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• *RAPID COMMUNICATION* •

Stool antigen tests in the diagnosis of *Helicobacter pylori* infection before and after eradication therapy

Lea Veijola, Eveliina Myllyluoma, Riitta Korpela, Hilpi Rautelin

Lea Veijola, Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, and Malmi Hospital, Helsinki, Finland
Eveliina Myllyluoma, Institute of Biomedicine, Pharmacology, University of Helsinki, and Foundation for Nutrition Research, Helsinki, Finland
Riitta Korpela, Institute of Biomedicine, Pharmacology, University of Helsinki, and Valio Ltd. Research Centre, Helsinki, Finland
Hilpi Rautelin, Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, and HUSLAB, Helsinki University Central Hospital Laboratory, Helsinki, Finland
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Correspondence to: Dr. Lea Veijola, Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, PO Box 21, Fin-00014 Helsinki, Finland. lea.veijola@helsinki.fi.
Telephone: +358-9-19126716 Fax: +358-9-19126382
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Abstract

AIM: To evaluate two enzyme immunoassay-based stool antigen tests, Premier Platinum HpSA and Amplified IDEIA HpStAR, and one rapid test, ImmunoCard STAT! HpSA, in the primary diagnosis of *Helicobacter pylori (H pylori)* infection and after eradication therapy.

METHODS: Altogether 1 574 adult subjects were screened with a whole-blood *H pylori* antibody test and positive results were confirmed with locally validated serology and ^{13}C-urea breath test. All 185 subjects, confirmed to be *H pylori* positive, and 97 *H pylori*-negative individuals, randomly selected from the screened study population and with negative results in serology and UBT, were enrolled. After eradication therapy the results of 182 subjects were assessed.

RESULTS: At baseline, the sensitivity of HpSA and HpStAR was 91.9% and 96.2%, respectively, and specificity was 95.9% for both tests. ImmunoCard had sensitivity of 93.0% but specificity of only 88.7%. After eradication therapy, HpSA and HpStAR had sensitivity of 81.3% and 100%, and specificity of 97.0% and 97.6%, respectively. ImmunoCard had sensitivity of 93.8% and specificity of 97.0%. HpSA, HpStAR, and ImmunoCard had PPV 77%, 80%, and 75%, and NPV 98%, 100%, and 99%, respectively.

CONCLUSION: In primary diagnosis, the EIA-based tests performed well. After eradication therapy, negative results were highly accurate for all the three tests. HpStAR had the best overall performance.

Key words: Diagnosis; Feces; *Helicobacter pylori*; Therapy

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INTRODUCTION

H pylori infection is one of the most common infections in human beings worldwide, strongly associated with peptic ulcer disease and gastric cancer[1,2]. There are several methods available to detect *H pylori* infection including invasive methods based on gastric biopsies and non-invasive methods like serology, urea breath tests (UBTs), and stool antigen tests[3,4]. Stool antigen tests have recently been welcomed with great expectations as they are convenient to the patients and can be easily performed even in small laboratories[5,6]. However, the accuracy of stool antigen tests in different clinical situations and outside of controlled studies is a matter of concern[7-9].

Several commercial stool antigen tests are available: enzyme immunoassays (EIAs) based on either polyclonal (Premier Platinum HpSA, Meridian Inc., Cincinnati, OH, USA) or mAbs (Amplified IDEIA HpStAR, also known as Femtolab, Dako, Glostrup, Denmark) and rapid bed-side tests like ImmunoCard STAT! HpSA (Meridian Bioscience Europe, Milan, Italy). HpSA is the most widely studied of these tests and it has shown acceptable performance in the primary diagnosis of *H pylori* infection but the accuracy in post-treatment setting and in special clinical situations (e.g. upper gastrointestinal hemorrhage, gastric surgery, PPI therapy) has been controversial[5,7,8]. The three stool antigen tests have rarely been compared in parallel in the same study. The differences in patient characteristics (e.g. peptic ulcer *vs* gastritis) and widely variable prevalence of *H pylori* in different studies make the comparisons between the tests difficult as the statistical parameters of the performance of the tests are often dependent on the prevalence of the infection.

Recently, we evaluated the three stool antigen tests in *H pylori*-positive patients before and after eradication therapy[10]. In the present study we also included *H pylori*-negative individuals. *H pylori* infection in all the subjects was verified by serology and ^{13}C-UBT.

MATERIALS AND METHODS

Subjects

Adults were invited with a newspaper announcement to participate in the study. Exclusion criteria were antibiotic treatment during previous 2 mo; use of H_2-receptor antagonists, bismuth or proton pump inhibitor therapy during previous 2 wk; *H pylori* eradication therapy during previous 5 years; gastric surgery; chronic gastrointestinal diseases; contraindications to drugs used in the study; pregnancy or lactation. Study subjects were screened for *H pylori* infection with rapid whole-blood antibody tests (Pyloriset Screen II, Orion Diagnostica, Espoo, Finland, or Biocard *Helicobacter pylori* IgG, AniBiotech Ltd, Vantaa, Finland). The present study was subsidiary to another study investigating the efficacy of probiotics in the eradication therapy of *H pylori*. Therefore, allergy to fruit juice containing the probiotics also belonged to the exclusion criteria.

The population screened comprised 1 574 subjects. Positive results in screening were confirmed with UBT and an in-house EIA-based serologic method. Of the 300 *H pylori*-positive subjects in screening, 196 were positive in both of the confirmatory tests, but 11 subjects met one of the exclusion criteria; thus 185 *H pylori*-positive subjects were included in the study (of the remaining 104 subjects positive in screening, 49 were negative in both of the confirmatory tests and for the rest either no confirmatory tests were performed or the results were discordant). From the subjects with *H pylori*-negative test result in screening, 114 (randomly selected by a computer program SPSS 12.0) were invited to bring the specimens for the confirmatory tests and 97 subjects followed this invitation. For these *H pylori*-negative study subjects, the infection was excluded with both of the confirmatory tests. Thus, the final study population consisted of 282 subjects: 185 were *H pylori* positive and 97 negative. The median age of the subjects was 52 years, range 23-71 years. The median age of *H pylori*-positive subjects was 55 years (range 25-71 years) and of *H pylori*-negative subjects 43 years (range 23-64 years). In total there were 186 females and 96 males.

H pylori eradication therapy

A total of 185 *H pylori*-positive subjects received the same eradication therapy: amoxicillin 1 g b.i.d., clarithromycin 500 mg b.i.d. and lanzoprazole 30 mg b.i.d. for 1 wk. Exclusion criteria for the therapy were penicillin allergy, prolonged QT-interval, and antifungal therapy for dermatophyte infection.

Serology

At baseline and 4 mo after the end of eradication therapy the subjects gave serum samples for locally validated in-house EIA[11]. At baseline, serum samples had been investigated in order to confirm the infection, and they were stored at -20 ℃ until further used. Serum samples before and after eradication therapy were analyzed in parallel for both immunoglobulin G (IgG) and IgA antibodies as described earlier[12]. *H pylori* eradication therapy was considered successful when antibody titers of at least IgG class had fallen 40% or more from the pre-treatment level[11].

UBT

UBT was performed at baseline and 4 wk after the end of eradication therapy. Diabact tablets were used (Diabact UBT, Diabact AB, Uppsala, Sweden) [13,14]. After overnight fast the subjects swallowed either one or two 50 mg Diabact tablets and blew into the test tube before and 10 min after ingesting the tablet(s). Results were analyzed by isotope ratio mass spectrometry (BreathMATPlus, Finnigan MAT GmbH, Bremen, Germany) and expressed as delta over baseline (DOB). Cut-off point for positive test result was DOB 2.2‰.

Stool antigen tests

All subjects gave stool specimens at baseline and those treated 4 wk after the end of eradication therapy. Stool specimens were stored at -20 ℃ before analysis and were thawed twice at most. Stool samples before and after therapy were always run in parallel in all three antigen tests.

The polyclonal antibody-based Premier Platinum HpSA test, later HpSA (Meridian Inc., Cincinnati, USA) was performed according to manufacturer's instructions. Diluted stool specimens were added to the microtiter wells with a peroxidase-conjugated polyclonal antibody. After washing, substrate was added. The results were read at 450 nm by a spectrophotometry (Titertek Multiskan analyzer, Eflab Oy, Helsinki, Finland). Optical density (OD) values <0.140 were negative, 0.140-0.159 equivocal (gray zone) and ⩾0.160 positive, as suggested by the manufacturer. In cases with gray zone values, the same stool samples stored at -20 ℃ were retested as recommended.

For the mAb-based Amplified IDEIA HpStAR test, later HpStAR (also known by name FemtoLab, Dako), the supernatant of stool suspension and peroxidase-conjugated mAbs were pipetted into the wells. After washing substrate was added, and the results were read by spectrophotometry. According to manufacturer's instructions, OD values ⩾0.190 (450 nm) were assessed as positive and <0.190 as negative.

ImmunoCard STAT! HpSA-test, later ImmunoCard (Meridian Bioscience Europe) is based on monoclonal *H pylori* antibodies and a lateral flow chromatography technique. The diluted stool sample was dispensed to the sample port of the test cassette, and after incubation of 5 min at room temperature, the appearance of a pink-red line in the reading window indicated a positive result.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the studies and all subjects

Table 1 Performance of the three stool antigen tests as compared with UBT and serology in 282 subjects at baseline

UBT, serology	HpSA		HpStAR	ImmunoCard
Positive 185	Positive	170[1]	178	172
	Negative	13[1]	7	13
	2 gray zone[2]			
Negative 97	Negative	93	93	86
	Positive	4[3]	4	11

[1]One subject originally had gray zone result.
[2]Gray zone result even in re-examination.
[3]Three subjects originally had gray zone results.

Table 2 Performance of the three stool antigen tests as compared with UBT and serology in 182 subjects after eradication therapy

UBT, serology	HpSA	HpStAR	ImmunoCard
Negative 166	Negative 161[1]	162	161
	Positive 4	4	5
	1 gray zone[2]		
Positive 16	Positive 13	16	15
	Negative 3[3]	0	1

[1]Six subjects originally had gray zone result.
[2]Gray zone result even in re-examination.
[3]One subject originally had gray zone result.

gave their written informed consent.

RESULTS

The performance of the stool antigen tests at baseline is shown in Table 1 and after eradication therapy in Table 2. Four patients were treated with antimicrobials after eradication therapy before the 4 wk had elapsed and thus, stool specimens and UBTs of these particular patients were not collected until they gave the serum sample for serology 4 mo after the therapy. For all the other subjects, UBT was performed and stool specimens were collected 4 wk after therapy according to the study protocol.

The results after eradication therapy are presented for 182 subjects; 3 subjects had the results only at baseline. One patient died before the follow-up. Serum sample was collected and another subject discontinued the study during antimicrobial therapy because of severe headache, which later turned out to be viral meningitis as examined by a neurologist. After eradication therapy, the confirmatory tests (UBT and serology) showed concordant results in all but one subject, who had eradication failure according to the UBT and all three stool antigen tests but successful eradication according to the serology: his results after eradication therapy were excluded from the analysis.

The performance of the tests at baseline is presented in Table 3 and after eradication therapy in Table 4. The adjusting of the cut-off points would not have had any beneficial effect to the results either before or after eradication treatment (data not shown). The false-positive test results in stool antigen tests were randomly distributed between the individual tests. However, half of the false-negative HpSA test results at baseline were also negative with the other two stool tests.

The HpSA tests with gray zone values were re-examined using the same stool specimens according to manufacturer's recommendations. However, no new stool specimen was collected (although recommended by the manufacturer) if the result was in gray zone even in re-examination. Out of the 464 samples analyzed, 15 (3.2%) fell into the gray zone but only three were equivocal when re-tested. Gray zone results obtained after re-examination were considered neither true positive nor true negative in statistical calculations.

Table 3 Performance of the three stool antigen tests at baseline

	Sensitivity	Specificity	PPV	NPV	Accuracy
	(%)	(%)	(%)	(%)	(%)
HpSA	91.9	95.9	97.7	87.7	93.3
HpStAR	96.2	95.9	97.8	93.0	96.1
ImmunoCard	93.0	88.7	94.0	86.9	91.5

PPV, positive predictive value; NPV, negative predictive value.

Table 4 Performance of the three stool antigen tests after eradication therapy

	Sensitivity	Specificity	PPV	NPV	Accuracy
	(%)	(%)	(%)	(%)	(%)
HpSA	81.3	97.0	76.5	98.2	95.6
HpStAR	100	97.6	80.0	100	97.8
ImmunoCard	93.8	97.0	75.0	99.4	96.7

PPV, positive predictive value; NPV, negative predictive value.

DISCUSSION

In the primary diagnosis of *H pylori* infection, the EIA-based HpSA and HpStAR tests had high sensitivities in accordance with our previous study[10] and those of others[6,8]. Earlier the specificities of these tests have varied between 63% and 100% for HpSA and 87% and 100% for HpStAR in studies with high prevalence of *H pylori* infection[6,8,15-19] and are in line with the specificity of 96% in our present study population. ImmunoCard had a good sensitivity, 93.0%, but a low specificity, 88.7%, at baseline, leading to a high number of false-positive test results. In previous studies, ImmunoCard has shown variable results in the primary diagnosis with sensitivities between 83% and 96% and specificities between 82% and 94%[8,10,20-25].

The positive predictive values (PPVs) for all the three stool antigen tests were very high (94.0-97.8%) at baseline in our study population with a high prevalence (65.6%) of *H pylori*. However, if these stool antigen tests had been used to detect the infection in the original group of 1 574 screened study subjects with the prevalence of *H pylori* being 12% (in assuming that all the screened but not confirmed *H pylori*-negative subjects would have been negative also in the both confirmatory tests), the PPVs for these tests would have been only as follows: HpSA 76.6%, HpStAR 77.5%, and ImmunoCard 54.8%. It has been earlier suggested that at an *H pylori* prevalence of lower than 30%, the most cost effective diagnostic strategy would be to use stool antigen test and confirm positive results with UBT[4]. In our study, the ImmunoCard test had the lowest specificity and thus a high number of false-positive test results emphasizing the need for a confirmation of a

positive test result by UBT or serology.

In post-eradication setting, the position of these stool antigen tests is most controversial[7,8]. This is true especially for the most widely studied HpSA test, which also in our study showed a low sensitivity after eradication therapy. We had an exceptionally low eradication failure rate in this study, only 8.8%, and HpSA test was unable to find 19% of our eradication failures, which is in accordance with our previous endoscopy-based study, in which 25% of eradication failures were unidentified with this test[10]. For the HpStAR test, the sensitivity has varied after eradication therapy between 86% and 100%, specificity 95% and 100%, PPV 83% and 100%, and NPV 96% and 100%[8,18,19]. Our results fell well into this range. The performance of ImmunoCard after eradication therapy in the few published studies available has varied widely. In a study in adults ImmunoCard showed very low sensitivity both before (83%) and after (73%) eradication therapy but high specificity 98%[23] whereas in the study of Gatta *et al*[21] the sensitivity was 92% and specificity 100%. In our study all the three stool antigen tests had false-positive results in 2.5%-3.1% of successfully eradicated subjects, figures comparable with UBT[3,26,27].

All patients except three in our study brought the follow-up UBT and stool specimens 4 wk after finishing the eradication therapy. In some previous studies using the HpSA test, it has been shown that the time elapsed after eradication therapy should not be less than 4 wk but extending the time beyond that would not clearly improve the results[8,10,19,28,29]. A positive HpSA test as early as 3 d after finishing eradication therapy has been highly predictive of eradication failure but a negative test result was reliable only after 3 wk[29]. Therefore, it is unlikely that after treatment a longer time before the collection of stool samples would have improved the results in our study.

In conclusion, in the primary diagnosis of *H pylori* infection, the EIA-based HpSA and HpStAR stool antigen tests performed well. However, in a population with a lower prevalence of *H pylori* infection, positive results even in these tests may be reasonable to confirm with UBT or serology. After eradication therapy, negative results were highly accurate for all the three tests and HpStAR even found all the subjects with an unsuccessful eradication. HpStAR had the best overall performance before and after eradication therapy.

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