New techniques in medicine

Non-invasive testing for *Helicobacter pylori*

Margaret A Stone

Summary

Confirmed and potential benefits of eradicating *Helicobacter pylori* have led to the development of a range of diagnostic tests. As well as techniques using biopsy tissue obtained during endoscopy, a number of non-invasive tests are now available. These may be appropriate for pre-endoscopy screening of younger dyspeptics, for use in research, particularly epidemiological surveys, to confirm successful eradication after treatment, and possibly in the future for screening in asymptomatic populations. Serology requiring laboratory analysis is likely to be the least expensive option, particularly suitable for testing large numbers, while urea breath tests should yield the most accurate results and are appropriate for confirming successful eradication since only current infection is detected. The performance of near-patient tests can lack consistency, but these may be useful for small numbers and where other non-invasive testing is unavailable. Tests should be used with an awareness of their potential limitations in terms of accuracy.

Keywords: *Helicobacter pylori*

Non-invasive tests for *H pylori* infection

- laboratory-based serology
- near-patient tests
- urea breath tests

Box 1

Gastrointestinal Research Unit,
Leicester General Hospital, Leicester,
UK
M A Stone

Correspondence to Mrs MA Stone, c/o
Dr J F Mayberry, Gastrointestinal Research Unit,
Leicester General Hospital NHS Trust,
Gwendolen Road, Leicester LE5 4PW, UK

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The importance of infection with *Helicobacter pylori* in peptic ulcer disease has been confirmed¹ and evidence for an association with gastric cancer^{2,3} has led to the bacterium being classified as a Class I carcinogen by the World Health Organisation.⁴ Evidence both for^{5,6} and against⁷⁻⁹ a link with ischaemic heart disease has been presented and the significance of *H pylori* infection in non-ulcer dyspepsia remains controversial.^{10,11} Confirmed and potential benefits of eradicating this common infection have led to the development of a wide range of diagnostic tests. Infection with the bacterium can be demonstrated using biopsy tissue obtained from patients undergoing upper gastrointestinal endoscopy, by means of histology, culture, rapid urease tests such as the CLO test® or, less commonly, polymerase chain reaction technology. Non-invasive tests are, however, now also available. The value of the most commonly available of these, namely laboratory-based enzyme-linked immunosorbent assay (ELISA), serology, near-patient blood tests, and urea breath tests are discussed, including comparative advantages and disadvantages. Although the levels of accuracy which may be expected from these tests are considered, a comprehensive evaluation of each commercially available test is not within the scope of this review. Non-invasive tests using faecal samples are being developed and may play an important role in the future.

A role for non-invasive diagnosis?

The diagnostic value of endoscopy in patients with gastrointestinal symptoms goes beyond the simple determination of *H pylori* status and samples sent for histological examination may yield important diagnostic information in addition to that relating to the infection. Samples sent for culture may provide information on antibiotic resistance, which can be useful in deciding on the choice of therapy, particularly after failed eradication treatment. However, endoscopy is an expensive and invasive procedure and in some situations non-invasive testing may be more appropriate and cost effective.

It has been proposed¹²⁻¹⁵ that younger patients with symptoms of dyspepsia could be screened non-invasively for the infection in order to reduce numbers referred for endoscopy, an invasive procedure for which resources are limited. Gastric cancer is rarely found in the younger age group (below 40 or 45 years); serious pathology would therefore be rare in a young *H pylori*-negative patient, since absence of infection would generally exclude peptic ulceration, except where an association with non-steroidal anti-inflammatory drugs was suspected. It has therefore been suggested that endoscopy may be unnecessary in younger dyspeptics testing negative for *H pylori*. Those with positive tests may be treated with eradication therapy or referred for endoscopy, either directly or if empirical treatment with antisecretory therapy proves ineffective. A positive effect in reducing endoscopy workload has been shown by studies using serology as a pre-endoscopy screening tool in younger dyspeptic patients,¹²⁻¹⁴ and also by a study in which salivary antibodies were measured as an alternative to serology.¹⁵

Further uses of non-invasive testing for *H pylori* are epidemiological and in research projects where endoscopy would be inappropriate. Urea breath tests can be used for follow-up after treatment with eradication therapy, as an alternative to repeat endoscopy. In addition, screening for the bacterium in asymptomatic populations is a possibility for the future. It has been proposed that infection with *H pylori* presents a major public health problem¹⁶⁻¹⁸ and it has been estimated that over 8000 deaths per year in England and Wales may be attributable to the infection through its association with gastric cancer and bleeding peptic ulcers.¹⁸ A study from the US has suggested that population screening for *H pylori* infection to prevent gastric cancer may be justified in terms of cost-effectiveness, particularly in high risk groups¹⁹ and it has also been proposed that in the UK expenditure on *H pylori* screening would be partially offset by a reduction in the high cost of treating dyspepsia.²⁰ Health benefits of screening for *H pylori* have yet to be convincingly demonstrated and good compliance would be necessary for such a strategy to be effective,²¹ but non-invasive testing for the infection would be the appropriate choice for routine screening if it were to be recommended.

Potential uses for non-invasive *H. pylori* tests

- pre-endoscopy screening of younger dyspeptics
- epidemiological surveys and other research
- screening in asymptomatic populations
- confirmation of eradication after treatment

Box 2**Laboratory-based serology***Advantages:*

- not limited by sampling error
- inexpensive
- convenient for testing large numbers

Disadvantages:

- past/current infection not distinguished
- accuracy may be limited
- laboratory service not always available

Box 3**Near-patient tests***Advantages:*

- not limited by sampling error
- special facilities not required
- convenient for small numbers
- rapid results

Disadvantages:

- past/current infection not distinguished
- accuracy may be limited
- possible problems with operator error and readability

Box 4**Laboratory-based serology**

H. pylori is capable of eliciting both local and systemic antibody response in infected persons²² and ELISA serology is generally based on detection of immunoglobulin G (IgG) antibodies to the bacterium. The cost of using a commercially available kit for this type of testing is relatively low at around £2–6 per patient,²³ depending on the kit selected and whether samples are tested singly or in duplicate. In-house ELISAs are also available in some laboratories. Although immunoblotting^{24–25} can be used on sera to provide more qualitative serological results with regard to reactivity with *H. pylori* antigens, this is not generally available as a diagnostic test.

Laboratory-based serological testing has the advantage of requiring very little patient time, since only a venous blood sample is required. It is therefore particularly suitable where large numbers are to be tested, for example, for epidemiological surveys. Whilst advantages in terms of convenience and cost are important considerations, the usefulness of serological tests depends largely on their sensitivity and specificity. A wide range of kits for carrying out these tests is available commercially and their accuracy has been shown to vary considerably.^{23–28} Sensitivity and specificity both of 100% were demonstrated for one kit (the Meridian Diagnostics/Launch Premier ELISA) in a study involving 84 patients.²⁶ However, in a much larger study²³ based on 588 patients and comparing 16 kits including the Meridian ELISA, sensitivities ranged from 92.6% to 75.5% and specificities from 82.4% to 51.6%, emphasizing the variability in performance of this type of test. In the latter study, the commercial kits ranked highest for overall accuracy (number of true results/number of patients tested) were the Sigma SIA (sensitivity 85.3%, specificity 79.9%), Meridian (Launch) Premier (sensitivity 85.0%, specificity 80.0%) and CDS HM-CAP (sensitivity 83.3%, specificity 80.0%). Attention must be paid to selecting an ELISA which will perform well in the population to be tested, ideally through local evaluation using other diagnostic tests. The specificity of one ELISA was found to be significantly reduced in ethnic minorities in one study¹³ and, in general, serological tests perform better in younger populations.^{23–26} Most ELISAs yield quantitative results and setting a local positive/negative cut-off point may also be advantageous.

Unlike biopsy-based tests, which are site-dependent, serology has the advantage of avoiding possible sampling error. However, since serological tests are based on antibody detection, past infection may lead to false-positive results where *H. pylori* is no longer present. For this reason, these tests are generally unsuitable for determining success of eradication after treatment, although it has been argued that successful eradication can be assumed following a substantial drop in antibody titre using repeat serology after a delay post-treatment. It has been suggested that a 50% decrease in antibody titre 6 months after treatment can confirm successful eradication,²⁹ whilst another study showed a 40% decrease after 3–4 months to be a reasonably reliable indicator of eradication.³⁰

Near-patient testing

Laboratory-based serology is not universally available, moreover it is a practical option only where a high number of samples are to be analysed together so that ELISAs can be run economically. A number of near-patient or 'office' tests have been developed, which are suitable for single use and require no special laboratory equipment or facilities, making them particularly convenient for use in general practice. In general, these are based on IgG antibody serology, although the use of salivary tests has also been investigated.^{15–31} Kits for near-patient blood testing vary from those requiring separation of a venous sample to those which use a finger-prick sample of whole blood. Cost varies, but a typical example is the commonly available Cortecs Helisal® test, currently costing £12 net excluding carriage for a single-patient kit, both in its original Rapid Blood or more recent One Step versions. In general, with near-patient kits, a result is available within a short time, so that the subject can be tested and the result obtained in a single visit. This adds to the convenience of the test, although it could be argued that there is no clinical advantage in access to an instant result from a test for an infection which is generally acquired in childhood^{32–33} and which most patients may consequently have already harboured for many years.

The accuracy of near-patient serology has been shown to vary widely. In one study good results were obtained using both the QuickVue kit (sensitivity 85.7%, specificity 93.0%) and Flexsure (sensitivity 94.8%, specificity 90.8%),³⁴ but the performance of this type of test may not be consistent. Evaluations of the Cortecs Helisal® Rapid Blood test, for example, have produced conflicting results,³⁵ with specificity particularly poor in some series. Although a sensitivity of 88% and specificity of 91% were shown in one study,³⁶ specificity below 60% has also been

demonstrated.³⁴⁻³⁷ As with laboratory-based serology, near-patient blood tests perform less well in older patients.³⁶⁻³⁷ In one evaluation of the Helisal® test, for example, specificity in particular was found to be unacceptably poor at 41–55% in those aged over 45 years, compared to 78–82% in younger patients.³⁷

H. pylori testing using this type of kit may involve a number of stages and where tests are carried out infrequently there is a danger of operator error. Moreover, since most results rely on a subjective reading, there is also the possibility of poor readability of results,³⁷ and inter- and intra-observer variation. There may be a role for near-patient kits where other non-invasive testing is unavailable, but tests should be used, and future management of patients considered, with an awareness of potential limited accuracy.

Urea breath tests

Urea breath tests

Advantages:

- not limited by sampling error
- good accuracy
- only current infection detected

Disadvantages:

- expensive
- more patient time required than for serology
- specialist equipment needed for ¹³C-urea version
- ¹⁴C-urea version uses radioactive isotope

Box 5

Like rapid urease tests performed on biopsy samples, the Urea Breath Test (UBT) for infection with *H. pylori*, relies on the bacterium's urease activity. Two versions, the ¹³C-urea³⁸⁻³⁹ and ¹⁴C-urea⁴⁰ have been developed. The patient drinks a solution of urea containing a labelled carbon atom and, in an infected patient, labelled carbon dioxide can subsequently be detected in expired air. A test meal, such as Calogen or Ensure, is usually given prior to the urea solution, in order to delay gastric emptying; orange juice, a citric acid solution or full cream milk have also been shown to be effective.⁴¹ Patients are generally required to fast prior to the test, although a non-fasting version may also give accurate results⁴² and would make the test method both more convenient and more acceptable to patients. Results of the ¹³C-UBT are generally expressed in terms of excess $\delta^{13}\text{CO}_2$ excretion and a post-urea increase greater than 5 $\delta^{13}\text{CO}_2/\text{ml}$ was originally determined as the negative/positive cut-off value. More recently, however, 3.5 $\delta^{13}\text{CO}_2/\text{ml}$ excess has been demonstrated to be the optimum cut-off value.⁴³

In common with laboratory-based serology and near-patient blood tests, breath testing has the advantage of being free from sampling error, since the whole stomach is involved. Unlike blood testing, it detects only current infection and it is therefore particularly appropriate as a non-invasive method of confirming successful eradication of *H. pylori* after treatment, both in clinical practice and research. This should, however, be delayed for at least four weeks after completion of therapy, to avoid misleading results.⁴⁴

Breath testing is more expensive than serology and requires more patient time than blood testing, since a delay of approximately 30 minutes between pre- and post-urea breath sampling is involved. Direct comparison has, however, suggested that ¹³C-UBT is more accurate than serology; sensitivity and specificity of 99% and 98%, respectively, has been demonstrated,³⁹ with 93% sensitivity and 100% specificity shown in another study.⁴⁵ In both these studies, serology provided less accurate results than the UBT.

The analysis of breath samples for the ¹³C-urea test requires costly and specialised equipment which is not always available on site, although a recent paper demonstrated only slightly reduced accuracy using a gas chromatograph mass selective detector, which is more generally available.⁴⁶ Where there are no facilities for on-site analysis, kits are available commercially from the Bureau of Stable Isotope Analysis at a current cost of £25 per single-patient kit, excluding VAT, test meal and carriage but including analysis of breath samples. This kit (Pylobactell™) is now available in the UK through pharmacies, on a prescription-only basis. In-house testing using a regional service for analysis of breath samples has been shown to give results comparable to commercial analysis,⁴⁷ but the high cost of a mass spectrometer would make the purchase of this equipment a feasible option only where large-scale testing was envisaged. One group have shown the feasibility of asking patients to collect breath samples at home, although the need for thorough instruction and some patient selection was suggested.⁴⁸

The ¹⁴C-UBT is generally more economical than the ¹³C-UBT, since the scintillation counter required for analysing samples is commonly available, but this version has the disadvantage of involving a very small but measurable dose of radiation. The ¹³C-UBT test, using a non-radioactive isotope, is suitable for use in children, pregnant women and for repeated tests on the same patient. It may also be considered more appropriate than the ¹⁴C-UBT for use in patients taking part in research, particularly those without related symptoms.

Conclusions

Non-invasive tests for infection with *H. pylori* do not supersede the use of tests based on biopsy tissue obtained during endoscopy, but do provide a

complementary strategy for diagnosing the infection. The role of pre-endoscopy screening for *H. pylori* in younger dyspeptic patients is still controversial, with wide variation in attitudes and practice shown by a UK survey of gastroenterologists and general practitioners with an interest in gastroenterology.⁴⁹ If this strategy is considered to be appropriate, however, then non-invasive testing has a role to play in this area. These tests are also useful for epidemiological surveys and other research projects where endoscopy would be inappropriate, and may be used for screening in asymptomatic populations. Successful eradication of the infection after treatment may also be confirmed non-invasively. The choice between the various tests available will depend on the relative importance of cost, practicality, sensitivity and specificity in relation to the use proposed. The costs of the various test methods mentioned above do not include operator time, but laboratory serology is likely to provide the cheapest method of testing high numbers, while urea breath tests will probably yield the most accurate results and are particularly appropriate for checking successful eradication. Near-patient tests may be useful where low numbers are to be tested and where other non-invasive testing is unavailable, although commercially available breath test kits are likely to perform better and should perhaps be preferred, particularly for testing older patients, except where cost is of paramount importance. It is important that all these non-invasive tests are used with an awareness of their potential limitations, particularly in terms of sensitivity and specificity.

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