Comment 1: PPIs are not essential for the H. pylori eradication especially in bismuth based treatment (Borody TJ, Cole P, Noonan S, Morgan A, Lenne J, Hyland L, et al. Recurrence of duodenal ulcer and Campylobacter pylori infection after eradication. Med J Aust 1989; 151:431–435 or George LL, Borody TJ, Andrews P, Devine M, Moore-Jones D, Walton M, et al. Cure of duodenal ulcer after eradication of Helicobacter pylori. Med J Aust 1990; 153:145–149). For this reason the sentence: PPI plays the cardinal role in the eradication regimen (Abastract section: line 4) is not correct. PPIs could be important but not essential.

Answer: Thanks for your suggestion. We had corrected our statement in Abstract and Introduction section: PPI is important in the eradication regimen.

comment 2 : The triple H. pylori regimen PPI, amoxicillin and clarithromycin now provides unacceptably low treatment success and their use could be discouraged. Chinese guideline for the treatment of H. pylori recommend bismuth-containing quadruple therapies for both first-line and rescue treatments for H. pylori infection. These aspects have to be discussed in the manuscript

Answer: We had added the following statement in the Introduction section:

According to the recommendation of the Asian Pacific Helicobacter pylori meeting 2012 in Singapore: 1. In areas with low clarithromycin resistance rates, standard triple therapy should be the primary choice, while bismuth-containing quadruple, sequential therapy and concomitant therapy could be alternative first-line therapies; and 2. In areas with high clarithromycin resistance, regimens including bismuth-containing quadruple, sequential therapy and concomitance should be the better choice for first-line regimens. So the antibiotics resistance should be analyzed in the high clarithromycin and / or levofloxacin resistant rate area.

Comment 3: Since the pattern of cytochrome polymorphism differs between Asian and Caucasian subjects, data on the latter group of patients would be useful. Indeed, the WJG is an International Journal, so that the manuscript should include a complete information. Therefore, we would invite the Authors to search for these data in literature, and to add the information by comparison with the Asian patients. Although the manuscript is clearly written, some stylistic improvements are advisable

Answer: Thanks for your suggestion. The WJG is an International Journal, so we presented a complete information about the differences between Asian and Caucasian in the part of **"The difference of geographic distribution"** as following:

The frequency of the CYP2C19 polymorphism is highly varied among different ethnic populations. According to previous reports, Asian people have a higher proportion of poor metabolizers compared to whites. Approximately 2-6% of Caucasians and 1% of African-Americans have been identified as PM, but this reaches more than 14.0% in Asian population. For example, the frequency of PM in Japanese (19-23%) is much higher.

On the other hand, the prevalence rate of HomEM is about 70% for Caucasians, but only 30–40% for Asians.

Comment 4: In the paper , the antibiotic resistance rates should be put into consideration and analysis at the same time, especially in high clarithromycin and /or levofloxacin resistant rate population.

Answer: Thanks for your suggestion. We had add following statement in the Introduction section:

The triple regimen should be abandoned when the CAM-resistance rate in the region is more than 15-20%, because many studies published recently have demonstrated that the intention to treatment (ITT) eradication rate is falling short of 80% . The same consideration is also suitable for high levofloxacin resistance area.

Comment 5: PPI don't always play the cardinal role in the eradication regimen.

Answer: Thanks for your suggestion. We had corrected our statement in Abstract and Introduction section: PPI is important in the eradication regimen.

Comment 6: H. pylori should be italicized ?

Answer: Thanks for your suggestion. We had corrected these mistakes.

Comment 7: What is the technique used for CYP2C19 genotyping? A short paragraph describing this aspect needs to be enclosed; ?

Answer: Thanks for your suggestion. We had added one paragraph describing the technique used for CYP2C19 genotyping:

Analysis of CYP2C19 Genotypes

For analysis of *CYP2C19* genotypes, all enrolled patients' peripheral blood leukocytes were obtained before the eradication therapy was begun. DNA was extracted from the leukocytes with a commercially available kit (QIAGEN K.K., Tokyo, Japan) and stored until use. Genotyping procedures for identifying the *CYP2C19 wild type* (*wt*) gene and two mutated alleles, *CYP2C19 m1* and *CYP2C19 m2*, were performed by a polymerase chain reaction–restriction fragment length polymorphism method with allele-specific primers.However, this technique is expensive and not all medical unit can carry out it. This is one of the limitations for managing *H. pylori* infection.

Comment 8: A table summarizing the main CYP2C19 polymorphisms and their clinical relevance is useful to make reading easier by the audience and, therefore, requires to be enclosed in revised manuscript?

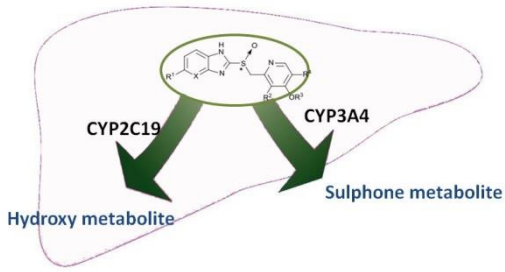
Answer:

	Genotype	**Ratio (Asian)**	**Ratio (Caucasian)**	**Metabolism of PPIs**
HomEM	wt/wt	30-40%	70%	at highest rates
HetEM	wt/m1 or wt/m2	45-55%	25-27%	at moderate rates
PM	m1/m2	13-23%	3-5%	at lowest rates

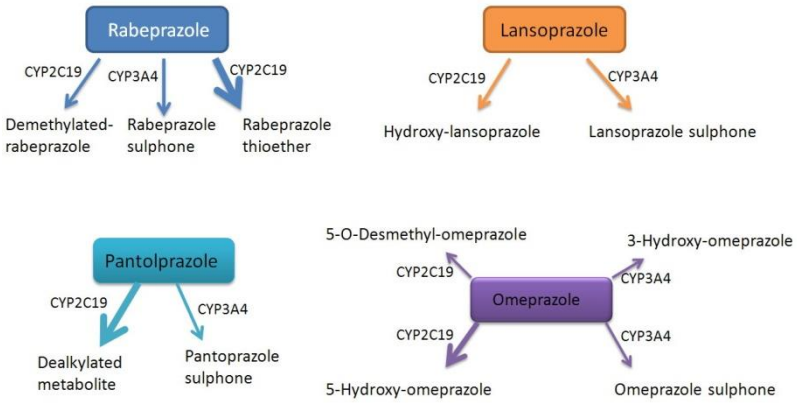
HomEM :Homozygous extensive metabolizer HetEM : Heterozygous extensive metabolizer PM: Poor metabolizer PPIs: proton pump inhibitors wt: wild-type allele m1/m2: mutated alleles

Comment 9: A figure with chemical formulas of PPIs, their metabolites and the most important metabolic pathways could be useful to enrich the content of this paper.

Answer: Thanks for yoursuggestion.We had added the figure with chemical formulas of PPIs, their metabolites and the most important metabolic pathways.



The hepatic metabolism of PPIs (except rabeprazole)



The metabolic pathways of PPIs and their cytochrome P450 (CYP) isoforms involved.

comment 10 : There are some new types of PPIs, e.g ilaprazole, tenatoprazole. Please add some information of CYP role on these PPIs.

Answer: We had added this part in our article:

There are some new types of PPIs, e.g tenatoprazole, ilaprazole reported in recent years. Tenatoprazole is a novel proton pump inhibitor with a seven-fold longer plasma half-life H(+)/K(+)-ATPase inhibitors . There are no much data about the impact of CYP2C19 polymorphism on tenatoprazole. Ilaprazole is a new proton pump inhibitor and its major metabolite is ilaprazole sulfone. It is predominantly metabolized by CYP3A4/5.

Comment 11: add some figures or tables to compare different effect of PPIs in H.pylori eradication.

Answer: as comment 8

Comment 12: English form may be revisited for some words (e.g. PPIs)

Answer: We had correct these mistakes.

Comment 13 Some references are omitted, please cite the paper of Serrano 2012 and explain the difference respect to it

Serrano D, Torrado S, Torrado-Santiago S, Gisbert JP. The influence of CYP2C19 genetic polymorphism on the pharmacokinetics/- pharmacodynamics of proton pump inhibitor-containing Helicobacter pylori treatments Curr Drug Metab. 2012 13(9):1303-12.

Answer: Thanks for your suggestion. We had cited the paper of Serrano et al. (2012) and explain the difference respect in the Introduction section.

Comment 14 Page 13: "We suggest the following strategies to avoid the influence on eradication: 1. Select PPI metabolized by the non-enzymatic pathway; and 2. Consider increasing dose of CYP2C19 sensitive PPI". Please change it because you must explain the criteria of selection of PPIs because these drugs are different respect to their ability to inhibit the proton pump, with a possible decrease in clinical efficacy. Moreover, you have write that the evaluation of CYP is expensive, but it is not possible to increase the dosage if you don't known the presence or not of a polymorphism

Answer: Thanks for your suggestion. We had modified this paragraph to avoid misunderstanding as following:

We suggest the following strategies to avoid the influence of CYP2C19 genotype after failure of eradication : 1. Select PPI metabolized by the non-enzymatic pathway; and 2. Consider increasing dose of CYP2C19 sensitive PPI.

comment 15 : Conclusions are very long please reduce.

Answer: Thanks for your suggestion. We had modified the conclusion as following:

The CYP2C19 variant carriage is an important factor of *H. pylori* eradication rate in patients taking omeprazole- or lansoprazole-based triple therapies. The efficacy of levofloxacin-based rescue triple therapy might be also affected by the CYP2C19 polymorphism, but CYP2C19 genotypes did not show obvious impact on levofloxacin-based quadruple rescue therapies. Other possible factors influencing gastric acid secretion (e.g. *IL-1*β- *511* polymorphisms) should also come under

consideration.

Comment 16: In respect to reference 60 by Dr. Liou JM,etal,the eradication rates were not affected by the CYP2C19 polymorphism, but in your conclusion: The efficacy of levofloxacin-based rescue triple therapy might be also affected by the CYP2C19 polymorphism, but the CYP2C19 genotypes did not show obvious impact on other levofloxacin- based rescue therapies. Is there any explanation?

Answer: Thanks for your comments. Our statement were consistent with the findings of Liou JM et al. We pointed out that the efficacy of levofloxacin-based rescue triple therapy might be also affected by the CYP2C19 polymorphism, but the CYP2C19 genotypes did not show obvious impact on other levofloxacin- based rescue therapies. According to their article, Liou used levofloxacin-based sequential therapy but not levofloxacin-based triple rescue therapies. So they stated that the eradication rates were not affected by the CYP2C19 polymorphism. This conclusion is not different with our statement.