

Dear Editor in BPG,

Greetings,

With warm thanks to all reviewers and editor for their comments on my paper, I should assert that I fully agree with all comments and in below, I first reply them one by one then sending you the revised manuscript as requested in instructions for paper revision in BPG. Once again I should thank everyone contributed and spent their valuable time for my paper at any position. Moreover, I put whole comments in below, thereafter, my reply to each one as a paragraph is incorporated. I need to mention that for request by two reviewers, I decided to revise my paper according to the **review** style, because of, 1- reviewers request, 2- many texts have been inserted which cannot be as an editorial! The paper is now with more than 3500 word counts! Which never can be considered as an editorial. The revised version of current manuscript is a novel panel for readers to see how a simple item can influences on antibiotic resistance of *H. pylori*. Three figures and a table were also the major changes in the revised manuscript, but actually I should confess that it improved a lot. Many of sections were also amended or inserted newly because of reviewers requests.

Best regards,

Amin

Reviewer code: 02997214, 02523689, 01548565, 02567669, and 00008633

In response to reviewer #00008633:

- I agree with reviewer, so final revised manuscript is in format of a review.
- I completely agree with reviewer, so I asked my English native friend to review whole manuscript again before resending to the BPG.
- Concerning the writing the PPI as abbreviation, I agree with the reviewer, thus changes had been made.

- With thanks to the reviewer for his/her constructive comment, I provided/suggested a novel roadmap for dealing with cases suspected to the clarithromycin resistant bacterium. I has been inserted in discussion section.

In response to reviewer #02567669

With thanks to reviewer constructive comments and also nice wording to my review, I agree with him/her, thus, in revised manuscript I incorporated those all opinions to enrich the main text.

In brief, I need to point out that global H. pylori elimination is an ambitious goal which may not happening at any situation, but we are suffering from H. pylori problematic face! So we have to make an action which antibiotic therapy is the closest one! No good and preventive vaccine! No useful probiotic are available, so we have to go back to the antibiotic. Now we have to select better ones that everyone! Clarithromycin was a good antibiotic, unfortunately, it became a candidate for being a good antibiotic against H. pylori. This is the main message from this paper and I guess the leaders in this field should have think more!

In response to reviewer #01548565

With thanks to reviewer constructive comment, I changed the whole format into the review for having better box to explain what is happening about H. pylori clr-resistant. In the end I should have thanks reviewer for interesting comment on my review.

In response to reviewer #02523689

First, I should thank the reviewer since his/her comments shaped my paper very well and I agree with this sort of commenting very much. I agree with him/her since the point mentioned is the major problem with gastroenterologists. I worked in many countries, not only in Iran, but also in developed countries, we are lacking in lateral trust. This is not a subject as focus of interests, but current review is aiming to increase attention on this topic to reduce skyrocketing speed of antibiotic resistance phenomena especially against clarithromycin. As a note, there is not too much complains of difficult procedure on endoscopy (at least not yet!) but we are quite familiar with hard situation for having successful HP- culture. Taking together, I agree with the reviewer for his/her interesting suggestion, so I mentioned the case suggested in my revised manuscript.

About **second major** comment presented by the reviewer, I fully agree, so new table has been designed showing increasing trend on clarithromycin resistance among the H.p STRAINS WORLDWIDE. With thanks to reviewer, I think this comment was also improving the main idea presented in this review.

In response to reviewer #02997214

I completely agree with very interesting comments suggested by the reviewer, so I consider them all in revised manuscript. In below, I mentioned replies one by one for each comments by reviewer;

About comment #1:

-I agree, so a new paragraph discussing whole involved mechanism acting in resistance against clarithromycin were explained for readers.

-Because of reviewer request, molecular diagnostic procedures were also well-discussed in revised manuscript (a novel table as table - 1) was designed to illustrate the current situation. Moreover, a new text were also incorporated to enrich the first proposed ideas.

-Because of reviewer request, importance of upper respiratory infections and its direct impact to increase clarithromycin resistance among the clinical *H. pylori* strains were also well-discussed in revised manuscript.

-The potential role of efflux pumps were also discussed to enrich the text as reviewer requested.

-Because of reviewer request, MALDI-TOF approach was also mentioned in our last section of the review. It seems that reviewer s constructive comment was improving the manuscript body very well.

- The comments for bilateral enforcement to reduce antibiotic resistance in HP strains was also inserted in the text. This sentence was also requested fairly by the reviewer. I agreement with him/her, I think this wording was obligatory to complete my manuscript.