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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

A review of *Helicobacter pylori* diagnosis, treatment, and methods to detect eradication

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Abstract

Helicobacter pylori (*H. pylori*) affects nearly half of the world's population and, thus, is one of the most frequent and persistent bacterial infections worldwide. *H. pylori* is associated with peptic ulcer disease, gastric ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Various diagnostic methods exist to detect infection, and the choice of one method or another depends on several factors, such as accessibility, advantages and disadvantages of each method, cost, and the age of patients. Once *H. pylori* infection is diagnosed, the clinician decides whether treatment is necessity, according to the patient's clinical condition. Typically, eradication of *H. pylori* is recommended for treatment and prevention of the infection. Cure rates with the standard triple therapy are acceptable, and effective quadruple therapies, sequential therapies, and concomitant therapies have been introduced as key alternatives to treat *H. pylori* infection. In this work, we review the main diagnostic methods used to identify *H. pylori* infection and to confirm eradication of infection. In addition, key factors related to treatment are reviewed.

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Key words: Diagnosis; *Helicobacter pylori*; Treatment; Hybrid therapy; Concomitant therapy; Sequential therapy

Core tip: This review focuses on diagnostic methods used to detect *Helicobacter pylori* (*H. pylori*) infection before and after eradication and on treatment regimens for *H. pylori* eradication. In this review, we emphasize the different regimens recommended in relation to differences in antibiotic resistance. Additionally, we review a test-and-treat strategy for and effective quadruple therapies, such as sequential, concomitant, and hybrid therapies. Furthermore, we review the use of probiotics as an additive to help increase *H. pylori* eradication rates.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is the microorganism re-

sponsible for the most frequent and persistent bacterial infection worldwide. *H. pylori* infection affects nearly half of the world's population. In developing countries, the prevalence of infection is as high as 90%, whereas in developed countries, excluding Japan, the prevalence is below 40%[1]. Diagnostic methods to detect *H. pylori* infection are diverse, and the choice of one method or another depends on several factors, such as the availability of diagnostic tests, need to perform an endoscopy, cost, accessibility, advantages and disadvantages of each method, and age of patients.

Triple therapy is the standard treatment for *H. pylori*. Although triple therapy offers acceptable cure rates, quadruple therapies that use various combinations of drugs, sequential therapies, and concomitant therapies have been introduced as effective alternatives for *H. pylori* treatment. In this paper, we review the main diagnostic methods for *H. pylori* infection, according to the principal priorities used by clinicians (*i.e.*, initial diagnosis and confirmation of eradication of infection), and discuss the key factors related to treating *H. pylori*.

DIAGNOSIS OF INFECTION

Several methods are currently available to detect the presence of *H. pylori*, each with its own advantages, disadvantages, and limitations. A classic way to categorize the methods is according to whether or not an endoscopy is necessary. Biopsy-based tests include histological evaluation, culture, polymerase chain reaction (PCR), and the rapid urease test (RUT), all of which are performed on tissue obtained during endoscopy. Alternatively, the urea breath test (UBT), serology, and stool antigen test (SAT) can be performed as non-invasive procedures. A second way to classify these tests is according to whether they are used before or after *H. pylori* eradication treatment. For the purposes of this review, we will classify diagnostic tests in this manner because this classification may be more useful to a clinician.

DIAGNOSTIC TESTS BEFORE TREATMENT OF *H. PYLORI* INFECTION

Invasive methods to detect H. pylori infection

Histology: As the standard method to diagnose *H. pylori* infection, histological examination provides critical information related to the mucosa (*e.g.*, presence and severity of inflammation, intestinal metaplasia, glandular atrophy, dysplasia, and neoplasia). Several studies have recommended that both antrum and corpus biopsies be collected[2-5]. The gold standard for gastric biopsy collection is the updated Sydney classification system, which indicates sampling from 5 biopsy sites. One specimen each should be obtained from the lesser curvature of the corpus about 4 cm proximal to the angulus (Ⅰ), from the lesser (Ⅱ) and greater curvature of the antrum (Ⅲ), both within 2 to 3 cm of the pylorus, from the middle portion of the greater curvature of the corpus, approximately 8 cm from the cardia (Ⅳ), and from the incisura angularis (Ⅴ)[6]. Despite the recommendations, this approach for biopsy collection is scarcely used in daily practice because of the large number of biopsies suggested. Endoscopy is an uncomfortable and time-consuming procedure. However, the analysis of fewer biopsy samples than recommended can lead to an underestimation of the presence of *H. pylori,* sampling error, and false negatives.

To detect *H. pylori* in biopsy samples, a routine hematoxylin and eosin (HE) stain is usually sufficient. When the results of this stain are inconclusive, special stains, such as Warthin-Starry, Giemsa, toluidine blue, acridine orange, McMullen, Genta, Dieterle, and Romanouski stains, or immunochemical methods can be used. Present guidelines suggest that at least 2 different stain techniques be used on biopsied tissue: HE to evaluate inflammatory cells, and Giemsa or Genta stain to detect *H. pylori*. Although the Genta stain is able to visualize both inflammatory cells and *H. pylori* by combining a silver stain, HE, and Alcian blue, it is technically complex. In contrast, the Giemsa stain is technically simple, highly sensitive, and inexpensive. Thus, the Giemsa stain is the preferred method in clinical practice. All other methods are used specifically for research proposes[7-10].

Histology has a few limitations. The tissue changes are assessed subjectively, which results in an interobserver variation in scoring for the evaluated parameters. Also, an endoscopy is needed to obtain the tissue samples for histology. Due to the patchy distribution of *H. pylori* in the gastric mucosa, tissue specimens should be obtained from different areas of the stomach. The sensitivity and specificity of histology for *H. pylori* diagnosis vary from 53% to 90%, depending on the pathologist's experience and density of colonization. Increasing the number of biopsies and employing specific stains can increase the sensitivity of histology[11].

In a histological section, *H. pylori* appear as a curved or spiral bacillus on the epithelial surface, in the mucus layer, and within gastric glands. Other *Helicobacter* species, such as *Helicobacter heilmanii* (*H. heilmanii*), are also detected in the human stomach. *H. heilmanii*, a zoonotic infection in humans that can be acquired from cats or dogs and can cause chronic gastritis, is present in about 0.1% of gastric biopsies. *H. heilmanii* is straight and much longer than *H. pylori;* thus, the two species can be easily distinguished[12].

Histopathologic studies are practiced less often in children because of the need to perform an endoscopy. A recent study that included an analysis of histopathologic lesions in 96 Brazilian children with *H. pylori* infection showed that *H. pylori* was identified in 51.8% of children[13]. Moderate to severe chronic active gastritis was present in the antrum (70.5%) and the corpus (45.2%), with more severe gastritis observed in the antrum than in the corpus ($P < 0.05$). The topographic distribution of inflammation was pangastritis (61.9%), followed by antral (32.1%) and corpus (5.9%). *H. pylori* density was higher in the antrum than in the corpus.

Fluorescent *in situ* hybridization (FISH) is a new method used on histological preparations that allows detection of a specific bacterial factor or feature, such as clarithromycin resistance, in addition to *H. pylori*[14,15]. FISH uses a set of fluorescent protein-labeled oligonucleotide probes that target a specific gene; common probes used are the 16S and 23S ribosomal RNA genes. It takes about 3 hours to perform this assay and probe for both for *H. pylori* and clarithromycin resistance. The ability to assess both probes in a short time adds value to the diagnosis of *H. pylori*. *In situ* hybridization and immunochemical methods have been used to detect the precise location of the bacteria in the gastric mucosa[16]. Despite the advantages of FISH is laborious, expensive, and not used in clinical practice.

Culture: A recently obtained gastric biopsy specimen is the ideal specimen for culturing *H. pylori* because no notable amount of commensal bacterial flora is expected (except in patients with reduced gastric acid production, in whom an overabundance of commensal bacteria is possible). Procedures that are less invasive than biopsy collection include gastric juice sampling or the string test. Specimens from gastric juice samples or the string test can also be used for culture; however, the sensitivity is lower than when biopsy specimens are used[17-19].

Culturing typically has a sensitivity greater than 90% and a specificity of 100% when performed under optimal conditions[20]. However, lower sensitivity values have been reported (85.4%) with a confirmed 100% specificity[21], and a culture sensitivity of 40.0% was reported in bleeding patients[22]. In patients with atrophy, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy for culture were 96%, 100%, 100%, 80%, and 97%, respectively[23]. In a pediatric population, sensitivity and specificity values of 95.8% and 96.4%, respectively, have been reported[24].

H. pylori is very delicate and needs to be cultured as soon as possible after sampling. Biopsies can be kept in a transport medium (*e.g.*, Stuart's transport medium) for up to 24 h at 4 ℃. Once isolated, *H. pylori* can be stored frozen at -80 ℃, preferably in broth with 15% to 20% glycerol. Several types of medium can be used for *H. pylori* culture, including selective agars (*e.g.*, Pylori-agar, Skirrow agar, Wang media, and others), which contain specific antibiotics to inhibit commensal bacteria, and nonselective agars (*e.g.*, blood agar, Columbia blood agar, and others). Cultures should be incubated under microaerobic conditions (85% N_2, 10% CO_2, 5% O_2) at 35 to 37 ℃ for at least 7 d before discarding cultures as negative. Positive identification of *H. pylori* is based on morphological characteristics and positive catalase, oxidase, and urease reactions[25].

Culturing is the most specific method for detecting *H. pylori*, although the results depend on the microbiologist's experience, specimen quality, and use of transport media[26]. For many years, the role of culturing *H. pylori* to diagnose infection was limited to research and epidemiologic studies. In clinical practice, culturing has mainly been used to confirm the antibiotic sensitivity of *H. pylori* after 2 treatment failures in patients. It is generally not considered a routine diagnostic method and is not available in most medical institutions worldwide. Yet, given the increase in antibiotic resistance rates, especially to clarithromycin and metronidazole, it would be desirable for more laboratories to be able to perform the culture and susceptibility test before 2 treatment failures have occurred.

Considering the increasing failure rate of standard therapies, bacterial culture may be an indispensable method for surveying antibiotic resistance in populations and managing antibiotic failure. A recent report described high antibiotic resistance rates in a pediatric population of Brazilian children and adolescents[27]. This study analyzed 77 *H. pylori* clinical isolates obtained from patients without previous eradication treatment for *H. pylori* infection, and 6 strains from patients in whom previous eradication treatment had failed. The study reported a global resistance rate of 49.3%, with 40% of strains resistant to metronidazole and 19.5% to clarithromycin. Another study of 61 *H. pylori* strains isolated from Japanese children[28] found overall resistance rates against clarithromycin, amoxicillin, and metronidazole of 36.1%, 0%, and 14.8%, respectively.

Polymerase chain reaction: PCR allows researchers and clinicians to identify *H. pylori* in small samples that have few bacteria present. It does not require any special processing supplies or transportation, and it can be performed on samples obtained by both invasive and noninvasive methods. Moreover, PCR can be performed faster than many other diagnostic methods, used to identify diverse bacterial genotypes, and employed in epidemiological studies. A considerable drawback of PCR is that it can detect DNA segments of dead bacterium in the gastric mucosa of patients after treatment; consequently, it can produce false-positive results[19,29,30]. Molecular detection of *H. pylori* using PCR is possible in materials obtained by non- or minimally invasive procedures, such as gastric juice, gastric content, saliva, stools, *etc*. Thus, molecular methods can be easily applied to specimens obtained by string tests or orogastric brushes. Molecular testing may be of particular value for samples that can no longer be successfully cultured because of prolonged transport or in cases where isolation of *H. pylori* is not feasible as a result of contamination.

In gastric biopsy specimens, molecular methods such as PCR have proved their worth in detecting pathogens and testing for clarithromycin resistance, which is attributable to mutations in the 23S rRNA gene[31]. Because of the increasing prevalence of antibiotic resistance in some populations with a high prevalence of *H. pylori*, molecular tests may have important implications as relevant alternatives for *H. pylori* diagnosis. In other Gram-negative species, efflux pumps have an important role in resistance to antibiotics, and options for treating some infections

caused by multidrug-resistant bacteria are limited[32].

Rapid urease test: The RUT utilizes the ability of *H. pylori* to produce large quantities of urea as the basis for diagnosing infection. Biopsies obtained during endoscopy are placed in a medium containing urea and a pH indicator. If urease is present, the urea is broken down into carbon dioxide and ammonia, which increases the pH of the medium and causes a subsequent color change in the pH indicator. The RUT produces a result in a range of minutes up to 24 h, depending on the number of bacteria in the biopsy. The RUT is inexpensive, rapid, widely available, and highly specific.

Although some members of the microbiota in the oropharynx produce urease that is swallowed in the saliva, this weaker enzyme is denatured rapidly because of the high acidity of the stomach. However, there is a high possibility of false-negative results with RUT due to decreased urease activity, which could be caused by a recent intake of antibiotics, bismuth compounds, or proton pump inhibitors (PPIs)[33]. A false-negative urease test can also be obtained in patients with achlorhydria. The RUT sensitivity is affected by the amount of bacteria in the biopsy; at least 10000 cells are required for a positive result.

Low sensitivity and specificity of the RUT have been reported in the presence of blood. The RUT specificity decreases (and, thus, the risk of a false positive increases) with increasing incubation time. When results from RUTs performed on individual gastric antrum and corpus tissue specimens and on combined specimens were compared to histology results (as the gold standard), combining the tissues increased *H. pylori* detection from 64% in separate specimens to 69.2%[34]. Commercial RUTs have specificities above 95% to 100%, but their sensitivity is slightly less (approximately 85%-95%). Commercially available RUTs include gel- (CLOtest, HpFast) and paper-based tests (PyloriTek, ProntoDry HpOne)[35,36].

Noninvasive methods to detect an infection

Serology: Several types of tests have been used to identify antibodies against *H. pylori*. The enzyme immunoassay (EIA) test has been the most prevalently used. Most commercial EIA tests are based on detecting IgG, with sensitivity and specificity values ranging from 60% to 100%. Critical factors important in evaluating the quality of serology tests for the detection of active *H. pylori* infection include the prevalence of infection, variations in geography, and characteristics of the study populations. Local validation of a serology test is necessary, and it is imperative to make adjustments to cut-off levels for specific populations. In general, tests containing complex antigen mixtures of various strains show the highest sensitivity[37].

Numerous characteristics should be considered when determining whether a serology test should be used as the method of choice. In particular, a serology test should be considered in patients with a recent use of antibiotics or PPIs, bleeding ulcers, or gastric atrophy[38]. Neither office-based whole-blood tests nor antibody detection in urine or saliva show similar reliability to laboratory-based tests, and they are not recommended to diagnose *H. pylori* infection[38].

Serology tests are relatively cheap and readily available. Indeed, the accessibility of these tests can result in their use by laboratories that are inexperienced in *H. pylori* diagnosis, which can result in misinterpretation of the data. Another drawback is the prolonged existence of antibodies in the host even after eradication therapy[39]. As a result, there can be a considerable amount of time between the administration of eradication therapy and the confirmation of a significant decline in antibody titers. This situation limits the utility of serology in confirming the eradication of infection. In contrast, serology results are not affected by recent antibiotic or PPI treatment. In general, the serology test is very good at correctly identifying patients with a negative result[40] and is a good alternative to the UBT test.

Serology has been used both for the detection of the whole bacterial cell and of specific *H. pylori* proteins. Not all *H. pylori*-infected subjects develop disease, and the wide spectrum of diseases associated with *H. pylori* infection may depend on the heterogeneity of *H. pylori* strains[41]. Between-strain heterogeneity can be due to the presence or absence of virulence factors, some of which have been used as serological markers. These factors include the *cagA* and *vacA* genes, which have been linked to increased pathogenicity of *H. pylori*.

The *cagA* gene encodes a 120- to 140-kDa protein, CagA[42]. Strains expressing the CagA protein induce more severe inflammation, a higher degree of gastric atrophy, and a higher incidence of duodenal ulcer and gastric adenocarcinoma of the intestinal type[43]. The *vacA* gene is present in all *H. pylori* strains; however, it is only expressed in 50% to 65% of strains. The *vacA* gene encodes an 81- to 91-kDa protein, VacA, which provokes vacuole formation in gastric epithelial cells[42]. Both proteins, CagA and VacA, are immunogenic, and serologic assays have been developed to diagnose *H. pylori* infection and the seroprevalence of virulence factors[44-46]. Recently, six highly immunogenic virulence factors, CagA, VacA, GroEL, gGT, HcpC, and UreA, were expressed in *Escherichia coli*, purified, and immobilized on nitrocellulose membranes to detect serologic immune responses against these virulence factors in the patient's sera. This new assay demonstrated sensitivity and specificity values of 97.6% and 96.2%, respectively[47].

TESTS USED TO DETECT THE ERADICATION OF INFECTION

Urea breath test

The UBT is based on the ability of *H. pylori*, if present in the gastric environment, to break down orally absorbed ^{13}C- or ^{14}C-labeled urea into CO_2 and ammonia. $^{13}CO_2$ or $^{14}CO_2$ diffuses into the blood, is exhaled via the lungs, and can be measured in the exhaled air. The test is easy

to perform and does not require endoscopy. ^{13}C is a non-radioactive innocuous isotope, and it can be safely used in children and women of childbearing age. An isotope ratio mass spectrometer is generally used to measure ^{13}C in breath samples; however, the machine is expensive[48]. In contrast, ^{14}C-urea is inexpensive but requires the use of a nuclear medicine department licensed for storage and disposal of radioactive reagents[49,50].

The sensitivity and specificity of the UBT exceed 90% in most studies[51]. The excellent sensitivity of the UBT, especially after eradication therapy, may be explained by the fact that the UBT is more likely to produce positive results than biopsy-based tests in cases of moderate colonization or patchy distribution of *H. pylori*. False-positive results due to other urease-forming pathogens are rare. In contrast to serology, the UBT may produce false-negative results if performed after the use of *H. pylori*- and urease-suppressive therapies, such as PPIs and antibiotics. Thus, if the patient has recently ingested PPIs, antibiotics, or bismuth compounds, the UBT may have limited value[50]. Corpus-predominant gastritis can also produce false-negative ^{13}C-UBT results. Misdiagnosis of corpus-predominant gastritis could lead to a major misassessment of patients that need endoscopy and/or eradication therapy[52].

Post-treatment UBT is usually performed 4 to 6 wk after eradication therapy[53]. A recent meta-analysis showed that the ^{13}C-UBT assay was accurate across all ages. The authors demonstrated a sensitivity of 95.9%, specificity of 95.7%, Likelihood-ratio ratio (LR)+ 17.4, LR- 0.06, and diagnostic odds ratio (OR) of 424.9. The ^{13}C-UBT had a high accuracy in children older than 6 years, with a sensitivity of 96.6%, specificity of 97.7%, LR+ 42.6, LR- 0.04, and diagnostic OR of 1042.7. In this study, they observed a greater variability in accuracy in children under 6 years old, with the test demonstrating a sensitivity of 95%, specificity of 93.5%, LR+ 11.7, LR- 0.12, and diagnostic OR of 224.8[54].

Stool antigen test

The SAT uses an enzyme immunoassay to detect the presence of antigens against *H. pylori* in stool samples. It is a reliable method to diagnose an active infection and to confirm an effective treatment of infection. Stool samples may be stored for 24 h at room temperature or 72 h at 4 ℃. Without refrigeration, the SAT suffers a significant reduction of sensitivity within 2 to 3 d[55]. Results of the SAT may be affected by disorders of the digestive tract, PPI treatment, or the presence of a bleeding ulcer.

The diagnostic accuracy of the SAT in detecting eradication of *H. pylori* infection has been evaluated. A recent study compared the ability of 2 SAT methods, the enzyme immunoassay (Premier Platinum HpSA) and immunochromatographic method (ImmunoCard HpSA STAT), to detect *H. pylori* after eradication therapy in dyspeptic patients. The sensitivity, specificity, PPV, NPV, and accuracy were 100%, 91.0%, 84.6%, 100%, and 94.0%, respectively, for ImmunoCard HpSA STAT, and 84.9%, 92.5%, 84.8%, 92.5%, and 90.0%, respectively, for Premier Platinum HpSA. Another study evaluated 5 SATs, including 2 monoclonal EIAs and 3 rapid immunochromatographic assay tests, for their ability to diagnose *H. pylori* infection in adult patients with dyspeptic symptoms before eradication therapy. For the 2 EIAs, the sensitivity and specificity were 92.2% and 94.4%, respectively, for the Premier Platinum HpSA Plus test, and 48.9% and 88.9%, respectively, for the *H. pylori* antigen test. For the 3 rapid immunochromatographic assays, the sensitivity and specificity were 86.7% and 88.9%, respectively, for the One Step HpSA test; 68.9% and 92.6%, respectively, for the ImmunoCard STAT HpSA test; and 78.9% and 87%, respectively, for the *H. pylori* fecal antigen test. The Premier Platinum HpSA Plus EIA test was the most accurate test to diagnose *H. pylori* infection in adult dyspeptic patients[56].

The sensitivity and specificity of the SAT vary in different clinical settings, and whether the test is given pre- or post-treatment[57,58]. In untreated patients, detection of *H. pylori* infection by the SAT is comparable to the UBT. However, posteradication, especially in populations with low *H. pylori* prevalence, the performance of the UBT is superior to the SAT.

The first SAT introduced was the polyclonal SAT (Premier Platinum HpSA, Meridian Bioscience Inc., OH, United States). This test was followed by a monoclonal test (Femtolab *H. pylori*, Connex, Germany), which is better than the polyclonal test in both testing untreated patients and following up with treated patients[59-61].

The superiority of the monoclonal SAT compared to the polyclonal test, both for early diagnosis of infection and for validation of *H. pylori's* eradication following treatment, has been reported[57]. According to European Guidelines, the monoclonal test and UBT are the only 2 noninvasive tests recommended for detecting the success or failure of eradication treatment.

Detection of *H. pylori* antigen in stool using a monoclonal enzyme-linked immunosorbent assay is one of the most efficient non-invasive tests for diagnosis of infection in children[62]. The *H. pylori* SAT seems to perform well in children, independent of the child's age[63-65]. An analysis of 20 studies of the SAT in a total of 2789 patients before they received treatment for *H. pylori* revealed values for sensitivity, specificity, PPV, and NPV of 90%, 96%, 93%, and 93%, respectively. In 8 studies examining a total of 307 children, encouraging results were achieved for the confirmation of *H. pylori* eradication after therapy using the SAT, with a sensitivity of 97%, specificity of 97%, PPV of 88%, and NPV of 99%[66].

TREATMENT OF *H. PYLORI* INFECTION

Since the discovery of *H. pylori* in 1983, this Gram-negative microaerophilic spiral bacillus has been studied extensively. It currently infects more than 50% of the world's population, and in the last decade, it has been recognized as a major human pathogen[67]. Today, the

involvement of *H. pylori* in active chronic gastritis, its association with gastroduodenal ulcer, and its well-accepted role as a risk factor for the development of gastric cancer are well documented[68].

There are many schemes for treating *H. pylori* infection; however, an optimal treatment has not been defined, and there is not a single antibiotic treatment that can eradicate it. Historically, a combination of various antibiotics has been used to eradicate the infection. The antibiotics used include clarithromycin, amoxicillin, metronidazole, tetracycline, fluoroquinolones, tinidazole, and others. These antibiotics are often used in combination with antisecretory agents, such as PPIs, or with bismuth salts. Various combinations of these agents have shown to be effective with different efficacy rates of eradication and tolerability.

The effectiveness of the most commonly used therapies has been increasingly compromised by the rapid emergence of antibiotic-resistant strains of *H. pylori* and by poor adherence to treatment by patients. These factors have reduced the effectiveness of treatment to unacceptable levels ($\leqslant$ 80%) in many geographic areas. Consequently, new treatment strategies have recently been validated and used to replace the standard triple therapy. These approaches have especially been used in areas with a high resistance to clarithromycin, which is a major risk factor for failure of treatment regimens[69]. Resistance to amoxicillin has remained relatively stable, while resistance rates to metronidazole and clarithromycin have been steadily increasing[70-74]. The prevalence of antibiotic resistance varies considerably by region and is related to the use of antibiotics, such as clarithromycin and metronidazole, for respiratory or gastrointestinal infections.

One of the first strategies developed for the treatment of *H. pylori* infection was the test-and-treat strategy. This therapy is recommended for patients younger than 45 years old that have persistent dyspepsia, peptic ulcer disease, low-grade MALT, and atrophic gastritis. The test-and-treat strategy is based on determining the existence of *H. pylori* and eradicating it when detected. An alternative to the test-and-treat strategy is desirable in dyspeptic patients that live in populations with a moderate-to-high prevalence of *H. pylori* infection ($\geqslant$ 10% to 20%), whereas the empirical PPI strategy may be preferable in populations with a low prevalence of *H. pylori* infection[75-77]. The test-and-treat strategy must be carefully used in populations with a low prevalence of *H. pylori* because diagnostic tests are less accurate in these populations[78]. Only a small proportion of patients that have functional dyspepsia experience long-term improvement in their symptoms after elimination of *H. pylori*[79-81].

It is currently recommended to split first-line empiric therapy into two large groups: populations with low and with high resistance to clarithromycin. For these groups, the acceptable resistance levels are set as < 15% to 20%[77]. The following information lists current recommendations and therapies available for the eradication of *H. pylori*. They are mentioned as first-, second-, and third-line treatments, according to clarithromycin resistance.

First-line treatment in areas with low clarithromycin resistance

The most frequently used strategy is triple therapy. This therapy is composed of a PPI (lansoprazole 30 mg/12 h, omeprazole 20 mg/12 h, pantoprazole 40 mg/12 h, rabeprazole 20 mg/12 h, or esomeprazole 40 mg/24 h), clarithromycin (500 mg/12 h), and amoxicillin (1 g/12 h), taken for 7 to 14 d. The duration of therapy is controversial, although a meta-analysis suggested that 14 d provides eradication rates 5% higher than those for 7 d. In cases of allergy to penicillin, metronidazole is an option to replace amoxicillin, as it is equally effective and considered equivalent[82].

There are several explanations for why clarithromycin susceptibility reduces the success rate of therapy. These explanations include a poor adherence to the drug regimen by the patient, gastric acidity, concentration of bacterial strains, bacterial mutations, and resistance to clarithromycin. There is also significant variability in these numbers. For example, in the Netherlands, where resistance to clarithromycin is not prevalent, it is between 1% and 5%[77].

The efficacy rates of triple therapy have shown to depend on PPIs; thus, various strategies, such as increasing the dose of PPIs and increasing the length of treatment, have been attempted to improve the success of triple therapy. A meta-analysis demonstrated an increase in the eradication rate from 6% to 10% compared with standard doses of PPI. The subanalysis specifically mentioned that a double dose of esomeprazole showed a greater beneficial effect. The presence of various polymorphisms in the host's metabolism can alter the effectiveness of PPIs, since PPI function depends on the cytochrome (CYP) 450 2C19 and MDR polymorphisms. A recent meta-analysis showed that hosts who are extensive PPI metabolizers (depending on CYP2C19 status) had lower cure rates. Furthermore, a lower cure rate was obtained with the MDR T/T genotype compared with the T/C and C/C genotypes[83].

In addition to the standard treatment for *H. pylori* infection, an adjuvant therapy is sometimes used. For example, lactoferrin has been used as adjuvant therapy. Two meta-analyses that examined the use of lactoferrin showed a decrease in the adverse effects of standard treatment[84,85], although the latest consensus of Maastricht (IV) mentions that more evidence and better designed studies are required[77] before definitive conclusions can be drawn. Another adjuvant that has been used is *Saccharomyces boulardii,* and some studies have shown encouraging results[86].

First-line treatment in areas with high clarithromycin resistance

Quadruple therapy: In areas that have high resistance to clarithromycin, a quadruple therapy can be used. This therapy includes a combination of a PPI, bismuth sub-

salicylate (525 mg, × 4 daily), and 2 antibiotics, metronidazole (250 mg × 4 daily) and tetracycline (500 mg, × 4 daily), for 10 to 14 d. This regimen is well tolerated, and patients tend to adhere to the schedule; however, this therapy is not available in all areas. It is recommended that doctors have other alternatives in mind, such as sequential therapy or quadruple therapy without bismuth[77].

Sequential therapy: Sequential therapy was proposed by a group of Italian researchers. It involves the combination of a PPI and amoxicillin (1 g, × 2 daily) for 5 d, followed by a PPI and tinidazole clarithromycin/metronidazole (500 mg, × 2 daily) for 5 d. Most studies have shown that sequential therapy and bismuth-based quadruple therapy have equivalent success in first-line therapy[82]. Sequential therapy was evaluated in a pediatric population with iron deficiency[87]. Children aged 12 to 15 years with an active *H. pylori* infection were evaluated for serum ferritin, and then were randomized into 2 groups to receive either standard or sequential eradication therapy. Six weeks after completing the therapy, eradication was detected by the UBT, and serum ferritin levels were measured. *H. pylori* eradication rates after either sequential or standard therapy were different; however, the serum ferritin levels were not significantly different between the two therapy groups or between the same group before and after treatment.

A recent meta-analysis evaluated *H. pylori* eradication rates in children after sequential therapy compared to triple therapy. This analysis included 857 children aged 3 to 18 years who met the inclusion criteria. Of the 409 patients who received sequential therapy, 318 (78%, 95%CI: 73%-82%) were cleared of the infection, compared with 314 of the 444 patients (71%, 95%CI: 66%-75%) who received standard triple therapy (RR = 1.14, 95%CI: 1.06-1.23). The authors concluded that sequential therapy is superior to 7-d standard triple therapy, but is not significantly better than 10- or 14-d triple therapy. Furthermore, they found no significant differences in the risk of adverse effects between groups that received different treatments.

Concomitant therapy: Concomitant therapy is used instead of sequential therapy in areas where the resistance to clarithromycin is greater than 20% and bismuth-based quadruple therapy is not available. Concomitant therapy involves the simultaneous administration of 3 antibiotics (metronidazole, clarithromycin, and amoxicillin) and a PPI for 10 d. This therapy is effective and well tolerated compared to conventional triple therapy[88].

A recent controlled trial compared concomitant therapy with triple therapy in Greece, where there is a high resistance to clarithromycin (25%) and metronidazole (40%). Concomitant therapy had an eradication rate of 90%, whereas triple therapy only had an eradication rate of 73.8%[89]. Unfortunately, the adverse effects of concomitant therapy were high, as 30.9% of subjects reported at least one adverse effect. However, the adverse effects were mild, and patients were able to complete their treatment despite them[90]. Another study analyzed a concomitant treatment with PPI, amoxicillin, rifabutin, and ciprofloxacin, and they observed *H. pylori* eradication rates of 95.2%. In patients with a penicillin allergy, the amoxicillin was replaced by bismuth with no significant effect on the eradication rate (94.2%)[91].

A clinical trial specifically compared concomitant and sequential therapies and found no difference in *H. pylori* eradication rates after treatment with these therapies. This clinical trial included *H. pylori*-infected patients from 11 Spanish hospitals. Patients were randomized to receive either sequential or concomitant therapy. Sequential therapy included omeprazole (20 mg/12 h) and amoxicillin (1 g/12 h) for 5 d, followed by 5 d of omeprazole (20 mg/12 h), clarithromycin (500 mg/12 h) and metronidazole (500 mg/12 h). Concomitant treatment included the same drugs, but the drugs were taken concomitantly for 10 d. Four weeks after treatment ended, *H. pylori* eradication was confirmed with ^{13}C-UBT or histology. The concomitant and sequential eradication rates were 87% and 81%, respectively, by intention-to-treat (P = 0.15) and 91% and 86%, respectively, per protocol (P = 0.131) They concluded that there was no significant advantage of concomitant over sequential therapy[92].

A second study that compared sequential and concomitant therapies included 164 patients infected with *H. pylori*. Patients received either 14 d of sequential (n = 86) or concomitant (n = 78) therapies. Patients in the sequential therapy group received rabeprazole (20 mg) and amoxicillin (1 g) in the first week, followed by rabeprazole (20 mg), clarithromycin (500 mg), and metronidazole (500 mg) in the second week. Patients in the concomitant therapy group received rabeprazole (20 mg), amoxicillin (1 g), clarithromycin (500 mg), and metronidazole (500 mg) for 2 wk. Four weeks after completion of treatment, *H. pylori* eradication was confirmed by ^{13}C-UBT. The intention-to-treat and per protocol eradication rates were 75.6% (95%CI: 66.3%-84.9%) and 76.8% (95%CI: 67.1%-85.5%) in the sequential therapy group, and 80.8% (95%CI: 71.8%-88.5%) and 81.3% (95%CI: 71.6%-90.7%) in the concomitant therapy group, respectively. The researchers concluded that the 2-wk concomitant and sequential therapies showed suboptimal efficacies. Furthermore, in this study, there were no significant differences between the two therapies with regard to the eradication rates, compliance, or side effects.

Hybrid therapy: Hybrid therapy is a recently reported therapy that consists of 2 steps: (1) treatment with a PPI and amoxicillin (1 g/12 h) for 7 d, followed by (2) a PPI and 3 antibiotics, amoxicillin (1 g/12 h), metronidazole (500 mg/12 h), and clarithromycin (500 mg/12 h), for 7 d. In a study comparing hybrid and sequential therapies, the eradication rates were 89.5% and 76.7% (P = 0.001), respectively. Similar severe adverse effects were observed in patients in both treatment groups. Specifically, 2.4% of patients in the hybrid therapy group and 3.8% of pa-

tients in the sequential therapy group reported adverse effects[93].

A recent study included non-ulcer dyspepsia patients that were infected with *H. pylori* and compared concomitant, sequential, and hybrid therapies[94]. Patients were randomized to receive one of the following 3 treatments: (1) concomitant therapy with omeprazole (20 mg), amoxicillin (1 g), clarithromycin (500 mg), and tinidazole (500 mg) for 5 d; (2) sequential therapy with omeprazole (20 mg) and amoxicillin (1 g) for 5 d, followed by omeprazole (20 mg), clarithromycin (500 mg), and tinidazole (500 mg) for 5 d; or (3) hybrid therapy with omeprazole (20 mg) and amoxicillin (1 g) for 7 d, followed by omeprazole (20 mg), amoxicillin (1 g), clarithromycin (500 mg), and tinidazole (500 mg) for 7 d. ^{13}C-UBT was used to detect *H. pylori* eradication 6 wk after treatment. In this study, the intention-to-treat and per protocol analyses revealed eradication rates of 85.5% and 91.6%, respectively, with the concomitant therapy regimen; 91.1% and 92.1%, respectively, with the sequential therapy; and 80% and 85.7%, respectively, with the hybrid therapy regimen.

Second-line treatment in areas that have a low clarithromycin resistance

Options available in areas with a low resistance to clarithromycin include bismuth-based quadruple therapy and therapies with a PPI and levofloxacin/amoxicillin[86,95]. However, levofloxacin use has been questioned, based on an increase in levofloxacin resistance[96]. Therefore, susceptibility studies should be performed before starting therapy.

Second-line treatment in areas that have high clarithromycin resistance

For the case in which bismuth-based quadruple therapy fails, a triple therapy containing a PPI, levofloxacin, and amoxicillin is recommended. Again, the increase in levofloxacin resistance should be taken into account[77].

Third-line treatment

After 2 failed treatments in areas that have either a low or high clarithromycin resistance, it is not advisable to prescribe further antibiotic treatments. Whenever possible, biopsy specimens should be obtained to culture and test for susceptibility[81]. "Rescue" or "salvage" therapies have obtained good results in these cases. One rescue therapy is the use of rifabutin (150 mg, × 2 daily), amoxicillin (1 g, × 2 daily), and ciprofloxacin (500 mg, × 2 daily) for 14 d. Although this therapy achieves an excellent response, severe adverse effects have been observed[97]. Other rescue therapies include a double dose of PPIs plus azithromycin (500 mg/d for 3 d), followed by a double dose of PPIs plus furazolidone (200 mg, × 3 daily) for 10 d in addition to a base therapy of furazolidone (200 mg, × 2 daily), bismuth subcitrate (120 mg, × 4 daily), and tetracycline (500 mg, × 4 daily) in combination with a PPI at the doses described. For this treatment, the rate of recurrence of *H. pylori* infection after a successful eradication has been estimated at 11.5%[90].

Eradication of H. pylori in pregnancy

If a patient is diagnosed with peptic ulcer during pregnancy or lactation, the condition should be managed only with acid suppression. Eradication of *H. pylori* should be completed after childbirth. Bismuth, quinolones, and tetracyclines are contraindicated in pregnancy, and metronidazole should be avoided[89].

To our knowledge, only one published report has examined eradication of *H. pylori* in pregnant women, specifically in pregnant women with iron deficiency anemia[98]. The researchers performed a randomized placebo-controlled trial on 40 women that were between 14 and 30 wk of gestation and had *H. pylori* infection detected by the SAT. Women were randomly divided into 2 groups: group I (n = 20) was treated with amoxicillin, clarithromycin, and omeprazole for 2 wk, and group Ⅱ (n = 20) was treated with placebo. Both groups received therapeutic doses of iron and folic acid. After 6 wk of therapeutic iron and folic acid supplementation, the rise in hemoglobin, packed cell volume, serum iron, and percentage of transferrin saturation were significantly greater ($P < 0.05$) in the group given *H. pylori* eradication therapy compared to the placebo group. The authors concluded that there is a high prevalence of *H. pylori* infection in pregnant women with iron deficiency anemia, and that eradication therapy resulted in a significantly better response to oral iron supplementation among *H. pylori*-infected pregnant women with iron deficiency anemia.

Use of probiotics in treating H. pylori infection

It has been suggested that probiotics compete directly with *H. pylori* by interfering with *H. pylori* adherence or by producing antimicrobial molecules. The efficacy of *Lactobacillus reuteri* (*L. reuteri*) in *H. pylori* eradication therapy has been investigated. In this study, *H. pylori* infection was identified by gastric histopathology and ^{13}C-UBT. Intervention consisted of 10^8 colony-forming units of *L. reuteri* (DSM 17938) plus pantoprazole (20 mg, × 2 daily) for 8 wk. Patients were examined 4 to 6 wk after therapy for *H. pylori* eradication by ^{13}C-UBT. They found that *L. reuteri* plus pantoprazole twice daily cured 13.6% (3/22; 95%CI: 2.9%-34.9%) of patients with *H. pylori* infection by intention-to-treat analysis and 14.2% (3/21; 95%CI: 3.0%-36%) by per protocol analysis. Researchers concluded that *L. reuteri* might have a potential role in *H. pylori* eradication therapy, if the cure rate can be improved by changes in dose, dosing interval, or duration of therapy[77].

A recent meta-analysis investigated whether a preparation of a *Lactobacillus*- and *Bifidobacterium*-containing probiotic could improve *H. pylori* eradication rates and reduce side effects[99]. The study included 10 clinical trials and 1469 patients, with 708 patients in the probiotic supplementation group and 761 patients in the control group. Pooled ORs by intention-to-treat and per-protocol analyses in the probiotic supplementation group *vs* the

control group were 2.066 (95%CI: 1.398-3.055) and 2.321 (95%CI: 1.715-3.142), respectively. The pooled OR of the incidence of total side effects was significantly decreased in the group that received probiotics supplementation (OR = 0.305; 95%CI: 0.117-0.793). They concluded that combining a *Lactobacillus*- and *Bifidobacterium*-containing probiotic with initial *H. pylori* eradication therapy in adults may have beneficial effects on the eradication rate and incidence of total side effects.

Another study aimed to determine whether adding probiotics to a standard anti-*H. pylori* regimen could minimize the prevalence of gastrointestinal side effects and improve the eradication rate. In a double-blind, randomized, placebo-controlled study, 66 *H. pylori*-positive children, diagnosed by RUT or histology, were treated with a triple drug treatment protocol (omeprazole, amoxicillin, and furazolidon) and randomly allocated to receive either a probiotic or a placebo[100]. All patients underwent esophagogastroduodendoscopy. *H. pylori* status was assessed by the SAT 4 to 8 wk after completion of treatment. The *H. pylori* eradication rate was significantly higher in the group that received probiotics ($P = 0.04$). Furthermore, during treatment, there was a lower rate of nausea/vomiting ($P = 0.02$) and diarrhea ($P = 0.039$) in the probiotic-supplemented children than in the placebo-treated children. The authors concluded that probiotics have a positive effect on the eradication of *H. pylori* infection and the side effects of *H. pylori* treatment.

CONCLUSION

Infection by *H. pylori* remains the most frequent and persistent bacterial infection worldwide; therefore, accurate diagnosis of infection is imperative. There are several alternatives for diagnosis of infection and detection of eradication after treatment for *H. pylori* infection. Additionally, there are several therapies used for treatment. Determining the diagnostic method and therapies to use for each patient depends on several factors, such as the clinical condition of the patient, the prevalence of infection, and the prevalence of clarithromycin resistance, among others.

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