Microbiological and serological diagnostic tests for *Helicobacter pylori* : an overview

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Abstract

Different invasive and non-invasive diagnostic tests are available for the diagnosis of *H. pylori* in the individual patient. In practice, endoscopic tests are best for a primary diagnosis of *H. pylori* infection because endoscopy allows assessment of treatment indications. The new rapid urease tests may help the clinician in treatment decision-making. Culture is currently not recommended for routine evaluation, but it is becoming increasingly important in certain populations with higher prevalence of drug resistance, since it allows to test for susceptibility to antibiotics. Serological testing has been recommended for initial pre-endoscopy or pre-treatment screening in dyspeptic patients. However, several current "in-office" tests appear insufficiently accurate or would need further validation before being recommended for use in clinical management strategies at a primary care level. The urea breath tests are best suited to confirm eradication early after treatment while laboratory serology tests are of limited use since 6 months are required before a result can be obtained. The serological office tests cannot be used for post-treatment assessment of *H. pylori* status. (Acta gastroenterol. belg., **1998**, 61, **321-326**).

Introduction

The recognition that *Helicobacter pylori* plays a pivotal role in the pathogenesis of several gastroduodenal pathologies makes its diagnosis necessary in many different circumstances. Since the original description of the organism by Marshall and Warren in 1982 (1), numerous reliable invasive and non-invasive diagnostic tests have been developed. Each has advantages and disadvantages which will make it more or less appropriate depending on the situation. The invasive biopsy-based tests which include rapid urease test, histology and culture are important in the assessment of *H. pylori* status pre-treatment, as endoscopy allows assessment of treatment indications such as ulcer disease (2). The non-invasive tests obviate the need for endoscopy and comprise serology and the urea breath test, using either ^{13}C or ^{14}C. In view of the irregular distribution of *H. pylori* all the biopsy-based tests may theoretically miss to diagnose the infection. The inherent risk of sampling error can however be virtually eliminated by obtaining several biopsy samples from the gastric corpus as well as the from the antrum (3). In contrast to biopsy-based methods, noninvasive tests assess the global presence of *H. pylori* in the stomach even when the bacteria are irregularly distributed on the gastric mucosa. Non endoscopic tests, particularly serology, are cheaper and more convenient, and thus should be preferred in situations where the extra-information yielded by an endoscopy is not needed.

The aim of this paper is to review current microbiological diagnostic modalities for *H. pylori* and to emphasise their preferential indications taking into account the particular settings in which a diagnosis is to be made (pre-treatment screening or follow-up after treatment). It also gives a brief overview of the gaps of the current tests and of the expected future developments.

Invasive tests

1. *Urease tests*

The urease tests provide a simple, rapid and cost effective method for the detection of *H. pylori*. However, the practical value of these tests depends not only on their sensitivity or specificity, but also on their speed, hence making them a practical tool for the endoscopist in decision-making as to whether or not therapy should be prescribed. Among the various rapid urease tests which have been described in the literature several were found to lack sensitivity when early reading was performed (within 1 hour). Different methods have been proposed to speed-up colour change, such as pre-heating of the kit or incubation at 37°C or higher.

Yousfi *et al.* (4) found that the diagnostic yield for detecting *H. pylori* by rapid urease test was not adversely affected by the size of the biopsy forceps while Laine *et al.* (5) showed that increasing the amount of tissue in CLO tests did significantly hasten the development of positive tests.

In another study, Woo *et al.* (6) investigated the best gastric site for obtaining a positive rapid urease test. They found that the gastric angle site had the highest sensitivity for the detection of *H. pylori* as compared to the prepyloric and corpus sites. Interestingly, the median time to positivity was similar with angle and prepyloric sites but it was significantly shorter than for the corpus biopsy (60 versus 180 minutes, respectively). Malfertheiner *et al.* (7) evaluated comparatively two commercial rapid urease tests, the HUT-test and the CLO-test. Both tests displayed comparable sensitivities and specificities (93% and 100% for the HUT test ; 88% and 100% for the CLO-test) despite the fact that two biopsy samples (antrum and distal gastric body) had been obtained for the HUT-test while only one antral specimen was sampled in the CLO-test. They concluded that the sampling of one additional gastric biopsy did

not improve significantly the diagnostic efficacy in untreated patients, but that it could be required following treatment with proton pump inhibitors, since in this circumstance *H. pylori* is more likely to be found only in the body mucosa and not in the antrum. Over the last years, newer generations of commercial tests have been introduced on the market. One of such strip test, the Pyloritek® is designed to give a 1-hour reading, without necessitating special incubation temperature and allow to test one to several biopsies at a time. Several studies have shown that the Pyloritek® provided a sensitivity (90 to 99%) and a specificity (95 to 100%) at least equivalent to those achieved by the CLO-test or other agar-based tests after 12 to 24 h (8,9,10). However, the average time required to achieve a positive result was only 20-30 min with the Pyloritek® versus 120-150 with the agar-based tests, and the former test was found to be significantly more sensitive at 1 hour than all other urease tests without compromise of its specificity.

2. *Culture*

Culture undoubtedly constitutes the most specific way to establish the diagnosis of *H. pylori* infection, but its sensitivity has been found to vary greatly between centres. The differences in performances observed between laboratories probably reflect differences in expertise with culture techniques. Although it is still generally considered as a tedious procedure, culture can nowadays be performed with minimal difficulties in almost every general hospitals with a standard microbiology laboratory. Culture is however not necessary for the routine diagnosis of *H. pylori* infection because other invasive tests will detect the organisms in most patients. One of the major advantage of culture is that it allows susceptibility testing of *H. pylori* to the agents used in the treatment. This is particularly important for the clinician who must manage patients in whom antibiotic-resistant isolates are suspected (e.g. in areas with high rates of resistance to antimicrobial drugs) or those who have failed with antimicrobial drug regimens known to select for the development of resistance (3). Although the risk of sampling error is probably lower than generally supposed, it is advisable to take two biopsy samples for culture. Culture from either the antrum or the corpus has an excellent diagnostic yield in the untreated patients, but sampling of both gastric sites is recommended following treatment in order to optimize the detection of *H. pylori* (11,12).

Another factor that may influence the success rate of culture involves the transport conditions from the endoscopy room to the laboratory. Several liquid or semi-solid transport media have been recommended but is not clear whether a specific medium composition is superior for this purpose. Roosendaal *et al.* (13) did not find qualitative differences between five different media, although they did not show the quantitative data. In several of the above mentioned studies (11,13), the recovery rates of *H. pylori* from gastric biopsies were not adversely affected by a delay of culture up to 24 h when transport media were held at room temperature. For transportation or storage longer than 24 h a lower temperature might however be an important factor for survival. Han *et al.* (14) found a 100% culture recovery from 16 gastric biopsies of *H. pylori*-positive patients stored in a cysteine-2% glycerol transport medium stored at -20°C for 4 weeks versus only 57% after 12-weeks storage. Recovery figures when storage was at +4°C were 81% and 19%.

Different culture media have been proposed to grow *H. pylori.* In one recent studies in which several conventional media were compared, brain heart infusion (BHI) agar supplemented with 7% lysed horse blood yielded the highest isolation rate and the highest number of *H. pylori* colonies (15). It is probable however that the use of freshly prepared media rather than the choice of the medium basis itself accounted for the success of BHI agar in this study. To suppress the growth of endogenous or exogeous contaminating bacteria selective media are required to increase the isolation of *H. pylori* from biopsy samples (3,11,12). Several selective culture media have been developed for optimal isolation of *H. pylori.* In a large comparative study, BHI agar supplemented with 10% sheep blood, polymyxin B, vancomycin, trimethoprim and amphotericin B yielded the highest isolation rate (99%) and was found much more superior than Skirrow's selective medium (71% isolation rate) for primary isolation of *H. pylori* from gastric biopsy specimens (16). However, combination of at least one selective and one non-selective culture medium is generally advocated since no single culture medium allows a 100% recovery rate of *H. pylori* and because culture contaminations occur in about 25% of the cases (11,12).

The patient's oro-phrayngeal flora can also markedly reduce the isolation rates and the colony numbers of *H. pylori.* In one study (17), rinsing of the biopsies in sterile saline was shown to improve the recovery of *H. pylori* in nearly 40% of the culture processed. Finally, failure to detect *H. pylori* by culture may be due to insufficient duration of incubation. Incubation periods for up to 10 days are usually recommended in order to optimise the culture isolation rates, especially in a post-treatment setting (11,12).

Polymerase chain reaction

Polymerase chain reaction (PCR) is regarded as the most sensitive technique for the detection of microorganisms. The detection of *H. pylori* in gastric biopsy samples or in gastric juice aspirates by PCR has been evaluated by several investigators and was found to perform well, with sensitivity and specificity usually over 95% as compared to other invasive methods (18,19,20,21). Given the usual high sensitivity of PCR, this test can be particularly useful for the post-treatment diagnosis of *H. pylori*, when the bacterial load may

be very low. However, in several comparative studies, the PCR test failed to detect significantly more treatment failures than culture or a combination of other conventional methods (3,22). Owing to its high sensitivity PCR unfortunately carries a risk of false positive results which may result either from residual *H. pylori* DNA on the fiberoptic endoscopes following inadequate cleaning and disinfection or from cross-contamination during processing of specimens in the laboratory (23). At present, PCR is still technically demanding and not generally available as a routine diagnostic tool. Recently however, methodological protocols have been simplified and improved by using hybridization and colorimetry to detect the amplification products (24). It can be anticipated that PCR will be used more readily in routine clinical settings once being fully automated and when commercial kits become available. It is also likely that in the near future, PCR or closely related molecular amplification techniques will be used in rapid test formats to detect antimicrobial resistance (i.e. resistance to macrolides) to *H. pylori* and possibly also in faeces to control eradication.

Non-invasive tests

Serology

H. pylori infection provokes both local and systemic antibody responses. The systemic response typically comprises a transient rise in IgM, followed by a rise in specific IgA and IgG maintained throughout infection. A large number of kits which detect these antibodies by enzyme-linked immunosorbent assay (ELISA) or latex agglutination have been developed and most clinical laboratories are experienced in performing serological tests. Such tests most commonly use serum, although detection of IgG in urine has also proved accurate (25). Several commercial or in-house tests have been adapted for use on saliva, but the detection of salivary IgA or IgG antibodies has proved overall less sensitive than serum-based tests (26,27).

The performance of different laboratory serological tests has been found to vary appreciably. In a large meta-analysis, several commercial ELISA kits appeared to perform well with sensitivity and specificity values averaging 90-95% and 80-90%, respectively (Table I). The lower specificity of serological tests observed in certain studies may have largely been explained by the inclusion of patients previously treated for *H. pylori* infection or having received antibiotics for the treatment of various intercurrent infections (21). A combination of reliable reference methods needs to be applied for evaluation of tests and difference in gold standard used may also have accounted for some of the differences that have been observed between studies. Furthermore, differences in test accuracy can be explained by the use of various antigen preparations or by differences in infecting strains that result in different immune responses. This has led to the general recommendation that any serological test for *H. pylori* should be validated and standardised locally before use. In many instances, this will imply the adjustment of the cut-off values recommended by the manufacturer. Numerous studies have evaluated the performance of a wide range of commercial tests (28,29,30,31). In most of these reports, the different tests performed equally well. Feldman *et al.* (32) recently reported a multi-laboratory comparison of eight commercially available *H. pylori* serology kits. As shown in Table II, some of the kits produced excellent results.

A number of rapid serological office tests have recently been developed for the serodiagnosis of *H. pylori* infection (33,34,35,36,37,38,39,40). They are based on a solid-phase ELISA (33,34) or on latex

Table I. — **Comparative performance values of various *H. pylori* ELISA commercial kits**

Test	Brand name	N° Patients	N° Series	Sensitivity (%) (average)	Specificity (%) (average)
Cobas Core®	Roche	1538	6	93-99 (95)	77-97 (88)
Helico-G®	Porton-Cambridge	1013	12	71-96 (82)	45-90 (70)
Malakit®	Biolab	308	3	87-96 (90)	79-96 (86)
GAP-IgG®	Bio-Rad	1077	9	77-100 (90)	26-91 (63)
Pylori Stat®	Bio-Whittaker	963	8	90-99 (96)	70-98 (90)
HM-CAP	Enteric Products	575	2	95-98 (97)	92-98 (93)
Premier *H. pylori*	Osi	209	3	87-93 (89)	81-96 (88)
Pyloriset® EIA G	Orion (old)	381	3	76-96 (91)	84-96 (86)
Pyloriset® EIA G*	Orion (new)	256	2	93-100 (97)	79-85 (83)

* The new version was introduced in 1995.

Table II. — **Sensitivity and specificity of eight commercial kits tested in 17 laboratories on identical serum samples from 59 patients (Optical density values in the grey zone were considered negative)**

Test	N° of laboratories	Mean sensitivity (SD)	Mean specificity (SD)
Amrad	17	89.4 (7.7)	93.9 (9.7)
Biolab	15	79.9 (9.1)	98.6 (2.6)
Bio-Rad	17	94.9 (6.8)	91.3 (13.2)
Orion	17	95.8 (3.9)	95.5 (4.8)
Porton	17	92.3 (6.1)	87.1 (12.6)
Radim	13	81.6 (7.0)	90.7 (17.6)
Roche	17	99.3 (1.3)	86.5 (5.2)
Whittaker	16	92.9 (4.9)	89.4 (11.1)

SD : standard deviation
Adapted from Feldman *et al.* (31).

agglutination (35). One major advantage of these tests over laboratory tests, is that they can be applied very easily in the office on whole blood obtained by finger-prick. Results are available on site within 5-10 minutes, usually by a simple colour change, and there is no need for any specific equipment. In a large meta-analysis of studies published in the literature, the rapid office tests overall appeared to be less accurate than the laboratory tests, with sensitivity and specificity values averaging 80 to 85% and 75 to 80%, respectively (Table III).

In some studies comparing the rapid tests with only one standard the sensitivity results were usually substantially better (33). In other reports (39), the "office" tests showed poor specificity in certain population age groups (patients over 45 years of age) as well as in some ethnic groups (e.g. South Asians) while they performed better in some other population subgroups (e.g. : patients less than 45 yrs and European natives). Moreover, problems of poor readability of results and inter-observer variations in interpretation of results were reported in a notable proportion of cases (up to 10% of all results) in some studies (38,39), which may limit the interest of certain kits.

Above all, it is important to stress that most reported evaluations of the rapid office-based serological tests have been undertaken in a secondary care setting and in patients referred for endoscopy. There are at present few reports of the evaluation of these tests in the environments for which they were designed and it will be particularly important to evaluate results obtained by general practitioners who will be the clinicians most likely to use such screening devices. In addition, it will also be very important to evaluate the short- and long-term impact that the office serological tests may have on the clinical management of patients in the primary care setting.

Immunoblot techniques also show promise. Heterogeneity has been observed in the immune response, but the predictive value of a given band or pattern for a specific pathology is still uncertain and its usefulness in patient follow-up has yet to be determined (41). However, some studies have shown that the use of recombinant antigen for cagA may be valuable for predicting the presence of peptic ulcer disease in a patient (42). As with the new serological tests, further work is needed to establish the utility of serological testing for selective pathogenic strains (e.g. cagA serology), but it may be useful in strategies aimed at narrowing the group of patients for whom *H. pylori* treatment should be considered.

Urea breath tests

The ^{13}C-urea breath test is highly sensitive and specific for the detection of *H. pylori* infection. In contrast to serology which cannot always distinguish between past and present infection, the urea breath test is a measure of current *H. pylori* infection. It is particularly well suited as a follow-up test in the early posttreatment period (4 to 6 weeks after end of therapy) since it has a good predictive value for the eradication of the bacterium. It is a non-invasive, global test which is easy to perform and is independent of transport conditions or the experience of the tester. Despite these advantages, however, this test is not yet widely available and it is still not approved in many European countries.

Table III. — **Performance values of various commercial *H. pylori* rapid tests ("Office-based tests")**

Test	Brand name	N° patients	N° series	Sensitivity (%) (average)	Specificity (%) (average)
Pyloriset Dry®	Orion Diagnostica	348	3	80-97 (89)	77-85 (81)
Pyloriset latex®	Orion Diagnostica	932	8	60-92 (75)	50-76 (63)
Latex	Oxoïd	202	1	86	75
FlexSure®	SmithKline Diagnostics	1169	5	74-95 (86)	69-89 (81)
Helisal®	Cortecs	788	5	82-92 (84)	56-91 (73)
Immunocard®	Meridian Diagnostics	78	1	92	98
Quick Vue®	Quidel	727	3	82-99 (91)	52-92 (79)
CLOser	Medical Instruments	86	1	95	72

Key points for clinical practice

With the continuous improvement of diagnostic techniques, the availability of new diagnostic tests and the high efficacy of modern of treatment regimens it is to be expected that the demand of *H. pylori* testing and treatment initiated at a primary care level will also increase. Several large-scale comparative studies have shown that invasive and non-invasive tests performed equally well, with a sensitivity and specificity, in the range of 90% (21,43). In practice, the choice of a particular test should be influenced by the local availability and expertise as well as by clinical circumstances.

The high urease activity of *H. pylori* can be used as a screening marker of infection in patients who present to endoscopy with upper gastrointestinal symptoms. The newer rapid urease strip tests which have been considerably improved in comparison to the initial urease tests may certainly help the endoscopist in decision-making as to whether or not therapy should be prescribed. Due to their low cost, these tests are the endoscopic tests of choice for initial evaluation. However, they should be used in addition to other invasive or non-invasive tests (e.g. serology) as some infected patients may still be missed on an initial screening.

Culture cannot be recommended for routine evaluation of *H. pylori* because of the restricted availability of good laboratory facilities and the many potential errors involved leading to false-negative results. However, it should be considered when treating the infection with a regimen that contains drugs to which *H. pylori* is possibly resistant. Likewise, culture should be favoured after documented treatment failure or in patients from a geographic area or of an ethnic origin with higher likelihood of antimicrobial drug resistance. PCR is presently not indicated for use in routine clinical setting. However, the rapid technologic improvements and the availability of commercial kits may render this technique more readily available in a near future. The urea breath tests are very accurate for assessing the *H. pylori* status posttreatment. However, they are still not yet widely available. Serology has only limited indication for the follow-up after treatment. Antibody titres to *H. pylori* vary markedly between infected individuals and following successful treatment take 1, 2 or even more years to return to the uninfected range, the exact time being dependent on the host response and on the test used. Rapid office tests are not quantitative and are not suited to be used for treatment follow-up. When using quantitative ELISA, a 50% drop in IgG titres at 6 months can accurately predict treatment success (43). However, matched pre- and 6 month post-treatment serum samples are needed, and preferably should be run together to avoid interbatch variation. This seems difficult to apply routinely because collecting and storing pre-treatment specimens may be problematic in clinical practice and also because 6 months is a too long time to wait for results. On the other hand, serological *H. pylori* screening appears particularly attractive as a pre-endoscopy or as a pre-treatment screening in young dyspeptic patients (aged less than 45 years) without alarm symptoms. Such recommendations are supported by a recent European consensus report on current concepts on the management of *H. pylori* infection (44). However, the feasibility of algorithms based on serological *H. pylori* status and age will greatly depend on the incidence of specific gastroduodenal pathologies in different populations as well as on the performances of the screening tests. Screening tests with optimal sensitivity would absolutely be required if used to select suitable groups of patients for endoscopy without missing significant disease. Conversely, tests yielding a high specificity would be necessary in order to avoid giving unnecessary eradication therapy to non infected patients. Some of the new office serological tests currently available may not appear sufficiently accurate in order to fulfil these requirements. Further research is clearly needed in order to delineate the place that rapid *H. pylori* serological tests may have in a primary care environment. The cost-effectiveness and clinical consequences of different serology-based strategies should also be established and may be found to differ between countries with different health-care systems and different economic constraints.

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