Author's response to reviews

Title: The diagnostic value of endoscopy and Helicobacter pylori tests for peptic ulcer patients in late post-treatment setting

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Version: 2 Date: 20 September 2004

Author's response to reviews: see over
Dear Dr. Deng-Chyang Wu and Prof. Francis Megraud

Thank you very much for your comments. Most of them were very valuable and we have introduced corresponding changes in our paper. The English language of the manuscript has been revised.

Referee 1:
Major Compulsory Revisions:
1) In page 4, the patient group was observed at 4 weeks, and thereafter one year and 5 years after treatment (127, 107 and 81 patients, respectively). That means 7 patients received post-treatment Hp evaluation after 1 year or 5 years. So, what is the definition of successful eradication? As time past, Hp could be re-infected or recrudesced during 5-year period. Of course, the aim of this paper focuses on detecting Hp with different methods. But detecting scanty Hp at 4 weeks and large amount Hp after 1 year with different methods and compared their accuracy, not a good way to do this.

Response: We completely agree with the Reviewer that after a 5-year period it is possible to have reinfection. Indeed, as our study group was part of a larger follow-up group, we registered two cases of reinfection during 5 years, but these cases were not included in the present group. As in this study our aim was not to evaluate the results of treatment and eradication success, we believe that comparison of different methods for detection of H. pylori is useful even in cases of unsuccessful eradication. In daily practice it is necessary to plan further management of patients who have been treated several years earlier but who still have complaints.
The Patients section in Methods has been rephrased (page 5).

2) Since recent proton pump inhibitor use leads to false negative UBT result. It’s necessary that author describe the percentage of patients underwent Hp exams during proton pump inhibitor use and the duration of cessation of proton pump inhibitor use and evaluation of residual Hp infection.
Response: Proton pump inhibitors were used for 7 days during triple therapy but not later. Some patients took H₂ receptor blockers on demand during the 5-year period. The use of drugs before 13C breath test was excluded.

3) In page 6, since the specimens from the antrum and corpus mucosa used for imprinting the cytology slides were the same with those used for culture, how do you explain the obvious difference between the cytology (24% positive) and culture (100% positive) results in UBT(+) cases?

Response: We found good accordance between all applied methods (separate specimens from the antrum and corpus mucosa), besides cytology. It was also surprising to us, as we have successfully used cytology in the investigation of peptic ulcer patients before treatment. We have even encouraged doctors to use it as a quick, inexpensive and simple method. After completing this study, we will be able to restrict the method to the cases where no antibacterial treatment is used.

4) The aim of this paper is to compare invasive and non-invasive methods for the detection of Hp in late post-treatment patients. Unfortunately, these can not be showed clearly in the result section and table 1. Please adjust this problem.

Response: Thank you for the suggestion. We made the necessary changes in Table 1, so it should be now clearer to understand (page 20).

5) In page 10 line 12, since the histologic finding of Hp completely correlated with the result of 13C-UBT, it was irrelevant with following sentence “Thus, endoscopy and gastric mucosal biopsy remain the best available methods…”.

Response: Considering your remark, we have rephrased the 2 important sentences appreciating 13C-UBT yet showing the importance of histological evaluation, page 11 lines 19-23.

6) In discussion section, our readers can’t easily find the crucial answer from the endpoint of this paper. Moreover, further discussion was relatively irrelevant to the result, though the author tried to address that the visual evaluation of mucosa did not well correlate with Hp infection.

Response: We tried to improve the Conclusion part (in Abstract and Discussion, pages 2-3 and 12-13).

7) In page 5, author diagnosed GU and DU, different with traditional definition? Could you explain this and provide reference?

antrum and corpus in relation to development of peptic ulcers and gastric carcinoma, served as the basis of our classification of ulcers. In page 5 we changed the text: Duodenal ulcer was diagnosed if the ulcer was found in the duodenal bulb area. Explanation: in this study we had no ulcers in prepyloric or pyloric area and all duodenal ulcers were located in bulbus area.

8) In page 5, the author performed E-test for clarithromycin, not for amoxicillin and metronidazole: which were main antibiotics used to treat these patients in this study (as shown in Line 5 Page 4).

Response: Our aim was not to establish the reasons for failure of H. pylori eradication after previous therapy by metronidazole and amoxicillin. Clarithromycin resistance was followed for clinical reasons as a promising preparation for repeat treatment of H. pylori positive patients.

9) In page 7, the endoscopic finding of these 34 patients were 6 patients with duodenal mucosa erosion and 4 peptic ulcer in line 9. However, in line 16, the author showed 6 patients with gastric mucosa erosions.

Response: Thank you for this remark. It should be duodenal erosions on both lines. We have now made the necessary correction (page 8).

Referee 1 generally:
Generally speaking, the result, discussion and conclusion part can not meet the aim of this paper. Secondly, this study lacks a good study design.

Response: Please accept that we have tried to improve all the problems concerned, as shown by the answers to your previous comments.

Referee 2:
General:
1) It would be interesting to know what the cause of the symptoms and endoscopic findings in the H. pylori negative group were.

Response: It is difficult to define the definite cause of the symptoms after treatment even if the ulcer has disappeared and H. pylori is eradicated. Quality of life studies of peptic ulcer patients after treatment show that there are persons who respond to H. pylori eradication with reduced symptoms and those who do not, due to capturing the patients experience of peptic ulcer disease complaints (Crawley J et al Dig Dis and Sci 2001;46:571-80).

2) It would also be nice to know more about the patients non-explored. Apparently 53 patients missed the 5-year follow-up. The reasons should be provided and among the remaining 81, only 34 were studied. Does this mean that none of the others had symptoms?

Response: For the comparison of the diagnostic methods 5 years after treatment, we included only 34 patients who met the Inclusion criteria as resistant complaints and compliance with all investigations (clinical symptoms, $^{13}$C breath test, endoscopy,
biopsy, bacteriology, PCR and cytology). This part has been rephrased in Methods/Patients section page 5.

3) Page 4, with regard to the 13C-UBT (no italics), please indicate if a test meal was used and the time of specimen collection.

Response: We included the suggested information in the manuscript, page 5.

4) Page 5, last line, the cut-off for clarithromycin resistance according to NCCLS is >1 mg/l.

Response: Sorry, we have now re-evaluated the data of clarithromycin resistance according to the new NCCLS criteria. After re-evaluating the data we found that three resistant *H. pylori* strains were highly resistant (> 256 mg/l), while the resistance of the others was below 1.0 mg/l (page 6).

5) A table showing the endoscopic findings according to the *H. pylori* status could be added.

Response: Thank you for the suggestion; we changed the Table 1 so that it includes now the information of the endoscopic findings (page 20).

6) The presence of atrophy and intestinal metaplasia in a small number of *H. pylori* negative cases should be interpreted as sequelae of this infection.

Response: We have added the suggested comment and the relevant reference of Sipponen to the Discussion section, page 11.

Minor Essential Revisions:
1) Page 4, 5 lines before the end; “13C-urea”
2) Page 7, line 10: “A poor concordance was found between…”
3) Page 7, 4 lines before the end: “histological tests, was *H. pylori* negative”
4) Page 8, line 5: “..intestinal metaplasia were rarely observed…” delete “with small frequency” line 6.
5) Page 8, lines 7 & 8: “Lymphoid follicles were more frequent…”

Response: Thank you for your valuable comments and suggestions. All minor essential revisions were performed during the improvement of the manuscript.