

Dear Editor in Chief:

Respectfully, we have revised the manuscript according to the comments of the reviewers. Changes are shown in Red and Green colors. Also, the answers to the comments are as follows:

Reviewer 00069819:

This is a comprehensive review of the various eradication therapies for H pylori in different West Asian countries, with a focus on resistance rates and alternative regimens. The manuscript is well written and sheds some light on this very important topic. My only comments/suggestions are the following:

1. Title should reflect the nature of the article (a review).

- The title is changed to “**Helicobacter pylori Eradication in Western Asia: A Review**”

2. The abstract should include a final paragraph describing the search methods and the most relevant methods.

- Search method is added to the abstract.

3. The aims of the study should be stated clearly in the abstract.

- The aim is added to the abstract

4. A brief comment by the Authors on the strengths and weaknesses of the various studies discussed should appear at the end of each paragraph.

- As it is mentioned in the method part, to minimize bias, two authors selected the studies and extracted the data; this process resulted in high inter-observer agreement. Furthermore, we just included randomized trials and excluded non-randomized ones. However, one of the main limitations of our study is that we included even those studies with less than 100 patients in each therapeutic arm. Therefore, we cannot judge the strength and weakness of the studies, promptly. It is mentioned at the end of the manuscript.

Reviewer 00077100:

This review tried to address the issues related to treatment and eradication of HP in Western Asia, it is an interesting topic. However the following issues have not been adequately described:

1. There is no information about the strategies on eradication of HP in Eastern Asia, therefore the clinical significance cannot be evaluated.

- Although we investigated H. pylori eradication regimens just in West Asia, the clinical significance of the results is not limited to those countries situated just in this geographic

region. The results can be useful for any country with the same pattern of resistance to antibiotics.

2. It is too descriptive, although the information is enormous, but the conclusion is lacking.

We added conclusion and a recommendation box at the end of the manuscript. Furthermore, we added and briefly stated the appropriate recommendations for first- , second- and third-line therapeutic options in the abstract.

3. It did not provide any significant management recommendation to the physicians or it will not change the management strategies significantly.

- As we replied to the previous comment, we have added recommendations to both Abstract and the end of the manuscript.

4. The search is limited by its language restriction and the search method is limited to Google Scholar, therefore for systemic review, it will carry notable bias.

- This study is not a systematic review and we just provided a narrative review. However, we have already changed the source of our research from Google Scholar to PubMed. Therefore, some studies have been omitted and significant changes in the results and recommendations have been made. All changes are shown in Red color.

Restriction of language is one of our limitations that is mentioned at the end of the manuscript.

Reviewer 00069406:

This is a systemic review on H. pylori treatment status in West Asia area. The author collected as much as possible data to analysis. However, there are some issues preventing it to be publishable.

1. Hp is a worldwide GI infection, so local area data is less important to other readers or clinicians in the rest area, hence is not so relevant.

- Although we investigated H. pylori eradication regimens just in West Asia, the clinical significance of the results is not limited to those countries situated just in this geographic region. In fact, the results are transferrable to any region provided the patterns of resistance are the same.

2. Too many tables contained in the text, which need to be re-organized and cut.

- Tables are re-organized and cut.

3. Google Scholar is not a scientific tool to search papers, instead Pubmed, Medline etc. will be better.

- We have already changed the source of our research from Google Scholar to PubMed. Therefore, some studies have been omitted and significant changes in the results and recommendations have been made. All changes are shown in Red color.

4. No obvious conclusion could be made by this review and the abstract style is not appropriate.

- We have changed the style of the abstract and have added conclusions and a Recommendation Box (table 5) to the end of the manuscript.

Reviewer 00058689:

This is a well written and important review on *Helicobacter pylori* eradication in the West Asia. There are some comments:

Generally *Helicobacter pylori*, *H. pylori*, in vivo and in vitro should be written in italic!

- Relevant changes have been made.

Antibiotics are written with small letter in the beginning.

- The beginning letter is changed to capital form.

Abbreviations should be explained the first time they are used throughout the manuscript.

- Relevant changes have been made.

Specific comments:

1. P2 line 4 from below: Basically *H. pylori* causes a chronic inflammation in the gastric mucosa which may be complicated by peptic ulcer etc.
 - The sentence has been corrected.
2. P6 line 1-3: Bismuth revert metronidazole resistance so metronidazole resistant *H. pylori* become sensitive to metronidazole.
 - The comment has been added to the text.
3. P6 line 5 from below: How does the author explain the effect of hybrid therapy on clarithromycin and metronidazole resistant *H. pylori* if it is not a coincidence?
 - The precise mechanism underlying these successful results is unknown, albeit synergistic effects between Clarithromycin and Tinidazole might be a plausible hypothesis. Also, Amoxicillin may weaken the cell wall layer and therefore, facilitating the transfer of Clarithromycin plus Tinidazole through the weakened cell wall layer.
4. P6 line 23 and P7 line 3: pp and ITT are new abbreviations that should be explained. Why are pp with small letters and ITT with capital letters? P8 line 11,22,232 and 24: PH should be pH.

-Relevant changes have been made and PP and ITT have been explained.

5. P8 line 8-24: If microorganisms are resistant in vitro they are also resistant in vivo but if they are sensitive in vitro they may be resistant in vivo because of the penetration distribution etc. Most antibiotics have the highest activity at neutral pH but especially clarithromycin has the highest activity at high pH (around 8) and metronidazole has the highest activity at lower pH (around 6). Thus clarithromycin is the only antibiotic that benefits from a high pH caused by PPI.

- The comment has been added to the text.

6. P.9 line 2: Why >80%, why not > 90%?

- The reference for the mentioned point is number 18:

Boyanova L, Mitov I. Geographic map and evolution of primary Helicobacter pylori resistance to antibacterial agents. Expert review of anti-infective therapy 2010; 8(1): 59-70 [PMID: 20014902 DOI: 10.1586/eri.09.113]

7. P9 line 9: delete the parentheses () around 90%.

- It is deleted.

8. P9 line 10-28: It should be specified what is "standard therapy" as several different ones have been proposed.

Standard triple therapy has been described in the paragraph of **"First-Line Treatment Regimens"**.

Respectfully,

Prof. Hafez Fakheri