ANSWERING REVIEWERS

Name of journal: World Journal of Gastroenterology

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Title: The importance of antimicrobial susceptibility testing for the management of eradication in *Helicobacter pylori* infection

Reviewer's code: 00227403

Reviewer's country: Italy

COMMENTS TO AUTHORS: Section introduction. The sentence: The eradication rate of first-line standard therapy is 55-57% in Western Europe, 74.5% in China, 84% in the Korea, 87% in Nigeria, 72% in Spain[8,20]. should be ameliorated. Since Spain is in Western Europe it should be reported as: The eradication rate of first-line standard therapy is 55-72% in Western Europe, 74.5% in China, 84% in the Korea, 87% in Nigeria[8,20]. In the section of Amoxicillin resistance could the authors add a sentence on the fact that an amoxicillin plus clavulanic acid-based triple therapy is not better that a simple "amoxicillin"-based triple therapy. All sentence regarding the Maastricht IV guidelines should be replaced and adapted with the new V Maastricht V in publication in Gut and in part reported in the review in Panminerva Medica 2016;58(4)304-17. This is more important considering the step by step indications for Helicobacter treatment and the new treatment with a single "three-in-one" capsule (quadruple therapy). Moreover indications on susceptibility testing are given.

Answers: i) The sentence is corrected as you recommended."The eradication rates of the first-line standard therapy are 55-57% in Western Europe, 74.5% in China, 84% in Korea and 87% in Nigeria"**(page 5, lines 28-29-30 in edited file).**

ii) Maastricht V/Florence Consensus Report is added and the any treatment strategy difference among Maastricht IV and V are considered. The new drug including three in one capsule is added by referring the publication you recommended (in the review in Panminerva Medica 2016;58(4)304-17). The treatment strategy of *H. pylori* is revised by step by step as **"The treatment regimens for *H. pylori* infection are generally based on the use of two antibiotics and one acid suppressant. Because *H. pylori* localizes on the acidic surface of the gastric mucosa, an acid suppressant**

(generally a proton pump inhibitor, PPI) is required for maintaining a constant pH and facilitating bacterial replication to increase the efficacy of antibiotics[3]. The standard triple therapy for *H. pylori* infection consists of a PPI in combination with clarithromycin and either amoxicillin or metronidazole[3,5,12-19]. Although the efficacy of this treatment regimen was high (>90%) in the 1990s, the eradication rate of the triple therapy has fallen below the rate of 80% recommended by the Maastricht IV Consensus in recent years, mainly due to high antibiotic-resistance rates[6,9,11,13] Many factors, such as antibiotic resistance, treatment compliance, dosage administered, duration of therapy, low gastric pH, cytochrome P450 2C19 (*CYP2C19*) gene polymorphisms, high bacterial load, impaired mucosal immunity and smoking, negatively affect the efficacy of the first-line triple therapy[6,8,20]. The eradication rates of the first-line standard therapy are 55-57% in Western Europe, 74.5% in China, 84% in Korea and 87% in Nigeria[8,21]. In cases of high clarithromycin resistance, bismuth-containing quadruple therapy (PPI, bismuth, tetracycline, and amoxicillin) or non-bismuth quadruple (concomitant) therapy has been recommended by more recent Maastricht Guidelines as the first-line therapy[12-14]. However, the success of these therapies remains controversial[22]. Other non-bismuth quadruple therapies, including the sequential and hybrid therapies suggested by the Maastricht IV/Florence Consensus Report, are no longer recommended by the latest Maastricht V/Florence guideline as the first-line treatment in regions with high clarithromycin resistance. After first-line treatment failure, bismuth-containing quadruple and levofloxacin-based triple therapies are recommended as a second-line treatment[12-14]. In addition, bismuth-containing levofloxacin quadruple therapy is recommended as a second-line therapy by the Maastricht V/Florence Consensus Report[12]. For cases of dual clarithromycin and metronidazole resistance (>15%), only bismuth-containing quadruple therapy is recommended. If bismuth is not available, levofloxacin, rifabutin, and high-dose dual (amoxicillin and PPI) therapies are also suggested[12,14]. Culture- or molecular-based antimicrobial susceptibility testing should be considered for third-line treatment[12,13]. A combination of bismuth with antibiotics or rifabutin-containing rescue therapy in regions with high fluoroquinolone resistance is recommended by the recent guideline after clarithromycin-based first-line treatment and bismuth-containing quadruple-based second-line treatment failure[12]. In addition, the new three-in-one capsule drug, which contains bismuth, tetracycline, and metronidazole, could be important in this clinical setting and shows better efficacy (93% intention to treat) than the standard therapy[14]. (pages 5 – 6 in edited file)"

iii) In the section of amoxicillin resistance, we thought that the sentence that" an amoxicillin plus clavulanic acid-based triple therapy is not better that a simple "amoxicillin-based triple therapy" is not suitable with content of the section. We want to mention standard treatment regimens recommended in recent Maastricht guidelines and focus on efficacy and applicability of the antimicrobial susceptibility based treatment. An amoxicillin-clavulanic acid based triple therapy is not mentioned in the relevant guidelines and also we could not realize this kind of regimen in publications about *H. pylori* treatment. So we could not understand clearly your suggestion.

Reviewer's code: 00058744

Reviewer's country: Japan

COMMENTS TO AUTHORS: This is an editorial description about antimicrobial susceptibility testing for *Helicobacter pylori* infection. The authors wrote about mechanisms of each main antimicrobial resistance and conventional and molecular-based tests to detect the resistance and about the contribution of antimicrobial susceptibility testing in the management of *H. pylori* eradication therapy in detail. The structure and overall description is excellent. Only one reference was missed. Please insert correct number of reference in line 27 in page 12.

Answer: Thank you for your comments and the attention about missed reference. We added the reference in "There is no consensus for levofloxacin, tetracycline and amoxicillin breakpoints in the treatment of *H. pylori* infection"[37,66]. "

Yes, indeed many thanks for your attention.