

# Swiss Tertiary Care Center Experience Challenges the Age-Cohort Effect in Helicobacter Pylori Infection

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## Abstract

**Background.** The epidemiology of Helicobacter pylori infection reflects the age-characteristics, developmental status and access to health care of the population in a given area. **Aim:** To assess the influence of demographic variables on the prevalence of H. pylori status among patients evaluated in a Swiss university medical center. **Methods.** Demographic data (i.e. age, gender, place of birth), indication for H. pylori testing, history of prior H. pylori eradication therapy, medical field and clinical setting of the referring physician were reviewed from patient's charts. H. pylori status was assessed by the <sup>13</sup>C Urea breath test. **Results.** Patients born in Switzerland had lower rates of positive <sup>13</sup>C Urea breath test results compared to those born outside of the country (12/101 [11.9%] vs. 67/252 [26.6%]; p=0.003). While there were no differences between males and females (p>0.05), patients 50 years and below were more likely to have a positive test result compared to those above the age of 50 years (59/106 [28.6%] vs. 20/147 [13.6%]; p<0.01). There were no major differences in the rate of positive <sup>13</sup>C Urea breath tests in patients with previous history of H. pylori eradication and those without. Patients with dyspeptic symptoms and those without had similar rates of positive tests (11/61 [18.0%] vs. 68/292 [23.3%]; p=ns). **Conclusion.** Epidemiologic characteristics of H. pylori infection in Western countries are influenced by changing demographics. Further studies are warranted to investigate reasons for the changing trends in the prevalence of H. pylori infection.

## Key words

Helicobacter pylori – <sup>13</sup>C urea breath test – dyspepsia.

## Introduction

Helicobacter pylori (H. pylori) is one of the most common human pathogens. Worldwide more than half of the population is colonized with this gram-negative spiral bacterium [1]. In developing countries including Eastern Europe the prevalence is as high as 80-90%. Unless eradicated, colonization usually persists lifelong increasing the risk of developing gastric cancer. In the Western world gastric colonization with H. pylori is decreasing presumably as a result of better hygienic standards and active eradication therapy [2, 3].

Infection with H. pylori frequently leads to histologic gastritis, but only few of the infected individuals develop clinical symptoms of this colonization. Therefore, contradictory evidence on the association between epigastric symptoms in the absence of structural lesions (i.e. non-ulcer dyspepsia) and H. pylori comes to no surprise [4]. Nevertheless, H. pylori infection plays a role in the pathogenesis of chronic active gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer [2, 5]. In addition, several extraintestinal conditions have been associated with H. pylori including coronary heart disease, dermatological, rheumatological, hematological and neurological disorders [6-8]. Pathogenic mechanisms of extra-gastrointestinal manifestations include accelerating atherosclerosis, chronic low-grade activation of the coagulation cascade and antigenic mimicry between H. pylori and host epitopes causing autoimmune disorders [9]. Although the linkage between H. pylori and extra-gastrointestinal manifestations is debated in clinical practice, H. pylori testing is requested for many of the above mentioned indications.

There are various factors influencing the prevalence of H. pylori infection. While there are no gender differences in the prevalence of H. pylori infection, studies indicate an increase in the prevalence of GERD with increasing age, non-Caucasian race and low socio-economic status [10, 11]. With regards to the influence of age, Graham et al reported an increase with age at 1%/year in the general population. On the other hand, living in developed countries with improved

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hygienic conditions has been shown to decrease the incidence of *H. pylori* infection [12]. As people living in improved hygienic condition are advancing in age, it becomes unclear how the interaction between these factors impact on the prevalence of *H. pylori* infection.

Several diagnostic methods are available for detecting *H. pylori* infection. Histological examination with culture for *H. pylori* is considered the gold standard for diagnosis of gastric colonization. While this approach is not always practicable in clinical settings, other tests have been developed. Rapid urease test of gastric biopsies has high sensitivity and specificity but implies an endoscopic examination. Non-invasive tests for the detection of *H. pylori* infection include urea breath test, stool antigen assays and serology [13, 14]. Among these, the urea breath test is the most frequently used test in clinical setting and, with sensitivities and specificities >95% compared to *H. pylori* culture it is considered the gold-standard of the non invasive tests [15]. At our institution  $^{13}\text{C}$  breath tests are performed in the gastrointestinal function laboratory and according to an open-access policy the indication for *H. pylori* testing is set by the referring physician.

Given the limited information on the prevalence of *H. pylori* infection in certain subgroups of patients we performed an exploratory study on the influence of age, gender, place of birth and indication for testing on the results of *H. pylori* testing at the tertiary care center in Zurich, Switzerland.

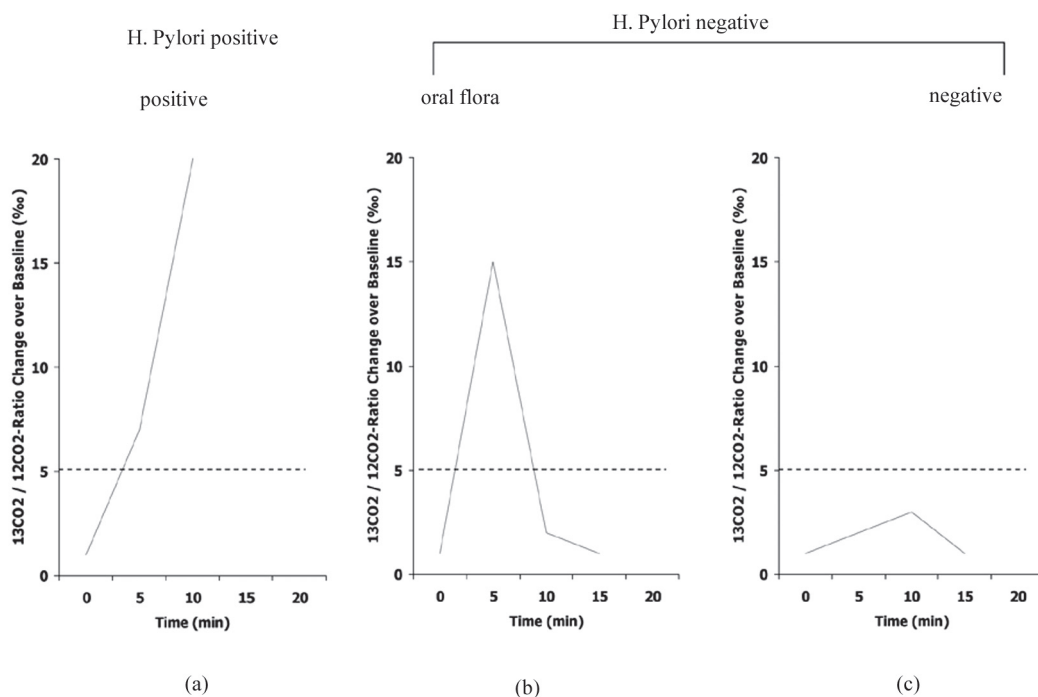
## Materials and methods

### Patient population

In the current study we included data from patients referred for *H. pylori* breath testing to our laboratory between January 2002 and December 2006. Permission to review medical records was obtained from the Ethics Committee of the Canton of Zurich. We excluded patients unable to complete the *H. pylori* breath test, studies aborted due to technical failures and datasets with insufficient clinical information on the indication for testing. We reviewed patient charts for demographic data (i.e. age, gender, place of birth), indication for *H. pylori* testing, history of prior *H. pylori* eradication, medical field (i.e. internal medicine, gastroenterology, dermatology, etc.) and clinical setting (i.e. private practice, hospital setting) of the referring physician in order to determine predictors for a positive *H. pylori* breath test. For the purpose of this study patients born in Switzerland were labeled “Swiss” while patients born outside of Switzerland were labeled “non-Swiss”.

### Urea-breath test

Urea breath tests for *H. pylori* were performed using the BreathID<sup>®</sup> breath monitoring system with the Oridion Idkit-hp<sup>™</sup> test kit (BreathID Inc. Jerusalem, Israel) and a 100mg  $^{13}\text{C}$  urea tablet (Medical Instruments Corporation, Solothurn, Switzerland). The patients were requested to come fasted for at least 4 hours prior to the test. After



**Fig 1.** *H. pylori* breath test results. The test was considered positive (a) if the  $^{13}\text{CO}_2 / ^{12}\text{CO}_2$  ratio change over baseline increased and remained above 5%. A short increase above 5% with subsequent values below this threshold (b) were indicative of the presence of urease positive oral flora. The test was considered negative (c) if the  $^{13}\text{CO}_2 / ^{12}\text{CO}_2$  ratio change over baseline remained below 5%.

dissolving the tablet into solution patients drank the  $^{13}\text{C}$  marked urea and were connected to breath monitoring system. The BreathID<sup>®</sup> system contains an analyzer that measures the ratio of  $^{13}\text{CO}_2/^{12}\text{CO}_2$  in the exhaled air by molecular correlation spectrometry. The system continuously samples the subject's breath via a nasal cannula connected to the analyzer.  $^{13}\text{CO}_2/^{12}\text{CO}_2$  ratios are expressed as delta over baseline and results are recorded graphically on a monitor online and available in real time. The ratio between  $^{13}\text{CO}_2$  and  $^{12}\text{CO}_2$  was monitored over 15 minutes. A persistent rise of the ratio above 5‰ indicated a positive test, a transitional rise with a final value below 5‰ indicated urease positive oral flora (i.e. negative test) while no increase above the mentioned threshold was considered a negative test (Fig. 1). Patients were not required to wash their mouths before undergoing urea breath testing.

### Statistical analysis

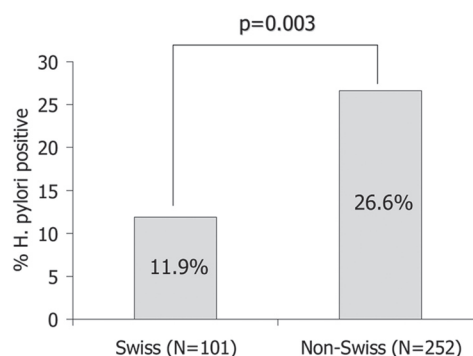
For this is a cross-sectional study evaluating the prevalence of H. pylori infection in the referred population, descriptive statistics were used to report prevalence data. Differences between proportions were compared using Chi-square or Fisher-exact tests. Continuous variables were compared using Student t-test or Mann-Whitney U-test depending on the distribution of data. For statistical significance alpha was set at 0.05.

## Results

Between January 2002 and December 2006, in the Gastroenterology Division of the University Hospital of Zurich 398  $^{13}\text{C}$  urea breath tests were performed [93 positive, 305 negative (including 56 patients with urease positive oral flora) test results] in 353 patients (198 women, mean age 47 years, range 18-85 years). Out of the 353 patients, 314 patients underwent one, 33 patients had two and 6 patients had three urea breath tests. The initial breath test was positive in 79/353 (22.3%) patients. Similar proportions of females and males tested positive [42/198 (21.2%) vs. 37/155 (23.9%);  $p=ns$ ]. Most referrals for  $^{13}\text{C}$  urea breath test came from general internal medicine (61.3% patients), gastroenterology (30.1% patients) and dermatology (6.4% patients). The proportions of patients with a positive H. pylori breath test were similar ( $p=ns$ ) in the groups of patients referred by general internists (45/212; 21.2%), gastroenterologists (28/104; 26.9%) and dermatologists (4/22; 18.2%).

### Influence of age and country of origin on the result of the $^{13}\text{C}$ urea breath test

A larger proportion of patients born outside Switzerland ("non-Swiss") tested positive ( $p<0.01$ ) compared to "Swiss" patients (Fig. 2). Also the proportion of H. pylori positive patients was higher ( $p<0.01$ ) in patients younger than 50 years compared to those 50 year and above (Fig. 3a). When separating patients into Swiss (Fig. 3b) and non-Swiss (Fig. 3c) patients we found a higher prevalence of positive tests in patients younger than 50 years (statistically significant for the non-Swiss sub-population but, due to the low numbers,



**Fig 2.** Prevalence of H. pylori positive patients originally from Switzerland (Swiss) and outside the country (non-Swiss).

not significant for the Swiss sub-population). The highest rate of H. pylori positive results was noted in "non-Swiss" individuals younger than 50 years (52/165 [31.5%]), the lowest rate in "Swiss" patients older than 50 years (5/60 [8.3%]).

### Indication for H. pylori testing

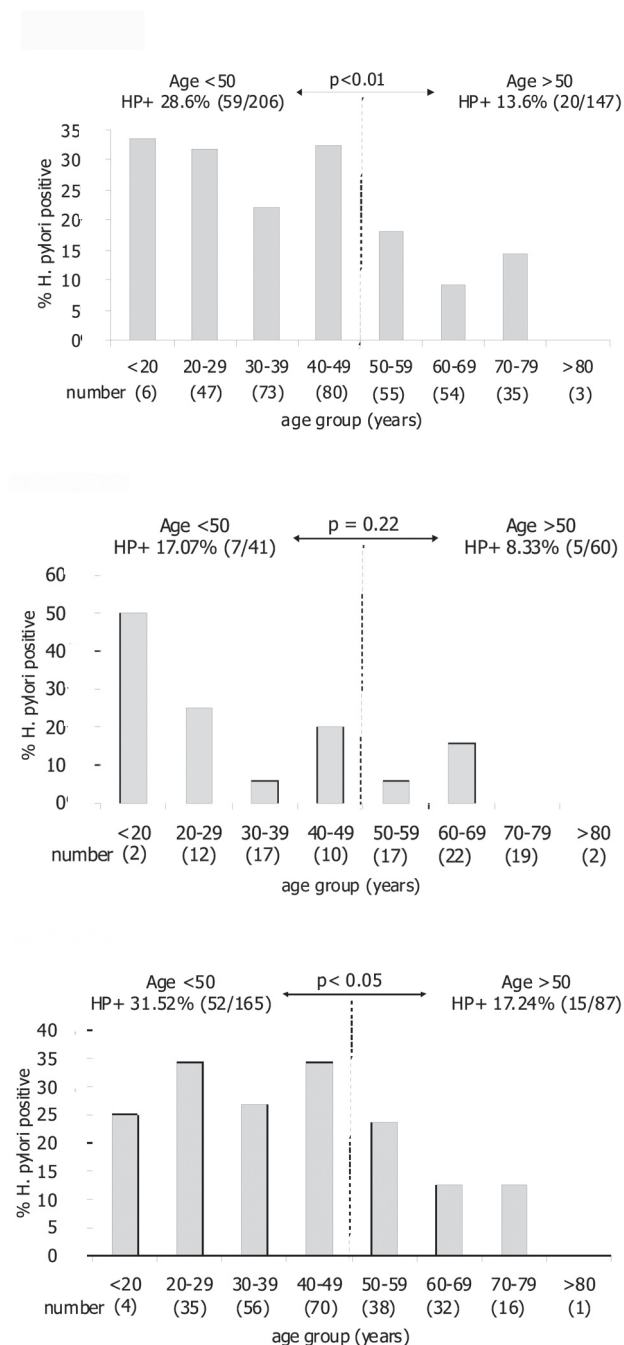
With regards to the indication for H. pylori testing, we focused the analysis on three groups of patients: patients with previous history of H. pylori eradication (i.e. verification of successful eradication), patients with dyspeptic symptoms and patients referred by dermatologists for evaluation of H. pylori status as a cause of urticaria.

Among patients with history of eradication therapy 22.0% (46/207) tested positive. In the group of patients without history of H. pylori eradication 33/146 (22.6%) patients also tested positive ( $p=ns$ ). The  $^{13}\text{C}$  urea breath test was positive in 18% (11/61) of patients referred for dyspeptic symptoms and 23.3% (68/292) of patients without history of dyspeptic symptoms ( $p=ns$ ).

Out of the 19 patients referred for  $^{13}\text{C}$  urea breath test as part of the work-up for urticaria three (15.8%) tested positive, while 76/334 (22.8%) patients without urticaria also tested positive ( $p=ns$ ).

## Discussion

In the present study we found a decrease in the prevalence of positive H. pylori breath tests with age, higher rates of positive  $^{13}\text{C}$  urea breath tests in non-Swiss patients compared to those born in Switzerland and no differences in H. pylori positivity with respect to gender, history of prior H. pylori eradication and indication for testing. While the results on the prevalence of H. pylori status related to the place of birth and gender are consistent with previous reports, the decreasing prevalence with age contradicts previous reports indicating an increased prevalence of H. pylori infection with age [2, 12, 16]. The decreasing prevalence of positive H. pylori breath test results in our population could be due to a referral bias. Patients under the age of 50 years migrating into Switzerland have a prevalence of H. pylori colonization similar to their country of origin whereas



**Figs 3a-c.** Variation in the prevalence of positive H. pylori test results with age in all patients (3a), Swiss patients (3b) and non-Swiss patients (3c). Patients age 50 and below were more likely to have a positive test in all three patient groups compared to patients above the age of 50 years. Numbers of patients in each age group are indicated in parentheses.

patients over the age of 50 years from Switzerland were more likely to have received antibiotics. In addition, given current clinical practice for patients with upper gastrointestinal (GI) symptoms, patients over the age of 50 were more likely to have had an upper GI endoscopy including H. pylori biopsy and would have undergone eradication by the time of the breath test. Given the retrospective nature of our study we were not able to accurately assess this but current results

provide the basis for future studies specifically designed to investigate the relationship between age and H. pylori status in industrialized countries.

Evaluating the prevalence and risk factors of H. pylori infection in Swiss adolescents, Heuberger et al [17] found one of the lowest H. pylori infection rates in Europe (9.7%). They also observed a significant disparity between the rate of H. pylori infection in the native population (13/176 [7.3%]) and the subjects from foreign countries (6/20 [30%]). Another Swiss study [18] evaluated the prevalence of H. pylori infection in 432 randomly selected asymptomatic children between the age of 5 and 7 years living in the eastern part of Switzerland. In this population the total prevalence of H. pylori infection was low (6.5%) with a significantly higher rate in children, whose parents had immigrated to Switzerland (19.2% vs. 3.9%). A study by Porsch-Ozcurumez M et al [19] presented similar results in 675 Germans, 260 Turks born and raised in Germany and 148 Turks living in Turkey. The proportion of H. pylori positive individuals (13.1% in Germans, 30.4% in Turks living in Germany and 44.5% in Turks living in Turkey) who underscored that of the country of origin is an important determinant of the H. pylori status. The results of our study with a significantly higher prevalence of positive H. pylori breath test results in the group of patients born outside the country compared to those born in Switzerland are in line with these findings. The demographic details available for the present retrospective analysis did not allow us to further sub-categorize the country of origin of the non-Swiss patients. As suggested by other recent studies, the most likely explanation for differences in H. pylori prevalence between industrialized and developing countries are better hygienic standards and active eradication therapy in the Western hemisphere [2, 3].

Similar prevalence of positive H. pylori breath tests in males and females indicate that H. pylori colonisation is not gender specific. Evaluating 485 asymptomatic individuals in the Houston, Texas area, Graham et al [13] found that H. pylori colonisation was present in 52% of these individuals. While age, race and socioeconomic status influenced the prevalence of H. pylori positivity, there were no gender differences in the studied population. Similar results on gender similarity were reported from regions with an even higher prevalence of H. pylori infection. A recent study [14] in 1567 patients from Turkey with various GI complaints reported similarly high positive  $^{14}\text{C}$  urea breath test results in males (67.7%) and females (68.2%) ( $p=0.865$ ). A population based epidemiological study from Sweden [20] comparing the prevalence of H. pylori infection in 150 adults with and without abdominal symptoms also reported no gender differences among the 55 H. pylori positive individuals. In summary, the results of our study are consistent with previous reports indicating that HP-positivity is not gender related.

Dyspeptic symptoms are common with a prevalence of 20-40% of the adult population in the Western hemisphere [2]. The role of H. pylori colonization in the pathogenesis of dyspepsia and data to support H. pylori testing in dyspeptic patients are controversial [21, 22]. In the present study we

found similar proportion of positive  $^{13}\text{C}$  urea breath test results in patients with and without history of dyspeptic symptoms. Evaluating 148 randomly selected residents of Olmsted County, Minnesota aged 20-50 years (36 with dyspepsia, 35 with irritable bowel syndrome without dyspepsia and 77 asymptomatic individuals), Locke et al [23] found a statistically borderline association ( $p=0.08$ ) between dyspepsia and CagA antibody positivity. A Swiss study by Verdú et al [24] comparing the prevalence of chronic dyspepsia in individuals from developing countries and individuals from industrialized countries found no difference between the two groups. In contrast, Nelson et al evaluating 435 healthy individuals (blood donors) and 102 patients in a general medical clinic found that patients were more likely to have dyspeptic symptoms and more likely to test seropositive for *H. pylori* compared to healthy individuals [25]. A logistic regression analysis of these data found CagA seropositivity to be an independent variable associated with dyspepsia, allowing the authors to interpret these results as supportive of the association between *H. pylori* infection and dyspepsia.

## Conclusion

The present data challenge the dogma on the increasing prevalence of *H. pylori* colonization with age. This relationship between age and *H. pylori* status in patients from industrialized countries referred to tertiary care centers warrants further investigations.

## Conflicts of interests

None to declare.

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