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Observational Study

Intraprocedural gastric juice analysis as compared to rapid urease test for real-time detection of Helicobacter pylori

Vasapolli R et al. Gastric juice-based H. pylori diagnosis

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#### Abstract

#### **BACKGROUND**

Endofaster is an innovative technology that can be combined with upper gastrointestinal endoscopy (UGE) to perform gastric juice analysis and real-time detection of Helicobacter pylori (H. pylori).

AIM

To assess the diagnostic performance of this technology and its impact on the management of *H. pylori* in the real-life clinical setting.

**METHODS** 

Patients undergoing routine UGE were prospectively recruited. Biopsies were taken to assess gastric histology according to the updated Sydney system and for rapid urease test (RUT). Gastric juice sampling and analysis was performed using the Endofaster, and the diagnosis of H. pylori was based on real-time ammonium measurements. Histological detection of *H. pylori* served as the diagnostic gold standard for comparing Endofaster-based *H. pylori* diagnosis with RUT-based *H. pylori* detection.

#### 15 RESULTS

A total of 198 patients were prospectively enrolled in an *H. pylori* diagnostic study by Endofaster-based gastric juice analysis (EGJA) during the UGE. Biopsies for RUT and histological assessment were performed on 161 patients (82 men and 79 women, mean age 54.8 ± 19.2 years). *H. pylori* infection was detected by histology in 47 (29.2%) patients. Overall, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value (NPV) for *H. pylori* diagnosis by EGJA were 91.5%, 93.0%, 92.6%, 84.3%, and 96.4%, respectively. In patients on treatment with proton pump inhibitors, diagnostic sensitivity was reduced by 27.3%, while specificity and NPV were unaffected. EGJA and RUT were comparable in diagnostic performance and highly concordant in *H. pylori* detection (κ-value = 0.85).

#### CONCLUSION

Endofaster allows for rapid and highly accurate detection of *H. pylori* during gastroscopy. This may guide taking additional biopsies for antibiotic susceptibility testing during the same procedure and then selecting an individually tailored eradication regimen.

**Key Words:** *Helicobacter pylori* diagnostic; Chronic gastritis; Gastric juice; Endofaster; Rapid urease test; Antimicrobial susceptibility testing

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**Tip:** Diagnosis of *Helicobacter pylori* (*H. pylori*) infection can be rapidly achieved within the framework of gastroscopy by rapid urease test (RUT) or by gastric juice

analysis with Endofaster. In this prospective observational study, we compared the accuracy of these two methods. Gastric juice analysis with Endofaster could reliably detect *H. pylori* with high accuracy, showing a diagnostic performance comparable to that of RUT and a major advantage of an immediate result. Intraprocedural *H. pylori* detection (or exclusion) is crucial to optimize the diagnostic approach and improve the management of infection. The diagnosis of Endofaster may guide additional sampling for antibiotic susceptibility testing in positive patients or avoid unnecessary biopsies in negative patients.

#### INTRODUCTION

Helicobacter pylori (H. pylori) infects nearly half of the world's population, with variable prevalence rates ranging from 20%-30% in Western countries to > 70% in Africa<sup>[1]</sup>. H. pylori infection causes chronic active gastritis and may lead to severe complications including gastroduodenal ulcers, gastric cancer and mucosa-associated lymphoid tissue lymphoma<sup>[2]</sup>. The diagnosis of active H. pylori infection is achieved by non-invasive tests such as the urea breath test (UBT) and stool antigen tests (SAT), as well as invasive methods based on endoscopy and gastric biopsies for histological assessment, rapid urease test (RUT), culture and molecular tests.

Current guidelines recommend testing for  $\overline{H}$ . pylori in all patients undergoing upper gastrointestinal endoscopy (UGE)<sup>[3]</sup>. The Endofaster has been introduced as new diagnostic device, which consents the detection of H. pylori by performing biochemical analysis of gastric juice aspirated during gastroscopy. Previous validation studies have shown that this device has high accuracy for H. pylori detection and reported diagnostic values similar to those of UBT and histology<sup>[4,5]</sup>. The diagnostic performance of the Endofaster has not been compared with that of the RUT, which shares a similar characteristic in terms of providing results in a short-term temporal context through endoscopic examination. This allows for therapeutic management immediately after the diagnostic procedure.

The aim of this prospective study was to validate the diagnostic performance of the Endofaster for *H. pylori* detection in patients who underwent UGE compared to conventional RUT.

#### **MATERIALS AND METHODS**

#### Study population

Consecutive patients undergoing routine UGE to investigate dyspepsia or other alarming symptoms (weight loss, anemia, vomiting, abdominal pain, or dysphagia) were prospectively recruited at the Ludwig Maximilians University Hospital in Munich from January to June 2022.

Subjects were recruited within the ERANET Bavaria and Helicopredict projects (German clinical trials register, DRKS-ID: DRKS00028629), large-scale prospective studies focused on studying different aspects of *H. pylori* infection, including improving the diagnosis and management of *H. pylori*, determining local antibiotic resistance spectrum, with the aim of developing a genotypic resistance testing database for predicting antibiotic susceptibility and evaluating the impact of the microbiome of the upper gastrointestinal tract on gastric carcinogenesis.

The study was approved by the local ethics committee and government authorities and was conducted in accordance with current Good Clinical Practice guidelines and the Declaration of Helsinki<sup>[6]</sup>. All recruited subjects provided written informed consent for participation. Previous gastric surgery and intake of anticoagulants or any antibiotic therapy within 4 wk prior to endoscopy were exclusion criteria. Regular use of proton pump inhibitors (PPI) or previous *H. pylori* eradication therapy did not represent exclusion criteria, but were recorded in detail. Only patients not taking a PPI or *H. pylori* treatment-naïve patients were considered to meet the desired minimum sample size.

#### Endoscopic procedure and histological assessment

Enrolled patients underwent a diagnostic UGE using standard video gastroscopes (GIF-HQ190, Olympus, Tokyo, Japan). All examinations were performed with sedation using Propofol and/or Midazolam. An analysis of gastric juice was performed at the beginning of the UGE by Endofaster. Special attention was paid during intubation: the stomach was handled first and no fluid was allowed to be sucked during passage through the oral cavity or esophagus. In order to avoid possible dilution of gastric juice prior to collection the administration of endoscopic premedications (*i.e.* dimethicone, N-acetylcysteine, pronase *etc.*) before endoscopy were not allowed. Furthermore, washing with water and cleaning the endoscopic lens were avoided until sampling was completed. After endoscopic assessment of the mucosa, gastric biopsies were obtained. Two biopsies - one from antrum and one from corpus (both from the greater curvature) - were taken for the RUT (Pronto Dry® New, Medical Instruments Corporation, Herford, Germany). RUT

was performed according to the manufacturer's instructions and assessed for positive response during gastroscopy and 1 h after biopsy sampling. The inspection time taken to perform the diagnostic UGE (excluding the time spent on gastric juice aspiration and on biopsy sampling) and the time it took until first detection of *H. pylori* positivity by RUT were recorded. Further biopsies (2 from antrum, 1 from angulus and 2 from corpus) were subjected to routine histology according to the updated Sydney system<sup>[7]</sup> and current guidelines<sup>[3]</sup>. In each biopsy sampling set the following stainings were performed: hematoxylin and eosin, periodic acid-Schiff and a *H. pylori* specific staining (modified Giemsa staining).

#### Endofaster analysis

Real-time gastric juice analysis was performed using an Endofaster 21-42 (NISO Biomed, Turin, Italy), which is interposed between the endoscope and the suction system (Figure 1). This innovative device analyzes the first 3.3 mL of gastric juice aspirated at the beginning of the UGE. The Endofaster provides information regarding gastric pH based on hydrogen ion concentration and *H. pylori* detection based on the measurement of ammonium derived from bacterial urease activity within 60-90 s<sup>[4,5]</sup>. Considering that approximately 10-20 s (max 30 s) are needed to aspirate the gastric juice through the scope a final *H. pylori* diagnosis is provided within the first 2 min from the beginning of the endoscopic procedure. Except for the time spent on the initial gastric juice collection no additional time is required for Endofaster use during the endoscopic procedure. In line with previous studies, we used a cut-off value of > 62 ppm/mL to indicate the presence of *H. pylori*<sup>[8]</sup>.

### Statistical analyses

Descriptive statistical analysis was performed using IBM SPSS Statistics 23.0.0 (IBM Corporation, New York, NY, United States). Numerical variables were expressed as mean ± SD. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated for both Endofaster and RUT using histology as

the gold standard. The concordance between Endofaster and RUT results was assessed by using Cohen's  $\kappa$ -value. The McNemar test was used to compare sensitivities and specificities between the two tests.

Sample size estimation was based on a 95%CI and the calculation methods of Buderer  $et\ al^{[9]}$  were applied using following formula:

$$n_{ ext{Se}} = rac{Z_{rac{lpha}{2}}^2 \widehat{ ext{Se}} (1-\widehat{ ext{Se}})}{d^2 imes ext{Prev}} \hspace{0.5cm} n_{ ext{Sp}} = rac{Z_{rac{lpha}{2}}^2 \widehat{ ext{Sp}} (1-\widehat{ ext{Sp}})}{d^2 imes (1- ext{Prev})}$$

Where Z is the normal distribution value set to 1.96, corresponding to the 95%CI, and d is the maximum acceptable width of the 95%CI, set at 10%. Based on a previous study, Endofaster had a sensitivity (*Se*) of 97.1% and a specificity (*Sp*) of 89.7% for H. pylori detection [5]. Recently, the prevalence of H. pylori infection (*Prev*) in Germany was estimated to be 35.3% (95%CI: 31.2-39.4)[1]. As a result, using the criteria listed above, this study required a minimum of 31 H. pylori-positive patients (n<sub>Se</sub>) and 55 H. pylori-negative patients (n<sub>Sp</sub>), resulting in a minimum total sample size of 86 subjects. Patients with PPI use or prior H. pylori eradication therapy were not considered to achieve the minimum sample size required. All authors had access to the study data and reviewed and approved the final manuscript.

#### **RESULTS**

#### Characteristics of the study cohort

A total of 198 patients undergoing elective UGE were enrolled. Of these, 182 underwent gastric juice analysis with the Endofaster. After excluding patients who reported antibiotic intake within the last 4 wk (n = 10, 5.2%), patients who could not undergo biopsy due to anticoagulation therapy (n = 8, 4.1%) and patients with insufficient volume of aspirated gastric juice for Endofaster analysis (n = 13, 6.7%) a total of 161 patients (male: 82, female: 79, mean age 54.8 ± 19.2 years) were included in the analysis. 67 (41.6%) patients were on ongoing PPI therapy and 94 patients (58.4%) did not report any PPI

therapy. The demographic, endoscopic, and histopathological characteristics of the study cohort are shown in Table 1. A flow chart of the study's recruitment is shown in Figure 2.

### Diagnostic performance of Endofaster and RUT for H. pylori detection

The average duration of the diagnostic UGE was 8.5 min.  $\overline{H}$ . *pylori* infection was diagnosed in 47 (29.2%) patients on histopathology. Endofaster results were positive in 51 patients (31.6%), while RUT was positive in 45 (28.0%) cases. A positive RUT reaction was detected during endoscopy in 37 subjects (78.7%), with a mean positive reaction time of 16.4 min. The overall diagnostic performances of Endofaster and RUT for *H. pylori* detection as compared to histology (gold standard) are shown in Table 2. Sensitivity, specificity, accuracy, PPV and NPV were 91.5%, 93.0%, 92.6%, 84.3% and 96.4% for Endofaster, and 93.6%, 99.1%, 97.5%, 97.8% and 97.4% for RUT, respectively. No significant differences were observed in the diagnostic performances of the Endofaster and the RUT (P > 0.05). This was confirmed by an almost perfect agreement of *H. pylori* detection between the two tests ( $\kappa$ -value = 0.85).

Both Endofaster and RUT showed excellent diagnostic performances when considering only patients without ongoing PPI therapy (n = 94). In this subgroup, 37 (39.4%) subjects were histopathologically diagnosed as positive for *H. pylori*.

Among patients treated with PPI (n = 67), the presence of H. pylori was detected by histology in 10 subjects (14.9%). In this subgroup, a reduction in sensitivity, PPV and accuracy was observed for both Endofaster and RUT, whereas specificity and NPV remained almost unchanged (Table 2). Again, in the subgroup analysis, there were no significant differences in diagnostic performances between Endofaster and RUT (P > 0.05).

#### DISCUSSION

Several diagnostic methods are performed on biopsies obtained during the UGE to detect *H. pylori* with high accuracy. They are highly accurate, but have the limitation to delay even a few days in providing diagnostic results, thus not allowing an immediate

therapeutic decision. RUT is the only exception in clinical practice that allows relatively rapid detection of *H. pylori*, usually within 1 h after UGE<sup>[10-12]</sup>.

Here, we report on the diagnostic performance of Endofaster-based gastric juice analysis (EGJA), an innovative technology that allows intraprocedural *H. pylori* detection compared to RUT. We found that the high accuracy (> 90%) of EGJA was comparable to that of RUT for *H. pylori* detection, confirming previous reports of the high accuracy of EGJA compared to histology<sup>[4,5,8,13]</sup>. A previous prospective study of EGJA in 182 patients determined the sensitivity, specificity and accuracy of *H. pylori* to be 97.1%, 89.7% and 92.6%, respectively, compared to histology being used as the gold standard as well as UBT, which was used for reclassification of *H. pylori* status in case of discordance between EGJA and histology results<sup>[5]</sup>. A multicenter study of 525 consecutive patients reported an overall sensitivity, specificity and accuracy of 87%, 84% and 85%, respectively, when compared to histology<sup>[8]</sup>.

We have observed impaired diagnostic sensitivity in patients with PPI in EGJA and RUT, which is a common phenomenon for all tests, including non-invasive tests<sup>[3,14]</sup>. In the context of PPI intake, only histology remains highly sensitive when gastric biopsies are taken from the proximal stomach<sup>[15,16]</sup>. This is related to the PPI-induced shift from antrum-predominant to corpus-predominant gastritis. We found that 3 out of 4 false negatives and 6 out of 8 false positives (75%) in EGJA were registered in patients on PPI therapy. Two of the three false negatives (66%) diagnosed by the RUT were PPI users. EGJA and RUT rely on the same principles related to ammonium concentration and H. pylori urease activity. Therefore, both tests are influenced by the reduction of bacterial load by PPI, which may lead to false negative results. Furthermore, an elevated pH in the stomach environment may lead to an overgrowth of other non-H. pylori bacteria with urease activity<sup>[17]</sup>. Several different urease-positive bacterial strains, such as Staphylococcus capitis subsp. urealyticus and Streptococcus salivarium, have been isolated in gastric juice and mucosal samples from patients with gastric hypochloridria<sup>[18]</sup>. The higher abundance of these strains may interfere with urea metabolism and explain the increased number of false-positive cases among patients on PPI therapy. It is necessary

to analyze the gastric microbiota and functionality profiles of PPI patients in order to further address this interesting topic. In our study, the low prevalence of *H. pylori*-infected subjects (only 14.9%) within the group of patients on PPI therapy is a limitation because of an underpowered statistical analysis. Using histology as the gold standard for *H. pylori*-diagnosis in a cohort with relatively low-prevalence of *H. pylori* may represent a further limitation of this study. Histopathological diagnosis of *H. pylori* may suffer from potential sampling error due to the patchy distribution of the bacterium<sup>[19]</sup>. However, by using the updated Sydney system based on biopsies from 5 different sites and applying different staining methods for *H. pylori* detection the accuracy of *H. pylori*-diagnosis by histology is not inferior to any non-invasive test (13C-UBT/SAT). In support for the validity of histology as gold standard for *H. pylori* detection, we found also no indirect signs of *H. pylori*-gastritis (*i.e.* neutrophils infiltration in the gastric mucosa) in the absence of *H. pylori*.

EGJA has the advantage of obtaining more rapid diagnostic results when performing endoscopy compared to RUT. During endoscopy (within a time period of approximately 10 min), a positive signal in the RUT for the presence of *H. pylori* was recorded in 78.7% of those producing *H. pylori* positivity at the end of the reading time in our study, consistent with the time interval of response reported in previous validation studies<sup>[12,20]</sup>, whereas EGJA resulted in the diagnosis of *H. pylori* within 2 min after starting with UGE. The intraprocedural detection of *H. pylori* infection combined with measurement of gastric pH can guide the endoscopist on the most appropriate approach to complete the diagnostic assessment, *i.e.*, whether or not to carry out additional biopsies for gastritis severity staging and antibiotic susceptibility testing (AST). This has become an absolute requirement for the selection of the eradication regimen due to the high antibiotic resistance rates of clarithromycin, metronidazole and fluoroquinolones<sup>[21]</sup>. Real-time detection of *H. pylori* suggests carrying out additional biopsies for AST during UGE and selecting an *H. pylori* eradication regimen accordingly.

Such a strategy would have a substantial impact on cost-effectiveness by reducing the duration of the procedure and lowering costs due to histological or microbiological analysis of negative gastric biopsies, an aspect that has been previously addressed by others<sup>[8]</sup>.

Future studies will explore the possibility of combining EGJA with *in situ* molecular genetic antibiotic resistance testing. Promising data in this field were revealed by a recent meta-analysis of four studies that evaluated gastric juice-based genotypic detection of *H. pylori* antibiotic resistance to clarithromycin compared to standard culture-based methods<sup>[22]</sup>.

#### **CONCLUSION**

In conclusion, Endofaster's gastric juice analysis is a highly accurate method for the diagnosis of *H. pylori* infection, comparable to RUT. EGJA-based *H. pylori* diagnosis has an advantage in terms of on-site immediacy of diagnosis. In patients on PPI therapy, sensitivity is reduced, but NPV and specificity are not affected. Real-time detection of *H. pylori* along with the determination of gastric pH during endoscopy adds important information on the need for additional biopsies for more detailed histological assessment and antibiotic susceptibility testing.

#### ARTICLE HIGHLIGHTS

#### Research background

Diagnosis of *Helicobacter pylori* (*H. pylori*) infection can be rapidly achieved within the framework of gastroscopy by rapid urease test (RUT) or by gastric juice analysis with Endofaster.

#### Research motivation

The diagnostic performance of the Endofaster has not been compared with that of the RUT, which shares a similar characteristic in terms of providing results in a short-term temporal context through endoscopic examination.

#### Research objectives

The objective of this prospective study was to validate the diagnostic performance of the Endofaster for *H. pylori* detection in patients who underwent gastroscopy compared to the diagnostic accuracy of a standard RUT.

#### Research methods

Patients undergoing routine upper gastrointestinal endoscopy were prospectively recruited. Biopsies were taken to assess gastric histology according to the updated Sydney system and for RUT. Gastric juice sampling and analysis was performed using the Endofaster, and the diagnosis of *H. pylori* was based on real-time ammonium measurements. Histological detection of *H. pylori* served as the diagnostic gold standard for comparing Endofaster-based *H. pylori* diagnosis with RUT-based *H. pylori* detection.

#### Research results

Gastric juice analysis with Endofaster could reliably detect H. pylori with an overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 91.5%, 93.0%, 92.6%, 84.3%, and 96.4%, respectively. Gastric juice analysis with Endofaster and RUT were comparable in diagnostic performance and highly concordant in H. pylori detection ( $\kappa$ -value = 0.85).

#### Research conclusions

Endofaster's gastric juice analysis is a highly accurate method for the diagnosis of *H. pylori* infection, comparable to RUT. EGJA-based *H. pylori* diagnosis has an advantage in terms of on-site immediacy of diagnosis.

#### Research perspectives

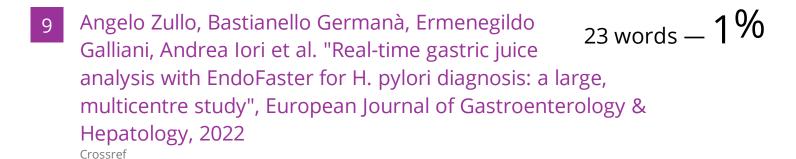
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