

Diagnosis and treatment of *Helicobacter pylori* for peptic ulcer bleeding in clinical practice - factors associated with non-diagnosis and non-treatment, and diagnostic yield in various settings

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ABSTRACT

Background/Aims: To study the practice of clinicians in the diagnosis and treatment of *H. pylori* for peptic ulcer bleeding, and the diagnostic yield of *H. pylori* tests in various situations.

Materials and Methods: All consecutive patients aged ≥ 18 years who underwent esophagogastroduodenoscopy for the indications of coffee-grounds vomitus, hematemesis or melena with endoscopically diagnosed peptic ulcers were included.

Results: 374 patients were included. *H. pylori* testing was performed during acute bleeding for 296 patients. 80% of patients who tested negative for *H. pylori* during the acute episode were planned for repeat *H. pylori* testing. 11/88 patients who tested negative for *H. pylori* during the acute episode were positive for *H. pylori* during repeat testing (diagnostic yield 12.5%). Prior proton-pump inhibitor and antibiotic ingestion within 4 weeks of presentation was associated with lower diagnostic yield for *H. pylori*. On multivariate analysis, patient's age, systolic blood pressure, heart rate, activated partial thromboplastin time, and need for endoscopic treatment were associated with failure to take biopsies for *H. pylori* testing during acute episode. 100/106 patients tested positive for *H. pylori* during the acute episode of gastrointestinal bleeding had *H. pylori* treatment.

Conclusion: Repeat *H. pylori* testing after index negative *H. pylori* testing during acute episodes gave a diagnostic yield of 12.5%, reinforcing the importance of repeat testing.

Keywords: *H. pylori*, gastrointestinal bleeding, peptic ulcer

INTRODUCTION

Upper gastrointestinal bleeding is an important cause of mortality worldwide (1-4). Peptic ulcer disease is the most common cause of upper gastrointestinal bleeding (4-5), and a significant proportion of peptic ulcers are caused by *Helicobacter pylori* (*H. pylori*) (6). Guidelines recommend the diagnosis and treatment of *H. pylori* in upper gastrointestinal bleeding secondary to peptic ulcers (7-9), but the preferred diagnostic test and the optimal timing of testing (during acute bleeding or after that) is not clear. Diagnostic tests for *H. pylori* include rapid urease test, histology and culture which requires endoscopic tissue biopsies, and non-endoscopic methods such as urea breath test, serology and rapid blood tests (10). Culture is usually used to determine the resistance after failure to eradicate *H. pylori*. Rapid blood tests have variable accuracy for the diagnosis of

H. pylori, but most kits perform poorly (11). Rapid urease test, histology, urea breath test and serology are more commonly used in the clinical setting. Diagnosis of *H. pylori* during the episode of acute bleeding has been reported to be less accurate (12). A recent international consensus recommends caution in the interpretation of initially negative *H. pylori* tests during the acute bleeding episode and the need for repeated testing at follow-up (7). Therefore, this might prompt one to question the role of *H. pylori* testing in the acute setting, as it appears that performing *H. pylori* testing only after the acute episode is a viable option. This international consensus stated that the optimal diagnostic approach remains unclear, but may include acute testing for *H. pylori* infection, followed by a confirmatory test outside the acute context of bleeding if the initial results are negative. This approach has not been previously

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studied, and there is limited data on the diagnostic yield of repeat testing for *H. pylori* after initial negative tests during the acute episode. The pattern of *H. pylori* testing by clinicians managing peptic ulcer bleeding in real-life clinical practice has not been extensively studied. We aim to study the percentage of upper gastrointestinal bleeding secondary to peptic ulcer disease which received diagnosis and treatment of *H. pylori* in the real-life setting of a tertiary centre, factors associated with non-diagnosis and non-treatment of *H. pylori*, and the diagnostic yield of *H. pylori* testing during and after the acute bleeding episode in this real-life setting, as well as during repeat testing after initial negative tests in the acute testing.

MATERIALS AND METHODS

Patients

Over an 18-month period in a university hospital, all consecutive patients aged at least 18 years who underwent esophagogastroduodenoscopy for the indications of coffee-grounds vomitus, hematemesis or melena and diagnosed endoscopically with peptic ulcers were included. Informed consent was obtained before EGD. All data, such as patient demographic data, indication for EGD, laboratory investigation results, comorbidities, symptoms at presentation, endoscopic findings, *H. pylori* test results and treatment, length of hospital stay, need for intervention, and all-cause in-hospital mortality, were prospectively collected and entered into the database by a research assistant (P.L.T.). The research assistant was trained in medical and endoscopic terminology, and given a template of medical information to collect.

The study was conducted in a tertiary hospital with a 24-hour endoscopy service for gastrointestinal bleeding. The on-call emergency endoscopy team consisted of a consultant endoscopist, a trainee endoscopist, and a trained endoscopy nurse. All endoscopies were performed with monitoring of vital signs. High-risk lesions with active bleeding or visible vessels were treated with hemoclips, heater probe, argon plasma coagulation (APC), alone or in combination with adrenaline injection. When hemostasis was not achieved with adrenaline injection plus another method, a third endoscopic treatment modality was added. Histoacryl glue injection was used when standard modalities of hemostasis failed. Blood clots were irrigated and underlying lesions were treated. Patients for whom endoscopic hemostasis could not be achieved were referred for surgery. Following endoscopy, patients with high-risk endoscopic stigmata (active bleeding or visible vessels) were continued on intravenous infusion of PPIs for 72 hours which was converted to oral PPIs for a total treatment of 8 weeks. Patients with no high risk endoscopic stigmata were treated with oral PPIs for 8 weeks. All patients with gastric ulcers were scheduled for repeat esophagogastroduodenoscopy to confirm gastric ulcer healing, as per the recommendations by the British Society of Gastroenterology (9). There was no standard protocol for *H. pylori* testing. Biopsies were taken for rapid urease test or his-

tology during endoscopy if deemed appropriate by the endoscopist, and patients might be sent for urea breath test post-endoscopy if deemed appropriate by the physician. Patients who were not tested for *H. pylori* during the index endoscopy were planned for *H. pylori* testing during follow-up endoscopy to check gastric ulcer healing or scheduled for urea breath test 3 months after the index endoscopy, giving a 4-week PPI-free period after 8 weeks of PPI therapy.

Definitions

In-hospital all-cause mortality referred to death during the hospital stay from any cause. Weekend was defined as between midnight on Friday and midnight on Sunday, as per the definition of "weekend" in previous studies (3,13-16). A patient was considered to have tested positive for *H. pylori* if he was tested with at least one of the three tests (rapid urease test, histology and/or urea breath test), with at least one positive result. A patient was considered to have tested negative for *H. pylori* infection if he was tested with at least one of the three tests (rapid urease test, histology and/or urea breath test), with none of the performed *H. pylori* test being positive. A patient was considered to have not been tested for *H. pylori* infection if he did not receive any of the tests (rapid urease test, histology and/or urea breath test).

Ethics approval

We viewed this evaluation as an assessment of service quality rather than research. All patients received current standard of care, without randomization or experimental intervention. All data collected were anonymized. Our Institutional Review Board approved the protocol, and deemed that apart from standard consent for EGD, no additional consent was required.

Statistical methods

Data were analyzed with SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean values with SDs, unless otherwise stated. Differences in categorical variables were evaluated using Pearson's χ^2 test. Differences in continuous variables were evaluated using Student's *t* test for independent samples, after verifying homogeneity of variance with Levene's test. Multivariate analysis was performed on variables which were significant on univariate analysis. A *p* value <0.05 was considered as statistically significant.

RESULTS

Patients

During the study period, 374 patients who presented with coffee-grounds vomitus, hematemesis or melena were diagnosed endoscopically with peptic ulcers. The mean age was 63.4±15.9 years. There were 264 (70.6%) males and 275 (73.5%) Chinese. The mean length of stay was 7.9±12.6 days. 20 (5.3%) patients were in intensive care unit at the time of endoscopy. 159 patients had at least one significant co-morbidities. All-cause in-hospital mortality was 4.5% (17/374). 203 patients (54.3%)

required endoscopic treatment, and 4 patients required surgery. 181 patients (48.4%) had gastric ulcers, 147 (39.3%) had duodenal ulcers, 42 (11.2%) had gastric and duodenal ulcers, and 4 (1.1%) had anastomotic ulcers.

Diagnosis of *Helicobacter pylori* (Figure 1)

H. pylori testing was performed during the acute episode of gastrointestinal bleeding for 296 patients (79.1%). 16 patients received empirical *H. pylori* treatment without getting any diagnostic tests for *H. pylori*. The remaining 48 patients who survived were planned for *H. pylori* testing after the acute episode.

Diagnosis during the acute bleeding episode

In total, 296 patients were tested for *H. pylori* infection with either rapid urease test, histology or urea breath test during the episode of acute gastrointestinal bleeding. Rapid urease test was done for 229 patients and histology was done was 222 patients. 18 patients had urea breath test. The diagnostic yield for *H. pylori* was 53 out of 229 (23.1%) for rapid urease tests, 63 out of 222 (28.4%) for histological examinations, and 6 out of 18 (33.3%) for urea breath tests. In total, 106 patients tested positive for *H. pylori* on at least one of the three tests (rapid urease test, histology and/or urea breath test), and 190 patients tested negative for *H. pylori* infection (none of the performed *H. pylori* test was positive).

Delayed index testing for *H. pylori*

Of the 62 patients scheduled for delayed *H. pylori* testing, 47 patients were planned for *H. pylori* testing during follow-up oesophagogastroduodenoscopy for confirmation of gastric ulcer healing, and 15 patients were planned to receive urea breath tests during follow-up outpatient clinic visits. 20 patients defaulted esophagogastroduodenoscopy, with only 27 patients

turning up for esophagogastroduodenoscopy, and all 27 were tested with rapid urease test. The diagnostic yield for *H. pylori* was 7 out of 27 (25.9%) for rapid urease test. Of the 15 patients planned for urea breath tests, only 7 patients (46.7%) did the tests, with a diagnostic yield for *H. pylori* of 42.8% (3 out of 7). When the patients who defaulted were included, the intention-to-diagnose diagnostic yield was 14.9% (7/47) for rapid urease test and 20% (3/15) for urea breath test.

Repeat *H. pylori* testing after initial negative tests

Of the 190 patients who tested negative for *H. pylori* during the acute episode, 34 patients received empirical *H. pylori* eradication. 87 out of the remaining 156 patients had repeat esophagogastroduodenoscopy, with 67 patients getting repeat *H. pylori* testing, of whom 9 tested positive for *H. pylori* (5 positive on rapid urease tests, 2 positive on histology, and 2 positive on both rapid urease test and histology). 20 out of these 87 patients who had oesophagogastroduodenoscopy did not have biopsies taken for repeat *H. pylori* testing. 4 of the 69 patients who did not have repeat esophagogastroduodenoscopy were sent for urea breath test, with 2 testing positive and 2 testing negative for *H. pylori*. Overall, 11 patients out of 71 patients tested positive on *H. pylori* during delayed testing although they tested negative during the acute episode, giving a diagnostic yield of 15.5%.

Factors associated with failure to take biopsies during index esophagogastroduodenoscopy

283 patients (75.7%) had biopsies taken during endoscopy for rapid urease test and/or histology. On univariate analysis, factors associated with failure to take biopsies for *H. pylori* testing included patient's age, systolic blood pressure, heart rate, intensive care unit at time of endoscopy, presentation on a week-

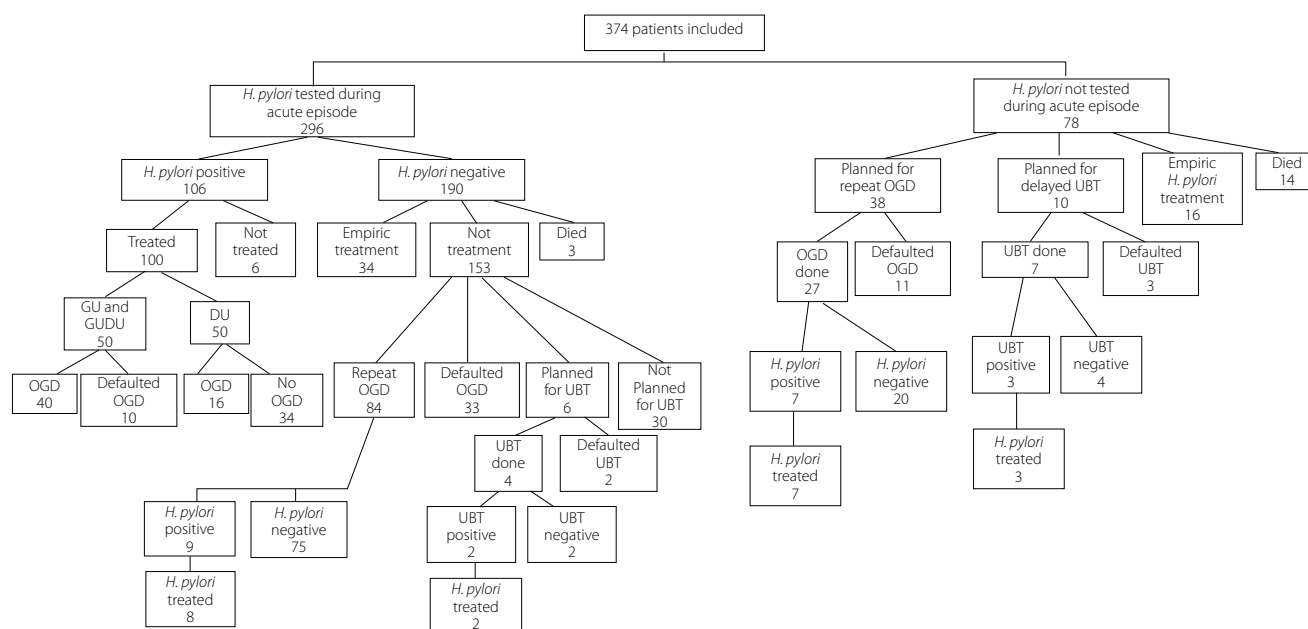


Figure 1. Flow chart showing the diagnosis and treatment of *H. pylori* in our study cohort.

end, haemoglobin, prothrombin time, activated partial thromboplastin time, and need for endoscopic treatment (Table 1). On multivariate analysis, patient's age, systolic blood pressure, heart rate, activated partial thromboplastin time, and need for endoscopic treatment were associated with failure to take biopsies for *H. pylori* testing (Table 2).

Treatment of *H. pylori*

Of the 106 patients tested positive for *H. pylori* during the acute episode of gastrointestinal bleeding, 100 patients (94.3%) were given eradication therapy for *H. pylori*, of whom 68 patients had subsequent confirmation of successful eradication, 7 patients failed eradication, and 25 patients defaulted *H. pylori* testing to confirm eradication. Six patients who were tested positive for *H. pylori* during the acute episode did not get treated because they were lost to follow-up after the histology came back positive for *H. pylori* infection. 34 out of 190 patients (17.9%) who

tested negative for *H. pylori* infection and 16 out of 78 patients (20.5%) who were not tested for *H. pylori* infection were given empirical treatment for *H. pylori*.

DISCUSSION

In our study, all patients were tested for *H. pylori* during the acute episode, scheduled for delayed testing, or treated empirically for *H. pylori* without prior testing. All patients who were tested positive for *H. pylori* received eradication therapy except for 5% who defaulted follow-up after histology showed *H. pylori* infection. These were consistent with the current recommendations. However, only 58% of the patients who tested negative for *H. pylori* during the acute bleeding episode received repeat testing, which was suboptimal as a recent international consensus recommended repeat testing if the initial tests were negative [7]. This recommendation was based on the variable evidence showing the poor negative predictive value of *H. pylori* testing in the setting of acute bleeding. The poor rate of repeat testing was due to defaulters and to endoscopists not taking biopsies for repeat *H. pylori* testing during repeat endoscopy. In our cohort, 15.5% of patients were subsequently diagnosed with *H. pylori* infection despite prior negative *H. pylori* tests during the acute episode. Clinicians should be made aware of the benefits of repeat *H. pylori* testing after the acute episode in order to increase the rate of repeat testing.

In our cohort, all patients with gastric ulcers were scheduled for repeat oesophagogastroduodenoscopy after the acute episode. This was in accordance with the British Society of Gastroenterology guidelines (9). There was no such recommendation for duodenal ulcers, although selected patients with refractory symptoms despite treatment might need repeat endoscopy, as pancreatic malignancies had been reported to present as duodenal ulcers (17). Repeat endoscopy provided an opportunity to check for ulcer healing, biopsy non-healing ulcers, and repeat testing for *H. pylori*. However, almost half of our patients did not return for repeat endoscopy. Similarly, half of the patients who were scheduled for urea breath test did not turn up. This might be because most patients felt better symptomatically after treatment and did not see a need for another endoscopy or a urea breath test. In addition, our local medical system requires patients to pay for the oesophagogastroduodenoscopy or urea breath test themselves, as these are not funded by the state, adding further disincentives for getting delayed or repeat *H. pylori* testing. This highlighted the importance of informing and educating patients regarding the repeat endoscopy and urea breath test.

This study describes real life clinical setting, and the tests for *H. pylori* are therefore not standardized, as is the case in most centres. Although this is a limitation of the study, it provides an opportunity to study the situation as it is in clinical practice, in particular the compliance to *H. pylori* testing and treatment.

Although index endoscopy provided an excellent opportunity for *H. pylori* testing, only 80% of our cohort was tested for

Table 1. Univariate analysis of factors associated with endoscopic biopsies not being taken for *H. pylori* testing during the acute episode

	Biopsy taken for <i>H. pylori</i> testing	No biopsy taken for <i>H. pylori</i> testing	p value
Age (years)	62.1±16.5	67.3±13.0	0.002
Intensive care unit (%)	3.5	11.0	0.006
Weekend presentation (%)	22.3	35.2	0.014
Systolic blood pressure (mmHg)	123.0±18.2	113.7±20.5	<0.001
Heart rate (/min)	81.3±11.6	88.2±16.9	<0.001
Hemoglobin (g/dL)	9.97±2.82	8.90±2.97	0.002
Platelet	297.0±118.4	294.9±161.1	0.909
Prothrombin time (sec)	15.0±4.0	17.3±6.0	0.001
Activated partial thromboplastin time (sec)	29.9±5.9	33.8±8.0	<0.001
Need for endoscopic treatment (%)	47.7	74.7	<0.001

Table 2. Multivariate analysis of factors associated with endoscopic biopsies not being taken for *H. pylori* testing during the acute episode

	Odds ratio	p value	95% CI
Age (years)	1.024	0.027	1.003-1.045
Intensive care unit (%)	0.764	0.631	0.255-2.288
Weekend presentation (%)	1.829	0.055	0.986-3.393
Systolic blood pressure (mmHg)	0.982	0.019	0.966-997
Heart rate (/min)	1.035	0.002	1.013-1.058
Hemoglobin (g/dL)	0.929	0.204	0.829-1.041
Prothrombin time (sec)	0.984	0.653	0.918-1.055
Activated partial thromboplastin time (sec)	1.093	0.001	1.037-1.153
Need for endoscopic treatment (%)	0.367	0.002	0.196-0.688

H. pylori during index endoscopy. On multivariate analysis, patient's age, systolic blood pressure, heart rate, activated partial thromboplastin time, and need for endoscopic treatment were associated with failure to take biopsies for *H. pylori* testing. Severe coagulopathy is a contraindication to obtaining tissue biopsies. However, in the absence of bleeding tendencies, ulcers which need endoscopic treatment do not preclude biopsy for histology or rapid urease test if the gastric mucosa away from the ulcer is biopsied. Given the possibility of loss to follow-up for another chance at *H. pylori* testing, endoscopists should take biopsies for *H. pylori* testing during index endoscopy whenever possible.

The large majority of patients either got tested for *H. pylori* during acute gastrointestinal bleeding or were scheduled for delayed testing. However, 40% of patients initially tested negative for *H. pylori* did not receive repeat testing. 16% of patients who tested negative initially during the acute episode subsequently tested positive, reinforcing the importance of repeat testing in this group. A significant proportion of patients defaulted delayed or repeat *H. pylori* testing, which support the algorithm of testing for *H. pylori* during the acute setting whenever possible, as well as repeat or delayed testing for patients who complies with follow-up.

Conflict of Interest: No conflict of interest was declared by the authors..

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