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Accuracy of Monoclonal Stool Antigen Test for the Diagnosis of *H. pylori* Infection: A Systematic Review and Meta-Analysis

Javier P. Gisbert, Ph.D.,[1] Felipe de la Morena, M.D.,[1] and Víctor Abraira, Ph.D.[2]
[1]*Department of Gastroenterology, "La Princesa" University Hospital, Universidad Autónoma; and* [2]*Clinical Biostatistics Unit, "Ramón y Cajal" University Hospital, Node of R_EBM Research Network, Departamento de Matemática Aplicada (Biomatemática), Universidad Complutense, Madrid, Spain*

OBJECTIVE: To perform a systematic review and a meta-analysis of accuracy of monoclonal stool antigen test (SAT) for the diagnosis of *Helicobacter pylori* infection.

METHODS: *Selection of studies:* assessing the accuracy of monoclonal SAT for the diagnosis of *H. pylori* infection. *Search strategy:* electronic and manual bibliographical searches. *Data extraction:* independently done by two reviewers. *Data synthesis*: meta-analyses combining the sensitivities, specificities, and likelihood ratios (LRs) of the individual studies.

RESULTS: Twenty-two studies, including 2,499 patients, evaluated the monoclonal SAT before eradication therapy. Pooled sensitivity, specificity, LR+, and LR− were: 0.94 (95% CI 0.93–0.95), 0.97 (0.96–0.98), 24 (15–41), and 0.07 (0.04–0.12). The accuracy of both monoclonal and polyclonal SAT was evaluated together in 13 pretreatment studies, and higher pooled sensitivity was demonstrated with the monoclonal technique (0.95 *vs* 0.83). Twelve studies, including 957 patients, assessed the monoclonal SAT to confirm eradication after therapy. Pooled sensitivity, specificity, LR+, and LR− were 0.93 (0.89–0.96), 0.96 (0.94–0.97), 17 (12–23), and 0.1 (0.07–0.15). Both tests were evaluated together in eight post-treatment studies and, again, the monoclonal technique showed higher sensitivity (0.91 *vs* 0.76). Heterogeneity among studies disappeared when a single outlier study was excluded. Subanalysis depending on the reference method, the study population, or the study quality showed similar results.

CONCLUSION: Monoclonal SAT is an accurate noninvasive method both for the initial diagnosis of *H. pylori* infection and for the confirmation of its eradication after treatment. The monoclonal technique has higher sensitivity than the polyclonal one, especially in the post-treatment setting.

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INTRODUCTION

Helicobacter pylori infection plays a fundamental role in the development of several gastroduodenal diseases and, therefore, the diagnosis of the infection represents a clinically relevant chapter. The methods for the diagnosis of *H. pylori* infection are classically divided into invasive and noninvasive (1). The former are based on the demonstration of the organism from gastric biopsy samples, therefore an endoscopy has to be performed. On the other hand, noninvasive methods, which require no endoscopic examination, are also available. Among noninvasive techniques, serology and urea breath test are the classically considered and the most widely used. Most recently, a novel noninvasive diagnostic test based on the detection of *H. pylori* stool antigen has been developed (1).

The first developed *H. pylori* stool antigen test (SAT), Premier Platinum HpSA™ (Meridian Diagnostics), used polyclonal antibodies to *H. pylori*. More recently, a novel SAT, a quantitative enzyme immunoassay (EIA) based on monoclonal—instead of polyclonal—antibodies, has been developed. Recently, two exhaustive reviews on the diagnosis of *H. pylori* infection by SAT have been performed, but they are mainly focused on the polyclonal method (2, 3). Since then, several articles have been published on that issue, adding a considerable amount of new information and making necessary an update of the role of monoclonal SAT. Furthermore, up to now, no formal meta-analysis has evaluated the accuracy of monoclonal SAT, nor has it directly compared monoclonal and polyclonal techniques. Theoretically, the monoclonal antibody-based SAT would have increased accuracy because of increased antigenic specificity.

Therefore, our objective was to perform a systematic review and a meta-analysis of accuracy of monoclonal SAT both for the initial diagnosis of *H. pylori* infection and for the confirmation of its eradication after treatment.

METHODS

Selection of Studies

Studies assessing the accuracy of monoclonal SAT for the diagnosis of *H. pylori* infection were considered. Gold standard for *H. pylori* infection should be based on at least one independent diagnostic method. "In-office" or "rapid" stool test, including MiniLab™ (Connex Diagnostics), Stick *H. pylori* (Operon S.A.), or ImmunoCard STAT HpSA (Meridian Bioscience, Europe), were not included, as controversial results have been reported with this novel technique (3). Studies evaluating the SAT in specific conditions, such as in patients with end-stage renal disease, cirrhosis, or partial gastrectomy, were also excluded, as these circumstances have been described to negatively influence the performance of the stool test (3).

Search Strategy

Bibliographical searches were performed, up to November 2005, in MEDLINE and EMBASE electronic databases, and in the Cochrane Library (issue 4, 2005), looking for the following words (all fields): "*Helicobacter pylori*" or "*H. pylori*" on one hand, and "stool" or "fecal" or "faecal" or "feces" or "faeces," on the other. We also conducted a manual search of abstracts available until November 2005 from the International Workshop on Gastroduodenal Pathology and *H. pylori* (EHPSG) and the American Digestive Disease Week (DDW). We included abstracts from congresses on the grounds that many negative or redundant studies are never published as a full article, and the inclusion of abstracts thus prevents, or at least reduces, publication bias. Abstracts of the articles selected in each of these multiple searches were reviewed and those meeting the inclusion criteria were recorded. References of reviews on diagnostic methods for *H. pylori* infection, and from the articles selected for the study, were also examined in search of articles meeting inclusion criteria. Articles published in any language, except Japanese, were included. Publications identified as duplicates were excluded.

Assessment of Study Quality

The quality of the studies was assessed using the "Quality Assessment of Diagnostic Accuracy Studies" (QUADAS) tool (4). This is the first tool for the assessment of the quality of diagnostic accuracy studies, which has been systematically developed and is evidence based (4). The tool is based on the 14 item questions summarized in Table 1, which should each be answered "yes," "no," or "unclear." Quality assessment of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus. The tool does not incorporate a (global) quality score, the reasons for this being justified in detail in the original article describing the QUADAS tool (4). Among these reasons, the most noteworthy is that quality scores ignore the fact that the importance of individual items and the direction of potential biases associated with these items may vary according to the context in which they are applied (4). Therefore, the application of quality scores, with no consideration of the individual quality items, may dilute or entirely miss potential association (4).

Data Extraction

The following variables were extracted from the original studies in a predefined data extraction form (see Table 2, including studies evaluating monoclonal *H. pylori* SAT for the diagnosis of the infection before therapy): Author, year of publication, publication format (abstract or journal article), study population (adults or children), *H. pylori* prevalence, gold standard (based on only one or at least two reference methods), and stool antigen diagnostic technique (monoclonal in all cases, and also polyclonal in some studies). In addition, for the studies evaluating *H. pylori* SAT to confirm *H. pylori* cure after therapy (see Table 3), eradication rate with the prescribed treatment, and number of weeks after completing antibiotic regimen—when eradication was assessed—were also extracted. True positives, false positives, false negatives, and true negatives with the monoclonal SAT were included. Finally, when the polyclonal SAT was also evaluated in these studies, true positives, false positives, false negatives, and true negatives with this test were also included. Extraction of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus.

Several studies have shown that the manufacturer's recommendations do not always coincide with the best cutoff point calculated by statistical methods. Nevertheless, as the use of the cutoff point arising from a study as a reflection of the performance accuracy of the test in the general population may flaw the results, we have always calculated the accuracy of SAT using the cutoff recommended by the manufacturer, except in those studies in which only the cutoff point calculated and proposed by the authors was available (see Table 2).

Data Synthesis

The sensitivity, specificity, positive and negative likelihood ratios (LRs), and their corresponding 95% confidence intervals (95% CIs) were calculated for each study. LRs state how many times more likely particular test results are in patients with disease than in those without disease (5). LRs can be used to adapt the results of a study to your patients. Using the Bayes theorem, the posttest odds that the patient has the disease are estimated by multiplying the pretest odds by the LR. Positive LRs >10 and negative LRs <0.1 have been noted as providing *convincing* diagnostic evidence, whereas those >5 and <0.2 give *strong* diagnostic evidence (6). To calculate LRs, if the event of one of the cells of the cross table contained a zero value, 0.5 points were added to all the cells.

The heterogeneity of all indexes was evaluated by the graphic examination of the forest plots, and statistically through a homogeneity test based on the χ^2 test. As a result of the low power of this test, a minimum cutoff p value of 0.1 was established as a threshold of homogeneity, lower values indicating heterogeneity. In addition, the I^2 statistic was calculated to assess the impact of heterogeneity on the

Table 1. "Quality Assessment of Diagnostic Accuracy Studies" (QUADAS) Tool

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Agha-Amiri *et al.* (11)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y
Andrews *et al*. (12)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	U	Y	Y
Asfeldt *et al*. (13)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Calvet *et al*. (15)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Chisholm *et al*. (16)	Y	N	Y	U	Y	Y	Y	Y	N	U	U	U	Y	Y
Chisholm *et al*. (17)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y
Dore *et al*. (18)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Erzin *et al*. (19)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y
Erzin *et al*. (42)	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U	U	Y	N
Hino *et al*. (22)	Y	N	N	U	Y	Y	Y	Y	Y	U	U	U	Y	N
Ignys *et al*. (23)	Y	Y	Y	U	Y	Y	Y	Y	N	U	U	U	U	Y
Koletzko *et al*. (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Konstantopoulos *et al*. (44)	Y	N	N	Y	Y	Y	Y	Y	N	U	U	U	Y	Y
Leodolter *et al*. (43)	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y
Makristathis *et al*. (26)	Y	U	N	Y	Y	Y	Y	Y	Y	U	U	U	Y	N
Malfertheiner *et al*. (27)	U	N	Y	Y	Y	Y	Y	Y	Y	U	U	U	U	N
Manes *et al*. (45)	Y	Y	Y	U	Y	Y	Y	Y	Y	U	U	U	Y	Y
Sykora *et al*. (28)	Y	N	Y	Y	Y	Y	Y	Y	N	U	U	U	U	Y
Trevisani *et al*. (29)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	U	Y	Y
Veijola *et al*. (30)	Y	N	N	Y	Y	Y	Y	N	N	U	U	U	U	N
Veijola *et al*. (31)	Y	U	N	U	Y	Y	Y	N	N	U	U	U	Y	Y
Veijola *et al*. (32)	Y	N	Y	U	Y	Y	Y	N	N	U	U	U	Y	Y
Veijola *et al*. (33)	Y	Y	N	Y	Y	Y	Y	Y	Y	U	Y	U	Y	Y
Weingart *et al*. (34)	Y	N	N	U	Y	Y	Y	N	N	U	U	U	U	Y
Weingart *et al*. (35)	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y
Zambon *et al*. (36)	Y	Y	N	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y = yes; N = no; U = unknown.
Items: Was the spectrum of patients representative of the patients who will receive the test in practice?
Were selection criteria clearly described?
Is the reference standard likely to classify the target condition correctly?
Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
Did the whole sample or a random selection of the sample receive verification using a reference standard?
Did patients receive the same reference standard regardless of the index test result?
Was the reference standard independent of the index test (*i.e.*, the index test did not form part of the reference standard)?
Was the execution of the index test described in sufficient detail to permit replication of the test?
Was the execution of the reference standard described in sufficient detail to permit its replication?
Were the index test results interpreted without knowledge of the results of the reference standard?
Were the reference standard results interpreted without knowledge of the results of the index test?
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
Were uninterpretable/intermediate test results reported?
Were withdrawals from the study explained?

results. This statistic describes the percentage of the variability in effect estimates that it is because of heterogeneity rather than sampling error (chance). A value >50% may be considered substantial heterogeneity (7).

Meta-analyses were performed combining the sensitivities, specificities, and LRs of the individual studies in the corresponding pooled indexes. Performing different meta-analyses depending on the setting in which the SAT was used to detect *H. pylori* infection (pre- or post-treatment) were planned *a priori.* LRs were pooled using a random effects model (DerSimonian and Laird). As a "threshold effect" was not detected (by the Spearman test and the examination of the plot of sensitivity and specificity on a ROC plane), summary receiver operating characteristic (SROC) curves were not constructed (8). The analyses were carried out using the statistical software Meta-DiSc (version 1.1.1) (9).

The accuracy of the monoclonal and the polyclonal SAT was compared with those studies evaluating together, in the same protocol, both techniques. A simple numeric comparison was made to compare monoclonal with polyclonal tests, because a rigorous comparison of pooled indexes taking into account the pairing of points within studies is not straightforward, as valid standard errors cannot be obtained readily from paired data and a meta-regression method is not well suited to these data.

Subanalysis/Sensitivity Analysis

As the accuracy of all *H. pylori* diagnostic methods in general (10), and of SAT in particular (3), seems to be lower when the test is aimed to confirm *H. pylori* eradication after therapy—as compared with untreated patients—the performance of the SAT was separately assessed in these two settings. Furthermore, subanalyses were planned *a priori* depending on: (1) the reference method or combination of methods considered as the gold standard (gold standard based on only one diagnostic method, or based on at least two reference methods); (2) the population study (adults or children); and (3) in the posteradication setting, depending on the time elapsed between finalizing eradication treatment and performing SAT. Finally, meta-regression was performed to

Table 2. Studies Evaluating the Monoclonal *H. pylori* Stool Antigen Test for the Diagnosis of the Infection Before Therapy

Author	Year	Format	Population	*H. pylori* Prevalence (%)	Gold Standard	Technique	True (+)	False (+)	False (−)	True (−)
Agha-Amiri *et al.* (11)	2001	JA	A	49	RUT, H, UBT, S	M	23	1	3	26
						P	23	2	3	25
Andrews *et al*. (12)	2003	JA	A	36	RUT, H, C	M	22	1	3	46
						P	16	2	9	45
Asfeldt *et al*. (13)	2004	JA	A	44	H, C, UBT	M	53	4	1	64
Calvet *et al*. (15)	2004	JA	A	71	RUT, H	M	50	5	1	16
						P	35	3	16	18
Chisholm *et al*.∗ (16)	2002	Ab	A	60	H, C	M	45	0	4	33
						P	43	1	6	32
Chisholm *et al*. (17)	2004	JA	A	57	H, C	M	60	0	4	48
						P	47	2	12	44
Dore *et al*.∗ (18)	2004	JA	A	52	RUT, H, UBT	M	37	2	1	33
Erzin *et al* (19)	2004	JA	A	86	RUT, H, C	M	121	2	9	19
						P	109	7	21	14
Hino *et al*. (22)	2004	JA	C	51	RUT, H	M	39	2	1	36
Ignys *et al*. (23)	2004	Ab	C	36	RUT, H	M	33	0	15	87
Koletzko *et al*. (24)	2003	JA	C	31	RUT, H, C, UBT	M	90	2	2	208
Makristathis *et al*. (26)	2000	JA	C	100	UBT, S	M	48	0	1	0
						P	46	0	3	0
Malfertheiner *et al*. (27)	2002	Ab	A	46	RUT, H, UBT	M	165	6	7	200
						P	136	4	35	202
Sykora *et al*. (28)	2003	Ab	C	28	RUT, H	M	25	1	1	66
Trevisani *et al*. (29)	2005	JA	A	57	RUT, H	M	53	0	7	44
Veijola *et al*. (30)	2002	Ab	A	100	RUT	M	30	0	1	0
						P	27	0	4	0
Veijola *et al*. (31)	2003	Ab	A	100	RUT	M	71	0	2	0
						P	68	0	5	0
Veijola *et al.* (32)	2004	Ab	A	32	UBT, S	M	44	4	2	93
						P	40	4	6	93
Veijola *et al*. (33)	2005	JA	A	100	RUT	M	80	0	2	0
						P	74	0	8	0
Weingart *et al*. (34)	2003	Ab	A	100	RUT, H, C	M	48	0	3	0
Weingart *et al*. (35)	2004	JA	A	100	RUT, H, C	M	47	0	3	0
Zambon *et al*. (36)	2004	JA	A	31	UBT	M	52	5	6	124
						P	39	1	19	128

Year = year of publication. Format: Ab = abstract; JA = journal article. Population: A = adults; C = children. Technique: P = polyclonal; M = monoclonal; Gold standard: RUT = rapid urease test; H = histology; C = culture; UBT = urea breath test; S = serology.
To calculate accuracy of stool antigen, the cutoff recommended by the manufacturer was considered, except in∗, in which only the cutoff point calculated and proposed by the authors was available.

evaluate the association between each quality item included in the QUADAS tool (Table 1) and the diagnostic odds ratio (DOR) in studies evaluating the monoclonal SAT.

RESULTS

With the aforementioned search strategy, we initially identified 633 articles in MEDLINE and 318 in EMBASE dealing with the diagnosis of *H. pylori* infection with the SAT, but only 35 studies assessed the performance of the monoclonal test in these patients (11–45). Two studies were excluded because they included patients with upper gastrointestinal bleeding (20, 21), one because the test was assessed in end-stage renal disease patients (25), and one more study was excluded because it included cirrhotic patients (14). Two studies were excluded because they did not provide information about the exact number of patients with *H. pylori* positive and negative SAT (37, 38). Finally, three more studies were excluded because they did not include a gold standard for *H. pylori* infection (based on at least one independent diagnostic method) (39–41). Therefore, 26 studies in total were finally included in the meta-analysis.

H. pylori SAT for the Diagnosis of the Infection Before Therapy

Twenty-two studies, including a total of 2,499 patients, evaluated the monoclonal *H. pylori* SAT for the diagnosis of the infection before therapy (Table 2) (11–13, 15–19, 22–24, 26–36). In some pretreatment studies, the prevalence of *H. pylori* infection was 100% and, therefore, only sensitivity but neither specificity nor LRs could be calculated (26, 30, 31, 33–35). Mean prevalence of *H. pylori* infection evaluated with monoclonal SAT was 62% (range, 28–100%). The included studies showed some degree of heterogeneity ($p < 0.001$), with sensitivities ranging between 0.68 and 0.99 (I^2 statistic, 61%), and specificities between 0.76 and 1.00 (I^2, 58%).

Table 3. Studies Evaluating the Monoclonal *H. pylori* Stool Antigen Test to Confirm Eradication After Therapy

Author	Year	Format	Population	Eradication (%)	Technique	Gold Standard	Time (wk)	True (+)	False (+)	False (−)	True (−)
Asfeldt *et al*. (13)	2004	JA	A	100	M	H, C, UBT	4–8	0	0	0	32
Erzin *et al*. (42)	2005	JA	A	69	M	UBT	6	14	4	1	29
					P			10	10	5	23
Konstantopoulos *et al.* (44)	2002	Ab	C	94	M	UBT	4–8	3	1	0	47
Leodolter *et al*.* (43)	2002	JA	A	76	M	UBT	4–6	31	7	4	106
					P			27	4	8	109
Makristathis *et al*. (26)	2000	JA	C	80	M	UBT	4	8	1	0	31
					P			8	2	0	29
Manes *et al*. (45)	2005	JA	A	71	M	RUT, H, C	4–8	83	12	11	219
					P			69	6	25	225
Veijola *et al*. (30)	2002	Ab	A	68	M	UBT	4	8	1	0	20
					P			7	2	1	19
Veijola *et al*. (31)	2003	Ab	A	78	M	UBT	4–6	15	2	1	55
					P			12	2	4	55
Veijola *et al*. (32)	2004	Ab	A	85	M	UBT, S	4	7	1	0	38
					P			5	0	2	38
Veijola *et al*. (33)	2005	JA	A	81	M	UBT	4–8	13	1	1	49
					P			11	3	3	47
Weingart *et al*. (34)	2003	Ab	A	80	M	UBT	4–6	10	0	0	40
Weingart *et al*. (35)	2004	JA	A	80	M	UBT	6	40	0	0	10

Year = year of publication. Format: Ab = abstract; JA = journal article. Population: A = adults; C = children; Eradication: *H. pylori* eradication rate with the prescribed treatment; Technique: P = polyclonal; M = monoclonal; Gold standard: RUT = rapid urease test; H = histology; C = culture; UBT = urea breath test; S = serology. Time: number of weeks after completing antibiotic regimen, when eradication was assessed.
To calculate accuracy of stool antigen, the cutoff recommended by the manufacturer was considered, except in*, in which only the cutoff point calculated and proposed by the authors was available.

Meta-analysis of studies evaluating sensitivity and specificity of monoclonal SAT for the diagnosis of *H. pylori* infection in untreated patients is shown in Figure 1. Pooled sensitivity was 0.94 (95% CI 0.93–0.95). Heterogeneity among sensitivities disappeared when a single outlier study (23) was excluded (I^2 statistic, 13%). Pooled specificity was 0.97 (95% CI 0.96–0.98), and heterogeneity among specificities also disappeared when another single outlier study (15) was excluded (I^2 statistic, 39%). Pooled positive LR was 24 (95% CI 15–41; statistically significant heterogeneity, $p < 0.01$), stating that the odds that a positive test is from a *H. pylori*-positive patient are 24 times higher than that originating from an *H. pylori*-negative patient. Finally, pooled negative LR was 0.07 (95% CI 0.04–0.12; heterogeneous results, $p < 0.001$). Again, heterogeneity of positive and negative LRs disappeared when this outlier study was not considered (15).

When subanalysis depending on the reference method was performed, and only pretreatment studies with a gold standard based on at least two reference methods were considered, the results of the meta-analysis were similar. Similarly, when subanalysis depending on the study population was performed, and only studies including adults or children were considered, the results of the meta-analysis were also similar. Finally, none of the 14 items included in the QUADAS tool showed statistically significant correlation with the DOR.

The accuracies of both the monoclonal and the polyclonal SAT were evaluated together, with the same protocol, in 13 pretreatment studies (11, 12, 15–17, 19, 26, 27, 30–33, 36). When only these studies were taken into account, accuracy (pooled data) of the monoclonal SAT was as follows: sensitivity, 0.95 (95% CI 0.93–0.96); specificity, 0.96 (0.94–0.98); positive LR, 20 (9.8–40); and negative LR, 0.08 (0.06–0.10). When the polyclonal technique was evaluated in these same 13 studies, specificity (0.96, 95% CI 0.94–0.97) and positive LR (15; 6–37) were similar, but sensitivity (0.83; 0.80–0.85) was lower and negative LR (0.24; 0.19–0.31) was higher than with the monoclonal test.

H. pylori SAT for the Confirmation of Eradication After Therapy

Twelve studies, including a total of 957 patients, assessed the monoclonal SAT to confirm eradication after therapy (Table 3) (13, 26, 30–35, 42–45). In one post-treatment study, *H. pylori* was eradicated in all patients (*e.g.*, prevalence of the infection was 0%) and therefore only specificity but not sensitivity nor LRs could be calculated (13). Mean prevalence of *H. pylori* infection post-treatment evaluated with monoclonal SAT was 20% (range 0–32%). The included studies evaluating accuracy of monoclonal SAT post-treatment showed no heterogeneity, with sensitivities ranging between 0.88 and 1.00 (I^2 statistic, 33%), and with specificities ranging between 0.88 and 1 (I^2, 21%).

Meta-analysis of studies evaluating sensitivity and specificity of monoclonal SAT for the diagnosis of *H. pylori* infection in treated patients is shown in Figure 2. Pooled sensitivity and specificity was 0.93 (95% CI 0.89–0.96) and 0.96 (0.94–0.97), respectively. Pooled positive and negative LRs were, respectively, 17 (12–23; nonheterogeneous results) and 0.1 (0.07–0.15; nonheterogeneous results).

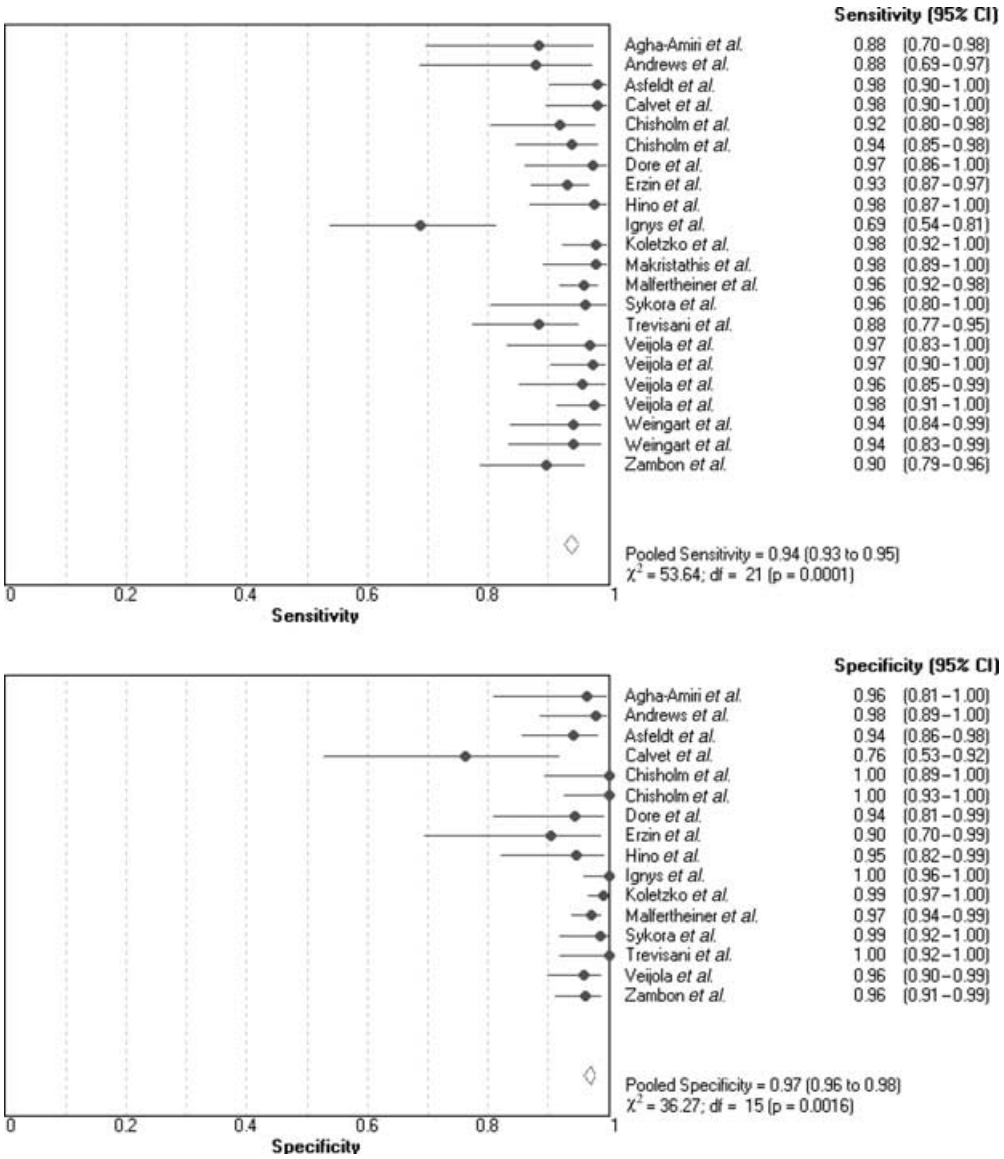

Figure 1. Meta-analysis of studies evaluating sensitivity and specificity of monoclonal *H. pylori* stool antigen test for the diagnosis of the infection before therapy. In the studies by Makristathis *et al*. (26), Veijola *et al*. (30, 31, 33), and Weingart *et al*. (34, 35), the prevalence of *H. pylori* was 100%, so they were excluded in the meta-analysis of specificity.

When subanalysis depending on the reference method or the study population was performed, the results of the meta-analysis were also similar (however, only three studies included a gold standard based on two or more reference methods, thus precluding adequate comparison of the study results). Regarding the time elapsed between finalizing the eradication treatment and performing SAT, this ranged between 4 and 8 wk (the time usually considered to confirm *H. pylori* eradication with other diagnostic methods) (46) in all studies, thus precluding the performance of subanalysis based on this variable. Finally, as was the case in the pretreatment setting, none of the 14 items included in the QUADAS tool was correlated with the accuracy of post-treatment SAT.

The accuracies of both the monoclonal and the polyclonal SAT were evaluated together, with the same protocol, in eight post-treatment studies (26, 30–33, 42, 43, 45). When only these studies were taken into account, accuracy (pooled data) of the monoclonal SAT was as follows: sensitivity, 0.91 (95% CI 0.86–0.94); specificity, 0.95 (0.93–0.97); positive LR, 16 (11–22); and negative LR, 0.11 (0.07–0.16). When the polyclonal technique was evaluated in these same eight studies, specificity (0.95, 95% CI 0.93–0.97) and positive LR (13; 5.3–32) were similar, but sensitivity (0.76; 0.69–0.81) was lower and negative LR (0.27; 0.22–0.35) was higher than with the monoclonal test.

DISCUSSION

H. pylori SAT is considered an accurate noninvasive method for the diagnosis of *H. pylori* infection. Accordingly, this diagnostic method has recently been approved by the U.S. Food

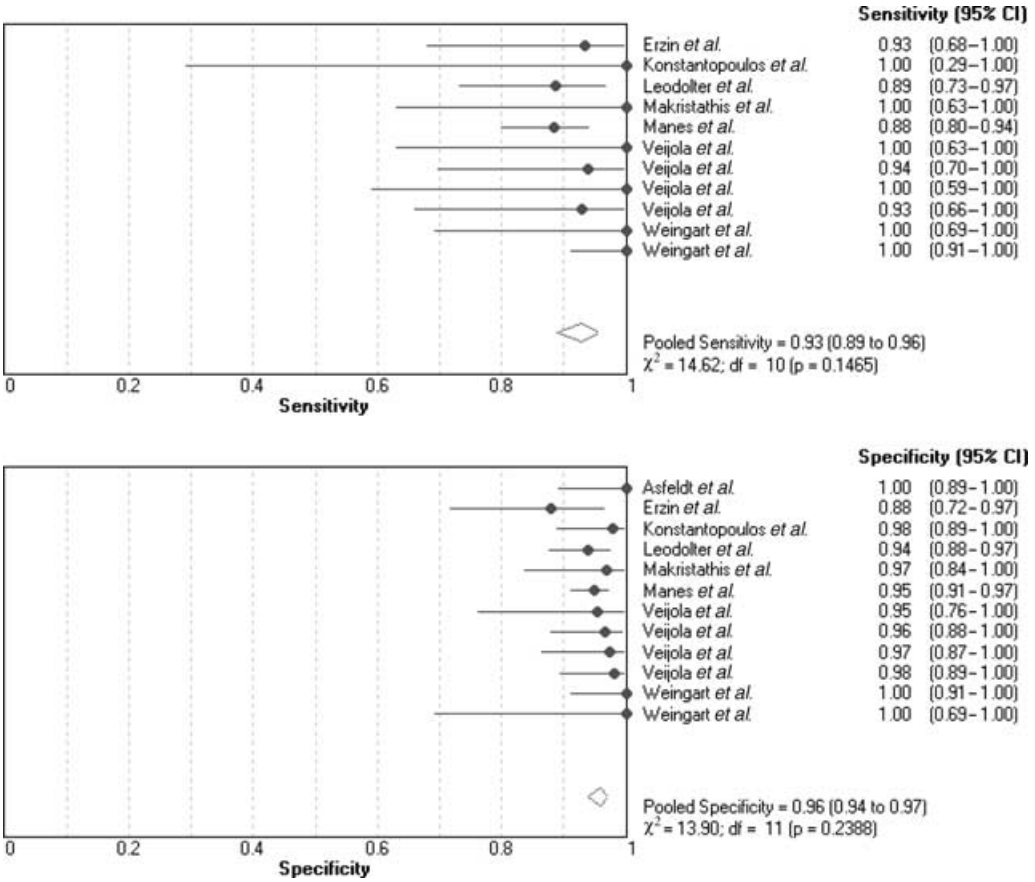

Figure 2. Meta-analysis of studies evaluating sensitivity and specificity of monoclonal *H. pylori* stool antigen test to confirm eradication after therapy. In the study by Asfeldt *et al*. (13), the prevalence of *H. pylori* was 0%, so it was excluded in meta-analysis of sensitivity.

and Drug Administration (FDA), with the indication for use in primary diagnosis of *H. pylori* and also in the monitoring of post-treatment outcome. Furthermore, in "The Maastricht 2–2000 Consensus Report" (47), the summary of the recommendations of the European *H. pylori* Study Group, it was stated that the "test and treat" approach is recommended in young adult patients presenting with persistent dyspepsia, and that "diagnosis of infection should be by urea breath test or SAT." However, these statements did not distinguish between the classical polyclonal test and the most recent monoclonal one, as the experience at that time with this last technique was very limited.

As shown in a recent review based on only eight pretreatment studies, the monoclonal SAT had high sensitivity (0.96) and specificity (0.97%) for the diagnosis of *H. pylori* infection (3). These encouraging results have been confirmed in the present meta-analysis, as the monoclonal SAT showed a pooled sensitivity and specificity as high as 0.94 and 0.97 when it was evaluated in 22 pretreatment studies, including a total of 2,499 patients. On the other hand, from the 12 studies, including a total of 957 patients, assessing the monoclonal SAT to confirm eradication after therapy, 0.93 sensitivity and 0.96 specificity were calculated. Although heterogeneity among studies was initially present, it disappeared when a single outlier study was excluded for both the sensitivity (23) and the specificity (15) calculation. When subanalysis depending on the reference method, the study population, or the quality of studies, was performed, the results of the meta-analysis were also similar.

The "classic" Premier Platinum HpSA^{TM} (Meridian Diagnostics) uses polyclonal antibodies obtained from intraperitoneal injection of *H. pylori* antigens to rabbits. This method obtains a profile of antibodies which is different in each animal, and this could generate, in theory, differences among diagnostic kits. In fact, considerable variability has been reported when several stool antigen determinations with the polyclonal method were performed in the same patients (3, 26); this, in turn, could explain remarkable differences among the different studies from the literature. On the other hand, the test based on monoclonal antibodies may have greater reproducibility of test results. In this respect, one study has reported excellent results in spite of the fact that the test was performed in three different laboratories using two different production lots (48). Furthermore, the differences between positive and negative results obtained with the monoclonal test are generally greater in comparison with the monoclonal technique and, therefore, the monoclonal test allows a better distinction between infected and noninfected patients (11,

16). Thus, in contrast to the polyclonal test, no gray zone seems to be necessary when the monoclonal test is used.

Of special interest are those studies that compare the monoclonal and polyclonal method in the same protocol. In the present systematic review, the accuracies of both tests were evaluated together in 13 pretreatment studies (11, 12, 15–17, 19, 26, 27, 30–33, 36), which allowed to demonstrate higher pooled sensitivity with the monoclonal SAT (0.95) than with the polyclonal one (0.83). This difference was even more evident when both methods were compared with the post-treatment setting (26, 30–33, 42, 43, 45), in which the monoclonal SATs maintained a high sensitivity (0.91), but the polyclonal technique was associated with an unacceptable low sensitivity (0.76). In this respect, some studies have shown that the polyclonal SAT has a significantly lower sensitivity than the urea breath test after eradication treatment (45, 49, 50). As the Premier Platinum HpSA^{TM} uses polyclonal antibodies to *H. pylori*, it has been suggested that the different antigenic composition of the test, that could differ from batch to batch, could explain these discordant results. Since such a variability is not expected in a monoclonal-based antibody test, the introduction of this novel technique based on monoclonal antigens is likely to represent an advantage.

To explain low sensitivity (that is, frequent false negative results) with the polyclonal SAT) in the post-treatment setting, it has been suggested that a reduction of *H. pylori* density grade observable shortly after treatment in patients from whom the microorganism has not been eradicated could be accompanied by low *H. pylori* stool antigen optical densities, leading to an erroneous diagnosis of eradication. Thus, when the density of the organism is small, the amount of antigens shed in the stool may not be sufficient to result in a positive polyclonal SAT. Our results suggest, therefore, that a smaller number of organisms is likely to be required for the accurate measurements in feces with the monoclonal SAT.

Until very recently, urea breath test was the only available noninvasive accurate diagnostic method for the confirmation of *H. pylori* eradication after treatment, because of the fact that serology, the other "traditional" noninvasive technique, requires several months for accurate detection of a significant fall in antibody titer (1). However, the results of the present meta-analysis indicate that the novel monoclonal *H. pylori* SAT can also be used in the post-treatment setting (51). In this respect, the U.S. FDA has approved SAT with the indication for use in the monitoring of post-treatment outcome. Similarly, the European "Maastricht 2, 2000 Consensus Report" suggested that SAT may be an alternative to urea breath test after treatment (47). Nevertheless, as previously shown, these encouraging results in the post-treatment setting have not been confirmed in some studies assessing the polyclonal SAT. Therefore, the "favorable" recommendation for the use of the SAT for the diagnosis of *H. pylori* infection, especially to confirm *H. pylori* eradication, should be restricted to the monoclonal technique.

In summary, this systematic review and meta-analysis shows that the novel monoclonal SAT is an accurate noninvasive method both for the initial diagnosis of *H. pylori* infection and for the confirmation of its eradication after treatment. Moreover, the monoclonal SAT is more accurate than the polyclonal method both in the pre- and, especially, in the post-treatment setting.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- A diagnostic test based on the detection of *H. pylori* stool antigen has been recently developed.
- The first developed *H. pylori* stool antigen test used polyclonal antibodies to *H. pylori*.
- More recently, a novel stool antigen test based on monoclonal antibodies has been developed.
- Theoretically, the monoclonal test would have increased diagnostic accuracy.

What Is New Here

- The monoclonal stool antigen test is an accurate non-invasive method.
- This test is accurate for both the initial diagnosis of *H. pylori* infection and for the confirmation of its eradication after treatment.
- The monoclonal technique has higher sensitivity than the polyclonal one, especially in the post treatment setting.

Reprint requests and correspondence: Javier P. Gisbert, M.D., Playa de Mojácar 29. Urb. Bonanza., 28669 Boadilla del Monte, Madrid, Spain.

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CONFLICT OF INTEREST

Guarantor of the article: Javier P. Gisbert
Specific author contributions: Javier P. Gisbert had the original idea for the study, developed the protocol, performed the search strategy for identification of studies, selected the studies, assessed study quality, extracted data, did the statistical analysis and wrote the manuscript. Felipe de la Morena assessed study quality and extracted data. Victor Abraira was involved in developing the protocol, reviewed the manuscript and did relevant suggestions.
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