Leading article

Blood, urine, stool, breath, money, and *Helicobacter pylori*

Helicobacter pylori infection can be diagnosed by invasive (that is, endoscopy and biopsy) and non-invasive techniques. The choice of a diagnostic test should depend on the clinical circumstances, the pre-test probability of infection, sensitivity and specificity of the test (or more correctly the likelihood ratio of a positive and negative test), the cost effectiveness of the testing strategy, and the availability of the test. Some clinical circumstances warrant invasive studies: patients who have failed eradication therapy may need culture and antimicrobial sensitivity testing to help determine an appropriate regimen, older patients with new onset dyspepsia, and those with "alarm" symptoms (bleeding, weight loss, etc) that raise the concern of malignancy. Non-invasive studies are preferable in epidemiological studies and in young children. Recent studies have also demonstrated that a strategy to test and treat *H pylori* in uninvestigated young (<50 years) dyspeptic patients in primary care is safe and reduces the need for endoscopy.[1]

Until recently, only two non-invasive methods of testing for *H pylori* have been available: (1) the ^{13}C or ^{14}C labelled urea breath test (UBT), which is based on detection of ^{13}C or ^{14}C labelled CO_2 in expired air as a result of *H pylori* urease activity[2–4] and (2) serology (which is based on detection of a specific anti-*H pylori* IgG antibody in the patient's serum.[5 6] Several new methods of detecting *H pylori* have recently been described and include detection of antibodies in saliva[7] and urine,[8] and detection of antigens in stool.

SEROLOGY

There are a number of different techniques for antibody detection in serum, including enzyme linked immunosorbant assay (ELISA), agglutination tests, and western blotting but ELISA is the most widely used clinically. Antibody levels persist in the blood for long periods of time. Not surprisingly, as more and more patients with *H pylori* infection are treated, the persistent antibody will lead to false positive tests with increasing frequency. A meta-analysis of 21 studies with commercially available ELISA serology kits reported overall sensitivity and specificity of 85% and 79%, respectively.[6] Recently, a large number of ELISA tests were evaluated by the Medical Devices Agency of Great Britain[5]: 588 samples of sera were evaluated with 16 different tests. The overall accuracy of the assays averaged 78% (range 68–82%) for all sera. The accuracy of these tests is no longer adequate to justify their clinical use on clinical or economic grounds.

SEROASSAYS FOR PATHOGENICITY MARKERS

There are several serological tests for determining the cagA status of a patient, either as an ELISA test or as a western blot assay. Determination of cagA status has value in epidemiological trials and in studies of pathogenesis but has limited use in clinical practice.

NEAR PATIENT TESTS

Near patient tests were developed to provide a rapid diagnosis of *H pylori* infection in the clinic or physician's office. They are technically simple to perform. Most of those currently used are one step tests that require a drop of whole blood, but others require separation of serum which diminishes their usefulness as near patient kits. Recent evidence accumulated in 3805 patients in eight studies performed in 1999/2000 suggests that these tests have considerably lower sensitivity and specificity than originally assumed. The mean sensitivity (weighted for number of patients studied) was 71.1% and specificity was 87.6%.[9–16]

SALIVARY AND URINE ANTIBODY ASSAY

Saliva and urine antibody testing have been proposed as non-invasive techniques for the detection of *H pylori* infection. Results with the salivary assay have been disappointing (sensitivity 81%, specificity 73%).[7] To date, only one study has reported on the urine assay with sensitivity and specificity of 86% and 91% in 132 patients.[8] These encouraging data do not appear to be supported by a multicentre European trial using the same urine assay in a large population (European *Helicobacter pylori* study group, unpublished data).

As a result of recent studies, the European *Helicobacter pylori* study group does not recommend serology except in high prevalence situations (prevalence 60%). Near patient tests, and urine and saliva tests are not recommended at the present time.

UREA BREATH TEST

Since their introduction, both ^{13}C and ^{14}C UBTs have been used widely in a number of patients both before and after therapy. Analysis of the results reported in studies in which the tests were evaluated against an accepted gold standard confirm the accuracy of the test. In 3643 patients studied in 1999/2000, the weighted means for sensitivity and specificity of the UBT were 94.7% and 95.7%, respectively.[17–22]

STOOL ANTIGEN DETECTION

Over the past two years, an enzymatic immunoassay which detects the presence of *H pylori* antigen in stool specimens has become available and has undergone testing in the initial diagnosis of *H pylori* infection and in the confirmation of eradication after treatment. A polyclonal anti-*H pylori* capture antibody absorbed to microwells is the most widely used test but a monoclonal antibody test has recently been described and is under investigation.[23] The polyclonal antibody test has been extensively evaluated in the diagnosis of *H pylori* infection before therapy. In 1999/2000, 2924 patients were evaluated using the stool antigen test and the weighted mean for sensitivity was 93.1% and specificity was 92.8% (fig 1).[17 24–41] Large carefully controlled trials with rigorous end points for the presence of infection suggest that the test is comparable with the UBT in the initial detection of *H pylori* infection. Consequently, the European *Helicobacter pylori* study group has recommended the use of the UBT or stool testing in the initial diagnosis of *H pylori* infection.

Abbreviations used in this paper: UBT, urea breath test; ELISA, enzyme linked immunosorbant assay.

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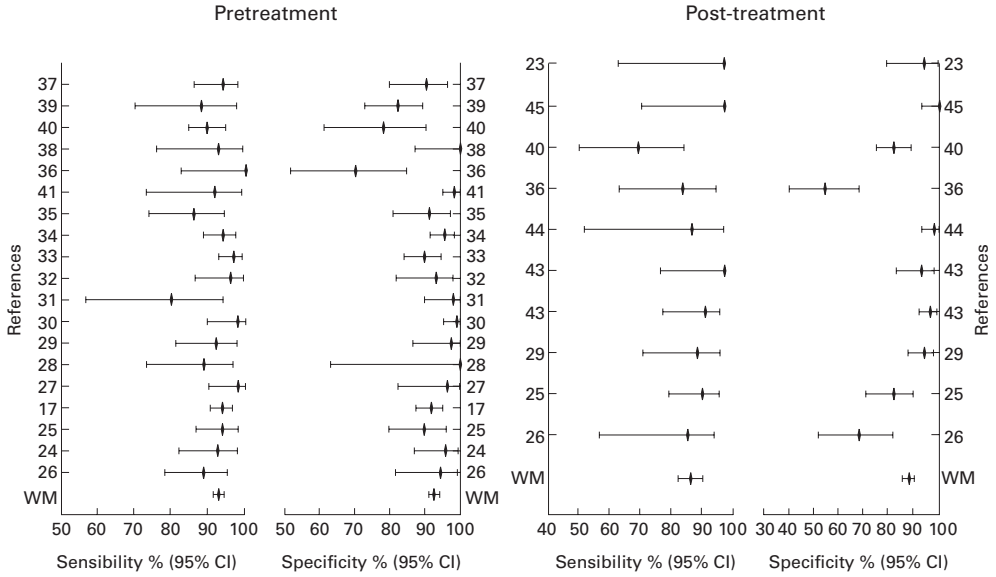

Figure 1 Sensitivity and specificity (with 95% confidence intervals) of the stool antigen test before and after therapy. WM, weighted mean.

There has been some variability in the results reported by different investigators in the post-therapy setting. Some of these differences may be due to the gold standard used for comparisons. A total of 945 patients were reported in recent studies with a weighted mean sensitivity of 89% and a specificity of 88.5%. In three studies (n=332) using two tests as a gold standard, as recommended by the working party of the European *Helicobacter pylori* study group,[42] the weighted mean of the sensitivity and specificity of the polyclonal tests were 92% and 88%, respectively.[25 26 43] In seven studies (n=613) using only the UBT as a comparator, the weighted mean of the sensitivity and specificity were 88% and 88%, respectively (fig 2).[23 29 36 40 43–45] Although more study in the post-therapy setting is necessary, the European *Helicobacter pylori* study group (Maastricht 2000) has suggested that the polyclonal stool test may be an alternative to breath testing after treatment.

PRE-TEST PROBABILITY AND THE CHOICE OF TEST

Diagnostic testing for *H pylori* has two critical aspects that must be considered when evaluating its accuracy. The first is how well it detects *H pylori* infection in patients who are infected with the organism (sensitivity) and the second is how well the test correctly identifies patients who do not have the infection (specificity). Values for sensitivity and specificity in clinical trials cannot be used to determine the utility of a given test in an individual patient. These values need to be combined with the physician's index of suspicion for the underlying condition (or pre-test probability) of the infection being present. Selection of tests for *H pylori* infection should be based on the prevalence of *H pylori* infection in the community and the pre-test probability of infection coupled with the cost and convenience of the test. Serology and near patient tests cannot be justified on economic or clinical grounds when the preva-

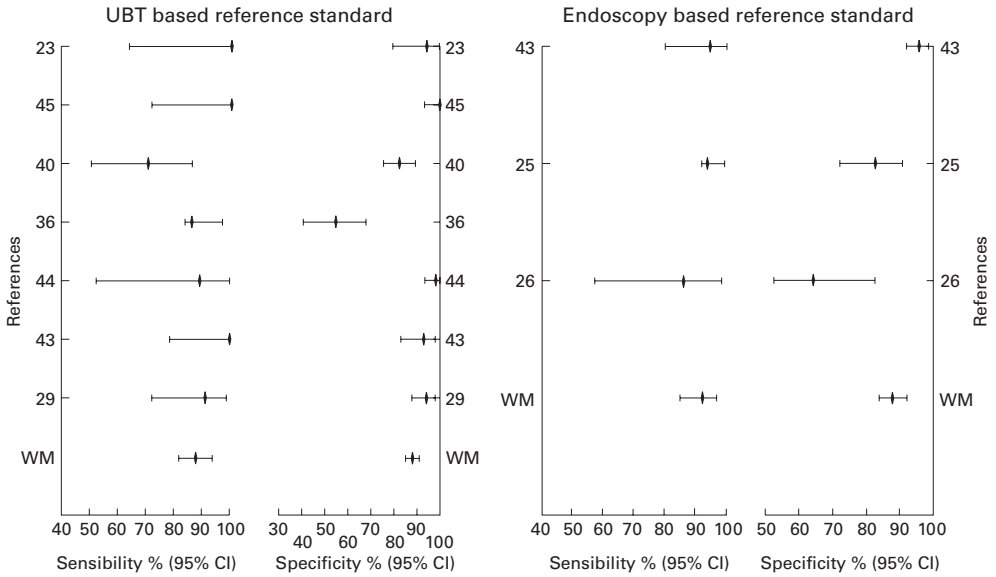

Figure 2 Sensitivity and specificity of the stool antigen test before and after therapy with different reference standards (urea breath test (UBT) as the sole reference standard; endoscopy based standard: two tests as the gold standard). WM, weighted mean.

lence of *H pylori* infection and the pre-test probability of infection are lower than 60%. In most developed countries, the prevalence of *H pylori* infection in uninvestigated dyspeptic patients is considerably less than this value and serology should not be used instead of the UBT or the stool antigen test under these circumstances.

COST EFFECTIVENESS

The cost effectiveness of diagnostic testing has been evaluated recently in an economic model.[46] In this model the cost of different testing strategies was evaluated when the pre-test probability was low, intermediate, or high. In general, the cost of serology is low in most countries while the UBT and stool antigen test are more expensive. Despite this, the improved accuracy of the stool and breath tests makes either of these tests cost effective compared with serology or near patient tests. The lower the prevalence (and the pre-test probability of infection), the less useful are serology and whole blood tests. Selection between the UBT and the stool antigen test will depend on the cost of the tests in individual countries, on convenience, and on patient preference.

Summary

The availability of affordable accurate tests (stool and breath) that detect active infection with *H pylori* has opened a new chapter in the diagnosis of *H pylori* infection. With the exception of high prevalence populations (now rare in developed countries), these tests should replace serology and near patient tests in most clinical situations particularly in the test and treat strategies now being recommended in primary care.

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