International Journal of Advances in Medicine
*Daivasikamai P. Int J Adv Med. 2014 Nov;1(3):217-221*
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: 10.5455/2349-3933.ijam20141105

**Research Article**

# Advantages of serological testing for *Helicobacter pylori* infection as a screening test

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**Received:** 20 August 2014
**Accepted:** 06 September 2014

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## ABSTRACT

**Background:** As the practicing physicians start treating all dyspeptic symptoms as peptic ulcer disease and some patients are treated for *Helicobacter pylori* infection without confirmation of infection. Hence, a simple and convenient test to identify the *H. pylori* infection is essential in the management of all dyspepsia. Serological test is a noninvasive test and result can be obtained within short time and treatment can be started early.
**Methods:** A total of 86 outpatients with dyspeptic symptoms underwent both serological test and endoscopy and biopsy for *H. pylori* infection. Serological testing for *H. pylori* is based on the immunoglobulin G antibody to *H. pylori* infection.
**Results:** Of 86 patients, 79 patients' biopsy were positive for *H. pylori* and 77 patients were positive by serology. Of them, 75 were both positive for *H. pylori* by biopsy and also by serology. Those 7, who are negative for histology is also negative for serology. Comparing endoscopic biopsy with serology, the specificity, sensitivity are 97.5, 98 for serology.
**Conclusions:** Serological tests assess the global presence of *H. pylori* in the stomach even when the bacteria are irregularly distributed on the gastric mucosa. Serology testing is cheaper and more convenient, and thus should be preferred in situations where the additional information yielded by an endoscopy is not needed.

**Keywords:** *Helicobacter pylori*, Serological testing, Stool antigen test, Endoscopy biopsy, Urease breath test, Non-ulcer dyspepsia, Peptic ulcer

## INTRODUCTION

Medical practitioners are coming across many patients with vague abdominal pain and were treated as peptic ulcer disease. As the *Helicobacter pylori* infection causes peptic ulcer disease with its complications and can produce chronic gastritis which leads on to carcinoma of stomach. Hence, the *H. pylori* infection must be identified early and appropriate treatment must be given. As endoscopy biopsy requires endoscopist, pathologist and there is time delay in starting the treatment. The endoscopy not only costly, but also an invasive procedure. The aim of the study was to compare the endoscopic gastric mucosal biopsy and the serology test for *H. pylori* for confirmation of *H. pylori* infection and the suitable test for rural Indian population. The current microbiological diagnostic modalities for *H. pylori* are reviewed and to emphasize their preferential indication taking into account, the particular settings in which a diagnosis is to be made. It also gives a brief overview of the deficiencies of current tests and of expected future developments. Serological tests are easy to perform, cost effective, do not require any preparation before testing and ideal for screening purpose.

## METHODS

Patients who are having dyspeptic symptoms, flatulent dyspepsia, indigestion, pain in empty stomach of more than 4 weeks duration were selected for this study. A total of 86 outpatients with above symptoms was taken up for

the study and endoscopic biopsy using H and E stain and serology for *H. pylori* was done for them. Serology is based on the presence of immunoglobulin G (IgG) antibody to the *H. pylori* infection. Positive testing denotes present or past infection to *H. pylori*. There is no need to stop the treatment before testing and previous antibiotic treatment do not change the test.

## RESULTS

Of 86 patients, 79 patients' biopsy was positive for *H. pylori* and 77 patients were positive by serology. Of them, 75 were both positive for *H. pylori* by biopsy and also by serology. Those 7, who are negative for histology is also negative for serology. Comparing endoscopic biopsy with serology, the specificity, sensitivity are 97.5, 98 for serology (Table 1).

## DISCUSSION

*H. pylori* is the bacterium responsible for most of the stomach and duodenal ulcers and many cases of superficial gastritis. Usually, *H. pylori* testing is done for

1. To diagnose *H. pylori* infection
2. If there is a gastric or duodenal ulcer
3. If treated gastric or duodenal ulcer in the past and were never tested for *H. pylori*
4. After treatment for *H. pylori* infection, to make sure there are no more *H. pylori* infection
5. Testing may also be done if the patient needs to take long-term ibuprofen or other nonsteroidal anti-inflammatory drugs medicines
6. The test may also be recommended for dyspepsia
7. Testing for *H. pylori* without endoscopy is most often done only when the indigestion is new, the person is younger than 55, and there are no other symptoms.

There are several methods to test for *H. pylori* infection.

### *Breath test (carbon isotope-urea breath test [UBT])*

Up to 2 weeks before, the test, antibiotics, bismuth medicines, and proton pump inhibitors must be stopped.

During the test, radioactive urea is swallowed. If *H. pylori* are present, the bacteria convert the urea into carbon dioxide, which is detected and recorded in the exhaled breath after 10 min. This test can identify almost all people who have *H. pylori*. It can also be used to check that the *H. pylori* infection has been fully treated.

**Table 1: Incidence of *H. pylori* positive serology and in both serology and biopsy.**

| | Serology (*n*=77) (%) | Both +ve (*n*=75) (%) |
|---|---|---|
| Sensitivity | 97.4 | 95 |
| Specificity | 98 | 94 |

*H. pylori: Helicobacter pylori*

### *Blood tests*

Blood tests are used to measure antibodies to *H. pylori*. Blood tests for *H. pylori* can only tell if the body has *H. pylori* antibodies. It cannot tell whether it is a current infection or past infection. This is because the test can be positive for years even if the infection is cured. As a result, blood tests cannot be used to see if the infection has been cured after treatment.

### *Stool test*

A stool test can detect traces of *H. pylori* in the feces. This test can be used to diagnose the infection and confirms that it has been cured after treatment.

### *Biopsy*

A tissue sample is taken from the stomach mucosa through endoscope is the most accurate way to diagnose *H. pylori* infection. Biopsy is taken during upper gastrointestinal (GI) endoscopy and stained with H and E, giemsa stain or silver stain and culture and sensitivity is done.

### *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 and 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. Yousfi et al.[1] found that the diagnostic yield for detecting *H. pylori* by the rapid urease test was not adversely affected by the size of the biopsy forceps, while Laine et al.[2] showed that increasing the amount of tissue in campylobacter-like organisms (CLO)-tests did significantly hasten the development of positive tests. In another study, Woo et al.[3] investigated the best gastric site for obtaining a positive rapid urease test. They found that biopsies from the gastric angulus had the highest sensitivity for the detection of *H. pylori* as compared to the pre-pyloric and corpus sites.

Culture can nowadays be performed with minimal difficulties in almost every general hospital 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 advantages of culture is that it allows sensitivity 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.[4]

### *UBTs*

The [13C]-UBT is highly sensitive and specific for the detection of *H. pylori* infection. UBT can diagnose current

*H. pylori* infection. It is particularly well-suited as a follow-up test in the early post-treatment period (4-6 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.

Serological testing for *H. pylori* infection is one of the diagnostic methods of choice. *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. Various commercial kits that use different antigens have been developed. Talley et al. evaluated the sensitivity, specificity, and predictive value of three IgG enzyme-linked immunosorbent assay (ELISA) kits, serum samples, and gastric biopsy findings from 76 patients. They found by using IgG enzyme linked study had overall sensitivities of 96, 96, and 88%, respectively, and specificities of 94, 86, and 96%, respectively, compared with gastric biopsy findings. They concluded that serology based on any of these commercial tests represents a reliable and valid method for the diagnosis of *H. pylori* whether or not highly purified antigens are used.[5] Such tests most commonly use serum, although detection of IgG in urine has also proved accurate. 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.[6,7] Positive results denotes the present or past infection with *H. pylori*.

Rapid serological office tests are based on a solid phase ELISA or on latex agglutination. 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 fingerpick. Results are available on site within 5-10 min, usually by a simple color 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 80-85% and 75-80%, respectively.[8-11]

The number of endoscopies were avoided using serology test intended primarily for use in primary care. The existing evidence suggests that screening for *H. pylori* in primary care and then referring positive cases for endoscopy are not a cost effective strategy. The Helisal test may be useful for preendoscopy screening of younger patients. The Helisal test may not have the power to satisfactorily exclude infection when the prevalence is high, but its performance as a screen before endoscopy looks promising; Mowat et al. compared the Helisal rapid blood (HRB) test and 14C-UBT for determining *H. pylori* status and predicting ulcer disease and found that the HRB test is inferior to the UBT for determining *H. pylori* status.[12]

Using serological test as a screening procedure can reduce endoscopy workload and cost. Used in conjunction with blood levels of gastrin and pepsinogen, these tests can suggest the presence of *H. pylori* associated gastritis and can be used to screen for serious gastro-duodenal pathology. Currently, eradication of *H. pylori* is only recommended in cases of PUD, and endoscopy is required to differentiate from non-ulcer dyspepsia (NUD).[13] Neither serological tests nor Urease Breath Test give any quantitative information that would help to differentiate between these two conditions. 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.[14,15] 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,[16] and authors do not recommend it as a routine practice.

A cost analysis of adopting a screening protocol using serological tests compared with empirical treatment with H2 receptor antagonists or an eradication protocol showed that although the eradication regimen was cheaper than suppressive treatment with H2 receptor antagonists, this was offset by the cost of screening to such an extent that savings were only achieved after eight years.[17] In children, the most cost-effective approach was empirical anti-secretory treatment.[18]

Another cost-benefit analysis showed that the efficacy of serological testing as a screening procedure depended on a response rate of more than 10% in NUD to eradication of *H. pylori*, a saving of more than $4000 for ulcer prevention.[19] Epidemiological evidence suggests that 31-87% of gastric cancers may be attributable to colonization by *H. pylori*, and it is feasible that eradicating *H. pylori* from an asymptomatic population may reduce the occurrence of gastric cancer.[20] However, a cost-benefit analysis showed that if 30% of gastric cancers were preventable by a screening eradication protocol, the cost effectiveness was $25,000/year of life saved, and this value was approximately maintained even if the success was only 5% if undertaken in high risk groups.[21]

As the endoscopy 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 the management of *H. pylori* infection 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.[22]

PCR is regarded as the most sensitive technique for the detection of micro-organisms. 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.[23,24]

Thijs et al. did upper GI endoscopy antral biopsy and specimens were taken for culture, polymerase chain reaction, histological examination (hematoxylin eosin and

giemsa stains), and rapid urease test for 105 outpatients. Serology (ELISA) and a 13C-UBT were also performed. They concluded that antral biopsy-based tests, as well as the 13C-UBT, are accurate for the diagnosis of *H. pylori* infection. The lower specificity of serological tests may be largely explained by previous treatment of *H. pylori*.[25]

Warthin-Starry staining had the best sensitivity and specificity, although CLO test, UBT, and IgG levels were not statistically different in determining the correct diagnosis. IgA was a better predictor in white patients. The noninvasive UBT and IgG serology test are as accurate in predicting *H. pylori* status in untreated patients as the invasive tests of CLO and Warthin-Starry.[26]

A simple, rapid serological test (FlexSure HP, SmithKline Diagnostics) for the detection of serum IgG antibodies against *H. pylori* with another rapid test (QuickVue, Quidel) and two enzyme immunoassays (HM-CAP, Enteric Products, and PyloriStat, BioWhittaker). The presence or absence of active *H. pylori* infections was determined using the [13C]-UBT. FlexSure HP had calculated sensitivity, specificity, and accuracy of 94.4, 87.6, and 91.1%, respectively, relative to the UBT. FlexSure HP is an excellent option for in-office tests for the physician who desires immediate results or for small laboratories that do not have the volume of *H. pylori* testing to justify ELISA test formats.[27]

### *UBT using capsule form*

Since the UBT indirectly detects gastric *H. pylori* infection by measuring urease activity, the possibility of false-positive results due to other urease-producing bacteria cannot be excluded. Previous studies have shown that increased $^{14}CO_2$ activity in early breath samples could be attributed to urea hydrolysis in the oropharynx. To overcome this problem, modified breath test done with 111kBq $^{14}$C-urea is supplied in a gelatin capsule, which prevents release of $^{14}$C before reaching the stomach.[28]

### *Monoclonal stool antigen test*

Gisbert et al. did a systematic review and a meta-analysis of accuracy of monoclonal stool antigen test (SAT) for the diagnosis of *H. pylori* infection. They concluded that monoclonal SAT is an accurate non-invasive method both for the initial diagnosis of *H. pylori* infection and for the confirmation of its eradication after treatment.[29] A commercial kit using an ELISA examined HpSA in the stool was done by Chang et al. and they found overall accuracy rate was 96.3%.The HpSA test is a new, simple, non-invasive method for accurate diagnosis of *H. pylori* infection.[30]

## CONCLUSION

Serological testing can be used as a screening test initial pre-endoscopy or pre-treatment screening in dyspeptic patients. In practice, endoscopic tests are best test to diagnosis *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 testing for susceptibility to antibiotics. The serological office tests cannot be used for post-treatment assessment of *H. pylori* status. The serological tests obviate the need for endoscopy. In view of the patchy distribution of *H. pylori*, all biopsy-based tests may theoretically fail to diagnose the infection. The H&E stain interpreted by the rotating pathology staff was the least sensitive method and one of the least specific tests. But serological 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 additional information yielded by an endoscopy is not needed.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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DOI: 10.5455/2349-3933.ijam20141105
**Cite this article as:** Daivasikamai P. Advantages of serological testing for *Helicobacter pylori* infection as a screening test. Int J Adv Med 2014;1:217-21.