

October 02, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12585-review.doc).

**Title:** Differential diagnosis in IBD colitis: state of the art and future perspectives.

**Authors:** Tontini GE, Vecchi M, Pastorelli M, Neurath MF, Neumann H.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 12585

The manuscript has been improved according to Reviewers' and Editor's suggestions.

1. The format has been entirely updated

2. The revision has been made according to the Editor's suggestions.

- The present version of the manuscript has received an extensive revision focusing on the English language by all the authors, as well as by one native English speaker currently working in our Gastroenterology Unit at IRCCS Policlinico San Donato. Please note that, according to the Journal authorship criteria, our language consultant has not been included in the authors' list.

- Authors' contribution format has been changed.

- References list and typesetting were corrected according to the Journal format and Reviewer#1 comment.

- Figure #1 format has been replaced according to Your comment.

We thank the Editor for the comments and for this opportunity.

3. The Revision has been made according to the Reviewers' suggestions.

- Reviewer #1, Comment #1: "Title can't accurately reflect the major topic and contents of the review."

We agree with the Reviewer's comment and we have replaced the original title ("Review article: differential diagnosis in IBD colitis") with the following: "Differential diagnosis in IBD colitis: state of the art and future perspectives".

- Reviewer #1, Comment #2: "Abstract doesn't give a clear delineation of the research methods, results and conclusions. No the innovative and significant points conform to the materials and methods, results and conclusions."

According to the journal guidelines, we designed an informed, unstructured abstract, thereby summarizing the main manuscript architecture and topics. The literature search (*i.e.* materials and

methods) was performed by two authors using PubMed and looking for scientific manuscripts (e.g. reviews, original articles, case reports, abstracts, book chapters) dealing with the topic of differential diagnosis in IBD and written in English language. The literature search was made in November-December 2013 and repeated in June-July 2014. Given this standard, non-innovative approach, we have preferred not to specify this information in the abstract, nor in the main text. However, all these detailed information can be easily added in both the abstract and the main text if needed.

- Reviewer #1, Comment #3: *"The results doesn't provide sufficient evidence or data to draw firm scientific conclusions."*

We agree with the Reviewer's Comment. Firm results and conclusions are still lacking in current literature and this topic represents an untangled issue in the setting of IBD. Nonetheless, we know that emerging evidences together with the optimization of all current diagnostic approaches have the concrete potential to improve both diagnosis and management of patient with IBD in the next future. According to Reviewer #2 and Reviewer #3, besides the lack of firm and resolute results and conclusions, we believe that such a comprehensive review can aid both clinicians and researchers in their daily approach to this still unsolved issue.

- Reviewer #1, Comment #4: *"Discussion is not well organized, and No valuable conclusions are provided."*

We thank the Reviewer but we respectfully disagree with this comment. The present manuscript is not structured into the standard chapters of original article but divided into the following: (1) introduction, (2) matter's size, (3) clinical relevance, (4) current approach, (5), future perspectives, and (6) conclusions. Each informative chapter (i.e. chapters 2-5) provides in detail all available results focused on one specific aspect and includes a final discussion with conclusion, thereby summarizing all data and authors' perceptions. Given the magnitude of provided data throughout the text, the final chapter entitled "conclusions" has been designed to summarize the hot topics already discussed by previous chapters, thereby focusing on "take home messages" instead of resuming all results.

- Reviewer #1, Comment #5: *"The references are too much, some is not relevant."*

We have extensively revised the reference list, updated some reference and deleted 38 units whose function was mostly or totally covered by other highly reliable citations.

- Reviewer #1, Comment #6: *"The tables and figures are not appropriately presented."*

Consistent with this comment, we have improved the citation of Figure 1 throughout the manuscript. No table is included in the manuscript.

- Reviewer #1, Comment #7: *"The conclusions is not clear, the lack of practical clinical significance."*

According with Reviewer's comment, we have revised this section and added a specific paragraph to summarize in a practical way the clinical meaning and the impact of either current or emerging diagnostic approaches for the differential diagnosis in IBD colitis.

We thank the Reviewer #2 again for the valuable comments which have offered us the opportunity to improve our manuscript.

- Reviewer #2: *"The article summarized the progress in the differential diagnosis in IBD colitis, putting an emphasis on the inflammatory bowel disease unidentified (IBDU). The reader will be interested both in the introduction of current advanced endoscopic imaging techniques (namely high definition, magnification, dye-less chromoendoscopy, confocal laser endomicroscopy, endocytoscopy and "molecular imaging", etc) and in the genetic/metabolic detections for the disease, including epigenetics, metabolomics and proteomics. The design of the figure 1 is concise and easy to read."*

Thank You for these comments.

- Reviewer #3: *"Classification of the inflammatory bowel disease facilitates clinical decisions, discussions with the patient, eligibility for clinical trials, the best treatment and follow up. If possible, the disease should be classified as either Crohn's disease or ulcerative colitis. This classification usually is accomplished with the combination of endoscopy, imaging, histopathology and lab tests. The provider should make every effort to classify the disease using standardized criteria. If the disease type remains uncertain after complete evaluation, the term "indeterminate" colitis is used. Some newer classifications schemes suggest using the term "colonic IBD, type unclassified", reserving "indeterminate colitis" for patients in whom the type of IBD remains uncertain after colectomy and pathological evaluation. Overall Gian Eugenio Tontini et al., provide an extensive overview on the available literature about the problem of differential diagnosis in IBD colitis. The review could be of interest for clinicians and could be suitable for publication. The manuscript is nicely presented, well structured, and the conclusions consistent with the entire manuscript."*

Thank You for these comments.

Once again, we thank the Editor and the Reviewers for all the valuable comments, which have highly improved our manuscript. After consideration of our responses to these comments, we hope that our revised manuscript will merit final acceptance and publication in the *World Journal of Gastroenterology*.

Sincerely yours,

Gian Eugenio Tontini, MD, PhD

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