

# A Retrospective Analysis of Three Non-Invasive Tests for Initial Diagnosis of *Helicobacter pylori* Infection in Children

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## Abstract

Proper diagnosis in the pediatric population is required to eradicate *Helicobacter pylori* (*H. pylori*) and prevent gastric cancer. Our aim was to assess the performance of non-invasive tests to diagnose *H. pylori* infection in pediatric patients. A retrospective analysis was performed on 141 pediatric patients requiring endoscopic evaluation and diagnostic tests for *H. pylori* infection to define the cause of abdominal symptoms. Non-invasive tests included the <sup>13</sup>C-urea breath test (UBT), a monoclonal stool antigen test using enzyme-linked immuno-sorbent assay (mSAT), and a serum immunoglobulin G antibody test using antigens derived from Japanese individuals (S-Ab). This study investigated sensitivity, specificity, likelihood ratios for a positive and a negative test (LR<sub>+</sub> and LR<sub>-</sub>), and accuracy of non-invasive tests, in comparison with invasive tests. Eighty two of 141 patients (58%) were recognized as *H. pylori* positive by invasive methods. When UBT, mSAT or S-Ab were analyzed, all were found to be effective over 94% accurate. Specificity ranged between 86.7% and 95.8%, and sensitivity ranged between 93.8% and 97.1%. When subjects were stratified into three distinct age groups, the best performance was achieved for 1 - 6 years old with mSAT at 100% for sensitivity, specificity, and accuracy. S-Ab yielded the best results for children 7 - 12 years old and the UBT test performed best for 13 - 18 years old. These results demonstrate the utility of UBT, mSAT, and S-Ab non-invasive tests in diagnosing *H. pylori* but suggest that certain tests may be optimal for children of distinct ages. Three non-invasive tests, UBT, mSAT and S-Ab showed sufficient sensitivity, specificity and accuracy for the initial diagnosis of *H. pylori* infection among pediatric patients. Non-invasive tests may contribute to achieving minimum invasive diagnosis with combining with a histological test and a culture test in children.

## Keywords

Accuracy, Non-Invasive Tests, Urea Breath Test, Stool Antigen Test, Serum Antibody Test

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## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is a microaerophilic Gram-negative spiral bacterial pathogen that resides in the stomach. Their production of urease helps protect the bacteria from the highly acidic environment. *H. pylori* infection is generally acquired in childhood and typically persists for life. *H. pylori* infection causes chronic gastric mucosal inflammation that is a risk factor for gastric cancer and the expression of the CagA oncoprotein is common [1]. Eradication therapy before the severe expansion of gastric atrophy is significantly beneficial in the prevention of gastric cancer [2] [3] [4] [5]. Therefore, early eradication therapy especially in early childhood may contribute to reduction in the incidence of gastric cancer. To eradicate *H. pylori* and prevent gastric cancer, proper diagnosis in the pediatric population is required.

Endoscopy remains the gold standard for diagnosis of *H. pylori* infection. There are however, several non-invasive diagnostic tools to detect *H. pylori* infection and these types of tests would be most desirable if their accuracy was shown to be comparable to invasive tests. There are predominantly three types of non-invasive tests used in Japan for the diagnosis of *H. pylori*. These tests include measuring specific antibodies in serum and urine using antigens derived from Japanese individuals, identifying *H. pylori* antigen in the stool using monoclonal antibodies, and the urea breath test. Although several studies have assessed the accuracy of the non-invasive methods, there has been no direct comparison of these three non-invasive methods in the same study in conjunction with diagnosis determined by invasive tests in Japan. The aim of this study was to perform a retrospective study to assess the accuracy of the <sup>13</sup>C-urea breath test (UBT), a monoclonal stool antigen test using enzyme-linked immuno-sorbent assay (ELISA) tests (mSAT), and a serum specific immunoglobulin G (IgG) antibody test against *H. pylori* using antigens derived from Japanese individuals (Serum Antibody Test: S-Ab) for the diagnosis of *H. pylori* pediatric patients already screened by endoscopy.

## 2. Methods

### 2.1. Patients

Esophagogastroduodenoscopy (EGDs), all diagnostic tests of *H. pylori* infection and eradication therapies were performed in Juntendo University Hospital in Tokyo, Japan. Subjects consisted of pediatric patients requiring endoscopic evaluation and diagnostic tests for *H. pylori* infection to define the cause of suffering from abdominal symptoms such as epigastralgia, nausea and vomiting.

Patients were excluded in the case of previous *H. pylori* eradication therapy, consumption of antibiotics or antacid agents in the previous 4 weeks of any examinations. Sample collection for the non-invasive tests was performed within a few days before or after EGDs. A signed informed consent was obtained from the parents of all children before assessment with EGDs.

## 2.2. Diagnosis of *H. pylori* Infection

Two gastric biopsy samples were taken endoscopically from both the antrum and the corpus of stomach for bacterial culture and histologic examination. All patients had no history of *H. pylori* eradication therapy. Positive *H. pylori* status was defined as a positive by either culture or histology. A negative *H. pylori* status was confirmed when both culture and histology gave concordant negative results.

## 2.3. UBT

Patients were fasted for at least 4 hours and then  $^{13}\text{C}$ -labeled urea dissolved in water was given without taking any test meals. The dose of  $^{13}\text{C}$ -urea was 100 mg for patients 12 years old or older, 75 mg for 6 - 11 years old patients, and 50 mg for patients less than 6 years old. To reduce the effect of urease-producing oral bacteria, patients rinsed their mouths with water immediately after ingestion of  $^{13}\text{C}$ -urea. Breath samples were collected in duplicate before ingestion of the  $^{13}\text{C}$ -urea and at 20 minutes afterwards. Breath samples were analyzed by carbon dioxide carbon isotope ratio analyzer (Spectral Analyzer POCone; Otsuka Electronics Co., Ltd., Osaka, Japan). The cut off value of  $\Delta^{13}\text{C}$  was defined to be 3.5‰ [6].

## 2.4. *H. pylori* Stool Antigen Test: mSAT

The mSAT was performed using commercial ELISA tests (Meridian HpSA ELISA II; Meridian Bioscience Inc., Ohio, USA). This test utilizes a panel of monoclonal anti-*H. pylori* capture antibodies adsorbed to microplate wells. The assay was performed according to manufacturer's instructions. An absorbance at 450 nm of  $<0.140$  was defined as negative, and  $\geq 0.140$  was defined as positive.

## 2.5. Serum Anti-*H. pylori* IgG Antibody Test: S-Ab

Serum IgG antibodies to *H. pylori* were measured using commercial EIA tests using antigens derived from Japanese individuals (E plate Eiken *H. pylori* Antibody II; Eiken Chemical Co., Ltd., Tokyo, Japan). Assays were performed according to manufacturer's instructions. A concentration of anti-*H. pylori* IgG antibody of  $<10$  U/mL was defined as negative, and of  $\geq 10$  U/mL was defined as positive.

## 2.6. Statistical Analysis

Sensitivity, specificity, likelihood ratios for a positive and a negative test ( $\text{LR}_+$  and  $\text{LR}_-$ ), and accuracy were calculated using standard methods.

## 2.7. Conflicts of Interest

No specific industry was linked to our study. The authors declare no conflicts of interest.

## 3. Results

The results from 141 pediatric patients examined from 1998 to 2016 by EGDs, *H. pylori* culture examinations and non-invasive *H. pylori* diagnostic tests were assessed. The population consisted of 68 boys and 73 girls with a mean age of  $11.77 \pm 3.45$  years (range, 1.33 to 18.92). Eighty-two patients (58%) were found to be *H. pylori* positive by *H. pylori* culture and/or histological examination. The UBT was used on 100 patients from 1998 to 2016, the mSAT was used on 56 patients from June, 2007 to 2016, and the S-Ab test was given to 92 patients from September 20<sup>th</sup>, 2005 to 2016. The characteristics of the 141 patients are presented in **Table 1**. The UBT, mSAT and S-Ab tests were positive in 70%, 57.1%, and 55.4% of children, respectively. The sensitivity, specificity, LR<sub>+</sub>, LR<sub>-</sub> and accuracy of the different noninvasive tests on this population when compared to the EGDs/Histology analysis are presented in **Table 2**. The parameter values indicating performance for each of the three tests were similar. The accuracy for all three tests was at least 94%. The UBT was found to have the highest sensitivity at 97.1%, but even the test with the lowest sensitivity, the mSAT test was 93.8%. The mSAT test however was demonstrated to have the highest specificity at 95.8% whereas the UBT test was the least specific at 86.7%.

**Table 1.** Characteristics of 141 pediatric patients.

	Number of patients	Rate of <i>H. pylori</i> Infection
Total	141	58.2%
Gender		
Male	68	61.8%
Female	73	54.8%
Age (years)		
1 - 6	16	43.8%
7 - 12	57	57.9%
13 - 18	68	61.8%
Non-invasive test		
UBT	100	70.0%
Mean age (years): 12.21 ± 3.11		
mSAT	56	57.1%
Mean age (years): 10.81 ± 3.88		
S-Ab	92	55.4%
Mean age (years): 11.87 ± 3.16		

<sup>13</sup>C-urea breath test, UBT; monoclonal stool antigen test, mSAT; serum antibody test, S-Ab.

**Table 2.** Performance of the non-invasive diagnostic tests.

	UBT	mSAT	S-Ab
Sensitivity	97.1%	93.8%	96.1%
Specificity	86.7%	95.8%	95.1%
LR <sub>+</sub>	7.29	22.5	19.7
LR <sub>-</sub>	0.033	0.065	0.041
Accuracy	94.0%	94.6%	95.7%

<sup>13</sup>C-urea breath test, UBT; monoclonal stool antigen test, mSAT; serum antibody test, S-Ab; likelihood ratio for a positive test, LR<sub>+</sub>; likelihood ratio for a negative test, LR<sub>-</sub>.

There were 36 patients (mean age,  $11.66 \pm 3.06$  years; range, 4.83 to 18.92) that underwent all three non-invasive tests. The sensitivity, specificity, LR<sub>+</sub>, LR<sub>-</sub> and accuracy of the different tests in these 36 patients are presented in **Table 3**. Within this group, the accuracy of the S-Ab test increased to 97.2% whereas the accuracy of the UBT test fell to 91.7%. The mSAT remained the same (94.4%). The sensitivity of all three tests was all similar (95.5%, 95.8%, and 95.8%). The specificity however varied greatly with the UBT falling to 83.3% and the S-Ab test at 100%. We then divided the 141 patients into 3 groups according to their ages. Group I included 16 patients from 1 to 6 years old with a mean age of  $4.95 \pm 1.73$  years (range, 1.33 to 6.67). Group II included 57 patients 7 to 12 years old with mean age of  $10.44 \pm 1.77$  years (range, 7.00 to 12.92). Group III included 68 patients 13 to 18 years old with mean age of  $14.48 \pm 1.21$  years (range, 13.00 to 18.92). The values of the non-invasive tests when assessed by the patient age are described in **Table 4**. The best performance was observed in Group I where the mSAT test sensitivity, specificity, and accuracy of 100%. The UBT test performed best on Group III with sensitivity, specificity, and accuracy at 97.2, 100, and 98% respectively, although both the mSAT and S-Ab test each performed well in this group as well.

#### 4. Discussion

There are two categories of examinations for detection of *H. pylori* infection, invasive methods and non-invasive methods. Invasive tests require samples taken from the gastric mucosa by EGDs for assessment of *H. pylori* on the mucosa directly. In contrast, non-invasive tests are performed using breath, stool, serum or urine, and assess general changes in the host due to *H. pylori* infection. There is no single test with 100% sensitivity and specificity. Culture is the only test with 100% specificity, however, its sensitivity is lower than other tests [7] [8]. Moreover, we should understand the factors that can lead to a false-positive or false-negative. Administration of antibiotics or antacid agents within 2 - 4 weeks of testing may result in a false-negative in all tests except for antibody examination [9] [10] [11]. In addition, the accuracy of UBT and antibody tests may be influenced by the age of the tested child [12]. The evidence-based guidelines from ESPGHAN and NASPGHAN [13] recommend the initial diagnosis of *H. pylori*

**Table 3.** Characteristics of 36 patients who underwent all 3 non-invasive tests and performance of the non-invasive diagnostic tests.

	Number of patients	Rate of <i>H. pylori</i> Infection	Mean age (years)
Total	36	66.7%	11.66 ± 3.06
Gender			
Male	20	60.0%	11.56 ± 2.77
Female	16	75.0%	11.78 ± 3.57
	UBT	mSAT	S-Ab
Sensitivity	95.5%	95.8%	95.8%
Specificity	83.3%	91.7%	100%
LR <sub>+</sub>	5.75	11.5	∞
LR <sub>-</sub>	0.050	0.045	0.041
Accuracy	91.7%	94.4%	97.2%

<sup>13</sup>C-urea breath test, UBT; monoclonal stool antigen test, mSAT; serum antibody test, S-Ab; likelihood ratio for a positive test, LR<sub>+</sub>; likelihood ratio for a negative test, LR<sub>-</sub>.

**Table 4.** Characteristics of three groups divided according to the ages and performance of the non-invasive diagnostic tests.

Group I	Number of patients	Rate of Infection	Mean age (years)
Total	16	43.8%	4.95 ± 1.73
Gender			
Male	9	22.2%	4.58 ± 1.80
Female	7	71.4%	5.42 ± 1.63
	UBT	mSAT	S-Ab
Sensitivity	83.3%	100%	75.0%
Specificity	66.7%	100%	100%
LR <sub>+</sub>	2.5	∞	∞
LR <sub>-</sub>	0.25	0	0.25
Accuracy	77.8%	100%	87.5%
Group II	Number of patients	Rate of Infection	Mean age (years)
Total	57	57.9%	10.44 ± 1.83
Gender			
Male	29	69.0%	10.95 ± 1.77
Female	28	46.4%	9.92 ± 1.67
	UBT	mSAT	S-Ab
Sensitivity	100%	93.3%	95.5%
Specificity	76.9%	90.9%	100%
LR <sub>+</sub>	4.33	10.27	∞
LR <sub>-</sub>	0	0.73	0.045
Accuracy	92.7%	92.3%	97.5%

## Continued

Group III	Number of patients	Rate of Infection	Mean age (years)
Total	68	95.8%	14.48 ± 1.21
Gender			
Male	30	66.7%	14.26 ± 1.04
Female	38	57.9%	14.66 ± 1.32
	UBT	mSAT	S-Ab
Sensitivity	97.2%	92.9%	100%
Specificity	100%	100%	89.5%
LR <sub>+</sub>	∞	∞	9.50
LR <sub>-</sub>	0.028	0.071	0
Accuracy	98.0%	95.2%	95.4%

<sup>13</sup>C-urea breath test, UBT; monoclonal stool antigen test, mSAT; serum antibody test, S-Ab; likelihood ratio for a positive test, LR<sub>+</sub>; likelihood ratio for a negative test, LR<sub>-</sub>.

infection based on either positive histology plus either a positive rapid urease test or a positive culture. They also refer to the indication of non-invasive tests such as UBT or stool antigen test when the results of histology and rapid urease test are discordant. Because invasive tests can confirm *H. pylori* infection directly, they are recommended as more suitable tests for the detection of infection than non-invasive tests. However, feasible accuracy of non-invasive tests for the initial diagnosis has been presented in many reports [14]-[20]. Additionally, false results from invasive tests may occur due to patchy density of *H. pylori*, active bleeding in the stomach, or the presence of other pathogens producing urease in stomach such as non-*Helicobacter pylori* *Helicobacters* [21] [22] [23].

This present study demonstrated high accuracy of non-invasive *H. pylori* diagnostic tests, UBT, mSAT and S-Ab, in pediatric patients as an initial diagnostic method. Sensitivity and specificity of all three tests were over 80% and the accuracy of all three tests was over 90%. As seen in **Table 2** and **Table 3**, parameter values for their performance for all three tests were similar when comparing either the results of our entire patient study group or the results of 36 patients who underwent all 3 non-invasive tests. These results suggest that selection bias of non-invasive tests was allowable and might have only limited effect on results. On the other hand, the age of the tested children may affect sensitivity, specificity and accuracy as seen in **Table 4**. In group I (1 to 6 years old), sensitivity for UBT and S-Ab were 83.3% and 75.0%, specificity were 66.7% and 100%, and accuracy were 77.8% and 87.5%. UBT requires patient cooperation such as rinsing their mouths with water immediately after ingestion of <sup>13</sup>C-urea to reduce the effect of oral urease producing bacteria. Therefore, it is more difficult to perform UBT in infants and toddler patients, and lower specificity has been obtained in children younger than 6 years old in past studies [18] [24]-[29]. Low sensitivity among young children with antibody tests has also been reported, and it was believed to result from immaturity of the immune response

and to be affected by transfer of maternal IgG antibodies to *H. pylori* [14] [30] [31] [32] [33]. In contrast, Okuda and Ueda *et al.* showed high sensitivity of antibody tests using antigens derived from Japanese individuals among young children [19] [20]. We found low sensitivity and specificity of UBT and low sensitivity of S-Ab in Group I with 1 to 6 years old patients as previously reported. In addition, the specificity of UBT and the sensitivity of S-Ab increased in older groups. Conversely, the sensitivity and specificity of mSAT in same group was 100%. Our results suggest more accuracy of mSAT than other non-invasive tests among young children.

In Japan, the increasing incidence of clarithromycin (CAM) resistance in *H. pylori* results in decreasing *H. pylori* eradication rates which have fallen to approximately 75% with a first line regimen with CAM [34] [35]. The prevalence of CAM resistance in young patients ranges from 29% - 43.4% in Japan [36] [37] [38] [39] [40]. Thus, clinical guidelines recommend antibiotic susceptibility testing for CAM prior to initial eradication therapy in children due to the high resistance rate (>20%) as clinical guidelines [13]. Therefore, 4 biopsies (2 for histology, 1 for rapid urease test, and 1 for culture and susceptibility testing) from both the antrum and the corpus are required to diagnose *H. pylori* infection and to prevent false results due to patchy density of *H. pylori* according to clinical guidelines [13]. Our study demonstrates reliable performance by non-invasive tests, UBT, mSAT and S-Ab, in pediatric patients for initial diagnosis of *H. pylori*. Histological findings are needed to confirm causes of symptoms indicating EGDs. However, a rapid urease test could only contribute to the detection of *H. pylori* infection. Consequently, we propose replacing a rapid urease test with a non-invasive test in children to reduce invasion by EGDs and to limit the taking of biopsies as much as possible. We can select non-invasive tests according to risk factors leading to false results such as age of patient, history of administration and stool condition.

In conclusion, all three non-invasive tests, UBT, mSAT and S-Ab, showed sufficient sensitivity, specificity and accuracy for the initial diagnosis of *H. pylori* in children. Non-invasive tests may contribute to achieving *H. pylori* diagnosis with reduced invasion when combined with a histological test and a culture test.

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