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

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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 peerreviewed articles in English on the epidemiology, screening, diagnosis, and treatment of H pylori 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.

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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 Evidence² 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 infection, with a focus on Hong Kong and China. The level of agreement using a Likert scale (1: completely

agree; 2: agree with some reservations; 3: agree with major reservations; 4: disagree with reservations; 5: completely disagree). Statements were modified as necessary, and voting was repeated online in November 2021. Consensus was achieved if at least 75% of the panel members agreed with a statement (completely or with reservations). Statements regarding consensus recommendations for the screening, diagnosis, and management of *H pylori* infection in Hong Kong are detailed below.

Epidemiology and burden

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.³ 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%).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%.4 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 2017.5,6

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.⁷

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 2018.⁸ In 2020, a prospective cohort study in China showed that the annual rate of *H pylori* reinfection was 1.5% per person-year.⁹

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).¹⁰ Moreover, the rate was

香港幽門螺旋桿菌感染篩查、診斷和管理的共識 建議

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幽門螺旋桿菌感染會導致慢性胃炎和多種胃及十二指腸疾病,包括消 化性潰瘍和胃癌。儘管地區差異很大,幽門螺旋桿菌感染所用抗生素 的耐藥性全球盛行率正在增加,進而妨礙根除療法的成功。為了提高 香港醫學界對幽門螺旋桿菌的認識並改善其診斷和治療,我們的專家 共識小組提出了一套管理幽門螺旋桿菌指導方針。我們對2011年至 2021年間發表的文獻進行了全面綜述,重點關注來自香港或中國其他 地區的文章。我們使用牛津循證醫學中心的2011年證據級別和推薦評 估、發展和評估(GRADE)系統來評估證據,並通過網上投票和隨 後的面對面會議尋求共識,制定和完善24條共識建議。本報告包括有 關幽門螺旋桿菌流行病學、篩查和診斷以及治療。關鍵指導語句包括 建議針對高風險人群使用試驗和治療方法,以及確認對於香港的成人 及小童而言,三重療法(質子泵抑制劑、阿莫西林和克拉霉素)仍然 是有效的一線選擇。

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.¹¹

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.¹² The estimated global burden of gastric cancer attributable to *H pylori* is 89%.¹³ The odds ratio of gastric cancer onset among patients with *H pylori* infection ranges from 5.9 to 34.5.^{14,15} Usually, a high incidence of gastric cancer is associated with a high prevalence of *H pylori* infection.^{12,16}

A reduced risk of gastric cancer after *H pylori* eradication has been demonstrated in interventional trials, including RCTs.¹⁷⁻²³ 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.²⁴ 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.²⁵ A metaanalysis of 24 studies also showed that the benefit of *H pylori* eradication for gastric cancer protection 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.²⁶ 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 100000 person-years).²⁶ The 2020 age-standardised incidence of gastric cancer in Hong Kong was 8.7 and 5.3 per 100000 person-years in male and female, respectively.³¹ 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.^{32,33} Therefore, it is prudent to test for and treat *H pylori* in patients with a family history or precancerous 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 non-steroidal aspirin, antiinflammatory 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.⁴²⁻⁴⁶ 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.⁴⁷⁻⁴⁹

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: 90%)

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*.^{50,51}

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%.^{52,53} The monoclonal stool antigen test has a sensitivity of 90% to 98% and a specificity of 90% to 97%.^{52,54}

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.³²

Statement 13: Serological testing is not recommended for initial diagnosis and post-eradication followup 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 diagnosis³²; it is not recommended for post-eradication follow-up because it can detect antibodies from past infections.⁵⁵ 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.³²

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.³² 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.^{32,56} 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.^{32,40,57,58}

The degree of gastric acid suppression is one of the most important factors in determining the success of *H pylori* eradication.^{2,59} 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.⁶⁰ Analyses of potassiumcompetitive acid blockers have shown that greater acid suppression can improve eradication success.⁶¹ 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 \geq 85%.^{32,57} Patients allergic to amoxicillin should receive metronidazole. If clarithromycin resistance exceeds 15%, bismuth quadruple therapy is recommended as another firstline 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

Therapy	Regimen	Recommendation
Adults		
Standard triple	 PPI standard dose* bid Amoxicillin 1000 mg or metronidazole 500 mg bid Clarithromycin 500 mg bid For 14 days 	 First-line regimen Suitable for regions with <15% clarithromycin resistance
Bismuth quadruple	 PPI standard dose* bid Bismuth qid Metronidazole 400 mg qid or 500 mg tid–qid Tetracycline 500 mg qid For 10-14 days 	 First-line regimen for high-resistance regions or for patients allergic to penicillin Suitable as second-line treatment and rescue therapy
High-dose dual	 PPI high dose, tid or qd Amoxicillin >2 g/day (eg, 750 mg qd) For 14 days 	Second-line regimenSuitable as rescue therapy
Levofloxacin triple	 PPI standard dose* bid Amoxicillin 1000 mg bid Levofloxacin 500 mg qd or 250 mg bid For 14 days 	Second-line regimen
Rifabutin triple	 PPI bid Amoxicillin 1000 mg bid Rifabutin 150 mg bid or 300 mg qd For 10 days 	 Suitable as rescue therapy May induce myelotoxicity and a <14-day regimen may be preferred
Children [†]		
Triple	 PPI Amoxicillin Clarithromycin or metronidazole +/- Probiotic For 14 days 	 First-line regimen if susceptible to clarithromycin and metronidazole Clarithromycin preferred; metronidazole to be used if there is drug resistance to clarithromycin Triple with metronidazole is a second-line option
Triple with high- dose amoxicillin and metronidazole	 PPI Amoxicillin Metronidazole +/- Probiotic For 14 days 	First-line regimen if susceptibilities are unknown
Bismuth quadruple	 PPI Amoxicillin Clarithromycin or metronidazole Bismuth subsalicylate +/- Probiotic For 10-14 days 	First-line regimen if susceptibilities are unknown

TABLE. Treatment options for *Helicobacter pylori* eradication in adults and children

Abbreviations: bid = twice daily; PPI = proton pump inhibitor; qd = once daily; qid = 4 times daily; tid = 3 times daily

* Omeprazole 20 mg, esomeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, or rabeprazole 20 mg

[†] Refer to the Table in the online supplementary Appendix for dosage

of resistance to metronidazole was 53% (95% confidence interval=39%-66%).⁶² 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 2018.⁶³ Compared with the 7-day regimen, a 14-day regimen of triple therapy is usually recommended because it produces better eradication rates.^{57,64}

Randomised trials have demonstrated eradication rates of >92% (intent-to-treat analysis) when bismuth quadruple therapy is used as empirical first-line treatment.^{65,66} Studies from Taiwan and Texas of the United States revealed that treatment intervals of 10 to 14 days led to eradication rates of >90%.^{65,67} However, the tolerability and availability of

bismuth compounds could limit the widespread use of bismuth-based therapy.⁶⁵

Statement 17: In the second-line setting for H pylori eradication (ie, after unsuccessful clarithromycinbased 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.³² 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).^{32,40,57} 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.^{32,40,57} Eradication rates may also be

improved when probiotics are administered before and after *H pylori* treatment, for an interval of >2weeks, 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, metaanalyses also revealed that eradication therapy was not significantly associated with the development of gastroesophageal reflux disease.^{80,81} 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.⁸² 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.⁸³⁻⁸⁶ 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.^{32,40} 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.^{32,40}

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

- Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. Gastroenterology 2018;155:1372-82. e17.
- 2. Malfertheiner P, Link A, Selgrad M. *Helicobacter pylori:* perspectives and time trends. Nat Rev Gastroenterol Hepatol 2014;11:628-38.
- 3. Hooi JK, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and metaanalysis. Gastroenterology 2017;153:420-9.
- Tam YH, Yeung CK, Lee KH, et al. A population-based study of *Helicobacter pylori* infection in Chinese children resident in Hong Kong: prevalence and potential risk factors. Helicobacter 2008;13:219-24.
- 5. Wong KK, Chung PH, Lan LC, Lin SC, Tam PK. Trends in the prevalence of *Helicobacter pylori* in symptomatic children in the era of eradication. J Pediatr Surg 2005;40:1844-7.
- Tang MY, Chung PH, Chan HY, Tam PK, Wong KK. Recent trends in the prevalence of *Helicobacter pylori* in symptomatic children: a 12-year retrospective study in a tertiary centre. J Pediatr Surg 2019;54:255-7.
- Hu Y, Wan JH, Li XY, Zhu Y, Graham DY, Lu NH. Systematic review with meta-analysis: the global recurrence rate of *Helicobacter pylori*. Aliment Pharmacol Ther 2017;46:773-9.
- Chiang TH, Chang WJ, Chen SL, et al. Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut 2021;70:243-50.
- Xie Y, Song C, Cheng H, et al. Long-term follow-up of *Helicobacter pylori* reinfection and its risk factors after initial eradication: a large-scale multicentre, prospective open cohort, observational study. Emerg Microbes Infect 2020;9:548-57.
- 10. Zhang Y, Dong Q, Tian L, et al. Risk factors for recurrence of *Helicobacter pylori* infection after successful eradication in Chinese children: a prospective, nested case-control study. Helicobacter 2020;25:e12749.
- 11. Sivapalasingam S, Rajasingham A, Macy JT, et al. Recurrence of *Helicobacter pylori* infection in Bolivian children and adults after a population-based "screen and treat" strategy. Helicobacter 2014;19:343-8.

- 12. Fock KM, Ang TL. Epidemiology of *Helicobacter pylori* infection and gastric cancer in Asia. J Gastroenterol Hepatol 2010;25:479-86.
- Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to *Helicobacter pylori*. Int J Cancer 2015;136:487-90.
- Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter* pylori infection and the development of gastric cancer. N Engl J Med 2001;345:784-9.
- 15. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001;49:347-53.
- Sipponen P, Kimura K. Intestinal metaplasia, atrophic gastritis and stomach cancer: trends over time. Eur J Gastroenterol Hepatol 1994;6 Suppl 1:S79-83.
- Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187-94.
- Zhou L, Lin S, Ding S, et al. Relationship of *Helicobacter pylori* eradication with gastric cancer and gastric mucosal histological changes: a 10-year follow-up study. Chin Med J (Engl) 2014;127:1454-8.
- 19. Leung WK, Lin SR, Ching JY, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut 2004;53:1244-9.
- 20. Saito D, Boku N, Fujioka T, et al. Impact of *H. pylori* eradication on gastric cancer prevention: endoscopic results of the Japanese Intervention Trial (JITHP-Study). A randomized multi-center trial. Gastroenterology 2005;128(Supp 2):A4.Abstract 23.
- 21. Li WQ, Zhang JY, Ma JL, et al. Effects of *Helicobacter pylori* treatment and vitamin and garlic supplementation on gastric cancer incidence and mortality: follow-up of a randomized intervention trial. BMJ 2019;366:15016.
- 22. Wong BC, Zhang L, Ma JL, et al. Effects of selective COX-2 inhibitor and *Helicobacter pylori* eradication on precancerous gastric lesions. Gut 2012;61:812-8.
- Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and *Helicobacter pylori* treatment. N Engl J Med 2020;382:427-36.
- 24. Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut 2020;69:2113-21.
- Leung WK, Wong IO, Cheung KS, et al. Effects of *Helicobacter pylori* treatment on incidence of gastric cancer in older individuals. Gastroenterology 2018;155:67-75.
- 26. Lee YC, Chiang TH, Chou CK, et al. Association between *Helicobacter pylori* eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology 2016;150:1113-24.e5.
- 27. Lanas A, Chan FK. Peptic ulcer disease. Lancet 2017;390:613-24.
- Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients. Cochrane Database Syst Rev 2006;(2):CD003840.
- 29. Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;2:CD002096.

- 30. Zullo A, Hassan C, Andriani A, et al. Eradication therapy for *Helicobacter pylori* in patients with gastric MALT lymphoma: a pooled data analysis. Am J Gastroenterol 2009;104:1932-8.
- 31. Hong Kong Cancer Registry, Hospital Authority, Hong Kong SAR Government. 10 most common cancers in Hong Kong in 2020. Available from: https://www3.ha.org.hk/ cancereg/default.asp. Accessed 19 Jun 2023.
- Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
- Du Y, Zhu H, Liu J, et al. Consensus on eradication of *Helicobacter pylori* and prevention and control of gastric cancer in China (2019, Shanghai). J Gastroenterol Hepatol 2020;35:624-9.
- Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 2013;145:105-12.e15.
- 35. Lanas Á, Carrera-Lasfuentes P, Arguedas Y, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. Clin Gastroenterol Hepatol 2015;13:906-12.e2.
- Chan FK, Ching JY, Suen BY, Tse YK, Wu JC, Sung JJ. Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. Gastroenterology 2013;144:528-35.
- 37. Ng JC, Yeomans ND. *Helicobacter pylori* infection and the risk of upper gastrointestinal bleeding in low dose aspirin users: systematic review and meta-analysis. Med J Aust 2018;209:306-11.
- 38. Venerito M, Schneider C, Costanzo R, Breja R, Röhl FW, Malfertheiner P. Contribution of *Helicobacter pylori* infection to the risk of peptic ulcer bleeding in patients on nonsteroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants, corticosteroids and selective serotonin reuptake inhibitors. Aliment Pharmacol Ther 2018;47:1464-71.
- Sostres C, Carrera-Lasfuentes P, Benito R, et al. Peptic ulcer bleeding risk. The role of *Helicobacter pylori* infection in NSAID/low-dose aspirin users. Am J Gastroenterol 2015;110:684-9.
- 40. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-39.
- 41. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut 2015;64:1353-67.
- 42. Queiroz DM, Harris PR, Sanderson IR, et al. Iron status and *Helicobacter pylori* infection in symptomatic children: an international multi-centered study. PLoS One 2013;8:e68833.
- 43. Yuan W, Li Y, Yang K, et al. Iron deficiency anemia in *Helicobacter pylori* infection: meta-analysis of randomized controlled trials. Scand J Gastroenterol 2010;45:665-76.
- 44. Qu XH, Huang XL, Xiong P, et al. Does *Helicobacter pylori* infection play a role in iron deficiency anemia? A metaanalysis. World J Gastroenterol 2010;16:886-96.
- 45. Xia W, Zhang X, Wang J, Sun C, Wu L. Survey of anaemia and *Helicobacter pylori* infection in adolescent girls in Suihua, China and enhancement of iron intervention

effects by *H pylori* eradication. Br J Nutr 2012;108:357-62.

- 46. Hudak L, Jaraisy A, Haj S, Muhsen K. An updated systematic review and meta-analysis on the association between *Helicobacter pylori* infection and iron deficiency anemia. Helicobacter 2017;22:e12330.
- 47. Stasi R, Sarpatwari A, Segal JB, et al. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. Blood 2009;113:1231-40.
- 48. Arnold DM, Bernotas A, Nazi I, et al. Platelet count response to *H pylori* treatment in patients with immune thrombocytopenic purpura with and without *H pylori* infection: a systematic review. Haematologica 2009;94:850-6.
- 49. Ikuse T, Toda M, Kashiwagi K, et al. Efficacy of *Helicobacter pylori* eradication therapy on platelet recovery in pediatric immune thrombocytopenic purpura—case series and a systematic review. Microorganisms 2020;8:1457.
- 50. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/ NASPGHAN Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr 2017;64:991-1003.
- 51. Kato S, Shimizu T, Toyoda S, et al. The updated JSPGHAN guidelines for the management of *Helicobacter pylori* infection in childhood. Pediatr Int 2020;62:1315-31.
- Calvet X, Sánchez-Delgado J, Montserrat A, et al. Accuracy of diagnostic tests for *Helicobacter pylori*: a reappraisal. Clin Infect Dis 2009;48:1385-91.
- 53. Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of *Helicobacter pylori* infection—a critical review. Aliment Pharmacol Ther 2004;20:1001-17.
- 54. Makristathis A, Barousch W, Pasching E, et al. Two enzyme immunoassays and PCR for detection of *Helicobacter pylori* in stool specimens from pediatric patients before and after eradication therapy. J Clin Microbiol 2000;38:3710-4.
- 55. Feldman RA, Deeks JJ, Evans SJ. Multi-laboratory comparison of eight commercially available *Helicobacter pylori* serology kits. *Helicobacter pylori* Serology Study Group. Eur J Clin Microbiol Infect Dis 1995;14:428-33.
- 56. Dechant FX, Dechant R, Kandulski A, et al. Accuracy of different rapid urease tests in comparison with histopathology in patients with endoscopic signs of gastritis. Digestion 2020;101:184-90.
- 57. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto Consensus for the Treatment of *Helicobacter pylori* infection in adults. Gastroenterology 2016;151:51-69.e14.
- 58. Graham DY, Moss SF. Antimicrobial susceptibility testing for *Helicobacter pylori* is now widely available: when, how, why. Am J Gastroenterol 2022;117:524-8.
- Shah SC, Iyer PG, Moss SF. AGA Clinical Practice Update on the management of refractory *Helicobacter pylori* infection: expert review. Gastroenterology 2021;160:1831-41.
- 60. Graham DY, Tansel A. Interchangeable use of proton pump inhibitors based on relative potency. Clin Gastroenterol Hepatol 2018;16:800-8.e7.
- 61. Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of *H pylori* infection in patients treated with proton pump inhibitor–based triple therapy regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162.
- 62. Kuo YT, Liou JM, El-Omar EM, et al. Primary antibiotic resistance in *Helicobacter pylori* in the Asia-Pacific region: a

systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:707-15.

- 63. Guo CG, Jiang F, Cheung KS, Li B, Ooi PH, Leung WK. Timing of prior exposure to antibiotics and failure of *Helicobacter pylori* eradication: a population-based study. J Antimicrob Chemother 2022;77:517-23.
- 64. Yuan Y, Ford AC, Khan KJ, et al. Optimum duration of regimens for *Helicobacter pylori* eradication. Cochrane Database Syst Rev 2013;(12):CD008337.
- 65. Liu KS, Hung IF, Seto WK, et al. Ten day sequential versus 10 day modified bismuth quadruple therapy as empirical firstline and secondline treatment for *Helicobacter pylori* in Chinese patients: an open label, randomised, crossover trial. Gut 2014;63:1410-5.
- 66. Hung IF, Chan P, Leung S, et al. Clarithromycinamoxycillin-containing triple therapy: a valid empirical first-line treatment for *Helicobacter pylori* eradication in Hong Kong? Helicobacter 2009;14:505-11.
- 67. Salazar CO, Cardenas VM, Reddy RK, Dominguez DC, Snyder LK, Graham DY. Greater than 95% success with 14-day bismuth quadruple anti–*Helicobacter pylori* therapy: a pilot study in US Hispanics. Helicobacter 2012;17:382-90.
- 68. Yang JC, Lin CJ, Wang HL, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. Clin Gastroenterol Hepatol 2015;13:895-905.e5.
- 69. Gao CP, Zhang D, Zhang T, et al. PPI-amoxicillin dual therapy for *Helicobacter pylori* infection: an update based on a systematic review and meta-analysis. Helicobacter 2020;25:e12692.
- 70. Xin Y, Manson J, Govan L, et al. Pharmacological regimens for eradication of *Helicobacter pylori*: an overview of systematic reviews and network meta-analysis. BMC Gastroenterol 2016;16:80.
- Marin AC, McNicholl AG, Gisbert JP. A review of rescue regimens after clarithromycin-containing triple therapy failure (for *Helicobacter pylori* eradication). Expert Opin Pharmacother 2013;14:843-61.
- 72. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. Aliment Pharmacol Ther 2006;23:35-44.
- 73. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacinbased triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a metaanalysis. Am J Gastroenterol 2006;101:488-96.
- 74. Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory *Helicobacter pylori* infection. Aliment Pharmacol Ther 2012;35:209-21.
- 75. Gisbert JP, Castro-Fernandez M, Perez-Aisa A, et al. Fourth-line rescue therapy with rifabutin in patients with three *Helicobacter pylori* eradication failures. Aliment Pharmacol Ther 2012;35:941-7.
- 76. Van der Poorten D, Katelaris PH. The effectiveness of rifabutin triple therapy for patients with difficult-toeradicate *Helicobacter pylori* in clinical practice. Aliment Pharmacol Ther 2007;26:1537-42.
- 77. Shi X, Zhang J, Mo L, Shi J, Qin M, Huang X. Efficacy and safety of probiotics in eradicating *Helicobacter pylori*: a network meta-analysis. Medicine (Baltimore) 2019;98:e15180.
- resistance in Helicobacter pylori in the Asia-Pacific region: a 78. Gingold-Belfer R, Niv Y, Schmilovitz-Weiss H, Levi Z,

Boltin D. Susceptibility-guided versus empirical treatment for *Helicobacter pylori* infection: a systematic review and meta-analysis. J Gastroenterol Hepatol 2021;36:2649-58.

- 79. Yaghoobi M, Farrokhyar F, Yuan Y, Hunt RH. Is there an increased risk of GERD after *Helicobacter pylori* eradication? A meta-analysis. Am J Gastroenterol 2010;105:1006-14.
- Saad AM, Choudhary A, Bechtold ML. Effect of *Helicobacter pylori* treatment on gastroesophageal reflux disease (GERD): meta-analysis of randomized controlled trials. Scand J Gastroenterol 2012;47:129-35.
- 81. Tan J, Wang Y, Sun X, Cui W, Ge J, Lin L. The effect of *Helicobacter pylori* eradication therapy on the development of gastroesophageal reflux disease. Am J Med Sci 2015;349:364-71.
- 82. Upala S, Sanguankeo A, Saleem SA, Jaruvongvanich V. Effects of *Helicobacter pylori* eradication on insulin resistance and metabolic parameters: a systematic

review and meta-analysis. Eur J Gastroenterol Hepatol 2017;29:153-9.

- Nwokolo CU, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of *Helicobacter pylori*. Gut 2003;52:637-40.
- 84. Furuta T, Shirai N, Xiao F, Takashima M, Hanai H. Effect of *Helicobacter pylori* infection and its eradication on nutrition. Aliment Pharmacol Ther 2002;16:799-806.
- 85. Liou JM, Chen CC, Chang CM, et al. Long-term changes of gut microbiota, antibiotic resistance, and metabolic parameters after *Helicobacter pylori* eradication: a multicentre, open-label, randomised trial. Lancet Infect Dis 2019;19:1109-20.
- 86. Lane JA, Murray LJ, Harvey IM, Donovan JL, Nair P, Harvey RF. Randomised clinical trial: *Helicobacter pylori* eradication is associated with a significantly increased body mass index in a placebo-controlled study. Aliment Pharmacol Ther 2011;33:922-9.