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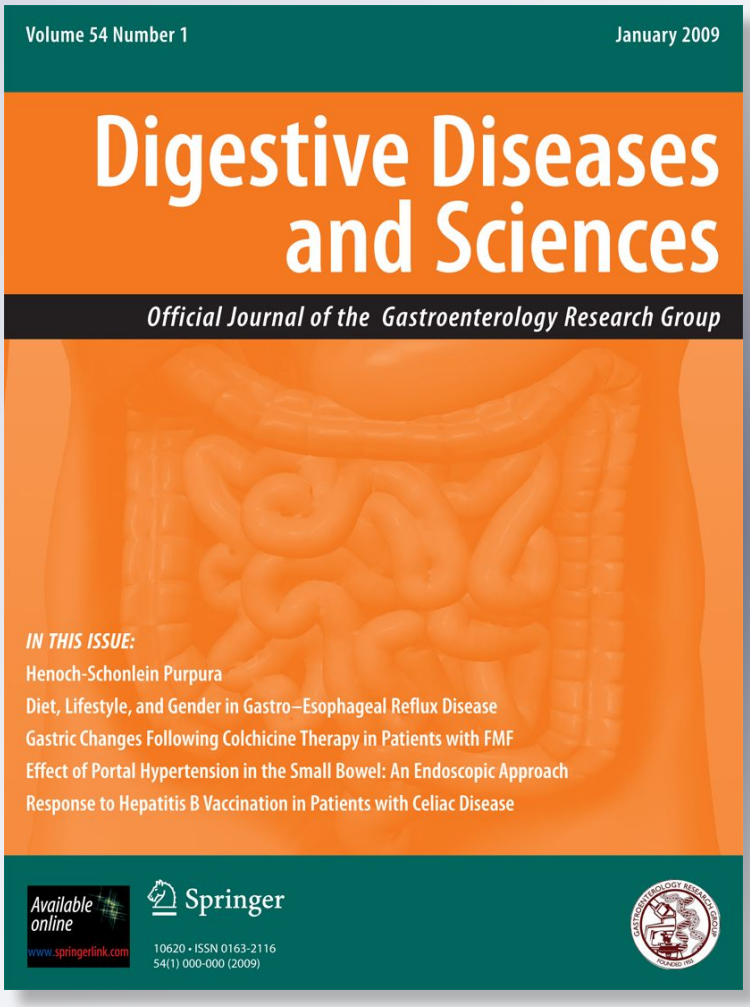

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ORIGINAL ARTICLE

Accuracy of Urea Breath Test Performed Immediately After Emergency Endoscopy in Peptic Ulcer Bleeding

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Abstract
Aims The aim of this work is to investigate the accuracy of the urea breath test (UBT) performed immediately after emergency endoscopy in peptic ulcer bleeding (PUB).
Methods Urea breath test was carried out right after emergency endoscopy in patients with PUB. The accuracy of this early UBT was compared to a delayed one after hospital discharge that was considered the gold standard. Clinical and epidemiological factors were analyzed in order to study their influence on the accuracy of the early UBT.
Results Early UBT was collected without any complication and good acceptance from all the 74 patients included. In 53 of the patients (71.6%), a delayed UBT was obtained. Comparing concordance between the two tests we have calculated an accuracy of 83% for the early UBT. Sensibility and specificity were 86.36 and 66%, respectively, with a positive predictive value of 92.68% and negative predictive value of 50% (Kappa index = 0.468; $p = 0.0005$; CI: 95%). We found no influence of epidemiological factors, clinical presentation, drugs, times to gastroscopy, Forrest classification, endoscopic therapy, hemoglobin, and urea levels over the accuracy of early UBT.
Conclusions Urea breath test carried out right after emergency endoscopy in PUB is an effective, safe, and easy-to-perform procedure. The accuracy of the test is not modified by clinical or epidemiological factors, ulcer stage, or by the type of therapy applied. However, we have found a low negative predictive value for early UBT, so a delayed test is mandatory for all negative cases.

Keywords Breath tests · Endoscopy · *Helicobacter pylori* · Peptic bleeding

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Introduction

Peptic ulcer is a major cause of gastrointestinal morbidity and mortality, mainly due to the risk of gastrointestinal bleeding, which has been estimated to be of 2–3% per year [1]. *Helicobacter pylori* (*Hp*) is the main etiologic agent for peptic ulcer disease in patients who are not under non-steroidal anti-inflammatory drugs (NSAIDs) [2]. It has been proven that correct diagnosis and treatment of this infection leads to a negligible rate of re-bleeding episodes [3].

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Although a delayed test can offer a high diagnostic yield [4], early detection of *Hp* infection in a bleeding patient discriminates patients with non-*Hp* ulcer and can lead to early therapy [5, 6]; it could save follow-up visits to diagnosis the infection.

Two large meta-analyses have evaluated the different methods for *Hp* detection in peptic ulcer bleeding (PUB) patients [7, 8]; however, clinical trials in this field have been scarce in the last years and the associations found by meta-regressions are observational, and weaker than derived from randomized comparisons [9].

On the other hand, most studies that analyze diagnostic tests for *Hp* detection in a bleeding patient are comparisons of different tests at the moment of the hemorrhage, which can result in false-negative tests [10], especially when invasive methods are used [11]. The accuracy of the urea breath test (UBT) in PUB patients has not been widely evaluated taking into account its performance at the moment of the hemorrhage and once the episode has resolved (delayed test); moreover, a group of experts have recently pointed out the importance of addressing this issue [8].

The aim of our study was to analyze if the diagnostic yield of UBT performed at the moment of the active bleeding episode (and as early as possible) is the same of the UBT once the bleeding has resolved, which is currently considered to be the best method (and the gold standard) for the diagnosis of *Hp* infection [12].

If the diagnostic performance were the same, we would have a non-invasive, innocuous, safe, and reproducible test for early diagnosis of *Hp* infection [13].

Materials and Methods

We have included in this prospective study 18-year-old or older patients who attended the Department of Gastroenterology of the University Hospital of Valladolid with a bleeding peptic ulcer for a period of 30 months. The study was approved by the Institutional Review Board of our institution and informed consent was obtained from the patients included.

Exclusion criteria were previous upper gastrointestinal tract surgery, pregnancy or breastfeeding, treatment with antibiotics, or proton pump inhibitors (PPI) in the previous 4 weeks to the bleeding episode, liver cirrhosis, severe pulmonary or cardiac dysfunction, chronic renal impairment, or any clinical or psychological situation that impaired informed consent or the realization of the UBT.

At all times, patients were treated routinely, with fluid reposition, oxygen and antihistamines, or PPI therapy at usual dosage. Time from admission to endoscopy was determined by the clinical condition of the patient. This time and that from first symptom to admission, form of presentation of the hemorrhage, age, gender, previous ulcer history, alcohol (more than 20 g/day), or cigarette consumption (more than 10 cigarettes/day), and NSAIDs intake were recorded in a database. Vital signs, hemoglobin levels, urea levels, and the presence or not of blood at the naso-gastric tube at admission were also recorded and analyzed.

Upper endoscopy was performed by an experienced endoscopist that applied conventional endoscopic therapy to stop bleeding as needed. No sedation or mild conscious sedation with midazolam were used; throat anesthesia was avoided. Invasive tests (rapid urease test or histology) were collected according to endoscopist criteria in some of the patients. The location of bleeding ulcers, Forrest classification, presence of blood in the stomach, and therapeutic procedures applied during endoscopy were also recorded.

After emergency endoscopy, UBT for the detection of *Hp* was performed by dispensing an oral tablet with 100 mg of C13-labeled urea (UBTest, Otsuka Pharmaceutical Europe Ltd ©, Middlesex, United Kingdom). The tablet was provided at the endoscopy room once emergency endoscopy had been accomplished. The procedure was performed following the manufacturer's instructions: initially with the patient in a sitting position. After a deep breath and a short period of apnea, exhaled air was collected. Afterwards, the solid form of C13-labeled urea was administered orally. The patient was asked to stay 5 min in a left lateral decubitus position; 20 min later, a second sample of exhaled air was collected. The two samples were then sent to a reference laboratory for determination. The test was considered negative if a value of $\Delta 13CO_2$ less than 2. 5‰ was obtained. No citric acid was used.

After hospital discharge, patients were referred to our outpatient clinic after 2–4 weeks under PPI therapy. Those patients who did not have a positive invasive test for *Hp* were assessed for *Hp* status by an ambulatory UBT, performed as it has been reported previously. PPIs were retired for 2 weeks before this test. This UBT was considered the gold standard, as it fulfilled all the requirements for ideal determination: ambulatory, PPIs retired, and non-active bleeding.

Statistical Analysis

Quantitative variables are presented as mean and standard deviation. Qualitative variables are presented as percentages. Qualitative variable associations were analyzed by Pearson's Chi-square test. Fisher's exact test and likelihood ratio were used when needed. Mann–Whitney *U* test was used to compare quantitative variables. Concordancy was assessed by Kappa index. SPSS version 18.0 for Windows and Epidat 3.1 were used for statistical analysis. A p value of <0.05 was considered to be statistically significant.

Results

Seventy-four patients with PUB and a UBT performed right after emergency endoscopy were included in the study. UBT was collected without any complication and good acceptance from all the patients.

In 53 of the patients (71.6%), a delayed ambulatory UBT was obtained in ideal conditions, showing a prevalence of *Hp* infection of 83%. Of the 21 patients with no delayed UBT, in 17 an invasive test of *Hp* diagnosis was obtained at the moment of endoscopy (histology or rapid urease test) (Fig. 1). The reasons for not obtaining a delayed UBT were: a positive invasive test collected at the moment of endoscopy with the consequent eradication therapy before the follow-up visit or patients failing to attend the follow-up visit.

Clinical and epidemiological characteristics of the 53 patients with a delayed UBT are shown in Tables 1 and 2.

Taking into account the 53 patients with two UBT, we found concordance between the two samples in 44 of them (38 positive in both samples and six negative in both cases). In three patients, early UBT was positive with a negative result in the delayed test and in six patients, the case was the contrary: negative in the early UBT at endoscopy and positive in the delayed ambulatory test (Fig. 1). From all these results we have calculated an accuracy of 83% for the early UBT. Sensibility and specificity were 86.36% (75.08–97.64%; CI: 95%) and 66.66% (30.31–100%; CI: 95%), respectively. The positive predictive value of the test was 92.68% (83.49–100%; CI: 95%) and the negative predictive value found was 50% (17.54–82.45%; CI 95%). Kappa index was 0.468 (0.174–0.761; $p = 0.0005$; CI: 95%), which means moderate concordance.

The influence of clinical or epidemiological factors on the concordance between early and delayed UBT was also analyzed. We studied age ($p = 0.687$), sex ($p = 0.272$),

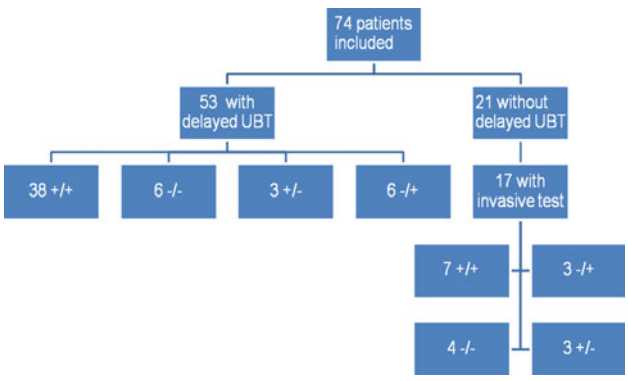

Fig. 1 Scheme and results of the study. The first + or − refers to the early UBT; the second one refers to the delayed UBT in the group of 53 patients and to the invasive test in the group of 21 patients

Table 1 Epidemiological, clinical, and endoscopic characteristics of the studied patients (qualitative variables) ($n = 53$)

Gender (%)	
Male	62.26
Female	37.74
Tobacco (%)	
Smokers	28.30
Non-smokers	71.70
Alcohol (%)	
Drinkers	16.98
Non-drinkers	83.02
History of peptic ulcer (%)	
Yes	33.97
No	66.03
Non-steroid anti-inflammatory drugs (%)	
Yes	45.28
No	54.72
Initial symptom (%)	
Hematochezia	3.77
Syncope	11.32
Hematemesis	20.75
Melena	64.16
Drugs until gastroscopy (%)	
200 mg PPI	1.89
240 mg PPI	1.89
320 mg PPI	1.89
120 mg PPI	3.77
160 mg PPI	5.66
Anti-H2	7.55
80 mg PPI	11.32
No medication	16.98
40 mg PPI	49.05
Naso-gastric tube (%)	
Bilious	1.89
No naso-gastric tube	1.89
Fresh blood	13.21
Coffee grounds	26.41
No blood	56.60
Forrest classification (gastric ulcers) (%)	
Forrest IIC	3.77
Forrest IB	5.66
Forrest IIA	7.55
Forrest III	33.96
No gastric ulcer	49.06
Forrest classification (duodenal ulcers) (%)	
Forrest IB	1.89
Forrest IIB	3.77
Forrest IIA	5.66
Forrest IIC	7.55
Forrest III	37.73
No duodenal ulcer	43.40

Table 1 continued

Blood at stomach when endoscopy (%)	
Coffee grounds	5.66
Fresh blood	9.43
No blood	84.91
Endoscopic therapy (%)	
Clips	3.77
Clips and sclerosis	5.66
Sclerosis	16.98
No endoscopic therapy	73.59

cigarette smoking ($p = 0.701$), alcohol consumption ($p = 0.640$), previous peptic ulcer ($p = 0.701$), NSAIDs intake ($p = 0.715$), form of clinical presentation of the hemorrhage ($p = 0.372$), use of PPI or antihistamines from admission to endoscopy ($p = 0.385$), presence of blood in the nasogastric tube ($p = 0.692$) or in the stomach ($p = 0.308$), Forrest classification in gastric ($p = 0.279$) and duodenal ulcers ($p = 0.408$), type of endoscopic therapy ($p = 0.586$), time from first symptom to hospital admission ($p = 0.505$), time from admission to endoscopy ($p = 0.543$), heart rate ($p = 0.152$), hemoglobin levels ($p = 0.507$), and urea levels ($p = 0.485$). We found no influence of any of the studied factors over the accuracy of early UBT in bleeding ulcer patients.

If we include in the study those patients without a delayed UBT but with an invasive test for *Hp* infection obtained at the moment of endoscopy, prevalence of the infection drops to 77.14%. Accuracy of the early UBT drops to 78.57%, while sensibility and specificity are 83.33% (72.46–94.19%; CI: 95%) and 62.5% (35.65–89.34%; CI: 95%), respectively; positive predictive value is 88.23% (78.41–98.05%) and negative predictive value found is then 52.63% (27.54–77.71%), with a Kappa index of 0.430 (0.188–0.671; $p = 0.0003$; CI 95%). Concordance remains moderate.

Discussion

Accurate diagnosis of *Hp* infection in PUB patients leads to eradication therapy and prevention of relapse [3]. It is necessary to establish which diagnostic tool is the best in this setting.

Although several studies have evaluated the prevalence of *Hp* in this group of patients, there is no "gold standard" test for its diagnosis [14]. Invasive tests like rapid urease test show a high rate of false-negative results [7] and UBT has not been widely used in this setting due to concerns on its feasibility in patients presenting with nausea and hematemesis [15]; on the other hand, the sensibility and specificity of UBT could be lower than usual in PUB patients [16].

In our group of patients, UBT could be easily performed with no complications in all patients right after emergency endoscopy, proving to be a safe and easy to perform test, as it has been suggested by other authors [17]. Patient acceptance was also as good as expected [18]. We think that the solid form of 13C-urea used (tablets) facilitated the procedure, minimizing the possibility of contamination with oropharynx bacteria [19] and so reducing the rate of false-positives [17].

A comprehensive meta-analysis has evaluated the accuracy of different diagnostic tests for *Hp* infection in PUB, proving the superiority of UBT over biopsy-based methods [7]; however, the analysis is based on studies that compared different tests obtained at the moment of the bleeding episode, without a reference or "gold standard" delayed test once the bleeding episode had resolved. Also, UBT accuracy determination was not the aim of most of the reviewed studies [17, 20–26].

Another regressive meta-analysis including 8,496 patients has shown that the most significant variable associated with a high prevalence of *Hp* infection in PUB is the use of a delayed diagnostic test [8]; however, accuracy of every single type of test was not evaluated and only

Table 2 Epidemiological, clinical, and endoscopic characteristics of the studied patients (quantitative variables) ($n = 53$)

	n	Minimum	Maximum	Mean	St. deviation
Age (years)	53	24	90	57.85	15.841
Time from symptom to admission (h)	53	2	336	40.30	53.804
Time from admission to gastroscopy (h)	53	1	72	19.79	17.576
Systolic blood pressure (mm/Hg)	53	78	155	124.45	18.513
Diastolic blood pressure (mm/Hg)	53	41	102	72.45	12.834
Cardiac frequency (bpm)	53	60	133	92.47	17.343
Hemoglobin (g/dl)	53	7.3	16.4	10.94	2.691
Urea (mg/dl)	53	18	206	67.30	38.734

eight out of 71 studies included a delayed test. The authors comment that the results are only observational and that more studies like the one we have conducted are needed [8].

Our patients showed a prevalence of *Hp* infection of 83%, taking as the gold standard the delayed UBT. This prevalence is somewhat higher than 70–72% obtained in two meta-analyses in a bleeding population [7, 8] although similar to that obtained from some studies included in these meta-analyses (32–100%) and also very similar to that published in our country by some experts [8, 27]. If we include for prevalence determination the 17 patients with no delayed UBT but who had an invasive test performed at endoscopy, prevalence drops to 77.4%; this fact could be explained by the high rate of false-negatives for invasive tests in the setting of a bleeding patient [7].

Sensitivity for early UBT was 86.3%, which is lower than previously reported in two large meta-analyses in PUB [7, 16], but within the same range as published in some of the studies included in this meta-analysis [20–26]; sensitivity for early UBT was higher to 78% reported for UBT in patients taking PPIs [28]. Tobacco or recent presence of blood or foods in stomach could have influenced this result in our patients [16] as well as PPIs from admission to endoscopy (it is accepted that UBT has a sensitivity higher than 90% when done in patients withouth PUB).

The specificity found in our study for early UBT was 66.6%, which is lower than that previously reported (78–100%) [16, 20–26, 29]. An explanation for this somewhat lower specificity could be the urease activity in oropharyngeal bacteria [17, 19], which could have been swept down to the stomach at endoscopy or even due to the oxygen flow, as well as the occurrence of some borderline results very close to the selected cut-off value [30] or maybe differences in sample collection between the early and the delayed UBT; however, all samples were collected by a physician either at the moment of endoscopy or at the outpatient clinic, and changes in the cut-off value would be expected to have little effect on clinical accuracy of the test [31]. Some studies have also reported high false-positive rates for UBT in non-bleeding patients in some specific settings [32]. We are aware of this limitation of our study, although other authors have found this unexpected false-positive rate and low specificity [33]. Technical aspects in the procedure like pretreatment with citric acid should be improved in order to increase these suboptimal results [34]. Taking into account the mild severity of side-effects related to eradication therapy [35], it could be rational to perform early UBT at endoscopy and eradicate all positive patients, as empiric therapy in PUB is no longer recommended in developed countries [36] (although in countries with a very high prevalence of *Hp*, empiric therapy could be an option in terms of cost-effectiveness).

Positive predictive value was 92.8% in our study, which is similar to or higher than that found in other studies [7, 16, 37]. This result encourages us to recommend early UBT in PUB as invasive tests have a low sensitivity [29] in this group of patients and can be hazardous (for example in patients under anticoagulant therapy). The unacceptable negative predictive value found for UBT in our study highlights the importance of confirming all negative results using additional tests if possible or in a delayed manner, as it has been proposed by some authors for invasive tests [4, 7, 35, 38].

However, we have not found any clinical or epidemiological situation that could modify the accuracy of early UBT in relation to delayed UBT. It has been proposed that PPI therapy lowers the sensitivity of UBT [39, 40]; our data show, as it has been proved for invasive tests [41], that short courses of acid suppressive therapy, as we used while the patient was hospitalized, do not alter the performance of UBT. The presence of blood in the stomach, which is a limiting factor for invasive tests [34, 42], does not seem to affect UBT accuracy either, as some authors say [43]. Unlike other studies [8], we did not find that age made any impact in UBT accuracy. Gender, ulcer location, or NSAID therapy also did not modify the results, as it has been previously reported [8, 27].

We are aware of some of the limitations of our study, as the sample size and lack of control group (UBT after emergency endoscopy in patients without PUB, but this was not accepted by the ethics committee). The low number of *Hp*-negative patients is also a limitation of our study but we think this fact only reflects the high rates of infection in a Spanish population [44]. We did not include patients with hemodynamic instability because we think that carrying out UBT in these patients would have been difficult, even though we are aware that excluding these patients could reduce the impact of the study. The fact that we used no sedation or mild sedation was crucial for the correct realization of the test by the patient.

Although we have included the 17 patients without a delayed UBT but with an invasive test, comparing different diagnostic methods was not the aim of our study. We are aware that determination of *Hp* status should be assessed by at least two different methods in clinical trials, although invasive tests are not always possible in bleeding patients (needing a quick endoscopy or with coagulopathies in some cases) and it is assumed the importance of a delayed test as gold standard for clinical practice [8], as we did. In any case, it is recommended to perform invasive tests if possible [36].

It is important to note that in 28.3% of the patients, a delayed UBT could not be obtained (although in half of them it was because of being treated previously due to positive invasive test); this fact emphasizes the value of an

early diagnosis for *Hp* infection whatever the test used because some patients will never attend to the follow-up visit and could be diagnosed and treated correctly before hospital discharge.

In conclusion, this study shows that early UBT carried out right after emergency endoscopy in PUB is an effective, safe, and easy-to-perform procedure. The accuracy of the test is not modified by clinical or epidemiological factors, ulcer stage, or by the type of therapy applied. This approach can allow early diagnosis and it could be cost-effective, reducing the number of follow-up visits; also, patients who will never attend the follow-up visit could be diagnosed and treated correctly before hospital discharge. However, we have found a low negative predictive value for early UBT, so a delayed test is mandatory for all negative cases, as it is recommended by the International Consensus on Non-Variceal Upper Gastrointestinal Bleeding.

Conflict of interest None.

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