa is the quantitation of intra-epithelial lymphocytosis (IEL). The normal duodenal IEL^[20,21] count remains contentious, with figures ranging from 11-25 IELs/100 enterocytes^[22-25]. Marsh used a computerised method to enumerate absolute values for IEL, against an invariant structure, the muscularis mucosae. He showed that the Ferguson technique (IEL/100 Enterocytes) grossly over-estimates IEL "counts" by a factor of 2^[23,26].

Moreover, he asserted that the IEL population is a graded characteristic (like height, weight, blood pressure, acid secretion *etc.*) and therefore cannot be separated as "normal" or increased: in other words, there is no

biphasic IEL population discernible, and the imposition of arbitrary "IEL cutoff norms" by various pathologists does not make sense and is therefore inappropriate. Whether the IEL population is abnormal is dependent on measurable changes following the appropriate treatment for the underlying disease. Finally, Marsh recognised that the IEL population is non-normally distributed, and therefore should be normalised by log-transformation. Even so his distributions of IEL counts for controls and coeliac disease overlapped. These factors complicate the histological analysis of ME, and ultimately need to be addressed.

The clinical significance of ME, although not fully determined, is increasingly being understood particularly in Crohn's disease (CD) where the majority of research has been focused. Recent studies have reported severe weight loss unrelated to the severity of duodenal mucosal damages^[7,27]. Despite growing interest and understanding of ME, there is little guidance for clinicians faced with interpreting pathology reports. To encourage targeted therapy against specific symptoms, a consensus on key aspects of ME is proposed. This work was undertaken in recognition of an increasing need to characterize disorders with microscopic and

Table 1 Results consensus agreement

	Total responses	Agreement	Comments
Definition	21/21	95%	
Clinical	21/21	95%	
Aetiology	21/21	95%	
Histological	21/21	100%	
Immunogenetic	21/21	90%	
Pathogenesis 1-2	21/21	80%-90%	
Diagnosis 1-3	21/21	85%-100%	
Investigation	21/21	95%	
Management	21/21	60%-100%	

submicroscopic presentations. To date, these have either been categorized as “functional” (clinical) or “non-specific” (histological), making it difficult to assess their clinical relevance. The consensus working party reviewed statements regarding the aetiology, diagnosis and symptoms associated with ME and to proposed an algorithm for its investigation and treatment.

RESEARCH

Following the 5th International Course of Digestive Pathology in Bucharest organised by Carol Davila University in November 2012 and 2013, a group of expert pathologists and gastroenterologists from around the world with an interest in small bowel disorders formed a working party to formulate a consensus statement on ME. A 5-step agreement score (from strongly agree to strongly disagree) was used independently by 21 experts, who reviewed 20 statements (Table 1).

Each panel member completed a pre-determined statement form relating to the definition, aetiology, diagnosis and treatment of ME. Statements were considered unanimously endorsed if more than 75% of the panel members shared a similar opinion (agree and strongly agree or disagree and strongly disagree). The consensus statements with supporting evidence are summarised below.

DEFINITION

ME is a histopathological condition that affects the small bowel and is characterised by microscopic and sub microscopic changes that may lead to micronutrient deficiencies (agreement: 95%).

ME is an early stage of mucosal abnormalities in several inflammatory conditions. It represents a common finding in patients with intestinal inflammation from different aetiologies. Recent advances in immunohistochemical staining techniques highlight sub-microscopic changes and enhanced detection of other microscopic abnormalities described by Marsh and others^[17,19].

The ill-defined mucosal lesions consistent with ME previously known as functional and non-specific

may affect the duodenum, jejunum and/or ileum with associated micronutrient malabsorption. It is well known that celiac disease with mild enteropathy is not necessarily a mild disease, as there is no correlation between mucosal lesion and clinical presentation of CD^[7].

Pathological changes can range from mild enteropathy with sub-microscopic abnormalities [alteration of enterocytes, shortening of microvilli and increased $\alpha/\beta/\gamma/\delta$ T cell receptors (Marsh 0)] to microscopic changes [increased IEL count (> 20 IEL/100 enterocytes) and/or crypt hyperplasia (Marsh I - II)] (agreement: 100%).

Marsh described a spectrum of small intestinal mucosal changes associated with CD but these are not specific and may be seen in other inflammatory disorders of the small intestine^[19]. Truly normal mucosal architecture and IEL count (Marsh stage 0) was considered possible but rare for CD. The mucosal appearance then progressed to an “infiltrative type”, characterised by normal architecture with increased IEL infiltration (Marsh stage I), ‘hyperplastic type’, characterised by crypt hyperplasia and increased mitotically active epithelial lymphocytes (Marsh stage II) and “destructive type”, characterised by partial or complete villous atrophy (Marsh stage III). The latter classification was modified to describe the degree of villous blunting in Marsh stage III destructive lesions: mild, marked and complete (IIIa, IIIb and IIIc respectively)^[25,28,29]. However, recent evaluations suggest that destructive lesions cannot be usefully subdivided into A, B, C subcategories with the basic tools available to most pathologists, and therefore is best abandoned.

Nevertheless the original widely used Marsh classification, seems to be the most reliable way of evaluating intestinal lesions not limited to CD. Inflammation associated with ME is better understood if the original Marsh classification is used as originally described. Several studies have observed that normal IEL counts are less than that initially defined by Marsh and may range between 11 and 25 IELs/100 enterocytes^[5,22-24,30].

Before the development of the ‘infiltrative type’ lesion of Marsh stage I has occurred, many other sub-microscopic abnormalities may occur, including subtle alteration to enterocytes, shortening of microvilli^[31,32] and altered ratio of T cell receptor $\alpha\beta$ and $\gamma\delta$ subsets of IELs^[18,33-36]. Interleukin (IL)-2 receptor upregulation may also be detected in conjunction with IEL T cell activation^[37].

These cases, with sub-microscopic changes but normal mucosal architecture and IEL counts, currently fall into Marsh stage 0. ME is characterised by mucosal changes of Marsh stages 0 to II and additional inflammatory changes not described in the current Marsh classification (Figure 1D).

From these critical studies, important conclusions arise: (1) A histologically “normal” mucosa doesn’t exclude an underlying intestinal disease process; and (2) the term

Table 2 Aetiology of microscopic enteritis

Conditions	Ref.
Celiac disease	[7,8]
Non coeliac gluten sensitivity	[52,53]
<i>Helicobacter pylori</i>	[15,57]
Other infections, parasites	[92]
Non-steroidal anti-inflammatory drugs	[64]
Bacterial overgrowth	[58-60]
Common variable immunodeficiency	[13]
Eosinophilic gastroenteritis	[90]
Collagenous gastroenteritis	[1]
Microvillous inclusion disease	[12]
Autoimmune enteropathy	[68]
Autoimmune disorders	[2,15,68]
Irritable bowel syndrome	[3,75]
Inflammatory bowel disease	[16]
Food allergy	[93]
Food intolerances	[76]
Idiopathic	[94]

“non-specific” should never be used diagnostically since every biopsy reflects the physiologic or pathological state of the small intestinal mucosa at the time of biopsy.

AETIOLOGY

ME is a multifactorial inflammatory process that may be caused by gluten intolerance, infections (including *H. pylori*), drug therapies and other systemic inflammatory processes (agreement: 100%).

ME results from an inflammatory process with several aetiological triggers. Recruitment and activation of IELs is pivotal and it is likely this is aetiology-specific with unique pro-inflammatory cytokine profile and triggering antigens. Established causes of ME include gluten exposure, infection, drug therapy, systemic inflammatory conditions and autoimmune diseases. In most cases an aetiology can be identified. Aziz *et al*^[3] and Brown *et al*^[38] found a definite cause for lymphocytic duodenitis (LD) in 66% of their patients^[3,38]. Multiple aetiologies may co-exist (Table 2) and a detailed diagnostic workup is imperative. Rosinach *et al*^[39] found more than one initial potential aetiology in 44% of patients with LD (Table 2).

Gluten related disorders

The gluten related disorders associated with ME are CD with minimal macroscopic changes, gluten/wheat allergy and non-coeliac gluten sensitivity (NCGS) (agreement: 83%).

Gluten related disorders are a major aetiology for ME affecting the small bowel and other organs in different ways. Gluten related disorders include CD, gluten/wheat allergy and NCGS. The triggering factor is exposure to the protein component of wheat and associated species of barley, rye and oats. Oats are safe in most CD patients. Innate and adaptive immune reactions lead to various abnormalities and

symptoms^[40] in and out of the gastrointestinal tract in genetically susceptible individuals^[41-45].

Subtypes of gluten intolerance have distinct mechanisms. In CD, ingestion of gluten and related prolamins stimulates adaptive immunity by tissue transglutaminase-mediated deamidation, human leucocyte antigen (HLA)-DQ2 complex formation and T-cell activation^[46-50]. In comparison, enteropathic gluten/wheat allergy results from an IgE-mediated or cell-mediated reaction to allergenic intra-luminal gluten and wheat-proteins^[51].

The nature and timing of reactions following oral or epicutaneous gluten challenge is crucial for diagnosis. NCGS is a re-discovered condition applicable to patients who fail to satisfy diagnostic criteria for CD or gluten/wheat allergy but benefit from GFD^[52,53]. The pathogenesis of NCGS is currently poorly understood but an enhanced innate immune response has been^[11,40,54,55]. Further research should clarify the differences between NCGS and CD.

ME is a common presenting histological finding in CD^[7,10,27]. Symptom severity may not correlate with the degree of enteropathy in patients with CD^[7,27]. Therefore recognition of subtle villous abnormalities is extremely important so that symptoms are not attributed inappropriately to a functional disorder. It should be noted that villous atrophy may be present in asymptomatic CD or persist despite treatment and clinical improvement. Similarly, deterioration of mild enteropathy into frank villous atrophy might not be associated with deterioration in symptoms or micronutrient deficiency.

Infection

Alongside more established associations with peptic ulceration, non-autoimmune chronic gastritis, primary gastric mucosa-associated lymphoid tissue (MALT) and gastric cancer, *H. pylori* infection is a prominent cause of intestinal ME. Mirbagheri *et al*^[56] found that *H. pylori* infection was associated with the presence and severity of microscopic duodenitis in patients with functional dyspepsia^[15,57]. A prospective study of 90 patients with LD attributed *H. pylori* infection as the single cause in 24.4% of cases^[39]. Furthermore *H. pylori* has been highlighted as the most frequent aetiology in patients with LD and abdominal pain^[58,59]. Santolaria *et al*^[58] found small bowel bacterial overgrowth caused LD in 22% of patients^[59,60] (Table 2).

The increased bacterial burden on the small intestine may cause ME by depleting of essential nutrients necessary for normal mucosal function and the subsequent generation of toxic metabolic products. Tropical sprue^[61], post-infective malabsorption and parasite infections including giardiasis and threadworm represent less prevalent infectious causes of ME^[2,62,63].

Drug therapy

NSAIDs and aspirin therapy are widely recognised

causes of ME with a prevalence of up to 14% reported in patients with LD^[4,39]. Epithelial damage may result from local exposure to the drug on ingestion or enterohepatic recirculation and/or due to systemic actions following absorption. Although *in vitro* mechanisms of NSAID-induced intestinal injury requires further evaluation, villous ischemia caused by focal slowing of villous blood flow and damage to surface microvasculature, have been identified in a murine model^[31]. Prior to mucosal ulceration, villous shortening and endothelial swelling were observed and may represent early NSAID-induced damage^[64]. More recently Olmesartan has been implicated in a severe sprue like enteropathy^[65,66].

Systemic inflammatory conditions

Microscopic abnormalities could be the presenting or at least the early stage of chronic inflammatory conditions including IBD and microscopic colitis (MC) (agreement 93%).

Systemic inflammatory conditions implicated in ME include sarcoidosis and IBD^[3]. Vidali *et al*^[67] identified microscopic duodenitis in 26.6% of patients with ulcerative colitis and significantly increased CD3+ and CD8+ IELs and lamina propria mononuclear cells compared with disease free controls. In some cases ME may be an initial non-specific finding that leads to diagnosis of a chronic inflammatory condition.

Autoimmune disease

Several autoimmune conditions may be associated with ME including rheumatoid arthritis, Hashimoto's thyroiditis, Graves' disease, psoriasis and multiple sclerosis^[15]. Mucosal changes may result from an associated autoimmune enteropathy characterised by elevated gut epithelial cell antibodies. The incidence of CD is greater in patients with autoimmune disease, so careful diagnostic workup is needed^[68].

ME AND MALABSORPTION

The malabsorption is due to activation of local and systemic cytokines leading to inhibition of the uptake of micronutrients (agreement: 80%).

Brar *et al*^[27] found that the clinical presentation in CD did not correlate with the degree of mucosal damage. Instead the underlying inflammatory process, common to each stage of enteropathy, may impair micronutrient uptake contributing to symptoms. Tumour necrosis factor α and IL-1, key pro-inflammatory cytokines, may act directly on the intestinal mucosa to cause malabsorption^[69,70]. This has been observed in non-gastrointestinal malignancies in which systemic cytokines are increased^[71].

Similarly IL-6 may impair iron transport in enterocytes by direct action at the local level or indirectly via hepcidin induction. Impaired iron absorption and elevated IL-6 levels were demonstrated

in patients with active CD compared with inactive disease controls^[72]. Future studies should further characterise the effects of cytokines on mucosal cells, specifically their absorptive function.

Malabsorption does not correlate with the length of small bowel micro/macrospectically affected (agreement: 80%).

Despite a macroscopically normal small bowel, microscopic and sub-microscopic mucosal abnormalities consistent with ME may exist with associated malabsorption. Brar *et al*^[27] found that clinical presentation did not correlate with the degree of villous atrophy in a retrospective study of 499 patients with CD. However patients with partial villous atrophy had greater haemoglobin and bone mineral density (measured at lumbar spine, hip and distal radius) than patients with subtotal and total villous atrophy.

This may be explained by ongoing inflammation, causing progressive bowel damage and cumulative systemic micronutrient deficiency. Instead, gastrointestinal symptoms may be the acute manifestation of micronutrient malabsorption that correlates with the severity of inflammation at that time. Therefore micronutrient absorption rate may not correlate with the degree of villous atrophy since it is not reflective of the duration of inflammation. Further studies are needed to test this theory and confirm that micronutrient absorption capacity does not relate to the degree of macroscopic small bowel damage.

DIAGNOSIS

The term ME can be proposed in cases of Marsh 0-II mucosal changes with clinical, serological, genetic and histological data supportive or unsupportive for a specific aetiology (agreement: 100%).

ME is confined to microscopic or sub-microscopic small intestinal enteropathy (Marsh 0-II) even if the aetiology is undetermined despite extensive clinical, serological, genetic and histological investigation. An underlying aetiology may not be detected on initial screening so further investigations become necessary to cover particular suspected diagnoses. Investigations may cover clinical suspicions according to the algorithm below.

A diagnosis of underlying aetiology of ME is dependent upon taking a careful history and detailed examination in suspected cases (agreement: 93%).

An accurate evaluation of ME requires a careful history and detailed clinical examination in the first instance. The findings elicited will help to select further investigations so that an accurate underlying diagnosis can be arrived at.

The history should pay particular attention to any chronic inflammatory conditions, drug therapies and symptoms affected by dietary changes (agreement: 100%).

Chronic inflammatory disease, drug therapies and

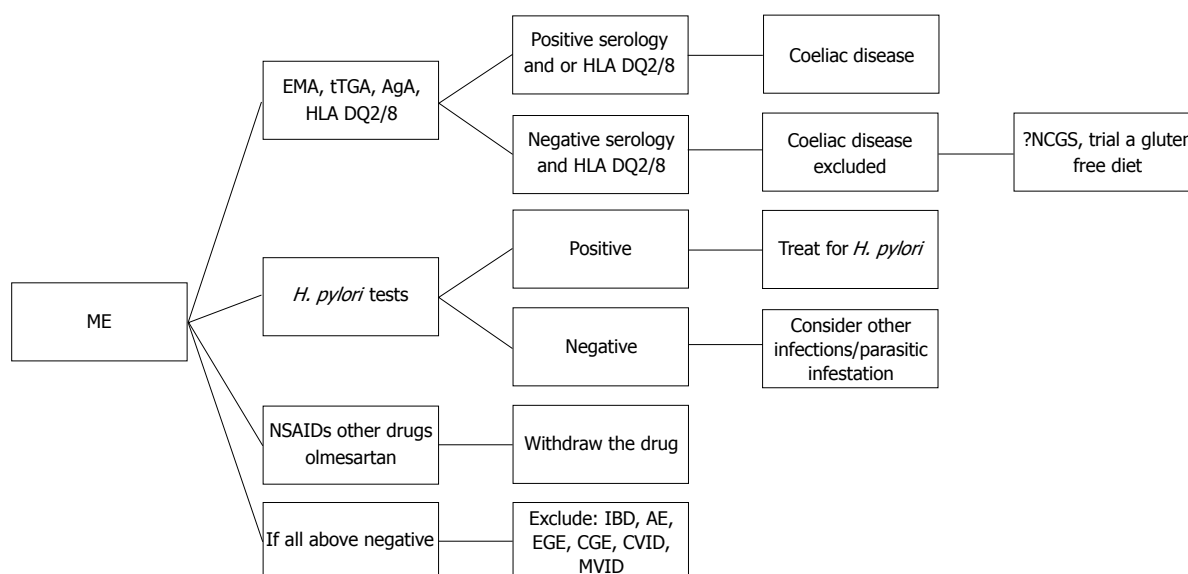


Figure 2 Algorithm for diagnosis the underlying condition behind microscopic enteritis. HLA: Human leucocyte antigen; EMA: Endomysial antibodies; tTGA: Tissue transglutaminase antibodies; AgA: Antigliadin antibodies; NCGS: Non coeliac gluten sensitivity; NSAIDs: Non-steroidal anti-inflammatory drugs; IBD: Inflammatory bowel disease; AE: Autoimmune enteropathy; EGE: Eosinophilic gastroenteritis; CVID: Common variable immunodeficiency; CGE: Collagenous gastroenteritis; MVID: Microvillous inclusion disease; *H. pylori*: *Helicobacter pylori*.

gluten intolerance are common causes of ME and hence should be evaluated with particular attention to the history. Occasionally an underlying occult chronic inflammatory disease may exist and therefore the practitioner should explore potential extra-intestinal features including arthritis, inflammatory ocular disease and dermatological peculiarities. Current and recently ceased medications should be reviewed, including NSAIDs angiotensin II inhibitors and “over the counter” medications. Time required for complete mucosal recovery following the cessation of medications is unclear. Many patients may have trialed particular diets in an attempt to alleviate symptoms following formal medical advice or, increasingly, attempted self-diagnosis. Others modify diet for weight loss. The effect of current or previous dietary modifications may provide useful diagnostic information.

Symptomatic improvement with gluten or lactose free diet suggests underlying gluten intolerance. Furthermore a current GFD may influence coeliac antibody serology results.

The clinical presentation of cases with ME with different aetiology may include gastrointestinal symptoms of abdominal discomfort, bloating, steatorrhoea, chronic diarrhoea and constipation; and systemic symptoms of lethargy and fatigue. Abnormal liver transaminases, specific micronutrient deficiency or weight loss may be present^[73,74]. Some studies suggest irritable bowel syndrome (IBS) may present with mild enteropathy^[3,75] and Fritscher-Ravens *et al*^[76] demonstrate exposing the food intolerant cases labelled as IBS to food antigens may cause immediate breaks, increased intervillous spaces and IEL in the intestinal mucosa. The symptoms are clearly similar in both cases with milder enteropathy

(ME) compared to severe mucosal damages despite the form of underlying conditions^[73,75,77] (Figure 2).

Investigations should include routine blood tests including a renal, liver and bone profile, serum B12, folate, ferritin and thyroid function tests, serum immunoglobulins, coeliac serology, *H. pylori* assessments (faecal antigen or blood serology) and HLA typing (agreement: 100%).

Initial investigations may help to establish the aetiology of ME and should evaluate micronutrient deficiency. Full blood count, renal and bone profile including vitamin D (25-OH-D3). Vitamin B12, folate and ferritin may reveal anaemia, electrolyte imbalance or specific micronutrient deficiency. Liver function tests may demonstrate elevated transaminases and cholestasis suggesting a chronic inflammatory disease such as primary biliary cirrhosis or sclerosing cholangitis potentially with concomitant IBD. Thyroid function tests are important. These investigation are useful in assessing systemic conditions that may affect any organs.

Coeliac serology should include anti-tissue transglutaminase (anti-tTg) and endomysial antibodies (EMA), immunoglobulin titres and HLA typing. Several studies have found that the sensitivity of coeliac antibody serology is poor in CD with mild enteropathy^[78,79].

Detection of HLA DQ2 and to lesser extent DQ8 genotypes (both strongly associated with CD) may be more useful when investigating patients with ME for underlying CD. HLA DQ2 and DQ8 genotype is however present in 25%-40% of the general population, so their absence is more useful in tending to exclude CD.

Evaluation for concomitant CD is particularly

important in patients with pre-existing autoimmune disease given its increased prevalence and since multiple potential ME aetiologies may co-exist^[39]. In ME with negative coeliac serology and no clear alternative aetiology the authors recommend a trial of GFD for potential underlying non-coeliac gluten sensitivity^[80-82]. Vande Voort *et al*^[79] found that 38% of patients with LD and non-HLA DQ2 or DQ8 genotype improved with initiation of GFD. In contrast Biagi *et al*^[83] recommend that patients with Marsh I or II intestinal lesions should only commence GFD if coeliac antibody serology becomes positive.

Further investigations should be guided by clinical suspicion based on the history, examination and initial serological screen.

Other investigations include colonoscopy, ideally with intubation of the terminal ileum, and multiple colonic biopsies to look for MC (agreement: 80%).

MC may rarely be a precursor of IBD. Therefore colonoscopy, ideally with intubation of the terminal ileum and multiple biopsies from right and left colon, may be a useful additional investigation when an aetiology for ME cannot be identified or in patients with other potential aetiology who do not respond to treatment. Microscopic colitis may cause a similar spectrum of clinical symptoms as ME including abdominal pain, cramping, bloating and diarrhoea. Early detection and treatment of IBD will minimise long term complications.

For ME upper gastrointestinal (GI) endoscopy with multiple duodenal biopsies (at least four) from the second part of the duodenum, 2 from first part of duodenum in cases with high risk for coeliac disease is required and additional biopsies should be taken to investigate for helicobacter infection and lymphocytic gastritis (agreement: 100%).

To detect ME the authors advocate upper GI endoscopy with at least four duodenal biopsies from D2. In a retrospective study of 132352 patients without known CD, a minimum of four biopsies was significantly more effective at achieving a pathological diagnosis of CD, defined as Marsh stage IIIA/B/C, compared with less than four biopsies (1.8% vs 0.7%, $P < 0.0001$)^[84]. Marsh stage I and II lesions were found in 4.5% of patients although the cause was not reported. There may be additional diagnostic yield from including a duodenal bulb biopsy particularly in patients with patchy villous atrophy. Bonamico *et al*^[85] found that in 16 children with patchy villous atrophy and positive coeliac serology (EMA, anti-tTg antibodies and HLA-DQ2/DQ8 heterodimers), villous atrophy was detected at the duodenal bulb in all patients and was the only duodenal biopsy demonstrating atrophy in 31% of cases.

Hopper *et al*^[86] advised at least three duodenal biopsies including one from the duodenal bulb to detect villous atrophy in patients with serology suggestive of CD. Concurrent antral gastric biopsies are

recommended to assess for lymphocytic gastritis and *H. pylori* infection (rapid urease test "RUT", biopsies from antrum and corpus), a common treatable cause of ME. C13 breath test should be considered as sensitivity of RUT is low. Biopsies from oesophagus and stomach might also be indicated in dyspeptic patients.

ME can progress to overt coeliac disease in genetically susceptible patients (agreement: 93%).

Following a diagnosis of ME, regular follow up is vital to detect initially silent but potentially treatable aetiology and to evaluate for evolving micronutrient deficiency. This includes CD which may not be detected on initial investigations. It is well documented that initially negative serology for CD may subsequently become positive. Duodenal abnormalities may progress from ME to Marsh stage III with continued ingestion of a gluten containing diet in genetically susceptible patients^[17].

TREATMENT

Treatment of ME is dependent on the aetiology: (agreement: 100%).

In coeliac and non-coeliac gluten sensitivity; dietetic review and initiation of a gluten free diet is the cardinal intervention (agreement: 100%).

The cardinal intervention for gluten related disorders is dietetic review and initiation of GFD^[87]. This supersedes advice that a GFD should only be recommended in CD patients with severe enteropathy. A GFD should be trialled to assess possible non-coeliac gluten sensitivity in patients with ME and no clear alternative aetiology. In the absence of clinical improvement repeat coeliac serology and follow-up duodenal biopsies may be required to assess for histopathological improvement before the patient is considered gluten tolerant. The optimal interval of GFD trial prior to repeat biopsy is poorly established but anecdotally at least six weeks seems to be appropriate. Aziz *et al*^[3] initiated a six week gluten challenge with repeat coeliac serology and duodenal biopsies in patients with LD of undetermined aetiology after primary investigation although the diagnostic yield was unclear.

For treatment of ME, any enteric infections including *H. pylori* should be eradicated (agreement: 93%).

Eradicating existing enteric infections is important both in the management of ME and to reduce potentially overlapping morbidity from alternative sources. *H. pylori* infection is also associated with peptic ulcer disease, non-ulcer dyspepsia, gastric cancer and gastric MALT lymphoma. Standard triple therapy eradication regimen is recommended for *H. pylori* infection in the first instance^[88]. Some enteric infections may cause concomitant microscopic colitis. Giardiasis is empirically treated with metronidazole^[89]. Other parasitic infections such as threadworm may require mebendazole or piperazine therapy.

Wherever possible any drugs associated with ME should be stopped (NSAIDs, aspirin or angiotensin II inhibitors) (agreement: 93%).

Currently a small group of medications, specifically NSAIDs, are known to cause ME however this will expand as clinical experience and understanding of the condition grows. Olmesartan has been described associated with severe enteropathy. But mild enteropathy might also be associated with this drug and so far this association has not been excluded. A thorough clinical assessment of drugs and their indication is essential when looking for the aetiology of enteropathy with different severity and contributory medications should be stopped where possible. In cases of ME where offending medication like NSAIDs or angiotensin II inhibitors cannot initially be ceased regular review is recommended to assess the ongoing need for the medication and to detect micronutrient deficiencies amenable to treatment.

Appropriate diet associated to medical therapy is required for eosinophilic enteritis (agreement: 93%).

Eosinophilic enteritis^[90], characterised by unexplained intestinal mucosal eosinophilia, is often associated with atopy and food allergies. Elimination of allergenic foods or initiation of an amino-acid based elemental diet may provide symptomatic benefit however some patients may need concomitant treatment with anti-inflammatory medications (e.g., oral corticosteroids).

Other causes of ME including systemic inflammatory conditions and autoimmune disease should be managed with targeted medical therapy guided by the appropriate specialist.

It is important to review progress and a repeat upper GI endoscopy should be considered to confirm response to therapy (agreement: 87%).

Following initiation of aetiology-targeted treatment it is important to assess clinical and/or histological improvement particularly in patients with multiple potential aetiologies, where a stepwise approach to treatment with regular review to determine response is recommended. If there is no improvement despite treatment the perceived aetiology should be re-evaluated. The duration of an ineffective treatment should be minimised since dietary modifications may be socially inhibiting and expensive and medical therapies may cause unpleasant side effects.

Patients should be considered for repeat assessments including an endoscopy and duodenal biopsies if symptoms persist (agreement: 87%).

In patients who fail to clinically improve despite treatment directed at the presumed aetiology, reassessments including endoscopy and gastroduodenal biopsies are indicated to evaluate for concomitant aetiology and to re-evaluate mucosal integrity. There is no known treatment for idiopathic ME. Regular assessments are keys to detecting initially undetected aetiologies and correcting micronutrient deficiencies, particularly in patients with persistent or worsening

symptoms. The increased IEL in so called idiopathic cases may normalise in the majority of cases at six weeks, although it is unclear whether this improvement correlates with symptom resolution^[3]. This suggests idiopathic ME may be self-limiting in a proportion of cases.

Further work is needed to better define the natural history and long-term clinical significance of ME, particularly whether it represents a precursor for more sinister pathology such as lymphoma which has a well-recognised association with CD^[91]. Whilst this remains unclear the authors advocate that all patients with ME including those who improve with treatment are monitored and considered for repeat upper GI endoscopy if clinically indicated.

SUMMARY AND RECOMMENDATIONS

The number of pathology reports identifying ME has increased markedly in recent years alongside advances in immuno-histochemical techniques and an increasing caseload of patients undergoing endoscopic investigation. This has created uncertainty amongst some clinicians faced with interpreting a finding of ME in the clinical setting. This expert consensus opinion provides evidence-based recommendations to aid clinical practice, particularly regarding the diagnosis, investigation and management of ME.

CONCLUSION

ME is a histopathological condition that affects the small bowel characterised by microscopic and submicroscopic changes (Marsh stage 0-II). Even sub microscopic abnormalities may lead to micronutrient deficiencies and symptoms. ME is associated with several recognised aetiologies including gluten intolerance, gastrointestinal infections, allergy, drug therapy, systemic inflammatory disease like IBD and autoimmune conditions. The severity of symptoms in Coeliac Disease is unrelated to the degree of mucosal damage or length of bowel affected and it clear that there is no correlation between the degree of mucosal abnormalities and malabsorption. A diagnosis of ME is indicated when Marsh I or II mucosal abnormalities exist. In the presence of gastrointestinal symptoms or evidence of malabsorption, a Marsh 0 lesion should be subjected to further detailed examination. Indeed and clinical, serological, genetic and histological and in some cases imaging data may all be needed to determine the aetiologies. ME should be investigated with a thorough history and examination, a full serological screen and upper GI endoscopy with gastric biopsies, *H. pylori* testing and ($\geq$ 4) duodenal biopsies from D2 and 2 from D1 in high-risk patients. A colonoscopy with biopsies taken from both the left and right side may be useful in selected cases. Treatment should be directed at the suspected underlying aetiology. Regular reassessment is important

in all cases particularly if symptoms persist and whilst the natural history of ME remains unknown. Future research should further evaluate the clinical significance, aetiology-specific pathogenesis, natural history, specific biomarkers and long-term sequelae of ME and the essential pathological/immunological mucosal features of each contributory cause.

REFERENCES

- Rustagi T**, Rai M, Scholes JV. Collagenous gastroduodenitis. *J Clin Gastroenterol* 2011; **45**: 794-799 [PMID: 21346601 DOI: 10.1097/MCG.0b013e31820c6018]
- Montgomery RD**, Shearer AC. The cell population of the upper jejunal mucosa in tropical sprue and postinfective malabsorption. *Gut* 1974; **15**: 387-391 [PMID: 18668848 DOI: 10.1136/gut.15.5.387]
- Aziz I**, Evans KE, Hopper AD, Smillie DM, Sanders DS. A prospective study into the aetiology of lymphocytic duodenitis. *Aliment Pharmacol Ther* 2010; **32**: 1392-1397 [PMID: 21050242 DOI: 10.1111/j.1365-2036.2010.04477.x]
- Kakar S**, Nehra V, Murray JA, Dayharsh GA, Burgart LJ. Significance of intraepithelial lymphocytosis in small bowel biopsy samples with normal mucosal architecture. *Am J Gastroenterol* 2003; **98**: 2027-2033 [PMID: 14499783 DOI: 10.1111/j.1572-0241.2003.07631.x]
- Veress B**, Franzén L, Bodin L, Borch K. Duodenal intraepithelial lymphocyte-count revisited. *Scand J Gastroenterol* 2004; **39**: 138-144 [PMID: 15000275 DOI: 10.1080/00365520310007675]
- Rostami K**, Villanacci V. Microscopic enteritis: novel prospect in coeliac disease clinical and immuno-histogenesis. Evolution in diagnostic and treatment strategies. *Dig Liver Dis* 2009; **41**: 245-252 [PMID: 18657490 DOI: 10.1016/j.dld.2008.06.008]
- Zanini B**, Caselani F, Magni A, Turini D, Ferraresi A, Lanzarotto F, Villanacci V, Carabellese N, Ricci C, Lanzini A. Celiac disease with mild enteropathy is not mild disease. *Clin Gastroenterol Hepatol* 2013; **11**: 253-258 [PMID: 23022697 DOI: 10.1016/j.cgh.2012.09.027]
- Zanini B**, Lanzarotto F, Villanacci V, Carabellese N, Ricci C, Lanzini A. Clinical expression of lymphocytic duodenitis in "mild enteropathy" celiac disease and in functional gastrointestinal syndromes. *Scand J Gastroenterol* 2014; **49**: 794-800 [PMID: 24941349 DOI: 10.3109/00365521.2014.919017]
- Fernández-Bañares F**, Carrasco A, García-Puig R, Rosinach M, González C, Alsina M, Loras C, Salas A, Viver JM, Esteve M. Intestinal intraepithelial lymphocyte cytometric pattern is more accurate than subepithelial deposits of anti-tissue transglutaminase IgA for the diagnosis of celiac disease in lymphocytic enteritis. *PLoS One* 2014; **9**: e101249 [PMID: 25010214 DOI: 10.1371/journal.pone.0101249]
- Bhatnagar S**, Gupta SD, Mathur M, Phillips AD, Kumar R, Knutton S, Unsworth DJ, Lock RJ, Natchu UC, Mukhopadhyaya S, Saini S, Bhan MK. Celiac disease with mild to moderate histologic changes is a common cause of chronic diarrhea in Indian children. *J Pediatr Gastroenterol Nutr* 2005; **41**: 204-209 [PMID: 16056100 DOI: 10.1097/01.mpg.0000172261.24115.29]
- Catassi C**, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zavallos V, Sapone A, Fasano A. Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. *Nutrients* 2013; **5**: 3839-3853 [PMID: 24077239 DOI: 10.3390/nu5103839]
- Thoeni CE**, Vogel GF, Tancevski I, Geley S, Lechner S, Pfaller K, Hess MW, Müller T, Janecke AR, Avitzur Y, Muise A, Cutz E, Huber LA. Microvillus inclusion disease: loss of Myosin vb disrupts intracellular traffic and cell polarity. *Traffic* 2014; **15**: 22-42 [PMID: 24138727 DOI: 10.1111/tra.12131]
- Malamut G**, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, Bouhnik Y, Lambotte O, Béchade D, Ziol M, Lavergne A, Hermine O, Cerf-Bensussan N, Cellier C. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. *Am J Gastroenterol* 2010; **105**: 2262-2275 [PMID: 20551941 DOI: 10.1038/ajg.2010.214]
- Ranganathan S**, Schmitt LA, Sindhi R. Tufting enteropathy revisited: the utility of MOC31 (EpCAM) immunohistochemistry in diagnosis. *Am J Surg Pathol* 2014; **38**: 265-272 [PMID: 24418860 DOI: 10.1097/PAS.000000000000106]
- Rostami Nejad M**, Rostami K, Yamaoka Y, Mashayekhi R, Molaei M, Dabiri H, Al Dulaimi D, Mirsattari D, Zojaji H, Norouzinia M, Zali MR. Clinical and histological presentation of Helicobacter pylori and gluten related gastroenteropathy. *Arch Iran Med* 2011; **14**: 115-118 [PMID: 21361718]
- Defendenti C**, Sarzi-Puttini P, Grosso S, Croce A, Senesi O, Saibeni S, Bollani S, Almasio PL, Bruno S, Atzeni F. B lymphocyte intestinal homing in inflammatory bowel disease. *BMC Immunol* 2011; **12**: 71 [PMID: 22208453 DOI: 10.1186/1471-2172-12-71]
- Sbarbati A**, Valletta E, Bertini M, Cipolli M, Morroni M, Pinelli L, Tatò L. Gluten sensitivity and 'normal' histology: is the intestinal mucosa really normal? *Dig Liver Dis* 2003; **35**: 768-773 [PMID: 14674666 DOI: 10.1016/S1590-8658(03)00457-2]
- Galipeau HJ**, Verdu EF. Gut microbes and adverse food reactions: Focus on gluten related disorders. *Gut Microbes* 2014; **5**: 594-605 [PMID: 25483329]
- Marsh MN**. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* 1992; **102**: 330-354 [PMID: 1727768]
- Robert ME**. Gluten sensitive enteropathy and other causes of small intestinal lymphocytosis. *Semin Diagn Pathol* 2005; **22**: 284-294 [PMID: 16939056 DOI: 10.1053/j.semdp.2006.04.004]
- Robert ME**, Ament ME, Weinstein WM. The histologic spectrum and clinical outcome of refractory and unclassified sprue. *Am J Surg Pathol* 2000; **24**: 676-687 [PMID: 10800986 DOI: 10.1097/00000478-200005000-00006]
- Dickson BC**, Streutker CJ, Chetty R. Coeliac disease: an update for pathologists. *J Clin Pathol* 2006; **59**: 1008-1016 [PMID: 17021129 DOI: 10.1136/jcp.2005.035345]
- Crowe PT**, Marsh MN. Morphometric analysis of intestinal mucosa. VI--Principles in enumerating intra-epithelial lymphocytes. *Virchows Arch* 1994; **424**: 301-306 [PMID: 8186895 DOI: 10.1007/BF00194615]
- Hayat M**, Cairns A, Dixon MF, O'Mahony S. Quantitation of intraepithelial lymphocytes in human duodenum: what is normal? *J Clin Pathol* 2002; **55**: 393-394 [PMID: 11986350 DOI: 10.1136/jcp.55.5.393]
- Rostami K**, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. *Am J Gastroenterol* 1999; **94**: 888-894 [PMID: 10201452 DOI: 10.1111/j.1572-0241.1999.983.f.x]
- Marsh MN**. Defining 'coeliac': Oslo Accord--or not? *Gut* 2013; **62**: 1669-1670 [PMID: 23514748 DOI: 10.1136/gutjnl-2013-304632]
- Brar P**, Kwon GY, Egbuna II, Holleran S, Ramakrishnan R, Bhagat G, Green PH. Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. *Dig Liver Dis* 2007; **39**: 26-29; discussion 30-32 [PMID: 16982222 DOI: 10.1016/j.dld.2006.07.014]
- Corazza GR**, Villanacci V. Coeliac disease. *J Clin Pathol* 2005; **58**: 573-574 [PMID: 15917404 DOI: 10.1136/jcp.2004.023978]
- Corazza GR**, Villanacci V, Zambelli C, Milione M, Luinetti O, Vindigni C, Chioda C, Albarello L, Bartolini D, Donato F. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. *Clin Gastroenterol Hepatol* 2007; **5**: 838-843 [PMID: 17544877 DOI: 10.1016/j.cgh.2007.03.019]
- Pellegrino S**, Villanacci V, Sansotta N, Scarfi R, Bassotti G, Vieni G, Princiotta A, Sferlazzas C, Magazzù G, Tuccari G. Redefining the intraepithelial lymphocytes threshold to diagnose gluten sensitivity

- in patients with architecturally normal duodenal histology. *Aliment Pharmacol Ther* 2011; **33**: 697-706 [PMID: 21255060 DOI: 10.1111/j.1365-2036.2011.04578.x]
- 31 **Kelly DA**, Piasecki C, Anthony A, Dhillon AP, Pounder RE, Wakefield AJ. Focal reduction of villous blood flow in early indomethacin enteropathy: a dynamic vascular study in the rat. *Gut* 1998; **42**: 366-373 [PMID: 9577343 DOI: 10.1136/gut.42.3.366]
 - 32 **Anthony A**, Dhillon AP, Thrassivoulou C, Pounder RE, Wakefield AJ. Pre-ulcerative villous contraction and microvascular occlusion induced by indomethacin in the rat jejunum: a detailed morphological study. *Aliment Pharmacol Ther* 1995; **9**: 605-613 [PMID: 8824647 DOI: 10.1111/j.1365-2036.1995.tb00429.x]
 - 33 **Han A**, Newell EW, Glanville J, Fernandez-Becker N, Khosla C, Chien YH, Davis MM. Dietary gluten triggers concomitant activation of CD4+ and CD8+ $\alpha\beta$ T cells and $\gamma\delta$ T cells in celiac disease. *Proc Natl Acad Sci USA* 2013; **110**: 13073-13078 [PMID: 23878218 DOI: 10.1073/pnas.1311861110]
 - 34 **Chan KN**, Phillips AD, Walker-Smith JA, Koskimies S, Spencer J. Density of gamma/delta T cells in small bowel mucosa related to HLA-DQ status without coeliac disease. *Lancet* 1993; **342**: 492-493 [PMID: 8102443 DOI: 10.1016/0140-6736(93)91616-T]
 - 35 **Spencer J**, Isaacson PG, MacDonald TT, Thomas AJ, Walker-Smith JA. Gamma/delta T cells and the diagnosis of coeliac disease. *Clin Exp Immunol* 1991; **85**: 109-113 [PMID: 1829988 DOI: 10.1111/j.1365-2249.1991.tb05690.x]
 - 36 **Chen Y**, Chou K, Fuchs E, Havran WL, Boismenu R. Protection of the intestinal mucosa by intraepithelial gamma delta T cells. *Proc Natl Acad Sci USA* 2002; **99**: 14338-14343 [PMID: 12376619 DOI: 10.1073/pnas.212290499]
 - 37 **Kirman I**, Nielsen OH, Kjaersgaard E, Brynskov J. Interleukin-2 receptor alpha and beta chain expression by circulating alpha beta and gamma delta T cells in inflammatory bowel disease. *Dig Dis Sci* 1995; **40**: 291-295 [PMID: 7851192 DOI: 10.1007/BF02065412]
 - 38 **Brown I**, Mino-Kenudson M, Deshpande V, Lauwers GY. Intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa: an increasing diagnostic problem with a wide differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1020-1025 [PMID: 16831028]
 - 39 **Rosinach M**, Esteve M, González C, Temiño R, Mariné M, Monzón H, Sainz E, Loras C, Espinós JC, Forné M, Viver JM, Salas A, Fernández-Bañares F. Lymphocytic duodenitis: aetiology and long-term response to specific treatment. *Dig Liver Dis* 2012; **44**: 643-648 [PMID: 22497904 DOI: 10.1016/j.dld.2012.03.006]
 - 40 **Peña AS**. Immunogenetics of non celiac gluten sensitivity. *Gastroenterol Hepatol Bed Bench* 2014; **7**: 1-5 [PMID: 25436091 DOI: 10.1371/journal.pmed.0010001]
 - 41 **Arentz-Hansen H**, Fleckenstein B, Molberg Ø, Scott H, Koning F, Jung G, Roepstorff P, Lundin KE, Sollid LM. The molecular basis for oat intolerance in patients with celiac disease. *PLoS Med* 2004; **1**: e1 [PMID: 15526039]
 - 42 **Sollid LM**. Molecular basis of celiac disease. *Annu Rev Immunol* 2000; **18**: 53-81 [PMID: 10837052 DOI: 10.1146/annurev.immunol.18.1.53]
 - 43 **Kupper C**. Dietary guidelines and implementation for celiac disease. *Gastroenterology* 2005; **128**: S121-S127 [PMID: 15825119 DOI: 10.1053/j.gastro.2005.02.024]
 - 44 **Küpper C**. [Dietary fiber--stepchild in nutrition, which has much benefit. Patients with diverticulosis must get their intestines functioning]. *Fortschr Med* 1998; **116**: 40-41 [PMID: 9577073]
 - 45 **Di Sabatino A**, Corazza GR. Coeliac disease. *Lancet* 2009; **373**: 1480-1493 [PMID: 19394538 DOI: 10.1016/S0140-6736(09)60254-2543]
 - 46 **Gujral N**, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol* 2012; **18**: 6036-6059 [PMID: 23155333 DOI: 10.3748/wjg.v18.i42.6036]
 - 47 **Srivastava A**, Yachha SK, Mathias A, Parveen F, Poddar U, Agrawal S. Prevalence, human leukocyte antigen typing and strategy for screening among Asian first-degree relatives of children with celiac disease. *J Gastroenterol Hepatol* 2010; **25**: 319-324 [PMID: 19929927 DOI: 10.1111/j.1440-1746.2009.06044.x]
 - 48 **Yachha SK**, Srivastava A, Mohindra S, Krishnani N, Aggarwal R, Saxena A. Effect of a gluten-free diet on growth and small-bowel histology in children with celiac disease in India. *J Gastroenterol Hepatol* 2007; **22**: 1300-1305 [PMID: 17565588 DOI: 10.1111/j.1440-1746.2007.04929.x]
 - 49 **Yachha SK**, Aggarwal R, Srinivas S, Srivastava A, Somani SK, Itha S. Antibody testing in Indian children with celiac disease. *Indian J Gastroenterol* 2006; **25**: 132-135 [PMID: 16877825]
 - 50 **Mohindra S**, Yachha SK, Srivastava A, Krishnani N, Aggarwal R, Ghoshal UC, Prasad KK, Naik SR. Coeliac disease in Indian children: assessment of clinical, nutritional and pathologic characteristics. *J Health Popul Nutr* 2001; **19**: 204-208 [PMID: 11761775]
 - 51 **Hischenhuber C**, Crevel R, Jarry B, Mäki M, Moneret-Vautrin DA, Romano A, Troncone R, Ward R. Review article: safe amounts of gluten for patients with wheat allergy or coeliac disease. *Aliment Pharmacol Ther* 2006; **23**: 559-575 [PMID: 16480395 DOI: 10.1111/j.1365-2036.2006.02768.x]
 - 52 **Cooper BT**, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology* 1980; **79**: 801-806 [PMID: 7419003]
 - 53 **Sapone A**, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders DS, Schumann M, Ullrich R, Villalta D, Volta U, Catassi C, Fasano A. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012; **10**: 13 [PMID: 22313950 DOI: 10.1186/1741-7015-10-13]
 - 54 **Volta U**, Caio G, Tovoli F, De Giorgio R. Non-celiac gluten sensitivity: questions still to be answered despite increasing awareness. *Cell Mol Immunol* 2013; **10**: 383-392 [PMID: 23934026 DOI: 10.1038/cmi.2013.28]
 - 55 **Rostami K**, Hogg-Kollars S. A Patient's Journey. Non-coeliac gluten sensitivity. *BMJ* 2012; **345**: e7982 [PMID: 23204003 DOI: 10.1136/bmj.e7982]
 - 56 **Mirbagheri SA**, Khajavirad N, Rakhshani N, Ostovaneh MR, Hoseini SM, Hoseini V. Impact of Helicobacter pylori infection and microscopic duodenal histopathological changes on clinical symptoms of patients with functional dyspepsia. *Dig Dis Sci* 2012; **57**: 967-972 [PMID: 22080417 DOI: 10.1007/s10620-011-1960-z]
 - 57 **Lebwohl B**, Blaser MJ, Ludvigsson JF, Green PH, Rundle A, Sonnenberg A, Genta RM. Decreased risk of celiac disease in patients with Helicobacter pylori colonization. *Am J Epidemiol* 2013; **178**: 1721-1730 [PMID: 24124196 DOI: 10.1093/aje/kwt234]
 - 58 **Santolaria S**, Dominguez M, Alcedo J, Abascal M, García-Prats MD, Marigil M, Vera J, Ferrer M, Montoro M. [Lymphocytic duodenitis: etiological study and clinical presentations]. *Gastroenterol Hepatol* 2013; **36**: 565-573 [PMID: 24007857 DOI: 10.1016/j.gastrohep.2013.06.003]
 - 59 **Molina-Infante J**, Santolaria S, Fernandez-Bañares F, Montoro M, Esteve M. Lymphocytic enteropathy, HLA-DQ2/DQ8 genotype and wheat-dependent symptoms: non-celiac wheat sensitivity or Marsh I celiac disease? *Am J Gastroenterol* 2013; **108**: 451 [PMID: 23459052 DOI: 10.1038/ajg.2012.433]
 - 60 **Villanacci V**, Bassotti G, Liserre B, Lanzini A, Lanzarotto F, Genta RM. Helicobacter pylori infection in patients with celiac disease. *Am J Gastroenterol* 2006; **101**: 1880-1885 [PMID: 16780559 DOI: 10.1111/j.1572-0241.2006.00621.x]
 - 61 **Marsh MN**, Mathan M, Mathan VI. Studies of intestinal lymphoid tissue. VII. The secondary nature of lymphoid cell "activation" in the jejunal lesion of tropical sprue. *Am J Pathol* 1983; **112**: 302-312 [PMID: 6614143]
 - 62 **Hanevik K**, Hausken T, Morken MH, Strand EA, Mørch K, Coll P, Helgeland L, Langeland N. Persisting symptoms and duodenal inflammation related to Giardia duodenalis infection. *J Infect* 2007; **55**: 524-530 [PMID: 17964658 DOI: 10.1016/j.jinf.2007.09.004]
 - 63 **Duncombe VM**, Bolin TD, Davis AE, Cummins AG, Crouch RL. Histopathology in giardiasis: a correlation with diarrhoea. *Aust N Z J Med* 1978; **8**: 392-396 [PMID: 104699 DOI: 10.1111/j.1445-5994.1978.tb04908.x]
 - 64 **Wallace JL**. Mechanisms, prevention and clinical implications

- of nonsteroidal anti-inflammatory drug-enteropathy. *World J Gastroenterol* 2013; **19**: 1861-1876 [PMID: 23569332 DOI: 10.3748/wjg.v19.i12.1861]
- 65 **Rubio-Tapia A**, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, Murray JA. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc* 2012; **87**: 732-738 [PMID: 22728033 DOI: 10.1016/j.mayocp.2012.06.003]
 - 66 **Fiorucci G**, Puxeddu E, Colella R, Paolo Reboldi G, Villanacci V, Bassotti G. Severe spruelike enteropathy due to olmesartan. *Rev Esp Enferm Dig* 2014; **106**: 142-144 [PMID: 24852741 DOI: 10.4321/S1130-01082014000200011]
 - 67 **Vidali F**, Di Sabatino A, Broglia F, Cazzola P, Biancheri P, Viera FT, Vanoli A, Alvisi C, Perego M, Corazza GR. Increased CD8+ intraepithelial lymphocyte infiltration and reduced surface area to volume ratio in the duodenum of patients with ulcerative colitis. *Scand J Gastroenterol* 2010; **45**: 684-689 [PMID: 20201621 DOI: 10.3109/00365521003663662]
 - 68 **Gentile NM**, Murray JA, Pardi DS. Autoimmune enteropathy: a review and update of clinical management. *Curr Gastroenterol Rep* 2012; **14**: 380-385 [PMID: 22810979 DOI: 10.1007/s11894-012-0276-2]
 - 69 **Chen H**, Xu H, Dong J, Li J, Ghishan FK. Tumor necrosis factor- α impairs intestinal phosphate absorption in colitis. *Am J Physiol Gastrointest Liver Physiol* 2009; **296**: G775-G781 [PMID: 19196948 DOI: 10.1152/ajpgi.90722.2008]
 - 70 **Sharma N**, Laftah AH, Brookes MJ, Cooper B, Iqbal T, Tselepis C. A role for tumour necrosis factor alpha in human small bowel iron transport. *Biochem J* 2005; **390**: 437-446 [PMID: 15901240 DOI: 10.1042/BJ20050256]
 - 71 **Suzuki S**, Goncalves CG, Meguid MM. Catabolic outcome from non-gastrointestinal malignancy-related malabsorption leading to malnutrition and weight loss. *Curr Opin Clin Nutr Metab Care* 2005; **8**: 419-427 [PMID: 15930968 DOI: 10.1097/01.mco.0000172583.25009.ab]
 - 72 **Semrin G**, Fishman DS, Bousvaros A, Zholudev A, Saunders AC, Correia CE, Nemeth E, Grand RJ, Weinstein DA. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis* 2006; **12**: 1101-1106 [PMID: 17119383 DOI: 10.1097/01.mib.0000235097.86360.04]
 - 73 **Shahraki T**, Rostami K, Shahraki M, Bold J, Danciu M, Al Dulaimi D, Villanacci V, Bassotti G. Microscopic Enteritis; clinical features and correlations with symptoms. *Gastroenterol Hepatol Bed Bench* 2012; **5**: 146-154 [PMID: 24834216]
 - 74 **Rostami-Nejad M**, Haldane T, Aldulaimi D, Alavian SM, Zali MR, Rostami K. The role of celiac disease in severity of liver disorders and effect of a gluten free diet on diseases improvement. *Hepat Mon* 2013; **13**: e11893 [PMID: 24348636 DOI: 10.5812/hepatmon.11893]
 - 75 **Catanzaro R**, Occhipinti S, Calabrese F, Anzalone MG, Milazzo M, Italia A, Marotta F. Irritable bowel syndrome: new findings in pathophysiological and therapeutic field. *Minerva Gastroenterol Dietol* 2014; **60**: 151-163 [PMID: 24780949]
 - 76 **Fritscher-Ravens A**, Schuppan D, Ellrichmann M, Schoch S, Röcken C, Brasch J, Bethge J, Böttner M, Klose J, Milla PJ. Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. *Gastroenterology* 2014; **147**: 1012-1020.e4 [PMID: 25083606 DOI: 10.1053/j.gastro.2014.07.046]
 - 77 **Rostami Nejad M**, Hogg-Kollars S, Ishaq S, Rostami K. Subclinical celiac disease and gluten sensitivity. *Gastroenterol Hepatol Bed Bench* 2011; **4**: 102-108 [PMID: 24834166]
 - 78 **Licata A**, Cappello M, Arini A, Florena AM, Randazzo C, Butera G, Almasio PL, Craxi A. Serology in adults with celiac disease: limited accuracy in patients with mild histological lesions. *Intern Emerg Med* 2012; **7**: 337-342 [PMID: 21468695 DOI: 10.1007/s11739-011-0585-8]
 - 79 **Vande Voort JL**, Murray JA, Lahr BD, Van Dyke CT, Kroning CM, Moore SB, Wu TT. Lymphocytic duodenosis and the spectrum of celiac disease. *Am J Gastroenterol* 2009; **104**: 142-148 [PMID: 19098862 DOI: 10.1038/ajg.2008.7]
 - 80 **Holmes G**. Non coeliac gluten sensitivity. *Gastroenterol Hepatol Bed Bench* 2013; **6**: 115-119 [PMID: 24834257]
 - 81 **Lewis NR**, Holmes GK. Risk of morbidity in contemporary celiac disease. *Expert Rev Gastroenterol Hepatol* 2010; **4**: 767-780 [PMID: 21108596 DOI: 10.1586/egh.10.72]
 - 82 **Whitaker JK**, West J, Holmes GK, Logan RF. Patient perceptions of the burden of coeliac disease and its treatment in the UK. *Aliment Pharmacol Ther* 2009; **29**: 1131-1136 [PMID: 19245681 DOI: 10.1111/j.1365-2036.2009.03983.x]
 - 83 **Biagi F**, Bianchi PI, Campanella J, Badulli C, Martinetti M, Klersy C, Alvisi C, Luinetti O, Corazza GR. The prevalence and the causes of minimal intestinal lesions in patients complaining of symptoms suggestive of enteropathy: a follow-up study. *J Clin Pathol* 2008; **61**: 1116-1118 [PMID: 18708422 DOI: 10.1136/jcp.2008.060145]
 - 84 **Lebwohl B**, Kapel RC, Neugut AI, Green PH, Genta RM. Adherence to biopsy guidelines increases celiac disease diagnosis. *Gastrointest Endosc* 2011; **74**: 103-109 [PMID: 21601201 DOI: 10.1016/j.gie.2011.03.1236]
 - 85 **Bonamico M**, Mariani P, Thanasi E, Ferri M, Nenna R, Tiberti C, Mora B, Mazzilli MC, Magliocca FM. Patchy villous atrophy of the duodenum in childhood celiac disease. *J Pediatr Gastroenterol Nutr* 2004; **38**: 204-207 [PMID: 14734885]
 - 86 **Hopper AD**, Cross SS, Sanders DS. Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate? *Endoscopy* 2008; **40**: 219-224 [PMID: 18058655]
 - 87 **Kurppa K**, Collin P, Viljamaa M, Haimila K, Saavalainen P, Partanen J, Laurila K, Huhtala H, Paasikivi K, Mäki M, Kaukinen K. Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. *Gastroenterology* 2009; **136**: 816-823 [PMID: 19111551 DOI: 10.1053/j.gastro.2008.11.040]
 - 88 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
 - 89 **Gardner TB**, Hill DR. Treatment of giardiasis. *Clin Microbiol Rev* 2001; **14**: 114-128 [PMID: 11148005]
 - 90 **Ingle SB**, Hinge Ingle CR. Eosinophilic gastroenteritis: an unusual type of gastroenteritis. *World J Gastroenterol* 2013; **19**: 5061-5066 [PMID: 23964139 DOI: 10.3748/wjg.v19.i31.5061]
 - 91 **Smedby KE**, Akerman M, Hildebrand H, Glimelius B, Ekblom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. *Gut* 2005; **54**: 54-59 [PMID: 15591504]
 - 92 **Lobo ML**, Augusto J, Antunes F, Ceita J, Xiao L, Codices V, Matos O. Cryptosporidium spp., Giardia duodenalis, Enterocytozoon bienuei and other intestinal parasites in young children in Lobata province, Democratic Republic of São Tomé and Príncipe. *PLoS One* 2014; **9**: e97708 [PMID: 24846205 DOI: 10.1371/journal.pone.0097708.eCollection2014]
 - 93 **Chen X**, Song CH, Liu ZQ, Feng BS, Zheng PY, Li P, In SH, Tang SG, Yang PC. Intestinal epithelial cells express galectin-9 in patients with food allergy that plays a critical role in sustaining allergic status in mouse intestine. *Allergy* 2011; **66**: 1038-1046 [PMID: 21426359 DOI: 10.1111/j.1398-9995.2011.02585.x]
 - 94 **Konorev MR**, Litviakov AM, Matveenko ME, Krylov IuV, Kovalev AV, Riashchikov AA. [Principles of current classification of duodenitis]. *Klin Med (Mosk)* 2003; **81**: 15-20 [PMID: 12685228]

P- Reviewer: Carroccio A, Leher P S- Editor: Qi Y L- Editor: A
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