Practice guidelines for the management of *Helicobacter pylori* infection: The Saudi *H. pylori* Working Group recommendations

Fahad Alsohaibani, Musthafa Peedikayil, Abdulaziz Alshahrani[1], Ali Somily[2], Raed Alsulaiman[3], Nahla Azzam[4], Majid Almadi[4,5]

Department of Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, [1]Department of Medicine, Najran University, Najran, [2]Department of Pathology and Laboratory Medicine, King Saud University Medical City, Riyadh, [3]Department of Medicine, King Fahad Hospital, Imam Abdulrahman bin Faisal University, Dammam, [4]Department of Medicine, College of Medicine, King Saud University Medical City, King Saud University, Riyadh, Kingdom of Saudi Arabia, [5]Division of Gastroenterology, McGill University Health Center, Montreal General Hospital, Montreal, QC, Canada

Abstract

The eradication rates for *Helicobacter pylori* globally are decreasing with a dramatic increase in the prevalence of antibiotic resistant bacteria all over the world, including Saudi Arabia. There is no current consensus on the management of *H. pylori* in Saudi Arabia. The Saudi Gastroenterology Association developed these practice guidelines after reviewing the local and regional studies on the management of *H. pylori*. The aim was to establish recommendations to guide healthcare providers in managing *H. pylori* in Saudi Arabia. Experts in the areas of *H. pylori* management and microbiology were invited to write these guidelines. A literature search was performed, and all authors participated in writing and reviewing the guidelines. In addition, international guidelines and consensus reports were reviewed to bridge the gap in knowledge when local and regional data were unavailable. There is limited local data on treatment of *H. pylori*. The rate of clarithromycin and metronidazole resistance is high; therefore, standard triple therapy for 10–14 days is no longer recommended in the treatment of *H. pylori* unless antimicrobial susceptibility testing was performed. Based on the available data, bismuth quadruple therapy for 10–14 days is considered the best first-line and second-line therapy. Culture and antimicrobial susceptibility testing should be considered following two treatment failures. These recommendations are intended to provide the most relevant evidence-based guidelines for the management of *H. pylori* infection in Saudi Arabia. The working group recommends further studies to explore more therapeutic options to eradicate *H. pylori*.

Keywords: Bismuth, quadruple therapy, clarithromycin, *Helicobacter pylori*, metronidazole, Saudi Arabia, sequential, triple therapy

Address for correspondence: Dr. Fahad Alsohaibani, Department of Medicine, King Faisal Specialist Hospital and Research Center, P.O. Box: 3354, Riyadh - 11211, Kingdom of Saudi Arabia.
E-mail: alsohaibani@hotmail.com

Submitted: 01-Jul-2022 **Revised:** 07-Aug-2022 **Accepted:** 19-Aug-2022 **Published:** 03-Oct-2022

Access this article online	
Quick Response Code:	**Website:** https://journals.lww.com/sjga
	DOI: 10.4103/sjg.sjg_288_22

How to cite this article: Alsohaibani F, Peedikayil M, Alshahrani A, Somily A, Alsulaiman R, Azzam N, *et al*. Practice guidelines for the management of *Helicobacter pylori* infection: The Saudi *H. pylori* working group recommendations. Saudi J Gastroenterol 2023;29:326-46.

EPIDEMIOLOGY

Helicobacter pylori is one of the most prevalent infections worldwide. Although the prevalence of *H. pylori* is rapidly declining in developed countries because of improved sanitation and the widespread use of antibiotics, it remains high (>50%) in the majority of other countries.[1,2] It is frequently acquired at an early age in developing countries compared with industrialized nations.[3] A recent systematic review and meta-analysis showed that North America had one of the lowest prevalence rates (37.1%), whereas Africa had the highest pooled prevalence (70.1%), followed by Latin America (63.4%) and Asia (54.7%).[4] Data from Saudi Arabia on prevalence of *H. pylori* were variable depending on geographical region, diagnostic methods, and period of study. The reported prevalence varied from 70% in 1989 to as low as 10.2% in 2018.[5-10] The overall prevalence and time trends are difficult to ascertain due to the methods used in detection as well as heterogeneity in the population studied in Saudi Arabia. The published data on the prevalence of *H. pylori* in six different Saudi cities using different diagnostic methods is shown in Table 1.

Transmission and risk factors

The risk of acquiring *H. pylori* infection is related to socioeconomic status and living conditions early in life. Factors such as density of housing, overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher acquisition rates of *H. pylori* infection. The mode of transmission is still unclear, but evidence shows clusters in family members indicating the importance of fecal–oral or oral–oral exposure.[11] Humans are the major reservoir of infection; however, *H. pylori* has been isolated from milk and gastric juices of sheep.[12] Contaminated water supplies in developing countries may serve as an environmental source for bacteria in endemic areas.[13,14] Isolation of *H. pylori* from the dental caries favor the risk of oral–oral exposure and transmission.[15]

Reinfection

The rate of reinfection in adults is uncommon and more likely related to recrudescence after partial suppression of *H. pylori* by antibiotics. In a large cohort from South Korea (10,468 eradicated subjects), reinfection of *H. pylori* was calculated to occur at the rate of 3.06% per person-year.[16] A prospective observational study performed in China including 3,728 patients with a median follow-up duration of 58.2 ± 13.6 months showed an annual reinfection rate of 1.5% per person-year. *H. pylori* reinfection was independently associated with ethnicity, lower education level, a family history of gastric cancer, and residence located in Western China.[17] Reinfection rates in Saudi Arabia have not been reported.

Diseases associated with *H. pylori*

H. pylori infection is responsible for a significant proportion of gastrointestinal morbidity worldwide, including acute and chronic gastritis, peptic ulcer disease (PUD), gastric adenocarcinoma, and gastric mucosal-associated lymphoid tissue (MALT) lymphoma.[18,19] In 1994, *H. pylori* was classified as a definitive (Class 1) carcinogen by the World Health Organization because of its association with gastric cancer. A meta-analysis showed that the incidence of gastric cancer in individuals with eradication of *H. pylori* infection is lower than those who did not receive eradication therapy (pooled incidence rate ratio, 0.53; 95%(CI), 0.44–0.64).[20]

H. pylori and non-steroidal anti-inflammatory drugs (NSAIDs) act synergistically to increase the risk of ulcers and bleeding. Eradication of *H. pylori* before the start of chronic NSAID therapy reduces this risk.[21] *H. pylori* infection can also cause iron deficiency; therefore, eradication of *H. pylori* together with oral iron leads to significantly increased hemoglobin, iron, and ferritin levels compared with iron therapy alone.[22,23] Idiopathic thrombocytopenic purpura (ITP) has been associated with *H. pylori*, and the American Society for Hematology recommends screening for *H. pylori*

Table 1: Prevalence of *Helicobacter pylori* in Saudi Arabia

Year (s) of Study	City Name	Targeted Patients	Test Method	Prevalence of *H. pylori*	Reference
1989	Riyadh	557 healthy individuals	ELISA-IgG	Age 5-10 years (40%) > 20 years (70%)	al-Moagel *et al*.[5]
2005	Riyadh	120 healthy medical students	UBT	35%	Almadi *et al*.[6]
2008	Makkah	314 intermediate and secondary school students	UBT	Overall was 27.4% and in those with chronic recurrent abdominal pain was 73%.	Telmesani[7]
2011-2012	AlMadinah	456 asymptomatic healthy individuals	ELISA-IgG	Seroprevalence was 28.3%. The highest Seroprevalence (36.8%) was seen among those aged more than 41 years.	Hanafi and Mohamed[8]
2014-2016	Jizan	404 patients with dyspepsia	Gastric biopsy PCR	46.5% (lower among those >55 years old)	Akeel *et al*.[9]
2018	Riyadh	411 primary care patients with gastrointestinal symptoms	Stool Antigen Test	Overall prevalence 10.2% <20 years old (0%) (31%) if >50	Alharbi and Ghoraba[10]

UBT=urea breath test, ELISA=enzyme-linked immunosorbent assay, PCR=polymerase chain reaction

in adults with ITP and treating it in those found to be positive.[24,25]

Epidemiology

- The prevalence of *H. pylori* in Saudi Arabia varies depending on geographical region, diagnostic methods and time of study. The prevalence varied from 70% in 1989 to as low as 10.2% in 2018.
- This decline in prevalence mirrors other countries and is attributed to better hygiene, improved sanitation, and the use of antibiotics.
- The mode of transmission is still unclear, but fecal-oral and oral-oral route transmission is important.
- The global reinfection rate is 3% per person-year.
- *H. pylori* infection is associated with gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric MALT lymphoma. *H. pylori* infection is also linked to iron deficiency anemia and ITP.
- Eradication therapy reduces the incidence of gastric cancer.
- The combination of *H. pylori* and NSAIDs increases the risk of ulcers and bleeding, and eradication of *H. pylori* before the start of chronic NSAID therapy reduces this risk.

MICROBIOLOGY

Clinical isolates of *H. pylori* demonstrate genetic diversity depending on the geographic location which might explain the geographic variability in virulence and probably the incidence of gastric cancer. Each pathogenic virulence factor has stronger association with a certain clinical syndrome and an antimicrobial susceptibility pattern different from others.[26]

Specimen Collection and Transport

Culturing of gastric biopsy tissue allows for *H. pylori* identification, and antimicrobial susceptibility testing. However, the majority of *H. pylori* infection is diagnosed by non-cultural methods, such as rapid urease test (RUT), histopathology, urea breath test (UBT), stool antigen test (SAT), and serology.[27] The complex nature of the organism, growth requirements, and slow culture are major challenges during cultivating *H. pylori*. The sensitivity of culture in detecting *H. pylori* in infected biopsies is 50–70% even in expert laboratories.[28-30] Before the endoscopy, the patient should be off all antibiotics or bismuth substances for at least 4 weeks, and off proton pump inhibitors (PPIs) for at least 2 weeks. It is recommended to obtain biopsies from an inflamed or ulcerated area of the stomach, with two biopsies from the antrum and two biopsies from anterior and posterior corpus, in addition to samples from the antrum and corpus for histology and RUT.[31]

Appropriate collection, transportation, and storage of gastric biopsy specimens are crucial for efficacious culture of *H. pylori*. A transport media must be used to keep the organisms viable. Semisolid transport mediums can be used for prolonged transportation (more than 4 h), such as Stuart's transport medium, Portagerm (bioMerieux, Durham, N.C.), or brucella broth with 20% glycerol.[32-34] For short transportation (less than 4 h) or when there is lack of transport media, saline with 20% glucose and glycerol act as a sufficient alternative.[35] The transported biopsy specimen requires to be maintained at a temperature less than 10°C for up to 16 h. If the culture of this specimen is not feasible to be performed within 24 h of collection, it is advised to freeze it at –70°C in dry ice, in a tube without medium, during transportation. It is recommended for long-term storage of *H. pylori* culture to use glycerol and maintain the culture at –70°C. Proper storage of biopsy specimen can allow 81% of recovery of *H. pylori* in the culture.[36]

Microbiology

- The organism is fastidious, slow growing, and requires specialized media. Culture is highly specific but has a low sensitivity.
- When gastric biopsies are obtained, it is recommended to target the inflamed area as well as from gastric antrum and body.
- Appropriate collection, transportation and storage of biopsy specimens are crucial for efficacious culture of *H. pylori*.

DIAGNOSIS

Indications for testing

Tests for *H. pylori* should only be performed when eradication is planned if the test is positive. PUD is the primary indication; therefore, all patients with a new diagnosis or those who had a history of PUD and have not been tested should be tested for *H. pylori* infection.[37] MALT lymphoma is an important indication to test and eradicate *H. pylori* infection as the regression of low-grade gastric MALT lymphoma was reported in 60–93% of patients.[38] Treatment may also be beneficial for patients diagnosed with diffuse large B-cell lymphoma of the stomach.[39] In addition, patients with early gastric cancer or following gastric cancer resection and patients who are first-degree relatives of patients with gastric cancer are all indications to test and treat for *H. pylori* infection.

Dyspepsia in patients less than 60 years of age without alarm features should have non-endoscopic testing for *H. pylori* infections. For patients who have dyspepsia and undergo upper endoscopy because of age or presence of alarm symptoms, testing should be conducted on gastric biopsy tissue. Functional dyspepsia (FD) includes epigastric pain syndrome or post-prandial distress syndrome. Some FD patients with *H. pylori* infection experience improvement following eradication therapy; therefore, it is recommended to test and treat *H. pylori* in patients with FD. When performing endoscopy in patients with dyspeptic symptoms, it is recommended to biopsy the normal appearing gastric mucosa to test for *H. pylori*.[40]

Aspirin and NSAIDs are well-known risk factors for PUD and can be complicated by upper gastrointestinal bleeding. *H. pylori* increases the risk of bleeding from ulcers during their use and, therefore, it is suggested to consider to test and treat for *H. pylori* when starting low-dose aspirin (ASA) or in patients requiring long-term NSAID therapy.[37,41,42]

Iron deficiency anemia (IDA) has been associated with *H. pylori* infection. A meta-analysis conducted in patients with IDA and *H. pylori* infection found statistically significant differences in favor of *H. pylori* eradication in combination with oral iron over oral iron alone for increases in hemoglobin, serum iron, and serum ferritin levels.[43] In patients with ITP, there is evidence that showed improvement in platelet counts after eradication of *H. pylori* infection. In 2019, the American Society of Hematology recommended to test and eradicate *H. pylori* in ITP patients.[44] In Japan, platelet counts have been reported to increase in 40%–60% *H. pylori*-positive patients with ITP following *H. pylori* eradication; thus, eradication therapy should be one of the therapeutic interventions.[45] *H. pylori* has been associated with a number of other extra-gastroduodenal conditions; however, the causality of these associations is not proven [Table 2].

Table 2: Indications to consider testing and treating *Helicobacter pylori* infection

To be tested
New diagnosis or a past history of gastritis or peptic ulcer disease.
Low-grade gastric mucosa-associated lymphoid tissue lymphoma.
Gastric mucosal atrophy and/or intestinal metaplasia.
Following resection of early gastric cancer.
Unexplained iron-deficiency anemia.
Idiopathic thrombocytopenic purpura.
First-degree relatives of patients with gastric cancer.
Functional dyspepsia (if prevalence of *H. pylori* >20%).
Patients taking long-term aspirin.
Patients initiating chronic non-steroidal anti-inflammatory drug (NSAID).
Consider testing (controversial)
Gastroesophageal reflux disease.
Vitamin B12 deficiency.
Patients taking long-term NSAID.
Patient request (asymptomatic).
Close contact to an individual with *H. pylori* infection.

Population-wide screening and eradication of *H. pylori* to prevent gastric cancer in highly infected areas have recently been proposed by several consensus reports, including a recent Chinese consensus report[46] and Houston consensus conference.[47] A family-based prevention and eradication strategy has been proposed as a suitable approach to prevent intra-familial transmission and related diseases. Whether this approach is cost effective to extend testing and treating all family members, particularly those in close contact with *H. pylori* infected individuals, is unknown, particularly in areas with low incidence of gastric cancer such as Saudi Arabia.

Studies conducted in Japan have shown that *H. pylori*-positive patients with gastroesophageal reflux (GERD) have increased levels of gastric acid secretion and experience transient emergence or worsening of acid reflux symptoms or increased reflux esophagitis after *H. pylori* eradication.[48] However, other reports have documented that the incidence of erosive GERD does not increase after treating *H. pylori* in patients with peptic ulcers, and GERD symptoms can improve by eradication of *H. pylori* infection.[49] Therefore, Japanese guidelines for *H. pylori* management recommend eradication treatment for GERD patients.[45]

DIAGNOSTIC METHODS

Non-endoscopic tests

Tests for *H. pylori* infection can be done by non-invasive or invasive methods. Test-and-treat strategies involve non-invasive testing, followed by treatment in cases where tests are positive. Non-invasive tests include UBT, SAT, and serology.[50] Low bacterial load in the stomach because of gastrointestinal bleeding, atrophic gastritis, gastric MALT lymphoma, and gastric adenocarcinoma can lead to a decreased sensitivity of all diagnostic methods except serology. Serologic tests employ enzyme-linked immunosorbent assay (ELISA) to detect immunoglobulin IgG antibodies to *H. pylori*. There is significant variability in the accuracy of serology test for *H. pylori*, with sensitivity and specificity of 90–100% and 76–96%, respectively.[51,52] Office-based kits that test whole blood can provide quick results and permit "point of care" testing. In most instances, serology remains positive for years after successful treatment of infection, this precludes the use of serology to confirm bacterial eradication after treatment.

UBT involves the ingestion of ^{13}C or ^{14}C-labeled urea. Hydrolysis of urea by bacterial urease generates ammonia and tagged CO_2, which can be detected in breath samples.[53,54] Patients should be fasting for at least 4 h before testing as this could increase the yield for diagnosis. UBT detects active infection and is useful for making the primary diagnosis and for documenting successful treatment with sensitivity and specificity of 88–96% and 93–100%, respectively.[55,56] False-negative results have been reported in patients taking PPIs, bismuth, or antibiotics. To improve diagnostic accuracy, PPIs should be stopped at least 2 weeks before UBT, and bismuth and antibiotics should be stopped at least 4 weeks before UBT. SAT detects *H. pylori* antigens in stool with an ELISA test. It has good accuracy with a sensitivity and specificity of 95% and 97%, respectively.[57] The sensitivity of SAT is also reduced by recent PPIs, bismuth, and antibiotics use.

Endoscopic tests

Endoscopy is recommended in patients aged more than 60 years or in those with alarm symptoms and those with a family history of gastric cancer.[40] When endoscopy is indicated, there are three methods to identify the organism in a gastric biopsy specimen: RUT, histology, and culture. For RUT, gastric biopsy is tested for urease activity by placing the tissue in a medium containing urea and a pH reagent. Bacterial urease hydrolyzes urea, liberating ammonia, which produces an alkaline pH and a resultant color change of the test medium. RUT is efficient, easy, accurate, fast, and allows for immediate treatment with sensitivity and specificity values of 90–97% and 94–100%, respectively.[58] Accuracy is negatively affected by blood in the stomach or by recent use of certain medications, such as antibiotics, bismuth-containing compounds, or PPIs. Taking multiple biopsy samples from the antrum and corpus may be attempted to improve the diagnostic yield.[59]

Direct examination of biopsy

Histological examination is an excellent diagnostic test for *H. pylori* and considered to be the gold standard test. Detection of *H. pylori* is possible with standard hematoxylin and eosin (H and E) staining, but is significantly improved with increase in the number of slides examined and special stains such as Giemsa, silver, Genta, or specific immune stains with reported sensitivity and specificity as high as 95% and 98%, respectively.[60-62] The use of immunohistochemistry may shorten the time required for the detection of bacteria in cases with a low level of organisms, with a sensitivity and specificity of 97–98% and 90–100%, when compared to Genta and H and E stains, respectively.[63,64] Histological examination of biopsy samples enables accurate detection of the bacterium, the assessment of inflammation and detecting gastritis, intestinal metaplasia, dysplasia, or malignancy. Histological sampling for *H. pylori* diagnosis should include an antrum and a corpus biopsy to account for the distribution of *H. pylori*.[65-67] Biopsies could be taken according to the Sydney protocol, which includes five biopsies encompassing the lesser curvature of the antrum within 2–3 cm of the pylorus, the greater curvature of the antrum within 2–3 cm of the pylorus, the lesser curvature of the body 8 cm distal to the cardia, the greater curvature of the body 8 cm distal to the cardia, and the incisura angularis.[68]

H. pylori culture and antibiotic susceptibility testing

H. pylori is difficult to culture because the organism is fastidious, slow growing (10–12 days), and requires specialized media and growth environment. The culture is highly specific with positivity rates ranging between 50% and 93%.[30,69] *H. pylori* culture with antibiotic sensitivity testing is recommended in patients with refractory infection to guide subsequent treatment; however, *in vitro* sensitivity testing does not always predict clinical treatment response.[70-72] Because of the rising incidence of antimicrobial resistance worldwide, it is recommended whenever possible to consider culture and antimicrobial susceptibility testing, particularly in regions with well-documented high antimicrobial resistance or after a failure of two regimens to tailor the treatment. Several studies using tailored treatments based on *H. pylori* susceptibility to antibiotics in comparison with standard empirical triple therapy have shown a better eradication rate and might be cost- effective.[50]

The rate of resistance varies from one country to another, a recent review showed a rate of resistance of about 10–30% to clarithromycin and levofloxacin and high resistance rate to metronidazole 23–56%.[73] In Saudi Arabia, a prospective study reported that *H. pylori* resistance was 48.5% for metronidazole, 23.3% for clarithromycin, 14.8% for amoxicillin, 11.1% for levofloxacin, and 2.3% for tetracycline.[74] Direct measurements with the agar dilution method is the gold standard for antibiotic susceptibility testing for *H. pylori*; however, it requires laborious preparation and may not be cost- or time-effective for

Table 3: Available PCR tests to detect *Helicobacter pylori* in gastric biopsies

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Ridagene	99	100	100	99
Amplidiag	100	99	99	100
Allplex	100	98	98	100

PCR=polymerase chain reaction

daily clinical practice. E-test uses different concentrations of antibiotics in a single strip as an alternative and maybe preferable in clinical practice because of the lower cost and for being less time-consuming.[75]

Polymerase chain reaction (PCR) assays are a rapid and highly sensitive and specific method for the laboratory diagnosis of *H. pylori* infection in gastric biopsies or stool. It is a sensitive method to detect *H. pylori*, and has gained in popularity lately. It allows detection of *23S rRNA*, *gyrA*, *rdxA*, *pbp1*, *16S rRNA*, and *rpoB* gene mutations associated with clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline, and rifabutin resistance, respectively. It is also useful for research purposes or to examine drinking water in a community setting, to type organisms in epidemiologic or transmission studies, and for "real-time" antibiotic resistance testing[76] [Tables 3 and 4].

Post eradication testing

Resolution of symptoms is not an accurate indicator of treatment success; therefore, all individuals treated for *H. pylori* should be offered a test to confirm successful eradication, in particular those with PUD, MALT lymphoma, early gastric cancer, and dyspepsia. False negative results for post eradication testing are usually associated with taking PPIs and antibiotics through inhibiting growth and by their bactericidal activity against *H. pylori*.[77,78] For this reason, eradication testing should be done at least 4 weeks following completion of antibiotics and at least 2 weeks following stoppage of PPI therapy.[79] UBT is the best option for *H. pylori* eradication test.[80] SAT is less accurate but can be used as an alternative.[81] Serology testing is not recommended for eradication confirmation as antibodies persist for months following clearance of infection. When endoscopy is performed, a biopsy from the antrum and the corpus should be taken for RUT that has a sensitivity and specificity for *H. pylori* detection post eradication of 44–88% and 98–100%, respectively.[82]

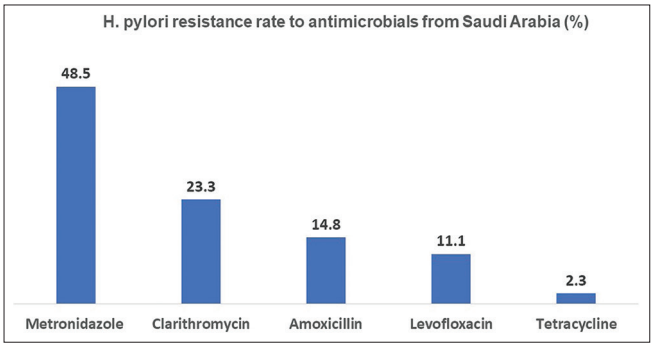

Figure 1: Rate of *Helicobacter pylori* antibiotic resistance in Saudi Arabia

Diagnosis

- *H. pylori* should be tested if there is a clear indication, and therapy will be pursued if the test comes to be positive.
- The main indications for "test then treat" includes; newly diagnosed or a past history of gastritis or peptic ulcer disease, MALT lymphoma, gastric mucosal atrophy or intestinal metaplasia, following resection of early gastric cancer, unexplained iron-deficiency anemia, ITP, first-degree relatives of patients with gastric cancer, functional dyspepsia and patients taking long-term aspirin or initiating chronic NSAID therapy.
- Tests for *H. pylori* infection include non-invasive methods (UBT, SAT and rarely serology). Invasive methods require gastric biopsy for (RUT, histology and culture). The sensitivity and specificity of each test varies.
- PCR assays from gastric biopsies or stool is rapidly developing. It is highly sensitive and specific method for diagnosing *H. pylori* infection and allows detection of gene mutations associated with antimicrobial resistance. However, it is limited by its availability and cost.
- The choice of test depends on its availability and the clinical indication. Presence of any alarm features is an indication for gastroscopy.
- Prior to any test with the exception of serology, the patient should be off any antibiotics or bismuth substances for at least 4 weeks and off PPI for at least 2 weeks.
- It is recommended to confirm the eradication by UBT or SAT at least 4 weeks following completion of antibiotics and at least 2 weeks following stopping PPI therapy.

MANAGEMENT

Factors affecting cure from *H. pylori* are the duration of treatment, compliance to treatment, high gastric acidity, high bacterial load, bacterial strains, and antimicrobial resistance.[50] However, knowledge on the geographical prevalence of *H. pylori* resistance to antimicrobials influences treatment regimens the most. For the successful eradication of *H. pylori* infection, a combination of effective antibiotics should be selected based on antibiotic resistance prevalence, given for an adequate duration; in addition, compliance to the given treatment and adequate acid suppression is essential.[37] The goal of *H. pylori* therapy is to achieve eradication in ≥90% of treated patients by

Table 4: Endoscopic and non-endoscopic diagnostic tests

Test	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
Serology	79-85	79–82	Widely available Inexpensive High NPV	Poor PPV: Not useful after treatment
UBT	88-96	93–100	Identifies active infection	Accuracy affected by PPI and antibiotic use
SAT	95	97	High PPV and NPV Cost effective Useful before and after treatment	
RUT	90-97	94–100	Rapid and easy	Requires endoscopy: Accuracy affected by PPI and antibiotic use
Histology	90-97	98–100	Excellent sensitivity and specificity: Provides additional information about gastric mucosa.	Expensive Inter-observer variability: Accuracy affected by PPI and antibiotic use
Culture	50-93	≈100	Very specific: Allows antibiotic sensitivity testing	Difficult culture protocol: Not widely available Expensive
PCR assay	99-100	98–100	Quick test (2 h) Excellent sensitivity and specificity Permits detection of antibiotic resistance	Not widely available: Technique not standardized and is expensive

UBT=urea breath test, SAT=stool antigen test, RUT=rapid urease test (CLO test, Hp fast), NPV=negative predictive value, PPV=positive predictive value, PCR=polymerase chain reaction

initially using the most efficacious therapies available. The therapeutic options depend on their availability, cost, convenience, resistance pattern, and presence of allergies.

Prevalence of antibiotic resistance of *H. pylori* strains in Saudi Arabia

H. pylori resistance to clarithromycin in Saudi Arabia ranges from 8.8% to 39.9%, fluoroquinolone resistance between 8.4% and 11.1%, and metronidazole between 48.5% and 80%. Resistance to amoxicillin and tetracycline was reported to be 14.6–14.8% and 2.3–9.5%, respectively.[74,83-85] When the prevalence of clarithromycin resistance in a geographical area is >15%, treatment regimens containing clarithromycin become less effective. Similarly, when fluoroquinolone resistance is high, the eradication with levofloxacin-based triple therapies reduces. Similarly, the eradication rates using metronidazole-based triple therapy diminishes significantly in areas where metronidazole resistance is high [Figure 1].

Treatment regimens available for *H. pylori*

When treating *H. pylori*, all efforts should be made to achieve eradication rates of ≥90%, keeping in consideration that failing to cure the infection from the first line of treatment might reduce the cure rate in subsequent therapies. Therefore, the most effective available regimen should be used first. The regimens with dosages, durations, and eradication rates are shown in [Table 5].

Triple therapy

Triple therapy consists of a combination of two antibiotics: amoxicillin, clarithromycin or metronidazole, and PPI. This combination is given from 7 to 14 days. The overall efficacy of standard triple therapy, including PPI, amoxicillin, and clarithromycin (PAC), in comparison with other treatment regimens was 60–82% on an intention-to-treat (ITT) analysis basis.[86-95] In most countries, standard triple therapy has a below therapeutic eradication rate.[96] Antibiotic resistance causes a decrease in the eradication rate of *H. pylori*.[97] In geographical areas where clarithromycin resistance is more than 15%, the eradication from clarithromycin-based triple therapies is generally suboptimum.[96] Seven days of triple therapy should be avoided because of very low eradication.[98] Longer duration (14 days) was associated with a higher eradication rate, but with a higher risk of events that lead to discontinuation.[96]

The data from Saudi Arabia show that the eradication rate of *H. pylori* with a combination of PAC for 14 days was 59% in ITT analysis, and in per-protocol analysis, the eradication was 67.6%. Clarithromycin resistance in this study was 23.3%.[74] Because of the very low eradication rate with standard triple therapy, alternative regimens should be tried as first-line treatment in Saudi Arabia. Different guidelines recommend or suggest clarithromycin or metronidazole-based triple therapies for 14 days only in geographical areas where this treatment has proven satisfactory efficacy and/or with low clarithromycin resistance for clarithromycin-based therapy and low metronidazole resistance for metronidazole-based triple therapy.[37,83] Meta-analyses comparing PPI, amoxicillin, and metronidazole (PAM) versus clarithromycin including triple therapies (PAC/PMC) showed total cure rates of all triple therapies as less than 90%, with a significant difference in favor of PAC (70% vs. 77.1%; OR = 0.70, 95% CI = 0.56–0.88) and PMC therapy (66.4% vs. 77.7%; OR = 0.55, 95% CI = 0.39–0.76). Sensitivity analyses showed a similar efficacy of PAM versus PAC when drugs were administered for 14 days (80% vs. 84%; OR = 0.70, 95% CI = 0.44–1.12). Number of antibiotic doses ($P = 0.012$), length of treatment ($P < 0.001$), and use of high metronidazole doses ≥1.5 g/day ($P = 0.021$) were

Table 5: Treatment regimens and mean pooled eradication rates from different meta-analysis

Treatment regimens	Recommended Dosages and Durations	Pooled Eradication Rate. ITT/PP (%)	Eradication Rate from the Arab World Given as ITT Response Rate (%)
Clarithromycin-based triple therapy	Amoxicillin 1,000 mg BID, Clarithromycin 500 mg BID, and PPI 20-40 mg BID for 14 days.	ITT 57-84 PP 60-83%	Saudi, the UAE, and Kuwait (59, 68, and 69%, respectively) as first line of treatment
Metronidazole-based triple therapy (in case of penicillin allergy)	Metronidazole 500 mg TID, Clarithromycin 500 mg BID, and PPI 20-40 mg BID for 14 days.	66-80%	No data available
Pylera®	3 capsules q6 hourly and PPI 20-40 mg BID for 10 days.	90%	Lebanon, Saudi Arabia, and Kuwait (50, 78, and 88%, respectively) as first line of treatment
Bismuth quadruple (PBMT)	Bismuth subcitrate (or subsalicylate) 120-300 mg QID, metronidazole 250 mg QID or 500 mg TID, tetracycline 500 mg QID, and PPI 20-40 mg BID for 10-14 days.	78-87%	No data available
PBMT with probiotics	Same as quadruple therapy with *Lactobacillus reuteri* (Biogaia®) 37.5 mg BID for 14 days.	91%	No data available
Concomitant	Amoxicillin 1,000 mg BID, clarithromycin 500 mg BID, metronidazole or nitroimidazole/tinidazole) 500 mg BID, and PPI 20–40 mg BID for 10–14 days.	78-91% PP 90%	No data available
Hybrid	Amoxicillin 1,000 mg BID and PPI 20–40 mg BID for 7 days, followed by amoxicillin 1,000 mg BID, clarithromycin 500 mg BID and tinidazole (or nitroimidazole) 500 mg BID and PPI 20–40 mg BID for 7 days.	ITT 79-87% PP 93%	No data available
Sequential standard	Amoxicillin 1,000 mg BID and PPI 20–40 mg BID for 5–7 days, followed by clarithromycin 500 mg BID, tinidazole 500 mg BID, and PPI 20-40 mg BID for 5–7 days.	76-86%	Saudi and the UAE (50 and 85%, respectively) as a first line of treatment. Egypt 75% for retreatment.
Sequential with quinolone	Amoxicillin 1,000 mg BID and PPI 20–40 mg BID for 5–7 days, followed by amoxicillin 1,000 mg BID, tinidazole 500 mg BID, levofloxacin 500 QD, and PPI 20–40 mg BID for 5–7 days.	88-91%	No data available
Vonoprazan-based therapy	Vonoprazan 20 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 400 mg BID for 7 days.	85-89%	No data available
High-dose dual therapy	Esomeprazole or rabeprazole 20 mg QID and amoxicillin 1,000 mg QID for 14 Days.	ITT 83-85% PP 88%	ITT 86% PP 88%
Levofloxacin-based triple therapy	Amoxicillin 1,000 mg BID, levofloxacin 500 mg QD, and PPI 20–40 mg BID for 10–14 days	77–81%	Saudi Arabia as a second line of treatment 36%
Moxifloxacin-based triple therapy	Amoxicillin 1,000 mg BID, moxifloxacin 400 mg QD, and PPI 20–40 BID for 10–14 days.	79%	No data available
Rifabutin-based triple therapy	Amoxicillin 1,000 mg, rifabutin 50 mg, and omeprazole 40 mg TID for 14 days	81% for Asians, 72.4% for non-Asians	No data available
Nitazoxanide-based quadruple therapy	Nitazoxanide 500 mg BID, doxycycline 100 mg BID, levofloxacin 500 QD, and PPI 20–40 mg BID for 14 days.	No data available	Egypt 83% as second-line treatment.

PP=per protocol, ITT=intention to treat, BID=Twice per day, TID=thrice per day, QID=four time per day, QD=once daily, PBMT=PPI, bismuth, metronidazole and tetracycline

associated with higher eradication rates. Giving antibiotics every 8 h instead of every 12 h increases eradication rates.[99]

Bismuth-containing quadruple therapy

Quadruple therapies (bismuth based and non-bismuth based) for 10–14 days are able to achieve ≥ 90% eradication rates. For the first-line treatment of *H. pylori*, 10–14 days course of bismuth-containing quadruple therapy has an overall eradication rate of 77.6–90% by ITT analysis.[88,93-95] In a meta-analysis, the efficacy of a 10-day course of single-capsule bismuth quadruple therapy (Pylera®) was 90% on ITT analysis as first-line therapy, 89% as a second-line treatment, and 82% as a third-line treatment. This treatment response was regardless of the type and dose of the PPI, including for patients with clarithromycin or metronidazole-resistant strains, and in those previously treated with clarithromycin.[94] In another meta-analysis, bismuth quadruple therapy and concomitant therapy were found good treatment options for *H. pylori* infection. However, bismuth quadruple therapy was superior to the current scheme of concomitant therapy in a subgroup analysis.[95] In a multicenter, prospective registry, Pylera®

had a modified ITT effectiveness of 92%, eradication was more than 90% in first-line treatment, and was maintained as a rescue therapy as both second (89%) and subsequent lines of therapy (92%).[100]

A study from Saudi Arabia found an eradication rate of 78.3% (ITT analysis) using Pylera® with PPI for 10 days and 87.8% in a per-protocol analysis; and previous treatment failure did not affect the treatment response.[101] This is higher than the treatment response obtained from standard triple therapy in Saudi Arabia.[74] It has been also reported that adding probiotics to bismuth-based quadruple therapy may improve the eradication rate of *H. pylori*, especially in patients receiving front-line eradication regimens or in patients who have had a failed triple therapy. Probiotics may reduce the adverse reactions when combined with other eradication agents.[102] We also recommend further studies to clarify if a 10-day course of quadruple therapy is as effective as a 14-day regimen.

Non-Bismuth-based quadruple (concomitant) therapy

In concomitant therapy, three antibiotics and a PPI are given in two divided doses for 10–14 days. In an open-label, randomized clinical trial, eradication rates for the concomitant group compared to the hybrid therapy group were 84.1% on ITT and 96.7% on per-protocol analysis.[103] In a meta-analysis, the efficacy of concomitant therapy was found to be duration dependent. In comparison with sequential therapy, a 10-day concomitant therapy was superior. Another observation was that when compared to sequential therapy, concomitant therapy was more efficacious for metronidazole-resistant strains, and metronidazole plus for clarithromycin-resistant strains. However, diarrhea was more frequent with concomitant therapy than with sequential therapy.[104]

Sequential therapy

In sequential therapy, in the first 5 days, one antibiotic and a PPI are given twice daily for 5–7 days; then, clarithromycin, metronidazole or tinidazole, and a PPI are given twice daily for the next 5–7 days. The treatment response to sequential therapy is generally influenced by the prevalence of resistance to clarithromycin and metronidazole. In areas with high resistance to clarithromycin, sequential therapy was superior to 14-day triple therapy. In areas with high metronidazole resistance, sequential therapy and 14-day triple therapy were equivalent. Overall, sequential therapy for 10 or 14 days was not significantly superior to 14-day triple therapy. However, 14-day sequential therapy was significantly more effective than 14-day triple therapy as first-line treatment.[105]

In a meta-analysis, sequential therapy was more effective than triple therapy, especially when sequential therapy was given for only 7 days. Nevertheless, the apparent advantage of sequential therapy has decreased over time, and more recent studies do not show sequential therapy to have a higher efficacy versus triple therapy when triple therapy is given for 10 days. Although sequential therapy offers an advantage when compared with triple therapy, it cannot be presented as a valid alternative, given that neither regimens achieved optimal efficacy (≥90% eradication rate).[106] The overall mean pooled eradication rate was 82% from different meta-analyses.[90,107,108] Sequential therapy has been tested in clinical trials from Saudi Arabia for first-line treatment of *H. pylori* and as second-line treatment in Egypt.[74,109] A randomized controlled trial has shown eradication rate from 10-days sequential therapy was 62.3% (ITT analysis). In addition, there was no statistical difference between sequential therapy and triple therapy. The treatment response was better with triple therapy (67.6%) than with sequential therapy.[74] In Korea, quinolone-containing sequential therapy for 14 days was found to be better than standard sequential therapy with a 91.4% eradication rate in the ITT analysis.[110]

Hybrid therapy

In hybrid therapy, we use PPI and amoxicillin for 7 days, followed by PPI, amoxicillin, clarithromycin, and metronidazole for 7 days. In a randomized study, the hybrid scheme resulted in an 85% eradication rate on ITT analysis and 91% as per protocol, and it was found to be significantly more effective than standard triple therapy.[111] From the meta-analysis, compared with sequential therapy or concomitant therapy, hybrid therapy gave a similar yield of eradication, high compliance rate, and acceptable safety profiles.[112] From a clinical trial from Taiwan, 96.4% eradication rate was achieved from the hybrid therapy on per protocol analysis compared to 81.9% with sequential therapy. It appeared that hybrid therapy was an appropriate eradication regimen in Taiwan.[113] There are no studies available from Saudi Arabia on hybrid therapy.

High-dose dual therapy

In high-dose dual therapy, a PPI and amoxicillin are given three times a day for 14 days or four times a day for 10 days.[114] In a network meta-analysis that compared sequential therapy, bismuth-based quadruple therapy, concomitant therapy, and hybrid therapy, high-dose dual therapy for 14 days appeared to be the most optimal first-line therapy for *H. pylori* among Asian populations, with comparable efficacy and compliance and with fewer adverse events. Pooled efficacy of high-dose dual therapy was found to be 83.2% versus 85.3% on ITT when

Table 6: Comparison of first-line treatment recommendations of *Helicobacter pylori* from international guidelines

	ACG 2017	Toronto Consensus	Maastricht 2016	Saudi 2022
PAC 14 days	Recommended	*Restricted	*Restricted	Not recommended
PAM	**Not discussed	*Restricted	*Restricted	Not recommended
PBMT 10-14 days	Recommended	Recommended 14 days	Recommended 14 days.	Recommended
Pylera® 10 days	**Not discussed	**Not discussed	Not discussed	Recommended
Concomitant 10-14 days	Recommended	Recommended 14 days	Recommended 14 days	Suggested
Sequential	Suggested	Not recommended	**Not discussed	Not recommended
Fluroquinolone sequential	Suggested	Not recommended	**Not discussed	***No data

ACG=American College of Gastroenterology, PAC=PPI, amoxicillin, and clarithromycin, PAM=PPI, amoxicillin, and metronidazole, PBMT=PPI, bismuth, metronidazole, and tetracycline. *Restrict use in areas with known low clarithromycin resistance (<15%) or proven high local eradication rates (>85%). **The guidelines did not suggest or recommend this regimen for the treatment nor was against it. ***No clinical trials to recommend or suggest this therapy for or against it

it was compared with other guidelines-recommended therapies.[115] There is no data from Saudi Arabia on high-dose dual therapy.

Levofloxacin-based regimens

The cumulative eradication rate of levofloxacin triple therapy in a systematic review was 80.7% (95%CI: 77.1–83.7) as first-line treatment and 74.5% (95%CI: 70.9–77.8) as second-line treatment. The efficacy of levofloxacin triple therapy before 2008 was 77.4% and after 2012 was 74.8%. The eradication rate was higher when levofloxacin was given once daily (80.6%, 95%CI: 77.1–83.7) than when given twice daily (73.6%, 95%CI: 69.7–77.2). The efficacy was significantly higher in levofloxacin-susceptible strains than in resistant strains (81.1% vs. 36.3%, risk ratio 2.18, 95%CI: 1.6–3, $P < 0.001$).[116]

Another meta-analysis showed that 7 days of levofloxacin triple therapy was found to be equal to 7 days of triple therapy as first line treatment. The crude eradication rate in the levofloxacin group was 79.05% versus 81.4% in the standard group (risk ratio 0.97; 95%CI: 0.93, 1.02).[117] There is no data available from Saudi Arabia exploring the role of levofloxacin-based triple therapies or sequential therapies as a first-line treatment for *H. pylori*. However, as rescue therapy, levofloxacin-based triple therapy was found to be suboptimum in Saudi Arabia. In a trial conducted by Alsohaibani *et al*.,[118] 55 patients who failed to respond to different kinds of *H. pylori* treatments were given levofloxacin, doxycycline, and esomeprazole for 10 days. *H. pylori* eradication was achieved in 20 out of 51 patients (39.22% per protocol analysis and 36.36% by ITT analysis). Therapy was well tolerated, and side effects were generally mild.

Moxifloxacin-based sequential therapy

In a study from South Korea, moxifloxacin-based sequential therapy (MBST) was found to be better than hybrid therapy; both treatments were given for 14 days. The eradication rates in the ITT analysis were 91.4% (128/140; 95%CI: 90.2–92.9%) in the MBST group and 79.2% (114/144; 95%CI: 77.3–80.7%) in the hybrid group ($P = 0.013$).[119] Pooled *H. pylori* eradication rates for first-line or second-line treatments were 79.03% (95%CI: 75.73–82.07) and 68.33% (95%CI: 64.44–72.04) for patients with moxifloxacin-based triple therapy or with standard triple or quadruple therapy, respectively, by ITT analysis.[87]

Rifabutin triple therapy

There is no data available on the efficacy of rifabutin-based therapy from the Middle East. The overall efficacy of rifabutin-containing regimens in Europe was 78%, 80%, and 66% by modified ITT as second-, third-, and fourth-line

Table 7: Second-line treatment regimens for the eradication of *Helicobacter pylori* after clarithromycin-triple therapy fails in first line

	ACG 2017	Toronto consensus	Maastricht 2016	Saudi 2022
PAC 14 days	Not recommended	Not recommended	Not recommended	Not recommended
PAM	*Not discussed	*Not discussed	*Not discussed	Not recommended
PBMT 14 days	Recommended	Recommended	Recommended	Recommended
Pylera® 10 days	*Not discussed	*Not discussed	*Not discussed	Recommended
Concomitant 10–14 days	Suggested	*Not discussed	*Not discussed	**No data
Sequential	*Not discussed	Not recommended	*Not discussed	Not recommended
High dose dual	Suggested	*Not discussed	Suggested	**No data
Levofloxacin triple therapy for 14 days	Recommended	Suggested	Recommended	Not recommended
Levofloxacin quadruple therapy for 14 days	*Not discussed	*Not discussed	Recommended	**No data
Nitazoxanide-based quadruple therapy for 14 days	*Not discussed	*Not discussed	*Not discussed	Suggested

PAC=PPI, amoxicillin, and clarithromycin, PAM=PPI, amoxicillin, and metronidazole, PBMT=PPI, bismuth, metronidazole, and tetracycline. *The guideline did not suggest or recommend this regimen for the treatment nor was against it. **No clinical trials to recommend or suggest this therapy for or against it

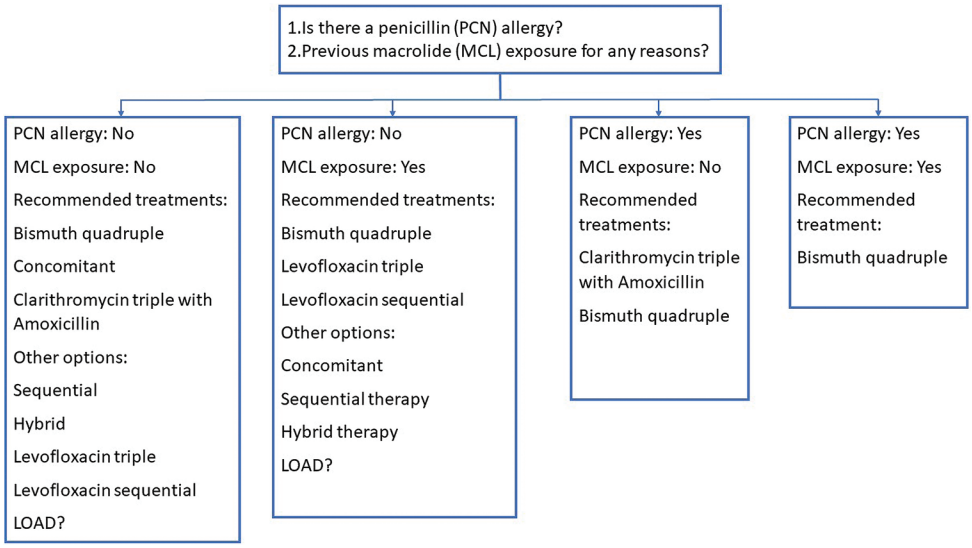

Figure 2: Selection of first-line *Helicobacter pylori* treatment regimen as recommended by American College of Gastroenterology (ACG). [37]*In regions where clarithromycin resistance is known to be >15%, use recommendations for patients with a history of macrolide exposure. **Levofloxacin, omeprazole, nitazoxanide, and doxycycline

regimens, respectively.[120] In a meta-analysis, only one randomized controlled trial had compared rifabutin therapy with control as first-line treatment (OR 3.78, 95%CI: 2.44–5.87, $P < 0.0001$). It was found that the treatment was more likely to be successful in Asian versus non-Asian populations (81.0% vs. 72.4%, $P = 0.001$), and when daily amoxicillin dose was ≥3,000 mg or PPI dose was ≥80 mg or treatment duration was 14 days (80.6% vs. 66.0%, $P = 0.0001$).[121] As second line therapy, 7-day rifabutin and amoxicillin regimen was compared to 7-day bismuth-based quadruple therapy. In a randomized trial, eradication achieved in an ITT analysis was 44.4% and 70.4% for rifabutin and bismuth-based quadruple therapy, respectively, (OR = 1.58, $P = 0.009$).[122]

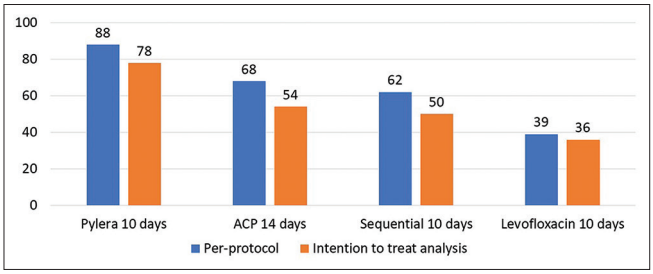

Figure 3: Eradication rates of *Helicobacter pylori* from Saudi Arabia as first-line or second-line treatment in intention-to-treat and per protocol analysis. Pylera® as first- or second-line: Bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg; 3 capsules four times daily for 10 days; and esomeprazole 20 mg bid for 10 days. Standard treatment as first line: Esomeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1,000 mg each bid for 14 days. Sequential as first line: Esomeprazole 20 mg bid for 10 days, amoxicillin 1,000 mg bid for 5 days, then clarithromycin 500 mg and tinidazole 500 mg bid for 5 days. Levofloxacin as second line: Levofloxacin 500 mg once daily, doxycycline 100 mg twice daily, and esomeprazole 20 mg twice daily for 10 days

PPI in the treatment regimens

Esomeprazole was found to be the most effective PPI, followed by rabeprazole, while no difference was observed among the three older generations of PPI for the eradication of *H. pylori*.[123] In one study, distribution of CYP2C19 phenotypes with extensive metabolizers was found to be 77.6% in Saudi Arabia.[124] This may affect the adequacy of acid suppression with conventional PPI. A clinical trial using potent acid suppressors other than a PPI, such as vonoprazan, would be of interest.

The role of vonoprazan-based treatments instead of PPI

The efficacy of vonoprazan (a potassium-competitive acid blocker) based triple therapy was found to be superior to that of PPI-based triple therapy for first-line *H. pylori* eradication. Additionally, vonoprazan-based triple therapy is better tolerated than PPI-based triple therapy.[125] Eradication rate was 77.5% in the esomeprazole group, 68.4% in the rabeprazole group, and 90.8% with vonoprazan.[126] A vonoprazan-based regimen has significant superiority over a PPI-based regimen for second-line *H. pylori* eradication therapy. Avonoprazan-based second-line *H. pylori* eradication regimen can be the first choice.[127] Almost all studies related to vonoprazan have been conducted in Japan. There are no data available from Saudi Arabia for vonoprazan as an acid suppression agent.

Which treatment regimens are appropriate to treat *H. pylori* in Saudi Arabia?

In Saudi Arabia, the available data from prospective studies suggest that triple therapy and sequential therapy are suboptimal for the treatment of *H. pylori* while bismuth-based quadruple

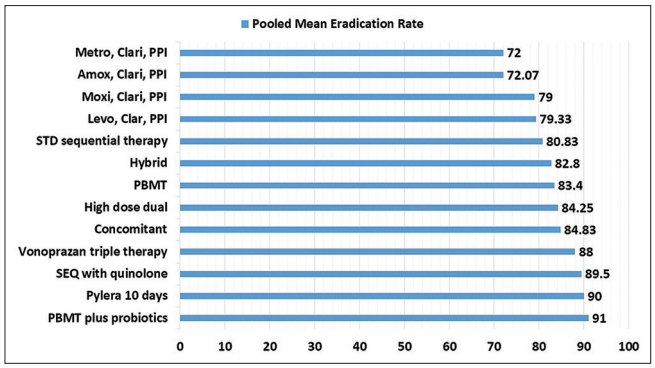

Figure 4: Pooled mean intention-to-treat eradication rates of *Helicobacter pylori* shown in this graph as first-line treatments from the meta-analyses published between 2011 and 2021. PBMT = PPI, bismuth, metronidazole, and tetracycline, SEQ with quinolone = sequential therapy containing quinolone, STD sequential therapy = standard sequential therapy, Metro Clr, PPI = metronidazole, Clarithromycin, and PPI

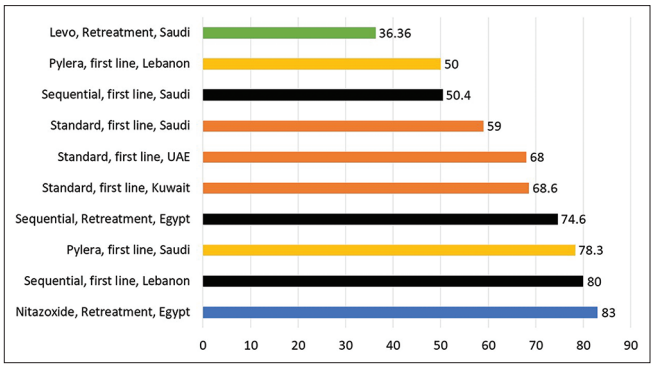

Figure 5: *Helicobacter pylori* eradication rates from clinical trials from the Arab World*. *Clinical trials testing the efficacy of Pylera® as a first line treatment for *H. pylori* is available from Saudi Arabia, Kuwait, and Lebanon. Clinical trials testing the efficacy of sequential therapy as first-line treatment is available from Saudi Arabia and the UAE. Clinical trials testing the efficacy of standard triple therapy is available from Saudi Arabia, the UAE, and Kuwait. Levofloxacin-based regimen as a second-line treatment was conducted from Saudi Arabia. From Egypt, sequential therapy and nitazoxide-based regimens were tested as a second-line treatment.

therapy (Pylera®) is superior as first-line treatment.[74,101] Until now, there are no clinical trials available from Saudi Arabia to assess the efficacy of concomitant therapy, hybrid therapy, and high-dose dual therapy; hence, clinical trials should be conducted to clarify their role. Until then, bismuth-based quadruple therapy (including Pylera®) should be considered as a first- and second-line treatment for *H. pylori* [Figures 2–4 and Table 6].

What are the treatment options when standard therapy fails?

Bismuth-based quadruple therapy, including Pylera®, for 10–14 days is recommended for patients who had failed to respond to standard therapy. Evidence to recommend or suggest a regimen as a second-line treatment is limited from Saudi Arabia because of the lack of sufficient clinical trials. Clarithromycin, metronidazole, amoxicillin, and levofloxacin resistance rates are high in Saudi Arabia. In one clinical trial from Saudi Arabia, eradication rate from a treatment regimen containing levofloxacin, doxycycline, and PPI was found to be substantially low.[118] In Egypt, in a randomized controlled trial using sequential therapy as a second-line treatment, the eradication rate was 74.6%.[128] Another trial carried out in Egypt with nitazoxanide, levofloxacin, doxycycline, and omeprazole for 14 days yielded 83% eradication on ITT analysis as second-line treatment.[129] Table 7 shows different second-line treatment regimens from various guidelines and suitable treatment options for patients from Saudi Arabia.

What are the treatment options when bismuth-based therapy fails?

Treatment regimens that have shown high eradication rates for the second-line treatments include bismuth-based quadruple therapy with probiotics, extending bismuth-based quadruple therapy to 14 days, levofloxacin–bismuth-containing quadruple therapy, vonoprazan-containing triple therapy, and combination of bismuth, clarithromycin, and tetracycline and high-dose dual therapy. The mean pooled eradication rates of the above-mentioned treatment range from 83% to 91%; however, no data are available from Saudi Arabia for these regimens.[127,130-136] In geographical areas where high resistance to clarithromycin and levofloxacin (or other macrolides or quinolones) are reported, clarithromycin and levofloxacin (or another quinolone) containing treatment should not be repeated to treat refractory cases.

What are the treatment options when second-line treatment regimens fail?

Many international guidelines recommend endoscopy to perform culture with susceptibility testing or molecular determination of genotype resistance when second-line treatment fails.[37,50,137] The treatment options for this group of patients are extending the duration of bismuth-based quadruple therapy to 14 days, high-dose dual therapy, or combination of bismuth, levofloxacin, and tetracycline or metronidazole. The data to support these treatment regimens are not available from Saudi Arabia [Figures 5–7].

Treatment of patients with a true penicillin allergy

Bismuth-based quadruple therapy should be the first- and second-line treatment for patients with true penicillin allergy. Standard triple therapy with metronidazole and clarithromycin might be a choice if bismuth-based quadruple therapy is not available and only in areas where this regimen has proven efficacy.[37]

Role of probiotics in the management of *H. pylori*

Probiotics have recently been added to the antibiotics regimen to

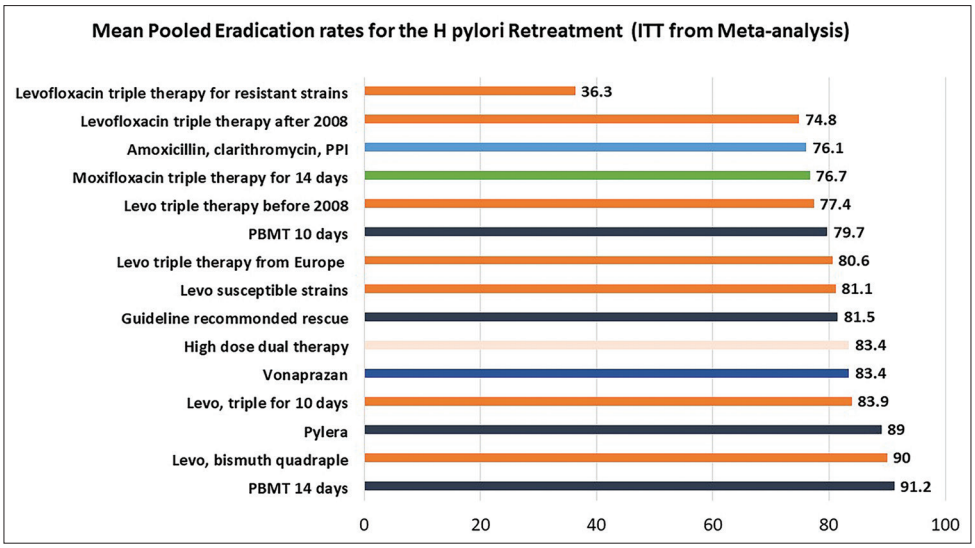

Figure 6: Pooled mean eradication rates (intention-to-treat analysis) of *Helicobacter pylori* from second-line treatment from the different meta-analyses published between 2011 and 2021. HDDT = high-dose dual therapy, PBMT = PPI, bismuth, metronidazole, and tetracycline, STD = standard triple therapy containing amoxicillin, clarithromycin, and PPI, Pylera® = bismuth, metronidazole, and tetracycline and PPI for 10 days

improve the eradication rate. The most used probiotic bacteria are *Lactobacillus* and *Bifidobacterium*. Recent data have shown an additional benefit of probiotics against *H. pylori* activity. Several studies have been conducted with favorable effects of different probiotics against *H. pylori*.[138-144] The possible mechanism of action of probiotics against *H. pylori* includes inhibiting the *H. pylori* growth by secreting short chain fatty acids that have antibacterial effect. It improves the strength of the mucosal barrier and has immunomodulatory mechanisms resulting in a reduction of gastric activity and inflammation.[145-147] It was also found that *H. pylori* infection is characterized by the release of various inflammatory mediators, such as chemokines and cytokines. Probiotics could modify the immunologic response by the modulation of anti-inflammatory cytokines secretion.

Several studies that assessed adding probiotic supplementation to *H. pylori* treatment showed positive results with improvement of *H. pylori* eradication rates and reduced side effects during therapy.[145,148,149] *Lactobacillus* species in particular have shown a stronger antibacterial activity against *H. pylori* in addition to *Bifidobacterium* strains and *Saccharomyces boulardii*.[140,150,151] Published data suggested that combining probiotics with a 14-day course of treatment by triple therapy did not improve the eradication of *H. pylori* infection compared to the placebo. However, probiotics did improve the adverse effects (AEs) of diarrhea and nausea.[136,150] Other meta-analyses showed positive results and concluded that probiotics supplementation can improve the eradication rate of *H. pylori* compared to the therapy alone.[140,144,152,153]

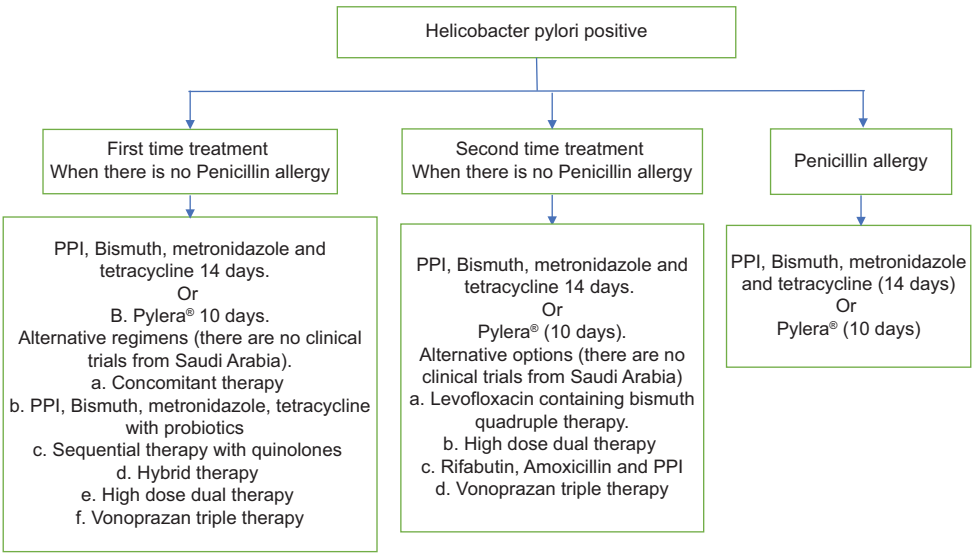

Figure 7: Suggested algorithm for management of *Helicobacter pylori* in Saudi Arabia

Nevertheless, randomized, placebo-controlled trials evaluated the effect of probiotics as an adjuvant to standard triple therapy for eradication of *H. pylori* infection in children and showed conflicting results.[154,155] Based on the current evidence, probiotics could not be recommended to be used in daily routine practice as an eradication regimen. However, its use as an adjunct therapy could improve the eradication rates and decrease treatment-related side effects.

Adherence to treatment regimen

H. pylori eradication can only be achieved if patients are adherent to the treatment regimen. Therefore, it is of utmost importance to educate patients regarding the adherence to treatment course and timing (PPI to be taken before meals and antibiotics after meals). It is important to ensure that adherence to treatment regimens were appropriate and satisfactory, otherwise subsequent treatment options will not be successful. It has been estimated that 10% of patients prescribed *H. pylori* eradication therapy will fail to take even 60% of medications. In one study, eradication levels of 96% were observed for patients who took 60% or more of medications compared to 69% for those taking less than 60% of prescribed medications. There are many factors behind the poor rate of adherence to treatment, including side effect of medication, duration and complexity of treatment, patient information, and physician motivation. The motivated physician can provide information to the patient that will lead to his or her empowerment to play an active role in their treatment by complying with therapy.[156-158]

Management

- The goal of *H. pylori* therapy is to achieve eradication in ≥ 90% of treated patients.
- The therapeutic options depend on their availability, cost, convenience, resistance pattern and presence of allergies.
- In Saudi Arabia, the eradication rates for *H. pylori* are declining due to many factors including high antimicrobial resistance to clarithromycin, metronidazole, amoxicillin and levofloxacin.
- For successful eradication, a combination of effective antibiotics with low resistance is selected and given for an adequate duration (minimum of 10 days and preferably for 14 days in most regimens).
- Given that clarithromycin resistance in Saudi Arabia is exceeding 15%, quadruple therapy for 10-14 days should be considered as a first line treatment for *H. pylori*.
- Quadruple therapy for 10-14 days is also recommended as second line treatment.
- Compliance to any given treatment and ensuring adequate acid suppression is essential for the treatment to be successful.
- Avoid repeating the same regimen with a prolonged duration, as the success rate will be very low.
- There is a limited data available for those who fail quadruple therapy. Concomitant therapy, rifabutin-amoxicillin, or levofloxacin-based quadruple therapy for 14 days can be considered.
- If two different regimens failed to eradicate the infection, it is recommended to perform culture and sensitivity or PCR assay (if available) before pursing any further treatment.

Table 8: Medications that need to be adjusted in chronic liver or renal diseases.[175,176]

Medications that need to be used with caution in patients with liver impairment	Medications that need to be used with caution in patients with renal impairment
Clarithromycin	Clarithromycin
Tetracycline	Tetracycline
Metronidazole	Levofloxacin
Rifabutin	

H. pylori Infection in pediatrics

H. pylori infection in pediatric patients is higher in developing countries with a prevalence of 3–10% compared to 0.5% in developed countries.[159] It was also found that the infection is usually acquired at a young age, and infection rates are similar in males and females. In developed countries, less than 10% of children younger than 12 years are infected; however, seropositivity increases with age.[160] Most children infected with *H. pylori* are asymptomatic. A recent meta-analysis reported no association between *H. pylori* infection and gastrointestinal symptoms in children.[161] The most common manifestation in children was antral gastritis; however, duodenal and gastric ulcers have been reported but are less common in children compared to adults.[162] The risk of gastric MALT lymphoma and adenocarcinoma is rare in the pediatric population.[163] Children differ from adults in different respects to *H. pylori* infection; therefore, the recommendations for adults may not apply in children.

In 2017, a joint European Society for Pediatric Gastroenterology Hepatology and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition made the following recommendations for the management of *H. pylori* in children and adolescents[164]:

1. Recommended against a "test and treat" strategy for *H. pylori* infection in children.
2. Recommended against diagnostic testing for *H. pylori* infection in children with functional abdominal pain disorders.
3. Recommended against diagnostic testing for *H. pylori* infection as part of the initial investigation in children with IDA.
4. Suggested that noninvasive diagnostic testing for *H. pylori* infection may be considered when investigating causes of chronic ITP.
5. If the strain is susceptible to clarithromycin, triple therapy with amoxicillin and clarithromycin for 14 days is the preferred choice.
6. Sequential therapy should not be given if the strain is resistant to metronidazole or clarithromycinor if susceptibility testing is not available.
7. The doses of PPI and antibiotics should be calculated based on the body weight.
8. Younger children need a higher PPI dose per body weight compared to adolescents and adults to obtain sufficient acid suppression.
9. For children younger than 8 years, bismuth quadruple therapy refers to bismuth, amoxicillin, and metronidazole. In children older than 8 years, bismuth quadruple therapy refers to bismuth, tetracycline, and metronidazole,
10. Current evidence does not support the routine addition of either single or combination probiotics to eradication therapy to reduce side effects and/or improve eradication rates.
11. When *H. pylori* treatment fails, rescue therapy should be individualized considering antibiotic susceptibility, the age of the child, and available antimicrobial options.

In 2020, a recent update for Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition recommended *H. pylori* eradication for children with the following conditions[165]:

a. Gastric and/or duodenal ulcers.
b. Histological evidence of chronic gastritis
c. Gastric MALT lymphoma.
d. Protein-losing gastro-enteropathy, if other etiologies for the gastrointestinal protein loss are not found.
e. IDA, when recurrent or refractory to iron supplement therapy.
f. Chronic ITP as the first line therapy.
g. Chronic idiopathic urticaria.

Adverse Effects (AE) of *H. pylori* treatments

The *H. pylori* eradication regimens are widely available in daily clinical practice. Overall, they are considered to be safe with good tolerability.[37] AEs of the standard *H. pylori* treatment have been observed in about 20% of the patients, with the majority being mild. However, severe type of AEs that necessitate medication discontinuations can occur in about 3% of patients. Nevertheless, serious adverse reactions were rarely reported. The common adverse reactions are fatigue (12%), anorexia (10%), abdominal pain/discomfort (9%), and diarrhea (8%).[166-168]

Headache, skin rash, and dizziness have been reported in (1–3%) of the patients on levofloxacin.[169] AEs have been recorded as well with the rescue therapy. For instance, myalgia and taste perversion were significantly more frequent with rifabutin compared to placebo.[170] Severe neutropenia and anemia have been reported in (0.4%) of patients treated with rifabutin.[171] In recent studies, myelotoxicity was the most significant adverse event of rifabutin. This complication is rare and occurred when a higher dose was used for a prolonged duration.[172,173] In a population-based study in Hong Kong, the use of clarithromycin was associated with an increased risk of myocardial infarction, arrhythmia, and cardiac mortality in the short term, but not with long-term cardiovascular risks.[174] All patients with chronic renal or hepatic diseases should have an adjustment for some of the antimicrobial doses [Table 8].

Protective role of *H. pylori*

There have been signals that the eradication of *H. pylori* has been associated with an increase in the incidence of allergic asthma and other allergy-mediated diseases.[177,178] This might be a direct AE from the drugs used in eradication therapy, or by losing the inhibitory effect of *H. pylori* on inflammation induced by T helper response; however, no convincing molecular mechanism has been proposed to support this theory. The risk of causing selective pressure on the organism and accelerating new antibiotic resistant strains causing loss of the efficacy of these drugs for its future use if needed. Also, where do antibiotic stewardship programs stand when it comes to universal eradication of *H. pylori* from the population?[179,180] These questions and more might be mitigated by targeting those who have developed complications from the infection or those at high risk of developing complications.[181-184] In addition, the potential downside of repeated antibiotic exposure in those who are at increased risk of adverse events, such as the elderly who have failed repeated courses of antibiotics, should be addressed on an individual level. Both epidemiological and basic experimental studies suggested a protective role of *H. pylori* infection against inflammatory bowel disease. In a meta-analysis, pooled relative risk depended on both, the region and the subtype (more protection against Crohn's disease in the East Asian region).

In a case–controlled study, the rate of *H. pylori* infection was significantly lower in patients with ulcerative colitis (UC) compared with the control group, suggesting a protective role of *H. pylori* against the occurrence of UC.[185-187]

Cost effectiveness of *H. pylori* eradication

Although eradication of *H. pylori* is cost effective in the prevention of gastric cancer on an individual level,[188] whether a nationwide program for *H. pylori* eradication should be adopted would depend on numerous factors, some of which would be *H. pylori* prevalence in the population, the virulence of the prevalent strain, the success and cost of therapy, the willingness to pay threshold, and other factors. In a cost-effective study from Japan, it was modeled that a population-based eradication for all would be cost effective.[189] The Taipei global consensus recommended that a "screen-and-treat" strategy would be most cost effective in young adults in regions with a high incidence of gastric cancer.[190] To the counter argument, in a long-term follow-up study (13 years) of a randomized trial with an economic impact analysis from Denmark, there was no effect in terms of quality of life, and the cost of screening was higher compared to no screening.[191] Another element that would influence whether the eradication of *H. pylori* would be cost effective is the cost and the efficacy of the therapy in a particular population. This would encompass a mixture of drug resistance, cost of medication and testing, the adherence rate to therapy, and other factors. In a study comparing the efficacy of two regimens for the eradication of *H. pylori* in Saudi Arabia, AlRuthia *et al*.[192] found that sequential therapy was more cost saving and more effective with 56.25% confidence level, in comparison to standard triple therapy.

Vaccination against *H. pylori*

A vaccine against *H. pylori* would be a very attractive strategy for prevention of its complications but has been hindered since the initial trials in 1992. This is related to numerous factors of which is its ability to immunomodulate and evade the immune response of the human body against it. Several antigens have been targeted in the development of a human vaccine against *H. pylori* some of which include urease, catalase, CagA, VacA, and others. In addition to the technical challenges associated with the development of a vaccine against *H. pylori*, there have been other factors related to the financing of the studies.[193]

Future direction

Further studies are required to know the exact incidence and prevalence of *H. pylori* in Saudi Arabia. In addition, *H. pylori* antimicrobial susceptibility testing to different antibiotics using culture or non-culture test with a new generation PCR and DNA extraction technology is recommended. Randomized clinical trials are needed to determine the most appropriate duration of many regimens, such as quadruple therapy (10-day vs. 14-day), and if higher dosages of PPI and antimicrobials, such as amoxicillin and metronidazole, will improve the eradication rate of *H. pylori* infection. The efficacy of other regimens to eradicate *H. pylori* in Saudi Arabia, such as concomitant therapy, hybrid therapy, high-dose dual therapy, and bismuth-based quadruple therapy along with probiotics, vonoprazan-based triple therapy, and rifabutin-based therapy are unknown, and further clinical trials are needed. Therapies for treating patients who failed multiple treatment regimens are necessary. Finally, the working group recommends reviewing and updating this consensus report within 5–10 years.

Acknowledgements

The authors thank Rhea Laguerta for her support in writing the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Malaty HM, Engstrand L, Pedersen NL, Graham DY. Helicobacter pylori infection: Genetic and environmental influences. A study of twins. Ann Intern Med 1994;120:982-6.
2. Testerman TL, Morris J. Beyond the stomach: An updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. World J Gastroenterol 2014;20:12781-808.
3. Mitchell H, Katelaris P. Epidemiology, clinical impacts and current clinical management of Helicobacter pylori infection. Med J Aust 2016;204:376-80.
4. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, *et al*. Global prevalence of Helicobacter pylori infection: Systematic review and meta-analysis. Gastroenterology 2017;153:420-9.
5. al-Moagel MA, Evans DG, Abdulghani ME, Adam E, Evans DJ Jr, Malaty HM, *et al*. Prevalence of Helicobacter (formerly Campylobacter) pylori infection in Saudia Arabia, and comparison of those with and without upper gastrointestinal symptoms. Am J Gastroenterol 1990;85:944-8.
6. Almadi MA, Aljebreen AM, Tounesi FA, Abdo AA. Helicobacter pylori prevalence among medical students in a high endemic area. Saudi Med J 2007;28:896-8.
7. Telmesani AM. Helicobacter pylori: Prevalence and relationship with abdominal pain in school children in Makkah City, western Saudi Arabia. Saudi J Gastroenterol 2009;15:100-3.
8. Hanafi MI, Mohamed AM. Helicobacter pylori infection: Seroprevalence and predictors among healthy individuals in Al Madinah, Saudi Arabia. J Egypt Public Health Assoc 2013;88:40-5.
9. Akeel M, Elmakki E, Shehata A, Elhafey A, Aboshouk T, Ageely H, *et al*. Prevalence and factors associated with *H. pylori* infection in Saudi patients with dyspepsia. Electron Physician 2018;10:7279-86.
10. Alharbi RH, Ghoraba M. Prevalence and patient characteristics of Helicobacter pylori among adult in primary health care of security

forces hospital Riyadh, Saudi Arabia, 2018. J Family Med Prim Care 2019;8:2202-6.
11. Weyermann M, Rothenbacher D, Brenner H. Acquisition of Helicobacter pylori infection in early childhood: Independent contributions of infected mothers, fathers, and siblings. Am J Gastroenterol 2009;104:182-9.
12. Dore MP, Bilotta M, Vaira D, Manca A, Massarelli G, Leandro G, *et al*. High prevalence of Helicobacter pylori infection in shepherds. Dig Dis Sci 1999;44:1161-4.
13. Kayali S, Manfredi M, Gaiani F, Bianchi L, Bizzarri B, Leandro G, *et al*. Helicobacter pylori, transmission routes and recurrence of infection: State of the art. Acta Biomed 2018;89:72-6.
14. Bellack NR, Koehoorn MW, MacNab YC, Morshed MG. A conceptual model of water's role as a reservoir in Helicobacter pylori transmission: Areview of the evidence. Epidemiol Infect 2006;134:439-49.
15. Alagl AS, Abdelsalam M, El Tantawi M, Madi M, Aljindan R, Alsayyah A, *et al*. Association between Helicobacter pylori gastritis and dental diseases: A cross-sectional, hospital-based study in Eastern Saudi Arabia. J Periodontol 2019;90:375-80.
16. Choi YK, Ahn JY, Won SH, Jung K, Na HK, Jung KW, *et al*. Eradication rate of Helicobacter pylori reinfection in Korea: A retrospective study. J Gastroenterol Hepatol 2019;34:1696-702.
17. Xie Y, Song C, Cheng H, Xu C, Zhang Z, Wang J, *et al*. Long-term follow-up of Helicobacter pylori reinfection and its risk factors after initial eradication: Alarge-scale multicentre, prospective open cohort, observational study. Emerg Microbes Infect 2020;9:548-57.
18. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: Aworldwide incidence analysis. Lancet Glob Health 2020;8:e180-90.
19. Gong EJ, Ahn JY, Jung HY, Park H, Ko YB, Na HK, *et al*. Helicobacter pylori eradication therapy is effective as the initial treatment for patients with *H. pylori*-Negative and disseminated gastric mucosa-associated lymphoid tissue lymphoma. Gut Liver 2016;10:706-13.
20. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, *et al*. Association between Helicobacter pylori eradication and gastric cancer incidence: A systematic review and meta-analysis. Gastroenterology 2016;150:1113-24.e15.
21. Samuel R, Bilal M, Tayyem O, Guturu P. Evaluation and management of Non-variceal upper gastrointestinal bleeding. Dis Mon 2018;64:333-43.
22. Tsay FW, Hsu PI. *H. pylori* infection and extra-gastroduodenal diseases. J Biomed Sci 2018;25:65.
23. Muhsen K, Cohen D. Helicobacter pylori infection and iron stores: Asystematic review and meta-analysis. Helicobacter 2008;13:323-40.
24. Kim BJ, Kim HS, Jang HJ, Kim JH. Helicobacter pylori eradication in idiopathic thrombocytopenic purpura: A meta-analysis of randomized trials. Gastroenterol Res Pract 2018;2018:6090878.
25. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, *et al*. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829-66.
26. Rizwan M, Fatima N, Alvi A. Epidemiology and pattern of antibiotic resistance in Helicobacter pylori: Scenario from Saudi Arabia. Saudi J Gastroenterol 2014;20:212-8.
27. Ashton-Key M, Diss TC, Isaacson PG. Detection of Helicobacter pylori in gastric biopsy and resection specimens. J Clin Pathol 1996;49:107-11.
28. Grove DI, Koutsouridis G, Cummins AG. Comparison of culture, histopathology and urease testing for the diagnosis of Helicobacter pylori gastritis and susceptibility to amoxycillin, clarithromycin, metronidazole and tetracycline. Pathology 1998;30:183-7.
29. Loffeld RJ, Stobberingh E, Flendrig JA, Arends JW. Helicobacter pylori in gastric biopsy specimens. Comparison of culture, modified giemsa stain, and immunohistochemistry. A retrospective study. J Pathol 1991;165:69-73.
30. Patel SK, Pratap CB, Jain AK, Gulati AK, Nath G. Diagnosis of Helicobacter pylori: What should be the gold standard? World J Gastroenterol 2014;20:12847-59.
31. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20:1161-81.
32. Fox JG, Yan L, Shames B, Campbell J, Murphy JC, Li X. Persistent hepatitis and enterocolitis in germfree mice infected with Helicobacter hepaticus. Infect Immun 1996;64:3673-81.
33. Ng VL, Hadley WK, Fennell CL, Flores BM, Stamm WE. Successive bacteremias with "Campylobacter cinaedi" and "Campylobacter fennelliae" in a bisexual male. J Clin Microbiol 1987;25:2008-9.
34. Grayson ML, Tee W, Dwyer B. Gastroenteritis associated with Campylobacter cinaedi. Med J Aust 1989;150:214-5.
35. Du MQ, Isaacson PG. Recent advances in our understanding of the biology and pathogenesis of gastric mucosa-associated lymphoid tissue (malt) lymphoma. Forum (Genova) 1998;8:162-73.
36. Han SW, Flamm R, Hachem CY, Kim HY, Clarridge JE, Evans DG, *et al*. Transport and storage of Helicobacter pylori from gastric mucosal biopsies and clinical isolates. Eur J Clin Microbiol Infect Dis 1995;14:349-52.
37. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol 2017;112:212-39.
38. Wundisch T, Dieckhoff P, Greene B, Thiede C, Wilhelm C, Stolte M, *et al*. Second cancers and residual disease in patients treated for gastric mucosa-associated lymphoid tissue lymphoma by Helicobacter pylori eradication and followed for 10 years. Gastroenterology 2012;143:936-42; quiz e913-34.
39. Ferreri AJ, Govi S, Ponzoni M. The role of Helicobacter pylori eradication in the treatment of diffuse large B-cell and marginal zone lymphomas of the stomach. Curr Opin Oncol 2013;25:470-9.
40. Yang YX, Brill J, Krishnan P, Leontiadis G, American gastroenterological association clinical practice guidelines C. American gastroenterological association institute guideline on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology 2015;149:1082-7.
41. Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Aliment Pharmacol Ther 2002;16:779-86.
42. Lanza FL, Chan FK, Quigley EM, Practice parameters committee of the American College of G. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104:728-38.
43. Yuan W, Li Yumin, Yang Kehu, Ma Bin, Guan Quanlin, Wang D, *et al*. Iron deficiency anemia in Helicobacter pylori infection: Meta-analysis of randomized controlled trials. Scand J Gastroenterol 2010;45:665-76.
44. Jackson S, Beck PL, Pineo GF, Poon MC. Helicobacter pylori eradication: Novel therapy for immune thrombocytopenic purpura? A review of the literature. Am J Hematol 2005;78:142-50.
45. Kato M, Ota H, Okuda M, Kikuchi S, Satoh K, Shimoyama T, *et al*. Guidelines for the management of Helicobacter pylori infection in Japan: 2016 Revised Edition. Helicobacter 2019;24:e12597.
46. Ding SZ, Du YQ, Lu H, Wang WH, Cheng H, Chen SY, *et al*. Chinese Consensus Report on Family-based Helicobacter pylori Infection control and management (2021 Edition). Gut 2022;71:238-53.
47. El-Serag HB, Kao JY, Kanwal F, Gilger M, LoVecchio F, Moss SF, *et al*. Houston Consensus Conference on Testing for Helicobacter pylori Infection in the United States. Clin Gastroenterol Hepatol 2018;16:992-1002.e6.
48. Kawanishi M. Development of reflux esophagitis following Helicobacter pylori eradication. J Gastroenterol 2005;40:1024-8.
49. Ishiki K, Mizuno M, Take S, Nagahara Y, Yoshida T, Yamamoto K, *et al*. Helicobacter pylori eradication improves pre-existing reflux esophagitis in patients with duodenal ulcer disease. Clin Gastroenterol Hepatol 2004;2:474-9.
50. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, *et al*. Management of Helicobacter pylori infection-the

Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
51. Leal YA, Flores LL, Garcia-Cortes LB, Cedillo-Rivera R, Torres J. Antibody-based detection tests for the diagnosis of Helicobacter pylori infection in children: Ameta-analysis. PLoS One 2008;3:e3751.
52. Loy CT, Irwig LM, Katelaris PH, Talley NJ. Do commercial serological kits for Helicobacter pylori infection differ in accuracy? A meta-analysis. Am J Gastroenterol 1996;91:1138-44.
53. Savarino V, Vigneri S, Celle G. The 13C urea breath test in the diagnosis of Helicobacter pylori infection. Gut1999;45(Suppl 1):18-22.
54. Ferwana M, Abdulmajeed I, Alhajiahmed A, Madani W, Firwana B, Hasan R, *et al*. Accuracy of urea breath test in Helicobacter pylori infection: Meta-analysis. World J Gastroenterol 2015;21:1305-14.
55. McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med 2010;362:1597-604.
56. Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection -- Acritical review. Aliment Pharmacol Ther 2004;20:1001-17.
57. Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: Asystematic review and meta-analysis. Am J Gastroenterol 2006;101:1921-30.
58. Roy AD, Deuri S, Dutta UC. The diagnostic accuracy of rapid urease biopsy test compared to histopathology in implementing "test and treat" policy for Helicobacter pylori. Int J Appl Basic Med Res 2016;6:18-22.
59. Midolo P, Marshall BJ. Accurate diagnosis of Helicobacter pylori. Urease tests. Gastroenterol Clin North Am 2000;29:871-8.
60. Montgomery EA, Martin DF, Peura DA. Rapid diagnosis of Campylobacter pylori by Gram's stain. Am J Clin Pathol 1988;90:606-9.
61. Zaitoun AM. Use of Romanowsky type (Diff-3) stain for detecting Helicobacter pylori in smears and tissue sections. J Clin Pathol 1992;45:448-9.
62. el-Zimaity HM. Accurate diagnosis of Helicobacter pylori with biopsy. Gastroenterol Clin North Am 2000;29:863-9.
63. Toulaymat M, Marconi S, Garb J, Otis C, Nash S. Endoscopic biopsy pathology of Helicobacter pylori gastritis. Comparison of bacterial detection by immunohistochemistry and Genta stain. Arch Pathol Lab Med 1999;123:778-81.
64. Anim JT, Al-Sobkie N, Prasad A, John B, Sharma PN, Al-Hamar I. Assessment of different methods for staining Helicobacter pylori in endoscopic gastric biopsies. Acta Histochem 2000;102:129-37.
65. Hsu WH, Wang SS, Kuo CH, Chen CY, Chang CW, Hu HM, *et al*. Dual specimens increase the diagnostic accuracy and reduce the reaction duration of rapid urease test. World J Gastroenterol 2010;16:2926-30.
66. Lan HC, Chen TS, Li AF, Chang FY, Lin HC. Additional corpus biopsy enhances the detection of Helicobacter pylori infection in a background of gastritis with atrophy. BMC Gastroenterol 2012;12:182.
67. van IMC, Laheij RJ, de Boer WA, Jansen JB. The importance of corpus biopsies for the determination of Helicobacter pylori infection. Neth J Med 2005;63:141-5.
68. El-Zimaity HM, Graham DY. Evaluation of gastric mucosal biopsy site and number for identification of Helicobacter pylori or intestinal metaplasia: Role of the Sydney system. Hum Pathol 1999;30:72-7.
69. Fiorini G, Vakil N, Zullo A, Saracino IM, Castelli V, Ricci C, *et al*. Culture-based selection therapy for patients who did not respond to previous treatment for Helicobacter pylori infection. Clin Gastroenterol Hepatol 2013;11:507-10.
70. Savarino V, Zentilin P, Pivari M, Bisso G, RaffaellaMele M, Bilardi C, *et al*. The impact of antibiotic resistance on the efficacy of three 7-day regimens against Helicobacter pylori. Aliment Pharmacol Ther 2000;14:893-900.
71. Megraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. Clin Microbiol Rev 2007;20:280-322.
72. Gerrits MM, van Vliet AH, Kuipers EJ, Kusters JG. Helicobacter pylori and antimicrobial resistance: Molecular mechanisms and clinical implications. Lancet Infect Dis 2006;6:699-709.
73. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in Helicobacter pylori: A systematic review and meta-analysis in World Health Organization regions. Gastroenterology 2018;155:1372-82.e17.
74. Alsohaibani F, Al Ashgar H, Al Kahtani K, Kagevi I, Peedikayil M, Alfadda A, *et al*. Prospective trial in Saudi Arabia comparing the 14-day standard triple therapy with the 10-day sequential therapy for treatment of Helicobacter pylori infection. Saudi J Gastroenterol 2015;21:220-5.
75. Valdivieso-Garcia A, Imgrund R, Deckert A, Varughese BM, Harris K, Bunimov N, *et al*. Cost analysis and antimicrobial susceptibility testing comparing the E test and the agar dilution method in Campylobacter jejuni and Campylobacter coli. Diagn Microbiol Infect Dis 2009;65:168-74.
76. Chisholm SA, Owen RJ. Application of polymerase chain reaction-based assays for rapid identification and antibiotic resistance screening of Helicobacter pylori in gastric biopsies. Diagn Microbiol Infect Dis 2008;61:67-71.
77. Vaira D, Vakil N, Menegatti M, van't Hoff B, Ricci C, Gatta L, *et al*. The stool antigen test for detection of Helicobacter pylori after eradication therapy. Ann Intern Med 2002;136:280-7.
78. Chey WD, Metz DC, Shaw S, Kearney D, Montague J, Murthy U. Appropriate timing of the 14C-urea breath test to establish eradication of Helicobacter pylori infection. Am J Gastroenterol 2000;95:1171-4.
79. Neil GA, Suchower LJ, Ronca PD, Skoglund ML. Time of Helicobacter pylori eradication assessment following treatment. Helicobacter 1997;2:13-20.
80. Gatta L, Ricci C, Tampieri A, Osborn J, Perna F, Bernabucci V, *et al*. Accuracy of breath tests using low doses of 13C-urea to diagnose Helicobacter pylori infection: Arandomised controlled trial. Gut 2006;55:457-62.
81. Gisbert JP, Pajares JM. Stool antigen test for the diagnosis of Helicobacter pylori infection: Asystematic review. Helicobacter 2004;9:347-68.
82. Nishikawa K, Sugiyama T, Kato M, Ishizuka J, Kagaya H, Hokari K, *et al*. A prospective evaluation of new rapid urease tests before and after eradication treatment of Helicobacter pylori, in comparison with histology, culture and 13C-urea breath test. Gastrointest Endosc 2000;51:164-8.
83. Eed EM, Hawash YA, Khalifa AS, Alsharif KF, Alghamdi SA, Saber T, *et al*. Molecular diagnosis of Helicobacter pylori antibiotic resistance in the Taif region, Saudi Arabia. Microbiol Immunol 2019;63:199-205.
84. Momenah A, Asghar A. Prevalence and antibiotic resistance among Helicobacter pylori clinical isolates from main Hospitals in the Western Region of Saudi Arabia. Pak J Med Sci 2008;24:100-3.
85. Eltahawy AT. Prevalence of primary Helicobacter pylori resistance to several antimicrobials in a Saudi Teaching Hospital. Med Princ Pract 2002;11:65-8.
86. Sezgin O, Aydin MK, Ozdemir AA, Kanik AE. Standard triple therapy in Helicobacter pylori eradication in Turkey: Systematic evaluation and meta-analysis of 10-year studies. Turk J Gastroenterol 2019;30:420-35.
87. Zhang G, Zou J, Liu F, Bao Z, Dong F, Huang Y, *et al*. The efficacy of moxifloxacin-based triple therapy in treatment of Helicobacter pylori infection: Asystematic review and meta-analysis of randomized clinical trials. Braz J Med Biol Res 2013;46:607-13.
88. Venerito M, Krieger T, Ecker T, Leandro G, Malfertheiner P. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of Helicobacter pylori infection. Digestion 2013;88:33-45.
89. Lee SW, Kim HJ, Kim JG. Treatment of Helicobacter pylori Infection in Korea: A systematic review and meta-analysis. J Korean Med Sci 2015;30:1001-9.
90. Kim JS, Ji JS, Choi H, Kim JH. Sequential therapy or triple therapy for Helicobacter pylori infection in Asians: Systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2014;38:118-25.
91. Kale-Pradhan PB, Mihaescu A, Wilhelm SM. Fluoroquinolone Sequential Therapy for Helicobacter pylori: A meta-analysis. Pharmacotherapy 2015;35:719-30.

92. Gong EJ, Yun SC, Jung HY, Lim H, Choi KS, Ahn JY, *et al*. Meta-analysis of first-line triple therapy for Helicobacter pylori eradication in Korea: Is it time to change? J Korean Med Sci 2014;29:704-13.
93. Luther J, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 2010;105:65-73.
94. Xiao SP, Gu M, Zhang GX. Is levofloxacin-based triple therapy an alternative for first-line eradication of Helicobacter pylori? A systematic review and meta-analysis. Scand J Gastroenterol 2014;49:528-38.
95. Guo B, Cao NW, Zhou HY, Chu XJ, Li BZ. Efficacy and safety of bismuth-containing quadruple treatment and concomitant treatment for first-line Helicobacter pylori eradication: A systematic review and meta-analysis. Microb Pathog 2021;152:104661.
96. Yeo YH, Shiu SI, Ho HJ, Zou B, Lin JT, Wu MS, *et al*. First-line Helicobacter pylori eradication therapies in countries with high and low clarithromycin resistance: Asystematic review and network meta-analysis. Gut 2018;67:20-7.
97. Zou Y, Qian X, Liu X, Song Y, Song C, Wu S, *et al*. The effect of antibiotic resistance on Helicobacter pylori eradication efficacy: A systematic review and meta-analysis. Helicobacter 2020;25:e12714.
98. Li BZ, Threapleton DE, Wang JY, Xu JM, Yuan JQ, Zhang C, *et al*. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: Systematic review and network meta-analysis. BMJ 2015;351:h4052.
99. Puig I, Baylina M, Sanchez-Delgado J, López-Gongora S, Suarez D, García-Iglesias P, *et al*. Systematic review and meta-analysis: Triple therapy combining a proton-pump inhibitor, amoxicillin and metronidazole for Helicobacter pylori first-line treatment. J Antimicrob Chemother 2016;71:2740-53.
100. Nyssen OP, Perez-Aisa A, Castro-Fernandez M, Pellicano R, Huguet JM, Rodrigo L, *et al*. European Registry on Helicobacter pylori management: Single-capsule bismuth quadruple therapy is effective in real-world clinical practice. United European Gastroenterol J 2021;9:38-46.
101. Alsohaibani F, Alquaiz M, Alkahtani K, Alashgar H, Peedikayil M, AlFadda A, *et al*. Efficacy of a bismuth-based quadruple therapy regimen for Helicobacter pylori eradication in Saudi Arabia. Saudi J Gastroenterol 2020;26:84-8.
102. Ko SW, Kim YJ, Chung WC, Lee SJ. Bismuth supplements as the first-line regimen for Helicobacter pylori eradication therapy: Systemic review and meta-analysis. Helicobacter 2019;24:e12565.
103. Mestrovic A, Perkovic N, Bozic J, PavicicIvelja M, Vukovic J, Kardum G, *et al*. Randomised clinical trial comparing concomitant and hybrid therapy for eradication of Helicobacter pylori infection. PLoS One 2020;15:e0244500.
104. Xu H, Wang W, Ma X, Feng R, Su Y, Cheng L, *et al*. Comparative efficacy and safety of high-dose dual therapy, bismuth-based quadruple therapy and non-bismuth quadruple therapies for Helicobacter pylori infection: Anetwork meta-analysis. Eur J Gastroenterol Hepatol 2021;33:775-86.
105. Losurdo G, Leandro G, Principi M, Giorgio F, Montenegro L, Sorrentino C, *et al*. Sequential vs. prolonged 14-day triple therapy for Helicobacter pylori eradication: The meta-analysis may be influenced by 'geographical weighting'. Int J Clin Pract 2015;69:1112-20.
106. Liou JM, Chen CC, Lee YC, Chang CY, Wu JY, Bair MJ, *et al*. Systematic review with meta-analysis: 10- or 14-day sequential therapy vs. 14-day triple therapy in the first line treatment of Helicobacter pylori infection. Aliment Pharmacol Ther 2016;43:470-81.
107. Nyssen OP, McNicholl AG, Megraud F, Savarino V, Oderda G, Fallone CA, *et al*. Sequential versus standard triple first-line therapy for Helicobacter pylori eradication. Cochrane Database Syst Rev 2016;2016:CD009034.
108. Wang Y, Zhao R, Wang B, Zhao Q, Li Z, Zhu-Ge L, *et al*. Sequential versus concomitant therapy for treatment of Helicobacter pylori infection: An updated systematic review and meta-analysis. Eur J Clin Pharmacol 2018;74:1-13.
109. Munteanu D, Etzion O, Ben-Yakov G, Halperin D, Eidelman L, Schwartz D, *et al*. Efficacy and safety of sequential versus quadruple therapy as second-line treatment for Helicobacter pylori infection-A randomized controlled trial. PLoS One 2017;12:e0183302.
110. Jung YS, Park CH, Park JH, Nam E, Lee HL. Efficacy of Helicobacter pylori eradication therapies in Korea: A systematic review and network meta-analysis. Helicobacter 2017;22.doi: 10.1111/hel. 12389.
111. Yurenev GL, Partzvania-Vinogradova EV, Andreev DN, Dicheva DT, Maiev IV. Evaluation of the efficacy and safety of the hybrid scheme for eradication therapy of Helicobacter pylori infection. Ter Arkh 2018;90:33-9.
112. Song ZQ, Zhou LY. Hybrid, sequential and concomitant therapies for Helicobacter pylori eradication: A systematic review and meta-analysis. World J Gastroenterol 2016;22:4766-75.
113. Chen KY, Lin TJ, Lin CL, Lee HC, Wang CK, Wu DC. Hybrid vs sequential therapy for eradication of Helicobacter pylori in Taiwan: A prospective randomized trial. World J Gastroenterol 2015;21:10435-42.
114. Zhang Y, Zhu YJ, Zhao Z, Zhao JT, Wang TY, Yang J, *et al*. Efficacy of modified esomeprazole-amoxicillin dual therapies for Helicobacter pylori infection: An open-label, randomized trial. Eur J Gastroenterol Hepatol 2020;32:563-8.
115. Gao CP, Zhang D, Zhang T, Wang JX, Han SX, Graham DY, *et al*. PPI-amoxicillin dual therapy for Helicobacter pylori infection: An update based on a systematic review and meta-analysis. Helicobacter 2020;25:e12692.
116. Chen PY, Wu MS, Chen CY, Bair MJ, Chou CK, Lin JT, *et al*. Systematic review with meta-analysis: The efficacy of levofloxacin triple therapy as the first- or second-line treatments of Helicobacter pylori infection. Aliment Pharmacol Ther 2016;44:427-37.
117. Peedikayil MC, Alsohaibani FI, Alkhenizan AH. Levofloxacin-based first-line therapy versus standard first-line therapy for Helicobacter pylori eradication: Meta-analysis of randomized controlled trials. PLoS One 2014;9:e85620.
118. Alsohaibani FI, Alharfi SA, Almadi MA. Efficacy of levofloxacin doxycycline based rescue therapy for Helicobacter pylori eradication: A prospective open-label trial in Saudi Arabia. J Health Spec 2017;5:155-61.
119. Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N. Efficacy of moxifloxacin-based sequential and hybrid therapy for first-line Helicobacter pylori eradication. World J Gastroenterol 2015;21:10234-41.
120. Nyssen OP, Vaira D, Saracino IM, Fiorini G, Caldas M, Bujanda L, *et al*. Experience with Rifabutin-containing therapy in 500 Patients from the European Registry on Helicobacter pylori Management (Hp-EuReg). J Clin Med 2022;11:1658.
121. Gingold-Belfer R, Niv Y, Levi Z, Boltin D. Rifabutin triple therapy for first-line and rescue treatment of Helicobacter pylori infection: A systematic review and meta-analysis. J Gastroenterol Hepatol 2021;36:1392-402.
122. Navarro-Jarabo JM, Fernandez N, Sousa FL, Cabrera E, Castro M, Ramírez LM, *et al*. Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate Helicobacter pylori infection. BMC Gastroenterol 2007;7:31.
123. Xin Y, Manson J, Govan L, Harbour R, Bennison J, Watson E, *et al*. Pharmacological regimens for eradication of Helicobacter pylori: An overview of systematic reviews and network meta-analysis. BMC Gastroenterol 2016;16:80.
124. Saeed LH, Mayet AY. Genotype-phenotype analysis of CYP2C19 in healthy saudi individuals and its potential clinical implication in drug therapy. Int J Med Sci 2013;10:1497-502.
125. Lyu QJ, Pu QH, Zhong XF, Zhang J. Efficacy and safety of vonoprazan-based versus proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: A meta-analysis of randomized clinical trials. Biomed Res Int 2019;2019:9781212.
126. Ozaki H, Harada S, Takeuchi T, Kawaguchi S, Takahashi Y, Kojima Y,

et al. Vonoprazan, a novel potassium-competitive acid blocker, should be used for the Helicobacter pylori eradication therapy as first choice: A large sample study of vonoprazan in real world compared with our randomized control trial using second-generation proton pump inhibitors for Helicobacter pylori eradication therapy. Digestion 2018;97:212-8.
127. Shinozaki S, Kobayashi Y, Osawa H, Sakamoto H, Hayashi Y, Lefor AK, *et al*. Effectiveness and safety of vonoprazan versus proton pump inhibitors for second-line Helicobacter pylori eradication therapy: Systematic review and meta-analysis. Digestion 2021;102:319-25.
128. Abuhammour A, Dajani A, Nounou M, Zakaria M. Standard triple therapy versus sequential therapy for eradication of Helicobacter pylori in treatment naive and retreat patients. Arab J Gastroenterol 2016;17:131-6.
129. Abd-Elsalam S, Kobtan A, El-Kalla F, Elkhalawany W, Nawasany SE, Saif SA, *et al*. A 2-week Nitazoxanide-based quadruple treatment as a rescue therapy for Helicobacter pylori eradication: A single center experience. Medicine (Baltimore) 2016;95:e3879.
130. Shah SC, Iyer PG, Moss SF. AGA clinical practice update on the management of refractory Helicobacter pylori infection: Expert review. Gastroenterology 2021;160:1831-41.
131. Nyssen OP, McNicholl AG, Gisbert JP. Meta-analysis of three-in-one single capsule bismuth-containing quadruple therapy for the eradication of Helicobacter pylori. Helicobacter 2019;24:e12570.
132. Chang YL, Tung YC, Tu YK, Yeh HZ, Yang JC, Hsu PI, *et al*. Efficacy of second-line regimens for Helicobacter pylori eradication treatment: Asystemic review and network meta-analysis. BMJ Open Gastroenterol 2020;7:e000472.
133. Yeo YH, Hsu CC, Lee CC, Ho HJ, Lin JT, Wu MS, *et al*. Systematic review and network meta-analysis: Comparative effectiveness of therapies for second-line Helicobacter pylori eradication. J Gastroenterol Hepatol 2019;34:59-67.
134. Yang X, Wang JX, Han SX, Gao CP. High dose dual therapy versus bismuth quadruple therapy for Helicobacter pylori eradication treatment: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e14396.
135. Munoz N, Sanchez-Delgado J, Baylina M, Puig I, López-Góngora S, Suarez D, *et al*. Systematic review, meta-analysis, and meta-regression: Successful second-line treatment for Helicobacter pylori. Helicobacter 2018;23:e12488.
136. Zhang M, Chen CY, Wang XT, Lyu B. [Levofloxacin-based triple therapy versus bismuth-based quadruple therapy in the treatment of Helicobacter pylori as the rescue therapy: Ameta analysis]. Zhonghua Nei Ke Za Zhi 2017;56:368-74.
137. Chen H, Dang Y, Zhou X, Liu B, Liu S, Zhang G. Tailored therapy versus empiric chosen treatment for Helicobacter pylori eradication: A meta-analysis. Medicine (Baltimore) 2016;95:e2750.
138. Zhang MM, Qian W, Qin YY, He J, Zhou YH. Probiotics in Helicobacter pylori eradication therapy: Asystematic review and meta-analysis. World J Gastroenterol 2015;21:4345-57.
139. Lionetti E, Indrio F, Pavone L, Borrelli G, Cavallo L, Francavilla R. Role of probiotics in pediatric patients with Helicobacter pylori infection: Acomprehensive review of the literature. Helicobacter 2010;15:79-87.
140. Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. J Clin Gastroenterol 2013;47:25-32.
141. Ki Cha B, Mun Jung S, Hwan Choi C, Song ID, Woong Lee H, Joon Kim H, *et al*. The effect of a multispecies probiotic mixture on the symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: Arandomized, double-blind, placebo-controlled trial. J Clin Gastroenterol 2012;46:220-7.
142. Sun YY, Li M, Li YY, Li LX, Zhai WZ, Wang P, *et al*. The effect of Clostridium butyricum on symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: Arandomized, double-blind, placebo-controlled trial. Sci Rep 2018;8:2964.
143. Srinarong C, Siramolpiwat S, Wongcha-um A, Mahachai V, Vilaichone RK. Improved eradication rate of standard triple therapy by adding bismuth and probiotic supplement for Helicobacter pylori treatment in Thailand. Asian Pac J Cancer Prev 2014;15:9909-13.
144. Zhu R, Chen K, Zheng YY, Zhang HW, Wang JS, Xia YJ, *et al*. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. World J Gastroenterol 2014;20:18013-21.
145. Aiba Y, Nakano Y, Koga Y, Takahashi K, Komatsu Y. A highly acid-resistant novel strain of Lactobacillus johnsonii No. 1088 has antibacterial activity, including that against Helicobacter pylori, and inhibits gastrin-mediated acid production in mice. Microbiologyopen 2015;4:465-74.
146. Gotteland M, Brunser O, Cruchet S. Systematic review: Are probiotics useful in controlling gastric colonization by Helicobacter pylori? Aliment Pharmacol Ther 2006;23:1077-86.
147. Kim TS, Hur JW, Yu MA, Cheigh CI, Kim KN, Hwang JK, *et al*. Antagonism of Helicobacter pylori by bacteriocins of lactic acid bacteria. J Food Prot 2003;66:3-12.
148. Wiese M, Eljaszewicz A, Andryszczyk M, Gronek S, Gackowska L, Kubiszewska I, *et al*. Immunomodulatory effects of Lactobacillous plantarum and Helicobacter pylori CagA(+) on the expression of selected superficial molecules on monocyte and lymphocyte and the synthesis of cytokines in whole blood culture. J Physiol Pharmacol 2012;63:217-24.
149. Kim MN, Kim N, Lee SH, The effects of probiotics on PPI-triple therapy for Helicobacter pylori eradication, *et al*. The effects of probiotics on PPI-triple therapy for Helicobacter pylori eradication. Helicobacter 2008;13:261-8.
150. Bhatia SJ, Kochar N, Abraham P, Nair NG, Mehta AP. Lactobacillus acidophilus inhibits growth of Campylobacter pylori in vitro. J Clin Microbiol 1989;27:2328-30.
151. Sgouras D, Maragkoudakis P, Petraki K, Martinez-Gonzalez B, Eriotou E, Michopoulos S, *et al*. *In vitro* and *in vivo* inhibition of Helicobacter pylori by Lactobacillus casei strain Shirota. Appl Environ Microbiol 2004;70:518-26.
152. Zheng X, Lyu L, Mei Z. Lactobacillus-containing probiotic supplementation increases Helicobacter pylori eradication rate: Evidence from a meta-analysis. Rev Esp Enferm Dig 2013;105:445-53.
153. Lu M, Yu S, Deng J, Yan Q, Yang C, Xia G, *et al*. Efficacy of probiotic supplementation therapy for Helicobacter pylori eradication: A meta-analysis of randomized controlled trials. PLoS One 2016;11:e0163743.
154. Li S, Huang XL, Sui JZ, hen SY, Xie YT, Deng Y, *et al*. Meta-analysis of randomized controlled trials on the efficacy of probiotics in Helicobacter pylori eradication therapy in children. Eur J Pediatr 2014;173:153-61.
155. Sachdeva A, Nagpal J. Effect of fermented milk-based probiotic preparations on Helicobacter pylori eradication: Asystematic review and meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol 2009;21:45-53.
156. Lee M, Kemp JA, Canning A, Egan C, Tataronis G, Farraye FA. A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy. Arch Intern Med 1999;15:2312-6.
157. Graham DY, Lew GM, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, *et al*. Factors influencing the eradication of Helicobacter pylori with triple therapy. Gastroenterology 1992;102:493-6.
158. O'Connor JP, Taneike I, O'Morain C. Improving compliance with Helicobacter pylori eradication therapy: When and how? Therap Adv Gastroenterol 2009;2:273-9.
159. Kalach N, Bontems P, Raymond J. Helicobacter pylori infection in children. Helicobacter 2017;22(Suppl 1).doi: 10.1111/hel. 12414.
160. Kato S, Abukawa D, Furuyama N, Iinuma K. Helicobacter pylori reinfection rates in children after eradication therapy. J Pediatr Gastroenterol Nutr 1998;27:543-6.
161. Muhsen K, Jurban M, Goren S, Cohen D. Incidence, age of acquisition

and risk factors of Helicobacter pylori infection among Israeli Arab infants. J Trop Pediatr 2012;58:208-13.
162. Spee LA, Madderom MB, Pijpers M, van Leeuwen Y, Berger MY. Association between Helicobacter pylori and gastrointestinal symptoms in children. Pediatrics 2010;125:e651-69.
163. Huang SC, Sheu BS, Lee SC, Yang HB, Yang YJ. Etiology and treatment of childhood peptic ulcer disease in Taiwan: Asingle center 9-year experience. J Formos Med Assoc 2010;109:75-81.
164. Jones NL, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, *et al*. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr 2017;64:991-1003.
165. Kato S, Shimizu T, Toyoda S, Gold BD, Ida S, Ishige T, *et al*. The updated JSPGHAN guidelines for the management of Helicobacter pylori infection in childhood. Pediatr Int 2020;62:1315-31.
166. Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: The effects of *Saccharomyces boulardii* supplementation on Helicobacter pylori eradication rates and side effects during treatment. Aliment Pharmacol Ther 2010;32:1069-79.
167. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, *et al*. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34-42.
168. Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of Helicobacter pylori infection: Past, present and future. World J Gastrointest Pathophysiol 2014;5:392-9.
169. Gisbert JP, Morena F. Systematic review and meta-analysis: Levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. Aliment Pharmacol Ther 2006;23:35-44.
170. Gisbert JP. Rifabutin for the treatment of Helicobacter pylori infection: A review. Pathogens 2020;10:15.
171. Apseloff G, Fluids G, LaBoy-Goral L, Kraut E, Vincent J. Severe neutropenia caused by recommended prophylactic doses of rifabutin. Lancet 1996;348:685.
172. Griffith DE, Brown BA, Girard WM, Wallace RJ Jr. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. Clin Infect Dis 1995;21:594-8.
173. Liu X, Wang H, Lv Z, Wang Y, Wang B, Xie Y, *et al*. Rescue therapy with a proton pump inhibitor plus amoxicillin and rifabutin for Helicobacter pylori infection: A systematic review and meta-analysis. Gastroenterol Res Pract 2015;2015:415648.
174. Wong AY, Root A, Douglas IJ, Chui CSL, Chan EW, Ghebremichael-Weldeselassie Y, *et al*. Cardiovascular outcomes associated with use of clarithromycin: Population based study. BMJ 2016;352:h6926.
175. Weersink RA, Bouma M, Burger DM, Drenth JP, Hunfeld NG, Kranenborg M, *et al*. Evaluating the safety and dosing of drugs in patients with liver cirrhosis by literature review and expert opinion. BMJ Open 2016;6:e012991.
176. Aloy B, Launay-Vacher V, Bleibtreu A, Bortolotti P, Faure E, Filali A, *et al*. Antibiotics and chronic kidney disease: Dose adjustment update for infectious disease clinical practice. Med Mal Infect 2020;50:323-31.
177. Salama NR, Hartung ML, Muller A. Life in the human stomach: Persistence strategies of the bacterial pathogen Helicobacter pylori. Nat Rev Microbiol 2013;11:385-99.
178. Malfertheiner P, Link A, Selgrad M. Helicobacter pylori: Perspectives and time trends. Nat Rev Gastroenterol Hepatol 2014;11:628-38.
179. Graham DY, Liou JM. Primer for development of Guidelines for Helicobacter pylori therapy using antimicrobial stewardship. Clin Gastroenterol Hepatol 2022;20:973-83. e971.
180. Leja M, Dumpis U. What would the screen-and-treat strategy for Helicobacter pylori mean in terms of antibiotic consumption? Dig Dis Sci 2020;65:1632-42.
181. Leung WK, Wong IOL, Cheung KS, Yeung KF, Chan EW, Wong AYS, *et al*. Effects of Helicobacter pylori treatment on incidence of gastric cancer in older individuals. Gastroenterology 2018;155:67-75.
182. Choi IJ, Kim CG, Lee JY, Kim YI, Kook MC, Park B, *et al*. Family history of gastric cancer and Helicobacter pylori treatment. N Engl J Med 2020;382:427-36.
183. Shah SC, Piazuelo MB, Kuipers EJ, Li D. AGA clinical practice update on the diagnosis and management of atrophic gastritis: Expert review. Gastroenterology 2021;161:1325-32.e27.
184. Wauters L, Dickman R, Drug V, Mulak A, Serra J, Enck P, *et al*. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia. United European Gastroenterol J 2021;9:307-31.
185. Yu Y, Zhu S, Li P, Min L, Zhang S. Helicobacter pylori infection and inflammatory bowel disease: Acrosstalk between upper and lower digestive tract. Cell Death Dis 2018;9:961.
186. Ali I, Abdo Q, Al-Hihi SM, Shawabkeh A. Association between ulcerative colitis and Helicobacter pylori infection: A case-control study. Heliyon 2022;8:e08930.
187. Imawana RA, Smith DR, Goodson ML. The relationship between inflammatory bowel disease and Helicobacter pylori across East Asian, European and Mediterranean countries: Ameta-analysis. Ann Gastroenterol 2020;33:485-94.
188. Han Y, Yan T, Ma H, Yao X, Lu C, Li Y, *et al*. Cost-effectiveness analysis of Helicobacter pylori eradication therapy for prevention of gastric cancer: A Markov model. Dig Dis Sci 2020;65:1679-88.
189. Kowada A, Asaka M. Economic and health impacts of introducing Helicobacter pylori eradication strategy into national gastric cancer policy in Japan: A cost-effectiveness analysis. Helicobacter 2021;26:e12837.
190. Liou JM, Malfertheiner P, Lee YC, Sheu BS, Sugano K, Cheng HC, *et al*. Screening and eradication of Helicobacter pylori for gastric cancer prevention: The Taipei global consensus. Gut 2020;69:2093-112.
191. Hogh MB, Kronborg C, Hansen JM, Schaffalitzky de Muckadell OB. The cost effectiveness of Helicobacter pylori population screening-economic evaluation alongside a randomised controlled trial with 13-year follow-up. Aliment Pharmacol Ther 2019;49:1013-25.
192. AlRuthia Y, Almadi MA, Alqahtani S, Alrasheed H, Al-Owairdhi M, Alsohaibani F. The cost-effectiveness of sequential versus standard triple therapy for Helicobacter pylori eradication in Saudi Arabia. Saudi J Gastroenterol 2021;27:217-22.
193. Dos Santos Viana I, Cordeiro Santos ML, Santos Marques H, Lima de Souza Gonçalves V, Bittencourt de Brito B, França da Silva FA, *et al*. Vaccine development against Helicobacter pylori: From ideal antigens to the current landscape. Expert Rev Vaccines 2021;20:989-99.