

# Urine-Based Enzyme-Linked Immunosorbent Assay for the Detection of *Helicobacter pylori* Infection in Children

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**ABSTRACT.** *Objective.* Serology and <sup>13</sup>C-urea breath test have been widely used as noninvasive tests to detect *Helicobacter pylori* infection. However, easier collection of samples and lower costs are desirable for diagnosis of the individual patient or for use in epidemiologic studies. Our aim was to study the diagnostic accuracy of a recently developed urine-based enzyme-linked immunosorbent assay (ELISA) kit for the detection of *H pylori*-specific immunoglobulin G (IgG) antibodies in children.

*Study Design.* Specimens of serum and randomly voided urine were collected from 816 children (0–15 years old) and were analyzed using 2 serum-based ELISA kits and a urine-based ELISA kit, respectively. Based on results of serology, the sensitivity, specificity, and accuracy of the urine-based ELISA kit were evaluated. With regard to false-positive and false-negative results, urinary IgG concentrations and IgG/creatinine levels were studied.

*Results.* Both serum-based ELISAs were positive in 41 children and were negative in 666, who were enrolled in this study. The remaining 109 children were excluded because of disagreement between the results of the 2 serum-based ELISAs, including indeterminate values. Overall sensitivity, specificity, and accuracy of urine-based ELISA test compared with serology were 85.4%, 95.5%, and 94.9%, respectively. On positivity rates, the urine-based ELISA was closely coincident with the serum-based ELISA in each age group. There was no correlation between antibody levels detected by urine-based ELISA and each serum-based ELISA. Urinary IgG concentrations and IgG/creatinine levels were significantly higher in false-positives and were lower in false-negatives than in true-positives plus true-negatives for serology. Most of those with false-positive results had trace to moderate proteinuria.

*Conclusions.* The urine-based ELISA is an alternative to serum-based ELISA for diagnosis of *H pylori* infection in children and should be suitable for large-scale epidemiologic studies concerning the organism. In children with proteinuria, results of the test should be interpreted with caution. It is possible that the urine-based ELISA

method would be applicable to diagnosis of other infectious diseases. *Pediatrics* 2001;107(6). URL: <http://www.pediatrics.org/cgi/content/full/107/6/e87>; enzyme-linked immunosorbent assay, *Helicobacter pylori*, immunoglobulin G, urine.

ABBREVIATIONS. IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; CI, cutoff index; SD, standard deviation.

Gastric infection with *Helicobacter pylori* occurs worldwide. Although the great majority of infected individuals have an asymptomatic mild chronic gastritis without sequelae, small subsets develop *H pylori*-associated peptic ulcer disease, gastric adenocarcinoma, or mucosa-associated lymphoid tissue lymphoma.<sup>1–4</sup> Furthermore, recent studies have also discussed a possible role of *H pylori* for extraintestinal involvements, such as ischemic heart disease,<sup>5,6</sup> iron deficiency anemia,<sup>7,8</sup> or chronic urticaria.<sup>9</sup>

Endoscopic biopsy tests (rapid urease test, histology, and culture) are recognized to be the most reliable method for detecting *H pylori* infection and its sequelae. However, endoscopy is invasive and gastric involvement may be patchy. Certain noninvasive methods, especially the <sup>13</sup>C-urea breath test for the urease activity and serology test for *H pylori*-specific immunoglobulin G (IgG) antibodies, have demonstrated high sensitivity and specificity in adults.<sup>3,10</sup> However, there are drawbacks to these tests. The <sup>13</sup>C-urea breath test is not inexpensive and may be technically difficult to perform in younger children, and several studies have pointed out that serologic tests are less reliable for children than for adults.<sup>11–13</sup> Another new noninvasive test is the stool antigen test, which uses an enzyme-linked immunosorbent assay (ELISA). In adults, the test has a sensitivity and specificity of ~90%.<sup>14,15</sup> However, it has the disadvantage of stool samples being difficult to collect.

Previous studies have shown that *H pylori*-specific IgG antibodies can also be detected in saliva<sup>16,17</sup> and urine,<sup>18,19</sup> suggesting a possibility of easy-to-use diagnostic tools. However, the salivary test has been shown to have poor sensitivity and specificity.<sup>17</sup> Recently, a urine-based ELISA method for the detection of the IgG antibodies has been developed and its clinical usefulness has been reported in adults.<sup>20–22</sup> In addition to its noninvasive nature, this test has the

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advantage of easy sample collection. The aim of our study was to assess the accuracy of the urine-based ELISA method in children.

## METHODS

### Participants and Samples

Sera and random voided urine specimens were collected from 816 children ( $7.2 \pm 3.9$  years old; range: 0–15 years) with various acute or chronic diseases. They did not have peptic ulcer disease, gastritis, or symptoms suggesting these diseases. Sodium azide (0.1 w/v% at final concentration) was added to the urine samples. Sera were frozen at  $-20^{\circ}\text{C}$  and urine samples were stored at  $4^{\circ}\text{C}$  until assayed. Informed consent was obtained from all children or their parents.

### Serum-Based ELISA Methods

Serum IgG antibodies to *H pylori* were measured using 2 commercial ELISA kits (HM-CAP, Enteric Products, Inc, New York, NY; HEL-p TEST, AMRAD Biotech, Victoria, Australia). Serum *H pylori*-specific immunoglobulin A (IgA) antibodies (PP-CAP, Enteric Products, Inc) were studied in some infants (<1 year of age). According to the manufacturer's instructions, the results of each assay were divided into positive, negative, and indeterminate.

### Urine-Based ELISA Method

Urinary IgG antibodies to *H pylori* were assayed using an ELISA kit (URINELISA *H pylori* antibody, Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan). The assay method was as follows. An OHPC-040 *H pylori* strain (*vacA* and *cagA* gene-positive) isolated from a Japanese patient with gastritis was chosen as the best strain for the antigen of the urine-based ELISA.<sup>20</sup> On *H pylori* extracted antigen-coated 96-well microtiter plate, 100  $\mu\text{L}$  of urine samples, 2 positive controls, and 3 negative controls were incubated in 0.2 M Tris aminomethane chloride buffer (pH 7.3) containing 0.001% *Escherichia coli* extracted proteins at  $37^{\circ}\text{C}$  for 1 hour. After washing the wells with buffer solution, 100  $\mu\text{L}$  of horseradish peroxidase-conjugated anti-human goat IgG antibody was added and incubated at  $37^{\circ}\text{C}$  for 1 hour. The wells were rinsed and incubated with 100  $\mu\text{L}$  of 3,3',5,5'-tetramethylbenzidine at room temperature for 15 minutes. After stopping the reaction with 100  $\mu\text{L}$  of stop solution, absorbance of each well was read at 450 nm. Calculations were as follows:

cutoff index (CI) = absorbance of sample tested/cutoff value. Cutoff value = (mean absorbance of 2 positive controls)/8.5 + (mean absorbance of 3 negative controls). CI of <1.0 was judged to be positive and CI of >1.0 was judged to be negative.

### Measurement of IgG Concentration

With regard to analysis of false-positive and false-negative results, serum and urinary IgG concentrations were studied using ELISA method. Anti-human IgG Fc goat IgG antibody was fixed to 96-well microtiter plate in 50 mM phosphate buffer and the walls of the plate were blocked with 0.5% bovine serum albumin (pH 7.4). After an addition of 150  $\mu\text{L}$  of 100 mM Tris-HCl buffer (pH 7.8) to the coated well, 50  $\mu\text{L}$  of IgG standard solutions (3.12–200 ng/mL) and diluted samples were added and incubated at room temperature for 1 hour with shaking. The optimal dilutions of urine and serum samples were 1:51 and 1:262 701, respectively. After incubation, the wells were washed 5 times with phosphate

buffer and 100  $\mu\text{L}$  of horseradish peroxidase-conjugated anti-goat IgG antibody at a dilution of 1:16 000 was added and incubated at room temperature for 1 hour. After washing, each well was incubated with 100  $\mu\text{L}$  of 3,3',5,5'-tetramethylbenzidine substrate solution at room temperature for 15 minutes. After adding 100  $\mu\text{L}$  of stop solution, absorbance of each well was read at 450 nm.

Urinary creatinine concentration was measured using an enzymatic method<sup>23</sup> and values of urinary IgG/creatinine were calculated.

### Statistical Analysis

The difference in positivity rates between serum-based and urine-based ELISAs was analyzed by Fisher's exact test. The differences in IgG concentrations and urinary IgG/creatinine levels between children with coincident and false results were analyzed by Mann-Whitney *U* test. Pearson's correlation coefficient was used to assess a correlation between levels of urine-based ELISA and each serum-based ELISA. A value of  $P < .05$  was regarded as statistically significant. Values were presented as means  $\pm$  standard deviations (SDs).

## RESULTS

### IgG Seroprevalence

Forty-one children were positive for both of 2 serum-based ELISAs and 666 children were negative. These groups were regarded as seropositive and seronegative, respectively. The 707 children who were enrolled in this study were divided into 6 age groups (Table 1). The remaining 109 children showed disagreement between the results of 2 serum-based ELISAs including indeterminate values. Overall seroprevalence was 5.8%. Seroprevalence of age groups of <1, 1 to 3, 4 to 6, 7 to 9, 10 to 12, and 13 to 15 years was 3.3%, 3.0%, 2.0%, 8.3%, 9.4%, and 11.5%, respectively (Fig 1).

### Urine-Based ELISA

Among 707 children studied, the urine-based ELISA was positive in 65 children and was negative in 642. For the urine-based ELISA, positivity rates of age groups of <1, 1 to 3, 4 to 6, 7 to 9, 10 to 12, and 13 to 15 years were 9.7%, 7.6%, 3.9%, 11.3%, 14.2%, and 16.5%, respectively (Fig 1). There were no statistical differences between positivity rates of urine-based and serum-based ELISAs in any age groups. Based on the results of serum-based ELISAs, the overall sensitivity, specificity, and accuracy of urine-based ELISA were 85.4%, 95.5%, and 94.9%, respectively (Table 1): 30 children were false-positive and 6 were false-negative. Although all age groups showed almost equal specificity, the sensitivity varied among the groups. In children in whom all 3 ELISAs were positive, there was no correlation between levels of

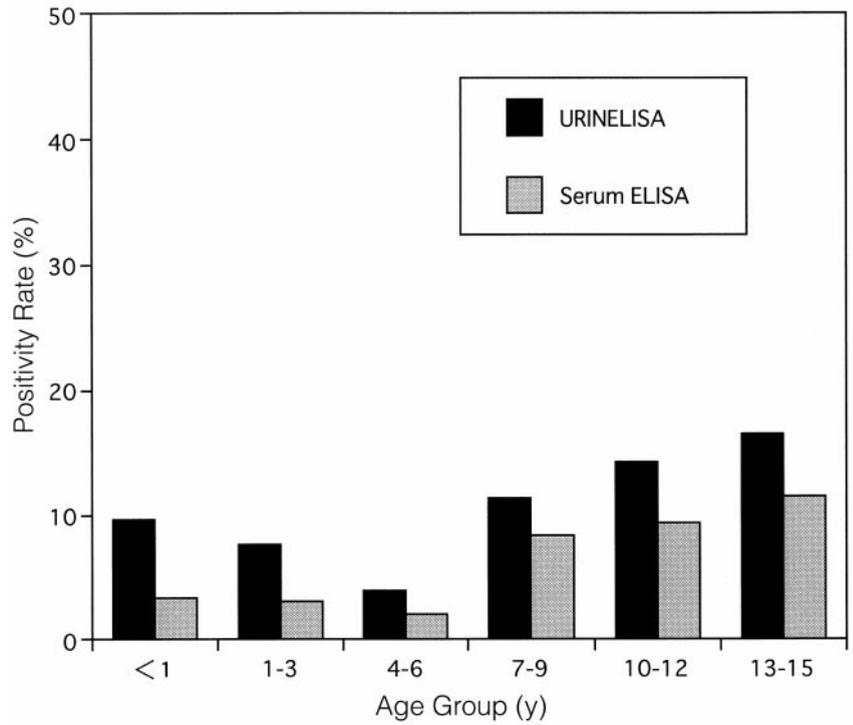
**TABLE 1.** Sensitivity and Specificity of Urine-Based ELISA Compared With Serum ELISA Methods\*

Age (Years)	Number of Patients	Sensitivity	Specificity	Accuracy	PPV	NPV
<1	60	50.0	93.1	91.7	20.0	98.2
1–3	134	100	94.7	94.8	22.2	100
4–6	151	100	99.3	99.3	75.0	100
7–9	133	81.8	95.9	94.7	64.3	91.7
10–12	117	72.7	93.4	91.5	47.1	97.1
13–15	112	100	94.0	94.6	66.7	100
Total	707	85.4 (83–88)	95.5 (94–97)	94.9 (93–96)	53.8 (50–58)	99.1 (98–100)

PPV indicates positive predictive value; NPV, negative predictive value. Ninety-five percent confidence intervals are in parentheses.

\* Based on a combination of 2 ELISA methods.

**Fig 1.** Positivity rates of urine-based ELISA and serum-based ELISAs in each age group. In serum-based ELISAs, a percentage of children in whom both of 2 tests were positive is presented. There were no significant differences of positivity rates between urine-based and serum-based ELISAs in each age group.



urine-based ELISA and those of HM-CAP (Fig 2) or those of HEL-p TEST (Fig 3).

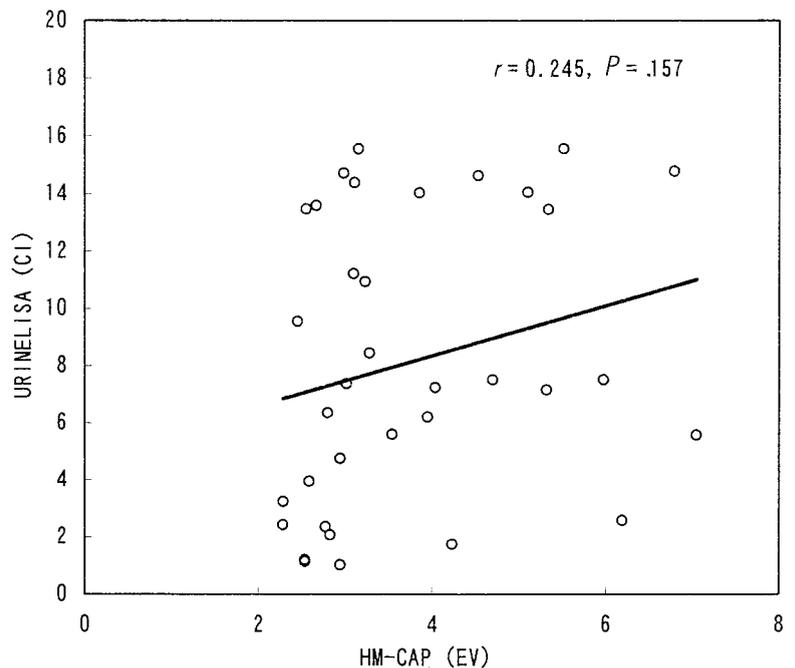
All 5 infants (<1 year of age) with true-positive results for IgG serology were negative for serum *H pylori*-specific IgA antibodies.

**IgG Concentrations**

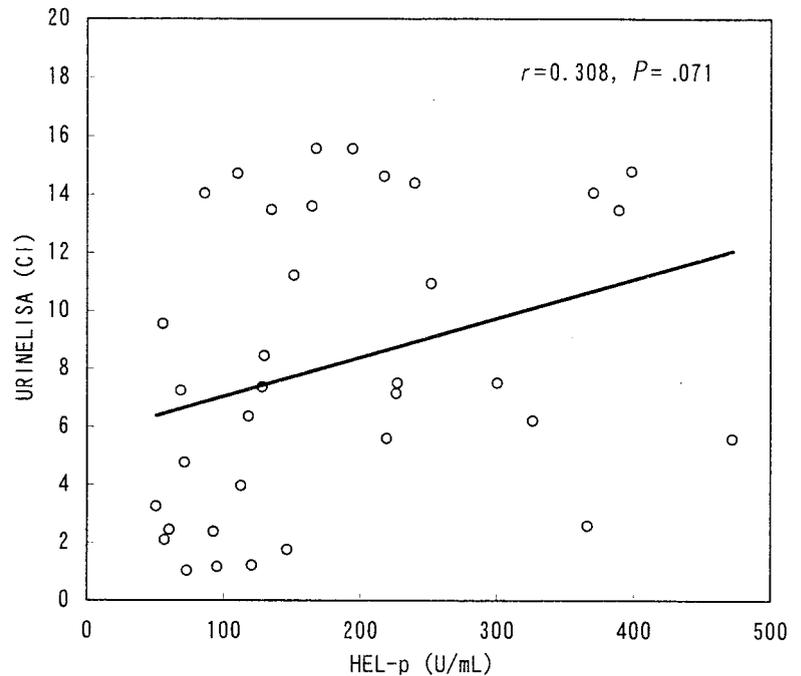
Compared with coincident group (true-positives plus true-negatives for serology), urinary IgG concentrations of false-positives were significantly higher and those of false-negatives were lower (Ta-

ble 2). In addition, statistical differences were also demonstrated in urinary IgG/creatinine levels. Serum IgG concentrations were significantly lower in the false-positive group than in the coincident group (Table 3). There was no difference between the false-negative group and the coincident group. One half of the false-positive children showed trace to moderate proteinuria: diseases included chronic nephritis ( $n = 3$ ), urinary tract infection ( $n = 2$ ), Kawasaki disease ( $n = 2$ ), or acute febrile illness, such as upper respiratory tract infection ( $n = 5$ ), acute enteritis ( $n = 1$ ),

**Fig 2.** A correlation between levels of urine-based ELISA and serum-based ELISA (HM-CAP) in children in whom all 3 ELISA tests were positive ( $n = 35$ ). There was no statistically significant correlation.



**Fig 3.** A correlation between levels of urine-based ELISA and serum-based ELISA (HEL-p) in children in whom all 3 ELISA tests were positive ( $n = 35$ ). There was no statistically significant correlation.



chicken pox ( $n = 1$ ), or mumps meningitis ( $n = 1$ ). In false-negatives, no particular diseases for decreased urinary excretion of IgG were demonstrated.

#### DISCUSSION

In an initial adult study with  $^{13}\text{C}$ -urea breath test,<sup>20</sup> the urine-based ELISA demonstrated the best sensitivity (99%) and specificity (100%) compared with 3 commercially available serum ELISA kits. A larger-scale Japanese study has also reported the excellent results of urine-based ELISA.<sup>21,22</sup> The high sensitivity of the test may be explained in part by the profiles of antigens extracted from the whole cell of *H pylori*.<sup>20</sup> Moreover, the addition of extracted proteins of *E coli* to the assay system reduces cross reactivity, probably contributing to the high degree of specificity. In this study, the specificity of the urine-based ELISA was consistently high, ranging from 93% to 99%. However, there was some variation of the sensitivity between different age groups. The sensitivity was lowest in infants below 1 year of age in particular, with sensitivity rates of 50%, although the number of infants tested was very small. As previously described,<sup>24,25</sup> most of the IgG-seropositive infants were considered to be false-positive, reflecting *H pylori*-specific IgG antibodies transplacentally transmitted from the mother. For this reason, we studied *H pylori*-specific IgA antibodies in these infants; these

antibodies, which represent a local immune response in the stomach, may be a more reliable indicator of active *H pylori* infection than IgG antibodies.<sup>26</sup> In this study, all infants below 1 year of age with positive urine-based ELISA were IgA antibody-negative. For these reasons, we believe that the IgG antibody test to *H pylori* should not be used in this age group.

The results of this study must be interpreted with some caution. It has been pointed out that there has been a lack of standardization and validation of commercial serum ELISA kits in children<sup>12</sup> and that the  $^{13}\text{C}$ -urea breath test or endoscopic biopsy tests are more reliable indicators of *H pylori* status. In this study with a large number of children, however, we could not perform these more reliable tests as the gold standard. We used the coincident positivity or negativity of 2 serologic tests for the presence or absence of *H pylori* infection. In pediatric patients with negative urine-based ELISA, however, additional noninvasive tests such as  $^{13}\text{C}$ -urea breath test may be considered.

Analysis of the ratio of IgG/creatinine levels excludes the possibility that the false-positive or false-negative results were attributable to concentration or dilution of urine samples. Other than the group of infants below 1 year of age, IgG concentrations of randomly voided urine samples were similar to those of healthy adult volunteers (data not shown). It

**TABLE 2.** Urinary IgG Concentrations and IgG/Creatinine Levels in Each Group

Urine-Based ELISA	Number of Patients	IgG Concentration ( $\mu\text{g}/\text{mL}$ )		IgG/Creatinine ( $\mu\text{g}/\text{mg} \cdot \text{Creatinine}$ )	
		Mean $\pm$ SD	P Value†	Mean $\pm$ SD	P Value†
Coincident*	356	3.1 $\pm$ 5.4		5.9 $\pm$ 9.8	
False-positive	30	68.0 $\pm$ 137.0	<.001	88.8 $\pm$ 151.1	<.001
False-negative	6	0.5 $\pm$ 0.5	.009	1.5 $\pm$ 1.5	.026

\* True-positive and true-negative cases.

† Compared with coincident group.

**TABLE 3.** Serum IgG Concentrations in Each Group

Urine-Based ELISA	Number of Patients	IgG Concentration (mg/mL)	
		Mean $\pm$ SD	P Value†
Coincident*	30	11.5 $\pm$ 3.7	
False-positive	30	8.5 $\pm$ 3.8	<.005
False-negative	6	12.8 $\pm$ 2.6	.270

\* True-positive and true-negative cases.

† Compared with coincident group.

is concluded that *H pylori*-specific IgG antibodies can be detected by a random collection of the urine. That there was no correlation between serum and urinary levels of specific IgG antibodies may be related to the random sampling of urine. Most children with false-positive results showed increased IgG concentrations in the urine and proteinuria in various degrees. In contrast, the mean serum IgG concentration of false-positives was lower than that of the coincident group. Increased urinary IgG concentrations seem to be associated with nonselective proteinuria but not with excessive urinary excretion of IgG. In children with transient or persistent proteinuria, the urine-based ELISA for the detection of *H pylori*-specific IgG antibodies should be cautiously interpreted. With regard to false-negative results, urinary IgG concentrations in such cases were significantly low. However, there was no difference of serum IgG concentrations between false-negatives and coincident group. No specific diseases that could link to reduced urinary IgG excretion have been demonstrated. The exact reason of decreased urinary IgG concentrations remains unclear.

Because of noninvasive and easier collection of samples, the urine-based ELISA is a desirable diagnostic method in children. Based on this study, we believe that the urine-based ELISA may be an alternative to serum-based ELISA for diagnosis of *H pylori* infection in pediatric patients in whom peptic ulcer disease or gastritis is suspected. If other *H pylori* tests are used together, the higher diagnostic accuracy of the infection is expected. *H pylori*-specific IgG antibodies in urine are stable for at least 60 days at 4°C.<sup>20</sup> Therefore, the method should be suitable for large-scale epidemiologic studies concerning the organism. In the near future, the urine-based ELISA method might be available for noninvasive diagnosis of various infectious diseases.

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