Methodological Validation and Clinical Usefulness of Carbon-14-Urea Breath Test for Documentation of Presence and Eradication of *Helicobacter pylori* Infection

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A simple [^{14}C]urea breath test (C-14-UBT) was validated with aims of determining accuracy in documenting both the presence and proof of eradication of *Helicobacter pylori* infection. **Methods:** Fifty-six dyspeptic patients had endoscopy with biopsies and C-14-UBT. Eleven biopsy-proven *H. pylori*-negative patients allowed C-14-UBT normal value determination. Forty-three patients with recurrent peptic ulcer disease and biopsy-proven *H. pylori* infection were included in an antimicrobial eradication protocol. Endoscopy with biopsies and C-14-UBT were done again 8 wk after initiation of treatment in 35 patients. For C-14-UBT, 185 kBq (5 μCi) of [^{14}C]urea was swallowed. Breath samples obtained up to 20 min were counted to calculate AS_{20}, [(% $^{14}CO_2$ dose excreted/mmol of CO_2) × kg] at 20 min. Combined histologic and microbiologic analyses of antral biopsies were used as a gold standard. **Results:** The positivity value was set as $AS_{20} > 0.33\%$ (mean + 3 s.d. of AS_{20} in *H. pylori*-negative patients). Diagnosis of *H. pylori* infection was correct with C-14-UBT in 55/56 patients (44 true-positive, 11 true-negative and 1 false-negative; sensitivity = 98%; specificity = 100%). As a proof of eradication, C-14-UBT correctly classified 33/35 patients (5 true-positive, 28 true-negative and 2 false-positive; sensitivity = 100%; specificity = 93%). The C-14-UBT global performance yielded sensitivity, specificity and accuracy of 98%, 95% and 97%, respectively. A significant correlation ($r = 0.84$) was found between AS_{20} and the number of *H. pylori* colonies on culture. **Conclusion:** This C-14-UBT is highly accurate both for diagnosis and proof of eradication of *H. pylori* infection and reflects the antral bacterial load. It is simple, fast and inexpensive, and it is therefore suitable for clinical practice.

Key Words: *Helicobacter pylori*; urea breath test; carbon-urea; peptic ulcer disease; gastritis

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Helicobacter pylori was first identified and isolated by Marshall in 1983 (*1*). It is a gram-negative, urease-producing spiraled rod that has since been proven to be responsible for type B chronic antral gastritis (*2–8*). *H. pylori* infection is now known to be the main cause of peptic ulcer disease and has been associated with atrophic gastritis, gastric carcinoma and nonulcer dyspepsia (*2–7*). Recent studies have showed presence of *H. pylori* in more than 95% of duodenal ulcers and in 80%–95% of gastric ulcers not associated with nonsteroidal anti-inflammatory drugs (*2–4,6*). The importance of *H. pylori* in the clinical setting is related to ulcer recurrence. After 1 yr, between 55% and 90% of ulcers recur when treated with anti-H2 therapy only, whereas the recurrence rate is only 10%–15% when a triple antibiotic regimen against *H. pylori* is added (*3,6*). The Consensus Development Conference of the National Institutes of Health (*9*) recommended that all patients with peptic ulcers who are infected with *H. pylori* receive antimicrobial therapy. *H. pylori* status determination has hence become a necessary tool to guide the therapy of peptic ulcer disease.

Diagnosis of *H. pylori* infection can be reliably achieved during endoscopy by histologic analysis or culture of biopsy specimens (*10–12*). The unique urease-producing capability of these bacteria has also been used to detect them through urease testing of endoscopic biopsies. However, these procedures that require endoscopy were invasive, and simpler means of detection were sought. While serology (ELISA) is simple, it cannot differentiate active from remote infection, nor can it quickly document *H. pylori* eradication after treatment (*3,6,10*). Urea breath testing was suggested as a promising noninvasive alternative for these purposes (*10,13–21*). If *H. pylori* is present in the stomach, its urease will hydrolyze urea labeled with carbon-13 or carbon-14 isotopes. The labeled $H^*CO_3^-$ will be absorbed in the stomach and will diffuse in blood to be excreted by the lungs as $^*CO_2$ that can be collected in breath samples. While both isotopes seem to offer similar diagnostic accuracy, the ^{13}C-urea breath test has the potential inconvenience of requiring more complex equipment, and it is more expensive. In addition, it usually requires the administration of a test meal and cold urea to the patient. This is not necessary with carbon-14, and the test is thus simpler, faster and more likely to achieve clinical acceptance.

This paper describes the use of a simple and quantitative ^{14}C-urea breath test (C-14-UBT) in our institution. The aims of this study were: (a) to present a methodological validation of the test and determine normal values; (b) to determine its accuracy for detection of *H. pylori* infection; (c) to determine its accuracy as a proof of *H. pylori* eradication after therapy; (d) to determine global performance of the test and (e) to show the ability of the test to provide a semiquantitative evaluation of the antral bacterial load.

MATERIALS AND METHODS

Patients

For the methodological validation part of the study, 56 referred patients with persistent dyspepsia were recruited. After informed consent was obtained, all underwent upper gastrointestinal endoscopy with antral biopsies as well as a ^{14}C-urea breath test within 1 wk. *H. pylori* status was determined as described in the following section, and the results of ^{14}C-urea breath tests were then analyzed against this gold standard in order to determine a cutoff value of

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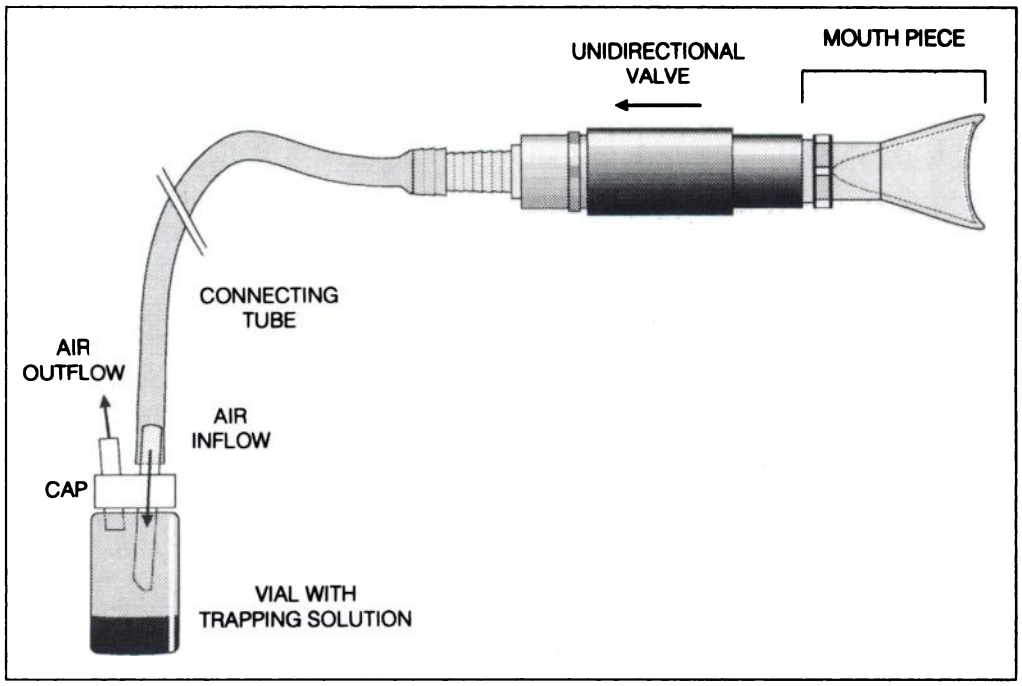

FIGURE 1. Apparatus for the ^{14}C-urea breath test. A disposable mouthpiece and unidirectional valve are linked to a connecting tube to a hole in the cap of a scintillation vial into which another hole is pierced to allow air to be expelled. Vials with CO_2 trapping solution are successively attached to this cap.

positivity. Evaluation of the accuracy of the ^{14}C-urea breath test for detection of *H. pylori* infection was then performed.

Of the 56 patients, all those shown to be *H. pylori*-positive by analysis of antral biopsies performed during the upper gastrointestinal endoscopy and known to have had at least one episode of ulcers in the past were recruited for a *H. pylori* eradication protocol. Forty-three patients were thus randomized to one of three therapeutic regimens against *H. pylori* (*22*). Thirty-five patients had both an upper gastrointestinal endoscopy and a ^{14}C-urea breath test done 8 wk after initiation of the 2-wk therapy against *H. pylori*. Using the same cutoff value of positivity as above, these patients allowed evaluation of the performance of the ^{14}C-urea breath test as a proof of eradication of *H. pylori* infection.

The global performance of our ^{14}C-urea breath test (i.e., for diagnosis and eradication) was also assessed by analyzing the 91 breath tests performed on the 56 patients. Finally, 48 of these patients who had antral biopsies and cultures for *H. pylori* were used to show the ability of our ^{14}C-urea breath test to provide a semiquantitative evaluation of the antral bacterial load. This was achieved by comparing the breath $^{14}CO_2$ specific activity with a semiquantitative evaluation (0–3+) of the number of *H. pylori* colonies on a culture plate.

Helicobacter pylori Status Determination

Upper Gastrointestinal Endoscopy. During the standard upper gastrointestinal endoscopy, three or four antral biopsies were obtained within 5 cm of the pylorus. Two were sent to pathology in formalin, one was sent to microbiology in an Eppendorf® microfuge tube containing one drop of saline, and another (if available) was used for rapid urease testing (CLOtest®).

Pathology. Tissue sections were stained with the Hematoxylin–Phloxin–Safran technique. If needed, an additional argentaffin stain (Dieterle) was used in cases not obviously positive with the Hematoxylin–Phloxin–Safran technique. All specimens were reviewed by the same experienced gastrointestinal pathologist and analyzed for presence of chronic active gastritis and histologic identification of *H. pylori*.

Microbiology. Biopsy specimens were inoculated within the same working day over the surface of an agar supplemented with a Skirrow selective supplement and on an *H. pylori* medium (*23*). All agars were incubated at 35°C under microaerophilic conditions. Readings were done at 3 and 7 days. The bacterial load was assessed semiquantitatively as 0 (no growth), 1+, 2+ or 3+, according to an estimate of the number of colonies on culture plate.

Our criteria for *H. pylori* positivity required the presence of at least one of the following: (a) histologic identification of *H. pylori* or (b) microbiologic evidence of *H. pylori* on culture. A patient was considered *H. pylori*-negative when both criteria were absent. These criteria we used are recognized in the literature as the gold standard for *H. pylori* status determination.

Carbon-14-Urea Breath Test

Materials. The apparatus is described in Figure 1 and consists of a 30-cm flexible plastic tube with, at one end, a mouthpiece connected to a unidirectional valve preventing any accidental aspiration of the trapping solution. The other end has an adapter linking the tube to a hole in the cap of a scintillation vial into which another hole is pierced to allow air to be expelled when patients breathe. The cap end allows vials to be attached for CO_2 trapping. Each 25-ml vial contains 4 ml of benzethonium hydroxide (0.5 mmol/ml) in pure ethanol with 100 μl of thymolphthalein (0.05%). This bluish solution turns colorless when 2 mmol of CO_2 are trapped in it. Four vials labeled T0, T5, T10 and T20 were initially used for patients in our protocol (0-, 5-, 10- and 20-min breath samples). Carbon-14-urea is supplied as a freeze-dried solid, sealed under nitrogen in a borosilicate vial containing 9.25 MBq (250 μCi). This is dissolved in 50 ml of ethanol and stored in a refrigerator. Each patient dose of 185 kBq (5 μCi) is obtained by pipetting 1 ml of the solution (185 kBq/ml). The three standard vials, each containing 18.5 kBq (0.5 μCi), are obtained by pipetting 0.1 ml. Each vial requires the addition of 15 ml of liquid scintillator after the CO_2 collection, to allow beta scintillation counting in an adequately calibrated instrument with quench correction.

Patient Preparation. For every patient, weight and medications were recorded. Antacids and anti-H2s were stopped at least 12 hr before the test while antibiotics and bismuth were stopped for 1 mo. History of gastric or abdominal surgery was noted. Patients were asked to fast for at least 4 hr. Then, they were asked to rinse their mouth and gargle twice with water, which they then spit out. The test was explained and patients practiced by breathing until there was a color change in T0, which served as background. Ingestion of ^{14}C-urea then followed. The patients swallowed 25 ml

of water containing 185 kBq (5 μCi) of ^{14}C-urea, as fast as possible with a straw, followed by another 25 ml of water. The test then proceeded with breath collections in vials labeled T5, T10 and T20.

Determination of $^{14}CO_2$ Specific Activity at a Given Time (AS_{time}). Each of the four vials filled with 15 ml of liquid scintillator was counted once for 20 min. The equation providing the percentage of the $^{14}CO_2$ dose excreted per mmol of CO_2 collected in a vial at a given time and corrected for the patient's weight is:

$$AS_{time} = (\%\ ^{14}CO_2 \text{ dose excreted/mmol of } CO_2) \times \text{kg}$$

$$= \frac{\text{net dpm sample } T_{time}}{\text{dpm standard} \times 10} \times \frac{\text{weight (kg)}}{2 \text{ mmol of } CO_2} \times 100,$$

where dpm sample T_{time} = counts from sample at T_{time} (time = 5, 10 and 20 min); dpm sample T0 = counts from sample at time 0 (beginning; background); net dpm sample T_{time} = dpm sample T_{time} − dpm sample T0; dpm standard = average of counts from three standard vials; 10 = multiplication factor to correct for 1:10 dilution of standard; and 2 mmol of CO_2 = quantity of CO_2 collected in each vial.

The AS_{time} value has theoretical advantages over reporting a dpm value. First, it is less likely to be affected by small variations in the dose given to patients. Second, considering that the basal metabolic excretion of CO_2 in man is 9 mmol/kg/hr, a heavier patient would exhale more CO_2 for a same quantity of $^{14}CO_2$, i.e., a lower specific activity. By providing correction for patient weight, the AS_{time} value can allow a semiquantitavive estimation of *H. pylori* urease activity. After beta scintillation counting, calculations can be done readily, and results can be made available the same day the test was performed.

Dosimetry. Dosimetry for the ^{14}C-urea breath test was described elsewhere (*24,25*) and is negligible, giving 0.10–0.20 μGy/kBq (0.38–0.69 rad/mCi) to the bladder wall and an effective dose equivalent of 38–80 μSv/MBq (0.14–0.30 mrem/μCi). For 185 kBq (5 μCi), this represents 30–40 μGy (3–4 mrad) to the bladder wall and an effective dose equivalent of 7–15 μSv (0.7–1.5 mrem).

Statistical Analysis

The cutoff value for the ^{14}C-urea breath test was set as the mean + 3 s.d. of AS_{time} in *H. pylori*-negative patients. The usual calculations of sensitivity, specificity, positive predictive value, negative predictive value and accuracy were then performed. To assess correlation between variables for the semiquantitative evaluation of the antral bacterial load, the Spearman regression analysis method was used. The 95% confidence intervals (95% CI) were also calculated for the above values.

RESULTS

Methodological Validation of Carbon-14-Urea Breath Test

The preliminary evaluation of data collected in the first part of the study with 56 dyspeptic patients who had endoscopy and a ^{14}C-urea breath test revealed that samples obtained at 5 and 10 min were not giving any additional information when compared to 20-min samples. Data analysis was then performed only on 20-min samples with calculation of AS_{20}. Forty-five patients were classified as *H. pylori*-positive and 11 patients were *H. pylori*-negative. For the *H. pylori*-negative group, statistics on AS_{20} showed a mean value of 0.125% with a 0.069% s.d. The cutoff value for the ^{14}C-urea breath test was determined to be the mean + 3 s.d. of AS_{20} in *H. pylori*-negative patients. A negative ^{14}C-urea breath test thus corresponded to a value of AS_{20} less than 0.33%. Figure 2 shows the AS_{20} scattergram in the 56 patients and demonstrates the excellent discrimination achieved with a 0.33% cutoff. As shown in Table 1, this cutoff

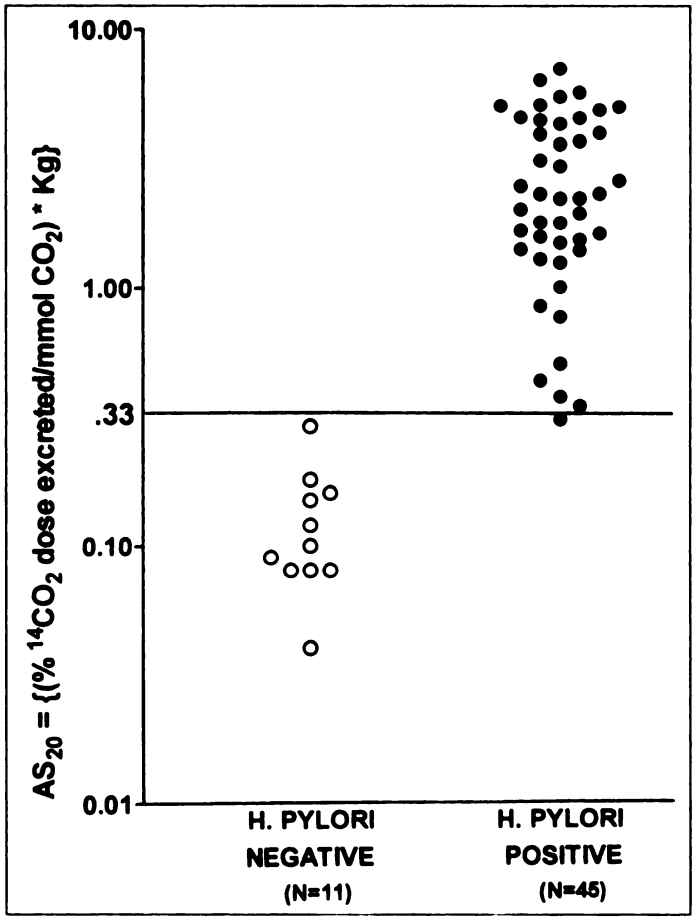

FIGURE 2. Scattergram of values of AS_{20} = [(% $^{14}CO_2$ dose excreted/mmol of CO_2) × kg] for *H. pylori*-negative and *H. pylori*-positive patients, as determined by combination of histologic and microbiologic criteria in 56 patients. Cutoff value was set as 0.33%.

allowed correct classification of patients as *H. pylori*-positive or *H. pylori*-negative in 55 of the 56 patients, with only one false-negative. To detect *H. pylori* infection, the sensitivity of the test was 44/45 = 98% (CI 95%, 94%–100%) and specificity was 11/11 = 100% (95% CI, 94%–100%). The positive predictive value was 100% (95% CI, 97%–100%) while the negative predictive value was 92% (95% CI, 76%–100%); the accuracy was 98%. It is true that a receiver operating characteristic analysis would have allowed a perfect discrimination of *H. pylori*-positive and -negative patients with a 0.30% value of AS_{20}. Nevertheless, we preferred to choose a 0.33% cutoff value, knowing there had been preparation and technical problems in the sole false-negative patient we obtained with this cutoff value (see Discussion).

H. pylori Eradication Protocol

Of the 43 patients randomized in our eradication protocol, 35 patients were submitted to a post-treatment urea breath test and upper gastrointestinal endoscopy with biopsies. Of those 35 patients, 28 patients with negative urea breath test all had eradication of *H. pylori* (true-negatives). Of the seven patients with a positive urea breath test, five were still infected with *H.*

TABLE 1
Diagnostic Performance of Carbon-14-Urea Breath Test

Breath test	*H. pylori*-positive	*H. pylori*-negative	Total
Positive	44	0	44
Negative	1	11	12
Total	45	11	56

TABLE 2
Performance of the Carbon-14-Urea Breath Test as Proof of *H. pylori* Eradication

Breath test	*H. pylori*-positive	*H. pylori*-negative	Total
Positive	5	2	7
Negative	0	28	28
Total	5	30	35

pylori (true-positives), and two patients did not present any residual infection on endoscopy (false-positives). Table 2 summarizes the results obtained when the urea breath test was used as a proof of *H. pylori* eradication after antibiotic treatment. In this setting, our ^{14}C-urea breath test presents a sensitivity of 100% (95% CI, 91%–100%), a specificity of 93% (95% CI, 84%–100%), a positive predictive value of 71% (95% CI, 37%–98%), a negative predictive value of 100% (95% CI, 96%–100%) and a 94% accuracy.

Global Performance of the ^{14}C-urea breath test

Table 3 provides the performance obtained by analysis of 91 breath tests in the 56 patients. Globally, our ^{14}C-urea breath test offered a sensitivity of 49/50 = 98% (95% CI, 94%–100%) and a specificity of 39/41 = 95% (95% CI, 88%–100%). With a 55% prevalence of disease, the positive predictive value was 96% (95% CI, 90%–100%), the negative predictive value was 98% (95% CI, 93%–100%) and accuracy was 97%.

Semiquantitative Evaluation of the Antral Bacterial Load

Figure 3 presents the comparison between the value of AS_{20} and the semiquantitative evaluation of the number of *H. pylori* colonies on culture on 48 antral biopsies performed with the same instrument. Regression analysis with the Spearman method demonstrated a very significant correlation (r = 0.84, 95% CI, 0.72–0.91). Our ^{14}C-urea breath test thus provides an estimation of the antral bacterial load.

DISCUSSION

The relative merits of the various modalities to diagnose *H. pylori* infection have been discussed (*10,11,18*). Many reports are now available to support the value of the urea breath tests with either ^{13}C or ^{14}C as a noninvasive means of documenting both the presence and eradication of *H. pylori* infection (*13–18,20,21,26–30*). It is also increasingly recognized now that the urea breath test will become the preferred method for the assessment of the success of antibiotic therapy against *H. pylori* infection (*6,18*). Studies have already documented the excellent prognostic value of a negative urea breath test post-treatment, with reinfection rates of 0.44%–2.2% per yr (*6,31,32*). Our results further confirm the utility of a simplified ^{14}C-urea breath test in *H. pylori* infection. In this study, performance of our urea breath test was high both for diagnosis of *H. pylori* infection and for documentation of *H. pylori* eradication. Globally, the accuracy of our urea breath test was remarkable, with a 98% sensitivity and a 95% specificity. Our protocol thus compares favorably with others (both with carbon-13 and carbon-14) published so far showing a sensitivity of 90%–100% and a specificity of 78%–100% (*10,11,18*).

TABLE 3
Global Performance of the Carbon-14-Urea Breath Test

Breath test	*H. pylori*-positive	*H. pylori*-negative	Total
Positive	49	2	51
Negative	1	39	40
Total	50	41	91

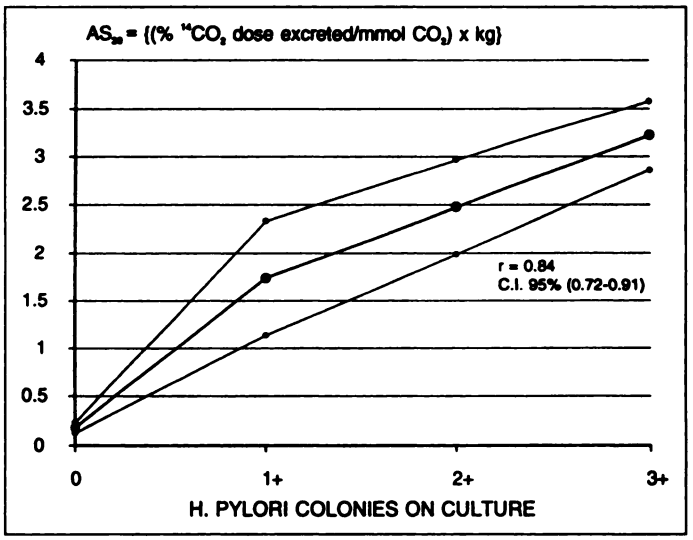

FIGURE 3. Values of AS_{20} = [(% $^{14}CO_2$ dose excreted/mmol of CO_2) × kg], expressed as mean ± s.d., as compared to a semiquantitative evaluation of the number of *H. pylori* colonies on culture.

Our ^{14}C-urea breath test protocol is interesting because of its simplicity. First, it does not require any special oral preparation like brushing teeth or antiseptic mouthwashing; it only requires gargling with water. Second, there is no need for test meal and/or cold urea administration, as usually required with ^{13}C-urea breath test. Third, only two breath samples need to be taken, one at T0 (background) and the other at T20. This compares favorably with multiple breath samples up to 60–120 min with some ^{13}C-urea breath tests (*18*). Fourth, ^{14}C-urea is inexpensive and is detected by liquid scintillation counting, which is already available in most hospitals (costs: $13 Canadian per patient for ^{14}C-urea, other reagents and disposable materials). Carbon-13-urea is expensive and traditionally requires analysis by isotope ratio mass spectrometry, an expensive apparatus with limited availability. These advantages of carbon-14 over carbon-13 largely compensate for the negligible radiation burden of 185 kBq (5 μCi) of ^{14}C-urea, which is approximately 50–100 times less than an upper gastrointestinal series (*16*).

In our protocol, we chose to show results as AS_{20}, although expressing results as raw dpm was shown to lead to approximately the same sensitivity and specificity for detection of *H. pylori* infection (*16*). AS_{20} can be calculated in less than 1 min and presents theoretical advantages (see Materials and Methods). This value correlated well with a semiquantitative evaluation of the antral bacterial load on culture in our study. Studies have also demonstrated a similar correlation with the severity and activity of the gastritis (*19*).

In our study, one infected patient had a false-negative urea breath test before antibiotic treatment with AS_{20} of 0.31%. For him, there was a small loss of liquid from the vial at the end of the breath sampling, and he had been on omeprazole for more than 3 wk until 12 hr before the test. At least one recent paper reported bacteriostatic and/or bactericidal effects of this medication against *H. pylori* (*33*). These two factors probably contributed to decrease the AS_{20} slightly below the cutoff value. Another patient with a history of partial gastrectomy and vagotomy had a false-positive urea breath test with AS_{20} of 0.43% after antibiotic treatment. It must be remembered that up to 3% of antral biopsy specimens are known to be false-negative when compared to urea breath test and serology (*34*). Moreover, patients with gastric surgery often have accelerated gastric emptying, and this could lead to the metabolism of urea

by urease-producing bacteria found in intestinal flora, thus falsely increasing AS_{20}. The last patient was also a false-positive after antibiotic treatment (AS_{20} = 1.44%) and was still significantly symptomatic. The discrepancy here could be related to the antro-fundal migration of *H. pylori* infection reported during treatment (*33*); antral biopsies would be negative, and the urea breath test would reflect the bacterial load now located in the fundus (*34*). Hence, in this case, it is very likely that the urea breath test is a true-positive and that the antral biopsy is falsely negative.

Adequate patient preparation is important to get accurate results with the ^{14}C-urea breath test. Antacids should be stopped for at least 12 hr (*35*). Antibiotics and bismuth should be stopped at least 4 wk before a diagnostic urea breath test and at least 4–6 wk before documenting eradication of infection. Since omeprazole and sulfasalazine are now known to cause a decrease in the bacterial load (*33,36*), it seems advisable to stop them before urea breath testing although the duration of abstinence is not well-documented yet.

CONCLUSION

This paper presented the methodological validation of a simple ^{14}C-urea breath test protocol and its role in documenting the presence and eradication of *H. pylori* infection. Our ^{14}C-urea breath test protocol, like others, is highly accurate both for diagnosis and for proof of eradication of *H. pylori* infection and provides a semiquantitative evaluation of the antral bacterial load. Our ^{14}C-urea breath test is simple, fast and inexpensive, and its radiation burden is negligible; it is therefore suitable for clinical practice.

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