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Blood tests in the management of *Helicobacter pylori* infection

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Summary
There are three main types of blood test available for the management of *Helicobacter pylori* infection: those that detect an antibody response; tests of the pathophysiological state of the stomach; and those that indicate an active infection. Enzyme linked immunosorbent assay (ELISA) based kits are the most numerous of the commercially available tests. Originally the kits used crude antigen preparations but many of the newer kits use a more purified antigen preparation giving increased specificity but a lower sensitivity. The sensitivity, specificity, and predictive values of the tests can also be affected by the population under test and coexistent disease in the patients. Near patient test kits are based on either latex agglutination or immunochromatography. Generally, they have low sensitivities compared with laboratory tests. Commerical western blotting kits have also been developed and are used to detect the presence of specific virulence markers. The exact role of serology in the management of *Helicobacter* infection has still to be defined, although there is evidence that, used as a screening procedure, it can reduce endoscopy cost and workload. Gastrin and pepsinogen blood concentrations may provide valuable information on the pathophysiological state of the stomach—for example, the presence of inflammation or gastric atrophy. A combination of serology and serum concentrations of gastrin and pepsinogen may be used effectively to detect serious gastroduodenal disease in patients.

Introduction
Helicobacter pylori has been linked with an increasing number of conditions since its first suggested association with gastritis, now well established. Knowledge about the pathogenesis of peptic ulcer disease (PUD) has been revolutionised by the isolation of *H pylori,* and, as a natural consequence of this, the management of PUD has completely changed from one of primarily acid suppression to one of primarily bacterial eradication. The causal association between colonisation by *H pylori*, PUD, and gastric cancer places *H pylori* as an important human pathogen. The link between colonisation by *H pylori* and the risk of developing various forms of gastric neoplasm raises the exciting prospect of reducing the risk of neoplasm development by some form of eradication therapy at a population or even individual level. A natural corollary of this is the requirement of an effective screening procedure to determine colonisation status. In addition, the possible association between the widespread pathophysiological effects of chronic inflammation in the stomach and the risk of ischaemic heart disease, growth retardation, and gall stones also suggests the need for cost-effective management protocols.

Generally, there are a number of factors that must be included in an effective protocol for all aspects of disease management. For example, there should be an accurate diagnostic procedure at an individual level and a cost-effective population screening procedure. Also, the ability to determine prognostic indicators may influence management of the disease and there should be an effective follow up protocol to establish efficacy of treatment and recurrence of disease. More specifically, with respect to determining colonisation by *H pylori* and associated disease, blood tests are one of the two non-invasive techniques available; the other is the urea breath test (UBT).

Antibody tests for *H pylori*

EVALUATION OF ANTIGEN
Several different antigen preparations have been tested. Initially, crude sonicates were used, and, although the sensitivity of the test was high, the specificity was relatively low compared with other diagnostic tests such as culture or histology, because of false positives caused by non-specific cross reactions with other organisms—for example, *Campylobacter* sp.

Comparison of a whole cell preparation and an acid-glycine extract[1] showed enrichment of some immunodiagnostic antigens in the acid-glycine extract (the 54 and 69 kDa proteins) but complete loss of others (the 29 and 120 kDa proteins). Further, although the intention was to reduce non-specific cross reactions, they were still detectable when assessed by western blotting. A more extensive study[2] compared crude sonicates with ultracentrifuged whole cell sonicates and acid-glycine extracts and antigen fractions separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis. The greatest discrimination between *H pylori* positive and negative sera was found with high molecular mass fraction antigens, but whole cell sonicates were better than acid-glycine extracted antigens. A further comparison of four different antigen preparations (crude sonicate, acid-glycine extract, acid-glycine extract of a flagellate organism, and urease enriched fraction) showed the crude sonicate to have the highest sensitivity but the lowest specificity.[3] A study using more purified antigen prepared by fast protein liquid chromatography (FPLC) or monoclonal antibody capture generally showed lower sensitivities of the purified antigens compared with an acid-glycine extract, with specificities of 100%

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Table 1 Sensitivity and specificity of the different antigens

Antigen preparation	Sensitivity (%)	Specificity (%)
Crude sonicate	94–100	60–100
Ultracentrifuged sonicate	84–97	95–100
Surface antigen	82	92
Acid-glycine extract	82–95	83–98
Acid-glycine extract*	89	96
Urease preparation	81–97	89–90
120 kDa protein (CagA)	84–96	92–98
Recombinant cagA	96	96
CagA + ultracentrifuged sonicate	97	100
CagA + acid-glycine extract	97	100
FPLC purified urease	91	91
FPLC purified flagelia	78	100
MAb purified urease	83	93

Prepared from references 1–11.
*Acid-glycine extract from an aflagellate organism.
FPLC, fast protein liquid chromatography; MAb, monoclonal antibody.

for most of the fractions.[4] In one serological assay using the 120 kDa (CagA) protein purified by size exclusion chromatography[5] and compared with a whole cell preparation, the sensitivities and specificities were 96 and 100% and 92 and 60% respectively for the whole cell preparation. Several other studies have also compared different antigen preparation as the basis for serological tests.[6–11]

These results show, not unexpectedly, that there is a trade off with antigen purification between loss of sensitivity and increased specificity. Immunoblots have shown qualitative and quantitative differences in the pattern of response in patients, and this emphasises that the type of strain of *H pylori* and the method of preparation of the antigens for serological tests may be critical to the test parameters. It is possible that a judicious combination of purified antigens may maximise both sensitivity and specificity, and many second generation serological tests use purified or combinations of purified antigens. Table 1 shows the sensitivity and specificity of some antigen preparations and combinations.

Table 2 Commercially produced serological assays for detection of Helicobacter pylori

Kit	Kit	Test format	Manufacturer
Helori-test	Helori-test	ELISA	Eurospital, Italy
Pyloristat	Pylori ELISA II*	ELISA	BioWhittaker, USA
Pyloriset	Pyloriset updata	ELISA	Orion, Finland
Helico G	Helico G2	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 IgG2	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	Cortecs, UK
H. pylori IgG		ELISA	Dako, Denmark
Autozyme		ELISA	Cambridge LS, UK
Pyloragen		ELISA	Hycor, USA
Enzygnost HP		ELISA	Behring, UK
Quidel HP EIA		ELISA	Quidel, USA
Enzywell HP EIA		ELISA	Dresse Monteriggioni, Italy
Color Vue Pylori		ELISA	Seradyn, USA
Pyloriset	Pyloriset Dry	LA	Orion, Finland
Helisal RBT	Helisal One Step	IMC	Cortecs, UK
FlexSureHPS	FlexSure WB†	IMC	SmithKline, USA
Genesis Dot		IMC	Genesis, UK
QuickVueOnestep		IMC	Quidel, USA
Launch		IMC	Meridian, USA
Immunocard			
Quadratech HEP		IMC	VEDA, France
CLOser		IMC	Medical Inst.Corp, Switzerland
HelicoBlot 2.0		WB	GeneLab, Singapore
RIBA		WB	Chiron USA

*Pyloriset and Pylori ELISA II are no longer avaliable and have been replaced by H pylori IgG ELISA (Wample, USA). †FlexSure HP (SmithKline) is replaced by FlexPack (Abbott). Other kits are on the market—for example, Elagen (Immunogen International), H pylori IgG assay (Cozart) but little information is available.
ELISA, enzyme linked immunosorbent assay; LA, latex agglutination; IMC, immunochromatography; WB, western blotting.

EVALUTATION OF COMMERCIALLY AVAILABLE SEROLOGICAL ASSAYS

ELISA kits

Many publications have compared either single or many kits one against another[12–18] in a defined population, usually patients with dyspepsia or PUD or symptomatic individuals. Table 2 lists the main commercial serological assays available for the detection of *H pylori*. A comparison of the use of three kits for 76 patients using known culture positive cases showed comparable sensitivity and specificity of between 88 and 96% and 86 and 96% respectively. The inter- and intra-laboratory assay variation was low. The three kits used antigens of different purity: Pyloristat (urease enriched fractions), HelicoG (acid-glycine extract), Premier HP (high molecular mass cell associated proteins).[19] In a further test on 95 dyspeptic patients, the Cobas Core anti-*H pylori* immunoglobulin EIA-G, which uses an FPLC purified antigen, had a sensitivity and specificity of 94 and 98% respectively and was superior to the rapid urease test (RUT) (88 and 96%) and culture (70 and 98%) when compared with histology.[20] A laboratory comparison of the three kits was carried out, which included modified Pyloriset EIA-G update kit and Malakit EIA-G[21], on serum samples from 154 dyspeptic patients. Serological results were compared with those using culture/histology/RUT as the "gold standard". The updated Pyloriset showed an improved sensitivity but reduced specificity compared with previous results for this kit from other studies on equivalent groups of patients. A single laboratory comparison of eight kits was undertaken[22] on 84 dyspeptic patients and compared with histology and UBT. The results showed that all the kits had comparable sensitivity (90–100%) but more variable and lower specificity (76–96%). Indeterminate (grey zone) results occurred with some kits in up to 12% of the readings, although Premier HP, Pyloriset EIA-G, and HelicoG were calibrated so as not to give grey zone results (the latest version of the last of these kits, HelicoG2, however, does not have a grey zone range). The kit giving the highest percentage of grey zone results was GAP IgG. In this study Pylori ELISA II and Premier HP were particulary effective.

A multilaboratory comparison of eight kits[23] also showed that all the kits tested were broadly comparable. Some laboratories experienced difficulties with some kits and some kits showed high inter-laboratory variation. Overall the Pyloriset EIA-G and Roche MTP kits seemed to be the best. Again most of the kits produced some indeterminate results but this varied between kits (Roche, 0.9%; Hel-p Test, 13%). Table 3 gives the published sensitivity, specificity, positive, and negative values of these kits.

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Table 3 Comparison of commercially available ELISA kits for detection of Helicobacter pylori infection

Kit	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Helori-test	98–99	88	94	88
Pyloristat	91–99	70–94	80	84
Pylori ELISA II	100	96	97	100
Helico G	71–97	65–95	89–90	65–98
Helico C 2	85	76	74	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	94–98	83–86	86	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 Sigma 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	86	63	87

Data taken from references 12–23, 36, 37.
PPV, positive predictive value; NPV, negative predictive value.

Latex agglutination kits

The agglutination format is not as frequently used as the ELISA format and there have been fewer published evaluations.[24–30] Pyloriset Dry has replaced Pyloriset LA; it differs in the test procedure, but both use latex beads coated with an acid-glycine extract of *H pylori*. Both tests detect IgM, IgA, and IgG. The latex agglutination test is more convenient than the ELISA format for near patient testing and has comparable sensitivity and specificity with the ELISA tests (table 4).

Near patient testing

There is a perceived unmet clinical need for near patient testing of patients for *H pylori* infection, and several companies have developed rapid tests. Most of the tests consist of one step using whole blood, but others require serum separation, which diminishes their usefulness as near patient kits. With one test kit, variation in sensibility and specificity were noted depending on whether capillary or venous blood was used. Comparatively few assessments have been published.[31 32] The Helisal rapid blood test (Helisal RBT, now superseded by Helisal One Step) had a sensitivity and specificity of 88 and 91% and a positive predictive value and negative predictive value of 92 and 86% when compared with histology, culture, RUT, and UBT in 154 dyspeptic patients.[33] These results compared with 93 and 87% sensitivity and specificity respectively for an ELISA test (HelicoG) in 109 of the patients. Another assessment on 203 patients[34] compared with RUT/histology gave a sensitivity and specificity of 82 and 91%, and 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% respectively.[35] Other studies have found much lower specificity (55%) when compared with RUT/histology/culture[36 37] (table 4). Inter- and intra-laboratory comparisons have not yet been performed and published for these kits, but a recent publication does not support the use of these kits as presently formulated for near patient testing.[38]

Table 4 Comparison of commercially available near patient tests for the detection of Helicobacter pylori infection

Kit	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Helisal RBT	82–89	55–91	56	89
FlexSure HP	76–96	77–95	72–96	83–95
Quick Vue	88–89	70–79	70–82	86–88
Pyloriset LA	68–92	56–76	68–85	62–84
Pyloriset Dry	64–97	75–95	72–95	75–93
Quadratech	83	57	60	81
CLOser	95	72	80	93

Data taken from references 24–37.
PPV, positive predictive value; NPV, negative predictive value.

EFFECT OF POPULATION ON SEROLOGICAL RESULTS

Most assessments have been made in adults who were dyspeptic or asymptomatic. It is recognised from sero-epidemiological studies that different ethnic populations have widely differing prevalences of infection and that the assay cut-off value may have to vary to reflect this. Similarly the positive and negative predictive values of the various serological tests may vary according to age, drug administration, or coexistent disease in the population or individual under investigation. Studies in a group of children and in the elderly have shown decreased specificity of the serological tests when compared with culture and histology.[39] In the elderly this can often be due to atrophic gastritis and reduction in colonisation by *H pylori.* Apart from this age related effect on the accuracy of serological tests, the use of non-steroid anti-inflammatory drugs[40] can also affect the test accuracy, as can coexistent disease such as HIV infection,[41] cystic fibrosis,[42] and cirrhosis.[43]

SEROLOGY IN DIAGNOSIS AND SCREENING

Serology can only give evidence of contact with *H pylori* and does not necessarily indicate a current infection. This is more accurately diagnosed using a UBT. Serology, however, like the UBT, is a global test and is not affected by sampling errors, as are the biopsy based tests. In a study comparing all the diagnostic methods available, serology had a sensitivity and specificity of 98 and 95% respectively compared with 98 and 100% (culture), 96 and 100% (PCR), 98 and 98% (histology), 90 and 100% (RUT), and 100 and 100% (^{13}C-UBT),[44] although lower values for the sensitivity and specificity have been obtained in other studies. For example, comparing serology with RUT, sensitivities of 74 and 90% and specificities of 89 and 96% respectively were obtained in one study[45] and sensitivities and specificities of 96 and 88% for serology were obtained in another study when compared with UBT (96 and 100%), RUT (92 and 92%), and histology (96 and 91%).[46] The relative sensitivity and specificity of serology obtained in another study, when compared with other diagnostic methods, depended on the population studied, the number of individuals investigated, and the type of serological assay

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used. Serological assays for *H pylori* infection may have value in both diagnosis and screening and to monitor the effect of eradication treatment. The decision to use one test rather than another depends on the clinical circumstances, the reported test parameters (sensitivity, specificity, positive predictive value, and negative predictive value), cost, and convenience.

There are several possible management algorithms: to treat empirically; to use a screening test and either treat or proceed to endoscopy on the basis of the results; to examine every symptomatic patient by endoscopy. As the latter is an expensive option, various screening strategies have evolved to decrease the number of endoscopies performed. Other factors that need to be taken into account in a management algorithm are age (if over 45 years the patient should proceed to endoscopy without necessarily having a serological test), use of non-steroid anti-inflammatory drugs, and worrying symptoms. Several studies have shown that screening dyspeptic patients using serological tests can be cost-effective in reducing the endoscopy workload by up to 30% without missing significant pathology.[47 48] Patients who are positive on serological testing can then go on to endoscopy to verify the presence of PUD and hence be started on treatment, or may proceed directly to treatment. However, other studies have shown that if a screening strategy is adopted, significant pathology in some populations can be missed,[49] and we do not recommend it as a routine practice.

An alternative screening strategy is the use of a symptom questionnaire, and these have been reported to save a similar percentage of endoscopies as serological screening. In one direct comparison of symptom questionnaires with serological screening in 315 patients,[50] the latter detected more PUD than the questionnaires, but one of the questionnaires was more cost-effective in avoiding unneeded endoscopies. In addition, a cost analysis[51] of adopting a screening protocol using serological tests compared with empirical treatment with H_2 receptor antagonists or an eradication protocol showed that, although the eradication regimen was cheaper than suppressive treatment with H_2 receptor antagonists, this was offset by the cost of screening to such an extent that savings were only achieved after eight years. In children, the most cost-effective approach was empirical antisecretory treatment; however, the cost benefit of screening or empirical treatment when compared with direct endoscopy was diminished if the relative costs of endoscopy were low or the recurrence rate of symptoms was high (>65%).[52] Another cost-benefit analysis[53] showed that the efficacy of serological testing as a screening procedure depended on a response rate of more than 10% in non-ulcer dyspepsia (NUD) to eradication of *H pylori*, a saving of more than $4000 for ulcer prevention and a prevalence rate of more than 10% of PUD in all dyspeptic patients. Other studies have shown that serological testing can be useful in screening long term dyspeptic patients on suppressive H_2 receptor antagonists in a general practice setting. In one practice of 7100 patients, 17 were confirmed as *H pylori* positive by serology and given an eradication protocol. Four months after successful eradication (confirmed by a UBT), 76% of the patients were symptom free.[54] Obviously these percentages may fall with prolonged follow up of the patient.

In addition to screening as a means of reducing the cost of managing dyspepsia, there may be a place for population screening for *H pylori* infection as a means of preventing gastric cancer. Epidemiological evidence suggests that 31–87% of gastric cancers may be attributable to colonisation by *H pylori*,[55] and it is feasible that eradicating *H pylori* from an asymptomatic population may reduce the occurrence of gastric cancer. Such interventional studies are underway, but it will be years before any accurate conclusions can be drawn. It is preferable to substantiate the reversibility of premalignant conditions such as atrophic gastritis and intestinal metaplasia after successful eradication of *H pylori* before wholesale screening is adopted. However, a cost-benefit analysis[56] showed that, if 30% of gastric cancers were preventable by a screening eradication protocol, the cost-effectiveness was $25 000 per year of life saved, and this value was approximately maintained even if the success was only 5% if undertaken in high risk groups.

SEROLOGICAL TESTS FOR THE ASSESSMENT OF ERADICATION OF *H PYLORI*

After successful eradication of *H pylori*, antibody levels fall slowly over several months. In one study of 144 patients given eradication treatment, the IgG titre had fallen by 30% by six weeks after eradication and continued to fall over the succeeding nine months.[57] Similar reductions in IgG have been found in other studies,[58] and, although this can be used to assess successful eradication, it is not as convenient as the UBT.

The length of time required to carry out the serological tests mitigates against their use for assessing the success of therapy, as most patients and doctors would prefer to have a more speedy answer, if available. However, the merits of a relatively delayed serological result compared with a more speedy result from the UBT have not been assessed.

SEROLOGICAL MARKERS OF PATHOGENICITY

The high prevalence of *H pylori* infection throughout the world compared with the relatively low prevalence of the gastroduodenal diseases linked with the infection raises the question of whether all *H pylori* have the same clinical impact. It has been shown that some genes (*vacA*, *cagA*, *iceA*) confer different biological properties, such as proinflammatory, cytotoxic, and vacuolating activity, which could enhance the in vivo pathogenicity of the bacteria.[59] CagA and VacA are the most studied of their gene products and are reported to be linked with the more serious diseases. Knowledge of the CagA and VacA status of *H pylori* infection could be relevant for treatment and for prevention of the possible complications of

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Table 5 Reactivity against Helicobacter pylori lysate, CagA and VacA by RIBA-SIA

	Reactivity (%)		
	Lysate positive	*CagA positive*	*VacA positive*
Blood donor (n=999)	42	32	15
Non-ulcer dyspepsia (n=571)	42	36	17
Duodenal ulcer (n=275)	82	70	38
Gastric ulcer (n=71)	77	68	38
Gastric cancer (n=570)	78	61	33
Extragastric cancer (n=438)	63	38	21

infection. It is therefore important to diagnose the type of infecting organism. This is serologically possible since CagA protein is highly immunogenic: in fact, more than 95% of subjects infected by *cagA* positive *H pylori* strains develop a serologically detectable response to the gene product (anti-CagA), compared with 0% of uninfected patients.[60] However, both the structure of the VacA proteins and the serological response to it are only just being clarified and data are still scanty. These and other as yet undiscovered proteins could therefore lead to the identification of "bad", "very bad", "neutral", or even "good" *H pylori* strains, as recently speculated by Blaser.[61] The serological techniques currently available to determine the cytotoxic type of infecting strains are western blotting and ELISA. A novel recombinant immunoblott assay (RIBA-SIA; Chiron Corp., Emeryville, California, USA) has recently been proposed which contains individual bands for whole *H pylori* lysate, recombinant CagA, and VacA. In a recent evaluation of anti-CagA and anti-VacA reactivity by RIBA-SIA in large populations of both asymptomatic subjects and patients with different pathologies, anti-CagA mainly but also anti-VacA reactivities were found to be more prevalent in patients with severe gastroduodenal pathology (table 5).[62] Similarly the seroprevalence of anti-CagA reactivity assessed by ELISA (Helori-CTX; Eurospital, Trieste, Italy) was confirmed as being higher in *H pylori* positive subjects with gastric or duodenal ulcer than asymptomatic subjects or patients with NUD.[63] The results of a large multicentre study carried out in Italy involving over 3000 patients examined by endoscopy in more than 90 endoscopy units have recently been published.[64] CagA prevalence was assessed by ELISA in this large population, and the preliminary results in over 1300 patients confirm the association between CagA and major gastroduodenal pathology (table 6).

Many similar, although smaller, studies have previously shown the association between CagA as a marker for PUD and gastric cancer,[65 66] although other studies have not found this association.[67]

MARKERS OF GASTRIC INFLAMMATION AND *H PYLORI*

To distinguish PUD (in which the eradication of *H pylori* is recommended) from NUD (in which the role of *H pylori* is controversial), it is necessary to perform an endoscopy. Neither serological tests nor UBT give any quantitative information that would help to differentiate between these two conditions.[68] However, measurement of blood markers of gastric inflammation may give some clinical information that is useful in the management of *H pylori* related disease.

Gastrin

H pylori infection is associated with a set of well recognised disturbances to normal gastric physiology. Plasma gastrin levels are elevated in *H pylori* infection (150 ng/ml) compared with control levels (50 ng/ml) as a consequence of inhibition of somatostatin production. After eradication of *H pylori* the plasma gastrin levels return to normal.

Higher levels of plasma gastrin are found in corpus gastritis than in antral gastritis,[69] but there is no significant difference between the levels in gastritis compared with ulceration.[70]

Pepsinogen

Variations in concentrations of pepsinogen (PG) I and II and the PGI:II ratio can occur with age, weight, smoking, and chronic renal failure. Increases in both PGI (73 ng/ml compared with 50 ng/ml) and PGII (24 ng/ml compared with 10 ng/ml) with a reduction in the PGI:II ratio (3.6 compared to 6.2) are found in *H pylori* associated gastritis compared with *H pylori* negative individuals.[71] Some studies have shown that PGI levels are even further elevated in *H pylori* associated PUD compared with those without PUD,[72] and the elevation correlates with the degree of inflammation. A high PGI:II ratio is found in ulceration associated with the Zollinger-Ellison syndrome. In *H pylori* associated gastritis the increase in PGI is least in corpus only gastritis and highest in predominantly antral gastritis. Reduction in both PGI and PGII and normalisation of the ratio can be used to confirm successful eradication of *H pylori*,[73 74] although a decrease in PGII is the most accurate biomarker of eradication compared with PGI, serology, and serum gastrin.[75]

Variation in the levels and ratio of PG can be used to predict the presence of more serious gastric pathology. Used as a screening test in an asymptomatic population, a low PGI combined with *H pylori* positivity can predict gastric atrophy with a sensitivity and specificity of 88 and 92% respectively.[76] A high serum IgA anti-*H pylori* antibody level associated with a

Table 6 Prevalence of CagA by ELISA in Helicobacter pylori positive patients according to endoscopic findings

	Normal	*Gastritis duodenitis*	*Gastric ulcer*	*Duodenal ulcer*	*Gastric cancer*	*Overall*
$CagA^+$	117 (55.7)	322 (59.6)	41 (80.4)	171 (85.1)	6 (85.7)	671 (64.7)
$CagA^-$	93 (44.3)	219 (40.5)	10 (19.6)	30 (14.9)	1 (14.3)	366 (35.3)
Overall	210 (20.2)	541 (39.3)	51 (4.9)	201 (19.4)	7 (0.7)	1037 (100)

Values in parentheses are percentages.

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decreased PGI (<50 ng/ml) correlates with an increased risk of gastric cancer, with an odds ratio of 5.95 in one study population.[77]

Conversely there is an inverse correlation between serum IgG anti-*H pylori* antibody levels and the extent of gastric metaplasia, but only in those individuals that have normal PGI levels.[78] Screening strategies have been developed to detect gastric adenocarcinoma using a combination of *H pylori* positivity and PG and gastrin levels.[79 80] A study of 686 patients, of which 150 had gastric adenocarcinoma, showed that age above 62 years, low PGI levels, low PGI × gastrin value, and low PGI:gastrin ratio were indicative of gastric adenocarcinoma, with the value of serum PGI being the most important.

Conclusions

The exact role of serological testing in the management of *H pylori* infection is yet to be defined. However, used as a screening procedure, it can reduce endoscopy workload and cost, although the savings may take several years to accumulate.

Used in conjuction with blood levels of gastrin and PGs, these tests can suggest the presence of *H pylori* associated gastritis and be used to screen for serious gastroduodenal pathology, although further work is required to clarify their usefulness in this aspect.

The role of *H pylori* in NUD will affect how these blood tests are used in the management of *Helicobacter* infections. Currently, eradication of *H pylori* is only recommended in cases of PUD, and endoscopy is required to differentiate PUD from NUD. Therefore blood tests that could achieve this differentiation may reduce the endoscopy workload even further.

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