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Testing of *Helicobacter pylori* by Endoscopic Biopsy: The Clinical Dilemma of Suppressive Conditions

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Keywords

Helicobacter pylori · *Helicobacter pylori* suppressive conditions · Esophagogastroduodenoscopy · Helicobacter urease test · Proton-pump inhibitors · Upper gastrointestinal bleeding · *Helicobacter pylori* eradication

Abstract

Background and Aims: Testing for *Helicobacter pylori* is frequently conducted during esophagogastroduodenoscopy (EGD). Suppressive conditions such as the intake of proton-pump inhibitors (PPIs), preceded antibiotic treatment or recent upper gastrointestinal bleeding impair *H. pylori* test quality. The aim of our study was to evaluate the frequency and pattern of *H. pylori* suppressive conditions in a large patient collective undergoing elective EGD in a German university hospital. ***Methods:*** The trial was performed as a single-center study. Only elective EGD from inpatients and outpatients were included. Prior to endoscopy, *H. pylori* suppressive conditions were collected using a standardized questionnaire. If *H. pylori* testing was indicated according to the guidelines, always both histology and helicobacter urease test were performed in analogy to the Sydney classification. ***Results:*** One thousand six hundred and thirty-one patients were included (median 61 years, 36.0% outpatients, 64.0% inpatients). Overall, 76.5% of patients were under *H. pylori* suppressive conditions. The main suppressive condition was the intake of PPIs (70.7%). In 819 (50.2%) of all included cases, *H. pylori* testing was performed. The following were the results: 17.3% (142) had a positive *H. pylori* testing and 82.7% (677) were negative. Of those with negative result, 70.0% were tested under suppressive conditions. ***Conclusion:*** Guidelines recommend *H. pylori* testing under non-suppressive conditions. However, this does not always meet the clinical practice. Our data show that de facto, many patients undergoing elective EGD are tested for *H. pylori* under suppressive conditions coming along with a higher risk of potentially false negative results. Particularly, concerning this issue, further research is needed to improve and clarify everyday clinical practice.

Introduction

The prevalence of infections with *Helicobacter pylori* has decreased over the last decades [1]. However, international population-based studies show that about 50% of the adult world population aged over 40 years remain infected [2, 3]. Prevalence shows a wide variety between

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industrial and developing countries but also in different regions as well as within a single population [4].

In Germany, the prevalence of *H. pylori* infection is low in children (3%) and ranges from 20 to 40% in adults [1, 5–7]. It is significantly higher for immigrants (36–86%) [1, 8].

The infection with *H. pylori* induces a chronic active gastritis that can possibly lead to gastroduodenal ulcer disease, dyspeptic syndromes, gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma as well as extra-intestinal diseases [5, 9]. To date, there are no sufficient prevention strategies. Particularly, an effective vaccine is not yet available [1].

Several methods for the detection of *H. pylori* have been adequately validated [10]. Noninvasive assays include urea breath test, stool antigen test with monoclonal antibodies as well as serologic immunoglobulin G antibodies. Invasive methods include culture, histology, helicobacter urease test (HUT), and polymerase chain reaction from gastric biopsies [1, 11]. The various methods have different sensitivities and specificities, and none is perfect in accuracy [12, 13]. Histology usually reaches a sensitivity and specificity of both around 94% [10]. The HUT shows sensitivity from 85 to 100% and specificity up to 100% [10, 14]. The indication for testing and the choice of the diagnostic test should be determined according to recommendations outlined in various guidelines [1, 15, 16]. In general, 2 positive test results should be available for a reliable diagnosis of *H. pylori* infection [1].

Importantly, endoscopic biopsy is a major tool to diagnose *H. pylori* in everyday clinical practice. In principle, the decision whether to test or not to test for *H. pylori* should be made during every esophagogastroduodenoscopy (EGD). If testing is indicated, it should be undertaken with biopsies for at least 2 different tests [1]. This approach is in accordance with the Sidney classification, since primarily histology and a rapid urease test are recommended [17, 18].

An existing clinical challenge is confounding factors that lead to a decreasing sensitivity and consequently to a higher rate of potentially false negative *H. pylori* test results. Apart from serology, sensitivity of all tests is derogated by conditions leading to a reduced *H. pylori* colonization density [19]. In particular, treatment with a proton-pump inhibitor (PPI), recent upper gastrointestinal bleeding and preceded *H. pylori* affecting antibiotic treatment may impair the diagnostic power [1, 20].

Guidelines recommend a minimal interval of 2 weeks after completing a PPI therapy and 4 weeks after previous antibiotic therapy [1]. Despite the clear statements, this still remains an unsolved clinical problem, since practically *H. pylori* testing is often conducted under suppressive conditions [21]. For instance, many patients with dyspepsia are primarily treated empirically with a PPI before an EGD with *H. pylori* testing is conducted [1].

Here, we performed a study with a high number of cases in order to investigate this relevant and common clinical dilemma. The purpose of this trial was to evaluate the overall rate and pattern of *H. pylori* suppressive conditions in a large patient cohort from a German university hospital and referral center.

Materials and Methods

The study was retrospectively conducted within a single-center gastroenterological patient collective of the University Hospital Marburg, a tertiary German referral center. The clinical standard concerning *H. pylori* testing at our center followed the indications according to the German S3-guideline [18]. Our study also conformed to the Helsinki Declaration and local legislation.

We included all patients who underwent elective EGD. In all patients undergoing EGD, the indication for *H. pylori* testing was assessed. If testing was indicated, both histology and HUT (AstraZeneca, London, UK) were conducted. Urease tests were interpreted 24 h after upper endoscopy. The study included inpatients as well as outpatients. Data were collected over a period of 6 months. EGDs were exclusively performed by experienced endoscopists. Biopsies were obtained from both the corpus (greater and lesser curvature) and antrum (greater and lesser curvature) as guidelines recommend in analogy to the Sydney classification [1, 17].

Data Collection

The medical history of every patient was routinely recorded prior to EGD by standardized questionnaire with regard to the evaluation of *H. pylori* suppressive conditions. Overall, we obtained the following parameters: age, date of EGD, previous intake of PPI (within the last 2 weeks), previous antibiotic treatment (within the last 4 weeks), signs of current upper gastrointestinal bleeding (hematemesis, melena within the last 2 weeks). If *H. pylori* testing was performed, the results of histology and HUT were recorded.

Statistical Analysis

Data analysis was performed using SPSS (version 24, IBM, Armonk, NY, USA). Chi-square-test was used for the statistical analysis of differences between the investigated sub-groups. For the analysis of age, Mann-Whitney U test was performed. p values <0.05 were considered statistically significant.

Results

Suppressive Conditions

One thousand six hundred and thirty-one patients were included with an age span from 15 to 93 years (me-

Table 1. Characteristics of tested and non-tested patients

	Tested patients	Non-tested patients	Statistic *p* value
Number	818	812	
Age, years, median (25–75% quantile)	56 (42–69)	65 (52–75)	0.021
Suppressive condition, %	68	85	<0.005
PPI intake	63	78	<0.005
Antibiotics	15	26	<0.005
GI-bleeding	8	20	<0.005
Outpatients, %	47	25	<0.005

p values <0.05 are considered statistically significant.
PPI, proton-pump inhibitor.

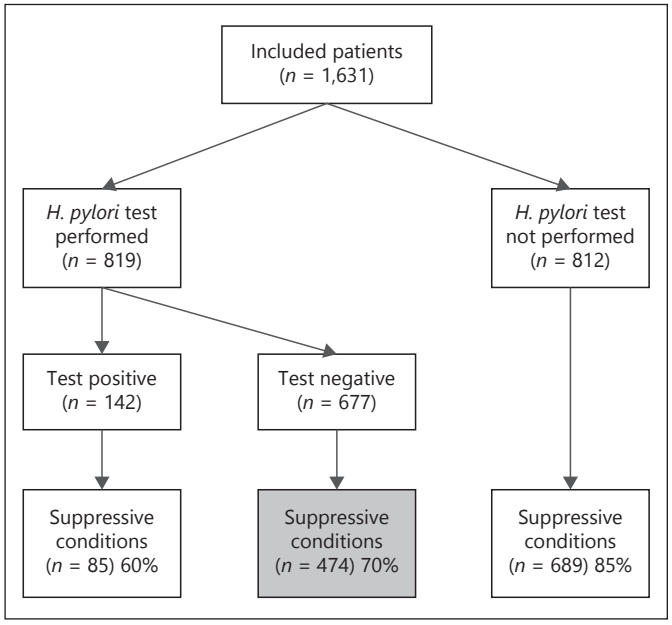

Fig. 1. Study design.

dian 61 years). Of these patients, 587 (36.0%) were outpatients and 1,044 (64.0%) were inpatients. In total, 1,248 (76.5%) patients had one or more *H. pylori* suppressive condition, whereas only 383 (23.5%) had no *H. pylori* suppressive conditions. The major suppressive condition was the intake of a PPI with 70.7% (1,153/1,631), followed by recent antibiotic treatment within the previous 4 weeks with 20.4% (332/1,631) and clinical signs of upper gastrointestinal bleeding (hematemesis, melena) within in the previous 2 weeks with 13.7% (223/1,631). Inpatients showed significant differences compared to outpatients. Inpatients were older (median age 52 vs. 65; $p < 0{,}005$) and showed more often *H. pylori* suppressive conditions (84.2% [879/1,044] vs. 62.9% [369/587]; $p < 0.005$).

H. pylori *Test*

Eight hundred and nineteen of all the included 1,631 (50.2%) patients had the indication for *H. pylori* testing; always conducted by both HUT and histology. Interestingly, patients with an indication for *H. pylori* testing were characterized by a reduced percentage of *H. pylori* suppressive conditions (68 vs. 85%; $p < 0.005$), a median lower age (56 vs. 65 years; $p = 0.021$) and a higher percentage of outpatients (47 vs. 25%; $p < 0.005$) compared to the non-tested patients. A detailed analysis of the different suppressive conditions between the tested and non-tested individuals revealed a reduced PPI intake (63 vs. 78%; $p < 0.005$), a reduced antibiotic intake (15 vs. 26%; $p < 0.005$), and reduced signs of GI-bleeding (8 vs. 20%; $p < 0.005$) within the tested patients. These results are shown in Figure 1 and Table 1.

Among the tested patients, 142 out of the 819 patients (17.3%) tested positive for *H. pylori*, whereas 677 out of the 819 (82.7%) tested negative for both histology and HUT. The comparison of these 2 groups (positive vs. negative testing) resulted in a significant lower amount of suppressive conditions among patients with positive *H. pylori* test (60.0 vs. 70.0%; $p = 0.018$), whereas no statistical differences concerning age or rate of out- or inpatients were observed. The analysis of the different suppressive conditions resulted in a reduced PPI (51 vs. 66%; $p < 0.001$) and antibiotic-intake (8 vs. 16%; $p < 0.02$) within the positively tested patients. These results are shown in Figure 1 and Table 2.

Taken together, 474 out of the 677 patients with negative results were investigated under suppressive conditions with an increased risk of a false negative test.

Of the 142 *H. pylori* positive patients, only 14 (9.9%) showed an incongruent result (1 test positive, 1 test negative). Incongruent results appeared only under *H. pylori* suppressive conditions, namely, exclusively PPI-intake, whereas without suppressive conditions, all positively tested patients showed positive results in both histology and HUT. The analysis of the incongruent tests showed a positive histology with negative HUT in 86% (12 out of 14). Conversely, only in 2 cases HUT was positive and histology negative. This reaches statistical significance ($p < 0.005$).

Table 2. Characteristics of patients who tested positive and negative for *Helicobacter pylori*

	Positive test	Negative test	Statistic, *p* value
Number	142	677	
Age, years, median (25–75% quantile)	53 (42–66)	56 (42–70)	ns
Suppressive condition, %	60	70	0.018
PPI intake	51	66	0.001
Antibiotics	8	16	0.020
GI-bleeding	9	7	ns
Outpatients, %	49	54	ns

p values <0.05 are considered statistically significant.
PPI, proton-pump inhibitor; ns, not significant.

Discussion

This study addresses the relevant issue of a high rate of *H. pylori* testing under *H. pylori* suppressive conditions leading to potentially more false negative results. Our trial was performed with a high number of patients in a real-world setting.

The main *H. pylori* suppressive conditions are treatment with PPI, upper gastrointestinal bleeding, and recent antibiotic treatment leading to a reduced sensitivity and specificity of all common *H. pylori* tests [1, 20]. Obviously, guidelines unanimously recommend testing under non-suppressive conditions [1]. However, this does not always meet the clinical practice in the real word setting. Especially, the withdrawal of PPIs can often not be realized, since many patients with dyspepsia have already been primarily treated with PPIs before an EGD is performed and *H. pylori* is tested [1].

Our study shows real world data of *H. pylori* suppressive conditions in patients who undergo EGD in a large German university hospital providing general and maximum care. It demonstrates that 63% of outpatients and up to 84% of inpatients show *H. pylori* suppressive conditions. In this respect, the interpretation of *H. pylori* test results poses a great challenge for gastroenterologists and the present guidelines might not be expedient enough.

According to the guideline recommendation, *H. pylori* testing was always conducted with histology and HUT [1, 18]. Interestingly, conflicting results between the 2 methods occurred exclusively under *H. pylori* suppressive conditions. In those cases, histology seemed to be superior to HUT in terms of its sensitivity under *H. pylori* suppressive conditions. Although this result reached significance in the statistical analysis, prospective studies are required to confirm this preliminary finding.

A large absolute and relative amount of negatively tested individuals exhibited *H. pylori* suppressive conditions throughout the test (474 out of 677 negatively tested patients; 70.0%). Under *H. pylori* suppressive conditions, histology and all urease tests exhibit a significant reduced sensitivity and specificity due to a reduction of *H. pylori* colonization density [1, 19, 20]. In this line of evidence, suppressive conditions were significantly increased within these 677 negatively tested patients compared to the positively tested patients for *H. pylori* test, thereby suggesting potentially false negative results in this group. This diagnostic "black box" of *H. pylori* might be clinically relevant for symptom control and long-term implications such as gastric cancer incidence. Our data provide preliminary evidence that in clinical practice histology could be superior to urease test under suppressive conditions.

There are certain limitations to our study concerning geographical differences of *H. pylori* prevalence. The trial was conducted monocentrically in a large German university hospital providing general and maximum care with a distinct patient collective that does not necessarily represent the general western population.

In summary, our study clearly illustrates the high frequency of patients with *H. pylori* suppressive conditions that undergo elective upper endoscopy in clinical everyday practice.

As a direct consequence, a relevant subgroup of patients with negative *H. pylori* testing under suppressive conditions exhibits an increased risk of a false negative test result. However, the exact rate of false negative results

under *H. pylori* suppressive conditions remains unclear at this point. Certainly, this is a question with high clinical relevance.

Further prospective clinical research is needed to address those relevant issues.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

R.F.K.: drafting manuscript. G.P., S.C.B.B., and A.A.: critical revision. T.M.G. and V.E.: supervision, critical revision. A.N.: data acquisition, critical revision. S.K.: study concept, data acquisition, data analysis, statistical analysis.

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