

Format for ANSWERING REVIEWERS



January 16, 2014

Dear Editor,

We appreciate very much the comments and suggestions from the reviewers. Those comments are valuable and very helpful for revising our paper. We have studied the reviewers' comments very carefully and tried our best to improve the manuscript. The followings are our point-by-point responses to the original reviewers' remarks underneath each comment.

Title: *Helicobacter pylori* infection *in vivo* by novel endoscopic techniques

Author: Ji Rui, Li Yan-Qing

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6497

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

(1)Reviewer 1:

This is a superficial review of novel endoscopic techniques which might help to prove *H. pylori* infection *in vivo* during endoscopy. No original work is being presented. The fact, that this manuscript is a review and not original work should be stated in the title already and be pointed out in the abstract more clearly. A Methods section should describe which search criteria, key words, search engines etc. have been used in order to find the most recent and complete set of original papers for the review. Are prospective and comparative studies available in the literature, which might allow more general conclusions for clinical application or future research? What is the role of culture techniques from "smart" biopsy samples? Are H.p. positive cultures found more frequently from "smart" biopsies than from blind biopsies? Where is the evidence? The Figures are difficult to interpret, especially Fig 1 A and Fig 3 A;

Response:

Thanks for your valuable comments and good suggestions. This manuscript is an invited review article for the special issue about *Helicobacter pylori*. More explanations have been added in the abstract and introduction of the revised manuscript to point out it according to your suggestion. Majority of the studies performed are prospective descriptive studies, we found only two comparative studies to compare standard endoscopy with magnifying endoscopy. Hence, well design prospective trials comparing current new techniques are needed to allow clear recommendations regarding which endoscopic imaging technique should be use in different clinical settings. These data have been added in the revised manuscript.

Previous researches have suggested that novel techniques with targeted biopsy could greatly reduce the number of biopsies needed per patient and significantly improve the diagnostic yield in Barrett's esophagus and ulcerative colitis. However, the study of "smart" biopsies in *H. pylori*-associated gastritis is rare. Using CLE-guided targeted biopsies, Kiesslich et al. reported that *H. pylori* infection was detected in a patient who had negative urease test results. However, further evidence is needed to exactly specify the diagnostic yield of targeted biopsy. Thanks for your good suggestion, more details have been added in the revised discussion.

We are sorry that some of the figures are difficult to interpret. In Fig 3 A, because the length of *H. pylori* was only 2.5~4.0 μ m, the CLE image was magnified and image resolution was decreased accordingly.

(2) Reviewer 2:

Grade A ,the same as above

Response:

Thank you very much for your kind comments.

(3) Reviewer 3:

This review addressed an interesting and clinically relevant topic on the "on-site" detection of *Helicobacter pylori* infection by endoscopic techniques during the endoscopy, without taking any samples. While the authors collected and summarized the all available techniques, comments on the performance and insights on the potential clinical application of these techniques are required. A table outlining the performance including sensitivity, specificity, PPV, NPV and accuracy, advantages and disadvantages would significantly improve the quality of the review. The manuscript, though fairly written, can be further improved in terms of presentation and language expression. In addition, literature search should be performed to ensure all latest relevant studies are included and updated in the review.

Response:

Thank you for your careful review and valuable suggestions. More comments on potential clinical application of these techniques have been revised in the revised manuscript according to your suggestion, and a table outlining the performance was added in order to facilitate the readers. The grammar and style of the revised manuscript have been intensively reviewed by professionals whose native language is English.

(4) Reviewer 4:

Very comprehensive and well written article. There are 2 writing errors and one important error related to reference number 5. "Hidaka et al. showed that the absence of RAC at two sites in gastric

body, indicated the absence (must be presence" of H. pylori infection with a sensitivity and specificity of 100% and 90% [5].

Response:

We are deeply sorry for the mistakes and thanks for your careful review. Corresponding revisions have been made in the revised manuscript.

(5)Reviewer 5:

A well written and comprehensive review regarding an interesting topic and merits publication in its existing form.

Response:

Thank you very much for your kind comments.

(6)Reviewer 6:

In the review paper the Authors present on the basis of the relatively recent literature (only one from 2013 y.) new techniques which might be useful in the diagnosis of the Helicobacter pylori infection during the endoscopic examination. The authors described shortly such novel methods like magnifying endoscopy, NBI, I-Scan, infrared Raman spectroscopy, endocytoscopy and confocal laser endomicroscopy. With these techniques endoscopists can observe such structures as gastric pit patterns, microvessels, cell morphology, and surface architecture of the mucosa. Authors conclude that these endoscopic methods can be useful in the diagnosis and treatment of diseases related to Helicobacter pylori infection. The subject of the review is important, however there is lack of convincing reports showing the significant advantage of the described methods used in detection of Helicobacter pylori infection over the currently used well established and inexpensive tests like CLO-test, histology or several non-invasive tests. The title does not reflect the review character of the paper. Since the progress in the endoscopic methods is observed I would suggest to describe the method of preparation of this review based on the literature search of the newest publications, e.g. Medline, Pubmed etc including good quality original papers. There is a lack of described clinical applications of novel techniques.

Response:

Thanks for your valuable comments and good suggestions. We totally agree with you that well design comparative controlled trials are needed to specify the diagnostic yield of new endoscopic techniques compared with the other well established and inexpensive tests. More explanations have been added in the abstract and introduction to point out this manuscript is a review. A PubMed search for relevant articles was performed using many key words such as "endoscopy", "Helicobacter pylori" "diagnosis", "magnifying endoscopy", "NBI", "I-Scan", "FICE", "AFI", "chromoendoscopy", "infrared Raman spectroscopy", "endocytoscopy" and "confocal laser endomicroscopy". We also added two new articles from Dec 2013 y in the revised manuscript.

(7)Reviewer 7:

This is a review paper about the recent advances in endoscopic technology concerning the possibilities of endoscopic visualization of *H. pylori* infection. The authors give an good overview about the advantages and limitations of new endoscopic techniques such as magnifying endoscopy, narrow band imaging, I-Scan, endocytoscopy and endomicroscopy, In this review the authors describes these techniques and theirs possibilities for diagnosis of presence of *H. pylori* in a time-efficient manner comparing it with the results of histological examination of gastric mucosa. This review is well-written, supplied with one Table and three Figures. The authors have reviewed 22 references. However, the follow point needs to be considered: 1.Figures 1 and 2 should be provided with the histopathological picture of the same gastric mucosa. 2.I agree with previous comment concerning the arrows of the microphotographs, the arrows should be defined.

Response:

Thanks for your kind comments and valuable suggestions. Corresponding histopathological pictures of Figures 1 and 2 have been added in the revised manuscript according to your suggestion. Arrows in the pictures were also have been defined.

(8)Reviewer 8:

In this review authors focus on novel endoscopic technique for in vivo diagnosis of *H. pylori* infection. Even though the topic remains a difficult challenge, the paper is clearly presented and provides the reader with a comprehensive and updated knowledge in the field. I would suggest to add the word ... might before "... lead us to easier diagnosis" in the last sentence of the abstract.

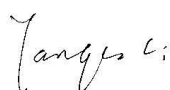
Response:

Thanks for your kind comments and good suggestions. The last sentence of the abstract has been modified in the revised manuscript according to your suggestion.

3.References and typesetting were corrected

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

Sincerely yours,



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