ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

We would like to thank both reviewers for critical review. Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Microscopic Enteritis: Bucharest consensus

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14670

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer and the changes are highlighted in red

3. A short commentary was added

4. The references adjusted

5. Authors contributions clarified and added

Reviewer 1

Dear Authors,

Good paper, interesting .

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). BUT THE BENEFIT FROM GFD MAY BE NOT DUE A SO-CALLED NCGS BUT TO THE REDUCTION OF 'FODMAP' (FERMENTISCIBLE OLIGOSACCHARIDE, DISACCHARIDE, MONOSACCHARIDE AND POLYOLS)++

Thank you for discussing this issue. We agree that gluten free products might also be low in FODMAP but the diagnosis for NCGS is based on improvement of gluten free only and these patients are allowed to consume other products high in FODMAP.

Furthermore H. pylori has been highlighted as the most frequent aetiology in patients with LD and abdominal pain (58, 59). Santoloria et al found small bowel bacterial overgrowth caused LD in 22% of patients (58-60). see table 2 WE'D LIKE TO KNOWN WHAT IS THE FREQUENCY OF ME RECOVERY AFTER HELICOBACTER PYLORI ERADICATION.

The current data in the literature doesn't fully answer this question. Based on existent data a successful H pylori eradication therapy should result in recovery from ME related to H pylori. If we agree with this statement than ME cannot be resolved if H pylori eradication hasn't been successful. Unfortunately eradication success rate usually is less than 100 %. In a study by R Mera1 et al (Helicobacter pylori Long term follow up of patients treated for Helicobacter pylori infection Gut 2005;54:1536-1540) Among patients that received anti-H pylori therapy at baseline (n=394), eradication rates at 3, 6, and 12 years were 51% (171/336), 75% (239/320), and 51% (153/300), respectively. We believe the recovery from ME might be directly proportional with the eradication success rate. In this paper we did not study the recovery rate from different condition behind ME but encourage to identify the potential cause for ME in order to implement appropriate treatment rather than symptomatic treatment leading to long term morbidities.

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). WE'D LIKE TO KNOWN AS WELL WHAT IS THE FREQUENCY OF ME RECOVERY AFTER TREATMENT OF THESE INFECTIONS.

Recovery from giardiasis and threadworm after adequate treatment is usually uneventful. Small bowel biopsy in patients with Giardia is usually not indicated at least in cases with positive stool test according to Barbara Grazioli, et al Giardia lamblia infection in patients with irritable bowel syndrome and dyspepsia: A prospective study World J Gastroenterol. 2006;28(12):1941–1944 and further biopsy to evaluate the recovery is not justifiable unless the symptoms will persist. Therefore we may only relay on the clinical improvement after treatment and the recovery has been estimated over 90% in most studies so far.

Drug therapy ….More recently Olmesartan has been implicated in a severe sprue like enteropathy (65, 66). WE'D LIKE TO KNOWN THE CAUSALITY OF OLMESARTAN, OR OTHER SARTAN, IN THE NEXT SECTIONS, THE CAUSALITY OF ACE INHITORS IS POINTED OUT: IS THERE A CONFUSION ? MAY I ADD SARTANS ARE ANGIOTENSIN II RECEPTOR ANTAGONIST AND NOT ACE INHIBITOR ? AND THE SAME QUESTION: WHAT IS THE FREQUENCY OF ME RECOVERY AFTER NSAID STOP?.

We agree that Sartans (angiotensin II inhibitor) have been associated with enteropathy and we will clarify this in the manuscript. The recovery after stopping the sartans is promising and leads to restoring the villous architecture in most cases in a few months time. Most cases on NSAID also will recover after stopping the drug. However chronic use of NSAIDs may cause chronic inflammation and fibrosis in some cases.

Systemic inflammatory conditions implicated in ME include sarcoidosis and inflammatory bowel disease (3). Vidali et al 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 (67). THE AUTHORS DO NOT COMMENT THESE STRANGE DATA: ENTERITIS ASSOCIATED WITH ULCéRATIVE COLITIS, WITHOUT REFERENCE ABOUT CRONH'S DISEASE!

Although Crohn's disease is usually the inflammatory condition that could be associated with upper GI tract inflammation, Ulcerative colitis (UC) is also a systemic inflammatory disease. There are some evidence suggesting the involvement of the upper gastrointestinal tract in this condition. The study by Vidali on 24 steroid free UC patients and 21 control showed that duodenum of UC patients is infiltrated by a higher number of CD8(+) IELs and as authors suggest further studies would be required to clarify whether the duodenum is a target organ in UC. Without a large randomized study, it would be difficult to comment. We are hopping this issue will be studied properly in the near future.

Diagnosis The term ME can be proposed in cases of Marsh 0-II mucosal changes with clinical, serological, genetic and histological data unsupportive for a specific aetiology (agreement: 100%) CONFUSING SECTION: WITH THE PREVIOUS AND FOLLOWING SECTIONS, WE CAN UNDERSTAND THAT ME CAN BE OBSERVED DURING MISCELLANEOUS CLINICAL DISORDERS (THE 'UNDERLYING AETIOLOGY') LEADING TO THE NEED OF AETIOLOGICAL INVESTIGATIONS. HERE, AT THE OPPOSITE, THESE CAUSES EXCLUDE THE DIAGNOSIS OF ME. OF COURSE, THIS DOES NOT CHANGE THE NEED OF THESE INVESTIGATIONS, BUT ONLY THE DEFINITION OF ME.

Thank you for the comment. Microscopic enteritis is not confined to the unknown etiology and in contrast it is caused by a large list of etiological factors as listed in the manuscript. The statement has been revised and corrected to histological data might be supportive or unsupportive for a specific etiology. We are hoping that organizing the mild histological changes under the umbrella of ME and the algorithm provided will encourage the clinician/pathologists to look for the etiology of this histological changes and implementing targeted effective treatment rather than symptomatic relief for an unknown non-specific condition that may lead to long term morbidities.

Current and recently ceased medications should be reviewed, including NSAIDs ACE inhibitors and 'over the counter' medications. SEE ABOVE COMMENT ON ACEI AND SARTANS …. 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. ? but very cautiously: see comment on FODMAP reduction. Liver function tests may demonstrate elevated transaminases suggesting a chronic inflammatory disease such as primary biliary cirrhosis or sclerosing cholangitis potentially with concomitant inflammatory bowel disease. ? NO. CHRONIC INFLAMMATORY DISEASE SUCH AS PRIMARY BILIARY CIRRHOSIS OR SCLEROSING CHOLANGITIS POTENTIALLY WITH CONCOMITANT INFLAMMATORY BOWEL DISEASE MAY BE SUGGESTED BY BIOLOGICAL CHOLESTASIS NOT BY ELEVATED TRANSAMINASES, WHICH ARE SUGGESTIVE OF CD. ….Vande-Voort et al found that 38% of patients with LD and non-HLA DQ2 or DQ8 genotype improved with initiation of GFD (79). In contras

We revised the statement

Reviewer 2

GENERAL COMMENT

The paper is signed by a very authoritative panel and it is an interesting work which attempts to define the histology picture of the microscopic enteritis (ME) and the clinical conditions which can be associated to it. However, I have some concerns; the main of these is that in this work the ME is considered as an "independent" clinical condition. In particular, in the paragraph regarding the "Diagnosis", the Authors seem to suggest a series of investigations to clarify the cause of ME. In the clinical practice, on the contrary, the histology evaluation of the duodenum (and the eventual finding of ME) is part of the investigations performed in the suspect of several diseases. In this way, on my opinion, the text is difficult to read and to understand. A similar comment is valid for the "Treatment". I would suggest to rewrite the paper, considering the different diseases which can cause ME, as the Authors made until page 9. Other useful considerations now suggested in the following para (Diagnosis and Treatment) could be included in the respective previous para (CD, NCGS, Infection, Drugs, etc)

Many thanks for the comments. The manuscript has been adjusted according to the comments in diagnosis section. In treatment section we mentioned at the beginning that Treatment of ME is dependent on the aetiology: (agreement: 100%).

SPECIFIC POINTS -

Page 4 4th para: "It has become clear that "non-specific" referred to multiple aetiological conditions, other than gluten sensitivity". I think that the Authors refer to Celiac Disease and not "gluten sensitivity". In general, to avoid confusion I would suggest to use the term "celiac disease" instead of "gluten sensitivity", throughout the text. –

The text has been adjusted and gluten sensitivity is changed to gluten related disorders where appropriate.

Page 5 "Definition". "ME is a histopathological condition that affects the small bowel and causes microscopic and sub microscopic changes....." I would suggest to change "cause" with "is characterised by" - Label of the figures is inaccurate

The definition has been revised and adjusted according to the comment

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

On behalf of authors

Kamran Rostami