July 27, 2015

Fang-Fang Ji
Science Editor, Editorial Office
Baishideng Publishing Group Inc

ESPS Manuscript NO: 18676: Antibiotic treatment for *Helicobacter pylori*: Is the end coming?

Dear Editor,

I would like to thank the editor and reviewers of the 'World Journal of Gastrointestinal Pharmacology and Therapeutics' for taking their time to review my article. Reviewer's comments were very helpful for us to correct and revise our manuscript. All changes we made are summarized below:

#Editorial comment

1. Please offer the signed pdf file. Thank you!

Answer: As you recommended above, we are willing to offer the signed PDF file at ESPS. Thank you very much for your careful concern.

2. Please offer the audio core tip, the requirement are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

Answer: As you recommended above, we are willing to offer the audio core tip at E SPS. Thank you very much for your careful concern.

#Reviewer 2535381

The submission includes an editing certificate. I recommend that the authors request the editor do a second pass at the manuscript. I found simple errors that the editors should have caught. They are relatively minor, but should be corrected. Additionally, I recommend that the authors work to summarize the efficacy reports from the numerous treatments better. The sections are challenging to read because it is simply one efficacy rate after another. Try to summarize in a rational way...maybe more generally by geography. I recommend the review for publication after minor revisions.

Answer: We appreciate your pointing out. As suggested by you and other reviewer, we have summarized the sections. In the sections (current antibiotic resistance in worldwide & sequential and concomitant therapy), we arrange antibiotic resistance and sequential therapy by geography as below (Page 6, line 2-25), (Page 10, line 17-24). In the Table 2~4, we also arrange contents by geography.

In Brazil, stomach biopsy specimens positive for H. pylori were analyzed by polymerase chain reaction (PCR) to detect the point mutation associated with clarithromycin resistance [33]. The results uncovered primary clarithromycin resistance in 16.5% patients. Recently, the clarithromycin resistance rate in Korea was reported to range from 17.2 to 23.7% [34]. In a study published in Japan, the clarithromycin resistance rate in 2002 was 18.9%; however, the clarithromycin resistance rate in 2006 increased to 27.2% [35]. Even with third-line eradication therapy, clarithromycin resistance rates in Japan were reported as 86.4% [36]. Several studies in China have reported increased resistance rates Shanghai [37], 21.5% resistance in the southeast coastal region [38], and a relatively high rate of 33% in Vietnam, which is near southeast China [39]. In western Asia, resistance to clarithromycin has been reported to be >10% in Iran and >20% in Turkey [12]. In one study, clarithromycin resistance was reported in 47.5% of patients with dyspepsia in Turkey [40]. In sharp contrast to other Asian countries, no resistance to clarithromycin has been reported in Malaysia [41] and the prevalence of resistance to clarithromycin in Gambia and Senegal also remains very low [42, 43]. Resistance to clarithromycin has also risen by >20% in southern Europe, although in northern Europe the resistance rate is less than 10% [44] compared to 1.5% in a random adult Swedish population [45] and 7.5% in central Germany [46]. During the last 15 years, a twofold increase in clarithromycin resistance was reported in Italy [47] and in Spain, where the mean

clarithromycin resistance rate was 18.3% in 1709 patients [48], and 34.7% in Portuguese children [49]. In contrast to the general trend, the rate of H. pylori strains resistant to clarithromycin decreased from 34 to 22% during 6 years in southern Poland [50].

In the study by Zhou et al., there was no significant difference between the eradication rates achieved with STT (66.4%) and sequential therapy (72.1%) by ITT analysis [92]. Moreover, the sequential therapy group with dual clarithromycin resistance and metronidazole resistance had a lower eradication rate (43.9%) compared to the rate seen with only clarithromycin resistance (88.9%) [92]. In a 2015 study from India that compared sequential therapy to ciprofloxacin-containing sequential therapy, the ITT cure rate in the sequential therapy group was 66% and only 73.5% in the ciprofloxacin group [93].

We work to summarize the efficacy of bismuth quadruple therapy sections, and two sections (standard therapy and bismuth quadruple therapy) were integrated into one section as below (Page 8-9).

The efficacy of standard triple therapy and bismuth quadruple therapy are decreasing

The first-line regimen for the eradication of H. pylori infection consists of STT using a PPI, amoxicillin and clarithromycin and was first introduced by Dr. Bazzoli. In studies conducted during the 1990s, STT yielded >80% treatment success with reports of >90% possible [65, 66]. However, the increased prevalence of clarithromycin resistance has accounted for the diminished efficacy of STT. Table 1 shows eradication rates from recent studies using STT. Generally, STT is not recommended as a first-line regimen when the clarithromycin resistance rate is >15–20%, and other therapies such as quadruple therapy or sequential therapy are suggested [24]. Thus, a steady increase in H. pylori resistance to amoxicillin and metronidazole has also resulted in reduced treatment success of STT [26, 67, 68]. The ideal outcome of H. pylori eradication is >80% by intention to treat (ITT) analysis and >90% by per protocol (PP) analysis. According to a recent study, the eradication rate was unacceptably low for treatment success, with only 18% exceeding 85% and ~60% failing to attain 80% eradication by ITT analysis [19]. Over the past 20 years, the efficacy of STT has decreased, with eradication rates <80% by ITT analysis [40]. According to the present formula by Dr. Graham, if clarithromycin resistance rate of 20%, the outcome of clarithromycin containing triple therapy is reduced to 77.2% by PP analysis [69]. Already in

some countries the eradication rates have been reported to be <50% and if this trend continues for another 20 years, the efficacy of STT will be negligible.

Various methods have been considered to circumvent the STT eradication rate decrease. The first method suggested that increasing the STT duration would improve treatment efficacy. In an early meta-analysis, a 14-day STT regimen raised the eradication rate compared to a 7-day regimen [70]. Another meta-analysis supported this result by showing that extending STT over 7 days improved the eradication rate [71]. However, other reports determined that extending STT was not cost-effective and increased adverse events and decreased compliance, resulting in no significant difference between the eradication rate and extended treatment duration [72]. Another means of addressing the decrease in STT eradication rate is to increase the dose of PPI, which has a positive effect on treatment success. PPIs delay gastric emptying and increase gastric pH, which improves the effect of antibiotics by preventing acid-related degradation [73]. A meta-analysis reported increased eradication rates from STT involving PPI administration twice per day compared with once per day [74]. Another systematic review reported that utilizing a high dose of PPI increased the H. pylori treatment rate [75] and the use of high-dose PPI increased the effectiveness of STT compared with a single does PPI [76]. In spite of these positive outcomes, STT is now regarded as an outdated therapy.

Bismuth quadruple therapy (bismuth subcitrate potassium, metronidazole, tetracycline, PPI) has been suggested as a first-line treatment option for regions with a high (> 20%) incidence of clarithromycin resistance [52]. In a meta-analysis of nine randomized controlled trials (RCTs), bismuth quadruple therapy and STT resulted in similar compliance rates, side effects, and eradication rates as a primary therapy for H. pylori infection [77]. For example, the ITT eradication rate with modified bismuth quadruple therapy was 92.7% in a recent randomized study in Chinese patients [78]. A pilot study in US Hispanics showed that 14-day bismuth quadruple anti-H. pylori therapy achieved a >95% eradication rate [79]. However, in some studies the eradication rate of bismuth quadruple therapy was <80% [80-82]. A decrease in the bismuth quadruple therapy eradication rate was highly associated with metronidazole resistance [19].

Reviewer #2535381

This is a detailed review regarding the treatment of Helicobacter pylori.

1. The details are exhaustive and the manuscript appears at times like a collage of various sometimes unrelated information. For example, the authors mix first, second and third line treatments within the same sections.

Answer: We agreed with reviewer's opinion. We have revised contents in the section and summarization as below (Page 9, line 16-27).

Bismuth quadruple therapy (bismuth subcitrate potassium, metronidazole, tetracycline, PPI) has been suggested as a first-line treatment option for regions with a high (> 20%) incidence of clarithromycin resistance [52]. In a meta-analysis of nine randomized controlled trials (RCTs), bismuth quadruple therapy and STT resulted in similar compliance rates, side effects, and eradication rates as a primary therapy for H. pylori infection [77]. For example, the ITT eradication rate with modified bismuth quadruple therapy was 92.7% in a recent randomized study in Chinese patients [78]. A pilot study in US Hispanics showed that 14-day bismuth quadruple anti-H. pylori therapy achieved a >95% eradication rate [79]. However, in some studies the eradication rate of bismuth quadruple therapy was <80% [80-82]. A decrease in the bismuth quadruple therapy eradication rate was highly associated with metronidazole resistance [19].

And, we are willing to integrate two sections (standard therapy and bismuth quadruple therapy) into one section (Page 8-9).

Also, we have deleted the sentence (*Recently Liang et al. evaluated levofloxacin-containing second-line therapy after STT, and presented an eradication rate of only 81% in PP analysis [120], which is an unacceptable PP for second-line treatment of H. pylori in Taiwan.*) and table (*Helicobacter pylori eradication rates following first- or second-line bismuth quadruple therapy.*) regarding the therapy of 2nd line. Thank you very much for your careful concern.

2. Some statements are too extreme and need review such as "The efficacy of standard triple therapy is disappearing" or "In order to prevent the end of H. pylori treatment, further studies must be required", etc.

Answer: We follow the review's suggestion. We are willing to correct the two sentences in each section as below (Page 8/ lines 7-8) (Page 20/ lines 6-7).

The efficacy of standard triple therapy and bismuth quadruple therapy are decreasing

In order to improve the eradication rate for H. pylori infection, further studies must be required.

3. The paper needs significant review regarding the English language

Answer: We agreed with reviewer's opinion. As the reviewer mentioned, we proofread our manuscript through Textcheck, professional proofread cooperation.

4. Triple therapy was first introduced in 1993 by Bazzoli not Graham

Answer: We agreed with reviewer's opinion. We are willing to correct the sentences as below (Page 8/ lines 9-10).

The first-line regimen for the eradication of H. pylori infection consists of STT using a PPI, amoxicillin and clarithromycin and was first introduced by Dr. Bazzoli.

I would like to confirm again that there is nothing to be declared and all authors have approved the revised manuscript. I hope that our revised manuscript will better meet the requirement of the 'World Journal of Gastrointestinal Pharmacology and Therapeutics' for publication. And I thank you for valuable comments by reviewers.

Sincerely,

Jun-Won Chung

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September 7, 2015

Fang-Fang Ji
Science Editor, Editorial Office
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ESPS Manuscript NO: 18676: Antibiotic treatment for *Helicobacter pylori*: Is the end coming?

Dear Editor,

I would like to thank the chief editor of the 'World Journal of Gastrointestinal Pharmacology and Therapeutics' for taking their time to review my article. Chief editor's comments were very helpful for us to correct and revise our manuscript. All changes we made are summarized below:

#Editor-in-chief comments to authors

1. This is an excellent overview, however, the manuscript might be substantially i mproved with critical discussion of the natural history of this agent in the etiopa thogenesis of disease, particularly gastrtis. Importantly, the authors should ackno wledge that Helicobacter infection may resolve spontaneously without treatment.
A reference that should be noted is as follows: Freeman HJ. Disappearance of H elicobacter without antibiotics in 12 patients with gastritis. Can J Gastroenterol 1 997; 11: 167-172 (PMID 9113817).

Answer: As you recommended above, we are willing to add the reference and sentence in introduction section (Page 5, line 14-15). Thank you very much for your careful conce rn.

In other report, some patients with gastritis resolved H. pylori infection without using antibiotic treatment[11].

I hope that our revised manuscript will better meet the requirement of the 'World Journal of Gastrointestinal Pharmacology and Therapeutics' for publication. And I thank you for valuable comments by editors.

Sincerely,

Jun-Won Chung

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