

## RESPONSE TO REVIEWER 1

### *Comment*

*In the section material and methods it should be specified how the patients were treated, with what kind of regimens (the same regimen or different) and for how many days? It is important to know, because this factor may affect the results of the study. The findings of the present study deserve to be discussed more deeply.*

### RESPONSE:

The data on applied eradication regimen are included into the revised manuscript.

The treatment with triple therapy containing omeprazole, amoxicillin and clarithromycin was administered to 33 (58%) patients; with triple therapy containing omeprazole, amoxicillin and metronidazole to 12 (21%) patients; with triple therapy containing omeprazole, clarithromycin and metronidazole to 12 (21%) patients.

I would like to stress, that the eradication after one-year follow-up was confirmed by two negative tests: histology and rapid urease test. So we consider, that these patients were true HP-negative. The reinfection rates were not different regardless the eradication regimen was used. These data will also be included in the revised manuscript.

### *Comment*

*The authors assumed that a high percentage of re-infection in the study is associated with socioeconomic status in Lithuania. However, there are many other factors that affect the reinfection as though the rate of resistance to antibiotics or recrudescence of infection. Also, recent reports suggest that other niches like oral cavity can affect the rate of reinfection. Moreover how authors may conclude that “ the reinfection rate of H. pylori in Lithuania is relatively high, suggesting that the prevalence of H. pylori remains high” and the most important cause of that is socioeconomic status when they did not examine the socioeconomic status of the patients. There are some studies published recently showing that in some populations the reinfection rate of H. pylori can be high even when the prevalence of H. pylori infection is low. The authors did not test the prevalence of H. pylori infection and did not show current data of the prevalence H. pylori infection in Lithuania. Final assumptions must be regarded cautiously (...it should be mentioned specifically in “this cohort “ of patients...), because the examined group was too small and results can not be applied to whole population in Lithuania.*

### RESPONSE:

We agree, that there are some other factors associated with the reinfection of HP. Nevertheless in our cohort of patients, the recrudescence is excluded as all patients were HP-negative by strict testing one year after the eradication regimen. At present, the main factors related with the prevalence and reinfection of HP are the poor socioeconomic conditions. That's correct: we did not investigate full socioeconomic status of our patients, but they were consecutive peptic ulcer patients, representing the general population of peptic ulcer patients.

Regarding the prevalence of HP in Lithuania: we do not have wide spectrum epidemiological studies, but the studies in some separate groups of patients are performed and we will cite these studies in the revised paper. The prevalence of HP is 69% in dyspeptic patients (among females - 65%, among males - 79%), older than 55 years of age<sup>[1]</sup>. The prevalence of HP is 30% in medical students<sup>[2]</sup>. The prevalence of HP is 69% in routine GP patients aged between 40 to 60 years old<sup>[3]</sup>. So we do not have any doubts that the prevalence of HP is quite high in Lithuania. But we accept the note, and we will regard our final assumption cautiously. Therefore, we change the statement to: *"the reinfection rate of HP in the cohort of peptic ulcer patients in Lithuania is relatively high, and this may be related to the relatively high prevalence of HP infection"*.

References:

1. **Jonaitis L**, Kiudelis G, Kupcinskas L, Kupcinskas J. Prevalence of Helicobacter pylori among outpatient middle-aged patients in Lithuania and its relation to dyspeptic symptoms. *Helicobacter* 2013; **18**(1):104.
2. **Jonaitis L**, Kiudelis G, Kupcinskas L. Prevalence of Helicobacter pylori among medical students in Lithuania decreased during last 17 years. *Helicobacter* 2012; **17**(1):88.
3. **Jonaitis L**, Ivanauskas A, Janciauskas D, Funka K, Sudraba A, Tolmanis I, Krams A, Stirna D, Vanags A, Kupcinskas L, Leja M, Lin JT. Precancerous gastric conditions in high Helicobacter pylori prevalence areas: comparison between Eastern European (Lithuanian, Latvian) and Asian (Taiwanese) patients. *Medicina* 2007; **43**(8):623-9. [PMID: 17895638]

*Comment*

*References: not updated, more than 70 % of the references are older than 5 years. It would be much better to insert more recent references In whole text there are many stylistic and linguistic errors. English corrector is urgently needed. Overall, the manuscript requires some formal revision, The sections, such as abstract, introduction and discussion should be clearly improved.*

RESPONSE:

The references are revised and updated as much as possible.

The additional stylistic and linguistic revision is applied.

The sections "abstract", "introduction" and "discussion" are revised.

## RESPONSE TO REVIEWER 2

### *Comment*

*Page 2, Abstract, line 3: HP should be given in full the first time.*

### RESPONSE:

Corrected.

### *Comment*

*Page 2, lines 17-18: I do not agree that it should be stated: "If most optimistic analysis is applied (considering that all non-responders are HP-negative),..." This statement should be removed from the abstract and may be mentioned briefly in the Discussion section.*

### RESPONSE:

This statement is removed from the abstract and briefly discussed in the appropriate section.

### *Comment*

*Page 4, Core tip, lines 7-8 : The authors state : ? According to our study, HP reinfection rate in Lithuania is relatively high (the annual rate being 3.36%), suggesting that the prevalence of HP remains high. "However, they speculate in the "optimistic case" that the annual rate of the reinfection would be 1.63%, and this percentage is similar to that in the developing countries (1.68%) as the authors state on page 5, line 13.*

### RESPONSE:

We accept this comment and agree that the speculations on "optimistic scenario" are probably too "optimistic" and not proven. We agree that all non-responders to the invitation could not be free of reinfection. Therefore we stress that this "optimistic case" is hardly possible. Anyway, we still cautiously and briefly discuss these theoretical numbers.

### *Comment*

*Page 6, Material and Methods: The patients should be described better according to their age, possible comorbidity and previous treatment.*

RESPONSE:

The patients are better described in the chapters "*Materials and Methods*" and "*Results*": the applied eradication regimens are added; it is stated if they were duodenal or gastric ulcer patients. We recognize that we did not include the data on concomitant comorbidities and treatments.

*Comment*

*Page 6, lines 17-19: How many patients were tested by RUT and histology, how many by 14C UBT and how many by serology?*

RESPONSE:

We added this information to the section "*Materials and Methods*": 43 patients were tested by RUT and histology. 14 patients (those who refused endoscopy) were tested by UBT and by additional serology.

*Comment*

*Page 6, lines 11-19: The methods (14C UBT, histology and serology) should be described.*

RESPONSE:

As the aim of the study was not to evaluate the methods of diagnosis of HP, we skipped the description of methods. Reflecting on Your comments, we added short description and links about the applied products and methods to the section "*Materials and Methods*".

*Comment*

*What method (rapid or quantitative) was used for the serology? The serology is not the optimal method (accuracy, most often <85%) to detect H. pylori eradication. For some tests, the cut-off should be validated locally and rapid serologic tests are unsuitable to control the eradication.*

RESPONSE:

We totally agree that mere serology is not the optimal method, therefore it was used not as a single test but additionally to 14C-UBT. Also, we used rapid (qualitative) serology test, which is now mentioned in the revised version of the manuscript.

*Comment*

*Page 8, Discussion, lines 16-19: see Notes #2 and 3*

RESPONSE:

Considered and updated in the revised version of the manuscript.

*Comment*

*Page 8, Discussion, lines 20-22: “This may indicate that in Lithuania the decrease of the prevalence of HP infection is not as fast as it was supposed” Are not there any studies about the current prevalence of the infection in Lithuania? If there are no such data, the past and present incidence of the gastric cancer could give some useful information about.*

RESPONSE:

Regarding the prevalence of HP in Lithuania: we do not have wide spectrum epidemiological studies, but the studies in some separate groups of patients are performed and we will cite these studies in the revised paper. The prevalence of HP is 69% in dyspeptic patients (among females - 65%, among males - 79%), older than 55 years of age<sup>[1]</sup>. The prevalence of HP is 30% in medical students<sup>[2]</sup>. The prevalence of HP is 69% in routine GP patients aged between 40 to 60 years old<sup>[3]</sup> (references mentioned above). The incidence of gastric cancer is established as we have cancer registry in Lithuania: it is 20,4%, according EASR (<http://www.nvi.lt/index.php?-1413089819>). So we do not have any doubts that the prevalence of HP is quite high in Lithuania.

*Comment*

*Table 1: The statement “The efficacy of eradication treatment assessed as “good” or “excellent”” needs clarification. 11. Table 1: Satisfied with general status of “digestion” needs clarification.*

RESPONSE:

There are data of the questionnaires which were completed by patients before the diagnostic procedures. But to avoid lengthy manuscript we removed these data from the revised manuscript as well as the data about the frequency of antisecretory medications used. These data do not actually add anything important to the manuscript.