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SOLICITED REVIEW

Helicobacter pylori management in ASEAN: The Bangkok consensus report

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Abstract

Helicobacter pylori (*H. pylori*) infection remains to be the major cause of important upper gastrointestinal diseases such as chronic gastritis, peptic ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. *H. pylori* management in ASEAN: the Bangkok consensus report gathered key opinion leaders for the region to review and evaluate clinical aspects of *H. pylori* infection and to develop consensus statements, rationales, and grades of recommendation for the management of *H. pylori* infection in clinical practice in ASEAN countries. This ASEAN Consensus consisted of 34 international experts from 10 ASEAN countries, Japan, Taiwan, and the United States. The meeting mainly focused on four issues: (i) epidemiology and disease association; (ii) diagnostic tests; (iii) management; and (iv) follow-up after eradication. The final results of each workshop were presented for consensus voting by all participants. Statements, rationale, and recommendations were developed from the available current evidence to help clinicians in the diagnosis and treatment of *H. pylori* and its clinical diseases.

Introduction

Eradication of *Helicobacter pylori (H. pylori)* infections plays an important role in curing many upper gastrointestinal tract diseases. Thinking about the best management strategy for these infections has continued to evolve. *H. pylori* management in ASEAN: the Bangkok consensus report gathered key opinion leaders for the region to review and evaluate clinical aspects of *H. pylori* infection and to develop consensus statements, rationales, and grades of

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recommendation for the management of *H. pylori* infection in clinical practice in ASEAN countries. This ASEAN Consensus consisted of 34 international experts from 10 ASEAN countries, Japan, Taiwan, and the United States (Fig. 1). The meeting mainly focused on four issues: (i) epidemiology and disease association; (ii) diagnostic tests; (iii) management; and (iv) follow-up after eradication.

Methodology of consensus process

Current clinical evidence and important studies were identified and analyzed by each working group before the face-to-face meeting. The working groups discussed and wrote preliminary clinical questions for each of the four areas. At the meeting, discussion of each clinical question was led by the chairman and secretary of each working group. Statements were then submitted to all experts and modified to fit a standard template. The level of evidence and grade of recommendation was developed using a standard reference (Table 1 and Fig. 2).[1–3] Consensus on all statements and rationales was determined at the face-to-face meeting. Consensus was defined as an agreement of 80% or more of all participants. Final statements and rationales were written by the secretary and proofed by the chairman of each working group. All final approved statements and rationales are summarized in this manuscript.

Epidemiology and disease association of *Helicobacter pylori* in the ASEAN countries

Statement 1:

1(a) *Helicobacter pylori* infection increases the risk of dyspeptic symptoms.

Level of evidence: High
Grade of recommendation: N/A
Consensus level A) Strongly agree 100%

1(b) In all patients with chronic dyspepsia, *H. pylori* infection should be tested and treated.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 95%, (B) Agree with reservations 5%

Rationale. *Helicobacter pylori* infection was shown to be more common in dyspeptic patients than asymptomatic controls.[4] Although the effects of eradication therapy have been variable, meta-analysis on the effects of eradication therapy clearly showed benefit in terms of symptomatic improvement (NNT = 15).[5] A recent meta-analysis including data such as the HEROES trial[6] indicated that eradication of *H. pylori* was beneficial in terms of symptomatic improvement (NNT = 13).[7] Furthermore, a meta-analysis of studies in the Chinese population reported the Number-Needed-to-Treat (NNT) of 3.[8] Eradication of *H. pylori* in dyspeptic patients was also shown to be cost-effective.[9] A test-and-treat strategy was also shown to be cost-effective in an Asian population.[10] As an additional benefit, *H. pylori* eradication was associated with a reduction of development of peptic ulcers among ulcer-like dyspeptic patients (0% in treated group *vs* 16.7% in control; difference between groups: −17%, 95% CI: −32% to −2%).[11] Thus, the statement that *H. pylori* should be tested in patients with chronic dyspeptic symptoms and patients who test positive should be offered the most effective eradication therapy in the area unless other competing conditions exist.[12,13]

Figure 1 All members for ASEAN Consensus on *Helicobacter pylori* Management in the Limited Resource Setting 2016. [Color figure can be viewed at wileyonlinelibrary.com]

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Table 1 Level of evidence and quality of evidence

Level	Quality	Comments
I	High	Further research is very unlikely to change our confidence in the estimate of effect.
II	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimated.
III	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
IV	Very Low	Any estimate of effect is very uncertain.

Statement 2: As *H. pylori* infection and/or nonsteroidal anti-inflammatory drug (NSAID) use is highly associated with peptic ulcer disease, the principal treatment for peptic ulcers is eradication of *H. pylori* and/or halting NSAID used.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. *Helicobacter pylori* causes chronic gastritis in virtually all infected individuals.[14] Such inflammation in *H. pylori* carriers leads to a 3-fold to 10-fold increase in risk of peptic ulcer disease as compared with *H. pylori*-negative subjects.[15,16] During long-term follow-up, peptic ulcers and the related complications occur in 10–15% of *H. pylori* carriers.[16] When a peptic ulcer is present, almost 100% of duodenal ulcers and approximately 80% of gastric ulcers have *H. pylori* infection in the absence of other risk factors, such as NSAID use or Zollinger–Ellison syndrome.[17] Moreover, the cause-and-effect relationship between *H. pylori* infection and peptic ulcers is supported by the substantial benefit of *H. pylori* eradication in terms of the healing of active ulcers[18] and decrease in ulcer recurrence.[19–21] A summary of 12 Randomized controlled trials (RCTs) showed that eradication therapy significantly reduced the risk of gastric ulcer by 69% compared with no eradication therapy.[22] In two meta-analyses including five and seven RCTs, significant reductions of 57% and 50% were found, respectively, in the prevention of peptic ulcers among NSAID users following *H. pylori* eradication.[23,24]

NSAIDs can also cause peptic ulcers through direct ulcerogenic effects as well as the inhibition of cyclooxygenase and depletion of endogenous prostaglandins, which impair mucosal defense mechanism.[25] As many as 25% of NSAID users will suffer from peptic ulcer disease, and among them, 2–4% may bleed or perforate.[26] A summary of nine case–control and seven cohort studies showed that the odds ratio of the risk of adverse gastrointestinal complications related to NSAID use was 2.74[27] and the risk was further increased in patients of older age, with higher dosage of NSAIDs, and the concurrent use of corticosteroids or anticoagulants.[26]

A summary of 25 studies showed that *H. pylori* infection and NSAID use increased the risk of peptic ulcer bleeding up to 1.79-fold and 4.85-fold, respectively. When both factors were present, this risk further increased to 6.13-fold, demonstrating a synergistic effect.[28] A meta-analysis including 34 RCTs showed that the adverse effect of NSAID on the peptic ulcer risk, however, was reduced by 56% and 63% by the use of H2RA and proton pump inhibitor (PPI), respectively.[29]

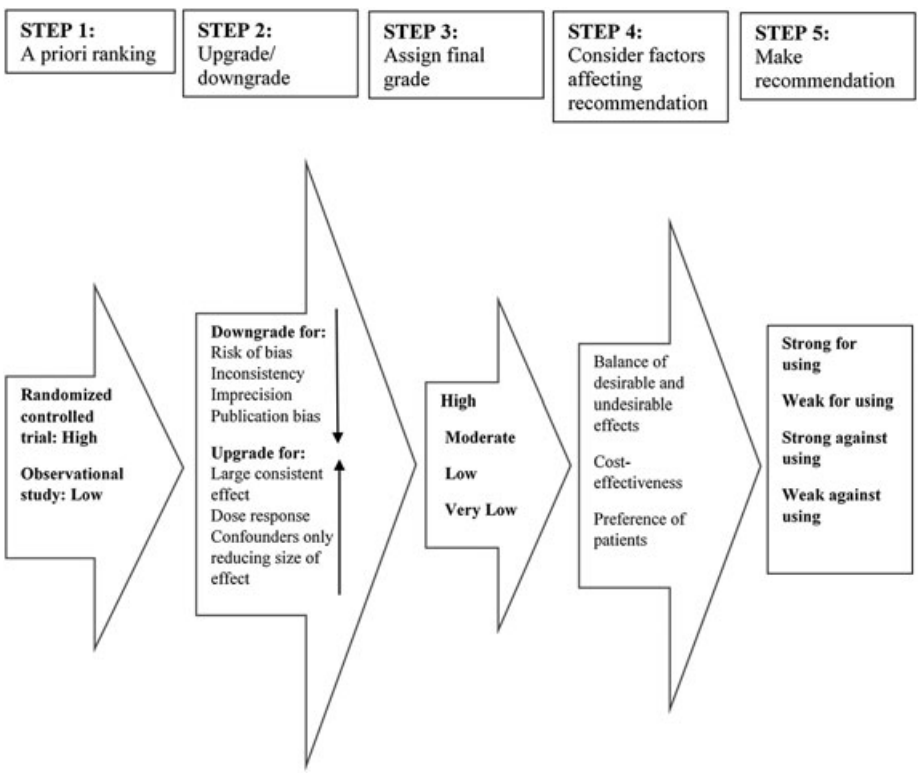

Figure 2 Grades of recommendation and quality of evidence.

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Statement 3: The age-standardized incidence rate of gastric cancer in ASEAN countries varies from 3.0 to 23.7 per 100 000 person-years. Gastric cancer remains one of the top 10 causes of cancer mortality in the majority of ASEAN countries. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is very rare.

Level of evidence: High
Grade of recommendation: N/A
Consensus level (A) Strongly agree 100%

Rationale. Although a decline in the prevalence of gastric cancer has been observed in many countries, some countries in South-East Asia, such as Singapore, Malaysia, and Thailand, the disease burdens on society and the economy remain enormous.[30–32] The age-standardized rates of gastric cancer incidence in the 10 ASEAN countries range from the highest, 23.7 per 100 000 person-years in Vietnam, to the lowest, 3.0 per 100 000 person-years in Lao[33] (Table 2). Only Vietnam was categorized as a high-incidence country (defined as $>$ 20 per 100 000 person-years), and the rest are intermediate-to-low-incidence countries. The mortality-to-incidence ratios (an indicator of patient prognosis)[34] range from 0.73 to 0.97 in ASEAN countries, except for Singapore (0.64) and Malaysia (0.47), which are substantially higher than those in Eastern Asian countries where gastric cancer screening programs are ongoing, such as Japan (0.41) and Korea (0.31).

In contrast, MALT lymphomas represent approximately 7% of newly diagnosed lymphomas.[35] It is a rare malignancy, with a worldwide incidence of 1–1.5 cases per 100 000 person-years. In comparison, gastric cancer is 5-fold to 10-fold more frequent.[35,36]

Statement 4: Eradication of *H. pylori* reduces the risk of gastric cancer, and family members of gastric cancer patients should be screened and treated.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. A recent meta-analysis, including eight randomized controlled trials and 16 cohort studies, indicated that eradication of *H. pylori* infection is associated with a significantly reduced incidence of gastric cancer (pooled incidence rate ratio: 0.53, 95% CI: 0.44–0.64), without heterogeneity among studies.[37] The benefit applied to all levels of baseline risk, from asymptomatic infected individuals (0.62, 95% CI: 0.49–0.79) to patients after endoscopic resection of early gastric cancer (0.46, 95% CI: 0.35–0.60). The result clearly showed that *H. pylori* eradication reduces gastric cancer risk in all risk groups and is consistent with the notion that the infection is a necessary but insufficient cause of gastric cancer.

According to a meta-analysis published in 2010, first-degree relatives of family number with a diagnosis of gastric cancer have a significantly higher prevalence of *H. pylori* infection, gastric atrophy, and gastric intestinal metaplasia than controls.[38] Moreover, first-degree relatives have a two to three times increased risk of developing gastric cancer; in particular, if more than one first-degree relatives have gastric cancer, the risk for the others is increased 10 times.[39–43] A recent consensus (Maastricht V) provided a strong recommendation to test and eradicate *H. pylori* in order to prevent gastric cancer.[44]

Statement 5: Gastric MALT lymphoma patients should be offered *H. pylori* eradication.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. If adequate diagnostic methods are used and if only low-grade lymphomas are considered, the prevalence of *H. pylori* infection is very high (almost 90%).[45] *H. pylori* eradication is effective in treating approximately 80% of patients with early-stage lymphoma.[46–51] In *H. pylori*-positive gastric high-grade lymphomas, antibiotic therapy should always be prescribed, as approximately 50% of them regress after *H. pylori* eradication.[52] Patients with early-stage MALT lymphoma negative for *H. pylori* might still benefit from antibiotic treatment as the sole treatment.[53,54] Complete remission of gastric MALT lymphoma after *H. pylori* eradication can take $>$ 12 months.

Statement 6:

6(a) Community screening for *H. pylori* by noninvasive tests followed by eradication for gastric cancer prevention can be cost-effective depending on the disease burden in that community.

Level of evidence: High
Grade of recommendation: Weak

Table 2 Disease burdens of gastric cancer in ASEAN countries

Country	Incidence rate*	Rank of the incidence	Mortality rate*	Rank of mortality	Mortality-to-incidence ratio
Vietnam	23.7	3	21.9	3	0.92
Myanmar	15.3	3	14.8	3	0.97
Singapore	10.9	5	7.0	4	0.64
Brunei	9.9	4	7.2	4	0.73
Malaysia	9.8	5	4.6	4	0.47
Cambodia	7.6	4	7.4	4	0.97
Philippines	4.8	6	4.3	5	0.90
Indonesia	3.9	9	3.5	8	0.90
Thailand	3.8	10	3.1	9	0.82
Laos	3.0	9	2.8	7	0.93

*Age-standardized rate per 100 000 person-years according to WHO World Standard Population 2000.

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Consensus levels (A) Strongly agree 86.4%, B) Agree with reservations 13.6%

Rationale. In 2014, the WHO published a new monograph entitled "*Helicobacter pylori* eradication as a strategy for preventing gastric cancer."[55] Systematic review and meta-analyses have confirmed that *H. pylori* eradication can lead to a reduction in the incidence of gastric cancer.[37,56] The degree of risk reduction depends on the presence, severity, and extent of atrophic damage at the time of eradication.[13,56] Additionally, the incidence and mortality of gastric cancer differ significantly by region, population, and race distribution.[57] Economic models suggest that *H. pylori* test and treat is cost-effective under most reasonable assumptions, and this provides a clear mandate for trials.[58] However, healthcare systems, health resources, and social and economic conditions may greatly affect gastric cancer prevention and screening strategies. For a population *H. pylori* test-and-treat strategy, serology is the most cost-effective and acceptable non-invasive test for a screening program when compared with stool antigen and carbon-labeled urea breath tests (UBTs).[59] Current data from a systematic review of cost-effectiveness studies suggested that population *H. pylori* screening and treatment is feasible and cost-effective in preventing gastric cancer depending on the cancer incidence and endoscopy cost (incremental cost-effectiveness ratio 6264–25 881 USD).[60] The models studied a variety of populations and made different assumptions, and all found population *H. pylori* screening and treatment to be cost-effective using a threshold of 50 000 USD per life-year saved.[61–72] A recent study in Taiwan showed the cost-effectiveness of *H. pylori* test-and-treat programs in preventing gastric cancer, referring to the nationwide reimbursement database. This program with serology was more cost-effective than 13C–UBT, especially beginning at the age of 30. Cost saving would be achieved in an endemic area where *H. pylori* prevalence was more than 73.5%.[73] Most models evaluated screening programs from a third-party payer's perspective. Although this is a valid approach, it could be argued that societal costs are more important for a national screening program. An economic model that did take this perspective also found population *H. pylori* screening and treatment to be cost-effective.[67] Another study in Hong Kong Chinese used the societal perspective and showed that the least costly and non-dominate strategy was the *H. pylori* serologic test-and-treat strategy.[74] One ASEAN study reported that there is a 75% certainty that population *H. pylori* screening and treatment is cost-effective for the Singaporean Chinese population.[66] The costs per life-year gained from *H. pylori* screening in six high-prevalence countries,[75] Singapore,[66] Thailand,[76] China,[68] Colombia,[62] Japan,[63] and Taiwan,[67] varied from 200 to 17 000 USD per life-year gained. The study concluded that screening in countries where gastric cancer incidence is higher is more cost-effective.

6(b) Currently, community-based gastric cancer screening by endoscopy is not feasible in most ASEAN countries.

Level of evidence: Moderate
Grade of recommendation: Weak
Consensus level (A) Strongly agree 91.7%, (B) Agree with revision 8.3%

Rationale. The East Asia region, particularly Japan and Korea with their high incidence rates of gastric cancer, has achieved tangible results from their screening programs, as well as from preventive interventions. In 2008, guidelines for gastric cancer screening were recommended.[77] They evaluated four screening methods: serum pepsinogen, *H. pylori* antibody, photofluorography, and endoscopy. On the basis of a benefit/harm balance, photofluorography was recommended for both population-based and opportunistic screening. However, endoscopy has subsequently replaced photofluorography as the initial mass screening method in several Japanese cities[78] because it is better for detecting early gastric cancer. Endoscopic mass screening is a promising method and can be effectively applied if a sufficient number of skilled endoscopists become available. In Korea, the guidelines recommend biennial gastric cancer screening by either upper gastrointestinal barium study or endoscopy for people aged 40 years or older.[79] According to the Korean National Cancer Screening Survey, the participation rate for opportunistic and organized gastric cancer screening has increased significantly, from 39.2% in 2004 to 70.9% in 2012.[80] A recent systematic review of cost-effectiveness studies for precancerous lesions or gastric cancer screening[61] concluded that endoscopy was more cost-effective than x-ray or no screening.[78,81–84] However, except for one from the United States, all these studies came from moderate- to high-risk populations of the Far East. In ASEAN countries, there are data from Singapore on opportunistic screening in patients with upper GI symptoms combined with *H. pylori* eradication through the selection of high-risk individuals. This combined procedure can be cost-effective.[85,86]

Statement 7: In ASEAN countries, different outcomes of *H. pylori* infection are determined by the interaction between *H. pylori* virulence factors, the host and environmental factors.

Level of evidence: High
Grade of recommendation: N/A
Consensus level (A) Strongly agree 100%

Rationale. *Helicobacter pylori* infections are typically lifelong and are associated with a decades-long acute and chronic inflammatory response that results in progressive mucosal damage. This results in the highly regulated acid secretory and digestive enzyme producing mucosa becoming transformed through a series of different types of metaplastic and dysplastic epithelium to eventually result in gastric adenocarcinoma.[87] There is also a strong environmental component involved in the outcome of *H. pylori* infections. One example is in Japan where the incidence of gastric cancer fell by approximately 60% between 1965 and 1995 despite no change in the virulence or prevalence of the most common infecting strains.[88] *H. pylori*-infected individuals living in areas where diets are seasonal with long periods without fresh fruits and vegetables and where food preservation is largely dependent on the use of salt and smoking have a strong tendency to develop progressive atrophy, which is linked to gastric ulcer and gastric cancer.[88] In contrast, in environments in ASEAN countries where fresh fruits and vegetables are available all year round, the mucosal damage tends to remain non-atrophic, the incidence of gastric cancer is low, and duodenal ulcers and their complications are the predominant clinical manifestations.[89]

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However, even in areas with a low incidence of gastric cancer, the presence of polymorphisms in host pro-inflammatory genes can result in early development of atrophic gastritis and an increased risk of gastric cancer, especially if the infected strain also contains virulence factors associated with an enhanced inflammatory response, such as cytotoxin-associated gene A product (*CagA*), the vacuolating cytotoxin (*VacA*), the outer inflammatory protein (*OipA*), and the duodenal ulcer-promoting factor (*DupA*).[90,91] Therefore, while *H. pylori*-host interactions play an important role in disease pathogenesis, bacterial virulence factors also play a role in determining outcome.[90,92] For example, although the incidence of gastric cancer is low in Thailand, the risk is higher in patients infected with *H. pylori* with East-Asian-type *CagA* than in those with Western-type *CagA*.[93]

Statement 8: All patients with gastric precancerous lesion should be tested and treated for *H. pylori* and risk stratified for gastric cancer.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. *Helicobacter pylori* infection is the primary cause of gastric cancer[94] and should be eradicated. Patients with *H. pylori* infection and severe gastric atrophy or gastric metaplasia are at increased risk of gastric cancer.[95] In contrast, the incidence of gastric cancer was not increased in patients with no precancerous lesion at 7.5-year follow-up regardless of the presence of an *H. pylori* infection.[94]

European guidelines for managing precancerous lesions in the stomach suggested scheduling endoscopic follow-up every 3 years in intestinal metaplasia of the stomach following *H. pylori* eradication.[96] However, the management of intestinal metaplasia in another guideline recommended the follow-up period of extensive-type (more than two locations or immature-type metaplasia) should be less than 1 year.[97,98] The longest follow-up study in Spain showed that gastric cancer developed in 18% of patients with immature intestinal metaplasia and 0.1% with mature intestinal metaplasia after a mean follow-up of 12.8 years.[99] According to the unpublished data at King Chulalongkorn Memorial Hospital, only those with immature-type intestinal metaplasia developed gastric cancer at 5-year follow-up.[100] Moreover, the diffuse pattern of intestinal metaplasia exhibited a 12.2-fold (95% CI: 2.0–72.9) increased risk of gastric cancer.[101]

For gastric dysplasia, endoscopic resection or follow-up is recommended for low-grade dysplasia whereas endoscopic or surgical resection should be offered in cases of high-grade dysplasia because of the high rate of intra-epithelial carcinoma.[102,103] Another option for low-grade dysplasia treatment is ablation therapy.[104]

A 5-year follow-up RCT study in 2004 reported that *H. pylori* eradication can reduce the progression of intestinal metaplasia by reverting to normal, inflammatory, atrophic change, or deterioration of intestinal metaplasia (in 47% of cases), whereas 1.8% progressed to gastric cancer even after successful *H. pylori* eradication.[105] Another recent meta-analysis (2015) emphasized that *H. pylori* eradication does not reduce either intestinal metaplasia or dysplasia.[58] Unfortunately, they combined intestinal metaplasia and dysplasia into the same category and did not provide information about each.[58]

Consequently, precancerous lesions should be followed up as follows:

1 Chronic atrophic gastritis and intestinal metaplasia in both the corpus and antrum OR immature-type intestinal metaplasia should be followed up the following year and then every 3 years if those findings remain;
2 Low-grade dysplasia should be followed up within 1 year. Immediate endoscopic resection is an optional treatment; and
3 High-grade dysplasia should be resected as soon as feasible.

Diagnostic tests for *H. pylori* infection

Statement 9: Diagnostic tests for *H. pylori* infection in the ASEAN region include the following: the UBT, the Stool Antigen Test (monoclonal), and locally validated rapid urease test **(RUT)/histology. The choice of test depends on patients' preference, availability, and cost.**

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. *Helicobacter pylori* is one of the most common infections in humans, and it plays an important role in relation to gastrointestinal diseases, such as peptic ulcer diseases and gastric cancer.[106–108] Given its intermediate to high prevalence in ASEAN countries,[107–109] diagnosis of the *H. pylori* infection[109–115] is crucial in order to eradicate and prevent disease. There are multiple non-invasive tests available for diagnosing *H. pylori*. These include the 13C–UBT, stool antigen tests and immunological tests. The UBT has been used for over 30 years and is one of the most popular and practical non-invasive tests for diagnosing *H. pylori* infection, with a diagnostic accuracy of more than 95%.[116,117] The monoclonal stool antigen test also provides a high sensitivity and specificity of $> 95\%$, although the process of stool collection is often associated with patient reluctance.[118] The RUT and pathology can be considered if endoscopy and gastric mucosa are obtained or if other tests are not available.

Statement 10: Biopsy-based testing should be performed in patients undergoing gastroscopy when *H. pylori* testing is indicated.

Level of evidence: Moderate
Grade of recommendation: Strong
Consensus level (A) Strongly agree 94.7%, (B) Agree with reservations 5.3%

Rationale. Whenever endoscopy is indicated, direct testing for *H. pylori* should be considered. Because it is inexpensive, rapid, and easy to perform, the RUT is the most useful test for diagnosing *H. pylori* infection for routine endoscopy practice. Other biopsy-based tests include histology, culture, tissue for polymerase chain reaction, and immunohistochemistry. Although most of these latter

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tests offer higher accuracy as well as clinical usefulness (e.g. antibiotic sensitivity profile), the limitations of these tests are that they are more expensive and there is a lack of standardization and availability, compared with the RUT.[118]

Statement 11: Proton pump inhibitor therapy should be discontinued at least 2 weeks before testing for *H. pylori*; antibiotics should be discontinued for 4 weeks before testing.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. Proton pump inhibitor and antibiotics produce false negative results for all tests except serology.[119] PPIs have anti-*H. pylori* activity and by suppressing the density of *H. pylori* can lead to false negative results in the urease test, UBT, and stool Ag test.[119] High intragastric pH reduces the viability of the organism and directly inhibits urease activity.[112] Antibiotics and bismuth compounds should be discontinued at least 4 weeks before the tests.[120] The effect of H2 receptor antagonists on the sensitivity of UBT has been inconclusive. Antacids do not impair the sensitivity of UBT or the stool Ag test. H2 receptor antagonists do not have anti-*H. pylori* activity.[121–124]

Statement 12: Testing for *H. pylori* infection in GERD patients is recommended when long-term PPI treatment is needed and/or endoscopy is performed.

Level of evidence: Moderate
Grade of recommendation: Strong
Consensus level (A) Strongly agree 68.2%, (B) Agree with reservations 27.3%, (C) Undecided 4.5%

Rationale. Results from previous epidemiologic studies have shown a negative association between the prevalence of *H. pylori* and Gastroesophageal reflux disease (GERD) in Asian countries.[125] This is supported by the Maastricht V Consensus Report, which stated that *H. pylori* eradication does not exacerbate preexisting GERD or affect treatment efficacy.[44] However, more recent studies, including a meta-analysis, revealed that the effect of *H. pylori* eradication in GERD among Asian countries remains unclear,[126–129] with regard to GERD patients who required long-term PPIs. Many studies of long-term maintenance of PPI treatment demonstrated that PPIs induce gastritis, progression of gastric atrophy, and intestinal metaplasia in *H. pylori* infection patients.[130,131] Therefore, in GERD patients, especially those whose clinical presentation mandates investigation for *H. pylori* (suspicion of gastric ulcer, duodenal ulcer, or in certain situations functional dyspepsia), testing for *H. pylori* is warranted. The current Asia–Pacific Consensus also recommends *H. pylori* eradication in GERD patients requiring long-term PPIs.[110]

Statement 13: *Helicobacter pylori* should be tested and treated in patients who need long-term NSAID treatment.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. *Helicobacter pylori* infection and NSAIDs independently increased the risk of peptic ulcers and ulcer complications. In addition, the risk increases significantly when both factors were present.[24,28] Two meta-analyses demonstrated that *H. pylori* eradication reduced the incidence of peptic ulcers in patients receiving NSAIDs, especially when *H. pylori* was eradicated before starting NSAIDs in an Asian population.[23,24] However, *H. pylori* eradication was less effective than PPI maintenance therapy for preventing NSAID-induced ulcers in either primary or secondary prevention.[23,132,133] Therefore, *H. pylori* eradication was recommended for long-term NSAID users, especially for patients with a previous history of ulcers and NSAID-naïve patients. Nonetheless, *H. pylori* eradication was not effective enough to replace PPI maintenance therapy in the high-risk group patients.

Statement 14: In patients with peptic ulcer bleeding and a negative initial biopsy-based *H. pylori* test, this should be reconfirmed by a subsequent *H. pylori* test.

Level of evidence: Moderate
Grade of recommendation: Strong
Consensus level (A) Strongly agree 87%, (B) Agree with reservations 8.7%, (C) Undecided 4.3%

Rationale. Data from a meta-analysis indicated that upper gastrointestinal bleeding significantly reduced the sensitivity of tests for diagnosing *H. pylori*.[134,135] In this situation, biopsy-based methods (RUT, histology, and culture) had a low sensitivity whereas the stool antigen test and serology had a low specificity. On the other hand, the 13C–UBT still had a very high accuracy.[134] However, a meta-regression study found that the use of a diagnostic test delayed until at least 4 weeks after the bleeding episode detected significantly more *H. pylori*-infected patients.[135] Currently, the 13C–UBT was recommended as a subsequent diagnostic test if biopsy-based methods at the time of endoscopy were negative and the diagnostic tests should be repeated after at least 4 weeks in patients with negative initial results.

Statement 15: Urea breath test is the best option after *H. pylori* eradication, and the stool antigen test is an alternative. The test should be carried out at least 4 weeks after discontinuation of eradication therapy. If endoscopy is indicated, then a biopsy could be performed.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 88.9%, (B) Agree with reservations 11.1%

Rationale. Urea breath test is a valid and reliable test in the assessment of *H. pylori* eradication for post-treatment evaluation.[136] The stool antigen test can be used as an alternative, although it is less accurate.[137,138] In the situation where repeat endoscopy is indicated, the RUT can be performed, but it is less sensitive than UBT. False negative results can occur in patients taking PPI and antibiotics. Testing to prove eradication should be performed at least 4 weeks after the completion of eradication therapy. PPI should be discontinued for at least 2 as it interferes with the sensitivity of UBT and the stool antigen test.[23,111,122,139] Antibiotics and PPI contribute to the false negative results obtained with post-eradication UBT by inhibiting growth and their bactericidal activity against *H. pylori*.

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Statement 16: It is recommended that the costs of HP diagnostic tests and treatment be reimbursed by national health polices within ASEAN countries.

Level of evidence: Low
Grade of recommendation: Strong
Consensus level (A) Strongly agree 81%, (B) Agree with reservations 14.4%, (C) Undecided 4.6%

Rationale. This question addresses the issue of healthcare policies and health economics when the cost of a specific individual test used for *H. pylori* diagnosis is relevant. For an individual already undergoing gastroscopy for upper gastrointestinal evaluation, the relevant tests would be the RUT or histology. In the context of non-invasive testing, the options for diagnosing active infection are the UBT and the stool antigen test. ELISA serology is another method of diagnosis, but it may only indicate past exposure and may not reflect current active infection. Positive tests would need to be further confirmed with another test.

Helicobacter pylori eradication has been shown in meta-analyses to prevent gastric cancer[140] and peptic ulcers.[141] Studies on the issue of the cost-effectiveness of screening and treating *H. pylori* have shown it to be useful in preventing gastric cancer,[75,77] peptic ulcers,[142,143] and dyspepsia.[144,145]

Management of *H. pylori* infection

Statement 17: The threshold for a first-line regimen with susceptible strains should be a reliable cure for at least 95% of patients per protocol. The intention-to-treat threshold is 90% or greater treatment success.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 90%, (B) Agree with reservations 10%

Rationale. Based on Real-world practice and Expectation of Asia-Pacific physicians and patients in Helicobacter Pylori eradication (REAP-HP) survey, the expectation eradication rate for a first-line regimen was 91.4%.[146] However, treatment success was defined as a cure rate of ≥ 95% (i.e. grade A) as described in prior study.[147] Physicians should have at least two first-line choice regimens that contain different antimicrobials so that they can offer a reliable first-line choice despite allergies or other reasons why one of the regimens cannot be used. Randomized trials showing that these results are achievable are available.[148,149]

Statement 18: Amoxicillin and tetracycline resistance is low and stable. Metronidazole resistance is generally high in ASEAN countries. Clarithromycin resistance has been increasing in many regions and reduces the eradication rate of standard triple therapy.

Level of evidence: High
Grade of recommendation: N/A
Consensus level (A) Strongly agree 95%, (B) Agree with reservations 5%

Rationale. In ASEAN countries, metronidazole-resistant *H. pylori* are common whereas amoxicillin resistance remains rare.[150,151] Clarithromycin resistance results in a significant decrease in the *H. pylori* eradication rate with clarithromycin-containing regimens.[150,152] The prevalence of clarithromycin resistance varies in ASEAN countries, being very high in Vietnam and Indonesia (25–73%),[153,154] moderate to high in Singapore (6–18%),[151,155] and low in Malaysia (0–6.8%).[156–159] In Thailand, clarithromycin resistance tends to be higher in large cities than in rural areas, where it remains low (~5%).[150] However, susceptibility data regarding clarithromycin resistance is not widely available in most ASEAN countries. ASEAN countries should develop a standard protocol for regular susceptibility testing of *H. pylori* so that clinicians would be better able to choose reliably effective empiric therapies. The wide-ranging prevalence of antimicrobial resistance in ASEAN countries suggests that the preferred regimen will vary by region and a single recommendation other than to use what works best locally cannot be given.

Statement 19: The clarithromycin resistance rate is considered high when it exceeds 10–15%, which separates regions into high- and low-resistance areas.

Level of evidence: Moderate
Grade of recommendation: N/A
Consensus level (A) Strongly agree 95%, (B) Agree with reservations 5%

Rationale. Clarithromycin resistance is all-or-none, such that resistance effectively eliminates clarithromycin from clarithromycin-containing therapies.[150,152] Thus, clarithromycin resistance results in a marked reduction in the *H. pylori* eradication rates of any clarithromycin-containing therapy. The cure rate with clarithromycin-resistant strains depends on the effectiveness of the remaining dual PPI amoxicillin therapy, which depends in part on the duration of the therapy and the effectiveness of the PPI in increasing intragastric pH.[160] The highest rates are obtained with 14-day therapy. Clarithromycin resistance rates of more than 10–15% will decrease the eradication rate below 90%.

Statement 20: For most therapies, a 14-day duration is optimal and should be used. Shorter durations are acceptable only if they are proven to reliably achieve the threshold cure rates of 95% PP or 90% for ITT.

Level of evidence: High
Grade of recommendation: strong
Consensus level (A) Strongly agree 95%, (B) Agree with reservations 5%

Rationale. The optimal duration is defined as the duration that will reliably yield 95% or greater cure rates with susceptible infections and adherent-to-regimen patients. In most instances, 14 days of therapy is optimal and should be used.[44] Shorter durations are effective in some regions and for some drug combinations provided that they are proven to reliably achieve the threshold of 95% Per-protocol analysis (PP) or 90% Intention-to treat analysis (ITT) cure rates.

Statement 21: The selection of recommended first-line treatments varies regionally, geographically, and per individual patient depending on the known or anticipated pattern of antimicrobial resistance.

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Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 80%, (B) Agree with reservations 20%

Rationale. If the local pattern of resistance is unknown, then the rule of thumb is to use what works best locally. Therapy is also individualized based on the patient's history of antibiotic use and other clues to a high likelihood of resistance to one or more specific antibiotics (Fig. 3). Clarithromycin should not be prescribed to a patient with known or highly suspected resistance to clarithromycin (e.g. after failure of clarithromycin triple therapy). For populations, the regimen and duration should be based on what is most effective and cost-effective (Fig. 4). Quadruple therapies are generally reserved for use as empiric therapy in situations where dual resistance (e.g. clarithromycin-metronidazole) is known to be low. Some therapies proven to reliably yield 95% or greater cure rates with susceptible infections are shown in Table 3. Lower doses and shorter durations will yield similar results in some regions.

Individual drugs are discussed in the following

Proton pump inhibitors. The effectiveness of PPI therapy is related to dose, frequency of administration, and the degree to which it is metabolized by CYP2C19. Patient factors that influence effectiveness include the presence and severity of corpus gastritis and CYP2C19 polymorphisms. Generally, a double dose (e.g. 40 mg of omeprazole) twice a day is sufficient. Rabeprazole or esomeprazole are preferred when minimal CYP2C19 metabolism is desired (e.g. in a population of generally high rapid proton pump metabolizer patients). Every 6 h, higher doses are typically required when used as dual PPI-amoxicillin dual therapy.

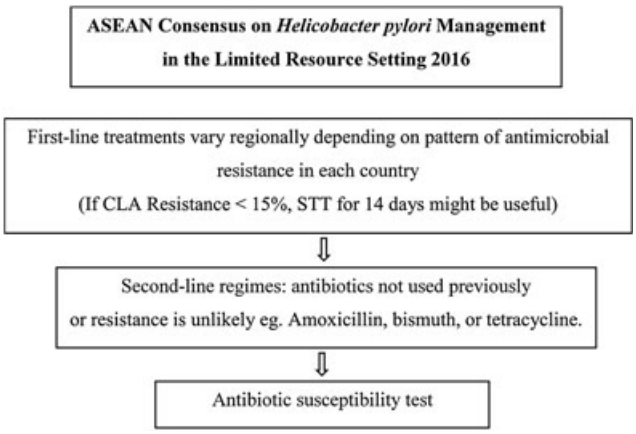

Figure 4 Algorithm for *Helicobacter pylori* management in ASEAN: the Bangkok Consensus Report.

Clarithromycin. Clarithromycin is typically administered twice a day. In some areas, long-acting clarithromycin is available allowing once-a-day administration. The most effective dose is undetermined and ranges from 200 to 500 mg twice a day. The dose chosen should reliably cure > 95% per protocol and 90% or greater susceptible infections and adherent-to-regimen in susceptible infections and adherent patients when given for the optimum duration. Resistance is all-or-none such that it eliminates the drug as an antimicrobial for that patient.

Metronidazole. Metronidazole is administered two to four times daily. The optimal dose is undetermined and ranges from

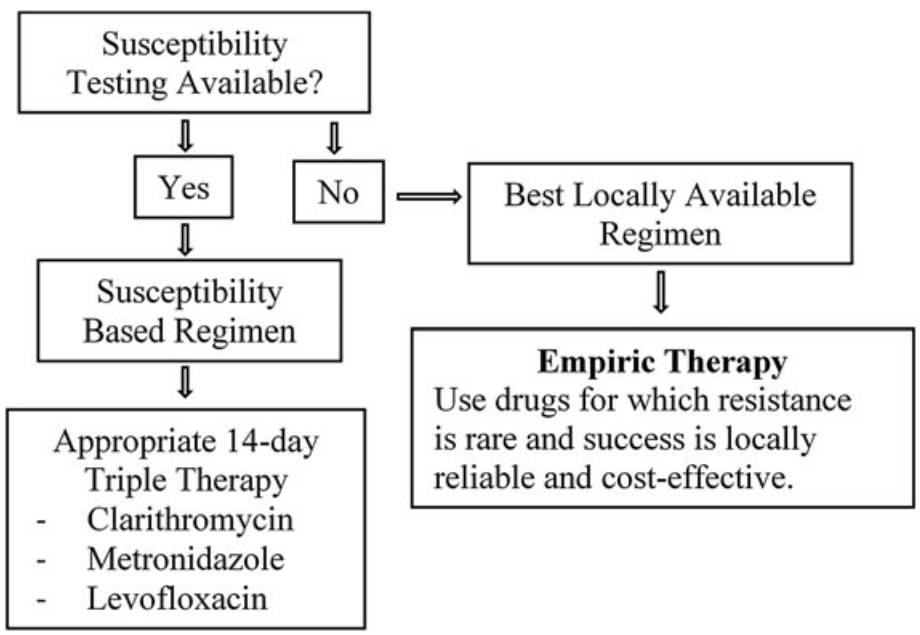

Figure 3 Rational approach to *Helicobacter pylori* therapy.

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Table 3 Effective regimens for *Helicobacter pylori* therapy with susceptible strains (doses and durations may vary in different regions and still achieve 95% or greater cure rates with susceptible strains)

Treatment	Drugs, dosages and duration
Empiric therapies	
Concomitant therapy	Amoxicillin (1 g), clarithromycin (500 mg), and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI (40 mg omep equivalent per dose) all given twice daily for 14 days
Sequential therapy (not recommended as concomitant is superior)	Amoxicillin (1 g) plus a PPI twice daily for 7 days, followed by clarithromycin (500 mg) and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI all twice daily for a further 7 days (total 14 days)
Hybrid therapy	Amoxicillin (1 g) plus a PPI twice daily (40 mg omeprazole equivalent per dose) for 7 days, followed by amoxicillin (1 g), clarithromycin (500 mg) and metronidazole (500 mg) plus a PPI twice daily for a further 7 days (total 14 days)
Bismuth quadruple therapy	Bismuth subsalicylate or bismuth subcitrate two tablets and tetracycline hydrochloride (500 mg) both four times daily with meals and at bedtime plus metronidazole/tinidazole (500 mg) three times daily with meals and a PPI twice daily for 14 days
New bismuth quadruple therapy (amoxicillin for tetracycline)	Bismuth two tablets two to four times daily with meals and at bedtime plus metronidazole/tinidazole (500 mg) three times daily with meals and amoxicillin 1 mg and a PPI twice daily for 14 days
For prepackaged bismuth quadruple therapy	PYLERA for 14 days, add a PPI bid (40 mg omep equivalent per dose)
Tailored therapy	(based on known susceptibility testing)
Triple therapy when *H. pylori* infection is known to be susceptible to clarithromycin	Amoxicillin (1 g) and either clarithromycin (500 mg) or tinidazole (500 mg) or metronidazole (500 mg) plus a PPI all given twice daily for 14 days (40 mg omep equivalent per dose)
Fluoroquinolone triple therapy when *H. pylori* is known to be susceptible to fluoroquinolones	Fluoroquinolone (e.g. levofloxacin 500 mg once daily), plus a PPI and amoxicillin 1 g twice daily for 14 days
Empiric salvage therapy	Known resistance or unknown in high resistance area
Furazolidone quadruple therapy with tetracycline	Bismuth subsalicylate or bismuth subcitrate two tablets and tetracycline hydrochloride (500 mg) both four times daily with meals and at bedtime plus furazolidone 100 mg tid, with means and PPI twice daily for 14 days
Furazolidone quadruple therapy with amoxicillin	Bismuth subsalicylate or bismuth subcitrate two, four times daily with meals and at bedtime plus furazolidone 100 mg and amoxicillin 1 g tid, with meals plus a PPI twice daily for 14 days
Rifabutin triple therapy	Rifabutin (150 mg daily), amoxicillin (1.5 g q.8.h.) and pantoprazole 80 mg (or an equivalent PPI) q.8.h. for 12 to 14 days (Borody formula)
High-dose PPI-amoxicillin dual therapy	PPI (e.g. rabeprazole 20 mg, esomeprazole 40 mg) plus amoxicillin (500–750 mg) all four times daily at approximately 6 h intervals for 14 days (can use 8-h interval at night)

Preferred proton pump inhibitor (PPIs): Esomeprazole 40 mg, rabeprazole 20 mg.

200 to 500 mg in twice-a-day therapies to 2 g/day when used in divided doses. The dose chosen should reliably cure $>$ 95% per protocol and 90% or greater susceptible infections and adherent-to-regimen in susceptible infections and adherent patients when given for the optimum duration. Resistance is dose and duration-dependent and can be partially overcome in bismuth-tetracycline and possibly bismuth-amoxicillin quadruple therapies when given in doses of 1500 mg/day or greater.[161]

Tinidazole is equivalent to metronidazole in relation to dosing and effectiveness.

Amoxicillin. Amoxicillin is administered two to four times daily. The optimal dose is unknown and ranges from 500 to 1 g twice or four times a day. The most common dose for twice-a-day therapy is 1 g twice a day. For dual PPI plus amoxicillin therapy, the dose ranges from 500 to 750 mg every 6 h. Resistance is rare in most countries.

Tetracycline. Tetracycline, oxytetracycline, and chlortetracycline are likely equally effective. Tetracycline is typically administered as 500 mg four times daily. The most common use of tetracycline is in four-drug (quadruple) therapies. In China, twice-a-day regimens are successfully used in quadruple therapies. Resistance is rare.

Levofloxacin. Levofloxacin is representative of the newer generation of fluoroquinolones. Fluoroquinolones are typically given once a day (e.g. 500 mg levofloxacin or 400 mg moxifloxacin) as part of triple therapies. Fourteen-day therapy is typically required to reliably achieve 95% cure rates with susceptible strains with fluoroquinolone triple therapies. Resistance is all-or-none such that resistance eliminates the drug as an antimicrobial for that patient.

Furazolidone. Furazolidone is most effective when administered as 100 mg three times daily as part of a bismuth-tetracycline or bismuth-amoxicillin quadruple therapy. Resistance is rare.

Statement 22: The second-line regimes should contain antibiotics not used previously, such as amoxicillin, bismuth, or tetracycline, or resistance is unlikely to have developed.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 80%, (B) Agree with reservations 20%

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Rationale. Antibiotic resistance is the most critical factor responsible for eradication treatment failure. The choice of a second-line treatment should be based primarily on antimicrobial susceptibility testing, chosen from treatments not used initially (e.g. bismuth or non-bismuth quadruple therapy), the local rate of fluoroquinolone resistance and the availability of either bismuth salts or tetracycline.

Bismuth-containing quadruple therapy

A systemic review by Marin *et al.*[162] showed that bismuth-containing quadruple therapy (BQT) had a mean eradication rate of 78% after the failure of standard clarithromycin-containing triple therapy. Its effectiveness increased with the duration of treatment, from 76% for a 7-day regimen to 82% for a 14-day regimen. However, most systematic reviews do not take into account the doses used, which limits their usefulness.

A recent study from China has evaluated the efficacy of 14-day bismuth quadruple therapies (PPI, bismuth salts, and two antibiotics) with different antibiotic combinations in patients with previous eradication treatment failure. Cure rates were excellent (> 90%), regardless of the presence of clarithromycin, levofloxacin, or metronidazole resistance, with the best results being for furazolidone-containing regimens.[163]

Fluoroquinolone-containing therapies

Recent studies have reported high levofloxacin resistance rates, ranging from 63% in China to 14% in Europe.[164] A recent review revealed that the efficacy of levofloxacin-containing rescue regimens was 76%.[163] This reflects the fact that 7- and 10-day triple fluoroquinolone therapy fails to achieve acceptable cure rates. Fourteen-day therapy and susceptible infections will reliably cure 95% of infections. The role of newer fluoroquinolones, such as sitafloxacin and gemifloxacin, needs to be validated in further studies.

Rifabutin-containing therapy

A recent systematic review disclosed that the mean *H. pylori* eradication rate with rifabutin-containing rescue regimens was 73%.[158] The main disadvantages are its high cost and the potential development of resistance to *Mycobacterium tuberculosis* in populations with a high prevalence of M. tuberculosis. A recent study suggested that 150 mg of rifabutin, 1 g of amoxicillin, two tablets of bismuth subcitrate, and a PPI twice a day might be effective.[165] That study was small and used a 10-day regimen. More studies are needed including those extending the regimen to 14 days.

The fluoroquinolone-containing therapy should be the preferred second-line treatment in limited resource areas if bismuth is not available. The use of rifabutin should not be considered in regions with a high prevalence of M. tuberculosis.

Statement 23: The primary indication for antibiotic susceptibility testing is to perform susceptibility-based or tailored therapy, and currently, this is most commonly carried out after failure of second-line therapy.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 100%

Rationale. The basic principle of antimicrobial therapy is to use susceptibility-based therapy. The primary indication for antibiotic susceptibility testing is to identify the best treatment for an individual patient and to provide population-based recommendations. Clarithromycin, fluoroquinolones, metronidazole, and rifabutin should not be used empirically except when the probability of resistance is low. When the probability is known or suspected to be high based on population data or prior use or treatment failure, susceptibility testing should be carried out.

Antibiotic resistance is the most important factor responsible for treatment failures. A susceptibility test should be available from culture and/or molecular testing and should be used except when the probability of resistance to the antimicrobials chosen is low. After two treatment failures with different drugs, antibiotic susceptibility testing is mandatory to enable an appropriate choice of rescue treatment based on the antibiotic resistance pattern.[159,166–170]

Statement 24: Rescue therapy should be based on susceptibility testing whenever possible. If not available, one should not include drugs to which resistance is common and use drugs to which resistance rarely develops or can be overcome.

Level of Evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 90%, (B) Agree with reservations 10%

Rationale. Rescue therapy should be based on susceptibility testing whenever possible. If not available, one should not include drugs to which resistance is all-or-none or drugs that have been used previously to which resistance often develops. Patients who fail two therapies with different drugs and are adherent can be considered to most likely have resistant infections. The goal of therapy is therefore to either test susceptibility to provide susceptibility-based therapy or, if unavailable, give a regimen where resistance is rare or can possibly be overcome (e.g. metronidazole resistance). The regimen should be full dose and last for 14 days.

Statement 25: The options to improve the antisecretory effect of PPIs to increase the *H. pylori* eradication rate can be based on the host's CYP2C19 genotype, by increasing the dose of heavily metabolized PPIs, or using PPIs little affected by CYP2C19.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 60%, (B) Agree with reservations 25%, (C) Undecided 15%

Rationale. The metabolism of PPIs and their pharmacokinetics depend on hepatic cytochrome P450, especially the CYP2C19 genotype. More than 20 variants of the CYP2C19 gene have been identified.[171–173] The majority of CYP2C19 genotypes can be classified into three genotypes: extensive metabolizer, intermediate metabolizer, and poor metabolizer.[174] The genotype influences the pharmacokinetics (peak plasma concentration and area under the curve of the plasma concentration) and pharmacodynamics (i.e. intragastric pH) of PPI.[175] Rabeprazole is metabolized to thioether-rabeprazole mainly via a nonenzymatic pathway with minor involvement of CYP2C19.[176] Esomeprazole is a pure S-

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isomer of omeprazole, is less sensitive, and, in minimal first pass metabolism, undergoes less hydroxylation via CYP2C19.[177]

Statement 26: Increasing the dose of metronidazole to 1500 mg/day or more and increasing the duration to 14 days have been shown to improve the cure rate of bismuth-containing quadruple therapies in the presence of metronidazole resistance.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 95%, (B) Agree with reservations 5%

Rationale. **1 Increased dose of antibiotics**

Metronidazole resistance is one of the major problems that reduce the effectiveness of *H. pylori* eradication. But increasing the dose of metronidazole in PPI-amoxicillin-metronidazole triple therapy appeared not to significantly improve the outcome.[178] The HOMER study (which used triple therapy) clearly showed a dose response as does the Fischbach meta-analysis.[179] This may need both dose and duration effects and possibly multiple dosing intervals (e.g. tid or qid). The overall eradication rate was approximately 80% with all three doses of metronidazole (800, 1200, 1600 mg/day). However, a randomized trial with a 10-day bismuth quadruple therapy with high-dose metronidazole (2000 mg/day) for second-line therapy showed an ITT eradication rate of 79.7% (95% CI: 70.5–88.7%) and a PP eradication rate of 90.8% (95% CI: 83.8–97.8%).[180]

According to the data for extended duration of treatment, 14-day standard triple therapy, 14-day BQT, 14-day hybrid therapy, 14-day fluoroquinolone triple therapy, and 10 to 14-day concomitant therapy induced a higher eradication rate than shorter durations (5–7 days). But only 14-day BQT and 10–14-day concomitant therapy can achieve high effective rates: ITT $>$ 90% and PP $>$ 95%.

1 Extended duration of treatment

Several strategies have been proposed to improve the eradication rates of existing therapies. The overall trend shows that longer treatment duration is more favorable for *H. pylori* eradication. But now there are many regimens that are used worldwide, some for first-line and some for second-line treatment. The evidence of each regimen has been shown separately.

Standard triple therapy. Extending the treatment duration of triple therapy (PCA) from 7 to 10 or 10 to 14 days was associated with significantly higher eradication. Thirty-four studies (n = 5801) revealed that the eradication rate significantly increased from 7 days (74.9%) to 14 days (83.5%) (RR = 0.65 [95% CI: 0.57–0.75]).[181] The optimal duration of therapy for triple therapy (PCA) is at least 14 days.[181–187]

Bismuth-containing quadruple therapy. Prolonged treatment duration of both first-line and second-line BQT was more effective in a 2-week course than for 1 week.[188–192] A randomized trial of BQT for first-line eradication showed significantly increased success: comparing 14 to 7-day ITT, 93.7% *versus* 80.0%; P = 0.01, PP 97.4% *versus* 82.0%; P = 0.0016.[189] For second-line therapy, the eradication rate of 14-day BQT was higher than for 7 days.[188,190–192]

Sequential therapy. A *Lancet* paper clearly shows that 14 days is better, with 10-day therapy giving an average cure rate of less than 95%, and 14 days giving $>$95%.[193] However, sequential therapy is greatly affected by metronidazole resistance and dual clarithromycin-metronidazole resistance and is considered obsolete, being replaced by concomitant therapy, which is only affected by dual clarithromycin-metronidazole resistance.

Concomitant therapy. Concomitant therapy is effectively giving clarithromycin and metronidazole triple therapies simultaneously such that only clarithromycin-metronidazole dual resistance reduces the effectiveness. With 14-day therapy, cure rates of 95% or greater are obtainable in most regions.

A prospective multicenter in Italy and Spain, which has high clarithromycin and metronidazole resistance, showed a high eradication rate of 14-day concomitant therapy: ITT 91.7% (95% CI: 87–95%) and PP 96.1% (95% CI: 93–99%).[194]

Hybrid therapy. A 14-day course of hybrid therapy, which consists of a dual therapy with a PPI and amoxicillin for 7 days followed by a quadruple regimen with a PPI, amoxicillin, clarithromcyin, and metronidazole for 7 days, was more effective than 10 days in the area of high clarithromycin and metronidazole resistance. But in a low clarithromycin and metronidazole resistance area, treatment for between 10 and 14 days showed no difference. A randomized trial in Taiwan showed similar efficacy between 10-day hybrid therapy PP at 95% (95% CI: 89.5–100%) and 14-day PP at 93.4% (95% CI: 87.2–99.7%).[195]

Fluoroquinolone triple therapy for second-line treatment. The 14-day regimen of fluoroquinolone triple therapy (levofloxacin, moxifloxacin) was significantly more effective for second-line treatment than the 7 or 10-day regimens.[178,196,197]

ITT eradication rates for 7 to 10-day *versus* 14-day therapy were 67.1–70.8% and 81.4–84.8%, respectively. PP eradication rates were 73.6–77.7% for 7 and 10-day therapy and 90.4–90.5% for 14 days.

Statement 27: Probiotics can be used as adjunctive treatments to reduce adverse effects and increase tolerability. The use of probiotics plus standard therapy may be associated with a modest increase in eradication rate. However, the benefits have not been shown to be cost-effective.

Level of evidence: High
Grade of recommendation: Weak
Consensus level (A) Strongly agree 80%, (B) Agree with reservations 20%

Rationale. Although antibiotic-based *H. pylori* eradication treatment in first-line therapy is 90% effective, it can cause

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antibiotic resistance associated with low compliance and other adverse effects. Many studies have tried new treatment approaches by using probiotics. Probiotics such as *Lactobacilli*, *Bifidobacteria*, and *Saccharomyces boulardii* exhibit inhibitory activity against *H. pylori* both *in vitro* and *in vivo*. Several studies demonstrated that standard triple therapy plus probiotics showed slightly better eradication rates than standard triple therapy only.[198–200] Probiotic combinations can reduce adverse effects induced by *H. pylori* eradication treatment and increase compliance by increasing tolerability.

Meta-analyses have clarified the role of probiotics in the treatment of *H. pylori* infection. A meta-analysis including 10 clinical trials evaluated the use of probiotics containing *Lactobacillus* and *Bifidobacterium* as adjuvant to standard triple therapy.[201] This meta-analysis showed a reduction of overall adverse effects in the probiotics supplement group compared with the group without probiotics (OR: 0.30, 95% CI: 0.11–0.79). McFarland *et al*. performed a meta-analysis including 25 randomized controlled trials (28 treatment arms, with a total of 3769 participants) that assessed one of six single probiotic strains as adjunctive treatments to standard eradication therapy.[202] They showed that *S. boulardii* improved the *H. pylori* eradication rate (pooled relative risks [pRR] = 1.11, 95% CI: 1.07–1.16) and significantly prevented any adverse effects (pRR = 0.42, 95% CI: 0.28–0.62). Both *S. boulardii* and *Lactobacillus rhamnosus* significantly reduced antibiotic-associated diarrhea (pRR = 0.47, 95% CI: 0.37–0.60 and pRR = 0.29, 95% CI: 0.17–0.48, respectively) associated with *H. pylori* eradication therapy. Another meta-analysis, including 11 randomized controlled trials (a total of 2200 participants), evaluated the effects of *S. boulardii* as supplementation to a standard eradication regimen on *H. pylori* eradication rates and therapy-associated side effects.[203] They showed that *S. boulardii* compared with control reduced the risk of overall *H. pylori* therapy-related adverse effects (RR 0.44, 95% CI: 0.31–0.64), particularly diarrhea (RR 0.51, 95% CI: 0.42–0.62) and nausea (RR 0.6, 95% CI: 0.44–0.83).

Statement 28: In patients with a penicillin allergy, one common solution would be to use bismuth quadruple therapy. The alternative options would depend on the local pattern of susceptibility.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 95%, (B) Agree with reservations 5%

Rationale. Few studies are available on evaluating the efficacy of *H. pylori* eradication treatment specifically in penicillin-allergic patients. A previous recommendation for using a PPI-clarithromycin-metronidazole regimen as the first-line therapy achieved disappointing results in most Asian countries where rates of primary resistance to clarithromycin and metronidazole are high.[204] Bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) provided a better eradication rate than PPI-clarithromycin-metronidazole triple therapy.[205,206] If metronidazole resistance exceeds 40%, 14-day therapy seems to be more prudent.[157] A recent study in penicillin-allergic patients demonstrated that levofloxacin-based triple therapy (PPI-clarithromycin-levofloxacin) provided an intention-to-treat eradication rate of only 64% after both triple and quadruple failure. Based on a high efficacy of culture-based tailored therapy reported from Korea,[207] if antibiotic susceptibility testing is available, tailored therapy may be a good alternative choice, especially in the area of high levofloxacin resistance.

Follow-up after eradication.

Statement 29: The reported annual reinfection rate of *H. pylori* in ASEAN countries varies from 0% to 6.4%.

Level of evidence: Moderate
Grade of recommendation: N/A
Consensus level (A) Strongly agree 90%, (B) Agree with reservations 10%

Rationale. Reported cases of *H. pylori* reinfection are often cases of recrudescent infection. "True" reinfection is defined as an infection with a new strain of *H. pylori* that is different from the original strain after complete eradication, while recrudescence is a relapse of the original strain, which was temporarily suppressed by eradication therapy.[208] However, the molecular evidence is usually not practical and feasible. The recurrence rates of *H. pylori* have been reported to decrease with time and decline sharply after the first year, and beyond the first year, recurrence rates come close to the rate of natural acquisition of *H. pylori* infection in adulthood.[209–211] Therefore, the confirmation of continuous *H. pylori* negativity for the first year after eradication therapy has been widely accepted as complete eradication.[212–214] A meta-analysis showed that the annual recurrence rate of *H. pylori* after eradication in developing countries was about 12%.[215] A later review showed that the actual annual reinfection rates in Asian countries were about 0–6.45% according to the previously mentioned definition.[205] Recent Asian studies published after this review also reported similar results.[216–218]

Statement 30: *Helicobacter pylori*-associated dyspepsia is a distinct entity. In *H. pylori*-infected patients with dyspepsia, symptoms can be attributed to *H. pylori* if successful eradication therapy is followed by sustained symptom remission.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 95.5%, (B) Agree with reservations 4.5%

Rationale. According to the Rome III consensus, functional dyspepsia is defined as "the presence of chronic dyspeptic symptoms (postprandial fullness, early satiation, epigastric pain or burning) without evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms."[219,220] In contrast, chronic dyspeptic symptoms that have an identified organic or metabolic cause will resolute or improve if that cause is eliminated or the disease is improved.[216] Several studies showed that a subset of *H. pylori*-infected patients with non-ulcer dyspepsia have symptomatic remission after successful eradication with a delay of at least 6 months from the cure of the infection.[6,221–223] This sustained remission of symptoms after

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eradication identifies *H. pylori* as the organic cause of the symptoms in this subgroup of patients. Therefore, *H. pylori*-associated dyspepsia can be considered a distinct clinical entity, and *H. pylori* should be tested and treated before one can reliably diagnose functional dyspepsia.

Statement 31:

31a Noninvasive tests are recommended to confirm eradication of *H. pylori* infection in duodenal ulcers.

31b A repeat endoscopy is recommended in gastric ulcers often at 8–12 weeks to document complete ulcer healing. In addition, gastric biopsy is recommended to exclude malignancy when ulcer healing is not achieved.

Level of evidence: High
Grade of recommendation: Strong
Level of consensus:
31(a). (A) Strongly agree 90.9%, (B) Agree with reservations 9.1%;
31(b). (A) Strongly agree 95.2%, (B) Agree with reservations 4.8%

Rationale. *Helicobacter pylori* eradication should be confirmed in all patients with *H. pylori*-induced peptic ulcer diseases in order to prevent ulcer recurrence. The tests of choice include UBT, the stool antigen test as an alternative, and endoscopy-based tests (as discussed in statement 7 of WG2). As duodenal ulcers are extremely unlikely to be malignant and more than 90% of duodenal ulcers heal with 4 weeks of PPI therapy,[224,225] surveillance endoscopy has a low yield if symptoms resolve after *H. pylori* eradication therapy and discontinuation of NSAIDs. Noninvasive tests, therefore, are recommended to confirm successful *H. pylori* eradication in this situation.

In contrast to duodenal ulcers, some gastric ulcers that initially appear to be endoscopically and histologically benign may eventually prove to be malignant.[226,227] It has been reported that 5% to 10% of gastric ulcers are malignant.[228] In addition, some studies have shown that the false negative biopsy rate is about 2% to 5% of malignant ulcers, and any unhealed ulcers at follow-up examination after 8 to 12 weeks of medical treatment should undergo repeat biopsy.[226,228,229] Endoscopic-based tests for *H. pylori* are appropriate in this situation.

Statement 32: In patients with early gastric cancer and MALT lymphoma associated with *H. pylori* infection, successful eradication must be confirmed at least 4 weeks after treatment. Follow-up endoscopy is recommended.

Level of evidence: High
Grade of recommendation: Strong
Consensus level (A) Strongly agree 90.5%, (B) Agree with reservations 9.5%

Rationale. *Helicobacter pylori* eradication reduces the development of gastric cancer, but the risk of metachronous gastric carcinoma (MGC) is not completely eliminated. A multicenter, randomized controlled trial in Japan reported the efficacy of *H. pylori* eradication on the incidence of MGC after endoscopic resection of early gastric cancer.[230] In that study, MGCs developed in nine patients in the eradication group and 24 in the control group at 3-year follow-up. The odds ratio for MGCs was 0.353 (95% CI: 0.161–0.775; P = 0.009). In another study, the cumulative incidence rate of MGCs in the successfully eradicated group was lower than that in the persistent group when the follow-up period was censored at 5 years (5.3% *vs* 18.2%; P = 0.007; log–rank test).[231] However, a long-term follow-up period of more than 10 years showed no significant difference in the cumulative incidence of MGC between the two groups. In the successfully eradicated group, two thirds of the MGCs were discovered more than 5 years after the endoscopic resection of the primary cancer. A recent cohort study showed that the cumulative incidence of MGC 5 years after successful *H. pylori* eradication was 15%. Eleven percent of MGCs (10 out of 94) were detected more than 5 years after successful *H. pylori* eradication.[232] Therefore, surveillance endoscopy for MGCs in patients who have undergone endoscopic resection for early gastric cancer should be performed even after successful *H. pylori* eradication.

As *H. pylori* causes most cases of gastric MALT lymphoma, the diagnosis and treatment of *H. pylori* infection has been recommended as the first step in the management of gastric MALT lymphoma independent of the stage of disease.[233] Successful eradication must be confirmed in patients with *H. pylori*-associated MALT lymphoma as 77.5% of patients with gastric MALT lymphoma will achieve complete regression.[51] Furthermore, several studies have shown that successful eradication of *H. pylori* cures the majority of patients from gastric MALT lymphoma.[231,232] All patients with *H. pylori*-associated MALT lymphoma should be followed up with endoscopy to document endoscopic regression and detect histological residuals of MALT lymphoma as alternative treatments (chemotherapy or radiotherapy) will be required if the lymphoma fails to respond or progresses.[233] In addition, several prospective studies showed that low-grade MALT lymphoma has recurrence rates of 3–13% over 5 years of follow-up.[234,235]

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