Breath Test Diagnosis of *Helicobacter pylori* in Peptic Ulcer Disease: A Noninvasive Primary Care Option

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Background: **Helicobacter pylori is implicated as the causative agent for most duodenal and gastric ulcers. Invasive (endoscopy and biopsy) and noninvasive (serology, breath test) methods are currently available for definitive diagnosis of infectious peptic ulcer disease.**

Methods: **Twenty-six patients with chronic gastritis symptoms underwent upper endoscopy, biopsy, rapid urease test, and [^{14}C]urea breath test for the detection of *H pylori*.**

Results: **Twenty of 26 patients (77 percent) had biopsy-proved *H pylori* infection. All 20 (100 percent) with definite *H pylori* proved by invasive diagnosis had strongly positive results on urea breath test. Six patients with absence of *H pylori* on biopsy had negative urea breath test results. The urea breath test displayed 100 percent sensitivity, specificity, and predictive value compared with endoscopy and biopsy.**

Conclusions: **[^{14}C]Urea breath testing is comparable to endoscopy and biopsy in the diagnosis of *H pylori* infection and could become useful in primary care settings for noninvasive evaluation of peptic ulcer disease. (J Am Board Fam Pract 1997;10:385-9.)**

A dramatic transformation in the understanding and treatment of peptic ulcer disease occurred during the past decade with discovery of the pivotal contribution of *Helicobacter pylori* to antral gastritis, gastric ulceration, duodenal ulceration, and ulcer recurrence.[1] The methods of diagnosing *H pylori* infection are numerous, as indicated by several recent clinical reviews.[2-6] Endoscopy is a central diagnostic method in all studies. With the introduction of a new nuclear medicine test suitable for the primary care setting, the noninvasive diagnosis and management of peptic ulcer disease might soon undergo considerable change as well.

A novel diagnostic radiopharmaceutical, urea labeled with radioactive carbon (^{14}C), shows promise as a noninvasive tool for detecting *H pylori* in humans. Previously, endoscopy was a frequent initial step in the detection of peptic ulcer disease and, coupled with biopsy, was considered essential for diagnosis of *H pylori* infection. This procedure, however, is invasive, expensive, and often dependent on referral to a specialist. Recent studies have emphasized the emerging role of the [^{14}C]urea breath test as a safe, precise, cost-effective, and easily performed outpatient diagnostic test.[7-12]

Marshall and Warren[13] were the first investigators to associate gastritis and peptic ulceration with a curved urease-producing organism identified as *Campylobacter pyloridis*. This organism, later reclassified as *H pylori*, is histologically detectable in most patients with active chronic gastritis. Moreover, *H pylori* is found in gastric antral biopsies in 90 to 95 percent of patients with visible duodenal ulcer and 65 to 80 percent of those with gastric ulcer.[14-16] Eradication of *H pylori* is also strongly linked to ulcer healing and prevention of ulcer recurrence.[17,18] Although gastric acid has long been recognized as one of many factors in the pathogenesis of ulcers, the causative evidence linking *H pylori* to ulceration is now compelling enough to regard duodenal and gastric ulcers as infectious diseases in the vast majority of cases.[19] Notable exceptions are patients with nonsteroidal anti-inflammatory drug (NSAID)-induced ulceration or Zollinger-Ellison syndrome.

A particular biochemical property of *H pylori* facilitates the use of the [^{14}C]urea breath test to

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diagnose the presence of the organism in gastric or duodenal mucosa. This microbe produces relatively high concentrations of urease, an enzyme that hydrolyzes urea into the alkaline buffers ammonium and bicarbonate.

$$\underset{\text{Urea}}{CO(NH_2)_2} + H_2O + H^+ \xrightarrow{\text{Urease}} \underset{\text{Ammonium}}{2NH_4^+} + \underset{\text{Bicarbonate}}{HCO_3^-}$$

Bicarbonate generated in gastric mucosa enters the blood stream, is transported to the lungs, and is rapidly excreted from the lungs as volatile carbon dioxide. In the [^{14}C]urea breath test, a capsule of urea tagged with radioactive carbon is administered orally to a patient; the patient's exhaled carbon dioxide is then collected in airtight balloons. Detection of elevated quantities of exhaled carbon dioxide tagged with carbon 14 ([^{14}C]O_2) indicates marked bacterial urease activity in the patient's stomach. Production of ammonium and bicarbonate could allow local buffering of highly acidic (pH 1.5) gastric secretions and confer on *H pylori* its unique microbiologic ability to survive in the hostile gastric lumen.[20] Vigorous urease activity, then, might be vital to the organism's ecologic niche, and the elevated [^{14}C]O_2 measurements of exhaled carbon dioxide labeled with carbon 14 from intense urea metabolism is a biologically plausible indirect measure of *H pylori* presence.

Methods

Carbon-14-labeled urea is supplied in a gelatin capsule containing 1 μCi (37 kBq) of the radiopharmaceutical. Before the breath test is administered, the patient must fast for 6 hours and refrain from ingesting antibiotics or bismuth salts for at least 4 weeks. The capsule, coated to prevent hydrolysis by oral flora, is swallowed with 30 mL of warm water to promote its dissolution in the stomach and release of [^{14}C]urea, a process that takes approximately 3 minutes. Radioactive carbon dioxide is usually detectable in the breath within 5 minutes, with peak excretion occurring between 10 and 15 minutes after capsule administration. Breath samples are obtained at 10, 15, and 20 minutes by having the patient exhale through a straw into a 1.5-L aluminized balloon. Carbon radioactivity is then counted in a liquid scintillation counter.

Under a study protocol approved by our institutional review board, 26 patients with symptoms underwent upper gastrointestinal endoscopy and biopsy in a nonblinded study of presumed peptic ulcer disease during a 20-month period. The group consisted of 14 men and 12 women; their mean age was 49.8 years (range, 24 to 82 years). Most were referred by primary care clinicians. Symptoms included postprandial epigastric pain, failure of acid suppression therapy, hematemesis, melena, and iron deficiency anemia determined by fecal occult blood testing. Each patient underwent endoscopic inspection, photography and biopsy of gastroduodenal mucosa, and the *Campylobacter*-like organism (CLO) test of gastric antral tissue specimens for bacterial urease. Hematoxylin and eosin and Giemsa stains of gastric antral mucosa were processed in the Medical College of Georgia Department of Pathology and reviewed by faculty pathologists. CLO tests were interpreted within 24 hours by the endoscopist who performed the biopsies. Serologic tests, while sensitive for *H pylori* infection, were not available for all patients and thus were not analyzed in this protocol. Patients were excluded from the study if they had ingested antibiotics or bismuth-containing drugs during the previous 28 days.

The [^{14}C]urea breath test was performed in our nuclear medicine outpatient clinic within 5 days of upper gastrointestinal endoscopy. We used specifications established by the manufacturer (Tri-Med Specialties, Charlottesville, Va) to interpret all breath samples. Samples were interpreted as negative if they contained fewer than 49 disintegrations per minute (dpm); indeterminate if 50 to 99 dpm; and positive if more than 100 dpm. Patients who had positive test results for *H pylori* were defined as those in whom characteristic curved bacteria were detected in the gastric mucus layer on Giemsa-stained antral histologic sections or who had a definite biochemical color reaction on the CLO rapid urease test.

Results

Seventeen (65 percent) of the 26 patients had endoscopic evidence of discrete ulceration: 11 with duodenal, 3 with gastric, and 3 with both gastric and duodenal ulcers. Fourteen with discrete ulcers had histologic evidence of *H pylori* on antral biopsy; in the other three cases, histologic examination was deferred as a result of a strongly

positive CLO test. Three additional patients (12 percent) had no visible ulceration but did have histologic evidence of active chronic gastritis on antral biopsy, *H pylori* organisms on Giemsa stain, and positive CLO test results. Of the 20 patients determined to have *H pylori* infection, 19 had positive CLO test results for rapid urease activity. One patient had duodenal ulceration and visible *H pylori* organisms on biopsy, but that patient's CLO test results were negative. In all 20 patients with evidence of *H pylori* infection, the [^{14}C]urea breath test had strongly positive results (more than 100 dpm), with counts in 15-minute exhaled samples averaging 1868 dpm (range: 345 to 2976 dpm).

Six (23 percent) of the 26 patients had no ulcer on endoscopy, normal antral histologic findings, absence of *H pylori* on Giemsa-stained sections, and negative CLO test results. Five had negative (fewer than 49 dpm) [^{14}C]urea breath test results. One case was indeterminate with 66, 97, and 93 dpm at 10, 15, and 20 minutes, respectively, and was regarded not to have *H pylori* infection. For the 6 patients who did not have *H pylori* infection, the average [^{14}C]urea breath test reading was 33 dpm.

All patients with evidence of *H pylori* infection were given prescriptions for a combination of antibiotics and bismuth subsalicylate, according to published recommendations, for at least 10 days.[21] Proton-pump inhibitors and histamine-2 blockers were prescribed infrequently and at the discretion of personal physicians. Of the 20 patients found to have positive breath test results before treatment, 7 underwent repeat testing 2 months after treatment was concluded. All 7 had negative (fewer than 49 dpm) breath test results on follow-up examination, and their ulcer symptoms were in remission. To date, no ulcer relapse has been documented by symptoms or esophagogastroduodenoscopy in these 7 patients for a mean follow-up time of approximately 17 months per patient. The other 13 patients with initially positive [^{14}C]urea breath test results had symptomatic improvement with antibiotic therapy and were not referred for retesting by their personal physicians. Serologic follow-up was not systematically obtained in any of our cohort.

We observed a disease prevalence of 77 percent (20 of 26) in our series. The [^{14}C]urea breath test is strongly associated with the reference standard for *H pylori* diagnosis by biopsy or the CLO test ($P < 0.0001$, Fisher exact test), showing an estimated sensitivity of 20 of 20 (100 percent; 95 percent confidence interval[CI]: 83.2 to 100.0) and specificity of 6 of 6 (100 percent; 95 percent CI: 54.1 to 100.0). The [^{14}C]urea breath test showed no diagnostic errors in this sample; thus, both positive and negative predictive values are 100 percent.

Discussion

In our series of patients with chronic gastritis symptoms and definite *H pylori* infection, the [^{14}C]urea breath test proved a simple and reliable method for documenting the presence of the organism in association with frank ulceration (17 patients) and active chronic gastritis (3 patients). Assuming that the reference standard of endoscopy and biopsy is 100 percent sensitive, then the [^{14}C]urea breath test, at least in our cohort, was 100 percent sensitive as well. Conversely, in the 6 patients who had no endoscopic ulceration and no evidence of gastritis or *H pylori* infection on biopsy, [^{14}C]urea breath test results were negative in all six cases. Specificity, then, would be 100 percent. Both positive and negative predictive values are likewise quite high in our cohort.

Such high sensitivity, specificity, and predictive values for a single test are unusual in clinical settings and might, at first glance, seem too good to be true. Yet *H pylori* status was carefully characterized clinically and by tissue diagnosis for all our cases. [^{14}C]Urea breath test performance procedures were meticulously observed. Patients whose test results were positive for *H pylori* had breath samples that had 60-fold higher average disintegrations per minute than those with negative results (1868 vs 33 dpm, respectively). Other investigators have also found extremely high (90 to 100 percent) sensitivity and specificity of the [^{14}C]urea breath test in larger series of patients at other institutions.[11,12,22,23] We believe the [^{14}C]urea breath test has an accuracy equal to endoscopy and biopsy in detection of symptomatic *H pylori* infection. The main limitation of our study is its small sample size; therefore, high predictive values might not apply to all ulcer patients seen in a diverse primary care setting or among dyspeptic primary care patients less rigorously selected than our cohort.

In the 7 patients undergoing a repeated [^{14}C]urea breath test after treatment for definite *H pylori* infection, the reversion to negative results in all 7 breath tests suggests successful eradi-

cation of the organism and predicts long-term remission. We observed no ulcer relapse for an average follow-up period of 17 months in this cohort. Longer periods of follow-up will be required to determine whether the predictive values of once-positive, now-negative [^{14}C]urea breath test results are significant or durable in our subset of patients.[17]

Carbon 14 is a naturally occurring isotope that is continuously formed in the earth's atmosphere. The 1-μCi dose administered in the [^{14}C]urea breath test is similar to the whole body dose received from natural background sources during an 11-hour period (0.3 mrem).[24] This low radiation dose is far less than the exposure received from mammography, intravenous pyelogram, computed tomography scanning, and upper gastrointestinal tract series and is not likely to confer any serious risk to patients with peptic ulcer disease. The usefulness of the [^{14}C]urea breath test in children and pregnant women needs further evaluation.

Our results show that a new noninvasive modality using [^{14}C]urea appears to be reliable for diagnosis of *H pylori* infection in symptomatic patients who have duodenal or gastric ulceration and have active chronic gastritis. The breath test is quick, simple, easily tolerated by a wide age range of patients, and highly sensitive and specific. This noninvasive modality can also document eradication of *H pylori* infection, thus predicting long-term remission from gastroduodenal ulceration and precise evaluation of curative outpatient treatment regimens in patients with peptic ulcer disease. This investigational radiopharmaceutical was recently released for widespread outpatient use in the United States and Canada. Estimated cost will be less than $200. Primary care clinicians will occupy a pivotal role in the efficient utilization and precise interpretation of [^{14}C]urea breath tests for patients who have a variety of upper gastrointestinal tract syndromes.

In conclusion, our data and discussion suggest these potential uses for [^{14}C]urea breath test:

1. Provide a reliable primary care alternative to endoscopy for the initial diagnosis of *H pylori* infection in patients with peptic ulcer
2. Document *H pylori* infection in patients known to have duodenal or gastric ulcers as shown by a noninvasive barium upper gastrointestinal tract series
3. Document *H pylori* infection in episodes of gastric or duodenal ulcer recurrence
4. Prove *H pylori* eradication after antibiotic regimens and therefore predict long-term ulcer remission
5. Evaluate for the presence of *H pylori* in dyspeptic patients refractory to histamine-2 blockers but without discrete ulceration by upper gastrointestinal tract examination or endoscopy
6. Estimate quantitative activity of *H pylori* infection in patients with seropositivity of uncertain clinical importance or duration.

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References

1. NIH Consensus Conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. JAMA 1994;272:65-9.
2. Peterson WL. *Helicobacter pylori* and peptic ulcer disease. N Engl J Med 1991;324:1043-8.
3. Brown KE, Peura DA. Diagnosis of *Helicobacter pylori* infection. Gastroenterol Clin North Am 1993; 22:105-15.
4. Graham DY, Go MF. *Helicobacter pylori*: current status. Gastroenterology 1993;105:279-82.
5. Marshall BJ. *Helicobacter pylori*. Am J Gastroenterol 1994;89(8 Suppl):S116-28.
6. Peura DA. *Helicobacter pylori*: a diagnostic dilemma and a dilemma of diagnosis. Gastroenterology 1995; 109:313-5.
7. Marshall BJ, Surveyor I. Carbon-14 urea breath test for the diagnosis of *Campylobacter pylori* associated gastritis. J Nucl Med 1988;29:11-6.
8. Debongnie JC, Pauwels S, Raat A, de Meeus Y, Haot J, Mainguet P. Quantification of *Helicobacter pylori* infection in gastritis and ulcer disease using a simple and rapid carbon-14-urea breath test. J Nucl Med 1991;32:1192-8.
9. Marshall BJ, Plankey MW, Hoffman SR, Boyd CL, Dye KR, Frierson HF Jr, et al. A 20-minute breath test for *Helicobacter pylori*. Am J Gastroenterol 1991; 86:438-45.
10. Raju GS, Smith MJ, Morton D, Bardhan KD. Minidose (1 μCi)^{14}C-urea breath test for the detection of *Helicobacter pylori*. Am J Gastroenterol 1994;89: 1027-31.
11. Peura DA, Pambianco DJ, Dye KR, Lind C, Frierson HF, Hoffman SR, et al. Microdose ^{14}C-urea breath test offers diagnosis of *Helicobacter pylori* in 10 minutes. Am J Gastroenterol 1996;91:233-8.
12. Faigel DO, Childs M, Furth EE, Alavi A, Metz DC. New noninvasive tests for *Helicobacter pylori* gastritis. Comparison with tissue-based gold standard. Dig Dis Sci 1996;41:740-8.

13. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311-5.
14. Laine L. *Helicobacter pylori*, gastric ulcer, and agents noxious to the gastric mucosa. Gastroenterol Clin North Am 1993:22:117-25.
15. Tytgat GN, Noach LA, Rauws EA. *Helicobacter pylori* infection and duodenal ulcer disease. Gastroenterol Clin North Am 1993;22:127-39.
16. Nomura A, Stemmerman GN, Chyou PH, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and the risk for duodenal and gastric ulceration. Ann Intern Med 1994;120:977-81.
17. Forbes GM, Glaser ME, Cullen DJ, Warren JR, Christiansen KJ, Marshall BJ, et al. Duodenal ulcer treated with *Helicobacter pylori* eradication: seven-year follow-up. Lancet 1994;343:258-60.
18. Tytgat GN. Treatments that impact favourably upon the eradication of *Helicobacter pylori* and ulcer recurrence. Aliment Pharmacol Ther 1994;8:359-68.
19. Blaser MJ. Hypotheses on the pathogenesis and natural history of *Helicobacter pylori*-induced inflammation. Gastroenterology 1992;102:720-7.
20. Dunn BE. Pathogenic mechanisms of *Helicobacter pylori*. Gastroenterol Clin North Am 1993;22:43-57.
21. Walsh JH, Peterson WL. The treatment of *Helicobacter pylori* infection in the management of peptic ulcer disease. N Engl J Med 1995;333:984-91.
22. Cutler AF, Havstad S, Ma CK, Blaser MJ, Perez-Perez GI, Schubert T. Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. Gastroenterology 1995;109:136-41.
23. Thijs JC, van Zwet AA, Thijs WJ, Oey HB, Karrenbeld A, Stellaard F, et al. Diagnostic tests for *H pylori*: a prospective evaluation of their accuracy with an independent "gold standard." Gastroenterology 1995;108:abstract 241.
24. Stubbs JB, Marshall BJ. Radiation dose estimates for the carbon-14-labeled urea breath test. J Nucl Med 1993;34:821-5.