

First regional consensus on the management of *Helicobacter pylori* infection in the Middle East.

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Author contributions: Sharara AI, Alsohaibani FI, Malfertheiner P, and Karam SA revised the Delphi questionnaire to align with the specific context of the Middle East; All authors reviewed the most up-to-date literature on *Helicobacter pylori* ; Al-Taweel TA was responsible for the final manuscript revision and submission; All authors read and approved the final manuscript.

Corresponding author: Talal Al-Taweel, MD, MRCP, Division of Gastroenterology, Department of Internal Medicine, Jaber Al-Ahmad Hospital, Block 1, King Khalid Bin Abdulaziz Street, Ministries Area 900015, Kuwait. taltaweel@moh.gov.kw

21 7 2025 21 7 2025 31 27 493984 107138 16 3 2025 16 4 2025 24 6 2025 21 07 2025 30 07 2025 31 07 2025 ©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved. 2025 <https://creativecommons.org/licenses/by-nc/4.0/> This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/> *Helicobacter pylori* (*H. pylori*), a widespread gram-negative bacterium that colonizes the stomach, causes chronic gastritis, which may progress to peptic ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. *H. pylori* infection affects over 50% of people in developing countries and 10%-20%

in developed countries. The Kyoto consensus classifies *H. pylori* gastritis as an infectious disease in the International Classification of Disease 11th Revision. The Maastricht/Florence consensus recommends treatment for all infected individuals, introducing a shift in the management strategies. The prevalence of *H. pylori* infection is high in the Middle East, with infection rates of 40%-70% and 85%-90% being reported among children and adults, respectively. The increasing resistance to antibiotics, including macrolides and fluoroquinolones, is a major challenge in the management of *H. pylori*. Clarithromycin resistance, which is associated with reduced effectiveness of standard triple therapy regimens, leading to higher rates of treatment failure, impacts the eradication rates. This emphasizes the need for routine antibiotic susceptibility testing at the national level, the use of alternative therapies, including new molecular methods, and antibiotic stewardship. An online panel of experts from the Middle East, along with an international expert, developed this consensus to provide comprehensive guidelines on the diagnosis, treatment, prevention, and role of gut microbiota in *H. pylori* infection, with the goal of improving clinical decision-making and reducing the impact of antibiotic resistance in the region. These guidelines are intended to support healthcare professionals involved in the diagnosis and management of *H. pylori*, including primary care physicians, gastroenterologists, and other specialists. They may also inform future clinical research aimed at optimizing treatment strategies and addressing regional challenges.

Core Tip: This expert consensus comprised comprehensive guidelines for the management of *Helicobacter pylori* infection in the Middle East, addressing its diagnosis, treatment, and prevention, with a focus on antibiotic resistance and gut microbiota interactions. Given the rising clarithromycin and fluoroquinolone resistance, this report emphasized the importance of antibiotic stewardship, routine susceptibility testing, and optimized first-line and rescue therapies. Incorporating regional epidemiological data, this consensus aligned with the recommendations of the Maastricht VI/Florence consensus and proposed tailored strategies to enhance eradication success and reduce the risk of gastric cancer, thereby improving the clinical outcomes and management of *Helicobacter pylori* infection.

Helicobacter pylori (*H. pylori*) is a widespread gram-negative bacterium that inhabits the human stomach and is known to lead to chronic gastritis, peptic ulcers, and mucosa-associated lymphoid tissue (MALT) lymphoma[1], and gastric cancer[2]. *H. pylori* infection, which affects > 50% of the population in developing countries and 10%-20% of the population in developed regions, represents one of the most widespread chronic infections globally[3]. *H. pylori* transmission generally occurs during childhood, and transmission among adults is unlikely under normal conditions.

H. pylori gastritis is defined as an infectious disease by the Kyoto consensus report on gastritis. The recommendation to treat all patients with *H. pylori* gastritis in the Maastricht/Florence consensus marks a significant shift in its clinical management[4]. This classification, which is now part of the 11th Revision of the International Classification of Disease, recommends treating all patients with *H. pylori* infection, irrespective of clinical symptoms. However, a re-examination of existing management strategies is critical, given the diverse clinical spectrum of *H. pylori*-related diseases[4 , 5].

The prevalence of *H. pylori* infection in the Middle East, with infection rates ranging from 40%-70% among children and 85%-90% among adults, is consistent with that observed in other developing regions. However, the specific prevalence rates in the region are highly variable, with prevalence rates of 55.5%, 52.0%-68.3%, 40.0%-70.0%, 40.9%, and 64.3%-78.4% being reported in Bahrain[6], Lebanon[7], Saudi Arabia[8], Qatar[9], and the United Arab Emirates (UAE)[10], respectively. Notably, the prevalence rate of *H. pylori* infection is 42.6% among patients with dyspepsia in Kuwait[11] (Figure 1). Studies conducted in countries such as Egypt, Iran, Oman, Saudi Arabia, the UAE, and Yemen have revealed that the infection rates among patients with gastritis and peptic ulcer are similar to those reported in Europe, the United States, and Africa[12].

Regional prevalence of *Helicobacter pylori* (studies are highly variable in terms of diagnostic method use, setting and study population, and year of study).

The growing resistance of *H. pylori* to standard antibiotic therapies, such as clarithromycin, metronidazole, and levofloxacin, presents a significant challenge. This resistance is particularly problematic in the Middle East where treatment regimens often vary and consensus on management strategies is lacking. This consensus report aimed to offer optimal recommendations for the diagnosis and clinical management of *H. pylori* infection in the Middle East. By comparing the existing international guidelines with the specific needs and practices in the region, the expert panel aimed to identify commonalities and differences and to develop regionally tailored recommendations that can address the unique challenges faced in this context.

Notably, gastroenterology experts from Saudi Arabia, the UAE, Kuwait, Qatar, Bahrain, and Lebanon came together to develop comprehensive practice guidelines to address this issue, given the lack of consensus on *H. pylori* management in various Middle Eastern countries. These experts aimed to establish clear and actionable recommendations tailored to the unique context of the Middle East through the thorough review of local, regional, and global literature on the management of *H. pylori* infection.

These guidelines aimed to address the requirement for improved antibiotic susceptibility testing, enhanced antibiotic stewardship, and careful selection of first line and rescue therapies. Notably, the consensus emphasized the importance of appropriate diagnostic testing and effective prevention strategies for the complications associated with *H. pylori* infection, including gastric cancer. Furthermore, these guidelines highlighted the importance of conducting further studies on the impact of *H. pylori* infection and its treatment on the gut microbiota, acknowledging the emerging role of the gut microbiome in overall health.

A panel of experts was set up to address the key clinical issues and challenges affecting the management of *H. pylori* infection in the Middle East. Their collective expertise, along with the regional insights in the context of currently available evidence, were instrumental in the formulation of these guidelines.

This consensus report provided comprehensive regional guidelines for the management of *H. pylori* infection and its clinical manifestations in the Middle East in addition to encouraging further research in this field. The topics were selected in accordance with the Maastricht VI consensus report to address the indications, associations, diagnosis, treatment, and prevention of gastric cancer as well as the association between *H. pylori* infection and the gut microbiota.

A panel comprising six experts from Bahrain, Lebanon, Saudi Arabia, Qatar, UAE, and Kuwait and an international expert from Germany was formed. This group provided a broad representation of perspectives and expertise. Panel members were selected based on their recognized experience in *H. pylori* research and clinical management, their history of publications in peer-reviewed journals, and their active involvement in regional and international clinical practice. These experts are considered key opinion leaders in the field across the Middle East. A senior European professor with expertise in consensus methodology moderated the process to ensure neutrality and methodological rigor.

The identification of the key clinical areas requiring consensus was the initial step of developing these guidelines. A systematic review of the literature was conducted to gather the latest and most robust evidence supporting each statement. Draft statements were formulated based on the findings of these reviews. A comprehensive literature search was conducted to guide the development of the guidelines with all authors actively engaging in writing and reviewing the content. International guidelines and consensus documents were reviewed to help fill the gaps in local and regional data. This approach ensured the formulation of evidence-based guidelines tailored to meet the specific needs and practices of the region.

The Delphi method is a structured communication technique often used to achieve consensus among a panel of experts. It involves multiple rounds of anonymous voting where participants independently rate a series of statements or questions. After each round a summary of the group's feedback is shared, and participants are encouraged to reconsider their responses in light of the group's views. This iterative process helps reduce the influence of dominant individuals, encourages equal participation, and refines the group's opinions toward consensus.

In our process, the Delphi questionnaire was designed based on the selection of relevant, evidence-based questions. The questionnaire was shared online with participants, who were given time to respond anonymously. They were asked to indicate whether they agreed, disagreed, or were undecided on each statement. If they disagreed, they were invited to provide written feedback explaining their reasoning.

Two rounds of voting were conducted. The participants were instructed to rate each statement using the following scale in each round: (1) Agree strongly; (2) Agree with reservation; (3) Undecided; (4) Disagree; and (5) Disagree strongly.

The statement was rephrased and subjected to a second vote if < 80% of the responses were 'agree strongly' or 'agree with reservation'. A consensus could not be reached initially for 12 questions; in-depth discussions were conducted for these questions during the meeting before commencing the second round of voting. Evidence-based discussions, including key references, supported each statement during the voting process.

Consensus was defined as $\geq 80\%$ of respondents strongly agreeing or agreeing with reservation.

All statements were reviewed and presented to the delegates for final voting during the final meeting held online on July 12, 2024. The statements were adopted from Maastricht VI as they remain crucial for general clinical education and practice. The validity of these statements was re-evaluated considering current knowledge and the Middle Eastern context. The statements were not modified unless necessitated by new scientific evidence.

The level of evidence and strength of each recommendation were assessed after the meeting using the Grades of Recommendations, Assessment, Development, and Evaluation system, which evaluates both the quality of evidence and strength of recommendations. The Grades of Recommendations, Assessment, Development, and Evaluation categories are defined as follows:

Quality of evidence: (1) High quality: Further research is very unlikely to alter confidence in the estimated effect; (2) Moderate quality: Further research may significantly impact confidence in the estimate and could change it; (3) Low quality: Further research is likely to have a significant effect on confidence in the estimate and is likely to change it; and (4) Very low quality: The estimate of effect is highly uncertain.

Strength of recommendation: (1) Strong recommendation: A strong endorsement either for or against the use of an intervention; and (2) Weak recommendation: A weak endorsement either for or against the use of an intervention.

Table 1 summarizes all the statements, indicating their corresponding levels of evidence and strengths of recommendation.

Statements, level of evidence, and strength of recommendation 1

Proton pump inhibitor, bismuth, tetracycline, and metronidazole prescribed separately is not a Food and Drug Administration-approved treatment regimen. However, Pylora[®], a combination product containing bismuth subcitrate, tetracycline, and metronidazole combined with a proton pump inhibitor for 10 days, is a Food and Drug Administration-approved treatment regimen. *H. pylori* :

Helicobacter pylori ; PPI: Proton pump inhibitor; IDA: Iron deficiency anemia; ITP: Idiopathic thrombocytopenic purpura; MALT: Mucosa-associated lymphoid tissue; OLGA/OLGIM: Operative link on gastric atrophy/operative link on gastric intestinal metaplasia; BQT: Bismuth quadruple therapy; GI: Gastrointestinal; UBT: Urea breath test.

Agreement 100% grade: A1: The presence of *H. pylori* , a gastric pathogen that causes gastritis, in the gastric mucosa triggers chronic active inflammation characterized by the infiltration of neutrophils and mononuclear cells, an effect that is absent in the absence of the bacteria[13 , 14]. According to Koch's postulates, *H. pylori* was identified earlier as a pathogen[15]. Eradication of *H. pylori* may restore the gastric mucosa, preventing the progression of mucosal lesions[16], alleviating symptoms, reducing the incidence of complications, and lowering the risk of gastric cancer, even in asymptomatic individuals. However, chronic changes and intestinal metaplasia (IM) may persist despite successful eradication[4 , 5 , 17]. Notably, a type of gastritis similar to *H. pylori* -induced gastritis that occurs without *H. pylori* infection has been reported; however, its clinical relevance is still uncertain[18].

Agreement 100% grade: A1: The test-and-treat strategy is an effective approach for managing uninvestigated dyspepsia, especially in younger patients without alarming symptoms[19 , 20]. This approach involves non-invasive testing of patients with dyspeptic symptoms, followed by treatment if *H. pylori* infection is confirmed. This approach differs from the more invasive scope-and-treat strategy requiring upper gastrointestinal (GI) endoscopy. The test-and-treat approach can resolve the majority of peptic ulcer cases and help prevent the development of serious complications associated with *H. pylori* gastritis, even in patients without visible mucosal lesions[21 , 22]. Previous studies have indicated that the efficacy of this strategy[19 , 23] is equivalent to that of empirical proton pump inhibitor (PPI) therapy for short-term symptom relief, with *H. pylori* eradication offering long-lasting benefits[19 , 20]. Endoscopy offers a slight improvement in detection rates; however, its high cost[20] limits its use to patients aged ≥ 60 years, those with alarming features, and those unresponsive to initial treatments[4 , 19 , 20 , 23].

Agreement 100% grade: A1: Compared with placebo or acid-suppressive therapy, *H. pylori* eradication offers greater long-term relief for dyspepsia; however, the benefit is modest[4]. Trials excluding *H. pylori* eradication have not been conducted since the adoption of the test-and-treat strategy for dyspepsia in the early 2000s owing to ethical concerns[24]. A recent meta-analysis involving 29 randomized control trials revealed that eradication therapy is more effective for symptom cure and improvement in patients positive for *H. pylori* with functional dyspepsia (FD)[25]. The test-and-treat approach was ranked as the most effective strategy for managing uninvestigated dyspepsia, especially for patients positive for *H. pylori* , in a network meta-analysis. However, long-term studies have reported mixed results, with some studies reporting no significant difference between those treated for *H. pylori* and controls in terms of dyspepsia symptoms[26 , 27]. PPIs are more effective than *H. pylori* eradication in the management of dyspepsia linked to acid reflux, indicating that the benefits of eradication are more specific to non-reflux-related dyspepsia.

Agreement 85.71% grade: B2: The diagnosis of *H. pylori* gastritis must be excluded before diagnosing FD, particularly in patients with dyspepsia who are *H. pylori* -positive with no other endoscopic pathologies. Sustained symptom relief following eradication therapy indicates that symptoms were attributable to *H. pylori* gastritis[28 - 31]. However, persistence of symptoms despite successful eradication indicates the diagnosis of FD[5]. Thus, the diagnosis of *H. pylori* gastritis must be ruled out before diagnosing FD. Some patients attribute their symptoms to stress rather than *H. pylori*. This makes treatment outcomes less predictable, thereby complicating the decision-making process regarding treatment guidelines.

Agreement 100% grade: A1: The use of aspirin or nonsteroidal anti-inflammatory drug (NSAID) elevates the risk of peptic ulcers and related complications in individuals with *H. pylori* . NSAIDs, aspirin, and *H. pylori* independently increase the risk of gastric and duodenal ulcers and related complications[32 , 33]. The majority of studies indicate that compared with individuals not infected with *H. pylori* , patients with *H. pylori* infection who receive NSAIDs, cyclo-oxygenase-2 inhibitors,

or aspirin are at a higher risk of developing peptic ulcer and its complications. A combined or greater risk is observed in cases with concomitant *H. pylori* infection and NSAID or aspirin use, exceeding the risk of each factor alone[34 - 36].

Agreement 85.71% grade: A1: *H. pylori* testing and treatment are recommended in patients who are high risk commencing long-term NSAID therapy or already receiving long-term aspirin. Clinical trials primarily focus on *H. pylori* eradication in patients who used NSAIDs, showing reduced peptic ulcer risk for those commencing NSAID therapy. However, the advantage is less certain for individuals on long-term NSAID therapy. Patients who are high-risk, particularly those with a history of peptic ulcer, may benefit from PPI therapy to further reduce the risk of recurrence while taking NSAIDs. In patients using low-dose aspirin, *H. pylori* infection raises the risk of peptic ulcers and bleeding; eradication of the infection can help decrease this risk. However, the widespread use of low-dose aspirin makes universal *H. pylori* testing and treatment less practical. Therefore, *H. pylori* testing and treatment should be considered for patients who are high-risk receiving aspirin, especially those with a history of peptic ulcer, along with additional PPI therapy[34 - 36]. Age > 65 years, a history of peptic ulcers, use of high-dose NSAIDs, and concomitant use of antiplatelets, anticoagulants, or high dose corticosteroids are risk factors for ulcer-related complications[37].

Agreement 85.71% grade: A1: Long-term administration of PPIs reduces gastric acid secretion, leading to hypergastrinemia. The prevalence of enterochromaffin-like cell hyperplasia in the gastric corpus in patients who are positive for *H. pylori* is 2.5-fold higher than that in patients without infection who use PPIs[38]. Prolonged PPI therapy results in gastritis extending from the antrum to the corpus, significantly increasing the risk of body atrophic gastritis, with an odds ratio of 11.5 for atrophy in patients who are positive for *H. pylori* . The mean corpus atrophy score in patients who are positive for *H. pylori* on PPIs is two to three times higher than that in those in individuals without infection[38]. These changes, mainly observed in Europe and the United States, indicate the increased risk of gastric cancer in patients who are positive for *H. pylori* owing to the association with gastric mucosal atrophy[39 , 40]. Confounding factors, such as the reason for PPI use and unknown *H. pylori* status, complicate these findings. PPI-induced hypochlorhydria or parietal cell loss from conditions such as *H. pylori* -related atrophy may also alter the non- *H. pylori* gastric microbiome[41]. Further studies must aim to understand how the microbiome changes and gastritis topography contributes to gastric mucosal atrophy and preneoplasia in patients with persistent *H. pylori* infection.

Agreement 100% grade: A1: Eradicating *H. pylori* in long-term PPI users is advantageous as the prolonged administration of PPI can shift the antrum-predominant pattern of gastritis to a corpus-predominant pattern and elevated gastrin levels. *H. pylori* eradication improves gastritis in these patients[38 - 40 , 42 - 44] and is particularly recommended for those receiving long-term PPI therapy owing to the potential risks associated with persistent infection. Notably, *H. pylori* eradication does not appear to increase the risk of esophageal adenocarcinoma[45].

Agreement 100% grade: A1: Eradicating *H. pylori* is recommended for managing patients with unexplained iron deficiency anemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency. Eradication can improve IDA and ITP; however, results may vary. Eradication enhances anemia and hemoglobin levels in patients with IDA, especially in those with moderate to severe anemia, with significant benefits being observed in children. The guidelines recommend *H. pylori* eradication for the management of recurrent unexplained IDA, especially when upper GI and colonoscopy results are normal[46 - 48]. Eradication is beneficial in adults with ITP as it can increase the platelet counts and response rates, particularly in those with atrophic gastritis and high *H. pylori* prevalence. Evidence for improving vitamin B12 deficiency is less clear; however, addressing *H. pylori* infection can be beneficial for these conditions[49 - 51].

Agreement 85.71% grade: A1: *H. pylori* eradication, the first-line treatment and standard of care for localized low-grade gastric MALT lymphoma, yields long-term remission rates of 70%-80%[52]. However, patients with the 11:18 translocation may not respond to this therapy. Endoscopic follow-up conducted every 3-6 months enables the monitoring of disease regression and screening

for premalignant conditions due to the heightened risk of gastric adenocarcinoma. The latest guidelines from the European Society for Medical Oncology advise comprehensive H. pylori testing using serological, stool, and breath tests if the tissue results are negative. Ensuring eradication and considering second-line treatments is necessary if the infection persists[52]. Complete endoscopic remission may require > 1 year; nevertheless, up to 30% of H. pylori -negative cases may achieve a complete response rate following eradication therapy[53 , 54]. The European Society for Medical Oncology guidelines recommend evaluating regression 3-6 months post-eradication before exploring treatments such as radiation or chemotherapy[52]. These guidelines now recommend H. pylori eradication for all cases of gastric marginal zone B-cell lymphoma irrespective of the stage, owing to occasional responses in disseminated cases[52 , 55 , 56]. In contrast to gastric adenocarcinoma, specific H. pylori gene products have not been linked to the development of lymphoma[57].

Agreement 100% grade: D2: H. pylori has been linked to various extra-gastrointestinal conditions, including cardiovascular diseases, metabolic disorders, neurodegenerative diseases as well as conditions such as migraine, chronic urticaria, and rosacea. Nevertheless, definitive causal relationships remain unclear, with conflicting evidence[58 - 60]. The decreasing H. pylori infection rates in some countries have been associated with the increased incidences of asthma, atopic conditions, obesity, and inflammatory bowel disease. Although H. pylori has been linked to several diseases, its role in these conditions is not fully established. Thus, eradication based solely on these associations is not justified[58 , 61 - 63].

Agreement 100% grade: A1: Non-invasive testing for H. pylori infection is recommended for patients with dyspepsia aged < 60 years without alarming symptoms or specific risks. The 13C urea breath test (UBT), stool antigen test (SAT), and serological test for IgG antibodies against H. pylori exhibit high sensitivity and specificity[64]. However, IgG antibody tests cannot differentiate between current and past infections, making them unsuitable for verifying eradication success. These tests have certain limitations, particularly in areas with low H. pylori prevalence where false positives are more likely. Thus, confirmatory tests are necessary. Although the typical age threshold for such testing is 60 years, it can vary between 45 and 55 years depending on regional differences in the risk of gastric cancer.

Agreement 100% grade: B1: An upper GI endoscopy is crucial for accurate diagnosis in patients with dyspepsia aged > 60 years. Functional serology can offer complementary insights. New-onset dyspepsia in younger individuals warrants attention despite the global decline in gastric cancer rates as 5% of cases of gastric cancer occur in patients aged < 40 years[65]. The age group of 50-60 years presents a gray zone influenced by regional differences where gastric cancer can develop earlier. Thus, a comprehensive evaluation considering the regional risk factors for gastric cancer is essential for patients in this age bracket. The likelihood of gastric cancer increases with age; consequently, upper GI endoscopy is particularly recommended for patients aged > 60 years, especially in the presence of additional risk factors. Functional serology, including tests for pepsinogen I-II and gastrin 17, yields valuable supplementary diagnostic information. With a 96% accuracy rate and a 98% negative predictive value, functional serology facilitates highly accurate non-invasive assessment of corpus atrophy[66].

Agreement 100% grade: A2: Endoscopy, when indicated, should be performed utilizing the best available technologies and include biopsy sampling per the Sydney protocol[16]. Gastric endoscopy, coupled with biopsy sampling, is the most accurate, sensitive, and specific diagnostic method for patients with alarming gastroesophageal symptoms[67 - 69]. High-resolution endoscopy, enhanced by virtual chromoendoscopy after proper training, provides a reliable assessment of inflammatory lesions, mucosal atrophy, and focal abnormalities, thereby enhancing diagnostic performance[70 - 74].

Upper GI endoscopy must meet specific quality requirements irrespective of the clinical indications[67 - 69 , 71 - 73] including mucosal washing, sufficient inspection time, endoscopic evaluation of all gastric mucosa regions (oxyntic vs antral), and photographic documentation. At least two samples

must be acquired from both functional compartments, antrum and fundus, and submitted in separate containers[69 , 71 , 72]. A biopsy from the incisura further completes the biopsy collection for histological staging of gastritis, including the operative link on gastric atrophy (OLGA) and operative link on gastric IM (OLGIM)[74 , 75]. Additional tissue samples should be taken to evaluate *H. pylori* status. Focal lesions that may contain dysplasia should be identified and submitted separately for microscopic analysis and potential endoscopic submucosal dissection[76].

Agreement 100% grade: A1: Notably, 13C-UBT is widely utilized for diagnosing *H. pylori* infection and verifying its eradication post-treatment. Given its ability to enhance accuracy and sensitivity, citric acid (CA) plays a crucial role in this procedure. CA delays gastric emptying, optimizes the distribution of the substrate within the stomach, and prolongs its interaction with *H. pylori* urease[77]. CA is preferred over other test meals such as semi-liquid or semi-fatty acid meals, apple juice, or orange juice as it is more cost-effective and palatable when sweeteners are added[21 , 26 , 77 , 78]. Incorporating CA into the test meal significantly enhances the sensitivity of the 13C-UBT, especially in populations with gastric atrophy, making it a preferred choice for reliable diagnostic outcomes[79 - 82].

Agreement 100% grade: A1: The detection of *H. pylori* -specific antigens in stool samples represents a convenient and non-invasive diagnostic method suitable for pretreatment and post-treatment evaluation. *H. pylori* releases bacterial antigens into the stool. Thus, SAT can effectively detect active infection[80 - 82]. Polyclonal antisera was used in these tests originally; however, modern SATs utilizing monoclonal antibodies have exhibited superior performance in comparative studies[80]. SATs are available as enzyme immunoassay kits for laboratory use and rapid immunochromatography tests for near-patient testing[80 , 83]. Laboratory-based enzyme immunoassays have generally outperformed rapid tests in comparative studies[81 , 84 , 85], and the sensitivity can vary widely among different rapid test options; nevertheless, rapid tests exhibit acceptable clinical performance[86 , 87]. Users must consider the specific limitations and performance characteristics of each test when interpreting the results[83 , 84].

Agreement: 100% grade: A1: Over the past decades the prevalence of antibiotic resistance in *H. pylori* has gradually increased[88]. Traditional phenotypical methods such as agar dilution testing, which require bacterial culture, remain the gold standard for antibiotic susceptibility testing but are time-consuming and labor-intensive[89]. Molecular techniques such as real-time PCR using gastric tissue or stool, whole genome sequencing, and digital PCR meet the requirement for faster and culture-independent methods. These methods can detect specific mutations associated with antibiotic resistance, particularly clarithromycin and levofloxacin resistance[90]. Clarithromycin resistance, primarily caused by mutations in the 23S rRNA gene (e.g. A2143G, A2142G, and A2142C), is well-characterized and can be accurately predicted using PCR or sequencing[89]. Levofloxacin resistance is predominantly caused by mutations in the *gyrA* gene; thus, PCR-based tests are effective in predicting quinolone resistance[90]. However, predicting resistance to metronidazole is more complex due to multiple genetic factors affecting susceptibility, including mutations in the *rdxA* gene. Molecular methods exhibit varying accuracy in predicting resistance across different antibiotics, with promising advancements being observed in whole genome sequencing to improve prediction accuracy, especially for antibiotics such as metronidazole and amoxicillin where multiple genetic mutations may contribute to resistance[91 - 94].

Agreement 100% grade: A1: *H. pylori* treatment suppresses the infection; however, eradication may fail owing to factors such as antibiotic resistance. The immediate post-treatment phase is termed 'clearance.' Definitive eradication is confirmed 4-6 weeks later[95]. During this crucial period it is essential to refrain from using antibiotics, bismuth, and PPI for at least 4 weeks and should be discontinued 14 days prior to prevent lingering bacteria from affecting test accuracy, potentially leading to false negatives. Alternative medications such as H2 receptor antagonists, gastric mucosal protectants, or antacids can be safely used without impacting *H. pylori* testing[96]. Owing to its inability to distinguish between current infection and past exposure, serology is inadequate for assessing the success of the eradication.

Agreement 85.71% grade: A1: Serum IgG antibody tests for *H. pylori* serve as crucial screening tools in clinical contexts, such as bleeding peptic ulcers, gastric MALT lymphoma, gastric cancer, gastric atrophy, and following recent antibiotic or PPI therapy[97 , 98]. ELISA-based tests are most reliable in patients who were untreated or were previously treated. However, their effectiveness depends on local validation, which can vary, as observed in Kuwait. Given the diversity of *H. pylori* strains, only validated tests should be used for testing. Serology cannot confirm active infection post-eradication as antibodies persist and may lead to false positives months later. Thus, establishing a validated cutoff value for positivity is crucial as equivocal results may necessitate additional follow-up rather than immediate action. No specific antigen combination is recommended for assessing progression to gastric cancer at present owing to insufficient data supporting their clinical use.

Agreement 85.71% grade: A1: Histological assessment of atrophy facilitates gastritis staging using systems such as OLGA and OLGIM, which evaluate atrophy in the antrum and corpus/fundus separately. OLGA staging considers all types of atrophy, including metaplastic and non-metaplastic[99]; in contrast OLGIM focuses on IM[100]. These staging systems do not require subtyping of IM[99]. The high-risk stages (OLGA/OLGIM III and IV) show a strong association with increased risk of gastric cancer[101]. Notably, OLGIM staging exhibits higher reproducibility than OLGA; however, it does not assess pseudopyloric atrophy, which is considered a precancerous lesion[102]. Studies have shown markedly increased risks of gastric epithelial neoplasia associated with OLGA III–IV [relative risk = 27.70, 95% confidence interval (CI): 3.75-204.87] as well as high-grade dysplasia linked to advanced OLGIM stages (relative risk = 16.67, 95%CI: 0.80-327.53)[101].

Agreement 100% grade: C1: Antimicrobial resistance (AMR) is a significant concern in the Middle East owing to the widespread misuse and overuse of antibiotics. Notably, in 2019 Bahrain reported 78 deaths directly attributed to AMR and 302 deaths associated with AMR. The corresponding number of deaths were 2500 and 9100 in Saudi Arabia, 66 and 266 in Qatar, 418 and 1700 in the UAE, 197 and 755 in Kuwait, and 454 and 1900 in Lebanon. During the coronavirus disease 2019 pandemic, there was a notable increase in the use of various antimicrobials, particularly macrolides, often without proper indications or adherence to guidelines[103]. This rampant use has exacerbated resistance. Thus, it is crucial to address and regulate antibiotic use more effectively to combat growing antibiotic resistance in these regions.

Agreement 100% grade: B1: First-line treatment should be based on local resistance patterns and the success rates of specific regimens if susceptibility testing for *H. pylori* cannot be performed. Owing to its high eradication rates (> 90%) and ability to overcome clarithromycin resistance, single-capsule bismuth quadruple therapy (BQT) (Pylera ®) is recommended[104] in areas with high (> 15%) or unknown clarithromycin resistance. Single-capsule BQT, a single-capsule formulation that combines bismuth subcitrate, tetracycline, and metronidazole with a PPI, has been approved by the Food and Drug Administration (FDA) and is effective globally with studies from Kuwait and Saudi Arabia reporting high eradication rates. Single-capsule BQT achieved an 88.0% eradication rate in Kuwait (clarithromycin-based triple therapy: 68.6%)[105]. A 10-day single-capsule BQT achieved eradication rates of 78.3% (intention-to-treat) and 87.8% (per-protocol) in Saudi Arabia. Availability issues may limit access to BQT in some regions despite its efficacy[106].

Non-bismuth concomitant quadruple therapy can be considered if BQT is unavailable; however, its eradication rates are lower, and it may contribute to broader AMR. This therapy yields better outcomes than sequential therapy, particularly in patients with clarithromycin resistance, but increases exposure to unnecessary antibiotics. Concomitant therapy is less effective in areas with high dual resistance to clarithromycin and metronidazole with a success rate of 79%[104 , 107]. Alternative treatment strategies such as high-dose PPI-amoxicillin dual therapy or rifabutin triple therapy may be considered; however, the use of rifabutin must be studied further owing to its potential adverse effects[108 - 110].

BQT remains the preferred option where available, owing to its high success rates and fewer issues with resistance. Single-capsule BQT, which simplifies BQT into a single capsule, further reduces the pill burden, thereby increasing convenience. Importantly, single-capsule BQT achieves *H. pylori* eradication in 90% of patients in real-world clinical settings, with a favorable safety profile[111]. The effectiveness of single-capsule BQT as both a first-line and rescue therapy was shown to be optimal in the largest study conducted to date[111]. Compliance was closely associated with treatment effectiveness. Thus, local success rates must be regularly monitored to ensure the selected treatment remains effective.

Data regarding *H. pylori* resistance to antimicrobials in most Middle Eastern countries is lacking. Thus, regular monitoring of local success rates and resistance patterns plays a crucial role in ensuring the continued effectiveness of the selected treatment (Figure 2).

Algorithm for empirical *Helicobacter pylori* eradication if individual antibiotic susceptibility testing is not available. 1 High-dose proton pump inhibitor (PPI) or potassium-competitive acid blocker (vonoprazan where available) plus amoxicillin may be another option. 2 Bismuth Quadruple Single Capsule[1]. Bismuth Quadruple Single Capsule: PPI; bismuth, tetracycline; and metronidazole. Clarithromycin triple: PPI; clarithromycin; and amoxicillin. It is only used if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI; clarithromycin; amoxicillin; and metronidazole. Levofloxacin quadruple: PPI; levofloxacin; amoxicillin; and bismuth. Levofloxacin triple: The same but without bismuth. In cases of high fluoroquinolone resistance (> 15%), the combination of bismuth with other antibiotics, high-dose PPI-amoxicillin dual, or rifabutin, may be an option. BQT: Bismuth quadruple therapy; HDDT: High dose dual therapy; P-CAB: Potassium-competitive acid blockers; PPI: Proton pump inhibitor.

Agreement 100% grade: D2: The optimal duration for administering single-capsule BQT is typically 10 days. Traditional bismuth regimens are generally administered for 14 days; however, single capsule formulations yield effective results with a 10-day course. The latest clinical guideline from the American College of Gastroenterology on the treatment of *H. pylori* infection indicates that the administration of single-capsule BQT for 10 days is an FDA-approved treatment regimen. Notably, prescribing the individual components of BQT separately is not approved by the FDA. Thus, the treatment duration must be extended to 14 days to improve adherence and ensure effectiveness when using separate components[50].

Bismuth salts, which act locally against *H. pylori* through complex and unclear mechanisms, are not associated with resistance. Bismuth subcitrate and bismuth subsalicylate are commercially available; however, head-to-head comparisons are lacking. Both agents have been deemed safe and were well-tolerated in various studies[28 , 112].

Shorter duration of BQT administration, such as 1-7 days, is less effective than the 10-14-day regimen[113]. The longer duration regimen consistently achieves eradication rates of $\geq 85\%$, even in areas with high metronidazole resistance. Notably, recent analyses have reinforced the effectiveness of a 10-day course with a single-capsule formulation, demonstrating eradication rates of approximately 90% for first-line therapy and slightly lower rates for subsequent lines of treatment despite the presence of metronidazole resistance[112 , 114 , 115].

The Hp-EuReg study, which included over 2000 cases across several European countries, reported eradication rates of > 90% and excellent compliance for a 10-day single-capsule regimen. The ideal duration for BQT remains debatable; however, current evidence suggests that a 10-day treatment regimen with a single-capsule BQT is effective and well-tolerated in diverse settings. Nevertheless, extending the duration to 14 days may improve compliance and treatment outcomes when using separate components of BQT[116].

Agreement 85.71% grade: B1: Concomitant therapy comprising a PPI, amoxicillin, clarithromycin, and metronidazole administered concurrently should be the preferred choice when selecting a

non-BQT treatment strategy. This recommendation stems from its simplicity and proven reproducible effectiveness compared with that of sequential and hybrid therapies[117]. Non-BQTs, including sequential, concomitant, and hybrid approaches, are effective against susceptible *H. pylori* strains. Moreover, they are particularly beneficial in settings with high rates of clarithromycin resistance (> 15%) or unknown susceptibility profiles. However, non-BQTs involve the administration of at least one unnecessary antibiotic, which can be avoided if susceptibility profiles are known[104 , 118].

Given that they require switching medications midway through the treatment course, sequential and hybrid therapies are more complex and increase the risk of prescription errors, thereby reducing patient compliance. Concomitant therapy has superior efficacy over sequential therapy, with an odds ratio of 1.49 (95%CI: 1.21–1.85) and consistently higher eradication rates[117 - 122]. Concomitant therapy for 14 days yields eradication rates of > 90%, comparable with those of BQT. In contrast sequential and hybrid therapies often result in lower success rates and increased complexity. Concomitant therapy may be associated with a slightly higher rate of adverse events than hybrid therapy; however, these differences are generally minor (risk difference = 0.03; 95%CI: 0.00–0.06)[123 , 125 - 127]. Thus, given its higher efficacy, fewer complications, and simpler regimen, concomitant therapy is recommended over sequential and hybrid therapies in the absence of BQT.

Agreement 100% grade: D2: Given its proven effectiveness in eradicating *H. pylori*, the recommended duration for non-BQT concomitant therapy is 14 days. This duration ensures extended antibiotic exposure, which is crucial for overcoming bacterial resistance and achieving high eradication rates. Notably, 14-day regimens yield success rates of > 90%, indicating their reliability in treating infections, especially in regions with high resistance[122]. Despite potential concerns regarding patient compliance, this timeframe balances efficacy and safety, thereby offering optimal treatment outcomes.

Agreement 100% grade: B1: First-line empirical treatment in regions with low clarithromycin resistance may comprise single-capsule BQT or clarithromycin-containing triple therapy, provided these regimens are locally effective. Single-capsule BQT offers a high eradication rate with a simplified dosing regimen. Clarithromycin-containing triple therapy is effective in regions with minimal clarithromycin resistance. As emphasized in the Practice Guidelines for the Management of *H. pylori* Infection by the Saudi *H. pylori* Working Group, a study conducted in Saudi Arabia reported an eradication rate of 87.8% following the administration of single-capsule BQT with PPI for 10 days in a per-protocol analysis. Previous treatment failure had no effect on treatment response. This rate is higher than that obtained with standard triple therapy in Saudi Arabia[123]. The eradication rates achieved with single-capsule BQT in Kuwait were higher than those achieved with clarithromycin[124]. Another study conducted in the UAE in 2019 assessed different treatment regimens among 239 patients. Single-capsule BQT achieved the highest overall eradication rate of 88% in this study, with other regimens, such as sequential therapy (62%), amoxicillin + clarithromycin + PPI (60%), and amoxicillin + levofloxacin + PPI (48%), demonstrating lower success rates[125].

Agreement 100% grade: B1: Recent evaluations and expert consensus have consistently recommended continuing PPI-clarithromycin-based triple therapy, including amoxicillin or metronidazole, for 14 days[126]. Although extensive audits, such as the Hp-EuReg analysis of over 21000 first-line *H. pylori* treatments across 27 European countries, have highlighted that the regimen comprising PPI, amoxicillin, and clarithromycin (PAC) was predominant, its usage has decreased over time[116]. Notably, 14-day, 10-day, and 7-day courses of PAC resulted in modified intention-to-treat eradication rates of 86.2%, 82.7%, and 84.2%, respectively[116]. Further updates involving nearly 30000 treatments confirmed these findings, revealing that the 14-day PAC course achieved an eradication rate of 87%, while shorter durations yielded lower rates. The efficacy of the 14-day regimen remains robust unless local clarithromycin resistance rates surpass 15%; shorter courses may be less effective in such cases[127]. Saudi Arabia has a high resistance rate; thus, regimens of shorter duration are not recommended as standard therapy[

123]. PPI–amoxicillin–metronidazole-based regimens have shown variable eradication rates depending on metronidazole resistance, with 14-day schedules demonstrating some ability to counteract resistance effects[127]. In summary, the 14-day duration is optimal for achieving high eradication rates with PPI-clarithromycin-based triple therapy, unless local data suggest otherwise.

Agreement 100% grade: C2: The effectiveness of triple therapy for *H. pylori* can be enhanced by administering PPIs twice daily as higher doses of these antisecretory drugs significantly increase the intragastric pH[114 , 116 , 128]. This change in pH improves the delivery, stability, and activity of antibiotics such as clarithromycin, amoxicillin, and metronidazole, making *H. pylori* more susceptible to treatment. This effect is particularly notable in extensive metabolizers of PPIs[129]. High-dose PPI, defined as 40 mg of omeprazole or an equivalent dosage of another PPI, has been documented to improve the eradication rates in triple therapies. However, whether high-dose PPI has a similar impact on the efficacy of quadruple therapies remains unclear. Higher PPI doses may enhance the effectiveness of non-BQT (concomitant or sequential therapy) and triple therapy plus bismuth; however, the evidence is inconsistent and limited[114 , 116]. The eradication efficacy of quadruple therapies such as BQT remains largely unaffected by variations in the PPI dosage. Nonetheless, the administration of large doses of PPIs such as lansoprazole or esomeprazole can maintain adequate gastric acid suppression, which is crucial for achieving effective eradication with amoxicillin alone[108 , 130 - 132].

Agreement 85.71% grade: B2: Potassium-competitive acid blockers (P-CABs) offer distinct advantages over conventional PPI-based therapies for *H. pylori* eradication. The superior acid suppression achieved by P-CABs is particularly beneficial as achieving a pH of 6-7 over a 24-h period is crucial for optimal bacterial eradication[133]. Traditional PPIs often fail to maintain this level of acid suppression throughout the day. In contrast P-CABs provide a more consistent and effective inhibition of gastric acid production. This characteristic makes P-CABs, such as vonoprazan and its successors in development, more effective in combination therapies, particularly in patients with AMR[134 , 135].

Vonoprazan-based triple therapies outperform standard PPI-based regimens in first-line and second-line treatment settings with notably high success rates being observed even in patients with clarithromycin-resistant *H. pylori* strains[136]. Vonoprazan-based therapies were superior to PPI-based therapies in a previous meta-analysis[137] with a more recent review confirming these findings, thereby highlighting its enhanced efficacy in resistant cases[138]. Exploratory trials have demonstrated promising results for dual therapy involving vonoprazan and amoxicillin with eradication rates of 63%-100% and particularly high success rates in clarithromycin-resistant infections[136 , 139].

Initial studies were primarily conducted in East Asia; however, research in North American and European contexts has also yielded results comparable with those of PPI-based treatments. Nevertheless, the eradication rate did not exceed 90%[140]. Ongoing research into dose adjustments and comparative trials in Western countries will further refine these therapies, thereby simplifying treatment regimens and addressing global resistance challenges effectively[141 , 142].

Agreement 85.71% grade: D2: Treatment decisions must be based on local resistance patterns and eradication rates to optimize the success of second line and rescue therapies for *H. pylori* . Antimicrobial susceptibility testing guides therapy by tailoring antibiotic use and minimizing the risk of developing further resistance. However, traditional susceptibility tests necessitate invasive endoscopy, which is costly and not universally accessible. Furthermore, culturing *H. pylori* is often challenging, with success rates dropping to < 80% in patients who failed to respond to previous eradication attempts[143].

Molecular tests offer a solution by detecting resistance without the requirement for endoscopy. Commercially available kits can identify resistance to clarithromycin and levofloxacin[144]. Nevertheless, current evidence comparing tailored therapy to empirical approaches remains inconclusive despite these advances[117 , 145 , 146]. A clear benefit of susceptibility-guided

therapy over empirical methods has not been consistently demonstrated with similar eradication rates being observed in patients who failed to respond to multiple treatment strategies[147 , 148].

The Hp-EuReg study revealed that empirical second-line therapies can achieve eradication rates of > 90%, highlighting the importance of monitoring local resistance patterns and eradication success[149]. Empirical therapies guided by local data will remain a practical approach until susceptibility testing becomes more routine and accessible. Further studies must be conducted to further evaluate the efficacy of tailored therapies compared with that of empirical treatments for *H. pylori* eradication.

Agreement 100% grade: C2: A clarithromycin-based regimen may not be feasible in clarithromycin high resistance areas. High-dose PPI-amoxicillin dual therapy can be an effective alternative, given its ability to overcome resistance against clarithromycin and metronidazole[150]. Compared with lower dosing schedules, high-dose PPI-amoxicillin therapy achieves higher eradication rates, especially when administered four times daily[151]. Alternatives such as rifabutin combined with other antibiotics may also be considered in regions with high fluoroquinolone resistance[109 , 110]. Thus, the selection of an appropriate therapy based on local resistance patterns and treatment history is crucial for optimizing eradication outcomes.

Agreement 100% grade: C2: Clarithromycin resistance must be considered in cases wherein PPI-clarithromycin-amoxicillin triple therapy fails; thus, repeating the same regimen would be unsuitable. A pooled analysis of eight studies revealed that repeated clarithromycin-based treatments yielded a low eradication rate of just 46%[152]. Single-capsule BQT or high-dose PPI-amoxicillin dual therapy should be recommended as second-line options if a first-line eradication attempt with this triple therapy fails[153].

Singlecapsule BQT yielded a significant eradication rate of 90.9% and 94.6% in the clarithromycin-resistant and clarithromycin-susceptible groups, respectively (per protocol arm)[154]. The efficacy of BQT as a second-line treatment is well-documented, especially in areas with high clarithromycin resistance. Notably, optimal eradication rates ($\geq 90\%$) were obtained with BQT in the Hp-EuReg study, making it a pivotal choice for second-line therapy, particularly in regions with high resistance to quinolones and clarithromycin[155].

High-dose PPI-amoxicillin dual therapy, with an eradication rate of 81%, may be an effective second-line option[156]. This regimen can overcome resistance to clarithromycin and metronidazole. Therapies involving vonoprazan, a P-CAB, in combination with amoxicillin have also exhibited high efficacy[142].

The use of PPI-clarithromycin-amoxicillin triple therapy as a second-line treatment is not advisable in Qatar, given the high rates of clarithromycin resistance[157]. Treatment decisions must be made based on local resistance patterns to ensure efficacy. Regimens containing fluoroquinolone while effective are associated with serious adverse effects. These regimens must be used only if the benefits outweigh the risks, particularly in areas with significant resistance. Therefore, BQT and high-dose PPI-amoxicillin dual therapy are preferred as second-line options, tailored to the resistance profile in the region.

In summary single-capsule BQT and high-dose PPI-amoxicillin dual therapy are recommended second-line treatments following the failure of PPI-clarithromycin-amoxicillin triple therapy. The choice of treatment is guided by local resistance patterns and eradication rates.

Agreement 85.71% grade: C2: Finding an effective empirical rescue treatment becomes challenging following the failure of a non-BQT, which often includes a PPI, amoxicillin, clarithromycin, and a nitroimidazole. The treatment options are limited since these patients have already received key antibiotics such as clarithromycin, amoxicillin, and metronidazole. Single-capsule BQT is an effective second-line treatment[154]. A triple or quadruple regimen

containing fluoroquinolone may also be effective with eradication rates exceeding 90% in some studies[158 - 162]. However, fluoroquinolone resistance can significantly reduce its efficacy. The addition of bismuth to a levofloxacin-based regimen can enhance effectiveness in such cases[153]. A quadruple regimen of PPI, amoxicillin, levofloxacin, and bismuth has exhibited promising results in overcoming levofloxacin resistance[155]. High-dose PPI-amoxicillin dual therapy, which has demonstrated an eradication rate of 81% as a second-line or further-line treatment, is another viable option comparable with other recommended therapies[155].

Agreement 100% grade: B2: After the failure of first-line treatment with clarithromycin-containing triple therapy or non-BQT regimens and second-line treatment with single-capsule BQT, a fluoroquinolone-containing regimen is recommended. For third-line therapy, a combination of a PPI, amoxicillin, and a third-generation quinolone, such as levofloxacin or moxifloxacin, is suggested by the Maastricht V Consensus Conference and has exhibited efficacy in several previous studies[153 , 163 - 165]. The addition of bismuth to this levofloxacin-containing regimen may further enhance its efficacy, especially in cases with levofloxacin resistance. However, the increase in the resistance to quinolones owing to specific *gyrA* mutations has impacted the success of these therapies in recent years[166]. Novel treatment strategies such as sitafloxacin, a fourth-generation quinolone, and vonoprazan, a novel P-CAB, have been introduced to improve the effectiveness of quinolone-based treatments[167]. In regions with high fluoroquinolone resistance, alternative strategies should be considered, including BQT with different antibiotics, rifabutin-based rescue therapy, or high-dose PPI-amoxicillin dual therapy[109 , 110 , 168].

Agreement 100% grade: B2: Single capsule BQT is recommended following the failure of first-line treatment with clarithromycin-containing triple therapy or non-BQT regimens as well as second-line treatment with fluoroquinolone-containing therapy. Clarithromycin and fluoroquinolone resistance have no effect on BQT, which includes bismuth, metronidazole, and tetracycline combined with a PPI. Thus, it is a successful third-line eradication option. Alternative strategies such as high-dose PPI-amoxicillin dual therapy or a rifabutin-containing regimen should be considered effective rescue therapies if single-capsule BQT is unavailable[169 - 172].

Agreement 85.71% grade: C2: Clarithromycin-based triple or quadruple therapy is recommended after the failure of first-line treatment with single capsule BQT and second-line treatment with fluoroquinolone-containing therapy only in areas with low clarithromycin resistance (< 15%). The use of clarithromycin may be effective as it has not been used previously in these areas[168]. However, alternative treatment strategies, such as high-dose PPI-amoxicillin dual therapy, a rifabutin-containing regimen[173 , 174], or a combination of bismuth with previously unused antibiotics, must be considered in areas with high clarithromycin resistance. Given the low resistance rates and optimized treatment duration, rifabutin-based therapies are particularly effective. Cumulative effectiveness with several consecutive rescue therapies, including rifabutin as a third-line option, can achieve eradication rates of nearly 100%[173].

Agreement 85.71% grade: C2: The eradication of *H. pylori* infection in patients with penicillin allergy, which affects about 5%-10% of individuals, poses a significant challenge. True immune-mediated hypersensitivity is not observed in most patients with a penicillin allergy. Negative allergy test results can facilitate the use of penicillin in these patients to receive the most effective therapy[175]. Single-capsule BQT is recommended as a first-line treatment in such cases, especially in regions with high clarithromycin and/or metronidazole resistance[176]. BQT should be considered an empirical second-line option along with fluoroquinolone-containing regimens despite the risk of acquired resistance to quinolones, if it has not been used previously. For patients with a penicillin allergy who fail to respond to initial PPI-clarithromycin-metronidazole triple therapy, adding bismuth to the treatment regimen or increasing antisecretory potency using a P-CAB such as vonoprazan are viable strategies[116]. Similarly, substituting amoxicillin with cefuroxime or using regimens containing sitafloxacin or semi-synthetic tetracyclines such as doxycycline or minocycline can enhance eradication success[177 , 178].

Agreement 85.71% grade: A1: H. pylori infection plays a significant etiological role in a subset of adenocarcinoma of the gastroesophageal junction (GOJ) zone. The International Agency of Research on Cancer classification deemed GOJ cancer a separate entity[179]; however, it is now considered a type of esophageal cancer[180]. The term cardia gastric cancer is no longer used owing to the limited presence of genuine cardiac mucosa, which if present is confined to a very narrow area within 5 mm from the GOJ. Cardia gastric cancer is currently classified as GOJ cancer or as proximal gastric cancer depending on the location of the tumor relative to the GOJ. H. pylori is a key risk factor for proximal gastric cancer; consistent with the concept of GOJ zone cancer, which comprises adenocarcinomas occurring 1 cm proximally and 1 cm distally to the GOJ, clarifying the pathogenic mechanisms in this region. The two primary factors contributing to GOJ adenocarcinoma are inflammation caused by gastroduodenal reflux and inflammation of junctional gastric mucosa, including cardiac-type mucosa, largely due to H. pylori infection[181 - 184].

Agreement 100% grade: A1: The eradication of H. pylori results in the removal of the active inflammatory response characterized by neutrophil infiltration in chronic non-atrophic gastritis, particularly in the antrum and corpus. Eradication therapy reverses neutrophil infiltration within a period of 2 weeks; however, mild chronic inflammation with lymphocyte infiltration may persist for up to a year[18 , 185]. The eradication of H. pylori is closely associated with the normalization of the surface epithelium and a reduction in inflammatory activity[186]. Successful eradication restores gastric mucosa to its normal state in most patients with non-atrophic gastritis. Furthermore, it prevents further progression to atrophy and IM[187]. Notably, studies such as those conducted on the Matsu Islands demonstrated that the eradication of H. pylori can significantly reduce the risk of progression to gastric atrophy with a notable prevention rate of 77.2%[188 , 189].

Agreement 100% grade: A1: The eradication of H. pylori has a beneficial effect on gastric atrophy and to a lesser extent on IM[149 , 190 , 191]. Eradication therapy significantly reduces gastric atrophy; however, its effect on reversing IM is more limited and gradual[192 , 193]. Improvements in gastric mucosal atrophy can be observed from 6 months to 6 years after treatment, with partial reversal of IM being observed in specific regions such as the lesser curvature of the corpus[194]. Long-term follow-up studies, including large population-based trials and mass eradication programs, have revealed a decrease in the presence and severity of atrophic gastritis and IM over time[188 , 189 , 195]. The eradication of H. pylori has been associated with a notable reduction in the risk of gastric cancer, with reductions of 53% and 50%-52% being observed in patients undergoing mass eradication and patients with early-stage gastric cancer or premalignant lesions, respectively[192 , 196]. These findings highlight the potential of H. pylori eradication in some patients to halt the progression of chronic atrophic gastritis to neoplastic lesions.

Agreement 85.71% grade: A1: The eradication of H. pylori is most effective in preventing gastric cancer when performed before the onset of severe chronic atrophic gastritis. Patients without any precancerous lesions such as gastric atrophy, IM, or dysplasia at the beginning of the study did not develop gastric cancer over a 7.5-year follow-up period following H. pylori eradication in a previous study[197]. This led to the development of the concept of a “point of no return”, suggesting that eradication may become less effective following the appearance of advanced precancerous changes. Recent analyses using machine learning have identified age and presence of IM as key factors predicting the risk of cancer post-eradication[198]. Severe atrophy identified through endoscopic criteria has also been associated with an increased risk of cancer post-eradication[199]. Preneoplastic changes may be partially reversed following the eradication of H. pylori ; however, severe atrophic gastritis does not progress to cancer in the majority of patients. Nonetheless, endoscopic monitoring is crucial in this population, and future advances in molecular gastritis characterization may enhance the ability to identify patients who would benefit from eradication and those who remain at risk[200 , 201].

Agreement 85.71% grade: A1: The use of non-invasive diagnostic methods is generally preferred while screening for H. pylori infection in the context of gastric cancer prevention. Tests such as UBT offer accuracy comparable with that of invasive procedures requiring endoscopy and biopsy[67 , 202]. Although more precise invasive tests are more expensive. Furthermore, they are associated

with potential risks related to the endoscopic procedure[202]. Consequently, the use of non-invasive options is favored during the mass screening of individuals at average risk[203]. Individuals at a higher risk of developing gastric cancer, such as those with a family history of the disease, should undergo endoscopic examination to rule out pre-existing gastric cancer or precancerous lesions[154 , 203].

Agreement 85.71% grade: A1: Compared with their younger counterparts, individuals aged ≥ 60 years are at a higher risk of developing gastric cancer even when asymptomatic. The rate of gastric cancer increases significantly after the age of 60 years among individuals in the Middle East. Given that these countries report incidence rates of > 20 cases per 100000 at age 40, individuals aged ≥ 50 are deemed to be at elevated risk[204]. Consequently, asymptomatic adults aged > 60 years must be prioritized while screening for gastric cancer and implementing preventive measures owing to their increased vulnerability to the disease.

Agreement 100% grade: B1: Patients with severe atrophic gastritis, classified as OLGA stages III or IV, must be regularly followed up using endoscopic biopsy[74 , 75 , 104]. The staging system for atrophic gastritis assesses the risk of gastric cancer by categorizing the severity of mucosal atrophy, thereby guiding tailored endoscopic surveillance protocols that prevent the incidence of secondary cancer. The eradication of *H. pylori* can lead to partial regression of atrophic gastritis and IM; however, it does not eliminate the risk of cancer in advanced stages[194 , 205]. High-resolution endoscopy with advanced imaging techniques is recommended to detect small neoplastic lesions and ensure thorough evaluation[106 , 206]. The European management of epithelial precancerous conditions and lesions of the stomach (MAPS II) guidelines recommend conducting high-quality endoscopic evaluation every 3 years to monitor and manage the risk of cancer in patients with advanced atrophic gastritis[72 , 206].

Agreement 100% grade: A1: *H. pylori* must be eradicated to mitigate the risk of developing metachronous gastric cancer following curative endoscopic resection or subtotal gastric resection for early gastric cancer[196]. The eradication of *H. pylori* results in a significant reduction in the likelihood of subsequent malignancies. A notable reduction in the risk of metachronous cancer risk with an odds ratio of 0.392 was observed in a meta-analysis encompassing five studies[193]. A recent randomized controlled trial involving 396 patients further substantiated these findings by demonstrating a reduction in the incidence of metachronous cancer compared with that in the placebo group following eradication therapy (hazard ratio of 0.50)[192]. A meta-analysis of 11 cohort studies and 3 randomized control trials confirmed that the eradication of *H. pylori* reduced the risk of metachronous gastric cancer by approximately 35%[207]. Eradication helps prevent the development of new cancers; however, it does not eliminate the risk, particularly in patients with atrophic gastritis and IM. Thus, endoscopic surveillance must be continued to monitor these high-risk individuals[72 , 176].

Agreement 85.71% grade: B2: Antibiotic use for the management of various infections may inadvertently select *H. pylori* strains that are resistant to treatment. Resistance to amoxicillin has not been observed in *H. pylori* strains despite prolonged use; however, this does not indicate that other antibiotics are as benign. Higher usage of macrolides and quinolones increased the resistance of *H. pylori* to these antibiotics[208]. The rising resistance rates following ineffective *H. pylori* eradication treatments with quinolones, macrolides, and metronidazole across various patient cohorts further indicate this trend[77 , 122 , 209]. However, prospective research on the effect of cumulative antibiotic use on *H. pylori* resistance over time is lacking.

This consensus focused on the clinically relevant aspects of *H. pylori* management and made key recommendations and considerations, including reusing the gastric biopsies from rapid urease test for PCR-based molecular testing to confirm infection and detect resistance without necessitating additional biopsies, thereby offering a cost-effective approach. Though its practical implementation varies, clarithromycin susceptibility testing is recommended before initiating therapy to prevent resistance and to optimize treatment. Follow-up endoscopy is generally unnecessary for low-stage gastritis post-eradication, unless specific risk factors are present. Routine susceptibility testing is

encouraged to improve antibiotic stewardship; however, its feasibility depends on logistical and economic factors. *H. pylori* infection remains the primary cause of gastric adenocarcinoma, highlighting the importance of targeted eradication efforts. Confirmatory tests such as UBT or SAT must be conducted following serological detection to ensure accurate diagnosis before treatment. Asymptomatic individuals aged ≥ 45 years with a family history of gastric cancer must be encouraged to undergo *H. pylori* testing. Eradication therapy can foster resistant gut microbiota strains. The use of certain probiotics may alleviate GI side effects; however, their effectiveness varies. These considerations emphasize the requirement for implementing a comprehensive and individualized approach to *H. pylori* management.

While these guidelines aim to standardize and optimize the management of *H. pylori* across the Middle East, several limitations and challenges must be acknowledged. First, the availability of reliable data across countries remains limited, with antibiotic resistance surveillance being inconsistent and many regions lacking centralized reporting systems. As a result, empirical treatment often remains the only practical option, particularly in the absence of routine susceptibility testing. Resource constraints also pose a significant barrier as advanced therapies like BQT (e.g., Pylera®) are not widely accessible across all levels of care. For instance, Pylera® may be available in main hospitals in Kuwait but remains unavailable in primary care settings, forcing physicians to rely on less effective regimens such as standard triple therapy. Patient adherence is another challenge as factors like pill burden, treatment duration, and side effects often lead patients to prefer fewer intensive therapies despite their reduced effectiveness. Public awareness campaigns are limited, and educational initiatives targeting both patients and healthcare providers may not be reaching all stakeholders involved in *H. pylori* management. Although no major cultural barriers were identified, over-the-counter access to antibiotics, particularly without proper prescriptions, was noted as a contributing factor to prior failed treatments, complicating eradication efforts in certain patients. Finally, while this consensus offers updated recommendations based on the best available evidence, it also reflects expert opinion in areas where local data are lacking. Continuous monitoring, enhanced regional research, and future updates will be essential to adapt to emerging evidence and evolving resistance patterns. It is critical to maintain *H. pylori* as a priority in public health discussions, recognizing that it is a chronic infection unlikely to resolve spontaneously without targeted intervention[210 , 211].

This expert consensus on the management of *H. pylori* infection in the Middle East highlighted the necessity of addressing the high prevalence and increasing antibiotic resistance of this pathogen. The recognition of *H. pylori* infection as an infectious disease that must be treated in all infected individuals marks a paradigm shift in clinical practice, as emphasized by the Kyoto consensus. The prevalence of *H. pylori* in the Middle East, mirroring that in other developing regions, highlights the importance of developing region-specific strategies.

This report drew inspiration from the quinquennial Maastricht *H. pylori* Guidelines Initiative, which summarized the latest advances and provided consensus guidance, to implement the most effective and practical approaches for routine patient care. However, logistical, economic, and healthcare system differences complicate the translation of these guidelines into clinical practice.

Critical issues must be addressed over the next 5 years to achieve optimal outcomes, including the global prevention of gastric cancer through population-based test-and-treat strategies tailored according to the local prevalence rates to meet the treatment needs. Understanding and controlling antibiotic resistance through the systematic use of molecular resistance testing, which is becoming increasingly reliable for diagnosing *H. pylori* and detecting antibiotic resistance, particularly to clarithromycin, is of paramount importance.

Advancements in treatment combinations, including optimal acid suppression and dual therapy with the P-CAB class of antisecretory drugs, have yielded promising outcomes. Future studies must aim to optimize these treatment strategies, especially in non-Asian populations. The development of novel antibiotics and the potential role of selective probiotics in the gastric microbiome offer hope for improved management strategies.

This consensus report represents a comprehensive guide for managing H. pylori infection in the Middle East. This report aimed to inspire further clinical research and improve patient outcomes through targeted, evidence-based strategies.

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Specialty type: Gastroenterology and hepatology

Scientific Quality: Grade A, Grade A, Grade A, Grade A, Grade B, Grade B

Novelty: Grade B, Grade B, Grade B, Grade B, Grade B, Grade B

Creativity or Innovation: Grade A, Grade B, Grade B, Grade B, Grade B, Grade B

Scientific Significance: Grade A, Grade A, Grade A, Grade B, Grade B, Grade B

P-Reviewer: Babani SA; Wang Z; Ying GH S-Editor: Liu H L-Editor: Filipodia P-Editor: Zhao S