Comparision of endoscopy-based and serum-based methods for the diagnosis of *Helicobacter pylori*

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Available commercial tests for the diagnosis of *Helicobacter pylori* infection are based on different types of antigen preparations and hence the diagnostic utility differs substantially.

OBJECTIVE: To assess the diagnostic value of the determination of Immunoglobulin (Ig) A and IgG antibodies to *H pylori* whole cell (WC) and IgG antibodies to cytotoxin associated gene A (*CagA*) using an in-house ELISA in relation to the results obtained with different invasive methods.

METHODS: The study population consisted of 251 Mexican adults, mean age 53 years, age range 15 to 92 years and female to male ratio of 1.5. Peptic ulcer disease was present in 10.8% of these patients, 5.2% had gastric cancer, 11.2% had esophagitis and 72.9% had nonulcer dyspepsia. Biopsy specimens from the body and the antrum of the stomach were obtained for culture, histology and rapid urease test. ELISAs to detect IgA and IgG WC and *CagA* antibodies were performed using serum.

RESULTS: *H pylori* status was established by the results of the invasive tests. Eighty (31.9%) patients positive to the three tests and 38 (15.1%) negative to all the tests were identified. Based on this result, the sensitivity and specificity of the serology assays were 97.5% and 78.9% for the IgG WC and 70% and 73.7% for the IgA WC, respectively. However, if *H pylori* status was defined by the positive result of at least one or two invasive diagnostic tests, the sensitivity for the IgG WC decreased to 87.3% and 66.7% respectively, but the specificity was essentially the same. Similar results were obtained for the sensitivity and specificity of IgA using the same criteria. A low *CagA* prevalence was observed (39%).

CONCLUSIONS: Testing for serological IgG antibodies to *H pylori* WC was the best to assess whether infection by *H pylori* was present. Neither the IgA WC nor the IgG *CagA* ELISAs add significant value in the diagnosis of *H pylori*.

Key Words: *Diagnosis; Helicobacter; Serology*

Comparaison entre un diagnostic d'*Helicobacter pylori* par endoscopie et par sérologie

Les tests commerciaux sur le marché permettant de diagnostiquer une infection à *Helicobacter pylori* dépendent de divers types de préparations antigéniques. Par conséquent, l'utilité diagnostique varie énormément.

OBJECTIF : Évaluer la valeur diagnostique de la détermination d'anticorps à l'immunoglobuline (Ig) A et IgG à la cellule entière d'*Helicobacter pylori* et d'anticorps IgG au gène A associé à la cytotoxine (*CagA*) au moyen d'un test ELISA maison par rapport aux résultats obtenus au moyen de diverses méthodes effractives.

MÉTHODOLOGIE : La population à l'étude se composait de 251 adultes mexicains d'un âge moyen de 53 ans, mais dont l'âge variait de 15 à 92 ans. Le ratio entre les femmes et les hommes s'établissait à 1,5. Un ulcère gastroduodénal s'observait chez 10,8 % de ces patients, tandis que 5,2 % avaient un cancer gastrique, 11,2 %, une œsophagite et 72,9 %, une dyspepsie non ulcéreuse. Les spécimens de biopsie prélevés dans l'organisme et dans l'antre de l'estomac out permis d'effectuer une culture, une histologie et un test rapide d'uréase. Des tests ELISA afin de déceler des CE IgA et IgG et des anticorps *CagA* ont été effectués à l'aide de sérum.

RÉSULTATS : Le statut du *H pylori* a été établi par les résultats des tests effractifs. On a repéré quatre-vingts (31,9 %) patients ayant obtenu des résultats positifs aux trois tests et 38 (15,1 %), des résultats négatifs. D'après ce résultat, la sensibilité et la spécificité des essais sérologiques étaient de 97,5 % et de 78,9 % pour ce qui est de la CE IgG et de 70 % et 73,7 % pour ce qui est de la CE IgA, respectivement. Cependant, si le statut du *H pylori* était défini par le résultat positif d'au moins un ou deux tests diagnostiques effractifs, la sensibilité à la CE IgG diminuait à 87,3 % et à 66,7 %, respectivement, mais la spécificité demeurait sensiblement la même. Des résultats similaires résultaient de la sensibilité et de la spécificité de l'IgA, selon les mêmes critères. On remarquait une prévalence de *CagA* peu élevé (39 %).

CONCLUSIONS : La vérification d'anticorps IgG sérologiques à la CE du *H pylori* était la plus efficace pour évaluer la présence d'une infection à *H pylori*. Ni la CE IgA ni les tests ELISA IgG *CagA* n'ajoutait de valeur significative au diagnostic de *H pylori*.

Different diagnostic methods are used to assess *Helicobacter pylori* infection. Upper gastroduodendoscopic analysis and gastric biopsy samples are required for invasive methods such as culture, histological analysis or rapid urease test (RUT) (1-4). These tests have been traditionally used as the gold standard because they demonstrate directly or indirectly the presence of the bacteria. However, those methods have some inconveniences such as the discomfort for the patient and the costly and

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time consuming methodologies involved in the procedure. Among the noninvasive tests, the carbon labelled urea breath test (UBT) and the detection of serum antibodies specific to *H pylori* antigens are the most commonly used (2). The UBT detects the activity of urease produced by the bacteria employing carbon labelled urea, which is administrated orally and detected later as radiolabelled carbon dioxide. This test has some inconveniences such as its cost, the requirement of a special instrument and the management of radioactive isotopes (1,2).

The determination of serum immunoglobulins (Igs) G and A to a whole cell (WC) antigen preparation is very useful for the diagnosis of infection by *H pylori*. It has some important advantages compared with other diagnostic methods because it is simple and inexpensive, and no major equipment is required. Commercial serological assays for detection of serum IgG and IgA WC antibodies have variable sensitivity and specificity mainly because they are based on various antigen preparations (1,5-7). For this reason, it is necessary to assess the diagnostic utility of these methods before using them to determine the prevalence of *H pylori* in a particular geographic location. The main goal of this study was to compare the traditional endoscopy-based diagnostic methods with serum diagnostic methods for the detection of *H pylori* infection.

MATERIALS AND METHODS

Patient population

The study population consisted of 251 Mexican adults patients (mean age 53 years, age range 15 to 92 years, female to male ratio 1.5) who were subjected to an upper gastroduodenoscopic analysis at the Gastroenterology Service, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Mexico from February to December 2000. Each patient signed an informed consent form approved by the hospital. The patients enrolled had not received antibiotics or proton pump inhibitory drugs during the four weeks before endoscopy.

The presence of gastric cancer or peptic ulcer disease was defined according to histological and endoscopic findings. The presence of nonulcer dyspepsia was defined when no organic disease was found and the patient presented with upper abdominal or epigastric pain, symptoms related to meals and other symptoms such as heartburn, nausea or vomiting (8).

A total of 13 biopsy specimens from the antrum and body of the stomach for culture, histology and RUT were obtained in each patient by upper endoscopy under local anesthesia using an EG-290P (Pentax Precision Instrument Corporation, USA) endoscope. Serum samples were also obtained and frozen at –20°C until tested.

Bacteria and growth conditions

Four stomach biopsy specimens (two from the antrum and two from the body) were placed directly in Stuart's transport media and carried to the laboratory immediately. Specimens were placed in Brucella broth and plated in 1% IsoVitaleX enrichment Columbia agar plates (Becton Dickinson, USA) supplemented with 10% of blood and incubated at 37°C for 96 h under microaerobic conditions using the Campy Pouch System (Becton Dickinson). Strains were identified by Gram staining, oxidase, catalase and urease tests.

Histopathological examinations

During the endoscopic procedure, eight biopsy specimens were obtained for detection of the bacteria and histological evaluation: two from the lower curvature, two from the greater curvature, two from the incisura angularis, and two from the prepiloric region of the stomach. All sample biopsies were fixed in 10% formalin and paraffin embedded. Multiple 4 mm thick histological sections were obtained from each biopsy fragment and stained with hematoxylin-eosin for histopathological evaluation. A single experienced pathologist performed all histological examinations unaware of the results of the other tests.

RUT

One single antrum biopsy specimen was placed in a test vial for the RUT, incubated at 37°C and read after a maximum of 24 h. A colour change from orange to magenta indicated a positive result. No change in colour indicated a negative result.

Serology

Enzyme-linked immunoabsorbent assays (ELISAs) were used to study the presence of IgA and IgG antibodies to WC in patient's serum samples as previously described (9).

CagA status was determined by an ELISA based on the presence of serum IgG antibodies against a recombinant *CagA* protein purified from *Escherichia coli* (9). This method has been previously validated in an American population and has a sensitivity of 94.4% and a specificity of 92.5% (9).

Each antigen suspension was used to coat microtitre well plates (Dynex Technologies, USA) and the serum dilutions used were 1:800 for IgG WC and 1:100 for IgA WC and IgG *CagA*. An anti-human IgG or IgA conjugated to horseradish peroxidase (Biosource International, USA) was used and the substrate for colour development was 2,2'-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (Sigma Chemical Company, USA). Absorbance was read at 405 nm and data were analyzed using the program Revelation 2.0 (Dynex Technologies, USA). To correct for plate-to-plate and day-by-day variation, the results were expressed as optical density ratio (ODR) in relation to the mean of four standard positive control sera. For IgG and IgA WC, an ODR value of one or higher was considered to be positive, while a value of less than one was considered negative. For the IgG *CagA*, an ODR value of 0.35 or greater was considered to be positive, while a value of less than 0.35 was considered to be negative. All serological assays were performed in duplicate on two different days.

Definition of *H pylori* status

H pylori status was established according to the results obtained by histology, UBT and culture, which were considered the gold standard methods in the diagnosis of *H pylori*. We defined a patient as infected with *H pylori* based on three criteria: a patient was considered to be positive when all three invasive tests were positive; a patient was positive if at least two invasive diagnostic tests were positive; and a patient was considered to be positive when at least one invasive test was positive. Patients were considered *H pylori* uninfected only if all the invasive tests were negative.

TABLE 1
Characteristics of the patient population studied

	n (251)
Female to male ratio	1.5
Mean age ± SD	53±18.7
Age range	15-92 years
Peptic ulcer disease (n [%])	27 (10.8)
Nonulcer dyspepsia (n [%])	183 (72.8)
Esophagitis (n [%])	28 (11.2)
Cancer (n [%])	13 (5.2)

Statistical analysis

Statistically significant differences were determined by Student's *t* test, χ^2 or Fisher exact test two tailed as dictated by sample size. $P<0.05$ was considered to be statistically significant.

RESULTS

Characteristics of the study population

The characteristics of the studied population are described in Table 1. The population consisted mainly of women. Among clinical presentation, most of the patients presented with nonulcer dyspepsia.

The patients entered the study consecutively as they underwent gastroduodenoscopy and fit the inclusion criteria. For this reason, the characteristics of the study population and the clinical outcomes may not be similar to the characteristics of the general population of the city where the study was performed.

Assessment of accuracy of IgG and IgA WC tests

The diagnostic value was determined for IgG (Table 2) and IgA (Table 3) WC tests using the three criteria of positivity for *H pylori* defined in the materials and methods section. The IgG performed better than the IgA based on the accuracy and the result of the positive likelihood ratio, whether the diagnosis of infection by *H pylori* was defined by the positive result in one, two or all three biopsy-based tests.

There were no observations of a major impact in the specificity of the serological tests when the criteria to define the *H pylori* status was changed. However, the changes in those criteria had a major effect in the accuracy and negative predictive value of the assays. These results are consistent with some of the major limitations of the serological assays. Overall, the IgG WC assay showed better sensitivity, specificity, positive predicitve values and negative predictive values than the IgA assay. According to the criteria that considered a patient *H pylori*

TABLE 2
Assessment of the diagnostic value of the IgG tests for *Helicobacter pylori* infection*

	IgG WC†	IgG WC‡	IgG WC§
Positive	78	89	142
Negative	2	13	71
Sensitivity (95% CI)	97.5 (94.1-100.9)	87.3 (80.8-93.7)	66.7 (60.3-73)
Specificity (95% CI)	78.9 (66-91.9)	78.9 (66-91.9)	78.9 (66-91.9)
Accuracy (95% CI)	91.5 (86.5-96.5)	85 (79-90.9)	68.5 (62.8-74.3)
PPV (95% CI)	90.7 (84.6-96.8)	91.8 (86.3-97.2)	94.7 (91.1-98.3)
NPV (95% CI)	93.8 (85.4-102.1)	69.8 (56-83.5)	29.7 (20.8-38.6)
LR+ (95% CI)	4.6 (2.5-8.6)	4.1 (2.2-7.7)	3.2 (1.7-5.9)
LR- (95% CI)	0.0 (0-.1)	0.2 (0.1-0.3)	0.4 (0.3-0.5)

**Patients with all invasive tests negative, eight were positive and 30 were negative; †*H pylori *status was defined on the basis of positive results of all three invasive tests; ‡*H pylori *status was defined on the basis of positive results at least in two invasive tests; §*H pylori *status was defined on the basis of a positive result in at least one invasive test. Ig Immunoglobulin; LR- Negative likelihood ratio; LR+ Positive likelihood ratio; NPV Negative predictive value; PPV Positive predictive value;WC Whole cell*

TABLE 3
Assessment of the diagnostic value of the IgA tests for *Helicobacter pylori* infection*

	IgA WC†	IgA WC‡	IgA WC§
Positive	56	71	80
Negative	24	31	133
Sensitivity (95% CI)	70 (60-80)	69.6 (60.7-78.5)	37.6 (0.3-0.4)
Specificity (95% CI)	73.7 (59.7-87.7)	73.7 (59.7-87.7)	73.7 (0.6-0.9)
Accuracy (95% CI)	71.2 (63-79.4)	70.7 (63.2-78.3)	43 (0.4-0.5)
PPV (95% CI)	84.8 (76.2-93.5)	87.7 (80.5-94.8)	88.9 (0.8-1)
NPV (95% CI)	53.8 (40.3-67.4)	47.5 (34.7-60.2)	17.4 (0.1-0.2)
LR+ (95% CI)	2.7 (1.5-4.6)	2.6 (1.5-4.6)	1.4 (0.8-2.5)
LR- (95% CI)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.8 (0.7-1)

**Patients with all invasive tests negative, eight were positive and 30 were negative; †*H pylori *status was defined on the basis of positive results of all three invasive tests; ‡*H pylori *status was defined on the basis of positive results at least in two invasive tests; §*H pylori *status was defined on the basis of a positive result in at least one invasive tests. Ig Immunoglobulin; LR- Negative likelihood ratio; LR+ Positive likelihood ratio; NPV Negative predictive value; PPV Positive predictive value WC Whole cell*

TABLE 4
Sensitivity of the serological assays for each combination of results of the invasive tests.

n	Invasive assay			n (%) positive		
	Histology	RUT	Culture	IgG WC	IgA WC	*CagA*
80	+	+	+	78 (97.5)	56 (70)	38 (47.5)
38	-	-	-	8 (21.1)	10 (26.3)	11 (29)
108	+	-	-	52 (48.1)	62 (57.4)	36 (33.3)
3	-	+	-	1 (33.3)	1 (33.3)	0 (0)
8	+	+	-	7 (87.5)	7 (87.5)	6 (75)
13	-	+	+	3 (23.1)	7 (53.8)	7 (53.9)
1	+	-	+	1 (100)	1 (100)	0 (0)

CagA *Cytotoxin associated gene A; Ig Immunoglobulin; RUT Rapid urease test; WC Whole cell*

positive if all three invasive tests were positive, 80 (31.9%) patients infected with *H pylori* and 38 (15.1%) noninfected patients were identified. Among the noninfected patients, eight had a positive response to IgG WC antibodies and 30 patients did not. However, the IgG WC ODR values in the noninfected seropositive patients were lower than the ODR values obtained in the infected seropositive patients (P<0.01; data not shown). In addition, the mean age of noninfected seronegative patients was lower than the mean age of noninfected seropositive patients (P<0.05; data not shown).

Assessment of accuracy of IgG and IgA WC tests for each combination of results of invasive tests

The sensitivity of IgG and IgA WC assays was calculated for each combination of results (Table 4). Patients with a positive result in histology as the only *H pylori* positive invasive test were the majority (81.2%). Patients with culture positive and negative results for the other two tests were not observed. According to these results, if *H pylori* status was defined by the result of the histology, the RUT, or by both RUT and culture, the calculated sensitivities of the IgG and IgA WC assays were significantly lower than the sensitivity described when the diagnosis was established with all three invasive tests positive (P<0.05). In contrast, if the status of *H pylori* infection was determined by the combined result of histology and RUT, nonsignificant difference in the sensitivity for both IgG and IgA WC serological tests was observed when compared with patients in whom all three invasive tests were positive. Interestingly, when histology and culture were positive and only the RUT was negative among the invasive tests, the determination of serum IgG and IgA WC has an excellent sensitivity (100%). However, because only one patient with this combination of results was found, meaningful comparisons could not be made.

Value of *CagA* serology in the assessment of *H pyloris* status

Serological response to *CagA* in patients classified as *H pylori*-positive (all three tests positive), *H pylori*-negative (all three assays negative) and in patients with only one or two invasive diagnostic tests positive were also evaluated and tabulated (Table 4). The overall prevalence of *H pylori CagA*-positive was 39%.

In *H pylori*-negative patients, 11 (29.0%) had a positive serological response to *CagA*. However, in five (13.5%) of those patients, the IgG WC *H pylori* ELISA was also positive, which may suggest that these patients were indeed infected with *H pylori* but the invasive tests missed them. In patients classified as true positive for *H pylori*, 47.5% were infected with *CagA*-positive *H pylori* strains.

No differences in serologic response to *CagA* were detected among the groups of patients with only one test positive, nor were there differences in response among the group with two positive invasive tests (RUT and culture). A higher (75%) prevalence of *CagA* was observed in the group of patients with positive histology and RUT. However, it was not significant when compared with the other groups.

No differences associated with age were found among the groups of patients with each combination of results of invasive tests.

Association of histology and the results of the diagnostic tests for *H pylori*

Histological findings in relation to the different combinations of results of the invasive and noninvasive tests were tabulated (Table 5). Based on the previous results, the IgG WC was considered to be the only noninvasive test.

The presence of gastritis, atrophic gastritis, hyperplasia, intestinal metaplasia, high-grade dysplasia and gastric cancer were some of the pathologies found among the patients in this study. As expected, the most frequent histological finding was chronic gastritis. None of the gastric cancer patients were positive for culture. The most frequent result was positive histology in patients with a positive status for *H pylori* compared with the other invasive tests (P<0.01). Among patients positive for IgG WC antibodies, the presence of atrophic gastritis, hyperplasia or intestinal metaplasia was associated to only one positive invasive test (P<0.05). The association between a single invasive test with a positive IgG WC was more significant in patients with gastric cancer or high grade dysplasia (P=0.02).

DISCUSSION

The selection of the proper tests for the diagnosis of infection by *H pylori* requires the consideration of different factors, such as clinical outcome, the diagnostic value of the test and the facilities to obtain the specimens required, as well as the cost. The gastroduodenoscopy is essential for primary diagnosis of infection by *H pylori* when a visual analysis of the upper digestive tract is necessary and/or to obtain biopsy samples for histo-

TABLE 5
Histological findings in the different combination of results in the invasive test in relation to the IgG WC status

Invasive test for *Helicobacter pylori* diagnosis			Histological finding n (%)		
	IgG WC	n	Gastritis	AG, Hyper or IM	HGD or GC
At least two positive tests	+	89	70 (78.7)	18 (20.2)*	1 (1.1)†
	-	13	10 (76.9)	3 (23.1)	0 (0)
One positive test	+	53	26 (49.1)	19 (35.8)*	8 (15.1)†
	-	58	49 (84.5)	7 (12.1)	2 (3.4)

**Among patients positive for Immunoglobulin (Ig) G whole cell (WC) antibodies, the presence of atrophic gastritis, hyperplasia or intestinal metaplasia was associated to only one invasive test positive (P<0.05); †Among patients positive for IgG WC antibodies, the presence of high grade dysplasia or gastric cancer was associated to only one invasive test positive (P=0.02).*

logical analysis, RUT and/or culture. Although these invasive tests are considered to be standards, they have some inconveniences that make them unreliable due to the patchy nature of the colonization of the gastric mucosa by *H pylori* or because they are not available in some cases, such as the study of the pediatric population or in epidemiological studies (10,11).

In general, nonendoscopic tests are more convenient and more comfortable for the patient. Serological tests inexpensively detect circulating IgG or IgA antibodies and are very useful if endoscopy is not indicated. It has been demonstrated that endoscopy can be omitted in 34% of seropositive cases, regardless of age, and in 27% of seronegative cases when screening for IgG antibodies against *H pylori* is used to detect the infection (12).

In our study population, we defined the *H pylori* status based on the results of three invasive tests, and we compared these results with the serological diagnosis that measured IgA WC, IgG WC and *CagA* antibodies. We found that IgG WC antibodies have the best serological diagnostic value to assess the presence of *H pylori*, whether the diagnosis of infection was done by the positive result of three, two or at least one invasive test. Furthermore, it is an accurate and a cost effective alternative for the diagnosis of infection by *H pylori*.

We assessed the diagnostic value of IgG and IgA using the positive result of only one invasive test (histology, RUT or culture) as the gold standard, and we found that the performance of both serological tests was lower than the diagnostic value obtained when the diagnosis of infection was performed by the positive result of all three or at least two diagnostic tests. It has been suggested that the diagnosis of *H pylori* infection should be done by the positive result of at least two diagnostic tests, and our results clearly confirm that suggestion.

Our results suggested that it is not necessary to carry out other serological tests to assess the infection, because the IgA WC ELISA does not represent a significant value in the diagnosis of *H pylori*. In patients with discrepancies in results from the invasive tests, the results of WC IgG and IgA tests were analyzed for each combination of results. In patients with histology and RUT positives, the sensitivity value was statistically equal to the value obtained when compared with the three invasive test positives, which suggests that the combination of results is convenient for routine diagnosis. In this combination only the culture was negative among the invasive tests. Several authors (11,13) have described that different factors may affect the results of culture, such as the transport medium, the time elapsed between the obtention and inoculation of biopsies, the culture medium used, the system to obtain microaerobiosis and the amount of microorganisms in the biopsies. Because all samples were cultured in basically the same conditions, it is possible that the amount of bacteria present was not enough to be detected by culture. This idea is also supported by the observation of a higher frequency of cancer and dysplasia in patients with only a positive histology; previous work has found that premalignant and malignant epithelia is not suitable for the growth of *H pylori* (14).

We found that among the noninfected seropositive patients, IgG WC ODR values were lower than the ODR values obtained in the infected patients. This may suggest that noninfected but seropositive patients have serum antibodies in the absence of infection, particularly in this study population where the prevalence is high (64.2%) (10). The ODR values were reanalyzed and no forceful cut-off value was obtained. The consideration of a grey zone for interpretation of the ELISA test is feasible.

The correlation of histological findings and the results of invasive tests with the IgG WC serology showed that among patients with atrophic gastritis, hyperplasia, intestinal metaplasia, high grade dysplasia or gastric cancer, only one invasive test and the presence of IgG WC antibodies were positive. These results confirmed that the likelihood of a positive result among invasive tests is markedly reduced if the patient has any of these histological findings.

Several groups (15-17) have reported a limited diagnostic utility in the determination of IgG WC antibodies to asses the eradication of *H pylori* after treatment mainly because antibody titres decrease slowly in patients whose *H pylori* has been successfully eradicated. However, some studies reported that pretreatment and post-treatment IgG titres are useful for monitoring the disappearance of infection in the human stomach (15-17). Our results showed the diagnostic utility of the serological assays for assessing the infection by *H pylori*, further studies should be done to define its utility to detect the eradication of the bacteria.

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