

Prospective Study

High rate of *Helicobacter pylori* reinfection in Lithuanian peptic ulcer patients

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Author contributions: Jonaitis L, Kiudelis G and Kupcinskis L designed and planned the study, recruited the patients, collected all the data, and performed all the investigations; Jonaitis L performed statistical analysis; Jonaitis L, Slepavicius P prepared the manuscript; all authors were involved in drafting and revising the manuscript.

Institutional review board statement: The study was reviewed and approved by the Kaunas Regional Biomedical Research Ethics Committee (Protocol No. 8/2011).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Laimas Jonaitis, Gediminas Kiudelis, Paulius Slepavicius, Limas Kupcinskis declare that there are no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at laimasj@takas.lt. Participants gave informed consent for data sharing. No additional data are available.

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Received: May 27, 2015

Peer-review started: May 29, 2015

First decision: June 19, 2015

Revised: August 19, 2015

Accepted: November 30, 2015

Article in press: December 3, 2015

Published online: February 15, 2016

Abstract

AIM: To evaluate the frequency of *Helicobacter pylori* (*H. pylori*) reinfection in peptic ulcer patients during 9 years after *H. pylori* eradication.

METHODS: We invited 117 peptic ulcer patients in whom eradication of *H. pylori* was confirmed 1 year after eradication treatment both by histology and by rapid urease test. In total, 57 patients were available for the study procedures: 34 (59.6%) male, 23 (40.4%) female; mean age 52.3 ± 13.0 years. There were 45 (78.9%) patients with duodenal ulcer and 12 (21.1%) with gastric ulcer. *H. pylori* was diagnosed by a rapid urease test and histology if endoscopy was performed. If endoscopy was refused, *H. pylori* was diagnosed by the C14-urea breath test and serology. *H. pylori* was established if at least one of the tests was positive.

RESULTS: The mean follow-up was 8.9 ± 1.0 years (range, 6-12). *H. pylori* was established in 15 patients. In 2 *H. pylori*-negative patients, *H. pylori* was established during the follow-up period and eradicated. Therefore, we consider that reinfection occurred in 17 patients. In the *per protocol* analysis, reinfection was established in 17 of 57 (29.8%; 95%CI: 19.2-42.2) patients during the follow-up period. The annual rate of infection was 3.36%. If all non-responders were considered *H. pylori*-negative, reinfection would be 14.5% (17/117), the annual rate

being 1.63%. The mean age of patients with reinfection was 51.8 ± 14.0 years, and without reinfection was 52.5 ± 13.0 years, $P > 0.05$; the mean body mass index of patients with reinfection was 27.2 ± 4.1 kg/m², and without reinfection was 25.7 ± 4.2 kg/m², $P > 0.05$. There were no differences in the reinfection rates according to the location of the peptic ulcer, the eradication regimen used, and smoking status.

CONCLUSION: The reinfection rate of *H. pylori* is relatively high in Lithuania and probably related to the high prevalence of *H. pylori*, what may reflect differences in the socioeconomic status between Western and Eastern European countries.

Key words: *Helicobacter pylori*; Reinfection; Prevalence; Peptic ulcer; Eradication

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Core tip: The reinfection rate of *Helicobacter pylori* (*H. pylori*) varies according to geographical area. In regions with higher socioeconomic status and lower prevalence of *H. pylori* it is only 1.68% of cases. In developing areas, the reinfection rate could be much higher. Lithuania, as well as other Eastern and Central European countries, is in transition, and the prevalence of *H. pylori* is not as low as in Western regions, but not as high as in developing countries. According to our study, the *H. pylori* reinfection rate in Lithuania is relatively high (the annual rate being 3.36%), probably because of the high prevalence of *H. pylori*. This could indirectly reflect differences in the socioeconomic status between Western and Eastern European countries.

Jonaitis L, Kiudelis G, Slepavicius P, Kupcinskas L. High rate of *Helicobacter pylori* reinfection in Lithuanian peptic ulcer patients. *World J Gastrointest Pathophysiol* 2016; 7(1): 181-185 Available from: URL: <http://www.wjgnet.com/2150-5330/full/v7/i1/181.htm> DOI: <http://dx.doi.org/10.4291/wjgp.v7.i1.181>

INTRODUCTION

It is well established that *Helicobacter pylori* (*H. pylori*) infection is the main cause of chronic gastritis and peptic ulcer disease, and a definite risk factor for gastric cancer^[1-4]. Consensuses from different parts of the world strongly recommend eradication of *H. pylori* to cure peptic ulcer disease and MALT lymphoma, and to decrease the risk of gastric cancer^[5-7]. *H. pylori* eradication is recommended to alleviate the burden of functional dyspepsia and some other digestive and extragastric pathologies^[8-13]. Current treatment modalities allow eradication of the *H. pylori* bacterium in up to 90% of cases (less if there is clarithromycin resistance). Nevertheless, in some cases, recrudescence or reinfection of *H. pylori* may occur. Reinfection is

considered when *H. pylori* is found after confirmed *H. pylori* eradication. The confirmation of eradication must be performed not earlier than 6 mo after eradication treatment. It has been reported that in highly developed countries reinfection is rare and may account no more than 1.68% of cases^[14]. In contrast, in developing areas the reinfection rate could be much higher and has been reported to reach 9.63%^[14]. Central and Eastern European countries are areas of medium to high *H. pylori* prevalence. The reinfection rates could be expected to be in between the rates indicated above^[8-32]. *H. pylori*-related diseases are common in these countries and *H. pylori* eradication treatment is widely applied. There are little data from Eastern and Central Europe about the reinfection of *H. pylori*. In the Maastricht consensus, the recommendation to regularly investigate the regional epidemiological status of *H. pylori* has been proposed, indicating that the data for prevalence, eradication rates, antibacterial resistance, and reinfection rates are important^[13].

Therefore, we carried out a long-term follow-up study to evaluate the frequency of *H. pylori* reinfection in peptic ulcer patients in Lithuania after confirmation of *H. pylori* eradication.

MATERIALS AND METHODS

Patients

We included peptic ulcer patients from our previous 1-year follow-up studies^[15,20]; 117 patients, who were *H. pylori*-negative 1 year after eradication treatment (therefore, considered to have true eradication), were invited to participate in the study by mail or telephone. Fifty seven patients responded and were available for the study procedures. Written informed consent from all participants and approval of the Kaunas Regional Biomedical Research Ethics Committee was obtained. During the visits, demographic and clinical data were obtained. The flowchart of the study is presented in Figure 1. The previous 1-wk eradication regimens of these patients contained omeprazole, amoxicillin, and clarithromycin [applied to 33 (58%) patients]; omeprazole, amoxicillin and metronidazole [applied to 12 (21%) patients]; omeprazole, clarithromycin and metronidazole [applied to 12 (21%) patients].

Diagnosis of *H. pylori*

According to the protocol of previous studies^[15,20], the final *H. pylori* status was determined after 12 mo following eradication therapy by a rapid urease test (RUT) and histology. Patients were considered as *H. pylori*-negative if both tests were negative.

The mean follow-up period was 8.9 ± 1.0 years (range, 6-12) after the confirmation of the negative *H. pylori* status. At this time *H. pylori* was tested by RUT and histology if patients agreed to undergo endoscopy. If endoscopy was refused, *H. pylori* was tested by the ¹⁴C-urea breath test (UBT) "Heliprobe"^[18,24-26] and serology (the quantitative test "SureScreen Diagnostics

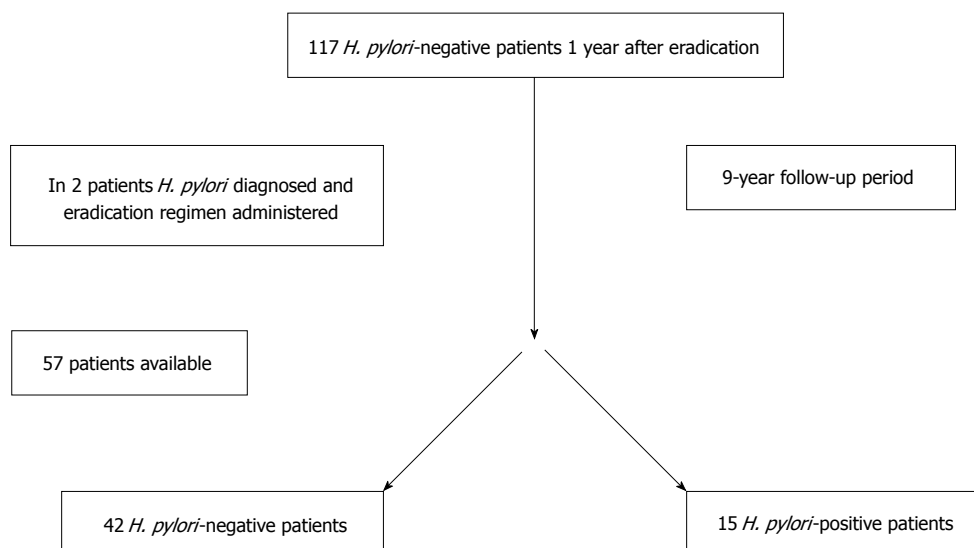


Figure 1 Flowchart of follow-up. *H. pylori*: *Helicobacter pylori*.

Table 1 Characteristics of patients with and without *Helicobacter pylori* reinfection *n* (%)

	Reinfection <i>n</i> = 17	No reinfection <i>n</i> = 40	<i>P</i> -value
Male	12 (70.6)	22 (55)	> 0.05
Smokers	7 (41.2)	19 (47.5)	> 0.05
Duodenal ulcer	13 (76.5)	32 (80)	> 0.05
Primary eradication regimen - 7 d triple therapy:			
Omeprazole, clarithromycin, amoxicillin	9 (52.9)	24 (60)	> 0.05
Omeprazole, metronidazole, amoxicillin	4 (33.3)	8 (20)	> 0.05
Omeprazole, clarithromycin, metronidazole	4 (33.3)	8 (20)	> 0.05

Ltd" which is CE Marked, Food and Drug Administration Approved^[17]). *H. pylori*-positivity was established, if at least one of the tests was positive.

Forty three patients were tested by RUT and histology; 14 patients (those who refused endoscopy) were tested by UBT and by additional serology.

Statistical analysis

The data were analyzed and compared using the χ^2 or Student *t* test. Values of *P* < 0.05 were considered significant.

RESULTS

The 57 patients consisted of 34 (59.6%) males and 23 (40.4%) females, with a mean age of 52.3 ± 13.0 years. There were 45 (78.9%) patients with a duodenal ulcer and 12 (21.1%) with a gastric ulcer.

Endoscopy was performed in 43 (75.4%) patients. *H. pylori* was established in 15 patients, and 42 patients were *H. pylori*-negative. In 2 *H. pylori*-negative patients *H. pylori* had been established by RUT during the follow-up period (both had peptic ulcer relapse), and successful eradication treatment had been administered. Therefore, we may count 17 patients with *H. pylori* reinfection during follow-up.

In the *per protocol* analysis, reinfection was established in 17 (29.8%; 95%CI: 19.2-42.2) of 57 patients, the annual rate being 3.36%. If we consider that all non-responders were *H. pylori*-negative (the most optimistic analysis), the reinfection rate would be 14.5% (17/117), the annual rate being 1.63%.

The mean age was 51.8 ± 14.0 years in patients with reinfection, and 52.5 ± 13.0 years in patients without reinfection (*P* > 0.05); the mean body mass index in the 2 groups was 27.2 ± 4.1 kg/m² and 25.7 ± 4.2 kg/m², respectively (*P* > 0.05). A comparison of characteristics of patients with and without reinfection is presented in Table 1.

DISCUSSION

The reinfection rate of *H. pylori* could be mostly dependent on the prevalence of *H. pylori* in the specific region. It could be considered as an indirect indicator of the socioeconomic status of the region. Yan *et al*^[14] analyzed the correlation between *H. pylori* recurrence rate and socioeconomic development [as represented by Human Development Index (HDI)], using data from 77 studies, which were considered reliable. Countries with very high HDI had a mean annual rate of 1.68%, which was significantly lower than that of high HDI countries at

6.05%, medium HDI countries at 7.04%, and low HDI countries at 9.63% (global annual rate being 2.82%)^[14]. Lithuania is placed in the very high HDI category.

The studies indicate that low socioeconomic status was one of the major risk factors for a high prevalence of *H. pylori* infection^[16,23]. Eastern and Central European countries are in a transitional area, where the prevalence of *H. pylori* is not as low as in Western regions, but not as high as in the developing countries^[27]. There are no large epidemiological studies on the prevalence of *H. pylori* in this region, but there are data on the prevalence of *H. pylori* in specific groups of patients. The prevalence of *H. pylori* in middle-aged outpatients was 69%^[21]. The prevalence of *H. pylori* in 22-year-old medical students established by serology was 30.4% and has decreased substantially during last 17 years^[22].

In our study, in the *per protocol* analysis, *H. pylori* reinfection was established in 29.8% (17/57) (95%CI: 19.2-42.2) of patients during our 9-year follow-up, the annual rate being 3.36%. We also calculated the reinfection rates on the assumption that all non-responders were *H. pylori*-negatives: In this case reinfection would be 14.5% (17/117), the annual rate being 1.63%. In reality, the reinfection rate is probably in between these numbers, and could be considered a relatively high *H. pylori* reinfection rate. This may indicate that in Lithuania the decrease in the prevalence of *H. pylori* infection^[21,22] is not as fast as was supposed, probably related to rather slow development of the socioeconomic status of the country, or the *H. pylori* prevalence is decreasing much slower than the speed of socioeconomic development. It is logical to believe that similar results could be found in neighboring countries.

The advantage of our study is that we established true reinfection, as all our patients were *H. pylori*-negative 1-year after the eradication regimen. We would like to stress that our study is the first to report on the reinfection rates of adult peptic ulcer patients from Central and Eastern Europe. In contrast to many South European countries, where the prevalence of antimicrobial drug resistance is significant, *H. pylori* susceptibility to the standard antibiotics in Lithuania remains high^[19]. Therefore, high reinfection rates could be the most important issue in the management of *H. pylori* infection in the country.

There are some limitations of the study. The low number of responses (57 out of 117 patients) to follow-up investigations allowed us to speculate with the most pessimistic and most optimistic numbers, not being able exactly to determine the rates of *H. pylori* reinfection. Besides, we did not have epidemiological data of our patients, thus we could not examine the reasons for reinfection. Our investigated demographic and clinical characteristics were not predictive of reinfection.

In conclusion, the reinfection rate of *H. pylori* in a cohort of peptic ulcer patients in Lithuania was relatively high, and this may be related to the relatively high prevalence of *H. pylori* infection in the country, suggesting that socioeconomic differences between Western and Eastern

European countries are probably still marked.

COMMENTS

Background

It is strongly recommended to eradicate *Helicobacter pylori* (*H. pylori*) in order to cure peptic ulcer disease and MALT lymphoma, to decrease risk of gastric cancer, and to alleviate the burden of functional dyspepsia and some other digestive and extragastric pathologies. At present, the eradication of *H. pylori* could be achieved in up to 90% of cases. Nevertheless, recrudescence or reinfection may occur over time.

Research frontiers

In the Maastricht consensus, the recommendation to regularly investigate the regional epidemiological status of *H. pylori* has been proposed, indicating that data of prevalence, eradication rates, antibacterial resistance, and reinfection rates are important. The reinfection of *H. pylori* has been reported to be not infrequent, especially in areas of high *H. pylori* prevalence. More studies are necessary to establish the rate of reinfection in different parts of the world. Factors which may contribute to the occurrence of *H. pylori* reinfection have to be elucidated.

Innovations and breakthroughs

There are few available data from Eastern and Central Europe on reinfection rates of *H. pylori*. This article presents a long-term follow-up study, which evaluates the frequency of *H. pylori* reinfection in Lithuanian peptic ulcer patients after confirmation of *H. pylori* eradication. These are probably the first data from Eastern-Central Europe regarding reinfection of *H. pylori* in peptic ulcer patients.

Applications

The results of the study add important scientific information on *H. pylori* reinfection rates in Central and Eastern Europe. This is important knowledge reflecting the current Maastricht consensus. It also encourages us to rethink the present epidemiological situation regarding the prevalence of *H. pylori* in Lithuania and the whole region. The reinfection rate of *H. pylori* in the cohort of peptic ulcer patients in Lithuania may be related to the relatively high prevalence of *H. pylori* infection in this region, suggesting that socioeconomic differences between Western and Eastern European countries are probably still marked.

Terminology

Reinfection of *H. pylori* is considered when a new strain of *H. pylori* is found after confirmed eradication. The confirmation of eradication must be performed not earlier than 6 mo after eradication treatment. Recrudescence of *H. pylori* is considered as a recurrence of the previous infection by the same *H. pylori* strain.

Peer-review

The subject of the present manuscript is interesting and important, as there are not many studies on the annual rate of *H. pylori* reinfection in this geographic area. However, some additions and clarifications should be performed to improve the manuscript.

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P- Reviewer: Boyanova L, Biernat MM

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