

October 27, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5749-edited.doc).

Title: Second and third line treatment options for *H. pylori* eradication

Authors: Mingjun Song, Tiing Leong Ang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5749

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

1. Format has been updated
 2. Revisions have been made according to the suggestions of the reviewers:
- (1) To reviewer 00035741: Thank you for the excellent suggestions. Sub headings are now included which makes the paper easier to read and reference. The paper "Multi-center randomized controlled study to establish the standard third-line regimen for *Helicobacter pylori* eradication in Japan." by Murakami K et al, *J Gastroenterol.* 2013, has been included as a useful reference.
 - (2) To reviewer 02462691: References for other patient factors contributing to treatment failure, smoking, obesity and poor compliance, are included. The role of high bacterial load is now mentioned under the sub heading "Other bacterium factors" for treatment failure. As suggested by the reviewer, we have briefly discussed the issue of reinfection, a significant problem in developing countries, in the introduction, highlighting the difference from failed therapy, which is the focus of our topic review. We did not go into great details about reinfection because our focus is failed therapy. Thank you for the input on the role of "3 in 1" capsule, we have made the appropriate corrections and acknowledge that more research is required to determine if this capsule is useful as 2nd line therapy. The suggested reference by Gisbert JP et al is noted and used in the discussion of levofloxacin-based second line therapy (reference no. 40). The suggested reference by Hsu PI was initially omitted due to the small patient numbers, however it is now included as a useful reference on the options of rescue therapy after first line concomitant or sequential therapies have failed.
 - (3) To reviewer 00030962: Thank you for the useful and comprehensive feedback. We have included more citations to discuss the differences in antibiotic resistance patterns across regions. A review written by Zullo A. and De Francesco V. "Predicting *Helicobacter pylori* eradication: how to teach an old dog new tricks!" *J Clin Gastroenterol.* 2012 has been cited, in addition to other references of work by these two authors that were suggested by the reviewer. Thank you for pointing out that esomeprazole actually has a similar hepatic metabolism as omeprazole and is not a second generation PPI; this has been duly corrected. The pill load for the "3-in-1" capsule is now reflected and we acknowledge the lack of data to support that this capsule may be used as rescue therapy. Excellent feedback regarding rifaximin has been given and this has induced us to conduct more literature research and include citations, which showed the unsatisfactory eradication rates of rifaximin and its limitations. Sitafloracin is marketed in Japan and is not available in many countries and we have included a brief note on this restriction.
 - (4) To reviewer 00503464: Thank you for the suggested citations. The paper "Proton pump inhibitor-amoxicillin-clarithromycin versus proton pump inhibitor-amoxicillin-metronidazole as first-line *Helicobacter pylori* eradication therapy" by Nishizawa T et al is interesting to read and we have included it in our references, when we mentioned the differences in success rates of first line therapy in our introduction. The paper "CagA protein of *Helicobacter pylori*: a hijacker of gastric epithelial cell signaling." by Handa O et al, is useful in the discussion of *H. pylori* carcinogenesis

pathophysiology. We have alluded to it as suggested by the reviewer by referencing it in our introduction. However, as our paper is focused on therapy, we did not discuss it in detail.

3. References and typesetting were corrected

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

Sincerely yours,



Dr Mingjun Song
MBBS, MRCP (UK)

Department of Gastroenterology
Changi General Hospital
2 Simei Street 3, Singapore 529889
Email: mingjun.song0950c@gmail.com



A/Prof Tiing Leong Ang
MBBS, MRCP (UK), FRCP Edin
Associate Professor
Department of Gastroenterology
Changi General Hospital
2 Simei Street 3, Singapore 529889
Email: tiing_leong_ang@cgh.com.sg

November 29, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5749-Review after 2nd round).

Title: Second and third line treatment options for *H. pylori* eradication

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5749

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

1. Format has been updated
2. Revisions have been made according to the suggestions of the reviewers:
 - (1) To reviewer 01436291: Thank you for the meticulous review. The appropriate changes have been made which should improve the content and presentation of this paper.
 - (2) To reviewer 01429020: Thank you for the suggestions. More details have been added with regards to the availability of Pylera and the limitations of available data to support its use as salvage therapy has been highlighted. The safety profile and availability of moxifloxacin is discussed briefly with the attachment of a useful reference. The sequential therapy mentioned is levofloxacin-based; the title has been made to be clearer. The report regarding rifaximin as a third line therapy was surprisingly positive for rifaximin; we think there may be some false negative results involved as the CUBT was conducted after stopping PPI or antibiotics for only a week; this point has been added.
 - (3) To reviewer 00073423: Thank you for the suggestion; we have summarized the various consensus published since 2000 in an additional table; there were minor differences noted but guidelines are largely similar.
3. References and typesetting were corrected

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

Sincerely yours,

Dr Mingjun Song
MBBS, MRCP (UK)
Department of Gastroenterology
Changi General Hospital
2 Simei Street 3, Singapore 529889
Email: mingjun.song0950c@gmail.com

A/Prof Tiing Leong Ang
MBBS, MRCP (UK), FRCP Edin
Associate Professor

Department of Gastroenterology
Changi General Hospital
2 Simei Street 3, Singapore 529889
Email: tiing_leong_ang@cgh.com.sg