

2015 Advances in *Helicobacter pylori***Diagnosis of *Helicobacter pylori* infection: Current options and developments**

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Author contributions: Wang YK wrote this manuscript; Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SSW, Wu JY and Kuo CH designed research; Huang YK and Wu DC polished the paper; Huang YK and Wu DC equally contributed to this manuscript.

Supported by (in part) Grants from the Kaohsiung Medical University "Aim for the Top Universities Grant", grant No. KMU-TP104G00, No. KMU-TP104G03 and No. KMU-TP104E25; and Ten Chan General Hospital, Chung-Li and KMU Joint Research Project, No. ST102004; and Kaohsiung Medical University Hospital, No. KMUH100-0R01.

Conflict-of-interest statement: The authors have no conflict of interest to disclose.

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Received: April 29, 2015
Peer-review started: May 12, 2015
First decision: July 13, 2015
Revised: August 6, 2015
Accepted: September 28, 2015
Article in press: September 30, 2015
Published online: October 28, 2015

Abstract

Accurate diagnosis of *Helicobacter pylori* (*H. pylori*) infection is a crucial part in the effective management of many gastroduodenal diseases. Several invasive and non-invasive diagnostic tests are available for the detection of *H. pylori* and each test has its usefulness and limitations in different clinical situations. Although none can be considered as a single gold standard in clinical practice, several techniques have been developed to give the more reliable results. Invasive tests are performed *via* endoscopic biopsy specimens and these tests include histology, culture, rapid urease test as well as molecular methods. Developments of endoscopic equipment also contribute to the real-time diagnosis of *H. pylori* during endoscopy. Urea breathing

test and stool antigen test are most widely used non-invasive tests, whereas serology is useful in screening and epidemiological studies. Molecular methods have been used in variable specimens other than gastric mucosa. More than detection of *H. pylori* infection, several tests are introduced into the evaluation of virulence factors and antibiotic sensitivity of *H. pylori*, as well as screening precancerous lesions and gastric cancer. The aim of this article is to review the current options and novel developments of diagnostic tests and their applications in different clinical conditions or for specific purposes.

Key words: *Helicobacter pylori*; Diagnosis; Invasive; Noninvasive; Oral specimen; Bleeding; Gastrectomy; Eradication

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Core tip: Nowadays, several tests are available for the diagnosis of *Helicobacter pylori* (*H. pylori*) infection. In this review, we focus on the usefulness and limitations of current diagnostic methods as well as the recent developments of these tests that contribute to improve the diagnostic accuracy. Furthermore, we also emphasize the detection of *H. pylori* in oral specimens and in patients with different clinical circumstances, including bleeding, post-gastrectomy and post-eradication therapy.

Wang YK, Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SSW, Wu JY, Kuo CH, Huang YK, Wu DC. Diagnosis of *Helicobacter pylori* infection: Current options and developments. *World J Gastroenterol* 2015; 21(40): 11221-11235 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i40/11221.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i40.11221>

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerobic human pathogen and *H. pylori* infection is strongly related with many gastroduodenal diseases including chronic active gastritis, peptic ulcer diseases, atrophic gastritis, mucosa associated lymphoid tissue (MALT) lymphoma and noncardia gastric cancer. *H. pylori* infection affects more than half of the adult population worldwide, but the prevalence of *H. pylori* infection varies widely by geographic area, age, race, and socioeconomic status. Usually, the prevalence of *H. pylori* increases with age in most countries, however a decline in prevalence of *H. pylori* infection has been observed in recent decades in time trend analysis of several large populations^[1]. More than 80% of peptic ulcer diseases are caused by *H. pylori* infection and the estimated lifetime risk for peptic ulcer disease in *H. pylori*-infected patients is approximately 15%^[2]. Gastric cancer is the third leading cause of cancer-

related death worldwide and *H. pylori* infection is responsible for 74.7% of all noncardia gastric cancer cases^[3,4]. Gastric cancer and peptic ulcer together cause more than a million deaths per year in the world and *H. pylori* infection always is an important health issue^[5]. Various diagnostic methods are developed to detect *H. pylori* infection and diagnostic tests with both high sensitivity and specificity, exceeding 90%, are necessary for accurate diagnosis of *H. pylori* infection in clinical practice. Although many diagnostic tests are available now, each method has its own advantages, disadvantages, and limitations. The choice of one method or another could be depended on availability and accessibility of diagnostic tests, level of laboratories, clinical conditions of patients, and likelihood ratio of positive and negative tests on different clinical circumstances. Diagnostic tests are usually divided into invasive (endoscopic-based) and noninvasive methods. Invasive diagnostic tests include endoscopic image, histology, rapid urease test, culture, and molecular methods. Non-invasive diagnostic tests included urea breath test, stool antigen test, serological, and molecular examinations. In the present article, we briefly review the current options and developments of diagnosis tests and associated applications in clinical practices, as well as choice of diagnostic tests on different clinical conditions (Table 1).

INVASIVE TESTS

Endoscopy

Conventional endoscopic exam is usually performed to diagnose *H. pylori*-associated diseases, such as peptic ulcer diseases, atrophic gastritis, MALT lymphoma and gastric cancer. Endoscopy is also an instrument routinely used to obtain specimens, usually gastric mucosa from biopsy, for further studies on other invasive tests, including rapid urease test, histology, culture, and molecular methods. Antrum is a preferential biopsy site for detecting *H. pylori* infection in most circumstances, but corpus biopsy from greater curve is suggested for patients with antral atrophy or intestinal metaplasia to avoid false negative results^[6,7]. The uneven distribution of *H. pylori* in the stomach in different clinical setting inevitably leads to sampling errors in biopsy-based examinations and several attempts have been made for real-time diagnosis of *H. pylori* infection during endoscopic examination.

Most gastric mucosal features, such as redness, mucosal swelling or nodular change, from conventional endoscopy are not specific enough for diagnosis of *H. pylori* infection and provide limited value in the accurate diagnosis^[8]. Although careful close-up observation of the gastric mucosa pattern with standard endoscopy may increase the diagnostic accuracy, but it may be time-consuming and not provide better results than other invasive tests^[9]. In addition to conventional endoscopy, chromoendoscopy with phenol red has also been evaluated for diagnosis of *H. pylori*

Table 1 Diagnostic options of *Helicobacter pylori* infection in different clinical circumstances and special applications of diagnostic tests

	Gastroduodenal bleeding	Post gastrectomy	Post eradication therapy	Special applications
Rapid urease test		√		
Histology		√		
Culture				√Antibiotic sensitivity
Polymerase chain reaction	√		√	√Antibiotic sensitivity √Virulence factors √Environmental/oral sample
Urea breath test	√		√	
Stool antigen test			√	
Serology ¹	√	√	√	√Virulence factors

¹Although serology is not affected by local change in stomach, result of serology should be interpreted with caution before further management.

infection under the basis of specific urease activity of *H. pylori*. However, this method is not a reliable test because of its low sensitivity (73%-81%) and low specificity (76%-81%)^[10,11]. Magnifying endoscopy provides direct observation of surface microstructure in the gastric mucosa and high resolution endoscopic patterns of gastric mucosa is highly correlated with histopathological changes, including *H. pylori* infection. The sensitivity and specificity for predicting *H. pylori*-positive corporal gastritis by using magnifying endoscopy with indigo carmine staining were 97.6% and 100% respectively. However the sensitivity and specificity decreased to 88.4% and 75.0% respectively in *H. pylori*-positive antral gastritis^[12]. Confocal laser endomicroscopy (CLE) is the other magnifying endoscopic technique which provide subsurface analysis and *in vivo* histology examination of gastric mucosa during endoscopy. Three features including white spots, neutrophils and microabscesses, based on CLE findings, were used for *H. pylori* diagnosis and the accuracy, sensitivity and specificity were 92.8%, 89.2% and 95.7% respectively^[13]. Magnifying narrow band imaging and I-scan were also used to detect *H. pylori* infection, but variable results were presented^[14-16]. Different classifications of image features from magnifying endoscopy provide different diagnostic accuracy and the accuracy of endoscopic test is also operator dependent, which means its use require training process from experienced supervisor and availability of equipment from local endoscopy unit^[17-20]. Moreover, careful examination by using magnifying with or without image-enhanced technique is also time-consuming and may make more discomfort to patient than other biopsy-based tests. Those factors usually limit the clinical use of magnifying endoscopy to detect *H. pylori* infection in routine practice.

Histology

Histology is usually considered to be the gold standard in the direct detection of *H. pylori* infection and is also the first method used for the detection of *H. pylori*. However, several factors influence the diagnostic accuracy of histology, such as site, size and number

of biopsies, staining methods, proton pump inhibitor (PPI), antibiotics and experience of the examining pathologist. PPI use may lead to controversial results of histological exam and stopping PPI 2 wk before performing histological test is recommended^[21]. More biopsy samples collected from appropriate site for analysis can decrease sampling error and false negative results in histological test as well as other biopsy-based tests. Biopsies from both antrum and corpus are usually recommended in clinical practice and the acquisition of at least two biopsy specimens from antrum and corpus is a most sensible strategy that guarantees the maximum diagnostic yield^[22,23]. As mentioned above, corpus biopsy is important for the diagnosis of *H. pylori* in a background of atrophic gastritis^[7].

Staining is the critical part of histological exam and several stains like routine HE staining, Giemsa, Warthin-Starry, Hp silver stain, toluidine blue, acridine orange, McMullen, Genta, Dieterle, and immunohistochemical stain have been used to detect *H. pylori*. Although immunohistochemical stain is the most sensitive and specific stain, HE stain is usually sufficient for diagnosis of *H. pylori* infection in routine clinical practice. Ancillary stain is usually recommended for biopsy specimens which revealed moderate or severe chronic gastritis, but no *H. pylori* identified in HE staining. Furthermore, immunohistochemical stain should be the first choice if ancillary stain is decided to use for detecting *H. pylori*^[24,25]. If immunohistochemical stains are not available, Giemsa stain is the preferred method in clinical practice because it is simple, highly sensitive and less expensive^[26].

Peptide nucleic acid fluorescent *in situ* hybridization (PNA-FISH), which can be used on histological preparations, is a highly sensitive (97% sensitivity) and specific (100% specificity) technique for the diagnosis of *H. pylori* infection. PNA-FISH can identify coccoid form of *H. pylori* which is usually undetectable by routine histological exam because this method could avoid individual biasness from morphological identification. Moreover, PNA-FISH is a rapid, accurate and cost-effective method for detection of *H. pylori* clarithromycin resistance in gastric biopsy specimens^[27-29]. FISH also has the potential role in the

detection of *H. pylori* in environmental samples and further studies on the transmission and environmental reservoirs of *H. pylori* could be conducted by using FISH^[30,31]. Despite the advantages of detection of *H. pylori* and clarithromycin resistance at the same time, the disadvantages of PNA-FISH, such as laborious prepare, requiring fluorescent microscope and particular expertise to read the slides, may limit the broadly use of this method.

RAPID UREASE TESTS

For routine clinical practice, rapid urease test (RUT) is the most useful invasive test for the diagnosis of *H. pylori* infection because it is inexpensive, rapid, easy to perform, highly specific and widely available. Based on the activity of the *H. pylori* urease enzyme, the presence of *H. pylori* in biopsy specimen convert the urea test reagent to ammonia, leading to an increase in the pH and a color change on the pH monitor. Several commercial urease tests including gel-based tests (CLOtest, HpFast), paper-based tests (PyloriTek, ProntoDry) and liquid-based tests (UFT300, EndoschHp) are available now, and different commercial RUTs have different reaction time to provide results. CLOtest usually takes 24 h to obtain accurate result, whereas PyloriTek takes 1 h and UFT 300 takes 5 min to provide more rapid results. Reading the urease tests earlier than recommended time may lead to false negative results^[32]. In addition to the designs of commercial kits, the density of bacteria present in the biopsy specimen also affects the reaction time and diagnostic accuracy of RUT, while the minimum of 10000 organisms are usually required for a positive RUT result. Other factors influencing the diagnostic accuracy of the urease tests include H₂-receptor antagonists, PPI, bismuth compounds, antibiotics, achlorhydria and presence of blood, all of which increase the possibility of false negative results. Furthermore, formalin contamination of biopsy specimens also decrease the sensitivity of RUTs^[21,33-35].

In general, the commercial rapid urease tests have specificity above 95%-100% and sensitivity above 85%-95%. Increasing the number of gastric antral biopsies could increase the sensitivity of RUTs and dual biopsy specimens from gastric corpus and antrum are preferred than only antrum biopsy specimens as additional corpus biopsy increase the diagnostic accuracy and avoid sampling bias due to uneven distribution of *H. pylori* in stomach. Moreover, combining antrum and corpus specimens prior to RUT, rather than separate specimens, also increased the sensitivity of RUT and accelerate the reaction time^[32,36-39]. Avoid medications that affect the urease activity and the density of bacteria is recommended before RUT to decreased false negative results, such as 2 wk for PPI and 4 wk for antibiotics. Bleeding significantly decreases the sensitivity and specificity of RUTs and make RUT become a more unreliable test

than other tests in this clinical condition^[40]. In a study evaluated the influence of different biopsy number and site on results of RUT in patients with peptic ulcer bleeding demonstrated that four biopsies from antrum or one biopsy from body increased the sensitivity of RUT as compared with only one biopsy from antrum. In this study, sensitivity of one biopsy from antrum was 64%, whereas sensitivity of four biopsies from antrum and one biopsy from body were 74% and 73% respectively^[41]. If RUT is still chosen for patient with gastrointestinal bleeding, biopsies from both antrum and corpus were suggested to increase the diagnostic accuracy.

Culture

Culturing of *H. pylori* from gastric biopsy specimen is a highly specific but less sensitive method. In general, culturing has almost 100% specificity, but the sensitivity of culture shows significant variation, between 85%-95%. Because of the delicate and fastidious nature of *H. pylori*, the cultivation in vitro requires particular transport medium, growth medium and incubation environment. Biopsy specimens can be kept in a transport medium, like Portagerm pylori or Stuart's transport medium, for up to 24 h at 4 °C. Several types of agar can be used for culture as *H. pylori* are isolated. The commonly used media include Pylori agar, Skirrow agar, Columbia blood agar, Brucella agar, Brain heart infusion or Trypticase soy agar, supplemented with sheep or horse blood. The agar plates are usually incubated in a microaerobic environment (80%-90% N₂, 5%-10% CO₂, 5%-10% O₂) at 35 to 37 °C for at least 5-7 d because *H. pylori* has been considered a microaerophile. However, a recent study showed growth of *H. pylori* is promoted by atmospheric oxygen levels with the presence of 10% CO₂, bringing a novel concept that *H. pylori* may be a capnophilic aerobe^[42]. Diagnosis of *H. pylori* from culture medium is based on morphological characteristics as well as positive urease, catalase, and oxidase reactions, which mean the microbiological laboratories should be equipped and trained to isolate this bacterium.

Conditions such as poor quality of specimens, delayed transport, exposure to aerobic environment or inexperienced microbiologist have adverse influence on the performance of culture and reduce the diagnostic accuracy^[43]. A recent study conducted in 26 hospitals to analyze the influence of transport time as well as temperature on culture rate showed positive culture rate decreased to 26.3% in 48 h transport group as compared to 32.8% in 24 h transport group ($P < 0.001$). This study also found the average temperature increased from 4.7 °C to 29.1 °C during transportation and this caused positive culture rate declined from 36.7% to 24.1%^[44]. The recent development of transport medium is a new transport medium, GESA transport medium. GESA transport medium is a semi-solid medium which can store gastric biopsy specimens

at 4 °C for up to 10 d and provide a quantifiable recovery rate of *H. pylori* (90.7%)^[45]. A new biphasic test which combined the selective enrichment broth and biochemical test using urea agar in a single vessel was also developed for culturing *H. pylori* in gastric biopsies. In this small study, biphasic test was conducted in 55 biopsy specimens and showed 100% positive predictive value after 48 h incubation. Moreover, this method had lower false positive rate and required lower bacterial load, approximately 10⁵ cfu/mL, as compared with CLOtest. At the same time, this test could be used under an aerobic condition and allowed culturing as well as antibiotic susceptibility testing^[46].

Host factors like high activity of gastritis, low bacterial load, bleeding, alcohol drinking, and use of H₂-receptor antagonists, PPI, antibiotics have adverse effect on culture positive rate. These medications, except for antibiotics which should be avoided at least 4 wk, were also suggested to be avoided 2 wk before culture. To avoid sampling bias from the patchy distribution of *H. pylori* in stomach, at least 2 biopsy specimens from the antrum and 2 biopsy specimens from corpus were also recommended^[47,48].

Although culture is a time-consuming, expensive and laborious test for *H. pylori* diagnosis, the antibiotic sensitivity test of *H. pylori* provided by culture is a particular advantage in clinical practice. As recommends from Maastricht IV Consensus Report, *H. pylori* culture and antibiotic susceptibility testing should be performed if primary resistance to clarithromycin is higher than 20% in a given geographical area or after failure of second-line treatment^[21]. Furthermore, culture also allows isolation of *H. pylori* for further analysis of phenotypic and genotypic characterization to have better understanding of the pathogens and, consequently, offer therapy evaluation. With the increasing prevalence of antibiotic resistance, culturing is still a reliable method for managing *H. pylori* treatment failure as well as surveying antibiotic resistance in population-based studies before other molecular tests are more widely available.

Polymerase chain reaction

Since the application of polymerase chain reaction (PCR) to detect *H. pylori* infection, PCR has been used extensively for the diagnosis of *H. pylori* from gastric biopsy specimens, saliva, stool, gastric juice and variable specimens. PCR provides excellent sensitivity and specificity, greater than 95%, as compared with other conventional tests and has more accurate results of detecting *H. pylori* in patients with bleeding. Several target genes including *UreA*, *glmM*, *UreC*, *16S rRNA*, *23S rRNA*, *HSP60*, and *VacA* genes, had been used for detection of *H. pylori* and using two different conserved target genes can increase the specificity, which in turn avoids false positive result, especially for samples other than gastric biopsy specimens. The other advantages of PCR, including fewer bacteria

required in sample, faster results, and no need for special processing supplies or transportation, enable clinicians to make quicker and more accurate decision on patient's treatment. Furthermore, PCR also allows concurrent detection of specific mutations leading to antibiotic resistance, such as macrolide- and fluoroquinolone-resistance, and virulence factors, such as *CagA* and *VacA*^[49-51].

As compared with agar dilution method (Etest) which is usually regarded as gold standard of antibiotic susceptibility test, real-time PCR (RT-PCR) had several advantages. First, using formaldehyde-fixed paraffin-embedded gastric tissue in PCR test is more convenient, rapid and sensitive than using fresh biopsy specimen in Etest, moreover, in this setting, RT-PCR also showed not inferior results of antibiotic susceptibility testing than Etest. In addition, PCR is more reliable to detect heteroresistant status which often cause false negative result in Etest, consequently, PCR can provide more accurate information for clinicians before starting antibiotic treatment^[52]. A recent study that used RT-PCR in formalin-fixed paraffin-embedded samples to detect *H. pylori* infection and associated clarithromycin-resistance status investigated the efficacy of genotypic resistance-guided quadruple therapy as the first-line treatment for 385 patients with functional dyspepsia. In this study, 136 patients (35.3%) were diagnosed with *H. pylori* infection and the sensitivities of RT-PCR and histological examinations were 95.6% and 69.9% respectively. Quadruple therapy with bismuth potassium citrate, rabeprazole, amoxicillin, and clarithromycin was used for genotypically sensitive patients, in contrast, genotypically resistant patients were treated with bismuth potassium citrate, rabeprazole, amoxicillin, and furazolidone. Authors found the eradication rates were 100% for patients with clarithromycin-susceptible *H. pylori* and 94% for patients with clarithromycin-resistant *H. pylori* respectively for per-protocol analysis^[53]. Second, RT-PCR is also a convenient method for epidemiological study on regional antibiotic resistance rate as a guidance for first-line empirical treatment. Furthermore, RT-PCR can detect the point mutations that cause antibiotic resistance as well as find the change of point mutation or occurrence of new mutation, which provide additional information for epidemiological studies and molecular research on genotype-phenotype relationships. Due to the possible change of mutations that cause antibiotic resistance with time, defining more than 5 point mutations when using PCR-based methods is important to achieve good accuracy in detecting antibiotic resistance^[54-56].

The genetic mutations causing resistance to clarithromycin (23S rRNA), quinolones (*gyrA* gene), tetracycline (16S rRNA), rifabutin (*rpoB* gene) and amoxicillin (*pbp-1a* gene) have been described in previous studies and several commercial kits such as MutaREAL *H. pylori* kit, ClariRes real-time PCR assay and Seeplex ClaR-*H. pylori* ACE

detection system are available for the detection of clarithromycin resistance^[57]. However, the precise mechanism of metronidazole resistance is less clear and the susceptibility genes such as *rdxA* and *frxA* have been implicated in previous studies with debated results. A recent study using Illumina next-generation sequencing to search candidate mutations for metronidazole resistance. This study confirmed mutations in *rdxA* gene had the major role in metronidazole resistance of *H. pylori* and mutations in *frxA* gene could enhance the metronidazole resistance only in the presence of *rdxA* mutations. Additionally, a new discovery of mutations in *rpsU* gene may have a role in metronidazole resistance to explain the metronidazole-resistant strains without the mutations in *rdxA* and *frxA* genes^[58]. GenoType HelicoDR assay is a molecular test that combine PCR and hybridization, allowing the molecular defecation of *H. pylori* as well as clarithromycin and fluoroquinolones resistance within 6 h. In previous studies, the GenoType HelicoDR assay using bacterial strains or gastric biopsy specimens is highly accurate for clarithromycin resistance with 94%-100% sensitivity and 86%-99% specificity respectively; the GenoType HelicoDR assay is also accurate for fluoroquinolone resistance with 83%-87% sensitivity and 95%-98.5% specificity respectively as compared to the culture-based method^[59,60]. However, a recent study evaluated the clinical usefulness of GenoType HelicoDR in Korea showed the sensitivity and specificity for clarithromycin resistance were only 55.0% and 80.0% respectively. The GenoType HelicoDR was also not accurate for fluoroquinolone resistance, showing the sensitivity and specificity were 74.4% and 70.0% respectively. The clinical applicability of GenoType HelicoDR in determination of antibiotic resistance may have some limitations which need further evaluations^[61]. RT-PCR is conventionally used to quantify the *H. pylori* DNA in biopsy specimens, but performing RT-PCR can be a problem for clinical laboratories because of expensive thermocyclers. A dual-priming oligonucleotide (DPO)-based multiplex PCR was developed to detect both *H. pylori* infection and clarithromycin resistance and this test can be performed in any conventional thermocycler that costs less than RT-PCR. With a particular DPO primer design to amplify the *H. pylori* 23S rDNA and to detect the most common mutations, A2142G and A2143G, conferring clarithromycin resistance, DPO-PCR was proved to be rapid and accurate for *H. pylori* diagnosis and determination of clarithromycin susceptibility by using gastric biopsy specimens^[62,63]. Furthermore, a recent study using tissue samples that had been processed by RUT to evaluate the diagnostic accuracy of DPO-PCR showed DPO-PCR had higher sensitivity than RUT and histology, and DPO-PCR could detect *H. pylori* infection in RUT-negative samples, meaning that this test can decreased the false negative result and reduce the need for re-endoscopic examination.

The concordance rate of DPO-PCR between gastric biopsy samples and samples proceeded by RUT was 94.4%^[64].

Detection of virulence factors by PCR helps to evaluate the genetic variation within virulence factors of *H. pylori* and gives more information to understand the clinical discrepancies between patients infected with different strains of *H. pylori*. Several studies showed presence of virulence factors, such as *CagA* and *VacA* gene, are associated with more severe gastric inflammation and higher prevalence of peptic ulcer disease and gastric cancer^[65-67]. Duodenal ulcer promoter gene A (DupA) was also proposed to be associated with *H. pylori* induced ulcer formation, but inconsistent results which were suspected to be caused by primer mismatches were reported by previous studies. A newly designed RT-PCR with a specific primer designed based on an alignment of all 221 DupA gene sequences was introduced recently to improve the detection rate of the DupA gene. This method increased the detection rate to 64.2%, whether the commonly used PCRs had detection rate between 29.9% to 37.8%. The authors pointed out that PCR design had great influence on the detection of virulence factor and the detection of specific DupA allele was not the same as detection of actual DupA gene^[68].

PCR is also helpful to detect *H. pylori* in environmental samples for epidemiological studies. A high prevalence of *H. pylori* detected in drinking water samples by PCR provided more information of *H. pylori* transmission through drinking water^[69]. Higher detection rate of *H. pylori* contamination in un-washed vegetable suggested accurate washing of vegetables decreased *H. pylori* contamination^[70]. PCR had also been used to detect genotyping of *H. pylori* in vegetable and high similarity in the genotyping pattern of *H. pylori* among vegetable samples and human specimens suggested that vegetable may be the sources of the bacteria^[71].

Except for more rapid and highly accurate results from PCR to detect *H. pylori* infection and antibiotic-resistance strains, concerns about cost, local available equipment and expertise in molecular techniques inevitably influence the feasibility of PCR in local laboratories.

NONINVASIVE TESTS

Several attempts have been made to avoid endoscopic diagnostic methods for several reasons. First and foremost, endoscopy is an invasive procedure which is discomfort and not suitable for patients with severe comorbidities or contraindications. Besides, cost of endoscopy and additional cost adding on endoscopy, such as disposable forceps and anesthesia, may be high. Last but not least, sampling bias is almost inevitably encountered in biopsy-based methods due to uneven distribution of *H. pylori* in stomach.

UREA BREATH TEST

Urea breath test (UBT) has been used for almost 30 years and is still the most popular and accurate noninvasive test for diagnosis of *H. pylori* infection. By the urease activity of *H. pylori*, the ^{13}C - or ^{14}C -labeled urea ingested by the patient is hydrolyzed to labeled CO_2 in stomach, then labeled CO_2 is absorbed in the blood and exhaled by breathing in which labeled CO_2 can be measured. Although several factors including patient, bacteria and the test itself influence the results of UBT, the UBT is a highly accurate and reproducible test with near 95% sensitivity and specificity under standardized procedures. A recent published meta-analysis to evaluate the diagnostic accuracy of UBT in adult patients with dyspeptic symptoms showed the pooled sensitivity was 96% (95%CI: 0.95-0.97) and pooled specificity was 93% (95%CI: 0.91-0.94)^[72]. UBT is also useful for epidemiological studies and for assessing the efficacy of eradication therapy^[21,73]. Patient should stop taking PPI 2 wk and antibiotic 4 wk before exam to avoid false negative results^[74]. Bleeding also influences the diagnostic accuracy of UBT and delayed UBT after recovery from bleeding is mandatory to decrease false negative result^[75]. Sometimes, although rare, the presence of other urease producing pathogens in stomach also causes the false positive results.

UBT is a suitable method with many advantages, such as simple, noninvasive and safe, to detect *H. pylori* infection in pediatric patients, although the accuracy of UBT in pediatric patients is not as good as it used in adult patients, especially for children younger than 6 years old, having 75% to 100% sensitivity and specificity^[76].

^{13}C -UBT is preferable to the ^{14}C -UBT to avoid exposure to radiation, even though ^{14}C -UBT is safe for children and pregnant women because radiation from ^{14}C -UBT is lower than radiation acquired from the natural environment. In the absence of expensive equipment and ability to pay high cost of ^{13}C -UBT, however, ^{14}C -UBT is more popular in the developing countries. The diagnostic accuracy between ^{13}C -UBT and ^{14}C -UBT is not different and both tests can be considered to be gold standard among the various noninvasive tests for the diagnosis of *H. pylori* infection^[77]. There are two protocols, nonencapsulated and encapsulated, used for the oral administration of ^{14}C -urea to patients for *H. pylori* diagnosis. Initially, encapsulated ^{14}C -UBT was developed to avoid the problem of ^{14}C -urea hydrolysis by the action of urease-producing oral flora and this method obviated the problem of false-positive results in early breath samples^[78]. Nonetheless, rapid transit of the ^{14}C -urea containing capsule from the gastric tract or its incomplete resolution in the stomach during the phase of breath collection causes encapsulated ^{14}C -UBT may not be a superior option than nonencapsulated protocol^[79]. A recent study used dynamic scintiscan technique to monitor gastric fate of capsule and

compared the sensitivity between nonencapsulated and encapsulated protocol in 100 dyspeptic patients. This study showed nonencapsulated protocol had higher sensitivity than encapsulated protocol and the sensitivity of encapsulated and nonencapsulated ^{14}C -UBT were 90.5% and 98.6% at 10 min and 91.8% and 97.2% at 15 min respectively. Incomplete or non-resolution of ^{14}C -urea capsule in stomach during the phase of breath collections noted by dynamic scintiscan images provided the explanation of lower sensitivity of encapsulated ^{14}C -UBT as compared with nonencapsulated ^{14}C -UBT^[80].

The precise cut-off value for delta over baseline (DOB) value to discriminate between *H. pylori*-positive and *H. pylori*-negative results is the other controversial issue. The cut-off value for the UBT was originally determined as 5.0‰, which had most widely recommended, whereas lower values, 3.0 or 3.5‰ were also proposed to improve its accuracy without compromising the sensitivity and specificity of this test. A "grey zone" in which the results of UBT are inconclusive were mentioned by previous studies and a borderline DOB value, like very close to the selected cut-off point, should be cautiously interpreted^[81]. A novel method of UBT using an optical cavity-enhanced integrated cavity output spectroscopy system was introduced recently to provide optimal diagnostic cut-off point. This preliminary test defined diagnostic cut-off point as cumulative percentage of ^{13}C dose recovered (c-PDR) = 1.47% at 60 min and exhibited 100% sensitivity and 100% specificity with an accuracy of 100% as compared with invasive endoscopic tests. However, small number of samples are used in this study and further larger study is necessary to confirm these results^[82].

STOOL ANTIGEN TEST

Stool antigen test (SAT) is the other noninvasive method with good sensitivity and specificity, 94% and 97% respectively in global meta-analysis, in the diagnosis of *H. pylori* infection^[83]. This method detects the presence of *H. pylori* antigen in stool samples. There are two types of SATs used for *H. pylori* detection, enzyme immunoassay (EIA) and immunochromatography assay (ICA) based methods, using either polyclonal antibodies or monoclonal antibodies. Many SATs are available now for the diagnosis of *H. pylori* infection and different diagnostic accuracy are showed from different studies with different SATs and different study design. In general, monoclonal antibody-based tests are more accurate than polyclonal antibody-based tests^[83] and EIA-based tests provide more reliable results than ICA-based tests^[84,85]. In a recent study, the Tesmate pylori antigen (TPAg) EIA utilizing a monoclonal antibody to check native *H. pylori* catalase showed 92.4% sensitivity and 100% specificity in adult when compared with RT-PCR and the accuracy of this test was 94.9%^[86]. Premier Platinum HpSA Plus test, the other monoclonal EIA-

based test, also showed reliable diagnostic results with 92.2% sensitivity, 94.4% specificity and 93.4% accuracy for diagnosing *H. pylori* infection as compared with the other 4 SATs, including 1 monoclonal EIA-based (*H. pylori* antigen test), 2 monoclonal ICA-based (ImmunoCard STAT! HpSA test and *H. pylori* fecal antigen test) and 1 polyclonal ICA-based (one-step *H. pylori* antigen test) tests, of which the accuracy were all lower than 90%^[84]. However, ICA-based tests are easy to perform and do not require specialized equipment, which make it suitable for in-office test and developing countries. A new monoclonal ICA-based SAT, Atlas *H. pylori* Antigen Test, was also introduced recently and provide better results than previous monoclonal ICA-based SATs, with 91.7% sensitivity, 100% specificity and 96.6% accuracy^[87].

As well as UBT, monoclonal EIA-based SAT is also a reliable test recommended by guidelines to assess the efficacy of *H. pylori* eradication therapy and the time for testing after the end of treatment should be as least 4 wk^[21,88]. In previous meta-analysis, the pooled sensitivity and specificity for monoclonal SAT to confirm eradication after therapy were 93% and 96% respectively^[83]. In recent studies, monoclonal EIA-based SATs have been confirmed to be a useful and accurate tool to determine the results of *H. pylori* eradication therapy, with 91.6%-100% sensitivity and 93.6%-98.4% specificity^[89,90]. Furthermore, monoclonal ICA-based SATs, RAPID Hp StAR and ImmunoCard STAT! HpSA, also provide promising results with 90.0%-100% sensitivity and 93.6%-94.9% specificity.

In addition to assessment of eradication therapy, monoclonal SAT is a convenient, noninvasive and useful test for the diagnosis of *H. pylori* infection in pediatric patients^[91]. A study applied SAT in children aged between 6 to 30 mo showed reliable results of SAT for diagnosing *H. pylori* infection in very young children^[92]. A recent meta-analysis, including 45 studies and 5931 patients, to evaluate the performance of SATs in children showed pooled sensitivity and specificity were 92.1% and 94.1% respectively. In subgroup analysis, the sensitivity and specificity of monoclonal SAT, polyclonal SAT and one-step rapid monoclonal SAT were 96.2% and 94.7%, 88.0% and 93.0%, and 88.1% and 94.2% respectively. Monoclonal SAT is a reliable test for diagnosis of *H. pylori* infection in children^[93]. Moreover, SAT is a useful tool for epidemiological study and screening programs^[94,95]. With regard to cost and equipment, SAT is more suitable than UBT for mass surveys. As compared with serological test, which are usually used for screening, SAT seems to provide more reliable results in diagnosis of *H. pylori* infection. However, a previous study found SAT was less accurate than serological test in patients with severe atrophic gastritis and the influence of this result need further evaluation to assess the role of SAT in screening *H. pylori*-associated diseases, like gastric cancer^[96]. Whereas the other study using a

new polyclonal EIA-based SAT (EZ-STEP *H. pylori*) found presence of atrophic gastritis and/or intestinal metaplasia did not significantly affect the results of SAT^[97].

The accuracy of SAT is influenced by several factors, like antibiotic, PPI, N-acetylcysteine, bowel movement and upper gastrointestinal bleeding. Preservation of the specimen, like temperature and transport time before testing, and cut-off valve also have impacts on the diagnostic accuracy of SAT^[98-100].

ANTIBODY-BASED TESTS

Numerous serological tests based on the detection of anti-*H. pylori* IgG antibody are widely available for *H. pylori* diagnosis and EIA test is the most common and accurate technique among them. Serological tests have also frequently been used in screening for epidemiological studies because of their inexpensive, rapid and acceptability to patients. Moreover, serological test is useful for evaluation of *H. pylori* infection in children. A recent study using E-Plate, a commercial serum antibody kit, to compare the performance of serological test with SAT in 73 children showed that the sensitivity, specificity, and positive likelihood ratio for serological test were 91.2%, 97.4%, and 35.6%, respectively. These results came from using recommended adult cutoff valve on children^[101]. Because the accuracy of serological tests depends on the antigen used in commercial kit and the prevalence rate of specific *H. pylori* strains employed as the source of antigen. Proper antigens, either using local strains as the source of antigen or pooling antigens from strains of different groups, as well as reliable cutoff value of serological test should be validated locally before investigating population^[102,103]. Several immunogenic proteins, like CagA, VacA, UreA, Omp and GroEL, have been used as candidates to detect infection. The *H. pylori* FliD protein, an essential element in the assembly of the functional flagella, is also recognized as a novel marker for serological diagnosis of *H. pylori* infection, with sensitivity and specificity of 99% and 97% respectively^[104]. A novel line immunoassay, recomLine *H. pylori* IgG, which using six highly immunogenic virulence factors (CagA, VacA, GroEL, gGT, HcpC, and UreA) was introduced recently for serological diagnosis of *H. pylori* infection. The recomLine, in contrast to EIA and immunoblot, allows the identification of specific antibody response against distinct *H. pylori* antigens and increased discriminatory power. As compared to histology, the recomLine showed sensitivity and specificity of 97.6% and 96.2% respectively. The recomLine is also a useful tool to identify specific virulence factors of *H. pylori*^[105,106].

The other advantage of serological test is that the accuracy of serological tests is not affected by ulcer bleeding, gastric atrophy as well as the use of PPI or antibiotics, which cause false negative results in other

invasive or noninvasive tests. However, serological test is not a reliable test to assess eradication therapy because antibody levels can persist in the blood for long periods of time even after successful eradication^[21]. Because the serological tests do not distinguish between active infection and past exposure to *H. pylori*, further confirmation by other tests is required before eradication therapy.

Like SAT, EIA-based serological tests have better accuracy than ICA-based tests. A recent study comparing 29 commercial serological test (17 EIA-based and 12 ICA-based) showed the accuracy of 9 of 17 EIA-based tests were higher than 90%, whereas only one of the 12 ICA based tests had an accuracy > 90%. Heterogeneous performances were also observed between different serological tests, revealing sensitivity ranged from 57.8% to 100% and specificity ranged from 58.7% to 96.8% in EIA-based tests; sensitivity ranged from 55.6% to 97.8% and specificity ranged from 60.3% to 96.8% in ICA-based tests. The serological tests should be chosen properly according to their specific performance parameters to achieve different goals, like screening, initial diagnosis or confirmation of another test^[107].

Serological test also play an important role in studies of pathogenesis and virulence factors because several antigenic proteins can be detected by immunological techniques and provide additional diagnostic value. Several attempts have been made to find potential biomarkers to identify patient infected with high-risk *H. pylori* strains by serological tests. Levels of pepsinogen (PG) I, PG II and PG I/II ratio combined with *H. pylori* antibody have been widely used to predict atrophic gastritis and risk of gastric cancer^[108,109]. PG I/II ratio can also be useful in gastric cancer surveillance in patients after eradication therapy^[110]. However, controversial results are presented on the clinical application of these serological makers. A recent study evaluating the accuracy of GastroPanel, which measures gastrin-17, *H. pylori* antibody, PG I and PG II, to detect atrophic gastritis showed only 50% sensitivity and 80% specificity, which were inferior to previous studies^[111]. Pepsinogen test was also not accurate enough for the diagnosis of gastric cancer, with 71.0% sensitivity and 69.2% specificity^[112]. Some virulence factors have also been evaluated to predict the prognosis of *H. pylori*-associated diseases. Presences of serum CagA, VacA, and GroEL antibodies in patients with *H. pylori* infection are associated with gastric precancerous lesions as well as gastric cancer and these serum markers might serve as potential predictors for patients infected with high-risk strains, which may be related to the development of gastric cancer^[106,113]. Although the association between virulence factors and clinical presentations had been found by previous epidemiological studies, serological tests are still not reliable enough for diagnosis of gastric cancer. In a recent meta-analysis, the pooled sensitivity and

specificity of CagA antibody using to diagnose gastric cancer were 71% and 40% respectively, and the diagnostic odds ratio were 2.11^[114].

Detection of *H. pylori* IgG in urine had also been evaluated in children in previous studies, however, variable results were presented^[115,116]. In addition, the diagnostic accuracy of EIA-based test to detect salivary *H. pylori* IgG was also not good enough as a reliable test^[117,118]. Antibody detection in urine or saliva is less accurate than other tests and is not suggested to be used in the management of patients^[119].

DIAGNOSIS OF *H. PYLORI* IN OTHER SPECIMENS

Utilizing PCR to detect *H. pylori* in stool is a reliable and rapid technique, which is especially attractive for children as a noninvasive test. Stool PCR also provides the advantages of identifying specific genotypes and antibiotic-resistance of the microorganism^[120,121]. Oral cavity has been implicated as an extra-gastric reservoir of *H. pylori*, even though the significance of *H. pylori* in oral cavity, either a source of re-infection or the route of transmission, is still unclear. Saliva and dental plaque were the specimens commonly used to detect *H. pylori* in oral cavity and PCR was the most common and reliable test used in recent studies. RUT and culture were also performed to detect oral *H. pylori* in early studies. The prevalence of *H. pylori* detection in oral cavity exhibited wide variations, from 0% to 100%, and lower prevalence in saliva as compared with dental plaque was usually found^[122]. The wide variations in the prevalence of *H. pylori* in oral cavity may be due to different methodologies, different populations and different primers used in studies. Recent studies focused on modification of primer to increase diagnostic accuracy or evaluation of new method to overcome the limitation of PCR. A novel PCR system, using a *H. pylori*-specific primer sets based on highly conserved sequences for the complete genomes of 48 *H. pylori* strains, was developed recently to increase the diagnostic accuracy of PCR in oral cavity^[123]. The Loop-mediated Isothermal Amplification (LAMP), a new method of highly specific and sensitive DNA amplification, was compared with PCR on the detection rate of *H. pylori* in dental plaque samples in a small study which enrolled 45 participants. This study showed LAMP had higher detection rate than PCR and the detection rate of *H. pylori* in dental plaque samples by LAMP and PCR were 66.67% and 44% respectively^[124].

DIAGNOSIS OF *H. PYLORI* IN SPECIFIC CLINICAL CIRCUMSTANCES

As mentioned previously, upper gastrointestinal bleeding (UGIB) decreases the diagnostic accuracy of many tests, including invasive and noninvasive, to

detect *H. pylori* infection. In a previous meta-analysis, RUT, histology and culture had low sensitivity and high specificity in patients with UGIB. UBT was still a reliable test, whereas SAT became less accurate in this clinical setting. Although serology was not influenced by UGIB, it could not be recommended as the first diagnostic test for *H. pylori* infection^[40]. When comparing CLO, culture and histology, histology was less influenced by ulcer bleeding and could be a reliable test even in the presence of blood^[125]. PCR had a significantly higher sensitivity than RUT, histology and culture, with sensitivity of 91%, 66%, 43% and 37% respectively and showed similar sensitivity as compared with serology and UBT, 94% and 94% respectively. PCR was similar to UBT in diagnostic accuracy for detecting *H. pylori* infection in bleeding peptic ulcers. However the specificity of PCR (100%) was only superior to serology (65%) and did not differ from other tests (RUT: 95%, histology: 95%, culture: 100%, UBT: 85%)^[126]. A study also found RT-PCR could detect *H. pylori* infection by using formalin-fixed paraffin-embedded biopsy specimens in which histology showed negative results in patients with peptic ulcer bleeding^[127]. Eradication of *H. pylori* is important in the management of *H. pylori*-associated ulcer bleeding for the purpose of preventing further bleeding and successful eradication therapy is even more effective than long-term maintenance antisecretory therapy with PPI to reduce rebleeding. Biopsy-based *H. pylori* testing is usually recommended during endoscopic survey of UGIB, even though bleeding decreases the sensitivity of biopsy-based tests. From the results of a meta-regression study, a delayed test, 4 wk after the UGIB episode, had higher detection rate of *H. pylori* in patients with UGIB. Because accurate determination of the etiology of bleeding ulcers is crucial in the management of ulcer bleeding, confirmation of a negative result with a subsequent noninvasive test has also been recommended by guidelines^[22,128,129]. A low negative predictive value was also found when UBT was performed right after emergent endoscopy and a delay test was also mandatory for all negative results of early UBT^[75]. Despite the importance of *H. pylori* testing in patients with UGIB, the proportion of patients who received direct *H. pylori* testing was quite low, about 12%-60% noted from previous studies. Concerns about decreased sensitivity related to bleeding or PPI use and increased risk of adverse events associated with gastric biopsies or increased procedure time to perform gastric biopsies may influence the decisions of *H. pylori* testing by clinicians^[130].

Diagnosis of *H. pylori* in patients with partial gastrectomy is the other issue, although, to which less attention has been paid because these patients represented a very small portion of general population. In a meta-analysis comparing three commonly used tests in patients with partial gastrectomy showed histology performed the best, followed by the RUT,

whereas the UBT had the poor diagnostic accuracy. These studies showed a high degree of heterogeneity and the pooled sensitivity and specificity of histology, RUT, and UBT were 93% and 85%; 79% and 94%; 77% and 89% respectively. The RUT was suggested as the initial choice of test on these patients and biopsy samples from gastric fundus or the upper body of the remnant stomach was recommended. Histology was recommended to be performed after negative result of RUT in these patients^[131]. SAT may be the other reliable test to detect *H. pylori* in patients with distal gastrectomy. A small study using HpSA test to evaluate the diagnostic accuracy of SAT in 59 patients with distal gastrectomy for gastric cancer demonstrated that the sensitivity, specificity and accuracy of HpSA test were 100%, 90.5%, and 96.6%, respectively^[132]. The possible reason for inadequate performance of UBT in the diagnosis of *H. pylori* in patients with distal gastrectomy may be not enough time for the urea stays in the gastric stump to interact with urease produced by *H. pylori*. The BreathID, a rapid continuous-real-time UBT, seemed to overcome this shortcoming and it showed better accuracy than RUT, 87% and 72% respectively. However lower sensitivity and specificity of RUT, 82% and 71% respectively, as compared with previous studies was also found in this study and biopsies were taken from the gastric body slightly distal to fundus in this study may influence the diagnostic performances of RUT^[133]. A recent study also demonstrated discordant results between UBT and biopsy-based tests in patients with partial gastrectomy after *H. pylori* eradication therapy. The authors suggested additional endoscopic biopsy-based tests would be helpful to avoid unnecessary treatment because high false positive rate and low positive predictive value of UBT, 19.1% and 44.7% respectively, were found in these patients after eradication therapy^[134].

Accurate determination of *H. pylori* status in patients after eradication therapy is important and UBT as well as SAT are recommended by guidelines to assess the efficacy of eradication therapy. These tests are usually recommended to perform more than 4 wk after end of therapy^[21,88]. However, high false positive rate of 52.9% was found by using ¹³C-UBT with current cutoff value (2.5‰), especially in patients with more than two times previous eradication therapies and in patients with moderate to severe gastric intestinal metaplasia^[135]. A recent study using nested PCR to detect *H. pylori* from gastric biopsy specimens after eradication therapy showed nested PCR is more sensitive than RUT, histology and culture. Furthermore, PCR based method is able to discriminate the reinfection or recrudescence after eradication therapy^[136].

CONCLUSION

The developments of current diagnostic methods

allow to have a more accurate diagnosis of *H. pylori* infection, which in turn improving the management of *H. pylori*-associated diseases. Although the golden standard test may not exist, the choice of test to detect *H. pylori* infection depends on the prevalence and strains of *H. pylori* on endemic areas, accessibility, advantages and disadvantages of each method as well as different clinical circumstances of each patient. To combine the results of two or more tests could be a reasonable strategy in routine clinical practice to achieve the most reliable result. We believe that there will be continuous attempts to evolve the diagnostic yield of *H. pylori* infection for different clinical purposes, specific populations, and genotypic characterizations to have more reliable and feasible diagnostic modalities of *H. pylori* infection in the future.

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P- Reviewer: Tosetti C S- Editor: Ma YJ L- Editor: A
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