

Point-by-point revision

Manuscript number: World Journal of Clinical Cases, No.74945

Manuscript title: Current guidelines for *Helicobacter pylori* treatment in East Asia 2022: Differences among China, Japan, and South Korea

Dear Editor:

Thank you for your meticulous review of our manuscript and valuable comments. We answered the reviewer's comments. The enclosed is the point-by-point reply to the comments. In the revised manuscript, the changes were highlighted by using red-colored text.

Sincerely yours,

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Round 1

Reviewer #1

1. The recommendations are not the same for each country which could be due to the local availability of some reagents or compounds. Indeed, Japan was the first country to use P-CABs which allow *H. pylori* eradication of some clarithromycin resistant strains (with MICs not much higher than the threshold). Korea had tests available from Seegene to detect clarithromycin resistance, first DPO-PCR then RT-PCR (Allplex) which is easy to perform. China which did not have specific drugs or reagents promoted bismuth-based treatments, another way to avoid antimicrobial resistance. They also recommend furazolidone for which there is no resistance instead of metronidazole. However, even with bismuth, clarithromycin should be avoided as well as levofloxacin because of the high resistance rates. - The authors should try to explain the difference using the above reasons or others.

Answer: Thank you for your important comment. In the conclusion section, we made a new paragraph to explain the difference of *H. pylori* regimens in China, Japan, and South Korea (as below). To highlight the objective of this review, we changed the 'comparison' to 'difference' in the manuscript title.

*At present, the availability of specific drugs and reagents differs among China, Japan, and South Korea. Bismuth is not licensed for use in Japan, whereas classic and modified BQTs are recommended in China and South Korea. Since 2015, VPZ was introduced to eradicate *H. pylori* in Japan. In contrast, there was few study about VPZ outside Japan. In South Korea, molecular tests for CAM-resistant *H. pylori* are commercially available. In Japan, a low rate of MDZ resistance results from the limited use of MDZ by the national health insurance system. Unlike in other two countries, MDZ was not approved as a component of first-line *H. pylori* regimens in Japan. Therefore, strategy for the treatment of *H. pylori* infection might be chosen due to antibiotic resistance rate and medical policy in each country.*

2. They could also explain why there is limited *H. pylori* resistance to metronidazole in Japan compared to the other countries.

Answer: Thank you for your valuable comment. As you mentioned, we added new

sentences in the section of *H. pylori* resistance to antibiotics in East Asia (as below).

A low MDZ resistance against H. pylori is thought to be correlated to antibiotic consumption in the community. The use of MDZ is strictly regulated in Japan, where it has been approved for the treatment of only selected diseases, such as trichomoniasis^[21].

3. Reference 4 on H. pylori prevalence dates back to 2010 and concerns studies from 2003 in China, 1999 in Japan and 2007 in Korea. Given the evolution, it is important to provide updated figures.

Answer: As you commented, we updated the prevalence rates in three countries based on the latest data (as below).

The overall seroprevalence rate of H. pylori infection is 44.2% in China, 37.6–43.2% in Japan, and 51.0% in South Korea^[4-6].

4. Reference 5 should be changed for the Globocan figure (2020) which ranks gastric cancer as the 4th cause of mortality by cancer and not the 3rd.

Answer: As you recommended, we changed the rank of gastric cancer-related mortality from third to fourth according to Globocan 2020 (as below).

Gastric cancer is the fourth most common cause of cancer-related mortality worldwide^[7].

5. Concerning reference 16 from Japan, instead of writing "recent", the year of publication "2019" should be indicated.

Answer: I am sorry not to understand your comment. In the submitted manuscript, reference 16 was not related to Japan. We have a question about whether you mentioned the recent Chinese consensus report (reference 9) in the introduction. We are ready to revise the manuscript if you comment again.

Reviewer #2

1. Why were these countries chosen? There are eleven countries in the South East.

Answer: Thank you for your careful comment. In this review, we included China, Japan, and South Korea in Asian countries. Since 2000, three countries have published their own *H. pylori* management guidelines. The latest guidelines were fifth edition in China, third edition in Japan, and fourth edition in South Korea, respectively. Furthermore, many studies have been reported from three countries (i.e. modified bismuth-containing therapies in China, P-CAB-based regimen in Japan, and tailored therapy using molecular test in South Korea). Then, their own guidelines were revised continuously based on the data from each country. Although three countries in East Asia are geographically close, however, there seems to be differences in the *H. pylori* treatment guidelines. Therefore, we wish to discuss their guidelines and up-to-date research from China, Japan, and South Korea.

2. When using bismuth, potassium-competitive acid blockers, dual or triple therapy, standard or conventional, concomitant, and sequential therapy?

Answer: Thank you for your important comment. The objective of this manuscript is to focus on the differences of *H. pylori* treatment regimens among three countries. In China, adding bismuth to all *H. pylori* regimens was recommended as the empirical first-line treatment. Furazolidone-based regimens showed a good *H. pylori* eradication rate. In Japan, standard triple therapy containing clarithromycin is still recommended as first-line *H. pylori* regimen. Bismuth is not licensed for use, and quadruple therapies are not approved in Japan. Since 2015, P-CAB has played an important role in increasing *H. pylori* eradication rate in Japan. There is few study about P-CAB-based eradication outside Japan. A revised South Korean guideline in 2020 is similar to those of Western countries. Concomitant and sequential therapies are used as first-line *H. pylori* regimens. Notably, molecular testing to detect CAM resistance is available for tailored *H. pylori* eradication. We think these differences may be due to the availability of specific drugs and reagents, antibiotic resistance rate, and medical policy in each country.

3. How much gastric cancer rate reduction and tolerability of any regimen (combination agent, dosage, duration)?

Answer: According to recent guidelines, *H. pylori* treatment is strongly recommended

for primary cancer prevention in regions with high prevalence of gastric cancer. The preventive effect depends on the timing of eradication before development of atrophic gastritis and intestinal metaplasia. When *H. pylori* infection is treated in younger subjects, reduction rate for gastric cancer development may be much lower. The patients' compliance to *H. pylori* eradication depends on the drug-related adverse event, dosage, and treatment duration. However, to my knowledge, there was no report about the gastric cancer preventive effect based on each eradication regimens.

4. what is the difference between empirical regimen therapy (first line, second line) in these three countries? regimen therapy algorithm following diagnostic test result (molecular testing, antimicrobial susceptibility testing)

Answer: Thank you for your valuable comment. In Chinese consensus, *H. pylori* therapies were not categorized into first- and second-line regimens. Any of the seven regimens can be prescribed to patients to eradicate *H. pylori*. The seven regimens include two of the following six antimicrobial agents: amoxicillin, clarithromycin, metronidazole, tetracycline, levofloxacin, and furazolidone. In Japan, clarithromycin-based triple therapy with PPI/P-CAB is recommended to eradicate *H. pylori* as a first-line regimen. Metronidazole-based triple therapy with PPI/P-CAB is recommended as the second-line eradication. Sitafloxacin-based triple therapy has been recommended as third-line therapy in combination with amoxicillin or metronidazole. In South Korea, first-line *H. pylori* therapies consist of three empirical regimens and one tailored eradication regimen. Tailored *H. pylori* eradication was based on the molecular test for detecting clarithromycin resistance. *H. pylori*-infected subjects without A2142G and A2143G point mutations are treated with the 7-day standard triple regimen. The classic bismuth-containing quadruple therapy is recommended when the A2142G and/or A2143G point mutations are present. For antibiotic susceptibility-based *H. pylori* therapy, tailored regimen should be selected according to the results of minimum inhibitory concentration including clarithromycin, metronidazole, and levofloxacin.

5. In addition, the authors should replace twelve out of ninety references published before 2012.

Answer: As you commented, we changed twelve references published before 2012 to new ones published after 2012. Please check the revised manuscript.

Round 2

Comments: Information in the introduction section implies that the background of the review is because *H. pylori* cause gastric cancer. The author should adjust the narrative in the Introduction section with the author's response to the reviewer comment, number 3.

Answer: As the reviewer mentioned, an additional sentence was described in the introduction section as below. "In *H. pylori*-infected stomach, gastric atrophy and intestinal metaplasia are linked to gastric cancer development[2]."