New immunological assays for the diagnosis of *Helicobacter pylori* infection

D Vaira, J Holton, M Menegatti, C Ricci, F Landi, A Ali', L Gatta, C Acciardi, S Farinelli, M Crosatti, S Berardi, M Miglioli

Summary

There are several types of immunological tests available for the diagnosis and management of *Helicobacter pylori* infection. Most commercially available serological kits use the enzyme linked immunosorbent assay (ELISA) test format. Originally the kits used crude antigen preparations although many of the newer kits use a more purified antigen preparation, with often increased specificity but lower sensitivity. Near patient test kits are based either on latex agglutination or immunochromatography. Generally they have low sensitivities compared with laboratory tests. Western blotting, ELISA, and recombinant immunoblot assays (RIBA) have also been developed into commercially available kits and can be used to indicate the presence of specific virulence markers. An antigen detection kit has been developed for the detection of *Helicobacter pylori* in faeces. Immunological reagents have also been combined with other diagnostic modalities to develop immunohistochemical stains and DNA immunoassays.

Introduction

Helicobacter pylori is now recognised as the cause of gastritis and most cases of peptic ulcer disease (PUD); its long term carriage increases the risk of gastric adenocarcinoma sixfold and it is designated as a class I carcinogen.¹ *H pylori* has also been implicated as a cause of gastric mucosa associated lymphoid tissue lymphomas. Its relation to non-ulcer dyspepsia remains controversial. Additionally, long term carriage of the organism may be associated with short stature in young girls and, in the general population, as a possible risk factor for the development of vasospastic disorders and possibly skin immunopathology such as urticaria. With the recognition of *H pylori* as an important human pathogen,² it has become one of the growing number of organisms to have its complete genome sequence mapped.³

Serology is an important method of determining colonisation status and can be used for diagnosis, as a screening procedure, or to follow the efficacy of eradication regimens. Most serological assays are in the ELISA format although some are based on the latex agglutination reaction. These latter are used principally as near patient assays. Most assays detect IgG in serum although some detect serum IgA. More recently developed assays detect IgA in saliva and the production of affinity purified antibodies has led to the development of an antigen detection assay for faecal specimens. Serological reagents have also been used in immunocytochemistry and to speed up

the detection of amplified products of the polymerase chain reaction (PCR)-DNA immunoassays.

Current non-invasive immunological tests

SEROLOGY

Several different techniques exist for antibody detection. Solid phase assays are by far the most numerous and convenient. ELISA is the most often used serological format. It is usually laboratory based, requiring both some technical competence to perform and the availability of an instrument to measure the optical density of the coloured product. Alternatively, latex agglutination tests are most suitable as near patient tests because they are technically simple to perform and provide a result within minutes rather than the hour or two for ELISA tests. In the technique for simultaneously detecting a serological response to all antigens, represented by a single value of colour intensity (optical density) as in the ELISA test, both the number and intensity of staining of antibody bound protein bands or antibodies to specific antigens are taken into account. A commercial western blot test (Helicoblot 2) for the detection of *H pylori* is also available.

ELISA kits

There have been many publications comparing either single or multiple kits⁴⁻¹⁴ in defined populations. Tables 1 and 2 list the kits and their reported sensitivity, specificity, and positive and negative predictive values.

Latex agglutination kits

The agglutination format is not as frequently used as the ELISA format but evaluations have been published.¹⁵⁻²¹ The latex agglutination test is more convenient than the ELISA format for near patient testing and has comparable sensitivity and specificity (table 3).

New immunological assays for *H pylori*

HISTOLOGY

The use of stains such as the Giemsa stain to detect *H pylori* in tissue sections relies on the experience of the histopathologist to recognise the typical morphological appearance of the organism. Clearly, small numbers of organisms may be missed. Developments of current

Abbreviations used in this paper: ELISA, enzyme linked immunosorbent assay; RIBA, recombinant immunoblot assays; PUD, peptic ulcer disease; UBT, urea breath test; RUT, rapid urease test; PCR, polymerase chain reaction.

Department of Internal Medicine, University of Bologna, Bologna, Italy

D Vaira
M Menegatti
C Ricci
F Landi
A Ali'
L Gatta
C Acciardi
S Farinelli
M Crosatti
S Berardi
M Miglioli

Department of Bacteriology, University College London Medical School, London, UK

J Holton

Correspondence to:
Dr D Vaira, Clinica Medica
I, Università di Bologna,
Policlinico S. Orsola,
Bologna, Italy.

Table 1 Commercially produced serological assays for detection of *Helicobacter pylori* infection

Kit name	Kit name	Test format	Manufacturer
Pyloristat	Pylori Elisa II ¹	ELISA	Biowhittaker, USA
Pyloriset	Pyloriset update	ELISA	Orion, Finland
Helico G	Helico G II	ELISA	Shield, UK
Premier Hp		ELISA	Meridian, USA
Cobas Core		ELISA	Roche, Switzerland
Hel-p Test	Hel-p Test II	ELISA	Amrad, Australia
MalaKit		ELISA	BioLab, Belgium
GAP IgG	GAP IgG II	ELISA	Biorad, USA
Roche MTP		ELISA	Roche, Switzerland
Hp-G screen		ELISA	Genesis, UK
Microstar EIA		ELISA	Kenstar, UK
SIA Helicobacter		ELISA	Sigma, USA
HM-CAP EIA		ELISA	Enteric Prod., USA
Helisal EIA		ELISA	Cortex, UK
Helori CTX		ELISA	Eurospital, Italy
H pylori IgG		ELISA	Dako, Denmark
Autozyme		ELISA	Cambridge LS, UK
Pyloragen		ELISA	Hycor, USA
Enzygnost HP		ELISA	Boehringer, UK
Quickvue HP EIA		ELISA	Quidel, USA
Enzywell HP EIA		ELISA	Dresde Monteriggioni, Italy
Color Vue Pylori		ELISA	Seradyn, USA
Autoplate		ELISA	Menarini
Biolife		ELISA	Biolife
Pyloriset	Pyloriset Dry	LA	Orion, Finland
Helisal RBT	Helisal One Step	IMC	Cortex, UK
Flexsure HPS	Flexsure WB	IMC	Smith-Kline, USA
Genesis Dot		IMC	Genesis, UK
Quickvue One Step		IMC	Quidel USA
Launch Immunocard		IMC	Meridian, USA
Quadrachek HEP		IMC	VEDA, France
CLOser		IMC	Medical Inst. Corp., Switzerland
HelicoBlot 2.0		WB	GeneLab, Singapore
RIBA		WB	Chiron, USA

LA, latex agglutination; IMC, immunochromatography; WB, western blotting.

Table 2 Comparison of commercially available ELISA kits for detection of *Helicobacter pylori* infection

Kit name	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pyloristat	91–99	70–94	80	84
Pylori Elisa II	100	96	97	100
Helico G	71–97	65–95	69–90	65–98
Helico G 2	85	76	84	87
Premier HP	85–100	80–100	76–100	88–100
Cobas Core	87–98	83–98	87	86
Pyloriset	81–97	69–97	76–97	51–98
Pyloriset update	100	79	95	100
Hel-p Test	89–100	62–93	65–90	91–100
Malakit	79–87	86–98	96	60
GAP IgG	76–100	26–99	76–100	71–100
HP kit Radim	81	90		
Roche MTP	94–99	83–86	88	90
HpG screen	83–93	68–91	66–84	84–100
Microstar	97	76	80	98
SIA sigma	85–90	80–98	76–96	88–100
HM cap EIA	83–98	80–96	76	86
Autozyme	89	52	58	87
Pyloragen	79	75	71	83
Enzygnost	80	74	70	83
Quidel EIA	89	66	68	89
Enzywell	90	71	71	91
Color Vue	88	66	63	87

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

Table 3 Comparison of commercially available near patient tests for detection of *Helicobacter pylori* infection

Kit name	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AccuStat	89	93	89	93
Helisal RBT	82–92	55–91	56–92	86–89
FlexSure HP	76–96	77–100	72–96	83–95
Quick Vue	78–89	70–93	70–82	86–88
Pyloriset LA	68–92	56–76	68–85	62–84
Pyloriset Dry	64–97	75–95	72–95	75–93
PyloriScreen	95	94	91	97
HpCheck	88	85	83	90
Quadrachek	83	57	60	81
CLOser	95	72	80	93

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

histological methods include the use of immunohistochemistry in order to increase both the sensitivity and specificity of the method. In a comparison of immunohistochemistry, using a polyclonal antiserum, with the Giemsa and Warthin-Starry stains, the method had a higher specificity and a lower interobserver variation.²² Immunocytochemistry also performs significantly better compared with culture and biopsy urease test when small numbers of bacteria are present and following eradication treatment.²³ Other histological developments include the fixing of the mucus layer using Carnoy's solution combined with immunohistochemistry, which reduces both the false positive and negative results obtained with conventional histological stains.²⁴

PCR AND DNA-ENZYME IMMUNOASSAY

Although most diagnostic PCR amplicons are detected by gel electrophoresis, there is a growing trend towards using a colorimetric method of detection as this is more rapid and can be automated.

Three DNA enzyme immunoassays have been developed to detect *H. pylori*. The GEN-ETI-K DEIA (Sorin, Italy) uses streptavidin coated microwell plates to which is added a biotinylated specific probe based on the UreC gene of helicobacter. The amplified product is added to the plate and the duplex DNA detected with an enzyme linked antibody against double stranded DNA. PYLORI-PROB (Biocode, Belgium) is a solid phase sandwich hybridisation assay. A specific capture probe (also based on the UreC gene) is bound to the microwell plate. The amplified product is added to the well and detected by a biotinylated probe to which are added streptavidin conjugated peroxidase and substrate. PCR-ELISA (Boehringer, Germany) uses a capture probe labelled with biotin (UreC) bound to the solid phase in a streptavidin coated microwell plate to which is added the amplified product labelled with digoxigenin and the hybridised product is detected with anti-digoxigenin peroxidase.

Assessment of these three kits²⁵ was performed on biopsy specimens from 199 patients and compared with PCR with gel electrophoresis and histology/culture as a gold standard. The colorimetric DNA immunoassays were 100 times more sensitive than the standard PCR and results were obtained within four hours. The sensitivity and specificity of the three tests were 85% and 88%, respectively, for GEN-ETI-K DEIA, 87% and 82% for PYLORI-PROB, and 80% and 68% for PCR-ELISA. The study assessed patients before and after treatment and before treatment the specificity of PYLORI-PROB and PCR-ELISA was only about 50%. This apparent lack of specificity may highlight limitations in the "gold standard" rather than reflect on the DNA-enzyme immunoassay kits.

SEROLOGY

There are several new areas in which serological tests are being developed to detect *H. pylori*. These include the detection of IgA; virulence

specific ELISA; immunoblot techniques; immunological tests for salivary antibodies; near patient tests; and antigen detection. Alternative formats that have been used as serological assays include flow microsphere immunofluorescence and immunochromatography, this latter for the rapid near patient testing of whole (capillary) blood. In the former, polystyrene microbeads are coated with complex antigen of *H pylori* derived from a whole cell sonicate or urease enriched fraction. The serum containing the analyte (antibodies to *H pylori*) is mixed with the coated microspheres and binding is detected with fluorescein isothiocyanate labelled anti-human IgG and a flow cytometer. This technique does not readily lend itself to commercialisation as not every laboratory has a flow cytometer. The principle of the immunochromatography format is binding of an antigen (in this case a purified antigen of *H pylori*) to a membrane, addition of whole blood, and subsequent addition of anti-human IgG labelled with coloured particles. The presence of anti-*H pylori* antibodies in the blood is detected by a coloured spot on the membrane. An adjacent area of the membrane with bound human IgG acts as control. Alternative arrangements of this format can be used in which the antigen coated coloured particles bound to anti-*H pylori* antibodies diffuse along the length of the membrane and are trapped by a line of anti-human IgG antibodies, thus concentrating the colour at a specific position.

Finally, isoelectric focusing can be used to investigate the serological response to infection, including that with *H pylori*, although it is more a research method rather than a commercial test used in the management of disease. The principle is the focusing of serum antibodies to their pH by means of electrophoresis along a pH gradient, followed by transfer to a membrane loaded with antigen. Bound antibody is detected in a fashion similar to that of western blotting. Using this technique one can detect a monoclonal, oligoclonal, or polyclonal response representing the cellular dynamics of antibody production.

Serum antibody assays

Assays for IgA have been neglected in favour of IgG. However, some commercial kits do assess serum IgA and in one study of 400 patients the sensitivity and specificity of the IgA assay was comparable with that of IgG.²⁶ Whether IgA levels give any clinical advantage over IgG is currently unknown.

The detection of CagA and VacA by ELISA or immunoblotting may provide additional information which could be of clinical relevance. Infection by Cag and Vac positive strains (type I strains) is generally more likely to be associated with more serious gastro-duodenal disease compared with negative (type II) strains. This association, however, is not seen in all countries. In one study of 98 patients detection of 125 kDa (Cag), 87 kDa (Vac), and a hitherto unidentified 35 kDa component of helicobacter was correlated with ulcer disease.²⁷

Salivary antibody assay

Because of the ease of collection, particularly in children, salivary antibody assays may be particularly useful. In one study of 157 patients referred for investigation of dyspepsia, using the Helisal (Cortex) salivary kit, the positive predictive value was very low (sensitivity 85%; specificity 55%; positive predictive value 45%; negative predictive value 90%) when compared with histology in a population in which the prevalence of helicobacter infection was 30%.²⁸ Similarly, in a study of 86 patients when compared with culture, histology, and the rapid urease test (RUT), the Helisal kit had a sensitivity and specificity of 88% and 71%, respectively, but was inferior to assessment on serum.²⁹

Using the OraSure salivary device (Epitope Inc.) to collect salivary antibodies from 100 children, sensitivity and specificity of 100% and 61%, respectively, were obtained with positive and negative predictive values of 100% and 92% when compared with a urea breath test (UBT).³⁰ Similarly good results were obtained in another study using the OraSure test. In this study,³¹ 740 children were tested with the saliva collected by the OraSure device and the serology performed by HM-CAP EIA (Enteric Products), giving a sensitivity and specificity of 85% and 93%. These results are encouraging and with further development salivary antibody tests may be of diagnostic utility.

Western blotting and CagA ELISA

Because western blotting determines the serological response to a range of antigens from an organism, it could provide more information than an ELISA. Initial studies showed that serological response to certain antigens was strongly correlated with infection and in particular the 120–138 kDa CagA protein was associated with PUD and gastric cancer. In one study, comparing immunoblotting with an in-house ELISA and a commercial ELISA (Color Vue EIA) that uses an unspecified purified antigen, western blotting was more sensitive and specific than the enzyme immunoassays²⁸ and serological reactions to specific proteins—for example, CagA could be detected. CagA is a highly immunogenic protein whose function is unknown. It is only present in about 50–60% of strains; the presence of CagA in a strain is correlated with increased interleukin 8 secretion by the gastric epithelium and is possibly associated with the presence of PUD and gastric cancer, at least in some populations. The detection of a serological response may therefore give clinically relevant information about the infecting strain. Western blotting has been developed into commercial kits, Helico-blot 2.0 and RIBA strip; the latter identifies immunological response to recombinant CagA and VacA proteins. In a large study of over 3000 subjects,³² the RIBA results were compared with ¹³C-UBT and western blotting and had a sensitivity and specificity of 92%. Furthermore, a positive reaction to the lysate or Cag and Vac correlated with current infection, but a positive result with

either Cag or Vac alone indicated a past infection. In some studies, however, serological detection of antibodies to Cag was no better than detection of anti-helicobacter antibodies.³³ In a comparison of Helicoblot 2, RIDA Blot Helicobacter, and RIBA HP SIA, the positive and negative predictive values for diagnosis of colonisation were 97% and 90% (HelicoBlot 2); 94% and 92% (RIDA), and 98% and 85% (RIBA). For CagA status, however, the positive and negative predictive values were, respectively, 96% and 55% (HelicoBlot), 94% and 100% (RIDA), and 95% and 55% (RIBA); and for VacA status, 100% and 46% (HelicoBlot), 78% and 100% (RIDA), and 95% and 76% (RIBA). Significant false positive and negative results were obtained. When used for pre-endoscopy screening the tests missed a significant number of patients with serious pathology.³⁴

Near patient tests

There is an increasing requirement for near patient testing as more patients are managed by general practitioners on a test and treat basis. Several new near patient tests are available but generally they lack diagnostic accuracy when compared with laboratory ELISAs. Most of the tests are one step tests using whole blood but others require serum separation, which diminishes their usefulness as near patient kits. Also, with one test kit, variations in sensitivity and specificity were noted depending on whether capillary or venous blood was used. Helisal Rapid blood test had a sensitivity and specificity of 88% and 91%, and positive and negative predictive values of 92% and 86% when compared with histology, culture, RUT, and ¹³C-UBT in 154 dyspeptic patients.³⁵ These results compared with 93% and 87% sensitivity and specificity for an ELISA test (Helico G) in 109 of the patients. Another assessment on 203 patients,³⁶ compared with RUT/histology, gave a sensitivity and specificity of 82% and 91%; in this study there was concurrence of results whether venous or capillary blood was used. When Helisal was compared with a laboratory ELISA its sensitivity and specificity were 83% and 78%.³⁷ Other studies have found much lower specificity (55%) when compared with RUT/histology/culture.³⁸ In a study of 200 patients, although the sensitivity was high (91–92%) the specificity was low (56–62%).³⁹ In a study comparing Helisal with the UBT on 351 patients the specificity of the near patient test was poor compared with the UBT and the specificity of the kit decreased with increasing age of the patient.⁴⁰

A study of the accuracy of a new rapid whole blood test kit Pyloriset Screen, compared with Pyloriset EIA and Pyloriset Dry, on 207 patients showed it had a sensitivity and specificity of 95% and 94%, respectively, with positive and negative predictive values of 91% and 97%.⁴¹ The QuickVue one step blood test had a sensitivity and specificity of 82% and 83% in a retrospective analysis of 193 patients and 89% and 93% in a prospective study on 24 patients. If venous blood was used rather than capillary blood the sensitivity decreased to

73%.⁴² Hp Chek was tested on 287 patients in 10 centres in the USA and gave a result within nine minutes. The results were similar if whole blood or serum was used and the sensitivity, specificity, and positive and negative predictive values were 88%, 85%, 83%, and 90%, respectively. Rapid immunochromatographic tests are also available. In a study of 1209 samples from children, the sensitivity and specificity of FlexSure HP were 83–90% and 90–100%, respectively, but the positive predictive value was low in asymptomatic children compared with that of an ELISA test.⁴³ However, a further study found FlexSure to have a positive predictive value of 88% which was equivalent to a laboratory based ELISA result.⁴⁴

Interlaboratory and intralaboratory comparisons have not yet been performed and published for these kits and a recent publication does not support the use of these kits as presently formulated for near patient testing.⁴⁵

Antigen detection

One of the most promising developments for the detection of *H. pylori* is faecal antigen detection because of its speed, technical simplicity, and ease of sample collection. The Premier platinum HpSA EIA (Meridian Diagnostics, USA) uses an affinity purified polyclonal antibody attached to microwell plates to which is added a faecal suspension followed by a peroxidase conjugated antibody and substrate. This kit has been assessed in several studies. In a European multicentre study from 12 participating centres, 501 patients were analysed and the efficacy compared with histology, RUT, culture, and UBT.⁴⁶ The sensitivity and specificity were reported as 94% and 91%, respectively, with positive and negative predictive values of 93% and 92% in a population where the overall prevalence was 55% helicobacter positive. A smaller number of patients was studied four weeks after the end of eradication treatment and gave a sensitivity and specificity of 100% and 90%. The faecal antigen kit has been tested in other studies,^{47–49} all giving comparable sensitivities and specificities (91–98% and 83–96%). After treatment, the antigen seems to disappear quite rapidly (within a few days) from the faeces⁵⁰ but the specificity was recorded as 79%.⁴⁷ However, in a further study comparing HpSA with PCR, antigen and DNA were still detectable in the faeces 35 days after treatment.⁵¹ Further development of the test is likely to improve its utility in monitoring eradication treatment. An emerging potential useful method in addition to antigen or DNA detection is the use of immunomagnetic beads to isolate the organism.

Conclusions

Although there are many well validated methods that can be used to detect *H. pylori*, there are nevertheless continued improvements to current tests and the development of new tests, driven by considerations of cost and a search for speed and technical simplicity. An increasing number of patients may be treated by their general practitioners and consequently there is

a requirement for a rapid, simple, accurate, near patient test. Furthermore, the emergence of antibiotic resistant isolates has given an impetus to the development of rapid molecular techniques to identify such resistant organisms. The current main areas of development in diagnostic tests are in the use of non-invasive salivary antibody and faecal antigen tests, the use of rapid near patient antibody tests, and the development of DNA immunoassays for the detection of both antibiotic sensitive and resistant *H. pylori*.

- 1 National Institute of Health Consensus Conference. Helicobacter pylori in peptic ulcer disease. *JAMA* 1994;272:65-9.
- 2 IARC. *Schistosomes, liver fluke and H. pylori*. IARC monograph on the evolution of carcinogen risks in humans. Lyon: International Agency for Research on Cancer, 1994; 61:177-240.
- 3 Tomb JF, White O, Kerlavage AR, et al. The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature* 1997;388:539-47.
- 4 van den Oever HL, Loffeld RJ, Stobberingh EE. Usefulness of a new serological test (BIORAD) to diagnose Helicobacter pylori-associated gastritis. *J Clin Microbiol* 1991;29: 283-6.
- 5 Goossens H, Glupczynski Y, Burette A, et al. Evaluation of a commercially available complement fixation test for diagnosis of Helicobacter pylori infection and for follow-up after antimicrobial therapy. *J Clin Microbiol* 1992;30:3230-3.
- 6 Aguirre PM, Pascual CY, Merino FJ, et al. Evaluation of two commercial enzyme immunoassays for the diagnosis of Helicobacter pylori infection. *Eur J Clin Microbiol Infect Dis* 1992;11:634-9.
- 7 Trautmann M, Moldrzyk M, Vogt K, et al. Use of a receiver operating characteristic in the evaluation of two commercial enzyme immunoassays for detection of Helicobacter pylori infection. *Eur J Clin Microbiol Infect Dis* 1994;13: 812-19.
- 8 Granberg C, Mansikka A, Lehtonen OP, et al. Diagnosis of Helicobacter pylori infection by using pyloriset EIA-G and EIA-A for detection of serum immunoglobulin G (IgG) and IgA antibodies. *J Clin Microbiol* 1993;31:1450-3.
- 9 Raymond J, Kalach N, Bergeret M, et al. Evaluation of a serological test for diagnosis of Helicobacter pylori infection in children. *Eur J Clin Microbiol Infect Dis* 1996;15:415-17.
- 10 Marchildon PA, Ciota LM, Zamaniyan FZ, et al. Evaluation of three commercial enzyme immunoassays compared with ¹³C urea breath test for detection of Helicobacter pylori infection. *J Clin Microbiol* 1996;34:1147-52.
- 11 Talley NY, Kost L, Haddad A, et al. Comparison of commercial serological tests for detection of Helicobacter pylori antibodies. *J Clin Microbiol* 1992;30:3146-50.
- 12 van de Wouw BA, de Boer WA, Jansz AR, et al. Comparison of three commercially available enzyme linked immunosorbent assays and biopsy dependent diagnosis for detecting Helicobacter pylori infection. *J Clin Microbiol* 1996;34:94-7.
- 13 Wilcox MH, Dent TH, Hunter JO, et al. Accuracy of serology for the diagnosis of H. pylori infection: a comparison of eight commercially available H. pylori serology kits. *J Clin Pathol* 1996;49:373-6.
- 14 Feldman RA, Deeks JJ, Evans SJW, et al. Multi-laboratory comparison of eight commercially available H. pylori serology kits. *Eur J Clin Microbiol Infect Dis* 1995;14:428-33.
- 15 Lozniewski A, de Korwin JD, Conroy MC, et al. Evaluation of Pyloriset Dry, a new agglutination test for H. pylori antibody detection. *J Clin Microbiol* 1996;31:1773-5.
- 16 Hirschl AM, Hirschl MM, Berger J, et al. Evaluation of a commercial latex test for the serological diagnosis of H. pylori infections in treated and untreated patients. *Eur J Clin Microbiol Infect Dis* 1991;10:971-4.
- 17 Hoek FJ, Noach LA, Rauws AJ, et al. Evaluation of the performance of commercial test kits for detection of H. pylori antibodies in serum. *J Clin Microbiol* 1992;30:1525-8.
- 18 Jensen AKV, Andersen LP, Wachmann CH. Evaluation of eight commercial kits for H. pylori IgG antibody detection. *APMIS* 1993;101:795-801.
- 19 Midolo PD, Lambert JR, Russell EG, et al. A practical single sample dry latex agglutination test for H. pylori antibody detection. *J Clin Pathol* 1995;48:969-71.
- 20 Schembri MA, Lin SK, Lambert JR. Comparison of commercial diagnostic tests for H. pylori antibodies. *J Clin Microbiol* 1993;31:2621-4.
- 21 Westblom TU, Madan E, Gudipati S, et al. Diagnosis of H. pylori infection in adults and paediatric patients by using Pyloriset, a rapid latex agglutination test. *J Clin Microbiol* 1992;30:96-8.
- 22 Jonkers D, Stobberingh E, de-Bruine A, et al. Evaluation of immunohistochemistry for the detection of Helicobacter pylori in gastric mucosal biopsies. *J Infect* 1997;35:149-54.
- 23 Marzio L, Angelucci D, Grossi L, et al. Anti-Helicobacter pylori specific antibody immunohistochemistry improves the diagnostic accuracy of Helicobacter pylori in biopsy specimens from patients treated with triple therapy. *Am J Gastroenterol* 1998;93:223-6.
- 24 Misaka K, Kumagai T, Shimizu T, et al. A new histological procedure for re-evaluation of the serological tests for Helicobacter pylori. *Eur J Clin Microbiol Infect Dis* 1998;17: 14-19.
- 25 Monteiro L, Cabrita J, Megraud F. Evaluation of performances of three DNA-enzyme immunoassays for detection of Helicobacter pylori PCR products from biopsy specimens. *J Clin Microbiol* 1997;35:2931-6.
- 26 Martin de Argila C, Boixeda D, Canton R, et al. Usefulness of the combined IgG and IgA antibody determinations for serodiagnosis of Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 1997;9:1191-6.
- 27 Aucher P, Petit ML, Mannant PR, et al. Use of immunoblot assay to define serum antibody patterns associated with Helicobacter pylori infection and with H. pylori-related ulcers. *J Clin Microbiol* 1998;36:931-6.
- 28 Loeb MB, Riddell RH, James C, et al. Evaluation of salivary antibodies to detect infection with Helicobacter pylori. *Can J Gastroenterol* 1997;11:437-40.
- 29 Christie JM, McNulty CA, Shepherd NA, et al. Is saliva serology useful for the diagnosis of Helicobacter pylori. *Gut* 1996;39:27-30.
- 30 Malaty HM, Peacock JS, Marchildon P, et al. OraSure salivary test for the screening of Helicobacter pylori infection in asymptomatic children [abstract]. *Gut* 1998;43(suppl 2):A53.
- 31 Passaretti N, Mina T, White E, et al. Evaluation of the diagnostic utility in children of a salivary EIA to detect IgG antibodies to H. pylori [abstract]. *Gut* 1998;43(suppl 2):A54.
- 32 Vaira D, Fusconi M, Menegatti M, et al. A novel recombinant immunoblotting assay (RIBA) for determination of serological reactivities of Helicobacter pylori (HP) [abstract]. *Gut* 1997;41:A77.
- 33 Yamaoka Y, Kodama T, Graham DY, et al. Comparison of four serological tests to determine the CagA or VacA status of Helicobacter pylori strains. *J Clin Microbiol* 1998;36: 3433-4.
- 34 Heikkinen M, Janatuinen E, Mayo K, et al. Usefulness of anti-Helicobacter pylori and anti-CagA antibodies in the selection of patients for gastroscopy. *Am J Gastroenterol* 1997;92:2225-9.
- 35 Moayyedi P, Carter AM, Catto A, et al. Validation of a rapid whole blood test for diagnosing H. pylori infection. *BMJ* 1997;314:119.
- 36 Borody TJ, Andrews P, Shortis NP. Evaluation of whole blood antibody kit to detect active H. pylori infection. *Am J Gastroenterol* 1996;91:2509-12.
- 37 Jones R, Phillips I, Felix G, et al. An evaluation of near patient testing for H. pylori in general practice. *Aliment Pharmacol Ther* 1997;11:101-5.
- 38 Stevens M, Livsey SA. *MDA evaluation reports*. Nos 15, 16, 17, 37, 43. Norwich: HMSO, 1997.
- 39 Stone MA, Mayberry JF, Wicks AC, et al. Near patient testing for Helicobacter pylori: a detailed evaluation of the Cortecs Helisal Rapid Blood test. *Eur J Gastroenterol Hepatol* 1997;9:257-60.
- 40 Mowat C, Murray L, Hilditch TE, et al. Comparison of helisal rapid blood test and ¹⁴C-urea breath test in determining Helicobacter pylori status and predicting ulcer disease in dyspeptic patients. *Am J Gastroenterol* 1998;93: 20-5.
- 41 Oksanen A, Veijola L, Sipponen P, et al. Evaluation of Pyloriset Screen, a rapid whole-blood diagnostic test for Helicobacter pylori infection. *J Clin Microbiol* 1998;36: 955-7.
- 42 Duggan AE, Hardy E, Hawkey CJ. Evaluation of a new near patient test for the detection of Helicobacter pylori. *Eur J Gastroenterol Hepatol* 1998;10:133-6.
- 43 Elitsur Y, Neace C, Triest WE. Comparison between a rapid office-based and ELISA serologic test in screening for Helicobacter pylori in children. *Helicobacter* 1997;2:180-4.
- 44 Anderson JC, Cheng E, Roeske M, et al. Detection of serum antibodies to Helicobacter pylori by an immunochromatographic method. *Am J Gastroenterol* 1997;92:1135-9.
- 45 Anon J. Helicobacter pylori testing kits. *Drugs and Therapeutics* 1997;35:23-4.
- 46 Vaira D, Malfertheiner P, Megraud F, et al. A novel antigen assay based on a stool specimen for Helicobacter pylori: European multicentre study [abstract]. *Gut* 1998;43(suppl 2):A47.
- 47 Trevisani L, Sartori S, Galvani F, et al. Evaluation of a new enzyme immunoassay for detecting Helicobacter pylori in faeces [abstract]. *Gut* 1998;43(suppl 2):A47.
- 48 Veldhuyzen van Zanten S, Bleau BL, Best L, et al. Use of the Helicobacter pylori stool antigen test (HPSAT) for detection of H. pylori infection. *Gut* 1998;43(suppl 2):A49.
- 49 Forne M, Dominguez J, Esteve M, et al. Detection of Helicobacter pylori antigen in stool specimens in the diagnosis of infection and post treatment check-up. Preliminary results [abstract]. *Gut* 1998;43(suppl 2):A50.
- 50 van't Hoff BW, van der Ende A, van der Hulst RWM, et al. Helicobacter pylori antigen in stool specimen as a possible monitoring tool for eradication therapy [abstract]. *Gut* 1998;43(suppl 2):A49.
- 51 Makristathis A, Pasching E, Schultz K, et al. Detection of Helicobacter in stool specimens by PCR and antigen EIA [abstract]. *Gut* 1998;43(suppl 2):A47.