

February 13th, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6428_review_edited_SS.doc).

Title: Antimicrobial susceptibility testing for *Helicobacter pylori* in times of increasing antibiotic resistance.

Authors: Sinéad M. Smith, Colm O'Morain, Deirdre McNamara.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6428

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 reviewers and highlighted in red.

(1) Reviewer 1 (ID: 00506501)

- (i) The title of the manuscript was not changed as it had been agreed with the journal editors prior to submission
- (ii) The usefulness of serologic tests that detect IgG antibodies to *H. pylori* is discussed in the "Introduction" (highlighted in red). In addition, the unsuitability of these tests for determining *H. pylori* eradication is mentioned in the second paragraph of the "Treatment for *H. pylori* infection" section.

(2) Reviewer 2 (ID: 00465176)

- (i) The most recent reports on the prevalence of *H. pylori* antimicrobial resistance were discussed in the original manuscript, as well as review articles on antibiotic resistance and testing, namely:

- a. Megraud F, Lehours P. *Helicobacter pylori* detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007; **20**(2): 280-322 [PMID: 17428887 PMCID: 1865594 DOI: 10.1128/CMR.00033-06]
- b. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**(8): 1143-1153 [PMID: 20525969 DOI: 10.1136/gut.2009.192757]
- c. Lehours P, Megraud F. *Helicobacter pylori* molecular diagnosis. *Expert review of molecular diagnostics* 2011; **11**(4): 351-355 [PMID: 21545252 DOI: 10.1586/erm.11.17]

In addition, the following recent review articles have now also been discussed in the revised manuscript:

- a. Ierardi E, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography? *World journal of gastroenterology : WJG* 2013; **19**(45): 8168-8180 [PMID: 24363506 PMCID: 3857438 DOI: 10.3748/wjg.v19.i45.8168]
- b. Iwanczak F, Iwanczak B. Treatment of *Helicobacter pylori* infection in the aspect of increasing antibiotic resistance. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University* 2012; **21**(5): 671-680 [PMID: 23356205]

(ii) A table indicating the sensitivity and specificity of molecular methods of antibiotic resistance detection compared to phenotypic assays, and the corresponding references, has been included (Table 2).

(iii) A table on the prevalence of antimicrobial resistance in different countries has been included (Table 4). This table indicates whether the study referenced reports primary resistance rates or overall resistance rates.

(iv) A figure on the mechanisms of resistance has been included (Figure 1)

(3) Reviewer 3 (ID: 00506467)

(i) The title of the manuscript was not changed as it was agreed with the editors prior to submission. A sentence to indicate that *H. pylori* treatment options are discussed in the review has been included in the abstract.

(ii) This typo has been corrected

- (iii) It has been mentioned in the “Treatment for *H. pylori* infection” section that non-compliance leads to treatment failure.
- (iv) The sentence relating to 16S rRNA mutations has been changed to reflect the reviewer’s suggestion.
- (v) 94.5% has been placed in parentheses according to the reviewer’s suggestion.
- (vi) A sentence based on the UK study finding that previous antibiotic use is associated with an increase in harboring an antibiotic resistant strain of *H. pylori* has been added to the abstract.

(4) Reviewer 4 (ID: 00058436)

- (i) It is mentioned in the “*H. pylori* culture and antimicrobial susceptibility testing” section that the use of PPIs or antimicrobials inhibits the growth of *H. pylori* and reduces the chances of successful culture and that patients should avoid taking PPIs for at least 2 weeks and antimicrobials for 4 weeks prior to endoscopy. The culture success rate (55-73%) of *H. pylori* from biopsies is described and the corresponding references indicated in the “Molecular testing for antibiotic resistance-associated mutations” section.
- (ii) The article on the cost-effectiveness of pre-treatment susceptibility testing by Yuan Wenzhen et al. 2010 was chosen, as to the best of our knowledge, it is the most recent meta-analysis to be performed in this area. However, the manuscript has been updated in the “Future perspectives” section to also reference the reports by Qasim et al 2004 and Faber et al. 2005. In addition, it is mentioned that the economic benefits of tailoring first line therapy is likely to depend on the local antibiotic resistance rates as a recent study by Cosme A. et al. (2013) reported that performing culture and antimicrobial susceptibility testing lead to higher eradication rates and increased cost efficiency in an area of high clarithromycin resistance (>15-20%).

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,
Sinead

Sinead M. Smith PhD
Rm 1.44
Dept. of Clinical Medicine
Trinity Centre
Adelaide and Meath Hospital
Tallaght
Dublin 24
Ireland
Phone: +353 18962998
Email: smithsi@tcd.ie