JGH Open An open access journal of gastroenterology and hepatology
JGHF
doi:10.1002/jgh3.12843

REVIEW ARTICLE

Management of *Helicobacter pylori* infection

Natsuda Aumpan,*,† Varocha Mahachai*,† and Ratha-korn Vilaichone*,†,‡

*Center of Excellence in Digestive Diseases and Gastroenterology Unit, Department of Medicine, Thammasat University, †Department of Medicine, Chulabhorn International College of Medicine (CICM) at Thammasat University, Pathumthani, Thailand and ‡Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Key words
Helicobacter pylori, management, treatment.

Accepted for publication 6 November 2022.

Correspondence
Ratha-korn Vilaichone, Center of Excellence in Digestive Diseases and Gastroenterology Unit, Department of Medicine, Thammasat University, Pathumthani, Thailand.
Email: vilaichone@hotmail.co.th

Declaration of conflict of interest: None of the authors has any conflict of interests.

Funding support: Bualuang ASEAN Chair Professorship at Thammasat University

Funding support: Center of Excellence in Digestive Diseases, Thammasat University, Thailand

Funding support: Thailand Science Research and Innovation Fundamental Fund

Abstract

Helicobacter pylori infection exhibits a wide disease spectrum ranging from asymptomatic gastritis, peptic ulcer disease, to gastric cancer. *H. pylori* can induce dysbiosis of gastric microbiota in the pathway of carcinogenesis and successful eradication can restore gastric homeostasis. Diagnostic testing and treatment for *H. pylori* infection is recommended in patients with active or past history of peptic ulcer, chronic dyspepsia, chronic non-steroidal anti-inflammatory drugs (NSAID) or aspirin use, precancerous gastric lesions, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma, family history of gastric cancer, family history of peptic ulcers, household family member having active *H. pylori* infection, iron deficiency anemia, idiopathic thrombocytopenic purpura, or vitamin B12 deficiency. Recommended first-line regimens for *H. pylori* eradication are classified according to clarithromycin resistance. In areas of high clarithromycin resistance (≥15%), we recommend 14-day concomitant therapy or 14-day bismuth quadruple therapy (BQT) as first-line regimen. In areas of low clarithromycin resistance (<15%), we recommend 14-day triple therapy or 14-day BQT as first-line treatment. Second-line regimens are 14-day levofloxacin triple therapy or 14-day BQT if BQT is not previously used. For patients with multiple treatment failure, antimicrobial susceptibility testing (AST) should be performed. If AST is not available, we recommend using antibiotics not previously used or for which resistance is unlikely, such as amoxicillin, tetracycline, bismuth, or furazolidone. High-dose potent proton pump inhibitor or vonoprazan is recommended to achieve adequate acid suppression. Probiotics can be used as an adjuvant treatment to reduce the side effects of antibiotics and enhance eradication rate.

Introduction

Helicobacter pylori (H. pylori), a spiral-shaped gram-negative bacterium, is one of the most common causes of serious chronic bacterial infections worldwide. *H. pylori* infection has been proven to be etiologically associated with chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.[1] Over 1 million new cases of gastric cancer and nearly 800 000 deaths occurred in 2020 making *H. pylori*-related disease the third leading cause of global cancer deaths.[2] *H. pylori* infection is designated as an infectious disease and it is recommended that it should be treated regardless of symptoms to prevent serious complications and transmission.[3]

The rapid emergence of antibiotic-resistant *H. pylori* has become the greatest global threat influencing treatment outcomes. For example, almost all World Health Organization (WHO) regions now experience resistance rates to clarithromycin, metronidazole, and levofloxacin of over 15%.[4] Clinical guidelines recommend different first-line treatments depending on antimicrobial resistance patterns in each region.[5–7] Appropriate antibiotic selection, adequate acid suppression, and adherence to therapy all affect successful eradication. Host CYP2C19 genetic polymorphisms are associated with decreasing effectiveness of some proton pump inhibitors (PPIs).[8] Second-generation PPIs (rabeprazole and esomeprazole) are less affected by CYP2C19 and are recommended. Furthermore, novel potent acid blockers such as vonoprazan have also been introduced and are not affected by CYP2C19.[9]

This review aimed to provide an overview of the prevalence, disease spectrum, diagnostic tests, and treatment options for *H. pylori* infection. Regimens for first-line, second-line therapy, and multiple treatment failures were recommended regarding the latest global antibiotic resistance patterns.

The prevalence of *H. pylori* infection

The global prevalence of *H. pylori* infection ranged widely from 18.9% to 87.7%, with an estimated 4.4 billion infected people worldwide in 2015. Regions with the highest prevalence of *H. pylori* are Africa (70.1%) and South America (69.4%), while Oceania (24.4%) and Western Europe (34.3%) have the lowest

prevalence.[10] The country with the highest prevalence of *H. pylori* infection was Nigeria (87.7%), whereas the lowest was Switzerland (18.9%).[10] *H. pylori* is known as a strong risk factor for gastric cancer. There were more than 2 billion *H. pylori*-positive patients and three-quarters of global gastric cancer cases residing in Asia.[10,11] Mongolia had the highest age-standardized incidence rate (ASIR) of gastric cancer, followed by Japan (ASIR of 32.5 and 31.6 per 100 000 persons, respectively).[11] Africa had high *H. pylori* prevalence but low incidence of gastric cancer.[11] This "African enigma" is likely related to the limited care available in many parts of Africa. Vietnam (70.3%), Myanmar (69%), Laos (68.7%), and Thailand (28.2%) were among the Association of Southeast Asian Nations (ASEAN) with varying prevalence of *H. pylori* infection.[12] Countries in ASEAN with high *H. pylori* prevalence also have high incidence of gastric cancer (ASIR > 10). The global prevalence of *H. pylori* infection and ASIR of gastric cancer in ASEAN are demonstrated in Figure 1.

Factors affecting the prevalence of *H. pylori* infection are age, ethnicity, and socioeconomic status.[13] The possible routes of transmission are fecal–oral, oral–oral, and gastric–oral routes.[14] Children became infected with *H. pylori* at a very young age (mean age of 32.78 months).[15] Intrafamilial clustering of *H. pylori* infection implied person-to-person transmission or common exposure to same contaminated source.[16] *H. pylori* prevalence gradually increased with age from adolescents (10%–30%) to the elderly (40%–60%)[17] and also varied between ethnic groups. In the United States, non-Hispanic Whites had *H. pylori* prevalence of 26.9%, while non-Hispanic Blacks and Mexican Americans had a prevalence of 51.1% and 57.9%, respectively.[18] Moreover, low socioeconomic class during childhood and crowded living conditions were related to *H. pylori* infection.[19] Higher prevalence of *H. pylori* infection in Asian countries than in Western countries might be explained by lower socioeconomic status in most countries in Asia.[10] Despite being in the same region, developing Asian countries also had higher prevalence than the developed ones.[20]

H. pylori and gastric microbiome

The human stomach harbors much less microbial density [10^1–10^3 colony forming units (CFUs)/g] than the colon (10^{10}–10^{12} CFUs/g) due to highly acidic environment.[21] The gastric microbiota is generally composed of dominant phyla including Actinobacteria (genus *Bifidobacterium*), Bacteroidetes (genus *Prevotella*), Firmicutes (genera *Lactobacillus*, *Streptococcus*, *Clostridium*, *Veillonella*), Fusobacteria, and Proteobacteria.[22] The most abundant phylum is Firmicutes, while the most common genera are *Streptococcus*, *Prevotella*, *Neisseria*, *Hemophilus*, *Fusobacterium*, and *Veillonella*.[22] The recent study reported that *H. pylori* had strong coexcluding interactions with *Fusobacterium, Neisseria, Prevotella, Veillonella*, and *Rothia* only in patients with advanced gastric lesions.[23] *H. pylori* can induce gastric dysbiosis resulting in decreased microbial diversity. Successful eradication can restore gastric microbiota resembling the status of *H. pylori*-negative controls, increase the abundance of *Bifidobacterium*, and hypothetical downregulation of drug-resistance mechanisms.[23] The dysbiotic gastric microbiota profile, decreased *H. pylori* abundance, and enriched oral or intestinal bacteria were found in patients with gastric cancer.[24] Interplays between *H. pylori* infection and gastric microbiome are demonstrated in Figure 2.

The disease spectrum of *H. pylori* infection

H. pylori infection exhibits a wide spectrum of clinical manifestations. *H. pylori*-related gastrointestinal diseases and extragastric manifestations are described below.

Gastrointestinal diseases

Dyspepsia. Young dyspeptic patients without alarm symptoms and no risk for gastric cancer are recommended to be tested for *H. pylori* infection by noninvasive testing, whereas older patients should undergo upper gastrointestinal (GI) endoscopy due to increased risk of gastric cancer.[7] The age cutoffs for performing upper GI endoscopy are different between countries according to the prevalence of gastric cancer.[25] The optimal cutoffs for endoscopy are 40 years for high-prevalence countries (e.g., China, Korea, Japan, Taiwan[26]), and 45 or 50 years for intermediate or low-prevalence countries (e.g., India, Malaysia, Singapore, Thailand, Africa, North America, Western Europe).[25] The age cutoffs for endoscopy in Vietnam are lower than most guidelines as 30 years for women and 35 years for men to detect 98.2% of upper GI malignancy.[27] Since *H. pylori* can be detected in visibly normal gastric mucosa, gastric biopsies should be obtained in dyspeptic patients undergoing gastroscopy. *H. pylori* eradication is recommended to provide symptomatic relief for dyspepsia.[28]

Gastritis. Persistent *H. pylori* infection causes chronic gastritis of varying severity. *H. pylori* typically causes antral-predominant gastritis. When inflammation continues, parietal cell destruction results in decreased acid secretion. Atrophic gastritis and intestinal metaplasia, which are precancerous lesions, subsequently develop.

Peptic ulcer disease. *H. pylori* and nonsteroidal anti-inflammatory drug (NSAID) are common causes of peptic ulcers. The guideline recommends testing for *H. pylori* infection for patients with active or a past history of peptic ulcer disease (PUD).[5] The prevalence of *H. pylori* infection was 90%–100% in duodenal ulcers and 60%–100% in gastric ulcers.[29] Recently, there has been a decreasing trend of *H. pylori* infection in patients with PUD in the United States.[30]

Gastric cancer. *H. pylori* can turn chronic gastritis into atrophic gastritis, intestinal metaplasia, dysplasia, and eventually adenocarcinoma via Correa's precancerous cascade.[31] *H. pylori*-induced chronic gastritis generates increased epithelial cell turnover and reactive oxygen species, resulting in DNA damage along with microRNA dysregulation.[32] Furthermore, *H. pylori* can induce DNA methylation changes, causing epigenetic aberrations in gastric epithelial cells. Promoter hypermethylation of E-cadherin, a tumor suppressor gene, is related to the development of gastric cancer.[32] Men, non-White racial and ethnic minority groups, and smokers were associated with higher risk of gastric cancer in *H. pylori*-infected patients.[33] Family history of

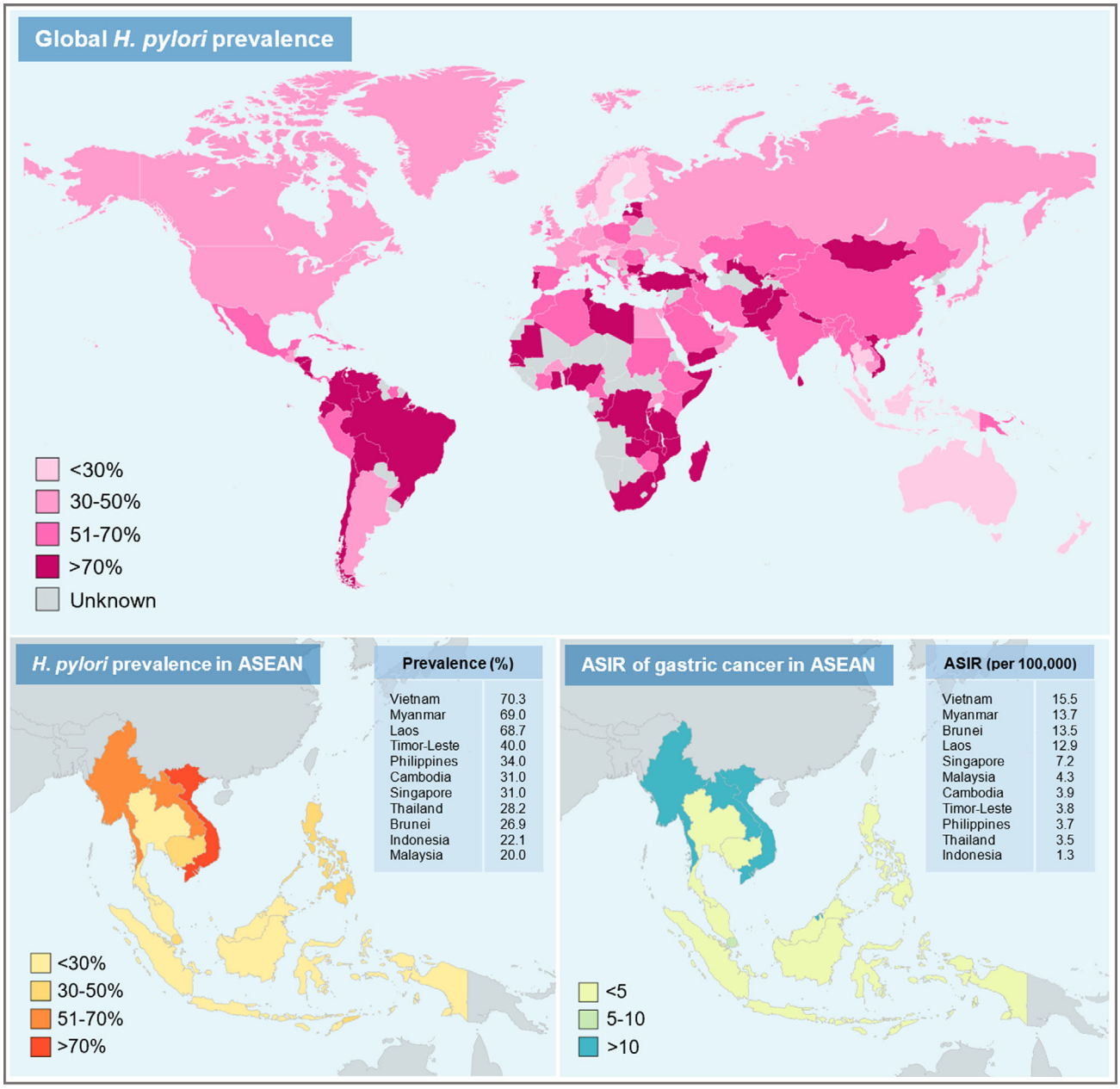

Figure 1 Global prevalence (upper panel), regional prevalence of *H. pylori* infection (lower left panel), and age-standardized incidence rate of gastric cancer in ASEAN (lower right panel).

gastric cancer in first-degree relatives was associated with approximately three-fold higher risk of gastric cancer.[34] *H. pylori* eradication not only decreases the risk of gastric cancer development,[35] but also reduces histologic progression to gastric dysplasia.[36] *H. pylori* testing is recommended in patients with a history of endoscopic resection of early gastric cancer (EGC). There were lower rates of metachronous gastric cancer in patients with EGC receiving *H. pylori* eradication than the placebo group during a median follow-up of 5.9 years [7.2% vs. 13.4% (HR 0.5; 95% CI 0.26–0.94, $P = 0.03$)].[37]

Mucosa-associated lymphoid tissue lymphoma. *H. pylori* infection is associated with over 90% of mucosa-associated lymphoid tissue (MALT) lymphomas.[38] The pathogenesis of MALT lymphoma might be related to direct antigenic stimulation of B-cell proliferation by *H. pylori*.[38] Previous studies revealed that majority of patients (80%) with low-grade gastric MALT lymphomas receiving *H. pylori* eradication could achieve complete remission with an annual recurrence rate of 5%.[39] *H. pylori* eradication is also recommended in patients with *H. pylori*-negative gastric MALT

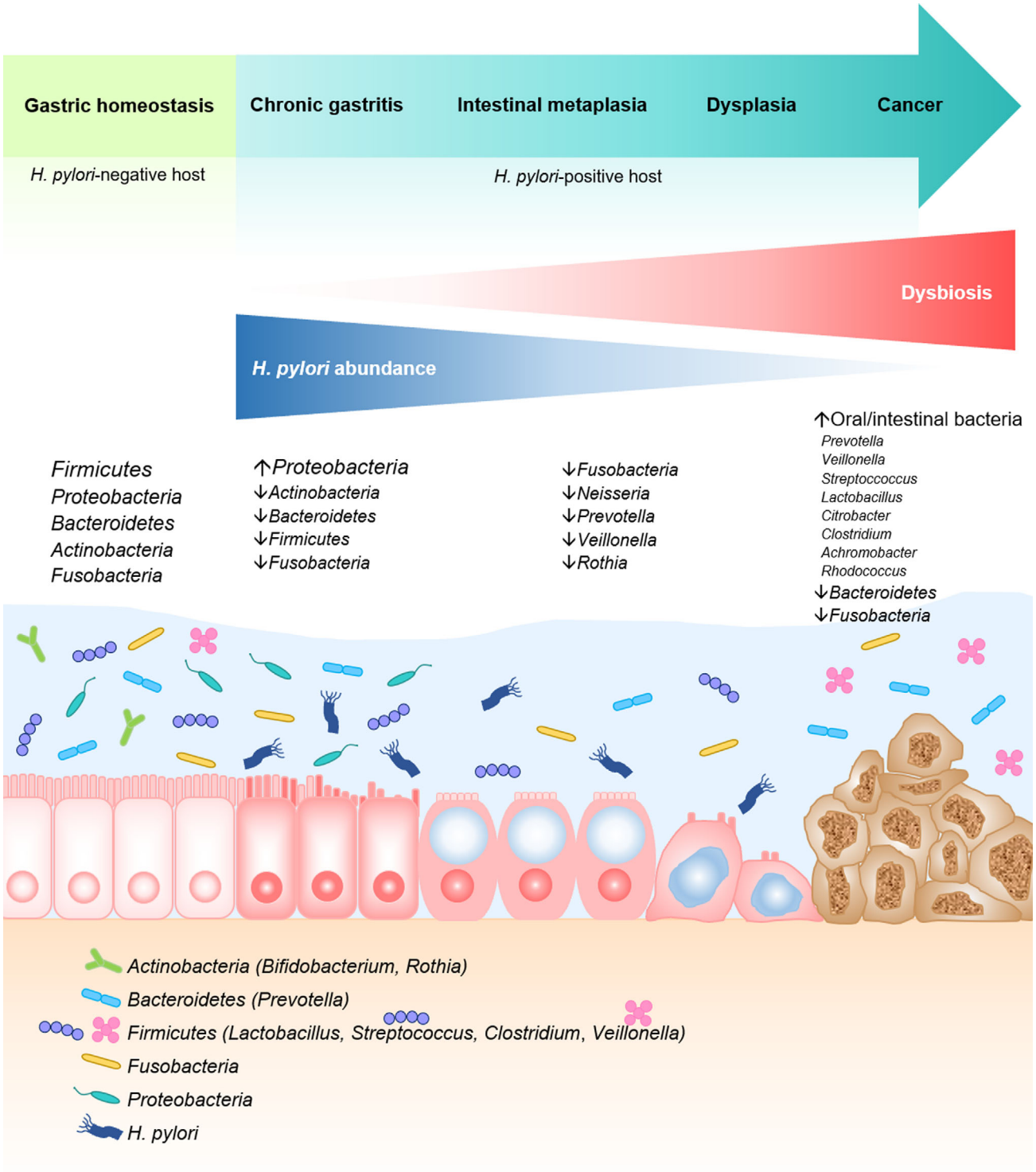

Figure 2 Interplays between *H. pylori* infection and gastric microbiome. In normal condition, the mucus layer over gastric epithelial cells is the habitat of highly diverse bacteria phyla. The most abundant phylum is Firmicutes, followed by Proteobacteria, and Bacteroidetes. In *H. pylori*-associated chronic gastritis, dysbiosis develops with decreased microbial diversity. There is higher abundance of Proteobacteria, but lower number of other phyla. As carcinogenesis continues, reduced *H. pylori* abundance and higher degree of dysbiosis are observed in intestinal metaplasia and dysplasia. In gastric cancer, oropharyngeal or intestinal commensals (*Streptococcus, Lactobacillus, Veillonella*, and *Prevotella*) are enriched.

lymphoma as this can induce complete remission in 29.3% of patients.[40]

Extragastric diseases

Iron deficiency anemia. *H. pylori* infection can induce depletion of iron stores by several mechanisms including chronic occult gastrointestinal blood loss, impaired iron absorption due to decreased intragastric acidity and ascorbic acid concentration,[41] and enhanced iron uptake for bacterial growth.[42] The previous study reported that the prevalence of *H. pylori*-related chronic gastritis was 60% in patients with unexplained iron deficiency anemia (IDA) compared with 43% of the control group without IDA ($P < 0.01$).[43] *H. pylori* infection was associated with IDA with pooled OR of 2.22 (95% CI 1.52–3.24, $P < 0.0001$).[44] The meta-analysis demonstrated significant improvement in IDA after combination of *H. pylori* eradication and oral iron compared with oral iron alone.[45]

Idiopathic thrombocytopenic purpura. Potential mechanisms of *H. pylori*-related idiopathic thrombocytopenic purpura (ITP) might be caused by molecular mimicry between *H. pylori*-induced antibodies and platelet glycoprotein antigens.[46] Moreover, antibodies to cytotoxin-associated gene A protein (CagA), one of *H. pylori* virulence factors, can cross-react with specific peptides expressed by platelets of ITP patients.[46] The prevalence of *H. pylori* infection was significantly higher in patients with ITP than in controls (90.6% vs. 43.8%, $P = 0.00006$) in the Colombian study.[47] The systematic review reported that among 696 ITP patients receiving *H. pylori* eradication, 42.7% achieved complete response (platelet count ≥100 × 10^9/L).[48] Higher response rate was observed in patients with milder degree of thrombocytopenia and in countries with high prevalence of *H. pylori* infection.[48] The American Society of Hematology recommends *H. pylori* eradication for infected patients with ITP (grade 1B) and also suggests *H. pylori* screening in patients with ITP (grade 2C).[49]

Diagnostic tests for *H. pylori* infection

Clinical guidelines recommend diagnostic testing for *H. pylori* infection in patients with conditions as follows: (1) active or past history of peptic ulcer, (2) chronic dyspepsia, (3) chronic NSAID or aspirin use, (4) precancerous gastric lesions, (5) gastric cancer, (6) MALT lymphoma, (7) family history of gastric cancer in a first-degree relative, (8) family history of peptic ulcer, (9) having household family member with active *H. pylori* infection, (10) unexplained IDA, (11) ITP, and (12) vitamin B12 deficiency.[5–7,50] As gastric cancer prevalence is relatively high in Asia, the Bangkok consensus recommends community screening and treatment for *H. pylori* infection to prevent gastric cancer, especially in the area with high cancer burden.[6]

Current diagnostic tests for *H. pylori* infection are classified into two groups, which are noninvasive and invasive methods. Invasive diagnostic tests are endoscopy-based tests including histology, rapid urease test, culture, and polymerase chain reaction. Noninvasive tests are urea breath test, stool antigen test, and antibody tests in serum, urine, and saliva.[51]

A patient should discontinue PPI for at least 2 weeks, antibiotics and bismuth compounds for at least 4 weeks before testing by histology, culture, rapid urease test, urea breath test, or stool antigen test to avoid a false negative result.

Invasive tests

Histology. Histologic examination is considered to be the gold standard in *H. pylori* detection with high sensitivity and specificity of 95% and 99%, respectively.[52] Histology can provide information about associated lesions such as atrophic gastritis, intestinal metaplasia, dysplasia, and MALT lymphoma.

Rapid urease test. Gastric biopsy specimens are placed in a medium containing urea and pH indicator. Urease from *H. pylori* converts urea to ammonia, which increases the pH resulting in color change of the pH indicator. Sensitivity and specificity are approximately 85%–95% and 95%–100%, respectively.[51]

Culture. Culture has lower sensitivity (85%–95%) than rapid urease test or histology, but the specificity is as high as almost 100%.[51] This test provides essential information about antimicrobial susceptibility.

Polymerase chain reaction. *H. pylori* can be detected by polymerase chain reaction (PCR) in several types of specimens such as gastric juice, gastric biopsies, stool, and saliva. PCR had high sensitivity of 100% and 98% for gastric biopsy and stool specimen respectively, while specificity was 98% for both specimens.[53] Antibiotic resistance can also be determined by amplification of resistance-associated genes using real-time PCR.

Non-invasive tests

Urea breath test. ^{13}C labeled urea is administered orally and hydrolysed by *H. pylori*'s urease producing ammonia and labeled CO_2, which is subsequently exhaled and collected as breath sample. Until now, urea breath test (UBT) has been the most popular and accurate noninvasive test for diagnosis of *H. pylori* infection with high sensitivity (96%) and specificity (93%).[54] In patients with upper gastrointestinal bleeding, the diagnostic accuracy of UBT is still high with sensitivity and specificity of 93% and 92%, respectively.[55] UBT can also be used after treatment to confirm *H. pylori* eradication.

Stool antigen test. There are two types of stool antigen tests that detect *H. pylori* antigens by using monoclonal or polyclonal antibodies. The monoclonal stool antigen test had higher pooled sensitivity (94% vs. 83%) than polyclonal stool antigen test but comparable specificity (97% vs. 96%).[56] Therefore, monoclonal stool antigen test should be used for diagnosis or confirmation of eradication.[56] PPI can decrease the sensitivity of stool antigen test from 95.2% to 88.9% and should be discontinued at least 2 weeks before the test.[57]

Antibody tests in serum, urine, and saliva. Serologic tests are inexpensive and noninvasive. The serological assay detects anti-*H. pylori* IgG in serum, which generally becomes positive 3 weeks after *H. pylori* infection and persists up to 6–12 months after eradication.[55] Serologic test had lower sensitivity and specificity of 85% and 79%, respectively.[58] Most serologic tests cannot

Table 1 *Helicobacter pylori* antibiotic resistance stratified by regions

Antibiotic resistance	ASEAN[12,63]	The United States[64] 2011–2021 $N = 2660$	Europe[65] 2008–2017, $N = 1211$	Africa[66] 1986–2017, $N = 2085$
Metronidazole	30%–73%	42.1%	38.9%	75.8%
Clarithromycin	17%–43%	31.5%	21.4%	29.2%
Levofloxacin	13%–34%	37.6%	15.8%	17.4%
Amoxicillin	0%–5%	2.6%	0.2%	72.6%
Tetracycline	0%	0.87%	0%	48.7%
Others	-	Rifabutin 0.17%, CLR-MNZ 11.7%	Rifampicin 0.9%	-

Abbreviations: ASEAN, the Association of Southeast Asian Nations; CLR, Clarithromycin; MNZ, Metronidazole.

differentiate past infection from current infection except for rapid test with current infection marker (CIM) test providing sensitivity and specificity of 93.2% and 96.2%, respectively compared with UBT.[59] Upper gastrointestinal bleeding did not affect the accuracy of serologic tests. There are less commonly used urine and saliva antibody tests. Urine-based tests had fair sensitivity (84.7%), specificity (89.9%), and accuracy (87%).[60] Salivary tests provided unsatisfactory results with fair sensitivity (81%) and specificity (73%).[61] Urine and saliva antibody tests still have high variability of diagnostic accuracy; therefore test usage is found only in research field.

Confirmation of cure

Confirmation of successful eradication should be performed to avoid further complications of *H. pylori* infection and prevent transmission to other family members. Posttreatment tests are UBT, stool antigen test, or biopsy-based test. UBT is recommended as the best option for confirmation of cure. Suitable timing for testing should be at least 4 weeks after treatment completion.

Antibiotic resistance patterns

Antibiotic resistance patterns are determined by *H. pylori* culture and antimicrobial susceptibility testing (AST). This test requires proper gastric biopsy handling, efficient specimen transportation, and microbiological expertise.[62] Moreover, traditional *H. pylori* culture is time-consuming and unavailable in some areas. Next-generation sequencing (NGS) is a new molecular-based test, which determines antibiotic resistance by identifying mutations or variances of the *H. pylori* DNA.[62] Fresh or formalin-fixed paraffin-embedded gastric biopsies, gastric juice, or feces can be used for NGS. Targeted genes associated with antibiotic resistance are as follows: 23 S rRNA for clarithromycin, 16 S rRNA for tetracycline, *gyrA* for fluoroquinolones, *rdxA* for metronidazole, *pbp1* for amoxicillin, and *rpoB* for rifabutin.[62] NGS reliably determined clarithromycin and levofloxacin resistance from culture isolates and formalin-fixed gastric tissue compared with agar dilution.[62]

Most of WHO regions had high pooled prevalence of primary and secondary resistance to metronidazole, clarithromycin, and levofloxacin (>15%).[4] The most common antibiotic resistance in all regions was metronidazole.[12,63–66] The ASEAN, the United States, and Europe had almost the same antibiotic resistance patterns, while extremely high resistance rates to all antibiotics were demonstrated in Africa.[66] Amoxicillin and tetracycline resistance rates were low in all regions except Africa. Antibiotic resistance rates stratified by regions are demonstrated in Table 1.

Treatment

Treatment goal for *H. pylori* infection is an intention-to-treat eradication rate of at least 90%.[67] Choosing the suitable first-line regimen depends on known or anticipated pattern of regional antibiotic resistance.[5–7] Treatment regimen comprises antisecretory drug and antibiotics. The choice of antisecretory drugs is either PPIs or potassium-competitive acid blockers (P-CABs). At least two antibiotics are generally chosen in regimens. Treatment guidelines for *H. pylori* infection recommend different first-line regimens regarding local antibiotic resistance as demonstrated in Table 2.

Antisecretory drugs

Proton pump inhibitors. Proton pump inhibitors (PPIs) irreversibly bind and inhibit H^+, K^+-ATPase on parietal cells causing effective gastric acid secretion blockage. PPIs are mainly metabolized by CYP2C19 enzyme. The meta-analysis reported that using high-dose PPI was more effective in *H. pylori* eradication than using standard-dose PPI (82% vs. 74%, RR 1.09; 95% CI 1.01–1.17).[68] High-dose PPI is defined as a double dose of 40 mg of omeprazole or equivalent.[7,69] Potency of PPI is determined based on omeprazole equivalent (OE). Equivalent doses of each PPI are as follows: pantoprazole 40 mg = 9 mg OE; lansoprazole 30 mg = 27 mg OE; esomeprazole 20 mg = 32 mg OE; rabeprazole 20 mg = 36 mg OE; dexlansoprazole 30 mg = 50–60 mg OE. This review suggests using twice-daily dosing of PPI because of its ability to maintain intragastric pH at 4 or higher for 15.6–20.4 h.[70] Potent PPI (e.g., esomeprazole, rabeprazole) is recommended and pantoprazole should be avoided due to its relatively lower potency than other PPIs.[69] The recommended dose of esomeprazole or rabeprazole is 20–40 mg twice daily.[69]

Potassium-competitive acid blockers. Potassium-competitive acid blockers (P-CABs) reversibly bind to K^+ ions and consequently block H^+, K^+-ATPase inhibiting acid secretion. These drugs have a rapid onset of action and are capable of achieving therapeutic levels after the first dose. At present, P-CABs released to the market are revaprazan, vonoprazan, and tegoprazan. Vonoprazan is mainly metabolized by CYP3A4/5. Exactly 10 mg of vonoprazan is equivalent to 60 mg of omeprazole.[70]

Table 2 Treatment regimens for *Helicobacter pylori* infection according to different guidelines

Regimen	ACG Clinical Guideline,[5] 2017	ASEAN Consensus,[6] 2018	Maastricht VI/Florence Consensus Report,[7] 2022
First-line therapy	Recommend • BQT (10–14 days) • Concomitant therapy (10–14 days) • If CLR resistance <15% Triple therapy (14 days) Suggest • Sequential therapy (10–14 days) • Hybrid therapy (14 days) • LVX triple therapy (10–14 days) • FQ sequential therapy (10–14 days)	Depends on antibiotic resistance • If CLR resistance <15% Triple therapy (14 days) • Concomitant therapy (14 days) • Hybrid therapy (14 days) • BQT (14 days)	Recommend routine AST before first-line therapy Empirical regimens if AST is not available • CLR resistance >15% or unknown ○ BQT (14 days) ○ If BQT is not available → concomitant (14 days) • CLR resistance <15% ○ BQT or CLR triple therapy (14 days)
Penicillin allergy	• BQT (14 days) • PPI-CLR-MNZ (14 days)	• BQT (14 days)	first-line: BQT (14 days) second-line: FQ regimen or BQT (if BQT is not previously used) (14 days)
Second-line therapy	• If first-line using CLR BQT or LVX salvage regimens • If first-line using BQT CLR or LVX salvage regimens	• Antibiotic not previously used, or resistance is unlikely (e.g., AMX, TET, Bismuth) • FQ triple therapy (14 days)	• BQT (if first-line using triple/concomitant) • FQ quadruple (or triple) therapy • High-dose PPI-AMX dual therapy • If high FQ resistance → bismuth with other antibiotics or rifabutin
Salvage therapy	Recommend • BQT (14 days) • LVX triple regimen (14 days) Suggest • Concomitant therapy (10–14 days) • Rifabutin triple regimen (10 days) • High-dose PPI-AMX (14 days)	• FRZ quadruple therapy (14 days) • Rifabutin triple therapy (12–14 days) • High-dose PPI-AMX dual therapy (14 days)	• Bismuth with other antibiotics • High-dose PPI-AMX dual therapy • Rifabutin triple therapy • If fail triple/concomitant → fail BQT therapy ○ FQ regimen • If fail triple/concomitant → fail FQ therapy ○ BQT • If fail BQT → fail FQ therapy ○ CLR triple or quadruple (low CLR resistance)
Antimicrobial susceptibility testing	No recommendation	After failure of second-line therapy	Recommend AST even before first-line treatment (if available) for implementation of antibiotic stewardship

Note: AST = Antimicrobial susceptibility testing, Hybrid therapy = PPI + AMX (7 days) then PPI + AMX + CLR + MNZ (7 days), FQ sequential therapy = PPI-AMX (5–7 days) then PPI-FQ-MNZ (5–7 days), FRZ quadruple therapy (14 days) = PPI + FRZ 100 mg tid + Bismuth + (AMX or TET), Rifabutin triple therapy (12–14 days) = PPI + rifabutin (150 mg daily) + AMX (1.5 g tid).

Abbreviations: AMX, Amoxicillin; BQT, Bismuth quadruple therapy; CLR, Clarithromycin; FQ, Fluoroquinolone; FRZ, Furazolidone; LVX, Levofloxacin; MNZ, Metronidazole; TET, Tetracycline.

Treatment regimens

Triple therapy. Standard triple therapy (STT) should not be used if the local clarithromycin resistance is >15%.[5,7] One study demonstrated that 14-day STT could provide 87.8% eradication in clarithromycin resistance rate of 14.8%.[71] The OPTRICON study demonstrated the eradication rate for 14-day STT of 82.3% without antimicrobial susceptibility data.[72] Another study revealed excellent eradication rate of 100% when using 14-day STT with high-dose PPI (lansoprazole 60 mg twice daily) in low clarithromycin resistance area.[73] Treatment duration of 14 days is recommended for *H. pylori* eradication. Although empiric STT yielded suboptimal eradication rates in some studies,[74] it could still be used in area with low clarithromycin resistance or available AST.

Concomitant therapy. Previous studies demonstrated high eradication rates (93.8%–96.4%) of 10-day concomitant regimen.[72,75] The European registry (Hp-EuReg) with 21 533 patients also reported a high eradication rate (92.2%) of 14-day concomitant regimens.[76] One Korean study reported that concomitant therapy had provided the best eradication rate (94.4%) compared with triple therapy and sequential therapy.[77] However, adverse effects, for example, nausea, vomiting, and diarrhea,

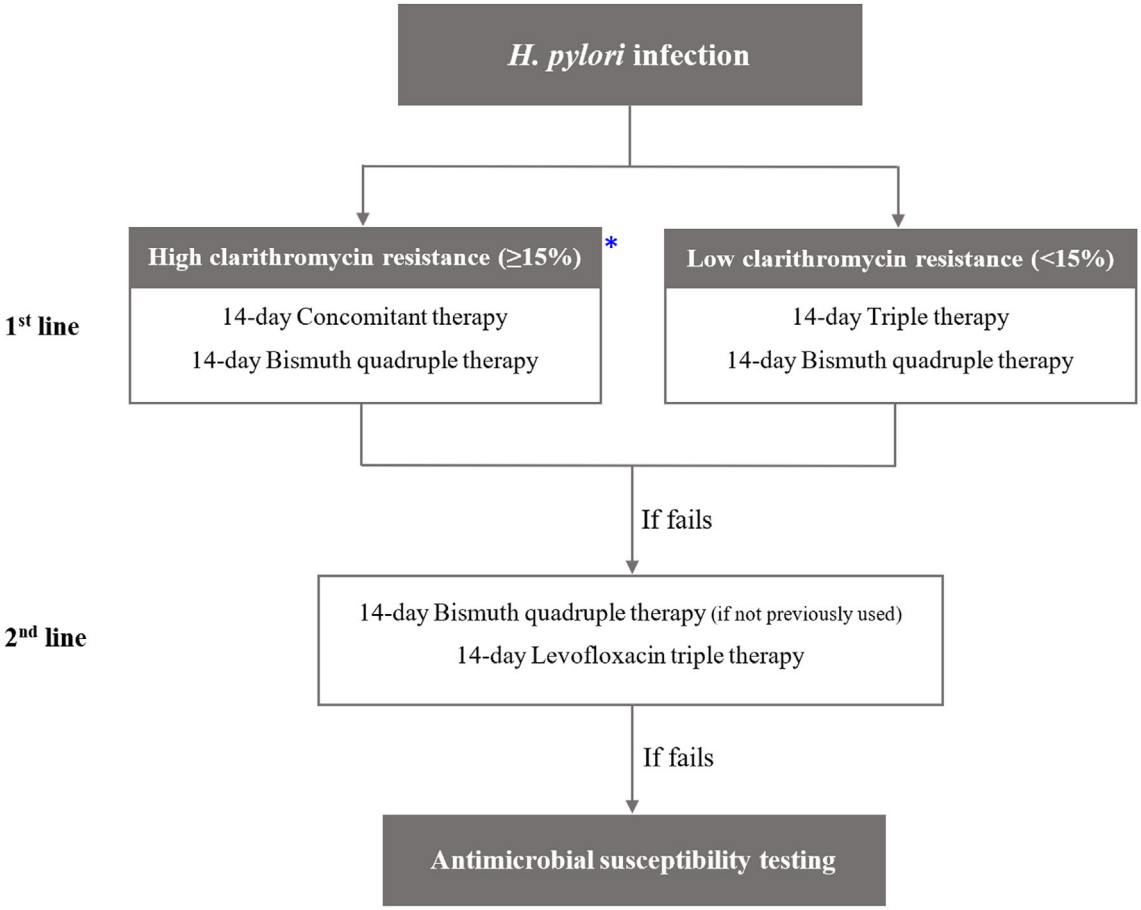

Figure 3 Algorithm for *H. pylori* management.

from concomitant regimen were significantly more common than from STT.[72] Although the concomitant regimen achieves high eradication rate, it can cause unnecessary antibiotic use accelerating antimicrobial resistance.

Sequential therapy. The meta-analysis including 13 532 patients reported an overall eradication rate for sequential regimen of 84.3% without superiority over STT, concomitant, and bismuth quadruple therapy (BQT).[78] In Thailand, 10-day sequential therapy has also demonstrated decreasing eradication rate to 59.7% in recent years.[63] This might be caused by low medication adherence associated with regimen complexity. Therefore, sequential therapy is not recommended for first-line treatment in this review.

Bismuth quadruple therapy. Bismuth results in rapid antimicrobial effect on *H. pylori* and also produces synergistic effect with metronidazole.[79] Bismuth quadruple therapy (BQT) can be used as first-line or second-line therapy. As first-line treatment, one study compared 14-day and 10-day BQT, revealing high efficacy (96% vs. 95%).[80] BQT provided high eradication rates of >90% in Taiwan and Europe.[74,76] The Thai study that evaluated 7-day BQT as first-line treatment using amoxicillin instead of tetracycline provided the eradication rate of 82.5% despite high metronidazole resistance rate (50%).[81] It is noted that metronidazole resistance can be overcome by increasing the dosage of metronidazole to at least 1500 mg/day and extending the duration of treatment to 14 days.[8] As second-line therapy, eradication rates were 76%–94.5%.[82,83]

Levofloxacin triple therapy. Levofloxacin triple therapy is primarily recommended for second-line therapy by most guidelines. The recent US study demonstrated high levofloxacin resistance (37.6%), making levofloxacin triple therapy not suitable to be a first-line regimen.[64] This regimen demonstrated fair eradication rates as first-line treatment (79.1%–85.2%).[76,84] As second-line therapy, eradication rates were 78%–92.9%.[82,85]

Table 3 Eradication rates and composition of each first-line and second-line regimen

Regimen and duration	Regimen composition	Eradication rates	Reference number
First-line regimens			
Concomitant therapy (10 days)	PPI + AMX (1 g bid) + MNZ (500 mg bid) + CLR (500 mg bid)	93.8%–96.4%	72,75–77
Triple therapy (14 days)	PPI + AMX (1 g bid) + CLR (1 g/day)	82.3%–87.8%	71,72,76
Bismuth quadruple therapy (14 days)	PPI + Bismuth subsalicylate (524 mg qid or 1048 mg bid) + MNZ (500 mg tid) + TET (500 mg qid)	88.2%–96.0%	74,76,80
LVX triple therapy (10–14 days)	PPI + AMX (1 g bid) + LVX (500 mg/day)	79.1%–85.2%	76,84
Sequential therapy (10 days)	PPI + AMX (1 g bid) (5 days) followed by PPI + CLR (1 g/day) + MNZ (500 mg bid) (5 days)	59.7%–84.3%	63,76,78
Vonoprazan triple therapy	VPZ (20 mg bid) + AMX (750 mg bid) + CLR (200 or 400 mg bid) (7 days)	88.9%–95.7%	86–88
	VPZ (20 mg bid) + AMX (1 mg bid) + CLR (500 mg bid) (14 days)	84.7%	91
Vonoprazan dual therapy	VPZ (20 mg bid) + AMX (750 mg bid or 500 mg tid) (7 days)	87.1%–94.4%	89,90
	VPZ (20 mg bid) + AMX (1 g tid) (14 days)	78.5%	91
Second-line regimens			
LVX triple therapy (14 days)	PPI + AMX (1 g bid) + LVX (500 mg/day)	78.0%–92.9%	82,85
Bismuth quadruple therapy (14 days)	PPI + Bismuth subsalicylate (524 mg qid or 1048 mg bid) + MNZ (500 mg tid) + TET (500 mg qid)	76.0%–94.5%	82,83

Abbreviations: AMX, Amoxicillin; bid, twice a day; CLR, Clarithromycin; LVX, Levofloxacin; MNZ, Metronidazole; PPI, Proton pump inhibitor; qid, four times a day; TET, Tetracycline; tid, three times a day; VPZ, Vonoprazan.

Vonoprazan-containing regimens. Recently, vonoprazan-containing regimens have been more popularly used due to P-CABs' potent acid inhibitory effect. Vonoprazan has been used in *H. pylori* treatment regimens since its first approval in Japan in 2015. Previous studies in Japan reported higher eradication rate of vonoprazan triple therapy (88.9%–95.7%) than PPI-based triple therapy (71.4%–86.7%) in a population with high clarithromycin resistance rate.[86–88] In Japan, the cure rates with PPI and vonoprazan in clarithromycin susceptible infection were high and similar. Other studies demonstrated no difference in eradication rates of approximately 90% between vonoprazan dual and vonoprazan triple therapy.[89,90] In the latest trial conducted in the United States and Europe, 1046 patients were randomized 1:1:1 to receive vonoprazan dual, vonoprazan triple, or lansoprazole triple therapy. This study demonstrated comparable eradication rates of vonoprazan triple (84.7%), vonoprazan dual (78.5%), and lansoprazole triple therapy (78.8%) in population with high clarithromycin resistance rates in each group (19.1%–23.7%).[91] The study also reported that both vonoprazan-based regimens provided significantly higher eradication rates than lansoprazole triple therapy in patients with clarithromycin-resistant strains (vonoprazan dual therapy 69.6%, vonoprazan triple therapy 65.8% vs. lansoprazole triple therapy 31.9%, $P < 0.001$).[91] Vonoprazan dual and triple therapies have been recently approved for *H. pylori* treatment by the US Food and Drug Administration since May 2022. For other vonoprazan-based regimens, pilot studies in Thailand revealed high efficacy of 7-day high-dose vonoprazan triple therapy (92.3%) and 14-day vonoprazan triple therapy plus bismuth (96.2%).[92] Another prospective study demonstrated high efficacy (95%) of 14-day vonoprazan bismuth quadruple therapy.[93]

The current trend in *H. pylori* eradication is adopting the principles of antibiotic stewardship to improve treatment outcome, minimize antibiotic resistance, and reduce healthcare costs. Since AST is not available in some areas, recent guidelines have also provided guidance on effective empirical regimens. Vonoprazan is increasingly used because of superior eradication rate for antibiotic-resistant strains and non-inferiority to PPI-based therapy. Recommended first-line regimens for *H. pylori* eradication are classified according to clarithromycin resistance. In areas of high clarithromycin resistance (≥15%), we recommend 14-day concomitant therapy or 14-day BQT as first-line regimen. In areas of low clarithromycin resistance (<15%), we recommend 14-day triple therapy or 14-day BQT as first-line treatment. Second-line regimens are 14-day levofloxacin triple therapy or 14-day BQT if BQT is not previously used. Recommended first- and second-line regimens are demonstrated in Figure 3. Eradication rates and composition of each first- and second-line regimen are summarized in Table 3.

Multiple *H. pylori* treatment failure

Multiple *H. pylori* treatment failure is an unsuccessful eradication after completing two or more courses of standard *H. pylori* treatment regimens.[8] Factors associated with successful eradication are interactions among host, bacteria, and systems. The most common causes of eradication failure are poor adherence to medical therapy and antibiotic resistance.[8] Barriers to adherence, for example, regimen complexity, adverse effects, should be explored and addressed. Antibiotic resistance has been increasing in the past decade except for low tetracycline and amoxicillin resistance. After second-line treatment failure, it is recommended to perform antimicrobial susceptibility testing (AST). If AST is available, we recommend using tailored treatment based on AST. If AST is not available, we recommend using antibiotic with low

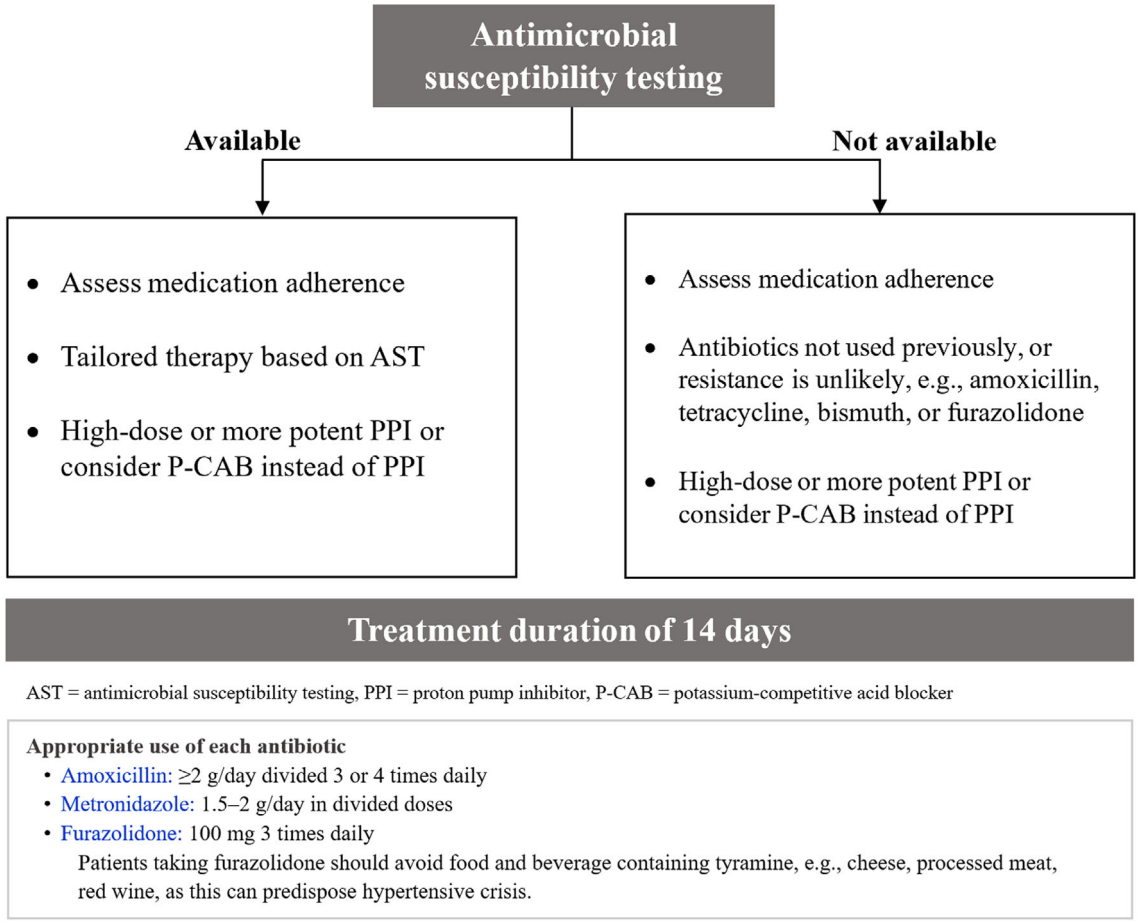

Figure 4 Algorithm for management of multiple *H. pylori* treatment failure.

resistance potential such as amoxicillin, tetracycline, rifabutin, or furazolidone in combination with antibiotic, which was not used in previously failed regimens. CYP2C19 polymorphisms also have an impact on PPI metabolism contributing to change in intragastric pH, and eventually affecting *H. pylori* eradication. It is recommended to use high-dose potent PPI or switch to use P-CAB to achieve adequate acid suppression. Bismuth has bactericidal activity on *H. pylori* and also produces synergistic effect with antibiotics.[79,94] The addition of bismuth to *H. pylori* treatment regimen can increase the eradication rate by an additional 30%–40% despite resistant infection.[79] Lastly, treatment duration of 14 days provided higher eradication rates than shorter duration.[8] Hence, we recommend treatment duration of at least 14 days for *H. pylori* treatment failure. The proposed algorithm for management of *H. pylori* treatment failure is demonstrated in Figure 4.

Adjuvant therapy for *H. pylori* infection

Probiotics are used as an adjuvant treatment to reduce the side effects of antibiotics, which may further increase tolerability and enhance the eradication rate. In vitro and in vivo studies demonstrated that *Lactobacillus*, *Bifidobacterium* species, and *Saccharomyces boulardii* could exert an inhibitory effect on *H. pylori*.[95,96] Shi et al. conducted the network meta-analysis including 40 studies (N = 8924) reporting that using probiotics could provide higher eradication rates and lower side effects. *Lactobacillus* and multiple strains contributed to better subgroup eradication rates. However, there were high heterogeneity, small sample size, and different strains of probiotics used in each study.[97] As *H. pylori*-associated gastric atrophy can cause reduced acid secretion, it was previously suspected that eradication therapy might aggravate gastroesophageal reflux disease (GERD).[98] Nevertheless, prior studies reported that *H. pylori* eradication was not associated with development of GERD[98] and did not increase risk of Barrett's esophagus and esophageal adenocarcinoma.[99] In any case, if patients develop reflux symptoms after eradication, probiotics might be used to improve heartburn or regurgitation.[100] More trials are still needed to evaluate the association of probiotics and GERD.

Statins can inhibit *H. pylori*-induced inflammation by inducing autophagy in macrophages. One randomized trial reported that patients receiving anti-*H. pylori* therapy with statin had significantly higher eradication rate than the group without statin.[101] However, this study did not provide data about antimicrobial susceptibility test. Another large prospective cohort revealed slightly higher eradication rates in statin users than non-statin group using empirical treatment (89%

vs. 86%, OR 1.3; 95% CI 1.1–1.5, $P = 0.002$).[102] Larger clinical trials are needed to confirm the efficacy of adding statin in treatment regimen.

Vaccine against *H. pylori*

H. pylori vaccine has been developed for a decade. The largest phase 3 trial conducted in China (Chinese children, $N = 4464$) concluded that an efficacy of oral recombinant *H. pylori* vaccine was 71.8% in the first year and decreased to 55% in the second year.[103] Protection against *H. pylori* infection was maintained for 3 years after vaccination. Mild adverse reactions such as vomiting, fever, and headache were detected in 7% of both vaccine and placebo groups.[103] In contrast, another study reported that parenteral vaccine was not superior to placebo in prevention of *H. pylori* infection in adult patients.[104] Future trials are required to study the safety and efficacy of vaccine against *H. pylori*.

Conclusions

H. pylori infection is a major risk factor for gastric cancer. Diagnostic testing and treatment for *H. pylori* infection are recommended. High-dose potent PPI or vonoprazan should be used to achieve adequate acid suppression. Fourteen-day concomitant therapy or 14-day BQT is recommended as first-line eradication regimen in high clarithromycin resistance area, while 14-day triple therapy or 14-day BQT is recommended in low clarithromycin resistance area. AST should be performed in patients with multiple treatment failures to provide best-tailored therapy and further increase eradication success.

Acknowledgments

This study was supported by Thailand Science Research and Innovation Fundamental Fund, Bualuang ASEAN Chair Professorship at Thammasat University, and Center of Excellence in Digestive Diseases, Thammasat University, Thailand.

References

1 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984; **1**: 1311–15.
2 Sung H, Ferlay J, Siegel RL *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2021; **71**: 209–49.
3 Sugano K, Tack J, Kuipers EJ *et al*. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut*. 2015; **64**: 1353–67.
4 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**: e17.
5 Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment Of *Helicobacter pylori* Infection. *Am. J. Gastroenterol.* 2017; **112**: 212–39.
6 Mahachai V, Vilaichone RK, Pittayanon R *et al*. Helicobacter pylori management in ASEAN: The Bangkok consensus report. *J. Gastroenterol. Hepatol.* 2018; **33**: 37–56.
7 Malfertheiner P, Megraud F, Rokkas T *et al*. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. *Gut*. 2022; **71**: 1724–62.
8 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.
9 Rokkas T, Gisbert JP, Malfertheiner P *et al*. Comparative effectiveness of multiple different first-line treatment regimens for *Helicobacter pylori* Infection: a network meta-analysis. *Gastroenterology*. 2021; **161**: e4.
10 Hooi JKY, Lai WY, Ng WK *et al*. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology*. 2017; **153**: 420–9.
11 Ferlay J, Ervik M, Lam F et al. Global cancer observatory: cancer today. Lyon, France: International agency for research on cancer. Available from: https://gco.iarc.fr/today, accessed [28 Jul 2022].
12 Vilaichone RK, Quach DT, Yamaoka Y, Sugano K, Mahachai V. Prevalence and pattern of antibiotic resistant strains of *Helicobacter pylori* infection in ASEAN. *Asian Pac. J. Cancer Prev.* 2018; **19**: 1411–13.
13 Vilaichone RK, Mahachai V, Graham DY. *Helicobacter pylori* diagnosis and management. *Gastroenterol. Clin. North Am.* 2006; **35**: 229–47.
14 Brown LM. *Helicobacter pylori*: Epidemiology and routes of transmission. *Epidemiol. Rev.* 2000; **22**: 283–97.
15 Rowland M, Daly L, Vaughan M, Higgins A, Bourke B, Drumm B. Age-specific incidence of *Helicobacter pylori*. *Gastroenterology*. 2006; **130**: 65–72 quiz 211.
16 Malaty HM, Graham DY, Klein PD, Evans DG, Adam E, Evans DJ. Transmission of *Helicobacter pylori* infection: Studies in families of healthy individuals. *Scand. J. Gastroenterol.* 1991; **26**: 927–32.
17 Breckan RK, Paulssen EJ, Asfeldt AM, Kvamme JM, Straume B, Florholmen J. The all-age prevalence of *Helicobacter pylori* infection and potential transmission routes. a population-based study. *Helicobacter*. 2016; **21**: 586–95.
18 Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J Infect Dis*. 2000; **181**: 1359–63.
19 Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. *Gut*. 1994; **35**: 742–5.
20 Fock KM, Ang TL. Epidemiology of *Helicobacter pylori* infection and gastric cancer in Asia. *J. Gastroenterol. Hepatol.* 2010; **25**: 479–86.
21 Sheh A, Fox JG. The role of the gastrointestinal microbiome in *Helicobacter pylori* pathogenesis. *Gut Microbes*. 2013; **4**: 505–31.
22 Chen CC, Liou JM, Lee YC, Hong TC, el-Omar EM, Wu MS. The interplay between *Helicobacter pylori* and gastrointestinal microbiota. *Gut Microbes*. 2021; **13**: 1–22.
23 Guo Y, Zhang Y, Gerhard M *et al*. Effect of Helicobacter pylori on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut*. 2020; **69**: 1598–607.
24 Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I *et al*. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. *Gut*. 2018; **67**: 226–36.
25 Miwa H, Ghoshal UC, Fock KM *et al*. Asian consensus report on functional dyspepsia. *J. Gastroenterol. Hepatol.* 2012; **27**: 626–41.
26 Liou JM, Lin JT, Wang HP *et al*. The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. *Gastrointest. Endosc.* 2005; **61**: 819–25.
27 Quach DT, Tran LT, Tran TL *et al*. Age cutoff and yield of prompt esophagogastroduodenoscopy to detect malignancy in Vietnamese with upper gastrointestinal symptoms: an endoscopic database review of 472,744 patients from 2014 to 2019. *Can. J. Gastroenterol. Hepatol.* 2021; **2021**: 1184848.
28 Moayyedi P, Lacy BE, Andrews CN *et al*. ACG and CAG Clinical guideline: Management of dyspepsia. *Am. J. Gastroenterol.* 2017; **112**: 988–1013.

29 Kuipers EJ, Thijs JC, Festen HP. The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Aliment. Pharmacol. Ther.* 1995; **9**: 59–69.
30 Sonnenberg A, Turner KO, Genta RM. Low prevalence of *Helicobacter pylori*-positive peptic ulcers in private outpatient endoscopy centers in the United States. *Am. J. Gastroenterol.* 2020; **115**: 244–50.
31 Correa P, Houghton J. Carcinogenesis of *Helicobacter pylori*. *Gastroenterology*. 2007; **133**: 659–72.
32 Graham DY. *Helicobacter pylori* update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology*. 2015; **148**: e3.
33 Kumar S, Metz DC, Ellenberg S, Kaplan DE, Goldberg DS. Risk factors and incidence of gastric cancer after detection of *Helicobacter pylori* infection: a large cohort study. *Gastroenterology*. 2020; **158**: e7.
34 Shin CM, Kim N, Yang HJ *et al*. Stomach cancer risk in gastric cancer relatives: interaction between *Helicobacter pylori* infection and family history of gastric cancer for the risk of stomach cancer. *J. Clin. Gastroenterol.* 2010; **44**: e34–9.
35 Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut*. 2020; **69**: 2113–21.
36 Aumpan N, Vilaichone RK, Pornthisarn B *et al*. Predictors for regression and progression of intestinal metaplasia (IM): A large population-based study from low prevalence area of gastric cancer (IM-predictor trial). *PLoS One*. 2021; **16**: e0255601.
37 Choi IJ, Kook MC, Kim YI *et al*. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. *N. Engl. J. Med.* 2018; **378**: 1085–95.
38 Parsonnet J, Hansen S, Rodriguez L *et al*. *Helicobacter pylori* infection and gastric lymphoma. *N. Engl. J. Med.* 1994; **330**: 1267–71.
39 Stolte M, Bayerdörffer E, Morgner A *et al*. Helicobacter and gastric MALT lymphoma. *Gut*. 2002; **50 Suppl 3**: III19-24.
40 Jung K, Kim DH, Seo HI, Gong EJ, Bang CS. Efficacy of eradication therapy in *Helicobacter pylori*-negative gastric mucosa-associated lymphoid tissue lymphoma: A meta-analysis. *Helicobacter*. 2021; **26**: e12774.
41 Annibale B, Capurso G, Lahner E *et al*. Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with *Helicobacter pylori* gastritis and associated iron deficiency anaemia. *Gut*. 2003; **52**: 496–501.
42 Muhsen K, Cohen D. *Helicobacter pylori* infection and iron stores: a systematic review and meta-analysis. *Helicobacter*. 2008; **13**: 323–40.
43 Nahon S, Lahmek P, Massard J *et al*. *Helicobacter pylori*-associated chronic gastritis and unexplained iron deficiency anemia: a reliable association? *Helicobacter*. 2003; **8**: 573–7.
44 Qu XH, Huang XL, Xiong P *et al*. Does *Helicobacter pylori* infection play a role in iron deficiency anemia? a meta-analysis. *World J. Gastroenterol.* 2010; **16**: 886–96.
45 Yuan W, Li Y, Yang K *et al*. Iron deficiency anemia in *Helicobacter pylori* infection: meta-analysis of randomized controlled trials. *Scand. J. Gastroenterol.* 2010; **45**: 665–76.
46 Stasi R, Provan D. *Helicobacter pylori* and chronic ITP. *Hematology Am. Soc. Hematol. Educ. Program*. 2008; **2008**: 206–11.
47 Campuzano-Maya G. Proof of an association between *Helicobacter pylori* and idiopathic thrombocytopenic purpura in Latin America. *Helicobacter*. 2007; **12**: 265–73.
48 Stasi R, Sarpatwari A, Segal JB *et al*. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. *Blood*. 2009; **113**: 1231–40.
49 Neunert C, Terrell DR, Arnold DM *et al*. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019; **3**: 3829–66.
50 El-Serag HB, Kao JY, Kanwal F *et al*. Houston Consensus Conference on testing for *Helicobacter pylori* Infection in the United States. *Clin. Gastroenterol. Hepatol.* 2018; **16**: 992–1002 e6.
51 Wang YK, Kuo FC, Liu CJ *et al*. Diagnosis of *Helicobacter pylori* infection: Current options and developments. *World J. Gastroenterol.* 2015; **21**: 11221–35.
52 Lee JY, Kim N. Diagnosis of *Helicobacter pylori* by invasive test: histology. *Ann Transl Med*. 2015; **3**: 10.
53 Schabereiter-Gurtner C, Hirschl AM, Dragosics B *et al*. Novel real-time PCR assay for detection of *Helicobacter pylori* infection and simultaneous clarithromycin susceptibility testing of stool and biopsy specimens. *J. Clin. Microbiol.* 2004; **42**: 4512–8.
54 Ferwana M, Abdulmajeed I, Alhajiahmed A *et al*. Accuracy of urea breath test in *Helicobacter pylori* infection: meta-analysis. *World J. Gastroenterol.* 2015; **21**: 1305–14.
55 Gisbert JP, Abraira V. Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 2006; **101**: 848–63.
56 Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 2006; **101**: 1921–30.
57 Kodama M, Murakami K, Okimoto T *et al*. Influence of proton pump inhibitor treatment on *Helicobacter pylori* stool antigen test. *World J. Gastroenterol.* 2012; **18**: 44–8.
58 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.
59 Wang XY, Yang Y, Shi RH, Ho B, Wang HD, Zhang GX. An evaluation of a serologic test with a current infection marker of *Helicobacter pylori* before and after eradication therapy in Chinese. *Helicobacter*. 2008; **13**: 49–55.
60 Quach DT, Hiyama T, Shimamoto F *et al*. Value of a new stick-type rapid urine test for the diagnosis of *Helicobacter pylori* infection in the Vietnamese population. *World J. Gastroenterol.* 2014; **20**: 5087–91.
61 Luzza F, Imeneo M, Marasco A *et al*. Evaluation of a commercial serological kit for detection of salivary immunoglobulin G to *Helicobacter pylori*: a multicentre study. *Eur. J. Gastroenterol. Hepatol.* 2000; **12**: 1117–20.
62 Hulten KG, Genta RM, Kalfus IN *et al*. Comparison of culture with antibiogram to next-generation sequencing using bacterial isolates and formalin-fixed, paraffin-embedded gastric biopsies. *Gastroenterology*. 2021; **161**: e2.
63 Aumpan N, Pornthisarn B, Chonprasertsuk S *et al*. Predictive factors for successful eradication in patients with *Helicobacter pylori* treatment failures: A large population-based study. *Gastroenterology*. 2022; **162**: S-874.
64 Ho JJC, Navarro M, Sawyer K, Elfanagely Y, Moss SF. *Helicobacter pylori* antibiotic resistance in the United States between 2011-2021: A systematic review and meta-analysis. *Am. J. Gastroenterol.* 2022; **117**: 1221–30.
65 Megraud F, Bruyndonckx R, Coenen S *et al*. *Helicobacter pylori* resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut*. 2021; **70**: 1815–22.
66 Jaka H, Rhee JA, Ostlundh L *et al*. The magnitude of antibiotic resistance to *Helicobacter pylori* in Africa and identified mutations which confer resistance to antibiotics: systematic review and meta-analysis. *BMC Infect. Dis.* 2018; **18**: 193.
67 Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy. *Helicobacter*. 2007; **12**: 275–8.
68 Villoria A, Garcia P, Calvet X, Gisbert JP, Vergara M. Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for *Helicobacter pylori* eradication. *Aliment. Pharmacol. Ther.* 2008; **28**: 868–77.
69 Lee YC, Dore MP, Graham DY. Diagnosis and treatment of *Helicobacter pylori* infection. *Annu. Rev. Med.* 2022; **73**: 183–95.
70 Graham DY, Tansel A. Interchangeable use of proton pump inhibitors based on relative potency. *Clin. Gastroenterol. Hepatol.* 2018; **16**: e7.

71 Phiphatpatthamaamphan K, Vilaichone RK, Siramolpiwat S *et al*. Effect of IL-1 polymorphisms, CYP2C19 genotype and antibiotic resistance on *Helicobacter pylori* eradication comparing between 10-day sequential therapy and 14-day standard triple therapy with four-times-daily-dosing of amoxicillin in Thailand: a prospective randomized study. *Asian Pac. J. Cancer Prev.* 2016; **17**: 1903–7.

72 Molina-Infante J, Lucendo AJ, Angueira T *et al*. Optimised empiric triple and concomitant therapy for *Helicobacter pylori* eradication in clinical practice: the OPTRICON study. *Aliment. Pharmacol. Ther.* 2015; **41**: 581–9.

73 Prasertpetmanee S, Mahachai V, Vilaichone RK. Improved efficacy of proton pump inhibitor - amoxicillin - clarithromycin triple therapy for *Helicobacter pylori* eradication in low clarithromycin resistance areas or for tailored therapy. *Helicobacter*. 2013; **18**: 270–3.

74 Liou JM, Fang YJ, Chen CC *et al*. Concomitant, bismuth quadruple, and 14-day triple therapy in the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. *Lancet*. 2016; **388**: 2355–65.

75 Kongchayanun C, Vilaichone RK, Pornthisarn B, Amornsawadwattana S, Mahachai V. Pilot studies to identify the optimum duration of concomitant *Helicobacter pylori* eradication therapy in Thailand. *Helicobacter*. 2012; **17**: 282–5.

76 Nyssen OP, Bordin D, Tepes B *et al*. European registry on *Helicobacter pylori* management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21,533 patients. *Gut*. 2021; **70**: 40–54.

77 Lee HJ, Kim JI, Lee JS *et al*. Concomitant therapy achieved the best eradication rate for *Helicobacter pylori* among various treatment strategies. *World J. Gastroenterol.* 2015; **21**: 351–9.

78 Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *BMJ*. 2013; **347**: f4587.

79 Dore MP, Lu H, Graham DY. Role of bismuth in improving *Helicobacter pylori* eradication with triple therapy. *Gut*. 2016; **65**: 870–8.

80 Dore MP, Farina V, Cuccu M, Mameli L, Massarelli G, Graham DY. Twice-a-day bismuth-containing quadruple therapy for *Helicobacter pylori* eradication: a randomized trial of 10 and 14 days. *Helicobacter*. 2011; **16**: 295–300.

81 Vilaichone RK, Prapitpaiboon H, Gamnarai P *et al*. Seven-day bismuth-based quadruple therapy as an initial treatment for *Helicobacter pylori* infection in a high metronidazole resistant area. *Asian Pac. J. Cancer Prev.* 2015; **16**: 6089–92.

82 Lin TF, Hsu PI. Second-line rescue treatment of *Helicobacter pylori* infection: Where are we now? *World J. Gastroenterol.* 2018; **24**: 4548–53.

83 Kim SE, Park MI, Park SJ *et al*. Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* eradication and impact of diabetes. *World J. Gastroenterol.* 2017; **23**: 1059–66.

84 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.

85 Antos D, Schneider-Brachert W, Bästlein E *et al*. 7-day triple therapy of *Helicobacter pylori* infection with levofloxacin, amoxicillin, and high-dose esomeprazole in patients with known antimicrobial sensitivity. *Helicobacter*. 2006; **11**: 39–45.

86 Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. *Gut*. 2016; **65**: 1439–46.

87 Maruyama M, Tanaka N, Kubota D *et al*. Vonoprazan-based regimen is more useful than PPI-based one as a first-line *Helicobacter pylori* eradication: A randomized controlled trial. *Can. J. Gastroenterol. Hepatol.* 2017; **2017**: 4385161.

88 Sue S, Ogushi M, Arima I *et al*. Vonoprazan- vs proton-pump inhibitor-based first-line 7-day triple therapy for clarithromycin-susceptible *Helicobacter pylori*: A multicenter, prospective, randomized trial. *Helicobacter*. 2018; **23**: e12456.

89 Suzuki S, Gotoda T, Kusano C *et al*. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: a multicentre randomised trial in Japan. *Gut*. 2020; **69**: 1019–26.

90 Furuta T, Yamade M, Kagami T *et al*. Dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin and clarithromycin for eradication of *Helicobacter pylori*. *Digestion*. 2020; **101**: 743–51.

91 Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan triple and dual therapy for *Helicobacter pylori* infection in the United States and Europe: Randomized clinical trial. *Gastroenterology*. 2022; **163**: 608–19.

92 Ratana-Amornpin S, Vilaichone RK, Sanglutong L *et al*. Pilot studies of vonoprazan-containing *Helicobacter pylori* eradication therapy suggest Thailand may be more similar to the US than Japan. *Gastroenterology*. 2022; **162**: S-872-S-873.

93 Tungtrongchitr N, Pornthisarn B, Chonprasertsuk S *et al*. High efficacy of 14-day vonoprazan-based quadruple therapy for *Helicobacter pylori* eradication in areas with high clarithromycin resistance: A prospective randomized study (VQ-HP trial). *Gastroenterology*. 2022; **162**: S-871.

94 McNicholl AG, Bordin DS, Lucendo A *et al*. Combination of bismuth and standard triple therapy eradicates *Helicobacter pylori* infection in more than 90% of patients. *Clin. Gastroenterol. Hepatol.* 2020; **18**: 89–98.

95 Zhang L, Su P, Henriksson A, O'Rourke J, Mitchell H. Investigation of the immunomodulatory effects of *Lactobacillus casei* and *Bifidobacterium lactis* on *Helicobacter pylori* infection. *Helicobacter*. 2008; **13**: 183–90.

96 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.

97 Shi X, Zhang J, Mo L, Shi J, Qin M, Huang X. Efficacy and safety of probiotics in eradicating *Helicobacter pylori*: A network meta-analysis. *Medicine (Baltimore)*. 2019; **98**: e15180.

98 Qian B, Ma S, Shang L, Qian J, Zhang G. Effects of *Helicobacter pylori* eradication on gastroesophageal reflux disease. *Helicobacter*. 2011; **16**: 255–65.

99 Doorakkers E, Lagergren J, Santoni G, Engstrand L, Brusselaers N. *Helicobacter pylori* eradication treatment and the risk of Barrett's esophagus and esophageal adenocarcinoma. *Helicobacter*. 2020; **25**: e12688.

100 Cheng J, Ouwehand AC. Gastroesophageal reflux disease and probiotics: A systematic review. *Nutrients*. 2020; **12**: 132.

101 Sarkeshikian SS, Ghadir MR, Alemi F, Jalali SM, Hormati A, Mohammadbeigi A. Atorvastatin in combination with conventional antimicrobial treatment of *Helicobacter pylori* eradication: A randomized controlled clinical trial. *J. Gastroenterol. Hepatol.* 2020; **35**: 71–5.

102 Caldas M, Perez-Aisa A, Tepes B *et al*. The role of statins on *Helicobacter pylori* eradication: Results from the European registry on the management of *H. pylori* (Hp-EuReg). *Antibiotics (Basel)*. 2021; **10**: 965.

103 Zeng M, Mao XH, Li JX *et al*. Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015; **386**: 1457–64.

104 Malfertheiner P, Selgrad M, Wex T *et al*. Efficacy, immunogenicity, and safety of a parenteral vaccine against *Helicobacter pylori* in healthy volunteers challenged with a Cag-positive strain: a randomised, placebo-controlled phase 1/2 study. *Lancet Gastroenterol. Hepatol.* 2018; **3**: 698–707.