

Format for ANSWERING REVIEWERS

August 2, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name:Revision NO: 21308 doc).

Title: [Five-year sequential changes in secondary antibiotic resistances of Helicobacter pylori in Taiwan](#)

I-Ting Wu, Seng-Kee Chuah, Chen-Hsiang Lee, Chih-Ming Liang, Lung-Sheng Lu, Yuan-Hung Kuo, Yi-Hao Yen, Ming-Luen Hu, Yeh-Pin Chou, Shih-Cheng Yang, Chung-Mou Kuo, Chung-Huang Kuo, Chun-Chih Chien, Yu-Shao Chiang, Shue-Shian Chiou, Tsung-Hui Hu, Wei-Chen Tai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 21308

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) **Reviewer 1:**

Reviewer report on manuscript number 20150705130732 Title: Five-year sequential changes in antibiotic resistances of Helicobacter pylori among patients who failed first line therapy

The paper discusses the resistance to antibiotic therapy among H. Pylori-treated subjects in Taiwan. The manuscript deals with an important issue. The study is well written and the authors presented their data and conclusions clearly. Comments In the introduction section: “The prevalence of antibiotic resistance for Helicobacter pylori (H. pylori) varies from countries to countries and may be partly determined by the geographical factors”. The authors should clarify what is meant by the geographical factors? and provide references for this. Some typing and grammatical mistakes are noted: “Antibiotics resistance ”.....” Antibiotic resistance “ “The resistances of amoxicillin and tetracycline”....” The resistance to amoxicillin and tetracycline” “did not increased”.... “did not increase” “None of these antibiotics resistances”..... “None of these antibiotic resistances”..... “ntibiotics resistance of H. pylori in Taiwan” “in Taiwan remained a problem for effective eradication in Taiwan” “Furthermore, the impact of increase levofloxacin resistance to efficacy” “Current study encounters some limitations” “Our results showed that theHigh resistance” “2010 but did not increased” “antibiotics resistances”

1. Comments In the introduction section: “The prevalence of antibiotic resistance for Helicobacter pylori (H. pylori) varies from countries to countries and may be partly determined by the geographical factors”. The authors should clarify what is meant by the geographical factors? and provide references for this.

[Answer:](#)

[Thank you very much!](#)

[It means the phenomenon of the increasing antibiotic resistance has been shown in controversial aspects either within the same geographic area such as each world continent \(Europe, America, Asia and Africa\).](#)

The values of resistance to main antibiotics (clarithromycin, amoxicillin, metronidazole and levofloxacin) are reported with large ranges depending from the different countries. [A reference has been added.](#)

[1]. Ierardi E, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography? *World J Gastroenterol.* 2013; **19**: 8168-8180.

2. Some typing and grammatical mistakes are noted: “Antibiotics resistance ”.....” Antibiotic resistance “ “The resistances of amoxicillin and tetracycline”....” The resistance to amoxicillin and tetracycline” “did not increased”.... “did not increase” “None of these antibiotics resistances”..... “None of these antibiotic resistances”..... “ntibiotics resistance of *H. pylori* in Taiwan” “in Taiwan remained a problem for effective eradication in Taiwan” “Furthermore, the impact of increase levofloxacin resistance to efficacy” “Current study encounters some limitations” “Our results showed that thehHigh resistance” “2010 but did not increased” “antibiotics resistances”

Answer: Thank you very much! They have been corrected in the text.

(2) **Reviewer 2**

This is an interesting paper looking at antibiotic resistance of *Helicobacter pylori* in patients who failed the first line of treatment. The authors are to be commended on their efforts to address such an important public health issue. I have only some minor comments: 1. Introduction, line 5: please check “mean seroprevalence rate”. It is not clear if you are referring to prevalence or incidence. 2. Although for this is intuitive for most of the clinicians, some other general readers may not be familiarised with the components of standard triple therapy and listing them in the introduction could be helpful. 3. Regarding the exclusion criteria, the use of antibiotics is so widespread that seem unlikely that an individual has never been exposed during his/hers lifetime. Could you please provide more details about the exclusion of isolates from patients who were previously treated for other diseases with antibiotics? 4. The information contained in table 1 is also contained in table 2, except the number of subjects. I would suggest including only one table, will all the information. 5. Discussion, paragraph 5: please clarify what is meant by “time ratio”. 6. Please provide a footnote explaining the meaning of the horizontal line around 15%.

1. Introduction, line 5: please check “mean seroprevalence rate”. It is not clear if you are referring to prevalence or incidence.

Answer: Thank you very much! It means the prevalence of *H. pylori* infection in Taiwan.

2. Although for this is intuitive for most of the clinicians, some other general readers may not be familiarised with the components of standard triple therapy and listing them in the introduction could be helpful.

Answer:

Thank you very much! We added it in the Introduction, “ If the resistance rates continue to rise, the use of first-line *H. pylori* eradication with standard triple therapy, **which consists of a proton pump inhibitor (PPI), clarithromycin and amoxicillin**, might lead to a poor outcome (<80%)”(page 5, lines 7-10)

3. Regarding the exclusion criteria, the use of antibiotics is so widespread that seem unlikely that an individual has never been exposed during his/hers lifetime. Could you please provide more details

about the exclusion of isolates from patients who were previously treated for other diseases with antibiotics?

Answer:

Thank you very much. You are right that the use of antibiotics is so widespread that seem unlikely that an individual has never been exposed during his/hers lifetime. However, we have reviewed and matched all the medical records for medication used in our hospital. Patients with history of previous antibiotics exposure in our medical records were all excluded. Therefore, we corrected this sentence to a more precisely one:

“All isolates from patients who had been previously treated for *H. pylori* infection or who had been exposed to any antibiotics according to our hospital’s chart recoding were excluded.”(Page 6, lines 14-16)

4. The information contained in table 1 is also contained in table 2, except the number of subjects. I would suggest including only one table, will all the information.

Answer: Thank you, we merged the tables.

				P value
		Patient number	Proportion(95% (%)	C.I.) Chi-square test for linear trend
Amoxicillin	2010	0/24	0 (-)	-
	2011	0/32	0 (-)	
	2012	0/20	0 (-)	
	2013	0/20	0 (-)	
	2014	0/41	0 (-)	
Clarithromycin	2010	17/24	70.8 (51.2-90.4)	0.736
	2011	21/32	65.6 (48.2-83.0)	
	2012	13/20	65.0 (42.1-87.9)	
	2013	15/20	75.0 (54.2-95.8)	
	2014	29/41	70.7 (57.9-85.3)	
Levofloxacin	2010	9/24	37.5 (16.6-58.4)	0.391
	2011	11/32	34.4 (17.0-51.8)	
	2012	6/20	30.0 (8.0-52.0)	
	2013	7/20	35.0 (12.1-57.9)	
	2014	11/41	26.8 (7.9-41.0)	
Metronidazole	2010	9/24	37.5 (16.6-58.4)	0.312
	2011	8/32	25.0 (9.1-40.9)	
	2012	6/20	30.0 (8.0-52.0)	
	2013	6/20	30.0 (8.0-52.0)	
	2014	18/41	43.9 (23.3-59.8)	
Tetracycline	2010	0/24	0 (-)	0.556

2011	0/32	0 (-)
2012	2/20	10.0 (0-24.4)
2013	0/20	0 (-)
2014	1/41	2.4 (0-7.4)

5. Discussion, paragraph 5: please clarify what is meant by “time ratio”.

Answer: Thank you very much.

The “time ratio” in original paper means time spending ratio for confirmed diagnosis and treatment of TB. In this case, it means it takes double time to diagnose TB and start treatment.

6. Please provide a footnote explaining the meaning of the horizontal line around 15%.

Answer: Thank you very much. The figure has been revised as suggested by providing a footnote explaining the meaning of the horizontal line around 15%.

* Values located above 15% horizontal line indicated intention-to-treat cure rate categories below C (fair, 85%-89%)^[39]

Editorial revisions:

- (1) Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).

For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in ‘**The Revision Policies of BPG for Article**’.

Answer: The manuscript has been revised by professional English language editing companies as suggested and language certificate letter has been attached. (American Journal Experts: <http://www.aje.com>)

- (2) Title should be no more than 10~12 words/60 bytes. Please revise it.

Answer: Five-year sequential changes in secondary antibiotic resistances of *Helicobacter pylori* in Taiwan

- (3) Besides, please provide these files, which are **necessary for final acceptance**, each in a **separate PDF file**, signed by the Correspondence author or a copy of Institution approval document(s)/letter(s) or waiver of confirmation. For sample wording and detailed information, please see the Revision policy in the attachment or Instruction to authors on our website. Thank you!

Answer: These files have been attached.

IRB: This study was approved by both the Institutional Review Board and Ethics Committee of Chang Gung Memorial Hospital, Taiwan (IRB104-1245B) as attached IRB file.

Informed consent: The Ethics Committee waived the requirement for informed consent, and the patient’s medical records was anonymized and de-identified prior to access as attached IRB file.

Conflict-of-interest: The authors have no conflict of interest related to the manuscript as attached in Conflict of Interest file

(4) Audio core tip:

In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

Answer: Audio Core Tip has been attached as mp3 formats

- (5) AIM** should be no more than 20 words: The purpose of the study should be stated clearly and with no or minimal background information, following the format of: "To investigate/study/determine..."

Answer: It has been revised

Aims: To determine changes in antibiotic resistances of *H. pylori* in Southern Taiwan after failure of first line standard triple therapy.

- (6)** Please put the punctuation behind reference. Please check throughout. Thank you!

Answer: It has been done throughout the paper as suggested

- (7)** Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>)

DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**)

Answer: PMID and DOI are added now.

Sincerely yours,

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