

# VALIDATION OF A NOVEL REAL TIME $^{13}\text{C}$ UREA BREATH TEST FOR RAPID EVALUATION OF *HELICOBACTER PYLORI* IN CHILDREN AND ADOLESCENTS

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We prospectively evaluated a  $^{13}\text{C}$  urea breath test (UBT) that involves passive continuous sampling for diagnosis of *Helicobacter pylori* in 72 children. Results were obtained within 10 minutes in 96% of patients. The test is rapid, user-friendly, and has 100% concordance with conventional diagnostic methods. (*J Pediatr* 2004;145:112-4)

Identification of *Helicobacter pylori* infection, a risk factor for duodenal ulcers and gastritis in children,<sup>1-3</sup> can be achieved by a variety of methods. Like the more invasive tests currently available, such as endoscopy and biopsy, urea breath tests (UBT) can detect active infection with high sensitivity and specificity. Therefore, the UBT may be considered the preferred method for epidemiological studies and for screening patients with dyspeptic symptoms. It also is the preferred method at present for monitoring eradication or recurrence of the infection.<sup>4-5</sup>

Conventional  $^{13}\text{C}$  UBT also requires  $^{13}\text{CO}_2$  analysis. This demands collecting, storing, and transporting the samples to isotope ratio mass spectrometer (IRMS) or gas chromatography laboratories. The test also requires active compliance, which can occasionally be problematic in children.<sup>5</sup>

An immediate result can be obtained if the sampling method is altered. One such option includes continuous sampling real time (CRT)  $^{13}\text{C}$  UBT technology. A device utilizing this technology (BreathID, Oridion, Israel) has been validated previously in adults.<sup>6</sup> This office-based system offers several advantages over conventional mass spectrometry-based UBTs, including an immediate test result, standardized test meal, and a sampling method that does not require active cooperation. The IDcircuit (Oridion), a nasal passive breath sampling device, continuously transports the breath sample from the patient to the BreathID device. Based on molecular correlation spectrometry, the BreathID continuously measures  $^{13}\text{CO}_2$  and  $^{12}\text{CO}_2$  concentrations from the patient's breath and establishes the  $^{13}\text{CO}_2/^{12}\text{CO}_2$  ratio, which is displayed onscreen, within 10 to 20 minutes. Because an apparatus of this type conceivably could be easier to use in the pediatric population and in ambulatory settings, we initiated a prospective study to evaluate the accuracy of CRT  $^{13}\text{C}$  UBT in children and adolescents.

## METHODS

Consecutive children and adolescents aged 5 to 18 years who were referred for gastroscopy or for  $^{13}\text{C}$  UBT served as the study population. Outpatients referred by pediatricians for UBT were not required to undergo endoscopy. Indications for isolated  $^{13}\text{C}$  UBT testing were persistent epigastric pain or verification of eradication after treatment of *H. pylori*. Exclusion criteria included use of antibiotics, histamine-2 receptor antagonists, or proton pump inhibitors over the proceeding 7 days.

Patients consumed a standard test drink, containing 75 mg  $^{13}\text{C}$  urea and 4.5 gm granulated citric acid-based powder dissolved in 200 mL water. All patients performed CRT  $^{13}\text{C}$  UBT for up to 20 minutes using the Oridion BreathID. In parallel, simultaneous breath samples at baseline and at the end of the CRT  $^{13}\text{C}$  UBT were collected and sent for isotope ratio analysis by previously validated IRMS (IRMS, Micromass, UK)<sup>1</sup> to Israel's largest central laboratory. The researchers were blinded to the results of IRMS testing. The determination of positive or negative results was based on a device algorithm, with

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Submitted for publication Oct 9, 2003; last revision received Jan 10, 2004; accepted Mar 16, 2004.

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0022-3476/\$ - see front matter

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10.1016/j.jpeds.2004.03.025

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CRT	Continuous sampling real time	UBT	Urea breath test
IRMS	Isotope ratio mass spectrometer		

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**Table I. Entry data**

Group	N	Age (y), mean $\pm$ SD	Male / Female	H pylori +/-
Total patients (Total UBT)	72 (76)	12.9 $\pm$ 3.6	29/43	30/42
Pretreatment UBT	62	12.5 $\pm$ 3.6	36/26	30/32
Posttreatment UBT	14	14.8 $\pm$ 2.5	7/7	4/10
Gastroscopy	26	13.4 $\pm$ 3.5	11/15	10/16

a previously validated cutoff of 5  $\delta$  over baseline.<sup>1,6,8</sup> In our study, the test automatically ended within 20 minutes.

Patients undergoing gastroscopy in addition to breath testing had biopsies taken from the antrum and gastric body for histopathologic diagnosis (hematoxylin & eosin and Giemsa stain) and had a rapid urease test (CUTest, Temmler Pharma, Germany) performed on an additional antral biopsy specimen, read at 24 hours. All pathological specimens were read by a single pathologist blinded to the results of breath testing. This study was approved by a hospital ethics committee.

### Statistical Analysis

Data were stored on Excel 97 (Microsoft Inc., Seattle, Wash, 1985-1997). Analysis of data was carried out using the Statistical Package for the Social Sciences software (SPSS Inc, Chicago, Ill, 1999). The *t* test for independent samples was used to detect differences in the means of age using *H. pylori* status as the categorical variable. All tests were two-sided and were considered significant at *P* < .05.

## RESULTS

Breath tests (n = 76) were performed in 72 enrolled children, mean age 12.9  $\pm$  3.6 years. All children enrolled completed the study without difficulty. Entry data are portrayed in Table I.

*H. pylori* was diagnosed by IRMS UBT in 34 of 76 tests. Gastroscopy with biopsies was performed in 26 of 72 patients; of these, 10 patients were *H. pylori* positive, and 16 patients were *H. pylori* negative. Findings on endoscopy included duodenal ulcer in 4 of 26 patients, erosive duodenitis or gastritis in 3 of 26 patients, isolated nodular antrum in 3 of 26 patients, and esophagitis in 1 patient.

A final printout of the results was available in 10 minutes or less in 73 of 76 tests (96%); the other three results were available within 15 minutes. Concordance between CRT-UBT, conventional UBT, and endoscopic methods in the subset undergoing gastroscopy was 100% for positive and negative results (Table II).

## DISCUSSION

We evaluated a new technology for the evaluation of *H. pylori* in children that differs significantly from standard

**Table II. Concordance of CRT BreathID (N=76) with other tests for diagnosis of *H. pylori***

Diagnostic Test	H pylori+	H pylori-	H pylori+	H pylori-	Concor- dance (%)
	Other test	Other test	Breath ID	Breath ID	
UBT IRMS	34	42	34	42	100
CU test (n = 26)	10	16	10	16	100
Histopathology (n = 26)	10	16	10	16	100

IRMS, Isotope ratio mass spectrometer; Cu test, rapid urease test.

breath tests in four aspects: use of passive continuous sampling, a shorter duration of test, immediate results, and a high-dose citric acid-based test meal. It was as effective as IRMS. Although our study population was small and 100% concordance may not stand up to the test of time, the high concordance was similar to the rate obtained with IRMS from studies involving adults to date.<sup>6-8</sup> A result was obtained in 10 minutes or less in 96% of patients, enabling an immediate decision regarding therapy.

Citric acid may improve the sensitivity of the <sup>13</sup>C UBT in comparison with orange juice, probably because fruit juice has a smaller content of citric acid. Although less palatable than juice, high-dose citric acid has been shown to preserve the accuracy of <sup>13</sup>C UBTs, even in patients receiving short-term treatment for up to 2 weeks with proton pump inhibitors.<sup>8-9</sup> Citric acid delays gastric emptying and decreases gastric pH. Bacterial urease activity is low at neutral pH. As the external pH decreases between 6.5 and 5.5, there is a 10- to 20-fold increase in activity that remains high through approximately pH 2.5.<sup>10-11</sup> The transport of urea into the bacteria is regulated by *UreI*-dependent specific H<sup>+</sup>-gated urea channels that also are pH dependent. High doses of citric acid may enhance the diagnostic accuracy of CRT by minimizing these pH dependent effects.

In conclusion, we have shown that use of CRT technique with a citric acid-based meal is user-friendly, accurate, and achieves immediate results. Because it does not require active participation, it may be especially useful in the pediatric population.

*BreathID kits for breath tests in this study were kindly supplied by Oridion.*

## REFERENCES

1. Drumm B, Koletzko S, Oberda G. *Helicobacter pylori* infection in children: a consensus statement. J Pediatr Gastroenterol Nutr 2000;30:207-13.
2. Gold B. Current therapy for *Helicobacter pylori* infection in children and adolescents. Can J Gastroenterol 1999;13:571-9.
3. Israel D, Hassall E. Treatment and long term follow-up of *Helicobacter pylori* associated duodenal ulcer disease in children. J Pediatr 1993;123:53-8.
4. Current European concepts in the management of *Helicobacter pylori* infection: the Maastricht Consensus Report. Gut 1997;41:8-13.

5. Kinderman A, Demmelmair H, Koletzko B, Krauss-Etschmann S, Weibecke B, Koletzko S. Influence of age of the  $^{13}\text{C}$ -urea breath tests results in children. *J Pediatr Gastroenterol Nutr* 2000;30:85-91.
6. Shirin H, Kenet G, Shevah O, et al. Evaluation of a novel continuous real time  $^{13}\text{C}$  urea breath analyzer for *Helicobacter pylori*. *Aliment Pharmacol Ther* 2001;15:389-94.
7. Shirin H, Frenkel D, Shevah O, et al. Effect of proton pump inhibitors on the continuous real time  $^{13}\text{C}$ -urea breath test. *Am J Gastroenterol* 2003;98:46-50.
8. Israeli E, Yaron I, Meir SB, Buena vida C, Goldin E. A novel  $^{13}\text{C}$  urea breath test device for the diagnosis of *Helicobacter pylori* infection: continuous online measurement allows for faster test results with high accuracy. *J Clin Gastroenterol* 2003;37:139-41.
9. Leodolter A, Dominguez-Munoz JE, Von Arnim U, Malfertheiner P. Citric acid or orange juice for the  $^{13}\text{C}$ -urea breath test: the impact of pH and gastric emptying. *Aliment Pharmacol Ther* 1999;13:1057-62.
10. Rektorschek M, Weeks D, Sachs G, et al. Influence of pH on metabolism and urease activity of *Helicobacter pylori*. *Gastroenterology* 1998;115:628-41.
11. Scott DR, Weeks D, Hong C, Postius S, Melchers K, Sachs G. The role of internal urease in acid resistance of *Helicobacter pylori*. *Gastroenterology* 1998;114:58-70.

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