Accuracy of a new innovative column-free miniaturized gas-mass spectrometer compared with a classic gas-mass spectrometer to diagnose and monitor *Helicobacter pylori* infection: a prospective single blind study

Matteo Pavoni[a], Marco Tartagni[b], Raffaele Correale[c], Luigi Gatta[c,d], Giulia Fiorini[e], Daniel Racca[c], Angelo Zullo[f], Luca Arlotti[a], Gabriella Massarenti[a], Beatrice Rosa[a], Cristina Marchesani[a], Giulia Collatuzzo[a], Raffaele Manta[g], Andrea Imbrogno[h], Claudio Borghi[a,e] and Dino Vaira[a,e]

Background *Helicobacter pylori* (*H. pylori*) is one of the most common bacterial infections, and it causes chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. *H. pylori* infection can be essentially detected by invasive [i.e. requiring an upper gastrointestinal endoscopy (UGE)], and noninvasive techniques. The principle of the urea breath test exploits the abundant quantities of urease produced by *H. pylori.* Recently, advances in the field of micro-electromechanical systems and nano-electromechanical systems have been proposed. This study aimed to evaluate the accuracy of this new miniaturized column-free portable gas-mass spectrometry (GMS) test compared with the standard GMS to diagnose *H. pylori* infection before and after eradication therapy.
Methods Consecutive patients never treated for *H. pylori* infection and referred to our unit to perform a UGE between April and November 2024 were evaluated for this blind prospective trial. Patients' samples were analysed with both methods and data were compared.
Results A total of 28 patients were enrolled and 92 were *H. pylori* positive. The data obtained from the two tests were compared, and no statistically significant difference was observed.
Discussion Our experience highlights the potential for introducing new diagnostic tools that are less demanding in terms of cost and labour, without compromising diagnostic accuracy. To our knowledge, this is the first time that an innovative diagnostic tool proves to be as compact and as reliable; for this reason, it deserves to be implemented in clinical practice. Eur J Gastroenterol Hepatol 38: 321–326

Background

Helicobacter pylori (*H. pylori*) is one of the most common bacterial infections, and it causes chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer [1–3]. Moreover, it was also associated with some important extra-gastric diseases, such as iron deficiency anaemia or idiopathic thrombocytopenic purpura [4]. *H. pylori* infection can be essentially detected by invasive [i.e. requiring an upper gastrointestinal endoscopy (UGE)] and noninvasive techniques [5]. The choice relies upon the patient's needs: presence of alarm symptoms clearly dictates a UGE evaluation; otherwise, noninvasive techniques, such as the urea breath test (UBT), are used to 'test and treat' for *H. pylori* infection [6–8].

The principle of the UBT exploits the abundant quantities of urease produced by *H. pylori*, which hydrolyses urea to form ammonia and soluble carbon dioxide, successively expired in the breath [9]. Labelling of urea with either a radioactive (^{14}C) or a stable isotope of carbon (^{13}C) allows the detection of them in the expired breath and consequently the presence of infection. Even though the dose of radiation of ^{14}C is small, the need of a nuclear medicine department or centres licensed for storage and disposal of radioactive substrates, as well as the impossibility of using the ^{14}C in some categories of patients, made the diffusion of this test not easy [5], with ^{13}C-UBT consequently becoming the most widespread UBT; however, major drawbacks of ^{13}C-UBT are the higher cost of

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Departments of [a]Medical and Surgical Sciences and [b]Electrical, Electronic and Information Engineering (DEI), University of Bologna, Bologna, [c]NanoTech Analysis S.R.L., Turin, [d]Oncologic Screening Unit, ASL Toscana Nord-Ovest (ATNO), Livorno, [e]Cardiovascular Medicine Unit, Heart, Chest and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, [f]Nuovo Regina Margherita Hospital, Gastroenterology and Digestive Endoscopy, Rome, [g]Gastroenterology and Digestive Endoscopy, 'Riuniti' Hospital, Livorno and [h]Maggiore Hospital Carlo Alberto Pizzardi, Emergency Room and Territorial Emergency Spoke Area, Bologna, Italy

Correspondence to Dino Vaira, MD, Department of Surgical and Medical Sciences, University of Bologna, Via Massarenti 9, 40138, Bologna, Italy
Tel: +39 51 2144140; e-mail: berardino.vaira@unibo.it

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the substrate [10], and the need for a isotope ratio mass spectrometry (IRMS). The IRMS represents the state-of-the-art technique for isotopic determination, which is a specialisation of gas-mass spectrometry (GMS), allowing for the precise measurement of the relative abundance of stable isotopes in a given sample [11]. This kind of instrument – currently used also for the ^{13}C-UBT – is complex, expensive, and relatively cumbersome [10,11].

Recently, the advances in the field of micro-electromechanical systems (MEMS) and nano-electromechanical systems (NEMS) determined the development of a new miniaturized, portable GMS able to sample and analyse the gas at ambient pressure through a nanometric orifice, without needing gas columns and equipped also with a machine-learning system resulting in quicker analysing processes [12,13].

The aim of this prospective study was to evaluate the accuracy of this new miniaturized column-free portable GMS test compared with the standard GMS to diagnose *H. pylori* infection before and after eradication therapy.

Methods

Patients

Consecutive patients never treated for *H. pylori* infection and referred to our unit to perform a UGE between April and November 2024 were evaluated for this blind prospective trial. Exclusion criteria were: (a) age less than 18 years; (b) previous upper gastrointestinal surgery; (c) use of proton pump inhibitors or H_2 receptor antagonist in the 4 weeks before the endoscopy; (d) use bismuth preparations or/and antimicrobial agents in the 4 weeks before the endoscopy; (e) previous eradication attempts, as this would skew the series toward negative tests [14]; (f) known history of allergic reaction to components of the eradication regimens; (g) patients with severe or unstable general conditions (e.g. cardiovascular, pulmonary, endocrine, renal, hepatic, haematologic diseases, etc.); (h) pregnant or breastfeeding women. Patients provided written informed consent for UGE and anonymous use of their clinical data for scientific purposes (i.e. sex and age).

Endoscopy, biopsies, rapid urease test

All patients enrolled underwent a UGE. During the procedure, biopsies were collected for histological examination (two specimens from *antrum* and *corpus*, respectively, and one from the *incisura*). Biopsies were stained with haematoxylin–eosin and Giemsa stains, and gastritis was scored using the updated Sydney system [15] and the operative link for gastritis assessment system [16]. Pathologists who performed the histological examination were blinded to the results of all of the other tests. Finally, a further sample from the antrum was obtained to make the rapid urease test (RUT) (BIOHIT *Helicobacter Pylori* UFT300; Biohit HealthCare Srl, Milan, Italy), performed as previously reported [17]. The technician who performed the RUT was blinded to the results of all of the other tests.

Urea breath tests

UBTs were carried out after an overnight fast, and collected using 20 ml disposable plastic straw containers. The containers were numbered using a random number generator (STATA SE Corporation 16.1, College Station, Texas, USA) to anonymize the patients' identities to the technicians who would analyze the samples. The association between containers and patient identity was made before starting the trial, and only one investigator (G.F.), who did not take part in the analysis of the samples and was also not aware of the results of all other tests. At the end of the study, the association of the results of ^{13}C-UBTs performed with the two GMSs and the identity of the patients was made.

For each patient, two consecutive breath samples were collected at baseline (T_0), and took an aqueous solution containing citric acid (1.4 g) and 100 mg of ^{13}C-urea. After 30 min of the ingestion of the solution, two consecutive new breath samples were collected (T_{30}). One of the two pairs of breath samples of each patient (i.e. T_0 and T_{30}) was subsequently analysed using the *standard UBT* (ABCA2; Sercon Limited, Crewe Trade Park, Gateway, Crewe, Cheshire, UK), while the second pair was assessed using NEMS technology, the new UBT [Helitron V CO_2 – (H_2) from Nanotech Analysis s.r.l., Turin, Italy] (a–c). The two GMSs were located in separate sites with dedicated technicians, blinded for the results from the other GMS and for the outcomes of the additional diagnostic tests.

Patients were classified as infected with *H. pylori* before treatment only if both RUT and histology were positive (gold standard before treatment). At follow-up, the gold standard was represented by the standard UBT, as described previously [18]. This criterion was established before the study began. For the standard UBT, a test was considered positive if the delta over baseline (DOB) was greater than or equal to 5‰, while for the new UBT, the result was considered positive if the DOB was greater than or equal to 9‰. All these criteria have been recommended by an expert panel for use in clinical trials of *H. pylori* and established before the study began [19].

Treatment of H. pylori-positive patients and follow-up

Patients who tested positive for *H. pylori* were offered a 10-day sequential therapy with esomeprazole 40 mg and amoxicillin 1 g. (both twice daily) for the first 5 days, followed by esomeprazole 40 mg, clarithromycin 500 mg, and tinidazole/metronidazole for the remaining 5 days, all twice daily. Both breath tests were repeated at least 4–6 weeks after the end of therapy to assess *H. pylori* eradication.

Statistics

This was a prospective comparison study designed to fulfil STARD (standards for reporting of diagnostic accuracy) recommendations [20]. Proportions, their differences, and 95% confidence intervals (95% CIs) were calculated using the method recommended by Newcombe and Altman [21]. Sensitivity, specificity with their respective 95% CIs, were calculated against the defined gold standards, using methods recommended by Altman [22]; however, as positive predictive value and negative predictive value are dependent on the prevalence of infection, these were not calculated as they are not indicative of values that might be observed in other clinical settings [23]. Therefore, likelihood ratios for a positive (LR+ve) or negative (LR-ve) test, with their respective 95% CIs, were also presented using methods

Table 1. Demographic characteristics of the patients enrolled in the study

Sex (M/F)	126/202
Age (years), median (IQR)	56.5 (45–67)
H. pylori-infected patients (%)	28.0% (95% CI: 23.5–33.1)
Peptic ulcer/erosions	8.2% (95% CI: 5.7–11.7)
Nonulcer dyspepsia	90.6% (95% CI: 86.9–93.26)
Neoplasia	1.2% (95% CI: 0.4–3.1)

CI, confidence interval; F, female; IQR, interquartile range; M, male.

Table 2. Receiver operating characteristic analysis of the conventional gas-mass spectrometry (standard urea breath test) and of the new miniaturized column-free portable gas-mass spectrometry [Helitron V CO_2 – (H_2) – new urea breath test] against the predefined gold standard in patients never investigated for *H. pylori* infection (see text for details)

	ROC value	SE	95% CI	*P* value
Standard UBT	0.9952	0.0025	0.99–1.0	–
New UBT	0.9916	0.0069	0.98–1.0	–
Difference between areas	0.00836	0.0148	-0.02–0.04	0.5720

CI, confidence interval; ROC, receiver operating characteristic; UBT, urea breath test.

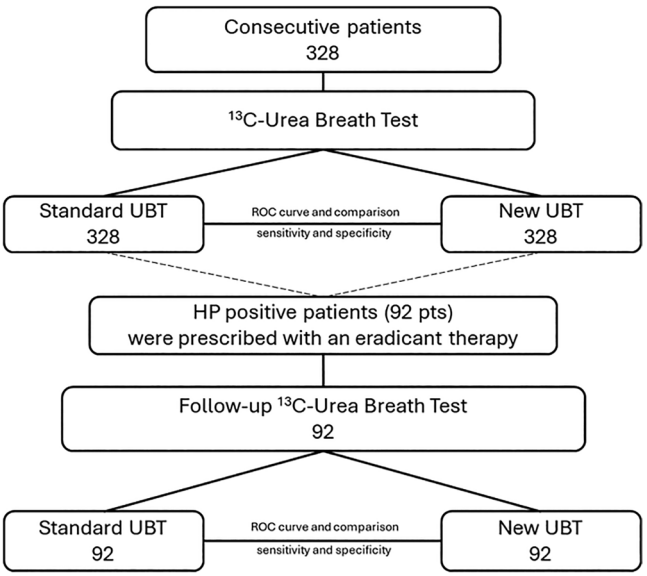

Fig. 1. Flow chart of the study. ROC, receiver operating characteristic; UBT, urea breath test.

recommended by Altman [22], and interpreted as suggested by Sackett and Sackett [24]. Receiver operating characteristic (ROC) analysis was performed using nonparametric methods [25]. Comparison of sensitivity, specificity, LR+Ve and LR-ve was assessed as recommended by Roldán-Nofuentes [26]. Cohen's κ coefficient was also calculated between the two breath tests (BTs) before and after treatment [27]. Eradication rates were assessed according to intention-to-treat (i.e. each patient receiving the treatment) and per protocol (i.e. each patient who was followed up). Statistical analysis was performed using MedCalc Statistical Software version 23.1.3 (MedCalc Software Ltd, Ostend, Belgium). A two-sided *P* value less than 0.05 was considered statistically significant.

Results

The design of the study is presented in Fig. 1. As shown in Table 1, 328 patients were enrolled. The median age was 56.5 years (25–75 percentile: 45–67 years), and 62.3% were women. Ninety-two patients (28.1%) were *H. pylori* positive. All 92 patients infected accepted to receive the eradication therapy.

When the ROCs of the standard and new UBTs were compared against the gold standard (histology + RUT), no difference was found between the two areas (Table 2, $P = 0.5720$ and Fig. 2). The values of sensitivity and specificity (Table 3) for both tests were greater than or equal to 98% with no difference between their values ($P > 0.1$). Also, LRs+ve and LRs-ve test were no different between them ($P > 0.1$), with values clearly indicating a significant and conclusive change to posttest probability of diagnosis [24]. Finally, the *k* agreement between the two BTs was 0.95 (standard error = 0.05; $P < 0.0001$).

At follow-up, data were available for all 92 infected patients. The eradication rate was 90.2% (95% CI: 82.4–94.8). The values of the area under the curve of the new UBT against the standard UBT was 0.9973 (95% CI: 0.96–100) as shown in Fig. 3. As reported in Table 4, the sensitivity was of 98% (95% CI: 92–99) and the specificity of 99% (95% CI: 97–100). Even in this case, the values of LR+ve and LR-ve test clearly indicated a significant and conclusive change to the posttest probability of diagnosis [24]. Finally, the *k* agreement between the two BTs was 0.90 (standard error = 0.10; $P < 0.0001$).

Discussion

H. pylori infection remains a key issue for physicians worldwide, given its direct relationship with gastritis, ulcer, and gastric neoplasia. Therefore, its diagnosis should be accurate and thorough [1–3].

Recent advancements in MEMS and NEMS, a new compact and portable GMS has been developed. This innovative device can sample and analyse gas at ambient pressure through a nanometric orifice, eliminating the need for gas columns. Furthermore, it incorporates a machine-learning system that significantly accelerates the analysis process [12,13].

IRMS represents the highest standard in isotopic determination techniques and constitutes a specialised branch of GMS.

Although the past two decades have seen innovations in optical technologies – such as laser-assisted ratio analyzers, cavity ring-down spectroscopy, integrated cavity output spectroscopy, and nondispersive infrared isotope spectroscopy – demonstrating sensitivity and specificity around 90%, no significant advancements have been made in IRMS technologies [28–30].

The first true breakthrough in gold standard IRMS techniques is represented by the instrument presented in this study, which revolutionises the compactness and portability of a GMS system while maintaining diagnostic reliability comparable to that of conventional GMS instruments.

From the analysis of the data obtained with both instruments in the present study, it was observed that there is no statistically significant difference between them; moreover,

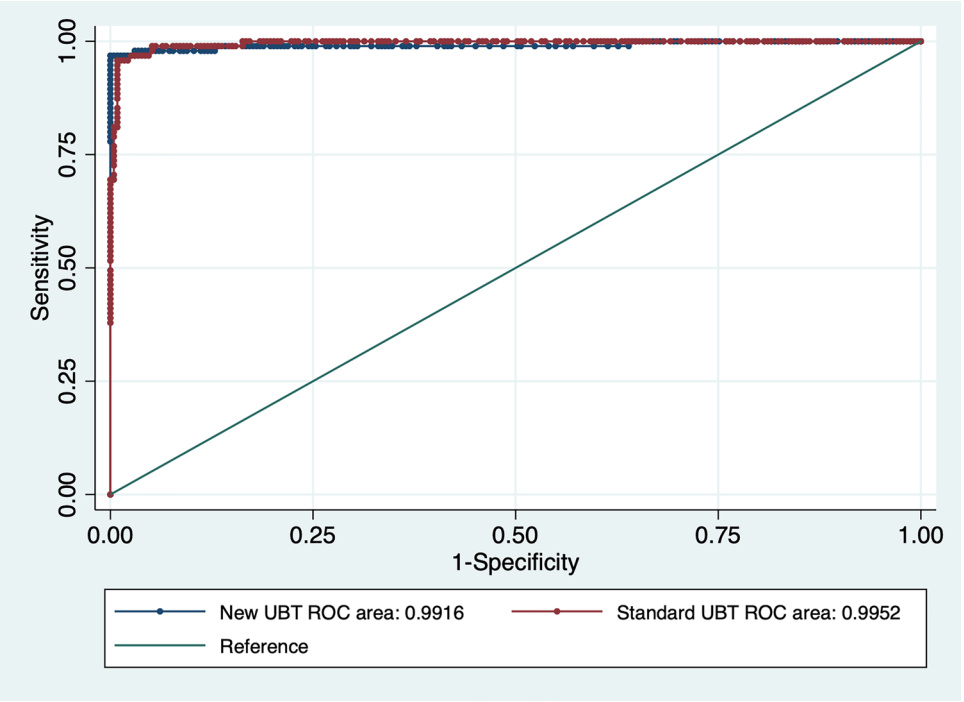

Fig. 2. ROC analysis of the conventional GMS (standard UBT) and of the new miniaturized column-free portable GMS [Helitron V CO_2 – (H_2)] against the predefined gold standard in patients never tested for *H. pylori* infection (see text for details). GMS, gas-mass spectrometry; ROC, receiver operating characteristic; UBT, urea breath test.

Table 3. Diagnostic accuracy of the standard[a] and new[b] urea breath tests in patients never tested for *H. pylori* infection

	Sensitivity (95% CI)[c]	Specificity (95% CI)[c]	LR+ve (95% CI)[c]	LR-ve (95% CI)[c]
Standard UBT	99% (94–100)	100% (98–100)	233 (33.01–1650)	0.01 (0–0.08)
New UBT[b]	98% (92–99)	99% (97–100)	115.43 (29.03–459)	0.02 (0.01–0.09)

[a]Standard GMS (ABCA2 breath test, Sercon Limited, Crewe, Cheshire, UK).
[b]New miniaturized column-free portable GMS [Helitron V CO_2 – (H_2)].
CI, confidence interval; GMS, gas-mass spectrometry; LR+ve, likelihood ratio for a positive test; LR-ve, likelihood ratio for a negative test; UBT, urea breath test.
[c]$P > 0.1$.

the positive and negative predictivity is similar with both tests. As far as we are concerned, given the comparable sensibility and specificity of the Helitron, different pros may be taken under consideration.

First, the price of the instrument and its maintenance are less expensive than the traditional mass spectrometry (MS), which implies a possible wider distribution on the territory. Furthermore, Helitron is extremely versatile in its application in breath tests; its possibility of detecting the presence of H_2, CH_4, and H_2S in patient breath samples allows its use in the study of small intestinal bacterial overgrowth and lactose intolerance. In addition, Helitron's autocalibration function should be emphasised, which allows the user to set an analysis start time on the instrument, thus having it ready without having to wait for calibration time, unlike MS standards. Moreover, Helitron applies a CO_2 correction factor technique to reduce errors from improper sampling. Furthermore, what makes Helitron a highly interesting instrument is the fact that it can be transported with considerable ease. This enables its use in the ambulatory or wherever necessary, in this way, the lab goes to the patient.

Specifically, these recent results confirm that Helitron is a fully functional GMS system with a volume approximately one order of magnitude smaller and reduced power consumption. Finally, it has been eliminated the need for a gas column for calibration and gas carrier containers.

In conclusion, our experience highlights the potential for introducing new diagnostic tools as Helitron that are less demanding in terms of cost and labour, without compromising diagnostic accuracy. This instrument combines the advantages of both classical MS and infrared, achieving results comparable to MS with practicality and costs comparable to infrared. For this reason, Helitron proves to be an extremely interesting tool that deserves to be more widely used in clinical practice.

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D.V., M.T., and R.C. conceived the study. D.V. included patients in the study. M.P. and D.R. performed the instrumental analyses. M.P. performed data management and L.G. performed statistical analysis. M.P. and L.G. wrote

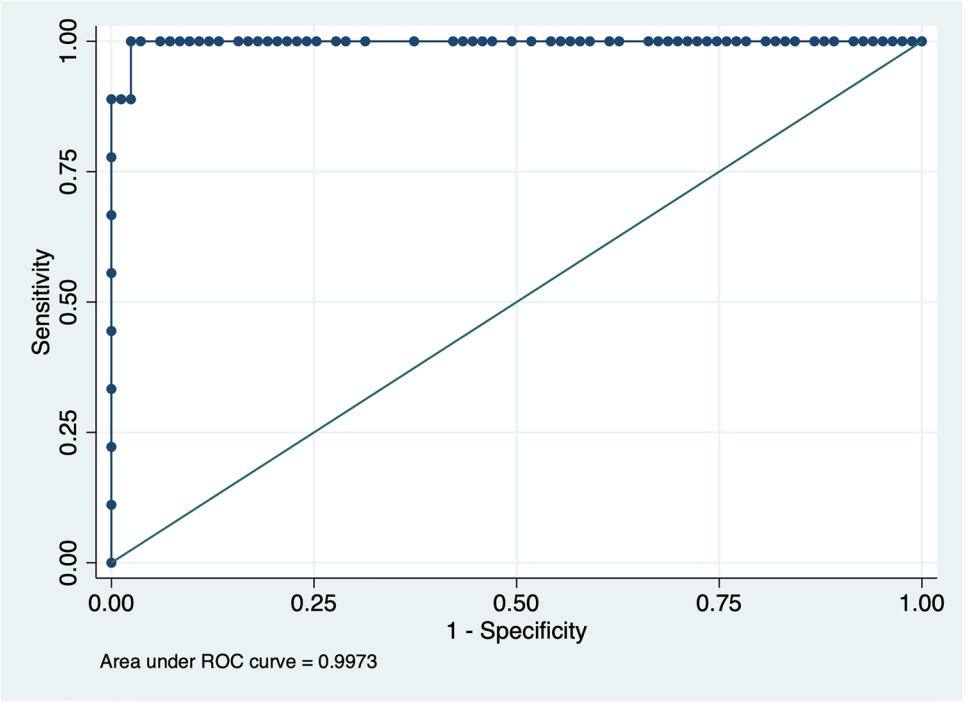

Fig. 3. ROC analysis of the new miniaturized column-free portable GMS [Helitron V CO_2 – (H_2)] against the predefined gold standard (conventional GMS - standard UBT) in patients followed up after treatment. GMS, gas-mass spectrometry; ROC, receiver operating characteristic; UBT, urea breath test.

Table 4. Diagnostic accuracy of the new[a] urea breath tests in patients followed-up after treatment

	Sensitivity (95% CI)	Specificity (95% CI)	LR+ve (95% CI)	LR-ve (95% CI)
New UBT[a]	98% (92–99)	99% (97–100)	115.4 (29–459)	0.02 (0.01–00.9)

[a]New miniaturized column-free portable GMS [Helitron V CO_2 – (H_2)].
CI, confidence interval; GMS, gas-mass spectrometry; LR+ve, likelihood ratio for a positive test; LR-ve, likelihood ratio for a negative test; UBT, urea breath test.

the manuscript. All the authors critically reviewed the manuscript and approved the final version of this manuscript.

The study was approved by the Ethical Committee of St. Orsola Polyclinic, University Hospital, Bologna, Italy (approval numbers: 47/2012/U/Oss).

Conflicts of interest

There are no conflicts of interest.

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