Helicobacter pylori: A Comprehensive Review of Virulence Factors, Diseases, Diagnosis, Antimicrobial Resistance and Eradication Strategies

Marwa Mostafa Elsaied [1], Shaymaa Abdelmalek [2], Jakeen El Jakee [2]

1. Postgraduate student at the Department of Microbiology, Faculty of Veterinary Medicine, Cairo University, Egypt
2. Department of Microbiology, Faculty of Veterinary Medicine, Cairo University, Egypt

* Corresponding author: Marwa Mostafa Elsaied, E-mail: sayedmarwa33@gmail.com

1. Abstract

Helicobacter pylori (*H. pylori*) is a global pathogen affecting both humans and animals, linked to gastritis and peptic ulcers that could be associated with the development of gastric carcinomas. Diagnosis of *H. pylori* infection involves both invasive methods [such as bacterial culture, histopathology, biopsy urease test (RUT), and *Campylobacter*-like organism (CLO) gel test] and non-invasive tests [including 13C-urea breath test (13C-UBT], serological test, and as tool antigen test using commercial enzyme-linked immunosorbent assay. This review systemically analysed 124 studies conducted to systematically review the accuracy of the different tests for *H. pylori* infection and compare the mean sensitivity and specificity of the diagnostic tests as well as antibiogram and control of the infection. Paper abstracts and PubMed database were the information resources of the review. Based on this review, it could be concluded that histological examination and rapid urease testing demonstrated excellent diagnostic reliability, while stool antigen testing proved to be a cost-effective, non-invasive method. Recently, loop-mediated isothermal amplification (LAMP) technique has emerged as promising, safe alternative for identifying *H. pylori* detection.

Keywords: Antibiogram; biopsy urease test; CLO gel test; *Helicobacter pylori*; Loop-mediated isothermal amplification (LAMP) technique; stool HPSA; urea breath test.

2. Introduction

Helicobacteriosis is a worldwide infection caused by *Helicobacter* species that affects both humans and animals. The global prevalence of *Helicobacter pylori* (*H. pylori*) infection indicates a capability to infect humans [1]. More than half of the world population is thought to be infected with *H. pylori*. Although the majority of infected people are asymptomatic, *H. pylori* infection can cause gastric ulcers and potential deadly gastric cancer [2]. *H. pylori*, previously known as *Campylobacter pylori*, is a Gram-negative, flagellated microaerophilic spiral-shaped bacterium [3]. The bacterium was first identified in 1984 by Marshall and Warren who succeeded in culturing the curved bacilli; *H. pylori*; obtained from the stomach of patients with gastritis and peptic ulceration. *H. pylori* produces oxidase, catalase, and urease [4]. Urease is the most abundant protein; its expression represents about 10% of the total protein weight [5]. The companion animals (dogs and cats) play an important role in zoonotic risks, public health hazards, and the transmission of *Helicobacter* species [6]. *H. pylori* is a causative agent of gastritis and peptic ulcers and is associated with the development of gastric carcinomas and MALT lymphoma [7]. *H. pylori* was detected in 29.6% (43/145) of patients by culture, 55.2% (80/145) by the urease test from gastric biopsies, 57% (65/114) by HpSA test and 71.3% (102/143) by PCR [8]. Out of 103 tested children, 41 (39.8%) and 39 (37.8%) were positive for *H. pylori* based on cultures of gastric biopsy and HpSA test results, respectively [9]. The detection rates were 81% by serology, 80% by histopathology, 9% by culture and 56% by urease test [10]. Epidemiological studies suggested that water might be a possible source of *H. pylori* transmission [11].

Currently, a range of accurate diagnostic tests is widely available. These include both invasive tests (bacterial culture, histopathology, and biopsy urease test) and non-invasive tests (such as 13C-urea breath test (13C-UBT), serological tests, and a commercial kit using ELISA to detect *H. pylori* antigen in the stool HpSA) [12, 13]. Initially *H. pylori* infection was diagnosed using invasive methods but non-invasive methods have been currently developed to simplify the diagnosis.

This review provides a general overview of *H. pylori* virulence factors, related diseases, both conventional and novel diagnostic methods including their sensitivity and specificity, as well as therapeutic approaches and treatment strategies for *H. pylori* infection. Bibliographical searches were performed using several electronic databases and abstracts.

3. *H. pylori* Infection Related Diseases

H. pylori infections which are common worldwide may be a risk factor for gastritis, gastric and duodenal ulcers, gastric adenocarcinoma and mucosa-

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

associated lymphoid tissue (MALT) lymphomas [14]. A close link was observed between *H. pylori* infection, antral intestinal metaplasia, and the development of gastric cancer [15]. Many researchers have reported that untreated *H. pylori* infection may lead to peptic ulceration and, particularly in adults, to gastric adenoid carcinoma and mucosa associated lymphoid tissue (MALT) gastric lymphoma [8, 16, 21]. The rate of *H. pylori* positivity was 87.5% (35 of 40) in patients with hyperemesis gravidarum [22]. *H. pylori* infection is closely related to the occurrence of Rosacea, an inflammatory disease affecting the central part of face characterized by persistent or recurrent episodes of erythema, papules, pustules and telangiectasias of unknown etiology [3]. *H. pylori* infection has been implicated in a number of malignancies and non-malignant conditions including peptic ulcers, non-ulcer dyspepsia, recurrent peptic ulcer bleeding, unexplained iron deficiency anaemia, idiopathic thrombocytopaenia purpura, and colorectal adenomas [23]. Colonization of the stomach with *H. pylori* can induce various gastric and extragastric disorders.

4. Virulence Factors of *H. pylori*

Urease production, formation of 2-7 flagella [24], outer membrane adhesion proteins, cytotoxin-related gene A (*cag*A) and vacuolar cytotoxin A (*vac*A) are the main virulence factors of *H. pylori* [1, 11, 25, 26]. Additionally, the cysteine-rich protein HcpA causes inflammation [27] and the virulence factor *DupA* is linked to duodenal ulcers [28]. Increasing antibiotic resistance is the main cause of initial treatment against *H. pylori* due to its ability to forming efflux pumps, and biofilms. It is noteworthy that pathogenic *H. pylori* posses numerous virulent factors [26, 29, 31].

5. Factors Affecting the Prevalence of *H. pylori*

Patients' age, family history of gastric cancer, presence of wasting or obesity, lifestyle habits such as: a history of smoking or alcohol consumption, preference for spicy food, frequent consumption of strong tea, high work pressure, high intake of fish and seafood, low intake of dairy products, vegetables, fruits or fats all impact the occurrence of *H. pylori* infection in patients [32]. The choice of testing method should be based on several factors including: patient age, presented symptoms, medication used and cost. Test reliability, availability, patient age, gender, and geographic location are also considered [21, 33]. The sensitivity of both urea breath and HpSA tests was affected by age while the sensitivity of the HpSA test was significantly lower among children under 6 years [33]. It was evidenced that *H. pylori* is a causative agent of gastric disorders regardless of patient age [34]. The prevalence of *H. pylori* has remained high in some areas and reinfection rate has varied in different countries due to socioeconomic and hygienic conditions.

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

Therefore, preventive measures should be considered in the living habits and dietary factors of people to reduce *H. pylori* infection [20].

6. Diagnostic Approaches to *H. pylori* Infection

Diagnostic methods of *H. pylori* infection have divided into invasive and non-invasive types. The first category is based on endoscopy (gastric mucosal biopsy, histology, culture, rapid urease test, PCR) and it has been considered the gold standard. In contrast, the noninvasive methods include detection of the bacterial antigen in stool, urea breath test and serology [8, 14, 35, 41]. The gold standard tests for diagnosis of *H. pylori* infection were defined as two or more tests (i.e., histology, IgG ELISA serology and 13C-urea breath test) [42]. Other methods considered gold standard for diagnosing H. *pylori* infection include gastroscopy, 13C breath test, rapid urease test, and pathological methylene blue staining [43]. The invasive tests include culture, urease test (CLOtest), histology, and PCR, while the noninvasive tests include 13C urea breath test, IgG serology (Pyloriset EIA-G), immunoblot (Helicoblot 2.1), and antigen stool detection (Premier Platinum HpSA) [44].

Of non-invasive tests, serology and stool HpSA are less sensitive than CLO however; they are equally sensitive to each other [38]. The urea breath test seems to be the most reliable diagnostic method for *H. pylori* infection in patients with chronic renal failure. Serology has a low specificity and the results of the fecal tests vary widely [45].

The sensitivity and specificity of various diagnostic methods using gastric biopsy specimens are as follows: culture (52.4% and 100%), PCR (96.3% and 62.3%), HpSA (80.3% and 81.4%) and urease test (86.6% and 85.7%) [8]. Specificity of the culture method was high while sensitivity of HpSA, PCR, and urease tests was relatively low compared to culture [8]. It was emphasized that the HpSA stool test may be useful for the primary diagnosis of *H. pylori* infection, with sensitivity similar to that obtained with 13C-urea breath test (UBT), histology (H), and rapid urease test (RUT), but with lower specificity [46].

According to the available information, the sensitivity and specificity values of different tests for diagnosis of *H. pylori* infection varied from a study to another. In an investigation, histological detection showed sensitivity and specificity of 100% and 86%, respectively. Culture resulted in 63% and 100% respectively, HpIgG (58% and 73%) rapid urease test (89% and 82%) and HpSA (84% and 82%) respectively [47]. In another study, the sensitivity and specificity by histopathology were 83% and 100%, serology (84% and 60%), culture (64% and 100%) and by urease test (67% and 85%) respectively [10]. The sensitivity and specificity of urea-breath test (94% and 96%), serology (97% and 64%), 3

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

fecal tests: FemtoLab *H. pylori* (86% and 100%), Premier Platinum HpSA (58% and 96%) and Simple *H. pylori* (61% and 78%) [45]. The sensitivity and specificity were: 42.5% and 69.2%, with histology; 69.2% and 42.9%, with stool antigens immunoassay (HpSAg); 64.2% and 47.7%, with serology (IgG serum of 'antibodies) respectively [48]. The sensitivities and specificities percentages of histology were 97.5 and 97.2, of HpSAg were 91.9 and 98.6, and of campylobacter-like organism CLO test were 79.7 and 97.2 tests against culture [49]. The sensitivity and specificity values of histopathology, urease and HpSA tests were 72.5% and 100%, 97.5% and 20.7%, 75% and 82.6% respectively [14].

6.1. Non-invasive Tests for Detection of *H. pylori*

Non-invasive tests for *H. pylori* infection include serological tests for antibodies (IgG), enzyme immunoassay for *H. pylori* antigens in stool (HpSA), and 13C-urea breath tests (UBT) using carbon-13 or radioactive carbon-14, which produces a labeled CO_2 that is detected in the breath [50]. Hahn *et al.* [51] noted that the non-invasive tests may provide a more rapid less expensive diagnosis. The urea breath test and the HpSTAR stool antigen kit are reliable tests for the non-invasive diagnosis of *H. pylori* [33, 52, 53]. The positivity rate of the stool antigen test (81.8%) was significantly lower than that of serology (88.7%) in patients with severe atrophic gastritis [54]. Non-invasive serological tests are useful as a screening test for *H. pylori* infection [55].

The non-invasive methods help patients to avoid the risks associated with invasive endoscopy.

6.1.1. *H. pylori* Stool Antigen (HpSA) Detection

One simple, fast and relatively inexpensive non-invasive method is the *H. pylori* stool antigen test [13]. It is based on a sandwich enzyme immunoassay the detection of *H. pylori* antigen in stool. This method is particularly suitable for developing countries where facilities for endoscopy are not readily available [56]. After the development of the polyclonal antibodies, enzyme immunoassay (Premier Platinum HpSA) that is a monoclonal based test (FemtoLab *H. pylori*) was developed. The sensitivity of monoclonal fecal *H. pylori* antigen test was found to be higher than that of the polyclonal test [57, 64].

In different investigations, the sensitivity and specificity of the HpSA test for the diagnosis of *H. pylori* infection were 89.5% and 77.8%, respectively [46], 97.6 and 76.2% [65], 75% and 100% [66], 88.6% and 93.5% [56], 86.21% and 98.18% [67], 96.6% and 94.9% [68], 87.1% and 93.7% [69], and 85% and 93% **[9]**.

The sensitivity and specificity of a monoclonal enzyme immunoassay for the

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

detection of *H. pylori* stool antigen were 91.9% and 70.7%, while those of a polyclonal enzyme immunoassay were 89.4% and 80.5%, respectively [70]. The monoclonal and polyclonal stool tests had 94% and 88% sensitivity, and 100% and 97% specificity, respectively, in the detection of *H. pylori* as compared to the 13C-urea breath test [62].

HpSA is a reliable diagnostic tool for diagnosis of *H. pylori* infection when gastric biopsy is contraindicated [71]. It is a practical and feasible alternative to traditional invasive diagnostic methods.

6.1.2 .The Urea Breath Test (UBT) for Detection of *H. pylori*

UBT is a rapid noninvasive diagnostic procedure applied to identify *H. pylori* infections by swallow a tablet containing urea and then measuring the amount of exhaled carbon dioxide. *H. pylori* produces an enzyme called urease, which breaks down urea into ammonia and carbon dioxide. The 13C-urea breath test (UBT) has become a highly reliable method for the noninvasive diagnosis of *H. pylori* infection [72]. UBT with a 10 minute breath collection is the most reliable non-invasive test for diagnosing *H. pylori* infection [73]. The UBT appears to be an excellent test for diagnosing *H. pylori* infection, with the best sensitivity, followed by serology, stool test, and antibody detection in urine [74]. Capsule UBT has a similar ability to detect *H. pylori* infection compared with conventional UBT and serology; its accuracy was higher than that of the conventional UBT and serology with an accuracy higher than that of conventional UBT and serology (98, 93 and 88%, respectively) [72].

Both the 13C-UBT and the HpSA tests are valuable effective non-invasive methods to detect of *H. pylori* [36, 75]. The overall agreement between UBT and monoclonal HpSA for detection of *H. pylori* was 90.5%, while the agreement between UBT and polyclonal HpSA was 76.9% [70]. The polyclonal HpSA test has a good sensitivity and specificity, but it is less accurate than UBT to establish the presence of *H. pylori* infection [60].

Through the literature, the sensitivity and specificity of the stool antigen test (HpSA) and urea breath test (UBT) were respectively 93.8% and 96.9%, and 90.6% and 99.2% [76], 88.9% and 94.0% and 100% and 98.9% [77], 98.3%, and 98.4%, and 95.0% and 98.4% [75], 93.3% and 98.7% and 93.3% and 95.5% [78], 94% and 81% and 98% and 89% [33], 77%, and 73% and 79%, and 80% [79].

6.1.3. Lateral Flow Immunoassay for Detection of *H. pylori*

H. pylori fecal antigen test using lateral-flow Immunochromatographic assay was found to be more sensitive than the enzyme immunoassays [80]. The immunochromatographic and immunoblot tests are non-invasive, reliable and useful for the diagnosis of *H. pylori* infection [55]. The Lateral flow

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

immunoassay (LFI), specifically the ImmunoCard STAT. HpSA stool antigen method, showed good sensitivity, specificity, and accuracy for diagnosing *H. pylori* infection [**75]**. The accuracy of two immunochromatographic lateral flow methods, the STAT-PAK and RAPIRUN tests, in detecting *H. pylori* antibodies in serum and in urine separately was evaluated by Hu *et al*. [81] who concluded that the urine RAPIRUN test is a faster and more accurate office-based test than the serum STAT-PAK test for detecting the *H. pylori* infection in untreated patients in Taiwan.

The sensitivity of the monoclonal test (ImmunoCard STAT HpSA, Meridian Diagnostics) using immuno-chromatographic lateral flow test was 96.3%, and its specificity was 95.1% [82]. The sensitivity and specificity of a commercially available enzyme-linked immunoassay (Novitec EIA) and a rapid near-patient immunochromatographic lateral flow stool test for the detection of *H. pylori* stool antigen were (82%, 86%) and (84% and 88%, respectively [83]. The sensitivity values of a polyclonal enzyme-linked immunosorbent assay, a monoclonal enzyme-linked immuno-sorbent assay, and a rapid monoclonal immunochromatographic lateral flow test were 74%, 94% and 60%, respectively [84]. The sensitivity and specificity of monoclonal immunochromatographic tests (RAPID Hp StAR) lateral flow test were 73% and 96% to 98%, for ImmunoCard STAT! HpSA 91% and 97%, for monoclonal EIA test (Amplified IDEIA Hp StAR) 73% and 97%, , and for polyclonal EIA test (Premier Platinum HpSA) 91% and 79% and all tests except Premier Platinum HpSA were highly accurate confirming eradication after treatment [**85]**. For the detection of *H. pylori*, the sensitivity and specificity for the Premier Platinum HpSA Plus test, the HP Ag test, the One Step HpSA test, the ImmunoCard Lateral flow test and the *H. pylori* fecal antigen test were as follows: 92.2% and 94.4% , 48.9% and 88.9% , 86.7% and 88.9, 68.9% and 92.6%, and 78.9% and 87%, respectively [86]. The rapid non-invasive Stool Antigen Lateral Flow Immunochromatography assay (HpSA-LFIA) was not accurate enough to be used as the sole test for diagnosing *H. pylori* infection [87].

6.1.4. ELISA for *H. pylori* IgG Antibodies

Serological tests are widely available and can be helpful in screening populations and in confirming the presence of *H. pylori* infection. The simplest and least expensive method is serology, however positive serology does not distinguish between active and chronic infection and is less specific as compared to other methods [10]. IgG ELISA exhibits low specificity and low negative predictive value for diagnosing *H. pylori* infection in patients with gastro-intestinal bleeding due to gastro-duodenal peptic ulcer **[**88]**.** The accuracy of anti *H. pylori* antibodies in serum also limited [47].

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

The urine-based ELISA kit for *H. pylori* immunoglobulin G antibody (urine-HpELISA) is a rapid, inexpensive, reliable, and easy-to-perform method for the diagnosis of *H. pylori* infection. It has a sensitivity of 94.4%, specificity of 96.9%, and an accuracy of 96.0% [89]. The sensitivity and specificity of URINELISA, RAPIRUN and anti *H. pylori* IgG ELISA were as follows: 74.4%, 73.2%, 100% and 81.0%, 78.6%, 35.7%, respectively [90].

6.1.5. Polymerase Chain Reaction (PCR) for Detection of *H. pylori*

PCR has been the most preferred technique of nucleic acid amplification over the years as a result of its high sensitivity [91]. Given the extended period required to culture *H. pylori*, detection would be improved by using PCR either in stool sample or gastric biopsy. The *H. pylori vac*A gene [92] and *ure*A gene specific primers or *H. pylori* 16S ribosomal RNA (rRNA) gene [93] can be used to detect *H. pylori* [18]. The genotyping protocols based on 2 *H pylori* specific biprobe real-time PCR assays using fragments of the *glm*M and the *rec*A genes as target sequences allow for both accurate detection and discrimination of *H. pylori* strains in stool samples [94]. *H. pylori* stool PCR seems to be a satisfactory test for pre-eradication as well as assessment of infection, it is a better indicator than HpSA test in the post-eradication assessment of infection [95].

The sensitivity and specificity of the PCR assay were 65.22% and 75%, respectively [18]. The sensitivity and specificity of stool PCR were 72.5% and 100%, respectively in untreated patients [95]. PCR had 89% sensitivity, and 100% specificity, and91% accuracy compared to HpSA [96]. The sensitivity and specificity of PCR (*ure*A) were 35% and 98%, respectively; HpSA had 67% sensitivity and 99% specificity; and FemtoLab had 90% sensitivity and 96%specificity, as recorded by Zambon *et al*. [73]. The sensitivity and specificity of various tests were as follows: ELISA with monoclonal antibodies 97%, each, ELISA with polyclonal antibodies 92% sensitivity and 93% specificity, one-step monoclonal antibody tests 88% sensitivity and 93% specificity, and PCR 80.8% sensitivity and 98% specificity [64]. The PCR test was negative for *H. pylori* DNA in 44.1% (26/59) and positive in 55.9 %, while *H. pylori* was not visible by histology in 57.6% (34/59) and was visible in 42.4 % [93]. PCR has been determined to be the most sensitive methods; however, the results should be confirmed with at least one of the other method, such as culture, urease test, or HpSA.

6.1.6. Loop- Mediated Isothermal Amplification (LAMP) for *H. pylori* Detection

It is a non-invasive molecular diagnostic test for detecting *H. pylori* in samples. The advantages of LAMP include its simplicity, cost-effectiveness,

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

rapidity, specificity, and the direct use of samples from the site of infection [91]. A novel LAMP-lateral flow dipstick method allows for specific detection of *H. pylori* without cross-reaction with non-*H. pylori* bacteria [97]. LAMP was found to be highly sensitive and rapid for detection of *H. pylori* in fecal specimens [98]. The assay can directly identify the *cag*A of *H. pylori* in the gastric juice of clinical patients with high sensitivity and specificity [99]. A LAMP was developed by Horiuchi *et al*. [98] for detecting the *H. pylori cagA* gene. A LAMP targeted *ureC* of *H. pylori* was evaluated by Yari *et al*. [100] on stool specimens. There are two specific virulence genes (*cagA* and *vacA*) of *H. pylori* that are closely related to the occurrence of gastric cancer, a LAMP assay was established by Wang *et al*. [101] for detecting *H. pylori* and its major virulence genes (*cagA, vacAs1* and *vacAm1*).

By LAMP assay, 123 out of 200 patients were confirmed as *H. pylori* positive using brushing technique samples, whereas only 100 were positive when biopsy samples were analyzed [102]. The prevalence of *ureC* by PCR, *ureC* by LAMP and *16s rRNA* by PCR were 26.67%, 38% and 61.67%, respectively [11]. *H. pylori*-positive fecal samples were detected in 13/20 patients using a novel LAMP-lateral flow dipstick method [97].

The LAMP technique is considered a useful and safe assay for identifying *H. pylori* infection and could be used as an alternative method for *H. pylori* detection.

6.2. Invasive tests for detection of *H. pylori* infection

The gold standard for the diagnosis of *H. pylori* infection requires an endoscopic biopsy of gastric mucosa for histological examination, urease test and culture [17, 43, 51, 55, 95, 103, 104]. The liquid urease test (LUT) is a rapid diagnostic test to demonstrate the presence of *H. pylori* in the endoscopy room with an overall accuracy of 90% compared with other available commercial tests [105]. The confirmatory diagnosis of *H. pylori* is made by endoscopic biopsy, followed by histopathological examination [23].

The most accurate method for detecting *H. pylori* infection is histopathological examination combined with either a urease test or microbial culture [106].

6.2.1. Biopsy-based Tests for Detection of *H. pylori*

Biopsy-based tests include histological examination and the rapid urease test.

6.2.1.1. Histopathology

It is an invasive (direct) method, which requires endoscopy for the examination of the gastric mucosa. Histopathology is routinely performed on gastric biopsies, allowing the evaluation of tissue injury and the classification of

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

the gastric inflammatory mucosal lesions associated with *H. pylori* [10, 39]. Histology was the most costly test compared to other tests [51]. The specificity of histology was higher than of the HpSA test, 13C-urea breath test, and rapid urease test for the diagnosis of *H. pylori* infection [46]. Guo *et al*. [107] concluded that the gold standard upper gastrointestinal endoscopic examination for diagnosis of *H. pylori* had no significant when difference compared to HpSA test.

In different studies, the sensitivity and specificity of histopathology were 100% and 86% [47], 83% and 100% [10], 42.5% and 69.2% [48], 72.5% and 100% [14]; 97.5 and 97.2 [49], respectively. The sensitivity and specificity of phenol red chromo-endoscopy were 90.1% and 88.9%, [71].

Gastric mucosal biopsy is widely used in the detection of *H. pylori* but is associated with several problems including massive bleeding after biopsy and false-negative results due to sampling error [102].

6.2.1.2 Rapid Urease Test (RUT) / Campylobacter Like Organism (CLO) Gel Test

RUT detects the urease enzyme of *H. pylori* in gastric mucosal biopsies using an indicator. The test indicates good sensitivity and specificity for the detection of *H. pylori* [108]. It is a practical, fast, and cost-effective method for diagnosis of *H. pylori* infection and its diagnostic utility is similar to the commercial test available [109]. The overall diagnostic accuracy of RUT was estimated as 98.5% [103].

The dry rapid urease (GUT) test appeared to be a good and reliable alternative for the widely used ClO test in diagnosing *H. pylori* infection as the test can best be read 60 to 120 minutes after endoscopy [110]. The fast agar-based urease (FABU) test is superior to other commercially available urease tests and provides rapid results of *H. pylori* status even before the patient is discharged from endoscopy suite [111].

Using biopsy specimens, the sensitivity and specificity of RUT were respectively recorded in different trials as 96.8% and 100% [42], 100% and 90% [112], 84.8 and 78.5%[40] and 98.2% and 99.0%, [103]. The sensitivity and specificity of the RUT at 4 and 24 hours were 65.45% and 100% while the specificity was 83% and 94% respectively [109]. Sensitivity and specificity of RUT were 23% and 100% after 30 minutes, 57% and 98% after 3 minutes and 81% 94% after 24 hours, respectively [113].

RUT has higher detection rate than histological examination of the biopsy specimens obtained from the margins of gastric ulcer for the diagnosis of *H. pylori* infection [114].

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

7. Antimicrobial Resistance of *H. pylori*

The increased rate of resistance of *H. pylori* to antibiotics, has led to a decreased *H. pylori* eradication rate [20; 115]. Antibacterial activity against *H. pylori* has been reported with amoxicillin, macrolides, tetracyclines, nitroimidazoles and bismuth [34]. One of the main antibiotics used in eradication therapies is the clarithromycin, but clarithromycin-resistant strains have become well-established [30]. The prevalence of clarithromycin resistance among PCR-positive samples was 31% [96]. Resistance of *H. pylori* to clarithromycin, metronidazole, and levofloxacin remains high in most countries [8, 20].

No resistance to amoxicillin was determined [8]. The resistance to amoxicillin and tetracycline remained low [20].

A biopsy culture with antibiotic testing is recommended in combination with histology, due to the development of antibiotic resistances [39]. To control the *H. pylori* diseases antibiotic-based therapy are recommended.

8. Eradication Strategies of *H. pylori*

Various antibiotic plus proton-pump inhibitor (PPI) drug regimens are used to eradicate *H. pylori* infection [116]. PPIs are recommended, because they increase the pH in the stomach, creating conditions that enhance the effectiveness of antibiotics [34]. Clarithromycin, amoxicillin, and a PPI given for 14–21 days were often being considered a first line treatment [117]. Levofloxacin-based or alternative macrolide-containing therapies are also options [21].

Guidelines in Europe, Canada, and the United States for the treatment of *H. pylori* infections recommend bismuth quadruple therapy as first-line treatment and replacing clarithromycin-based triple therapy [115]. A one- or 2-week treatment with PPI and 2 antibiotics (clarithromycin and amoxicillin) is recommended as first-line regimen and in the case of treatment failure, one or 2 weeks of PPI, metronidazole, tetracycline and bismuth is recommended [118, 120].

The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, a bismuth salt and a PPI. In addition, the combination of PPI-amoxicillin-levofloxacin is also a good option for second-line therapy [121].

Gisbert *et al*. [122] recommended a bismuth-containing quadruple regimen as an acceptable third-line strategy and a safe alternative in case of the failure of the above mentioned two eradication protocols with standard clarithromycin- and levofloxacin-containing triple therapies. Quadruple therapy for two weeks with bismuthsubsalicylate, tetracycline, metronidazole and a PPI recommended in case of treatment failure [19].

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

In 2018, WHO listed *H. pylori* as a high priority pathogen for research and development of new drugs and treatments [123]. Plant extracts primarily target urease activity and adhesion to treat *H. pylori*, while probiotics prevented *H. pylori* infection through both immune and non-immune pathways [1]. Probiotics exert a suppressive effect on *H. pylori* infection and may improve the eradication rates [124]. Testing after eradication should not be done until at least four weeks after treatment has ended [19].

Due to the important role of *H. pylori* in gastric ulcer and cancer as well as increasing resistance to antibiotics, vaccine, phytotherapy and probiotics have emerged as alternative novel treatment strategies for *H. pylori* infection.

9. Conclusion

The discovery of new therapeutic drugs, probiotics and vaccine for treatment and eradication of *H. pylori* infections should be focused on urgently. In cases where endoscopy cannot be performed, the HpSA method can be used as a screening test for *H. pylori* diagnosis and treatment monitoring. Although the HpSA test is a useful tool for the evaluation of eradication therapy and a combination of the HpSA test and UBT is clinically recommended, are needed further comparative studies to obtain more reliable evidence of the relative accuracy between these tests.

The available molecular tests are still unreliable. Since LAMP conforms to the criteria set by the World Health Organization, it will continue to be a valuable diagnostic tool in developed and developing countries.

Conflict of interest

The authors declare no conflict of interest.

10. References

1. Liu, M., Gao, H., Miao, J., Zhang, Z., Zheng, L., Li, F., *et al*. *Helicobacter pylori* infection in humans and phytotherapy, probiotics, and emerging therapeutic interventions: a review, Front Microbiol, 2024; 14:1330029.
2. Bangpanwimon, K., Mittraparp-Arthorn, P., Srinitiwarawong, K., & Tansila, N. Non-Invasive Colorimetric Magneto Loop-Mediated Isothermal Amplification (CM-LAMP) Method for *Helicobacter pylori* Detection, J Microbiol Biotechnol, 2021; 31(4):501-509.
3. Yang, X. Relationship between *Helicobacter pylori* and Rosacea: review and discussion, BMC Infect Dis, 2018; 18(1):318.
4. *Kusters, J.G., van Vliet, A.H., & Kuipers, E.J*. Pathogenesis of *Helicobacter pylori* infection, *Clinical Microbiology Reviews, 2006; 19 (3): 449–90*.
5. Alzahrani, S., Lina, T.T., Gonzalez, J., Pinchuk, I.V., Beswick, E.J., & Reyes, V.E. *Effect of Helicobacter pylori on gastric epithelial cells*, World J

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

Gastroenterol, 2014; 20 (36): 12767–80.

6. Moussa, I.M., Jakee, J.E., Beder, M., *et al*. Zoonotic risk and public health hazards of companion animals in the transmission of *Helicobacter* species, Journal of King Saud University – Science, 2021; 33:1-5.
7. Shimada, T., Yoneda, M., Hiraishi, H., & Terano, A. Guidelines in the management of *Helicobacter pylori* infection in Japan--in comparison with the guidelines published in other countries, Nihon Rinsho, 2003; 61 (1): 7-12. Japanese.
8. Cağdaş, U., Otağ, F., Tezcan, S., Sezgin, O., Aslan, G., & Emekdaş, G. Detection of *Helicobacter pylori* and antimicrobial resistance in gastric biopsy specimens. Mikrobiyol Bul, 2012; 46 (3): 398-409.
9. Iranikhah, A., Ghadir, M.R., Sarkeshikian, S., Saneian, H., Heiari, A., & Mahvari, M. Stool antigen tests for the detection of *Helicobacter pylori* in children, Iran J Pediatr, 2013; 23(2):138-42.
10. Taj, Y., Essa, F., Kazmi, S.U., & Abdullah, E. Sensitivity and specificity of various diagnostic tests in the detection of *Helicobacter pylori*, J Coll Physicians Surg Pak, 2003; 13 (2): 90-3.
11. Abiri, R., Bagherabadi, S., Kashef, M., Hasanvand, B., Pajavand, H., *et al*. Detection of *Helicobacter pylori* in Drinking Water by Loop-Mediated Isothermal Amplification, Jundishapur J Microbiol, 2017; 10 (4): e41895.
12. Chang, M.C., Wu, M.S., Wang, H.H., Wang, H.P., & Lin, J.T. *Helicobacter pylori* stool antigen (HpSA) test--a simple, accurate and non-invasive test for detection of *Helicobacter pylori* infection, Hepatogastroenterology, 1999; 46 (25): 299-302.
13. Sharbatdaran, M., Kashifard, M., Shefaee, S., Siadati, S., Jahed, B., & Asgari, S. Comparison of stool antigen test with gastric biopsy for the detection of *Helicobacter pylori* infection, Pak J Med Sci, 2013; 29 (1): 68-71.
14. Kalem, F., Ozdemir, M., & Baysal, B. Investigation of the presence of *Helicobacter pylori* by different methods in patients with dyspeptic complaints, Mikrobiyol Bul, 2010; 44 (1): 29-34.
15. Kim, N., Park, R.Y., Cho, S.I., Lim, S.H., Lee, K.H., Lee, W., *et al*. *Helicobacter pylori* infection and development of gastric cancer in Korea: long-term follow-up, J Clin Gastroenterol, 2008; 42 (5): 448-54.
16. Lin, H.J., L.O., W.C., Perng, C.L., Li, A.F., Tseng, G.Y., Sun, I.C., & Ou, Y.H. *Helicobacter pylori* stool antigen test in patients with bleeding peptic ulcers, Helicobacter, 2004; 9(6):663-8.
17. de Haan, S.N., Kindermann, A., Dahhan, N., & Bosman, D.K. Diagnostic methods for *Helicobacter pylori* infection in children, Ned TijdschrGeneeskd, 2005; 149 (24): 1326-9.

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

18. Sen, N., Yilmaz, O., Simşek, I., Küpelioğlu, A.A., & Ellidokuz, H. Detection of *Helicobacter pylori* DNA by a simple stool PCR method in adult dyspeptic patients, Helicobacter, 2005; 10 (4): 353-9.
19. Bytzer, P., Dahlerup, J.F., Eriksen, J.R., Jarbøl, D.E., Rosenstock, S., & Wildt, S. Danish Society for Gastroenterology. Diagnosis and treatment of *Helicobacter pylori* infection, Dan Med Bull, 2011; 58 (4): C4271.
20. Hu, Y., Zhu, Y., & Lu, N.H. Novel and Effective Therapeutic Regimens for *Helicobacter pylori* in an Era of Increasing Antibiotic Resistance, Front Cell Infect Microbiol, 2017; 7:168.
21. Guevara, B., & Cogdill, A.G. *Helicobacter pylori*: A Review of Current Diagnostic and Management Strategies, Dig Dis Sci, 2020; 65 (7): 1917-1931.
22. Guven, M. A., Ertas, I.E., Coskun, A., & Ciragil, P. Serologic and stool antigen assay of *Helicobacter pylori* infection in hyperemesis gravidarum: which test is useful during early pregnancy, Taiwan J Obstet Gynecol, 2011; 50 (1): 37-41.
23. Best, L. M., Takwoingi, Y., Siddique, S., Selladurai, A., Gandhi, A., Low, B., *et al*. Non-invasive diagnostic tests for *Helicobacter pylori* infection, Cochrane Database Syst Rev, 2018; 3 (3): CD012080
24. Duan, Q., Zhou, M., Zhu, L., & Zhu, G. Flagella and bacterial pathogenicity, J Basic Microbiol, 2013; 53 (1): 1–8.
25. Doohan, D., Rezkitha, Y.A., Waskito, L.A., Yamaoka, Y., & Miftahussurur, M. *Helicobacter pylori* BabA-SabA Key Roles in the Adherence Phase: The Synergic Mechanism for Successful Colonization and Disease Development, Toxins (Basel), 2021; 13 (7): 485.
26. Baj, J., Forma, A., Sitarz, M., Portincasa, P., Garruti, G., Krasowska, D., et al. *Helicobacter pylori* Virulence Factors-Mechanisms of Bacterial Pathogenicity in the Gastric Microenvironment, Cells, 2020; 10 (1): 27.
27. Dumrese, C., Slomianka, L., Ziegler, U., Choi, S.S., Kalia, A., Fulurija, A., et al. The secreted *Helicobacter* cysteine-rich protein A causes adherence of human monocytes and differentiation into a macrophage-like phenotype, FEBS Letters, 2009; 583 (10): 1637–43.
28. Alam, J., Sarkar, A., Karmakar, B.C., Ganguly, M., Paul, S., & Mukhopadhyay, A.K. Novel virulence factor dupA of *Helicobacter pylori* as an important risk determinant for disease manifestation: An overview, World J Gastroenterol, 2020; 26 (32): 4739–4752.
29. Soto, S.M. Role of efflux pumps in the antibiotic resistance of bacteria embedded in a biofilm, Virulence, 2013; 4 (3): 223–9.
30. Cai, Y., Wang, C., Chen, Z., Xu, Z., Li, H., Li, W., et al. Transporters

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

HP0939, HP0497, and HP0471 participate in intrinsic multidrug resistance and biofilm formation in *Helicobacter pylori* by enhancing drug efflux, *Helicobacter*. 2020; 25 (4): e12715.

31. Elshenawi, Y., Hu, S., & Hathroubi, S. Biofilm of *Helicobacter pylori*: Life Cycle, Features, and Treatment Options, Antibiotics, 2023; 12 (8): 1260.
32. Li, P., Zhu, W., Ding, J., & Lei, F. Study of *Helicobacter pylori* infection in patients with chronic atrophic gastritis and its relationship with lifestyle habits and dietary nutrient intake: A retrospective analysis, Medicine (Baltimore), 2024; 103 (2): e36518
33. Frenck, R.W., Fathy, H.M., Sherif, M., Mohran, Z., El Mohammedy, H., Francis, W., *et al*. Sensitivity and specificity of various tests for the diagnosis of *Helicobacter pylori* in Egyptian children, Pediatrics, 2006; 118 (4): e1195-202.
34. Dzieniszewski, J., & Jarosz, M. Guidelines in the medical treatment of *Helicobacter pylori* infection, J Physiol Pharmacol, 2006; 57 Suppl 3:143-54.
35. Gallo, N., Basso, D., Zambon, C.F., Navaglia, F., Di Mario, F., Rugge, M., & Plebani, M. Diagnosis of *Helicobacter pylori* infection: comparison of techniques, Recenti Prog Med, 2001; 92 (5): 332-5.
36. Chang, M.C., Chang, Y.T., Sun, C.T., Wu, M.S., Wang, H.P., & Lin, J.T. Quantitative correlation of *Helicobacter pylori* stool antigen (HpSA) test with 13C-urea breath test (13C-UBT) by the updated Sydney grading system of gastritis, Hepatogastroenterology, 2002; 49 (44): 576-9.
37. Sýkora, J., Valecková, K., Hejda, V., Varvarovská, J., & Stozický, F. Accurate noninvasive diagnosis of *Helicobacter pylori* infection using antigen determination in the feces in the pediatric population, Cas Lek Cesk, 2002; 141 (13):4 25-7. Slovak.
38. Baqai, R., Qureshi, H., Arian, G., & Mehdi, I. Diagnostic efficacy of stool antigen test (HPSA), CLO test and serology for the detection of *Helicobacter pylori* infection J Ayub Med Coll Abbottabad, 2003; 15 (4): 34-6.
39. De Korwin, J.D. Advantages and limitations of diagnostic methods for *H. pylori* infection, Gastroenterol Clin Biol, 2003; 27(3 Pt 2):380-90. French.
40. Aguilar-Soto, O., Majalca-Martńez, C., León-Espinosa, F., Avila-Vargas, G., Sánchez-Medina, R., Figueroa, S.A., et al. Comparative study between rapid urease test, imprint and histopathological study for *Helicobacter pylori* diagnosis, Rev Gastroenterol Mex, 2004; 69(3):136-42. Spanish.
41. Ricci, C., Holton, J., & Vaira, D. Diagnosis of *Helicobacter pylori*: invasive and non-invasive tests, Best Pract Res Clin Gastroenterol, 2007; 21 (2): 299-313.

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

42. Bermejo, F., Boixeda, D., Gisbert, J.P., Defarges, V., Sanz, J.M., Redondo, C., *et al*. Rapid urease test utility for *Helicobacter pylori* infection diagnosis in gastric ulcer disease, Hepatogastroenterology, 2002; 49 (44): 572-5.
43. Wu, H., Zhou, Y., & Huang, Y. Accuracy of gastric nodule combined with rapid urease test prediction in diagnosing *Helicobacter pylori* infection in children, Eur J Clin Microbiol Infect Dis, 2024; doi: 10.1007/s10096-023-04711-9. Epub ahead of print. PMID: 38182925.
44. Monteiro, L., de Mascarel, A., Sarrasqueta, A.M., Bergey, B., Barberis, C., Talby, P., *et al*. Diagnosis of *Helicobacter pylori* infection: noninvasive methods compared to invasive methods and evaluation of two new tests, Am J Gastroenterol, 2001; 96 (2): 353-8.
45. López, T., Quesada, M., Almirall, J., Sanfeliu, I., Segura, F., & Calvet, X. Usefulness of non-invasive tests for diagnosing *Helicobacter pylori* infection in patients undergoing dialysis for chronic renal failure, Helicobacter, 2004; 9 (6): 674-80.
46. Forné, M., Domínguez, J., Fernández-Bañares, F., Lite, J., Esteve, M., Galí, N., *et al*. Accuracy of an enzyme immunoassay for the detection of *Helicobacter pylori* in stool specimens in the diagnosis of infection and post treatment check-up, Am J Gastroenterol, 2000; 95 (9): 2200-5.
47. Aksoy, D.Y., Aybar, M., Ozaslan, E., Kav, T., Engin, D., Ercis, S., *et al*. Evaluation of the *Helicobacter pylori* stool antigen test (HpSA) for the detection of *Helicobacter pylori* infection and comparison with other methods, Hepatogastroenterology, 2003; 50 (52): 1047-9.
48. Gómez, N.A., Alvarez, L.R., Zapatier, J.A., & Vargas, P.E. Efficacy of stool antigen and serologic tests in the diagnosis of *Helicobacter pylori* in Ecuadorian population, Rev Gastroenterol Mex, 2005; 70 (2): 146-50.
49. Al-Humayed, S.M., Ahmed, M.E., Bello, C.S., & Tayyar, M.A. Comparison of 4 laboratory methods for detection of *Helicobacter pylori*, Saudi Med J, 2008; 29 (4): 530-2.
50. Jambi, L.K. Systematic Review and Meta-Analysis on the Sensitivity and Specificity of (13) C/(14)C-Urea Breath Tests in the Diagnosis of *Helicobacter pylori* Infection, Diagnostics, 2022; 12 (10): 2428.
51. Hahn, M., Fennerty, M.B., Corless, C.L., Magaret, N., Lieberman, D.A., & Faigel, D.O. Noninvasive tests as a substitute for histology in the diagnosis of *Helicobacter pylori* infection, GastrointestEndosc, 2000; 52 (1): 20-6.
52. Kato, S., Ozawa, K., Okuda, M., Fujisawa, T., Kagimoto, S., Konno, M., *et al*. Accuracy of the stool antigen test for the diagnosis of childhood *Helicobacter pylori* infection: a

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

multicenter Japanese study, Am J Gastroenterol, 2003; 98 (2): 296-300.

53. Calvet, X., Sánchez-Delgado, J., Montserrat, A., Lario, S., Ramírez-Lázaro, M.J., Quesada, M., *et al*. Accuracy of diagnostic tests for *Helicobacter pylori*: a reappraisal, Clin Infect Dis, 2009; 48 (10): 1385-91.
54. Shimoyama, T., Oyama, T., Matsuzaka, M., Danjo, K., Nakaji, S., & Fukuda, S. Comparison of a stool antigen test and serology for the diagnosis of *Helicobacter pylori* infection in mass survey, Helicobacter, 2009; 14 (2): 87-90.
55. Treepongkaruna, S., Nopchinda, S., Taweewongsounton, A., Atisook, K., Pienvichit, P., Vithayasai, N., et al. A rapid serologic test and immunoblotting for the detection of *Helicobacter pylori* infection in children, J Trop Pediatr, 2006; 52 (4): 267-71.
56. Osoba, A.O., Ibrahim, M.B., Al-Shareef, B.A., Yassen, A.A., & Hussein, B.A. Comparison of *Helicobacter pylori* stool antigen test with CLO test in the diagnosis of *Helicobacter pylori* associated dyspepsia in a Saudi population, Saudi Med J, 2004; 25 (12): 1906-8.
57. Leodolter, A., Peitz, U., Ebert, M.P., Agha-Amiri, K., & Malfertheiner, P. Comparison of two enzyme immunoassays for the assessment of *Helicobacter pylori* status in stool specimens after eradication therapy, Am J Gastroenterol, 2002; 97 (7): 1682-6.
58. Sýkora, J., Valecková, K., Stozický, F., Schwarz, J., & Varvarovská, J. Diagnosis of *Helicobacter pylori* infection in childhood with a novel immunoenzyme method (HpStAR) which detects antigens in feces using monoclonal antibodies, Cas Lek Cesk, 2003; 142 (11): 687-90.
59. Asfeldt, A.M., Løchen, M.L., Straume, B., Steigen, S.E., Florholmen, J., Goll, R., *et al*. Accuracy of a monoclonal antibody-based stool antigen test in the diagnosis of *Helicobacter pylori* infection, Scand J Gastroenterol, 2004; 39 (11): 1073-7.
60. Dore, M.P., Negrini, R., Tadeu, V., Marras, L., Maragkoudakis, E., Nieddu, S., *et al*. Novel monoclonal antibody-based *Helicobacter pylori* stool antigen test, Helicobacter, 2004; 9 (3): 228-32.
61. Manes, G., Zanetti, M.V., Piccirillo, M.M., Lombardi, G., Balzano, A., & Pieramico, O. Accuracy of a new monoclonal stool antigen test in post-eradication assessment of *Helicobacter pylori* infection: comparison with the polyclonal stool antigen test and urea breath test, Dig Liver Dis, 2005; 37 (10): 751-5.
62. Paimela, H.M., Oksala, N.K., Kääriäinen, I.P., Carlson, P.J., Kostiala, A.A., & Sipponen, P.I. Faecal antigen tests in the confirmation of the effect of

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

Helicobacter eradication therapy, Ann Med, 2006; 38 (5): 352-6.

63. Faruqui, A.N., Majid, U., Ahmad, L., Khalil, M., & Hassan, M.U. *Helicobacter pylori* stool antigen test (HpSA) for the diagnosis of gastric infection, J Coll Physicians Surg Pak, 2007; 17 (6): 316-9.
64. Leal, Y.A., Cedillo-Rivera, R., Simón, J.A., Velázquez, J.R., Flores, L.L., & Torres, J. Utility of stool sample-based tests for the diagnosis of *Helicobacter pylori* infection in children, J Pediatr Gastroenterol Nutr, 2011; 52 (6): 718-28.
65. Morales, A., Hurtado, C., Madrid, A.M., Pimentel, C., & Espinosa, M.N. An ELISA stool test to detect *Helicobacter pylori* infection, Rev Med Chil, 2002; 130 (1): 61-5.
66. El-Nasr, M.S., Elibiary, S.A., Bastawi, M.B., Hassan, A., Shahin, Y., Hassan, L., et al. Evaluation of a new enzyme immunoassay for the detection of *Helicobacter pylori* in stool specimens, J Egypt Soc Parasitol, 2003; 33 (3): 905-15.
67. Leszczyńska, K., Jakoniuk, P., & Namiot, Z. The study of the presence of HpSA antigens in the faeces in *Helicobacter pylori* infection, Med DoswMikrobiol, 2007; 59 (1): 51-8.
68. Nguyen ,T.V., Bengtsson, C., Nguyen, G.K., & Granström, M. Evaluation of a novel monoclonal-based antigen-in-stool enzyme immunoassay (Premier Platinum HpSA PLUS) for diagnosis of *Helicobacter pylori* infection in Vietnamese children, Helicobacter, 2008; 13 (4): 269-73.
69. Falaknazi, K., Jalalzadeh, M., & Vafaeimanesh, J. Noninvasive stool antigen assay for screening of *Helicobacter pylori* infection and assessing success of eradication therapy in patients on hemodialysis, Iran J Kidney Dis, 2010; 4 (4): 317-21.
70. Domínguez, J., Forné, M., Blanco, S., Prat, C., Galí, N., Latorre, I., *et al*. Comparison of a monoclonal with a polyclonal antibody-based enzyme immunoassay stool test in diagnosing *Helicobacter pylori* infection before and after eradication therapy, Aliment Pharmacol Ther, 2006; 23 (12): 1735-40.
71. Ibrahim, E.A., Moustafa, M.A., & Monis, W. Comparison between phenol red chromo-endoscopy and a stool rapid immunoassay for the diagnosis of *Helicobacter pylori* in patients with gastritis, J Microsc Ultrastruct, 2015; 3 (4): 175-180.
72. Peng, N.J., Lai, K.H., Lo, G.H., & Hsu, P.I. Comparison of noninvasive diagnostic tests for *Helicobacter pylori* infection, Med Princ Pract, 2009; 18 (1): 57-61.
73. Zambon, C.F., Basso, D., Navaglia, F., Mazza, S., Razetti, M., Fogar, P., *et al*. Non-invasive diagnosis of *Helicobacter pylori* infection: simplified 13C-urea breath test, stool antigen testing, or DNA PCR in human feces in a clinical laboratory setting, Clin Biochem, 2004; 37 (4): 261-7.

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

74. Mégraud, F. European Paediatric Task Force on *Helicobacter pylori*. Comparison of non-invasive tests to detect *Helicobacter pylori* infection in children and adolescents: results of a multicenter European study, J Pediatr, 2005; 146 (2): 198-203.
75. Kato, S., Ozawa, K., Okuda, M., Nakayama, Y., Yoshimura, N., Konno, M., et al. Japan Pediatric *Helicobacter* Study Group. Multicenter comparison of rapid lateral flow stool antigen immunoassay and stool antigen enzyme immunoassay for the diagnosis of *Helicobacter pylori* infection in children, Helicobacter, 2004; 9 (6): 669-73.
76. Vaira, D., Malfertheiner, P., Mégraud, F., Axon, A.T., Deltenre, M., Gasbarrini, G., et al. Noninvasive antigen-based assay for assessing *Helicobacter pylori* eradication: a European multicenter study The European *Helicobacter pylori* HpSA Study Group, Am J Gastroenterol, 2000; 95 (4): 925-9.
77. Konstantopoulos, N., Rüssmann, H., Tasch, C., Sauerwald, T., Demmelmair, H., Autenrieth, I., Koletzko, S. Evaluation of the *Helicobacter pylori* stool antigen test (HpSA) for detection of *Helicobacter pylori* infection in children, Am J Gastroenterol, 2001; 96 (3): 677-83.
78. Dondi, E., Rapa, A., Boldorini, R., Fonio, P., Zanetta, S., & Oderda, G. High accuracy of noninvasive tests to diagnose *Helicobacter pylori* infection in very young children, J Pediatr, 2006; 149 (6): 817-21.
79. Hafeez, A., Bilal, R., Haseeb, H.A., Khan, U.F., Latif, Z., & Hassan, M. Comparison of diagnostic accuracy of non-invasive tests for *Helicobacter pylori* infection in children, J Coll Physicians Surg Pak, 2007; 17 (5): 261-4.
80. Kesli, R., Gokturk, H.S., Erbayrak, M., Karabagli, P., & Terzi, Y. Comparison of the diagnostic values of the 3 different stool antigen tests for the noninvasive diagnosis of *Helicobacter pylori* infection, J Investig Med, 2010; 58 (8): 982-6.
81. Hu, H.M., Kuo, C.H., Lo, Y.C., Wu, M.T., Wu, I.C., Lu, C.Y., et al. Evaluation of the two immunochromatographic methods for detecting urine and serum IgG antibodies to *Helicobacter pylori* and comparison of accuracy and clinical utility, Hepatogastroenterology, 2007; 54 (73): 119-23.
82. Nares-Cisneros, J., Jaramillo-Rodríguez, Y., Martínez-Ordaz, V.A., Velasco-Rodríguez, V.M., Madero, A., Mena-Arias, G., et al. Immunochromatographic monoclonal test for detection of *Helicobacter pylori* antigen in stool is useful in children from high-prevalence developing country, Helicobacter, 2007; 12 (4): 354-8.
83. Kyrlagkitsis, I., Ladas, S.D., Mallass, E.G., Raptis, S., Mentis, A., Delliou, E., *et al*. Evaluation of a conventional ELISA (Novitec) and a near patient

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

immunochromatographic test (Stick H. pyl) for *Helicobacter pylori* antigen detection in stool, Hepatogastroenterology, 2007; 54 (75): 799-802.

84. Gisbert, J.P., Trapero, M., Calvet, X., Mendoza, J., Quesada, M., Güell, M., *et al*. Evaluation of three different tests for the detection of stool antigens to diagnose *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding, Aliment Pharmacol Ther, 2004; 19 (8): 923-9.
85. Quesada, M., Calvet, X., Dosal, A., Calvet, V., Sanfeliu, I., Ribera, L., *et al*. Evaluation of four different fecal tests for determination of cure after *Helicobacter pylori* treatment, J Clin Gastroenterol, 2006; 40 (9): 790-4.
86. Korkmaz, H., Kesli, R., Karabagli, P., & Terzi, Y. Comparison of the diagnostic accuracy of five different stool antigen tests for the diagnosis of *Helicobacter pylori* infection, Helicobacter, 2013; 18 (5): 384-91.
87. Abdelmalek, S., Hamed, W., Nagy, N., Shokry, K., & Abdelrahman, H. Evaluation of the diagnostic performance and the utility of *Helicobacter pylori* stool antigen lateral immunochromatography assay, Heliyon, 2022; 8 (3): e09189.
88. García-Díaz, E., Castro-Fernández, M., Romero-Gómez, M., & Vargas-Romero, J. The effectiveness of (IgG-ELISA) serology as an alternative diagnostic method for detecting *Helicobacter pylori* infection in patients with gastro-intestinal bleeding due to gastro-duodenal ulcer, Rev Esp Enferm Dig, 2002; 94 (12): 725-36.
89. Okuda, M., Nakazawa, T., Booka, M., Miyashiro, E., & Yosikawa, N. Evaluation of a urine antibody test for *Helicobacter pylori* in Japanese children, J Pediatr, 2004; 144 (2): 196-9.
90. Demıray Gürbüz, E., Gönen, C., Bekmen, N., Dölek, D., Soytürk, M., Sağol, Ö., *et al*. The diagnostic accuracy of urine IgG antibody tests for the detection of *Helicobacter pylori* infection in Turkish dyspeptic patients, Turk J Gastroenterol, 2012; 23 (6): 753-8.
91. Agbaje, S. Loop-Mediated Isothermal Amplification: A Rapid Tool for Microbial Diagnosis, Annals of Clinical and Laboratory Research, 2022; 10 (8), 1-5.
92. Vilaichone, R.K., Mahachai, V., Tumwasorn, S., & Kullavanijaya, P. Gastric juice urease test and brushing urease test for *Helicobacter pylori* detection, J Med Assoc Thai, 2002; 85 Suppl 1: S74-8.
93. Yakoob, J., Jafri, N., Jafri, W., Zaman, S., Bian, L.C., Islam, M., *et al*. Polymerase chain reaction in the detection of *Helicobacter pylori* infection, J Coll Physicians Surg Pak, 2004; 14 (3): 153-6.
94. Puz, S., Innerhofer, A., Ramharter, M., Haefner, M., Hirschl, A.M., Kovách, Z., et al. A novel noninvasive genotyping method of *Helicobacter pylori* using stool specimens,

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

Gastroenterology, 2008; 135 (5): 1543-51. Erratum in: Gastroenterology. 2009; 136 (5): 1844.

95. Mishra, S., Singh, V., Rao, G.R., Jain, A.K., Dixit, V.K., Gulati, A.K., & Nath, G. Detection of *Helicobacter pylori* in stool specimens: comparative evaluation of nested PCR and antigen detection, J Infect Dev Ctries, 2008; 2 (3): 206-10.
96. Booka, M., Okuda, M., Shin, K., Miyashiro, E., Hayashi, H., Yamauchi, K., et al. Polymerase chain reaction--restriction fragment length polymorphism analysis of clarithromycin-resistant *Helicobacter pylori* infection in children using stool sample, Helicobacter, 2005; 10 (3): 205-13.
97. Liu, W., Lu, G., Wang, Y., Chen, Z., Gao, Y., Yin, Z., *et al*. A novel loop-mediated isothermal amplification-lateral flow dipstick method for *Helicobacter pylori* detection, Front Microbiol, 2023; 14: 1094600.
98. Horiuchi, S., Nakano, R., Nakano, A., Hishiya, N., Uno, K., Suzuki, Y., *et al*. Development of a loop-mediated isothermal amplification assay for rapid *Helicobacter pylori* detection, Journal of Microbiological Methods, 2019; 163: 105653
99. Zhang, J., Wang, M., Shi, Y., Wang, Q., & Zhao, W. Rapid detection of *Helicobacter pylori* using cytotoxin-associated gene A based on loop-mediated isothermal amplification assay and magnetic nanoparticles Mater, Express, 2020; 10: 283-289.
100. Yari, F., Abiri, R., Aryan, E., Ahmadi Jouybari, T., Navabi, J., & Alvandi, A. Loop-mediated isothermal amplification as a fast noninvasive method of *Helicobacter pylori* diagnosis, J Clin Lab Anal, 2016; 30 (5): 464–470.
101. Wang, B., Gan, Q., Tong, Y., Qiao, Y., Han, M., Zhang, R., *et al*. A visual diagnostic detection of *Helicobacter pylori* and the gastric carcinoma-related virulence genes (*cag*A and *vac*A) by a fluorescent loop-mediated isothermal amplification (LAMP), Talanta, 2023; 256: 124260.
102. Minami, M., Ohta, M., Ohkura, T., Ando, T., Torii, K., Hasegawa, T., & Goto, H. Use of a combination of brushing technique and the loop-mediated isothermal amplification method as a novel, rapid, and safe system for detection of *Helicobacter pylori*, J Clin Microbiol, 2006; 44 (11): 4032-7.
103. Goh, K.L., Cheah, P.L., Navaratnam, P., Chin, S.C., & Xiao, S.D. HUITAI rapid urease test: a new ultra-rapid biopsy urease test for the diagnosis of *Helicobacter pylori* infection, J Dig Dis, 2007; 8 (3): 139-42.
104. Tepes, B. Comparison of two invasive diagnostic tests for *Helicobacter pylori* after antimicrobial therapy, Scand J Gastroenterol, 2007; 42 (3): 330-2.

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

105. Montes, H., Salmen, S., Dolfo, W., Sotolongo, A., Petrosino, P., Donis, J., & Berrueta, L. Evaluation of a liquid urease test (LUT) for detection of *Helicobacter pylori*, Acta Gastroenterol Latinoam, 2003; 33 (2): 73-6.
106. *Logan, R.P., & Walker, M.M*. ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of *Helicobacter pylori* infection, BMJ, 2001; 323 (7318): 920–2.
107. Guo, J.X., Han, J., Chen, L., Xu, J., Liu, J., Zhao, J., *et al*. Evaluation of the *Helicobacter pylori* stool antigen test, Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi, 2011; 25 (6): 495-6. Chinese.
108. Makaju, R.K., Tamang, M.D., Sharma, Y., Sharma, N., Koju, R., Bedi, T.R., & Khanal, S. Comparative study on a homemade rapid urease test with gastric biopsy for diagnosis of *Helicobacter pylori* infection, Nepal Med Coll J, 2006; 8 (2): 97-100.
109. Cifuentes, P., Topor, J., Avagnina, A., Elsner, B., Moore, R., Barberis, C., *et al*. Validation of a rapid urease test for the diagnosis of *Helicobacter pylori* infection, Acta Gastroenterol Latinoam, 2002; 32 (1) :29-34.
110. Van Keeken, N., van Hattum, E., & de Boer, W.A. Validation of a new, commercially available dry rapid urease test for the diagnosis of *Helicobacter pylori* infection in gastric biopsies, Neth J Med, 2006; 64 (9): 329-33.
111. Abdul-Razzak, K.K., Odeh, A.M., & Bani-Hani, K.E. Fast agar-based urease test for detection of *Helicobacter pylori* infection in the stomach, Saudi Med J, 2007; 28 (3): 379-81.
112. Nunthapisud, P., Lertpocasombat, K., Hanvivatvong, O., Tatiyakavee, K., Thong-Ngam, D., Kullavanijaya, P., *et al*. Evaluation of in house rapid urease test for detection of *Helicobacter pylori* from gastric biopsy specimens, J Med Assoc Thai, 2002; 85 Suppl 1: S355-9.
113. Perko, Z., Blazanović, A., Katić, M., Mimica, Z., Cala, Z., & Druzijanić, N. *Helicobacter pylori* in biopsy specimen of gastric mucosa: frequency and correlation of rapid urease test with histology, LijecVjesn, 2002; 124 (6-7): 190-4.
114. Ho, C.Y., Chen, T.S., Chang, F.Y., & Lee, S.D. Rapid urease test from non-ulcer part of stomach is superior to histology from ulcer in detection of *Helicobacter pylori* infection in patients with gastric ulcer, Hepatogastroenterology, 2004; 51 (60): 1877-80.
115. Fallone, C.A., Moss, S.F., & Malfertheiner, P. Reconciliation of Recent *Helicobacter pylori* Treatment Guidelines in a Time of Increasing Resistance to Antibiotics, Gastroenterology, 2019; 157 (1): 44-53.
116. Burkitt, M.D., Duckworth, C.A., Williams, J.M., & Pritchard, D.M. *Helicobacter pylori*-induced gastric

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036

pathology: insights from in vivo and ex vivo models, Disease Models & Mechanisms, 2017; 10 (2): 89–104.

117. Azer SA, Awosika AO, Akhondi H. Gastritis. [Updated 2024 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544250/

118. Kim, N., Kim, J.J., Choe, Y.H., Kim, H.S., Kim, J.I., & Chung, I.S. Diagnosis and treatment guidelines for *Helicobacter pylori* infection in Korea, Korean J Gastroenterol, 2009; 54 (5): 269-78.

119. Park, J.M., & Hahm, K.B. The Korean perspective of *Helicobacter pylori* infection: lessons from the Japanese government's policy to prevent gastric cancer, Dig Dis, 2014; 32 (3): 290-4.

120. Chey, W.D., Leontiadis, G.I., Howden, C.W., & Moss, S.F. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection, Am J Gastroenterol, 2017; 112 (2): 212-239. Erratum in: Am J Gastroenterol. 2018 Jul;113 (7): 1102.

121. Suzuki, H., Nishizawa, T., & Hibi, T *Helicobacter pylori* eradication therapy, Future Microbiol, 2010; 5 (4): 639-48.

122. Gisbert, J.P., Perez-Aisa, A., Rodrigo, L., Molina-Infante, J., Modolell, I., Bermejo, F., et al. *H. pylori* Study Group of the Spanish Gastroenterology Association. Third-line rescue therapy with bismuth-containing quadruple regimen after failure of two treatments (with clarithromycin and levofloxacin) for *H. pylori* infection, Dig Dis Sci, 2014; 59 (2): 383-9.

123. Sukri, A., Hanafiah, A., Patil, S., & Lopes, B.S. The Potential of Alternative Therapies and Vaccine Candidates against *Helicobacter pylori*, Pharmaceuticals (Basel), 2023; 16 (4): 552.

124. Violeta Filip, P., Cuciureanu, D., Sorina Diaconu, L., Maria Vladareanu, A., & Silvia Pop, C. MALT lymphoma: epidemiology, clinical diagnosis and treatment, Journal of Medicine and Life, 2018; 11 (3): 187–193.

Online ISSN: 2537-1045
Print ISSN: 1110-1423
DOI: 10.21608/vmjg.2024.304754.1036