Consensus recommendations for the screening, diagnosis, and management of Helicobacter pylori infection in Hong Kong

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ABSTRACT

Helicobacter pylori infection causes chronic gastric inflammation that contributes to various gastroduodenal diseases, including peptic ulcer and gastric cancer. Despite broad regional variations, the prevalence of resistance to antibiotics used to manage H pylori infection is increasing worldwide; this trend could hinder the success of eradication therapy. To increase awareness of H pylori and improve the diagnosis and treatment of its infection in Hong Kong, our consensus panel proposed a set of guidance statements for disease management. We conducted a comprehensive review of literature published during 2011 and 2021, with a focus on articles from Hong Kong or other regions of China. We evaluated the evidence using the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and sought consensus through online voting and a subsequent face-to-face meeting, which enabled us to develop and refine the guidance statements. This report consists of 24 statements regarding the epidemiology and burden, screening and diagnosis, and treatment of H pylori. Key guidance statements include a recommendation to use the test-and-treat approach for high-risk individuals, as well as the confirmation that triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin remains a valid first-line option for adults and children in Hong Kong.

Introduction

Antibiotics are the primary treatment for Helicobacter pylori; however, resistance to common antibiotics used in eradication therapy (eg, clarithromycin, metronidazole, and quinolones) is increasing worldwide, thereby reducing the expected therapeutic benefit.1 Thus, there is an urgent need for an updated management guide that considers susceptibility patterns, disease prevalence, and patient factors in Hong Kong. Accordingly, a panel of 10 experts from Hong Kong gathered to review recently published evidence regarding the management of H pylori infection to develop this consensus report.

PubMed was searched for published peer-reviewed articles in English on the epidemiology, screening, diagnosis, and treatment of H pylori infection, with a focus on Hong Kong and China. The search included clinical trials (randomised controlled trials [RCTs] and controlled clinical trials), practice guidelines, meta-analyses, systematic reviews, and observational studies from January 2011 to August 2021.

In September 2021, the panel assigned consensus topics to specific members for literature review and statement drafting, followed by a discussion in October 2021. The Oxford Centre for Evidence-Based Medicine’s 2011 Levels of Evidence and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system were used to evaluate level of evidence and classify recommendations, respectively. Details of GRADE classification are shown in the online supplementary Table.

All participants were asked to indicate their level of agreement using a Likert scale (1: completely
Statement 1: Although the prevalence of *H pylori* infection in many developed countries has declined in recent decades, epidemiological data for Hong Kong, except in children, are limited. (quality of evidence: 2/3; strength of recommendation: not applicable; level of consensus: 100%)

Global and regional estimates published in 2017 revealed that the prevalences of *H pylori* infection were 55.8% in China and 53.9% in Taiwan. No prevalence data for Hong Kong have been reported since 2011. Although the prevalences in many countries in Europe and Northern America have declined since 2000, the prevalences in Asia before and after 2000 were similar (53.6% vs 54.3%).

Two retrospective studies and a population-based study explored the *H pylori* infection rate in Hong Kong children. In 2008, the estimated rate of *H pylori* infection in healthy school children (n=2480) was 13.1%. Among 602 children who underwent esophagogastroduodenoscopy at a tertiary centre for peptic ulcer symptoms, the *H pylori* infection rate decreased from 25.6% in 2005 to 12.8% in 2017.

**Epidemiology and burden**

Statement 2: Although the rate of *H pylori* reinfection remains low (<2%) in the Chinese population, it may be higher in children than in adults. (quality of evidence: 3; grade of recommendation: not applicable; level of consensus: 80%)

In a systematic review of 132 studies, the global annual rates of *H pylori* recurrence, reinfection, and recrudescence were 4.3%, 3.1%, and 2.2%, respectively. The global rates of *H pylori* recurrence generally remained stable in the 1990s, 2000s, and 2010s, but data varied according to region.

Data regarding the rates of *H pylori* recurrence, reinfection, and recrudescence in Hong Kong adults are limited. A community-based study showed that the rate of *H pylori* reinfection in Taiwan was 0.34 to 0.95 per 100 person-years between 2008 and 2018. In 2020, a prospective cohort study in China showed that the annual rate of *H pylori* reinfection was 1.5% per person-year.

The rates of *H pylori* reinfection may be higher in children. In a study from Baoding in Hubei, China, the recurrence rate was 18.8% (41/218 children with successful follow-up). Moreover, the rate was higher in children aged ≤10 years than in children aged >10 years (22.8% vs 7.1%, P=0.01). Similarly, a Bolivian population-based study showed a higher annual recurrence rate in younger children than in older children: 20% for children aged <5 years, 20% for children aged 5 to 9 years, 8% among children aged 10 to 14 years, and 8% among individuals aged ≥15 years.

Statement 3: *Helicobacter pylori* infection in adults has been associated with increased risks of gastric adenocarcinoma, peptic ulcer disease, non-ulcer dyspepsia, and mucosa-associated lymphoid tissue (MALT) lymphoma. Eradication of *H pylori* has been shown to reduce gastric cancer incidence, reduce peptic ulcer recurrence, and provide symptomatic relief in *H pylori*-positive patients with non-ulcer dyspepsia. (quality of evidence: 1; grade of recommendation: not applicable; level of consensus: 90%)

*Helicobacter pylori* infection is considered an important causal risk factor for non-cardia gastric adenocarcinoma. The estimated global burden of gastric cancer attributable to *H pylori* is 89%. The odds ratio of gastric cancer onset among patients with *H pylori* infection ranges from 5.9 to 34.5. Usually, a high incidence of gastric cancer is associated with a high prevalence of *H pylori* infection.

A reduced risk of gastric cancer after *H pylori* eradication has been demonstrated in interventional trials, including RCTs. To prevent one case of gastric cancer in *H pylori*-positive patients from a region with a high risk of gastric cancer (eg, China), the minimum number needed to treat was 15 according to a meta-analysis of six RCTs. In 2018,
a territory-wide study of 73,237 H pylori–infected patients in Hong Kong showed that eradication was associated with a reduced risk of gastric cancer, particularly among patients aged ≤60 years.29 A meta-analysis of 24 studies also showed that the benefit of H pylori eradication for gastric cancer prevention was greater in patients with endoscopically resected early gastric cancer compared with asymptomatic patients; moreover, eradication was associated with a reduced incidence of metachronous recurrence.30 The available evidence suggests that, even when H pylori treatment is initiated after the development of atrophic gastritis and metaplasia, the risk of gastric cancer is reduced.

Helicobacter pylori is a causal risk factor for peptic ulcer disease; its eradication therapy is effective in treating and preventing the recurrence of both gastric and duodenal ulcers.27,28 There is a potential causal link between H pylori infection and dyspeptic symptoms. Helicobacter pylori eradication had a small but statistically significant effect on the relief of dyspeptic symptoms in H pylori–positive patients.29

Gastric MALT lymphoma was also associated with H pylori infection; remission was achieved in 77.8% of patients after successful eradication.30

Screening and diagnosis

Statement 4: Considering the declining incidence of gastric cancer in Hong Kong, screening for H pylori in the general population is not recommended. (quality of evidence: 1; grade of recommendation: conditional; level of consensus: 90%)

A screen-and-treat strategy for H pylori is most cost-effective in regions with high gastric cancer incidence (ie, 20 per 100,000 person-years).26 The 2020 age-standardised incidence of gastric cancer in Hong Kong was 8.7 and 5.3 per 100,000 person-years in male and female, respectively.25 Because of this declining incidence, a screen-and-treat strategy may not be cost-effective for gastric cancer prevention in Hong Kong.

Statement 5: Among adults without gastric symptoms, individuals at high risk of gastric cancer (eg, individuals with a family history of gastric cancer) should be tested and (if they test positive) treated for H pylori. Otherwise, routine testing of asymptomatic household members or family members of H pylori–infected adults is not recommended. (quality of evidence: 1; grade of recommendation: strong; level of consensus: 90%)

Statement 6: Adults with non-ulcer dyspepsia, peptic ulcer disease, and early gastric cancer after endoscopic treatment should be tested and (if they test positive) treated for H pylori. (quality of evidence: 1; grade of recommendation: strong; level of consensus: 100%)

Statement 7: Adults with gastric biopsy results showing atrophy, intestinal metaplasia, or dysplasia should be tested and (if they test positive) treated for H pylori. (quality of evidence: 1; grade of recommendation: strong; level of consensus: 100%)

Family history, atrophic gastritis, and intestinal metaplasia are established risk factors for gastric cancer.35,31 Therefore, it is prudent to test for and treat H pylori in patients with a family history or pre-cancerous gastric lesions.

Statement 8: Adults planning to begin long-term low-dose aspirin treatment should be tested and (if they test positive) treated for H pylori. (quality of evidence: 3; grade of recommendation: conditional; level of consensus: 90%)

Statement 9: Adult patients planning to begin other non-aspirin non-steroidal anti-inflammatory drugs, antiplatelets, and anticoagulants should be tested and (if they test positive) treated for H pylori. (quality of evidence: 3; grade of recommendation: conditional; level of consensus: 70%)

Low-dose aspirin, non-steroidal anti-inflammatory drugs, anticoagulants, and antiplatelets can increase the risk of gastrointestinal (GI) bleeding.34,35 There is limited and conflicting evidence regarding the interaction among these agents, H pylori, and GI bleeding.36-39 Therefore, the benefit of testing and treatment for all users of these agents is unclear. However, the treatment of H pylori infection along with the use of gastroprotective strategies could mitigate the risk of GI complications, particularly in patients at high risk of GI bleeding.32,40,41 Thus, despite the conflicting evidence, the consensus panel also favoured testing and treatment for H pylori infection in these patients.

Statement 10: Adults with unexplained iron deficiency anaemia, vitamin B12 deficiency, or immune thrombocytopenic purpura should be tested and (if they test positive) treated for H pylori. (quality of evidence: 1/2; grade of recommendation: conditional; level of consensus: 90%)

Iron deficiency anaemia was associated with H pylori infection in both adults and children. The effect of iron therapy for iron deficiency anaemia may be enhanced with H pylori treatment.32-46 In recent decades, systematic reviews have shown that H pylori eradication can also improve platelet counts in adult and paediatric patients with idiopathic thrombocytopenic purpura.47-50 However, this panel does not recommend testing and treatment for all children with chronic idiopathic thrombocytopenic purpura. Additionally, the identification of iron deficiency anaemia aetiology in children should be prioritised over the detection and treatment of H pylori.
Statement 11: Routine H pylori testing in asymptomatic children is not recommended. However, children with peptic ulcer disease should be tested and (if they test positive) treated for H pylori. (quality of evidence: 2/3; grade of recommendation: strong; level of consensus: 100%)

Helicobacter pylori infection in children is mainly asymptomatic and rarely causes complications; thus, routine non-invasive testing in an otherwise asymptomatic child is not usually recommended. When a child presents with GI symptoms, the clinical investigation should focus on identifying the cause of the child’s symptoms, rather than solely confirming the presence of H pylori.

Statement 12: Non-invasive tests, including the urea breath test and (preferably monoclonal) stool antigen test, are highly accurate for the initial diagnosis and follow-up of H pylori. (quality of evidence: 2; grade of recommendation: not applicable; level of consensus: 90%)

The carbon-13 urea breath test and stool antigen test are non-invasive diagnostic tests with high accuracy in the detection of H pylori. The carbon-13 urea breath test has a sensitivity of 95% to 98% and a specificity of 90% to 97%. The monoclonal stool antigen test has a sensitivity of 90% to 98% and a specificity of 90% to 97%.

For post-eradication therapy follow-up, reliable results can be obtained at 2 weeks after discontinuation of proton pump inhibitors (PPIs) and at least 4 weeks after discontinuation of antibiotics and bismuth.

Statement 13: Serological testing is not recommended for initial diagnosis and post-eradication follow-up of H pylori. (quality of evidence: 2; grade of recommendation: conditional; level of consensus: 100%)

Serological testing has low accuracy and high false-negative rates for initial diagnosis; it is not recommended for post-eradication follow-up because it can detect antibodies from past infections. However, it may be useful in the management of some clinical conditions characterised by decreased bacterial load (eg, GI bleeding, atrophic gastritis, gastric MALT lymphoma, and gastric cancer); other tests can lose sensitivity for these conditions.

Statement 14: For all patients who undergo endoscopy, the initial diagnosis of H pylori can be made by the following methods: rapid urease test, histology with or without specific staining, and culture. (quality of evidence: 2; grade of recommendation: strong; level of consensus: 100%)

Gastric biopsies are ideal specimens for diagnostic rapid urease tests or histopathological assessments. Samples generally should be collected from both the antrum and corpus. Rapid urease tests can be used for quick assessment, but specimens with low bacterial loads can yield false-negative results. Culture-based detection of H pylori has comparatively low sensitivity and is usually reserved for instances where antimicrobial susceptibility testing is needed.

Additional information about screening for H pylori in pregnancy and diagnosis for H pylori in children are shown in the online supplementary Appendix.

**Treatment**

Statement 15: The choice of H pylori eradication therapy should be based on H pylori microbial resistance patterns and antibiotic stewardship in Hong Kong, as well as the efficacy of gastric acid suppression. The regimen should be simple to use and well-tolerated, with good compliance and high efficacy (>85%). (quality of evidence: 1; grade of recommendation: strong; level of consensus: 100%)

In addition to tolerability and compliance, key H pylori treatment considerations include its susceptibility and resistance to antimicrobials, both of which demonstrate temporal and geographical variability.

The degree of gastric acid suppression is one of the most important factors in determining the success of H pylori eradication. The dose, frequency, and potency of PPIs, as well as host genetics (hepatic cytochrome P450 2C19 polymorphism), can influence gastric pH. The most effective acid suppression regimen should be used to increase antibiotic bioavailability. Analyses of potassium-competitive acid blockers have shown that greater acid suppression can improve eradication success. A longer eradication therapy interval could also improve the eradication rate.

Statement 16: In the first-line setting for H pylori eradication, possible therapies include (a) triple therapy with a PPI, clarithromycin, and amoxicillin for 14 days; and (b) bismuth quadruple therapy with a PPI, tetracycline, metronidazole, and a bismuth salt for 10 to 14 days. (quality of evidence: 1/2; grade of recommendation: strong/conditional; level of consensus: 100%)

Triple therapy with a PPI, clarithromycin, and amoxicillin (Table) remains the first-line option in regions with clarithromycin resistance <15% and a local eradication rate of ≥85%. Patients allergic to amoxicillin should receive metronidazole. If clarithromycin resistance exceeds 15%, bismuth quadruple therapy is recommended as another first-line option (ie, a PPI, tetracycline, metronidazole, and a bismuth salt). According to a meta-analysis published in 2018, the prevalence of resistance to clarithromycin was 10% (95% confidence interval=5%-17%) in Hong Kong; the prevalence
of resistance to metronidazole was 53% (95% confidence interval=39%-66%). A more recent population-based study in Hong Kong showed that the overall failure rate of clarithromycin-based triple therapy was 10.1% during the period from 2003 to 2018. Compared with the 7-day regimen, a 14-day regimen of triple therapy is usually recommended because it produces better eradication rates.

Randomised trials have demonstrated eradication rates of >92% (intent-to-treat analysis) when bismuth quadruple therapy is used as empirical first-line treatment. Studies from Taiwan and Texas of the United States revealed that treatment intervals of 10 to 14 days led to eradication rates of >90%. However, the tolerability and availability of bismuth compounds could limit the widespread use of bismuth-based therapy.

**Statement 17: In the second-line setting for H pylori eradication (ie, after unsuccessful clarithromycin-based triple therapy), possible therapies include (a) bismuth quadruple therapy with a PPI, tetracycline, metronidazole, and a bismuth salt for 10 to 14 days; (b) high-dose PPI–amoxicillin dual therapy for 14 days; and (c) levofloxacin-containing triple therapy with a PPI and amoxicillin for 14 days. (quality of evidence: 1/2; grade of recommendation: conditional; level of consensus: 100%)**

Second-line treatment should not repeat the previous regimen. The reuse of antibiotics that were
previously unsuccessful (eg, clarithromycin and levofloxacin, both of which commonly cause post-exposure resistance) should be avoided. However, as amoxicillin and tetracycline have low rates of resistance, they can be reused. Metronidazole can also be reused if administered in combination with bismuth salt.57

If testing is feasible, the choice of therapy should be guided by antimicrobial susceptibility testing and administered with the optimal treatment interval.52 Bismuth quadruple therapy can be regarded as second-line treatment when antimicrobial susceptibility testing is unavailable.32 High-dose dual therapy (ie, high-dose PPI and amoxicillin) is emerging as a second-line treatment because of its favourable eradication rates.68,69 Levofloxacin-based triple therapy with amoxicillin and a PPI may be considered if bismuth-based therapy was used as first-line treatment.70-73 However, a recent report showed that the prevalence of levofloxacin resistance in Hong Kong was 17%.63

Quinolones and antibiotics in the tetracycline class are not currently licensed for use in young children, further limiting second-line treatment options. However, the inclusion of levofloxacin or tetracycline in triple therapy may be considered for adolescents.50

Statement 18: After unsuccessful second-line treatment, rescue therapies include (a) bismuth quadruple therapy with a PPI, tetracycline, metronidazole, and a bismuth salt for 10 to 14 days; (b) high-dose PPI–amoxicillin dual therapy for 14 days; and (c) rifabutin-containing therapy with a PPI and amoxicillin for 10 days. (quality of evidence: 2; grade of recommendation: conditional; level of consensus: 100%)

Similar to the approach involved in selection of second-line treatment, previously unused regimens may be regarded as rescue therapy. Regions with high fluoroquinolone resistance may consider a rifabutin-containing regimen (usually with a PPI and amoxicillin).32,46,57 Rifabutin use should be limited because of its potential for myelotoxicity; a 10-day regimen of rifabutin (300 mg/day) is usually recommended.74-76 Another concern regarding the use of rifabutin is the potential for acquired rifamycin resistance, particularly in regions where tuberculosis is endemic.

Statement 19: The use of probiotics as adjunctive therapy to reduce the side-effects associated with H pylori eradication therapy should be individualised. (quality of evidence: 1; grade of recommendation: qualified; level of consensus: 90%)

Probiotics (eg, Lactobacilli) may help to ameliorate treatment-related side-effects such as diarrhoea.32,46,57 Eradication rates may also be improved when probiotics are administered before and after H pylori treatment, for an interval of >2 weeks, or in combination with bismuth quadruple therapy.77

Statement 20: Antibiotic susceptibility testing can be considered after at least two empirical therapies with different antimicrobial agents have been unsuccessful. (quality of evidence: 1; grade of recommendation: conditional; level of consensus: 90%)

A recent meta-analysis showed that antimicrobial susceptibility–guided therapy was slightly more effective than empirical therapy.78 The available evidence suggests that an understanding of the antimicrobial susceptibility profile can guide antimicrobial selection and improve eradication, particularly in patients for whom multiple therapies have been unsuccessful.

Statement 21: There are insufficient data to provide solid recommendations concerning medical treatment for H pylori infection in children. The optimal age for eradication therapy in children also requires further investigation. (quality of evidence: 2/3; grade of recommendation: conditional; level of consensus: 100%)

The treatment of H pylori in children is not usually recommended. There are a few indications for which treatment should be carefully considered: incidental findings during endoscopy, findings of ulceration or erosion, refractory iron deficiency anaemia, and chronic idiopathic thrombocytopenic purpura.50

Statement 22: H pylori eradication may worsen gastroesophageal reflux disease in some patients. (quality of evidence: 3; grade of recommendation: not applicable; level of consensus: 90%)

In a meta-analysis, the pooled results of five cohort studies suggested that there is an increased risk of erosive gastroesophageal reflux disease in patients with peptic ulcer disease who are undergoing eradication therapy; however, this risk was not supported by the pooled results of seven RCTs in the same meta-analysis.79 In the past decade, meta-analyses also revealed that eradication therapy was not significantly associated with the development of gastroesophageal reflux disease.46,81 Generally, H pylori treatment does not have a clinically significant effect on acid production.

Statement 23: Patients may gain weight after H pylori eradication; therefore, lifestyle advice should be offered as needed. (quality of evidence: 2; grade of recommendation: qualified; level of consensus: 90%)

A meta-analysis showed that H pylori eradication increased body weight and body mass index, but it did not influence insulin resistance,
fasting blood glucose, or lipid parameters. The mechanisms that underlie weight gain after *H. pylori* eradication may be multifactorial, including increased appetite related to changes in ghrelin level, the resolution of dyspepsia and changes in gut microbiota. Weight monitoring is advisable after eradication therapy.

**Statement 24:** All patients should be tested for *H. pylori* after eradication therapy. (quality of evidence: not applicable; grade of recommendation: strong; level of consensus: 100%)

From a practical perspective, the confirmation of eradication therapy success is strongly recommended, particularly because persistent *H. pylori* infection can lead to complications. Considering the increasing prevalence of antibiotic resistance, there is an emerging clinical need to confirm *H. pylori* clearance after eradication.

The urea breath test, stool antigen test, and endoscopy-based assessments (eg, rapid urease test and histology) have comparatively high sensitivity and specificity for *H. pylori*; these approaches may be selected according to availability and patient circumstances. Non-endoscopic tests should be performed at least 4 weeks after eradication therapy and/or 2 weeks after PPI treatment.

Additional information regarding treatment for *H. pylori* in children is shown in the online supplementary Appendix.

**Conclusion**

After thorough review of the most recent evidence, the consensus panel highlighted the importance of appropriate diagnosis and treatment for patients with *H. pylori* infection to prevent complications. Our current recommendations may differ from other regions; in particular, standard triple therapy remains a first-line option because clarithromycin resistance is still relatively low in Hong Kong. Moreover, our recommendations may preclude unnecessary testing (particularly in asymptomatic children), facilitate rational use of antibiotics, and improve eradication rates and clinical outcomes.

**Author contributions**

Development of clinical questions: WK Leung, JCY Wu.

Retrieval of evidence: All authors.

Analysis or interpretation of evidence: All authors.

Discussion and finalisation of evidence and statements: All authors.

DRAFTING OF THE MANUSCRIPT: All authors.

Critical revision of the manuscript for important intellectual content: WK Leung, JCY Wu.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

**Conflicts of interest**

WK Leung has participated in advisory boards for Roche Diagnostics and Harbour BioMed. KS Cheung has received research grants from the Hong Kong SAR Government, consultant fees from the Xela Group, honoraria from Janssen Pharmaceuticals, meeting support from Takeda Pharmaceutical Company, and has participated in advisory boards for Janssen Pharmaceuticals and AstraZeneca. RSY Tang has received support from AstraZeneca for laboratory test kits.

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**References**


