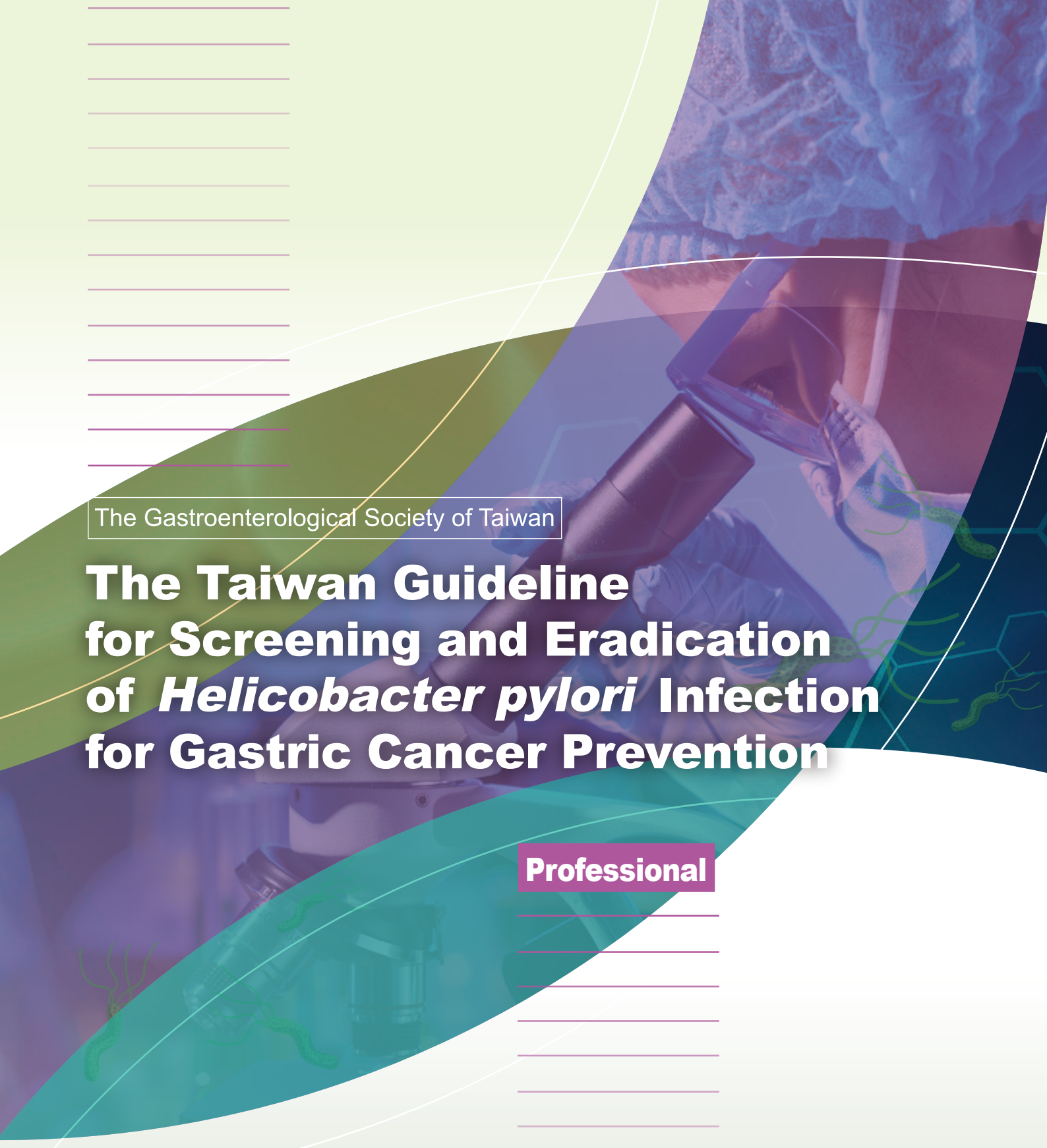

The Gastroenterological Society of Taiwan

The Taiwan Guideline for Screening and Eradication of *Helicobacter pylori* Infection for Gastric Cancer Prevention

Professional

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Health Promotion Administration, Ministry of Health and Welfare, Taiwan

Preface

Cancer is the most common cause of death in Taiwan, and gastric cancer ranks among the top ten causes of cancer deaths in Taiwan. About 2,300 people die of gastric cancer each year. Data over the years show that the ranking and number of deaths from gastric cancer have declined year by year, but it is still an important health threat to people in Taiwan. *H. pylori* infection is an important risk factor for the development of gastric cancer. Eradication of *H. pylori* is an effective method to prevent gastric cancer. Since 2017, the National Health Administration has used carbon-13 urea breath test to detect the *H. pylori* infection in the moderate and high risk areas of gastric cancer, and provided eradication therapy for those with positive test. In order to allow medical units and professional medical personnel at all levels to follow the screening and treatment methods for gastric *H. pylori*, the Health Promotion Administration has commissioned the Gastroenterological Society of Taiwan to develop this guideline based on international and local evidence, and has gone through 4 expert meetings to develop this guideline. I would like to express my special thanks to Ming-Shiang Wu, Chairman of the Gastroenterological Society of Taiwan, Dr. Jyh-Ming Liou, Dr. Yi-Chia Lee, and Dr. Hsiu-Chi Cheng, and many other doctors of the expert meetings. They jointly developed this guideline which will provide the basic of our National screening program of *H. pylori* for gastric cancer prevention in Taiwan. It is hoped that all medical staff can make good use of it and work together to fight against cancer, to reduce the incidence and mortality of gastric cancer, and to improve the quality of life of people in Taiwan.

Chao-Chun Wu, Director-General, the Health Promotion Administration

Preface

Gastric cancer is the fifth most common cancer in the world. In 2018, there were more than 1 million new cases of gastric cancer worldwide. Gastric cancer ranked eighth among the top ten causes of cancer deaths in Taiwan. Although the age-standardized mortality rate has declined, the number of new cases of gastric cancer has not decreased in the past 10 years due to increase of the elderly population in Taiwan. The number of cancer cases is expected to increase significantly if preventive interventions are not taken. Not only will resources be spent on the treatment of advanced cancer patients, but also the prognosis of patients will be poor. How to reduce the incidence of gastric cancer by elimination of the causal factor of gastric cancer is an important topic in the prevention and treatment of gastric cancer.

H. pylori has been proven to cause chronic gastritis. Long-term inflammation will lead to the destruction of gastric glands and gastric mucosal atrophy, the decrease of gastric acidity and the change of the bacterial phase in the stomach, resulting in gastric mucosal intestinal metaplasia and eventually gastric cancer. The World Health Organization has classified *H. pylori* as a first-level carcinogen in 1994. Therefore, if the screening and eradication of *H. pylori* can be carried out, it is expected that the incidence of gastric cancer can be greatly reduced and the effect of primary prevention can be achieved. Taiwan, Japan, China, and South Korea are countries with a high incidence of gastric cancer. They have all actively evaluated pylori screening and sterilization therapy to prevent gastric cancer, but this policy requires guidelines on implementation.

In view of this, the Heath Promotion Administration of the Ministry of Health and Welfare entrusted the Taiwan Gastroenterology Medical Association to hold an expert group meeting to jointly formulate Taiwan's guidelines on screening and eradication of *H. pylori*. The guidelines for endoscopy screening and tracking are expected to allow colleagues in the relevant medical practitioners in Taiwan to have a clear and followable standard, and to allow the public to better understand the prevention methods of gastric cancer. The most valuable thing about this guideline is that it not only comprehensively collects the latest relevant international literature and guidelines, but also includes many local evidences accumulated in Taiwan for gastric cancer prevention and *H. pylori* treatment over the years, making this guideline more practical.

I am very grateful to the experts from the Gastroenterological Society of Taiwan and the Internal Medicine Association for their participation, and also to the public health and clinical experts for their strong assistance and encouragement to the gastric cancer prevention plan over the past years, as well as colleagues for their assistance in the process of compiling the guidelines. I would like to express my highest thanks for collecting and arranging relevant literature. If there are any omissions or inadequacies in the literature review, I would like to ask all colleagues for providing any corrections or comments.

Ming-Shiang Wu, President, the Gastroenterological Society of Taiwan

Contents

Summary of guidelines

No.	Clinical Question	Statement	Evidence level	Strength of recommendation
1	*H. pylori* infection and gastric cancer	*H. pylori* infection is the major etiological factor of gastric cancer, with the attributable fraction of about 90%. Screening and eradication of *H. pylori* is an important strategy for gastric cancer prevention.	moderate	strong
2	*H. pylori* infection and gastroduodenal disease	All *H. pylori* infection will result in chronic gastritis; some of them will lead to peptic ulcer, precancerous conditions (atrophic gastritis and intestinal metaplasia), or gastric cancer. Eradication therapy can prevent the recurrence of peptic ulcer disease and reduce the severity of gastritis and precancerous conditions.	moderate	strong
3	How is *H. pylori* infection transmitted?	The most important route of *H. pylori* infection is through oral ingestion. Person-to-person transmission within families is an important source of infection.	low	recommended
4	Who are at high risk of developing gastric cancer?	Screening of *H. pylori* is recommended in those at higher risk of gastric cancer, such as those with a family history of gastric cancer in their first-degree relatives, who are aged 50 years or older, or those living in regions with a high incidence of gastric cancer.	moderate	strong
5	Does eradication of *H. pylori* reduce the risk of gastric cancer?	Eradication of *H. pylori* can reduce the risk of gastric cancer so this strategy is recommended for all infected subjects, except for those with severe comorbidities.	moderate	recommended
6	Who should we screen *H. pylori*?	Screening of *H. pylori* infection for gastric cancer prevention is recommended for subjects at higher risk of gastric cancer.	high	strong
7	Is eradication of *H. pylori* cost-effective for gastric cancer prevention?	Eradication of *H. pylori* for gastric cancer prevention is cost-effective in regions with intermediate or high incidence of gastric cancer.	moderate	recommended

No.	Clinical Question	Statement	Evidence level	Strength of recommendation
8	How is the accuracy of the ^{13}C-urea breath test?	The sensitivity and specificity of the ^{13}C-urea breath test are both higher than 95% for the diagnosis of *H. pylori* infection.	high	strong
9	How accurate is the *H. pylori* stool antigen test?	The *H. pylori* stool antigen test can accurately detect the presence of *H. pylori* infection and can be used to confirm the treatment response after eradication therapy.	moderate	recommended
10	How accurate is the *H. pylori* serology test?	The serology test can detect previous and current *H. pylori* infection. It can be used in epidemiological studies but is not recommended to guide the decision for eradication therapy or to confirm the treatment response.	moderate	recommended
11	Screening strategy for subjects at intermediate or high risk of gastric cancer in community	Screening and eradication of *H. pylori* for subjects at intermediate or high risk of gastric cancer can be integrated or included in the routine screening programs to optimize the national resources for health care.	moderate	strong
12	What is the recommended screening strategy for high risk subjects in the hospitals?	The ^{13}C-urea breath test (^{13}C-UBT), stool antigen test, or the serology test can be used for screening of *H. pylori* infection for subjects at moderate or high risk of gastric cancer in the hospital setting. However, the positive result of a serology test should be confirmed by tests that can detect active infection, in order to guide the decision for antibiotic treatment.	low	recommended
13	How to improve the screening efficiency in population? (family unit)	Family-based screening and eradication of *H. pylori* may detect higher proportion of infected subjects, increase the compliance to therapy, and reduce the risk of reinfection after eradication therapy.	moderate	weak
14	Consideration of *H. pylori* infection and reinfection rate	*H. pylori* is transmitted through the per-oral route. Improvement of sanitation, hygiene, dietary habits, and lifestyles can reduce the risk of *H. pylori* infection.	low	weak

No.	Clinical Question	Statement	Evidence level	Strength of recommendation
15	Which regimens are recommended for the first-line therapy in subjects with *H. pylori* infection?	The quadruple therapy, including the bismuth quadruple therapy for 10-14 days or the non-bismuth quadruple therapy for 14 days, is recommended as the first-line therapy. The triple therapy for 14 days is acceptable as an alternative in regions with the lower clarithromycin resistance.	moderate	strong
16	What is the first line treatment of *H. pylori* infection in penicillin allergic individuals?	The bismuth quadruple therapy for 10-14 days is suggested as the first-line therapy for patients who report penicillin allergy. Antibiotic susceptibility testing guided therapy can be an alternative choice.	low	recommended
17	Is confirmation test needed after *H. pylori* eradication?	Confirmation of treatment response is suggested after eradication therapy for *H. pylori* infection.	low	strong
18-1	Which regimens are recommended for the second-line therapy in subjects with *H. pylori* infection?	The bismuth quadruple therapy, levofloxacin based triple therapy, or levofloxacin based quadruple therapy can be used as the second-line treatment for *H. pylori* infection.	moderate	strong
18-2	What is the treatment suggestion after first line *H. pylori* treatment failure in penicillin allergic individuals?	The susceptibility testing guided therapy or the empirical levofloxacin-based therapy is suggested for patients with penicillin allergy after failure from bismuth quadruple therapy in the first-line treatment.	low	recommended
19	How to treat patients who fail after two or more eradication therapies?	The susceptibility testing guided therapy is recommended after two or more treatment failures. Bismuth or non-bismuth quadruple therapies containing the high dose of proton pump inhibitors for 14 days are recommended.	moderate	strong

No.	Clinical Question	Statement	Evidence level	Strength of recommendation
20	Does *H. pylori* eradication increase the risk of long-term antibiotic resistance of gut microbiota?	The short-term increase of antibiotic resistance of the gut microbiota may be restored months after eradication therapies.	low	recommended
21	How is the accuracy of methods for *H. pylori* detection which requiring gastric biopsies obtained during an endoscopy?	Accuracies of the rapid urease test, histology, and the culture are 90% or higher but may be affected by the site and number of endoscopic sampling. The accuracy of the rapid urease test is reduced by the recent use of antibiotics, bismuth, and proton pump inhibitors. The accuracy of histology is associated with the inter-observer variations. The successful rate of culture is affected by the endoscopic sampling and the laboratory quality.	moderate	strong
22	For those with *H. pylori* screening positive, who need additional endoscopy?	Endoscopic examinations are indicated for those with the first degree relatives of gastric cancer, abnormal results of pepsinogen testing, and those with alarm symptoms, in order to exclude the presence of gastric cancer.	high	strong
23	Who needs surveillance endoscopy after successful *H. pylori* eradication?	After *H. pylori* eradication, endoscopic surveillance is indicated for patients with advanced precancerous conditions, such as the operative link for gastritis assessment (OLGA) and/or operative link on gastric intestinal metaplasia assessment (OLGIM) stages III-IV on histology, severe or open-type gastric atrophy by endoscopy, abnormal results of pepsinogen testing by serology, and for those with dysplasia or gastric cancer following surgical or endoscopic resection.	low	recommended

Background

Gastric cancer remains the fifth most common cancer in the world. In 2018, there were more than 1 million new cases of gastric cancer worldwide, and more than 70% of the new cases were reported in Asia. Gastric cancer remains the third most common malignancy in the world in terms of mortality[1]. Gastric cancer ranks eighth among the top ten causes of cancer death in Taiwan. Although the age-standardized mortality rate has declined, new cases of gastric cancer in Taiwan have not decreased in the past decade due to the increase in the elderly population in Taiwan, and they have remained at an annual 3,500 people, so gastric cancer is still an important disease globally and in Taiwan[2]. With the aging population structure in Taiwan, the number of cancer cases is expected to increase significantly if preventive interventions are not made for carcinogenic factors. Not only will resources be spent on the treatment of advanced cancer patients, but also the prognosis of patients will be poor. Our primary goal is to reduce the incidence of gastric cancer through removal of the casual factor in the population.

Researches in the past 20 years have shown that *Helicobacter pylori (H. pylori)* can cause chronic gastritis. Long-term inflammation will lead to the destruction of gastric glands, gastric mucosal atrophy, gastric acid decline and changes in the gastric microbiota in the stomach, resulting in gastric intestinal metaplasia, and finally leads to gastric cancer[3]. It is estimated that more than 50% of the global population is infected with *H. pylori*, and the prevalence in undeveloped countries is higher than that in developed countries. The infected population in the Asia-Pacific region accounts for more than 60% of the global infected population[1]. In the 1990s, the prevalence of *H. pylori* among adults in Taiwan was about 55% [4]. With the improvement of economic conditions and public health environment, the prevalence of pylori among adults over 20 years old in Taiwan is now 30%, and the prevalence of children and adolescents is about 10% [5]. Using these results and data on Taiwan′ s population composition, the age-standardized prevalence of *H. pylori* among adults over the age of 20 in Taiwan is 32%, and it is estimated that a total of 5.79 million adults in the country are infected with *H. pylori*.

The risk of gastric adenocarcinoma in people with *H. pylori* infection is 6-10 times higher than in people without infection, based on estimates from the results of the cohort study[5]. Animal studies also confirmed that 37% of Mongolian gerbils developed gastric adenocarcinoma one year after infection with *H. pylori* [6]. Animal studies showed that early eradication of *H. pylori* can reduce the risk of gastric cancer in *H. pylori* infected hypergastrinemic mice[7]. Therefore, the World Health Organization has listed *H. pylori*

as a class I carcinogen in 1994. According to epidemiological estimates, 90% of gastric cancers can be attributed to *H. pylori*. Therefore, screening and eradication of *H. pylori* can significantly reduce the incidence of gastric cancer and achieve the effect of primary prevention[1]. Taiwan, Japan, China and South Korea are countries with a high incidence of gastric cancer. Screening and eradication of *H. pylori* can reduce the risk of gastric cancer. In addition to *H. pylori* screening, treatment and endoscopic surveillance are also important issues to be addressed. Therefore, we aimed to provide the national guidelines for screening and eradication of *H. pylori* and surveillance endoscopy for gastric cancer prevention based on current evidence.

Methods

We organized a working group for screening guidelines for *H. pylori*, and invited 3 experts to serve as group leaders to promote the formulation of topics, literature review, meta-analysis, interpretation of results, holding group meetings, and drafting the first draft of treatment guidelines for each group. In addition, a total of 19 experts, scholars, and practitioners in academic, clinical and other related professional fields in the field of *H. pylori* and gastric cancer prevention and treatment were invited to participate in the consensus cohesion and promotion of this guideline. The topics to be discussed were put forward in the form of PICO (P: patient; I: intervention; C: comparison; O: outcome), and the personnel in charge of each topic formulated the inclusion and exclusion criteria, search keywords, methods and results evaluation basis. After completing the systematic literature review and analysis, the person in charge of each topic wrote the first draft of the guidelines based on the results of the systematic literature review and integrated analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used for grading the level of recommendations and evidence[8].

Recommendation levels were classified as strongly recommended, recommended, weakly recommended, weakly against, or strongly against. We determined the strength of the recommendation according to the results of the experts′ vote on the strength of the agreement. We held a total of four meetings, and all the members of the expert group discussed and revised the content of the guideline according to the Delphi process. The Red Cap system was adopted for the voting. We asked scholars and experts to indicate whether they agree or not with the provisional guideline, and expressed their reasons for disagreement with the level of evidence and with each statement. Guidelines with at least 80% agreement among experts are defined as guidelines with consensus. Guidelines for which no consensus has been reached were discussed further, revised and voted on again. If the statement failed to pass three rounds of voting, the statement was defined as guidelines that have not reached consensus and was discarded. We reached consensus in a total of 23 statements after rounds of voting.

Results

1

Clinical question ***H. pylori* infection and gastric cancer**

Statement *H. pylori* infection is the major etiological factor of gastric cancer, with the attributable fraction of about 90%. Screening and eradication of *H. pylori* is an important strategy for gastric cancer prevention.

Evidence level moderate

Grade of recommendation strong

Comments:

The World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) expert consensus demonstrated that there is sufficient epidemiological and histological evidence to classify *H. pylori* as a carcinogen which causes gastric cancer[9]. One meta-analysis including 12 case-control studies with a total of 1,228 gastric cancer patients showed that *H. pylori* infection was associated with increased risk of the non-cardia gastric cancer (NCGC). (OR: 3.0; 95% CI: 2.3-3.8). Besides, a higher risk for NCGC (OR: 5.9; 95% CI: 3.4-10.3) was noted if the serological samples were collected ten years or more ago, suggesting that the association between *H. pylori* infection and gastric cancer may be underestimated in this retrospective case-control study[5].

A Japanese cohort study including a total of 1246 cases, with a mean follow-up period of 7.8 years (1-10.6 years), found that 2.9% of those patients with *H. pylori* infection and 0% of those without *H. pylori* infection eventually developed gastric cancer[10]. Another German cohort study of 9,449 people showed that *H. pylori* infection increased the incidence of gastric cancer (HR: 2.99), especially for NCGC (HR: 12)[11].

About 89% of NCGC and 20-30% of cardia gastric cancer (CGC) are attributable to *H. pylori* infection. *H. pylori* is the most important infectious agent in cancer etiology, accounting for approximately 5-6% of the total global cancer burden[12, 13]. Assumption of eliminating *H. pylori* infection in the population, most gastric cancers might be prevented.

H. pylori infection is the most important risk factor for gastric cancer. The effective screening and successful elimination of *H. pylori* infection are the important method to prevent gastric cancer.

2

Clinical question ***H. pylori* infection and gastroduodenal disease**

Statement All *H. pylori* infection will result in chronic gastritis; some of them will lead to peptic ulcer, precancerous conditions (atrophic gastritis and intestinal metaplasia), or gastric cancer. Eradication therapy can prevent the recurrence of peptic ulcer disease and reduce the severity of gastritis and precancerous conditions.

Evidence level moderate

Grade of recommendation strong

Comments:

Gastritis usually refers to an inflamed structural change in the gastric mucosa, and the most common cause of chronic gastritis is *H. pylori* infection[14]. The Kyoto consensus regarded " *H. pylori* infection" as infectious disease and suggested aggressive *H. pylori* eradication, despite for those subjects without symptoms or *H. pylori* associated disease, such as peptic ulcer disease, etc[15, 16]. The *H. pylori* eradication can improve chronic gastritis and reduce the recurrence of peptic ulcer disease [17]. The *H. pylori* gastritis may progress to more severe gastritis or precancerous conditions, such as atrophic gastritis or intestinal metaplasia of gastric mucosa[18, 19].

The elimination of *H. pylori* infection can improve chronic gastritis, atrophic gastritis and intestinal metaplasia of gastric mucosa [20, 21], and reduce the risk of gastric cancer. For those patients with chronic gastritis or precancerous conditions, the elimination of *H. pylori* infection can reduce the risk of gastric cancer for those patients with chronic gastritis and atrophic gastritis, and the effect of risk reduction is less significant for those with gastric intestinal metaplasia and dysplasia[18, 22, 23]. For gastric cancer prevention, early screening and elimination of the *H. pylori* infection is recommended before the development of gastric intestinal metaplasia or dysplasia.

3 **Clinical question** **How is *H. pylori* infection transmitted?**

Statement The most important *route of H. pylori infection* is through oral ingestion. Person-to-person transmission within families is an important source of infection.

Evidence level low

Grade of recommendation recommended

Comments:

The exact route of transmission of *H. pylori* remains uncertain, but the fecal-oral and oral-oral routes are considered the most likely routes of transmission[24]. *H. pylori* can be cultured from the vomitus, laxative feces, and saliva of infected subjects in previous studies, suggesting that it may be transmitted through saliva, vomit, and feces [25]. *H. pylori* can transform into the coccoid form when facing with critical environments, and contaminated water sources are potential reservoirs[26] . According to epidemiological studies, transmission within family is an important source of acquisition of *H. pylori* infection [27-30]. Random amplification of DNA polymorphisms (RAPD-PCR) genotyping revealed 56% (10/18) concordance of mother-child strains within families. In 81% (29/36) of families, at least two siblings had similar strains[28]. However, transmission between spouses remains controversial [27-29]. Some studies have shown that 22%-44% of the strains in couples are homologous[27, 28] , but another study showed that although 5 out of 13 couples had similar strains, further analysis by restricted Dicer HhaI of RFLP revealed heterogeneous strains between these 5 couples[29]. New sequencing techniques and assays can further explore the routes of transmission of *H. pylori* in families and communities.

4

Clinical question **Who are at high risk of developing gastric cancer?**

Statement Screening of *H. pylori* is recommended in those at higher risk of gastric cancer, such as those with a family history of gastric cancer in their first-degree relatives, who are aged 50 years or older, or those living in regions with a high incidence of gastric cancer.

Evidence level moderate

Grade of recommendation strong

Comments:

The high-risk groups for gastric cancer include family history of gastric cancer in first-degree relatives, males, elderly groups, and special groups – aborigines. A recent systematic review and meta-analysis covering 32 relevant studies (n = 80690 people) showed that people with a history of gastric cancer in first-degree relatives had a 2.4 fold (95% CI: 2.0-2.8) increased risk of developing gastric cancer compared with those without a family history of gastric cancer [31]. Smoking, high salt and pickled foods are also important risk factors for gastric cancer[32, 33]. Statistics from the Taiwan Cancer Registry and the International Agency for Research on Cancer of the World Health Organization show that the incidence of gastric cancer in males is approximately twice that of females (Table 1)[34]. The elderly are also at a higher risk of gastric cancer. Statistics from the Taiwan Cancer Registry showed that the incidence of gastric cancer in men aged 55-59 has increased to 27.7 per 100,000 population, and the incidence of gastric cancer in men aged 60-64 It was 49 people per 100,000 population in 2018, all of which were groups with a high incidence of gastric cancer (Table 2)[34]. Previous studies have shown that eradication of *H. pylori* before the occurrence of gastric precancerous lesions can significantly reduce the risk of gastric cancer[35], but even in people with gastric precancerous lesions, early eradication of *H. pylori* can significantly reduce the risk of metachronous gastric cancer[36, 37]. Therefore, it is recommended that the above-mentioned high-risk groups for gastric cancer should be prioritized for screening for *H. pylori*.

Table 1. The number and standardized incidence of gastric cancer in males and females in Taiwan Cancer Registry (per 100,000 population)

	Male		Female	
	Case number	Standardized incidence*	Case number	Standardized incidence*
2000	2,212	18.94	1,139	10.18
2001	2,365	19.50	1,137	9.83
2002	2,485	19.97	1,209	10.09
2003	2,215	17.30	1,145	9.20
2004	2,390	18.10	1,294	9.99
2005	2,260	16.58	1,248	9.28
2006	2,408	17.27	1,277	9.15
2007	2,372	16.59	1,334	9.10
2008	2,360	15.92	1,304	8.66
2009	2,430	16.03	1,466	9.31
2010	2,469	15.79	1,461	9.00
2011	2,453	15.37	1,422	8.42
2012	2,408	14.67	1,432	8.14
2013	2,464	14.55	1,379	7.70
2014	2,354	13.49	1,482	7.93
2015	2,382	13.40	1,521	7.79
2016	2,343	12.82	1,367	6.74
2017	2,350	12.64	1,439	6.96
2018	2,334	12.18	1,464	6.76

* per 100,000 population

Table 2. The number of gastric cancer cases and normalized incidence rates (per 100,000 population) in males and females of each age group in the Taiwan Cancer Registry in 2018

	Male		Female	
Age of diagnosis	Case number	Standardized incidence*	Case number	Standardized incidence*
15~19	1	0.15	1	0.16
20~24	1	0.12	2	0.27
25~29	4	0.48	1	0.13
30~34	9	1.07	7	0.86
35~39	24	2.41	28	2.75
40~44	35	3.72	44	4.53
45~49	85	9.63	60	6.58
50~54	145	16.11	80	8.66
55~59	247	27.74	128	13.79
60~64	384	49.06	192	22.94
65~69	323	51.85	205	29.90
70~74	269	79.25	140	35.89
75~79	254	94.45	191	56.75
80~84	238	138.68	189	79.27
85+	315	185.51	196	93.31

5 Clinical question: Does eradication of H. pylori reduce the risk of gastric cancer?

Statement Eradication of *H. pylori* can reduce the risk of gastric cancer so this strategy is recommended for all infected subjects, except for those with severe comorbidities.

Evidence level moderate

Grade of recommendation recommended

Comments:

We searched the randomized trials addressing the following issue in the literature

- P (Patient): *H. pylori* infection subjects
- I (Intervention): Eradication therapy
- C (Comparison): No eradication therapy
- O (Outcome): incidence of gastric cancer

Through literature search, we identified 7 randomized trials of primary prevention for gastric cancer through *H. pylori* eradication, including a total of 8323 patients with *H. pylori* infection, of which 4206 received *H. pylori* eradication therapy, and the other 4177 did not receive eradication therapy or received placebo (Table 3)[35, 38-46]. At the end of the trial (interval 4-22 years), gastric cancer occurred in 68 treated and 125 untreated subjects, respectively (Hazard ratio (RR) 0.55, 95% CI 0.42-0.74) [35, 38-46].

It is worth noting that in two of the several trials, eradication of *H. pylori* appeared to be ineffective in preventing gastric cancer, possibly because all participants in both trials had precancerous lesions in the stomach[38, 42, 43]. In a subgroup analysis, Wong et al. found that in subjects without precancerous lesions at the beginning of the trial, eradication therapy was significantly more effective than placebo in the prevention of gastric cancer[42, 43]. These results suggest that *H. pylori* eradication therapy before gastric precancerous lesions can provide better gastric cancer prevention[42, 43]. Our population-based screening and eradication program for *H. pylori* in Matsu Islands further showed that the incidence of gastric cancer in Matsu was significantly reduced by 53% 12 years after mass screening and eradication of *H. pylori*. Based on the above evidence, we concluded that eradication of *H. pylori* can reduce the risk of gastric cancer[47]. Professor Chun-Ying Wu mentioned that eradication therapy should be reserved for subjects at high risk of gastric cancer. However, there is currently inadequate evidence to estimate the risk of gastric cancer in individual *H. pylori* infected subjects. Therefore, it is recommended that all infected patients should receive eradication therapy of *H. pylori* in addition to competing considerations, such as those with severe comorbidities.

Table 3. Clinical trials that assessed the efficacy of *H. pylori* eradication on gastric cancer prevention

Study	Country/ Trial start year	% with precancerous lesion at baseline*	Follow-up period (years)	GC/Total in treated vs non-treated	Risk ratio (95% CI)
Correa 2000[1]	Columbia/1994	100%	6 years	3/437 vs. 2/415	1.42 (0.24-8.48)
Leung 2004& Zhou 2014[5,6]	China/1996	44.6%	10 years	2/276 vs. 7/276	0.29 (0.06-1.36)
Wong 2004[10]	China/1994	38.4%	7.5 years	7/817 vs. 11/813	0.63 (0.25-1.63)
Saito 2005[7]	Japan/n.a.	n.a.	≥4 years	2/379 vs. 3/313	0.55 (0.09-3.27)
Ma 2012[3] **& Li 2019**[4]	China/1995	75.7%	22 years	41/1130 vs. 78/1128	0.52 (0.36-0.76)
Wong 2012[8]	China/2002	100%	5 years	6/510 vs. 3/514	2.02 (0.51-8.02)
Choi 2020[9]	Korea/2012	57.4%	9 years	10/912 vs. 23/914	0.44 (0.21-0.91)
		Meta-analysis			0.55 (0.42-0.74)

6

Clinical question **Who should we screen *H. pylori*?**

Statement Screening of *H. pylori* infection for gastric cancer prevention is recommended for subjects at higher risk of gastric cancer.

Evidence level high

Grade of recommendation strong

Comments:

We search the literatures, including randomized controlled trials and meta-analysis, addressing the following issues:

- P (Patient): subjects at higher risk of gastric cancer
- I (Intervention): screening of *H. pylori* infection
- C (Comparison): no screening of *H. pylori* infection
- O (Outcome): gastric cancer incidence

According to the randomized controlled trials in Japan and Korea for patients with early gastric cancer after receiving endoscopic submucosal dissection, those who received *H. pylori* treatment had 50% decreased incidence of metachronous gastric cancer compared to patients who did not treat *H. pylori* [36, 37]. Eradicate *H. pylori* can reduce 55% risk of gastric cancer in persons with a family history of gastric cancer in first-degree relatives during 14-year follow-up[45]. According to the randomized controlled trial in Shandong province of China, *H pylori* treatment could decreased 52% risk of gastric cancer incidence during 22 years of follow-up[41]. An effectiveness in reducing gastric cancer incidence of 53% is demonstrated in Matsu Islands of Taiwan after 6 rounds of mass *H. pylori* eradication in 16 years[47, 48]. The benefits of *H. pylori* treatment can be observed early especially in high risk population; the meta-analysis also confirmed that population with a high incidence of gastric cancer, *H. pylori* treatment significantly reduces the risk of gastric cancer (47-54%)[49-51]. A recent study also addresses the cost-effectiveness of screen-and-treat for *H. pylori* infection in persons with a family history of gastric cancer and finds that this strategy can be cost-effective even in the low-risk of United States[52].

7 Clinical question: Is eradication of *H. pylori* cost-effective for gastric cancer prevention?

Statement Eradication of *H. pylori* for gastric cancer prevention is cost-effective in regions with intermediate or high incidence of gastric cancer.

Evidence level moderate

Grade of recommendation recommended

Comments:

We searched the literature on the following issues

- P (Patient): *H. pylori*-infected subjects
- I (Intervention): *H. pylori* test-and-treat
- C (Comparison): observation without *H. pylori* eradication
- O (Outcome): gastric cancer and cost-effectiveness

There were two systemic reviews, one randomized control trial, and 23 studies using the Markov model or others for this clinical question. The variables which correlated to cost-effectiveness of *H. pylori* test-and-treat to prevent gastric cancer included the prevalence rate of *H. pylori* infection, the incidence rate of gastric cancer, the cancer reduction achieved by *H. pylori* eradication, the starting age of treatment, and cost of gastroscopy and cancer treatment[53].

H. pylori test-and-treat was cost-effective to prevent gastric cancer in the region where the prevalence rate of *H. pylori* infection was high, such as Columbia and Singapore Chinese[54], or in the region where the prevalence rate of *H. pylori* infection was not high but the reduction in gastric cancer risk by *H. pylori* eradication could be > 15%, such as United States. In Japan, it was cost-effective if the reduction in gastric cancer risk by *H. pylori* eradication was > 0.6% [55, 56]. In East Asia, where the incidence rate of gastric cancer was intermediate to high, including Taiwan, it was cost-effective for *H. pylori*-positive subjects to receive *H. pylori* eradication starting at age of 30 [57-59] and it was more cost-effective if screening was conducted by serology or *H. pylori* stool antigen than by ^{13}C-urea breath test[58].

In Taiwan, gastric cancer not only had a significant economic loss, the lifetime health expenditure of gastric cancer, from diagnosis, treatment, to death was about 500,000 NT dollars (16,992 USD) per case[58], but also had the expected years of life lost, i.e., 12.3 years in females and 9.3 years in males[60]. We proposed two scenarios, one without *H.*

pylori eradication and the other with. The cost of risk of gastric cancer was 3,659 NTD (124.8 USD) per person in the former and 2,331 NTD (79.5 USD) per person in the latter. Thus, *H. pylori* eradication saved 1,328 NTD (45.3 USD)[58], which was a target for us to control cost of *H. pylori* test-and-treat to make it cost saving. The prevalence rate of *H. pylori* may be changed with time, or different between the urban and aboriginal area. Taking the variables which determined the cost-effectiveness into consideration, the sensitivity analysis showed that the incremental cost-effectiveness ratio (ICER) of *H. pylori* test-and-treat, which was conducted by serology screening, would be 0 in Taiwan if the *H. pylori* prevalence rate and absolute risk reduction of gastric cancer achieved by *H. pylori* eradication were 40% and >0.70%, 54.4% and >0.58%, and 65% and >0.53%, respectively. The incremental cost-effectiveness ratio (ICER) < 0 meant that *H. pylori* test-and-treat could save the expenditure for gastric cancer. In view of prevention of *H. pylori*-related diseases, including peptic ulcer, gastric cancer, and others, cost of *H. pylori* test-and-treat would be less and the effectiveness would be higher if starting at a younger age[59].

8

Clinical question **How is the accuracy of the ^{13}C-urea breath test?**

Statement The sensitivity and specificity of the ^{13}C-urea breath test are both higher than 95% for the diagnosis of *H. pylori* infection.

Evidence level high

Grade of recommendation strong

Comments:

We search the literatures of meta-analysis addressing the following issues:

- P (Patient): subjects with *H. pylori* infection or not
- I (Intervention): ^{13}C-urea breath test
- C (Comparison): other tests
- O (Outcome): sensitivity and specificity

H. pylori infection can be confirmed by non-invasive methods, including ^{13}C-urea breath test (UBT), *H. pylori* stool antigen test, and serology; its advantages, disadvantages and applicable timing are shown in Table 5. The invasive methods for *H. pylori* detection which requiring gastric biopsies obtained during an endoscopy include histology, rapid urease test, and culture; its advantages, disadvantages and applicable timing are shown in Table 6. According to Cochrane Database of Systematic Reviews of UBT for *H. pylori* infection at the most commonly reported threshold of delta over baseline > 4% (30 minutes after administration of urea) compared to histology or combined culture as reference standard (Table 4), the sensitivity and specificity of UBT are 95% (95% CI: 79-99%) and 95% (95% CI: 87-98%), respectively[61]. Before testing with UBT, proton pump inhibitor should be discontinued at least 2 weeks; antibiotics and bismuth compounds also should be discontinued at least 4 weeks[62, 63].

Table 4. Studies evaluating the accuracy of the 13C-urea breath test

Study	Case No.	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Delvin 1999	79	combination	100% (74-100%)	100% (95-100%)
Bosso 2000	95	histology	97% (84-100%)	90% (80-96%)
D′ Elios 2000	256	histology	97% (93-99%)	99% (95-100%)
Mana 2001	182	combination	99% (94-100%)	96% (90-99%)
Germana 2001	100	combination	98% (90-100%)	98% (88-100%)
Schilling 2001	68	histology	52% (31-72%)	93% (81-99%)
Korstanje 2006	20	combination	83% (36-100%)	79% (49-95%)
Hafeez 2007	54	histology	91% (76-98%)	60% (36-81%)
Adamopoulos 2009	104	combination	85% (73-92%)	98% (89-100%)
Meta-analysis			95% (79-99%)	95% (87-98%)

Table 5. Comparison of non-invasive methods for confirmation of the *H. pylori* infection

Non-invasive methods for *H. pylori* detection	Advantages	Disadvantages	Sensitivity and specificity (This is an estimate; the accuracy will vary depending on the brand and the tested group)	It is recommended when to use
^{13}C-UBT (^{13}Carbon urea breath test)	Simple operation; high accuracy	1. It takes more than 2 hours for fasting, and it takes 30-40 minutes to complete the collection of samples 2. Avoid proton pump inhibitors for 2 weeks and antibiotics for 4 weeks before test	Sensitivity: 97% Specificity: 96%	Screening: V Decide whether to treat or not: V Assess treatment effectiveness: V
HpSA (*H. pylori* stool antigen test)	The subjects only need to collect stool samples, which is non-invasive and easy to operate	1. Instruct the subjects (eg collection methods, storage and transportation of stool samples) 2. Since the test is not collected immediately, the subject′ s adherence (compliance) may be poor 3. Avoid proton pump inhibitors for 2 weeks and antibiotics for 4 weeks before test	Sensitivity: 90-92% Specificity: 90%	Screening: V Decide whether to treat or not: V Assess treatment effectiveness: V
Serology test	The serology test can be done simultaneously as regular blood sampling, which is very convenient	1. Blood collection needs to be carried out by professionals 2. Since serology test can′ t distinguish active and past *H. pylori* infection, it is recommended to confirm whether to treat with ^{13}C-UBT or HpSA	Sensitivity: 85-90% Specificity: 79%	Screening: V Decide whether to treat or not: Not applicable Assess treatment effectiveness: Not applicable

Table 6. Comparison of invasive methods for confirmation of the *H. pylori* infection

Invasive methods for *H. pylori* detection	Advantages	Disadvantages	Sensitivity and specificity (This is an estimate; the accuracy will vary depending on the brand and the tested group)	It is recommended when to use
Histology	1. High accuracy 2. Can simultaneously assess the severity of gastritis and the detections of precancerous lesions	1. Gastroduodenoscopy and biopsy are required 2. Sampling location and number of specimens can affect accuracy 3. Higher cost	Sensitivity: 92% Specificity: 92% Accuracy: 92%	Screening: V Decide whether to treat or not: V Assess treatment effectiveness: V
Rapid urase test (CLO)	High accuracy and specificity of test	1. Gastroduodenoscopy and biopsy are required 2. Sampling location and number of specimens can affect accuracy 3. Sensitivity is slightly lower. 4. Avoid proton pump inhibitors for 2 weeks and antibiotics for 4 weeks before test	Sensitivity: 87% Specificity: 95% Accuracy:92%	Screening: V Decide whether to treat or not: V Assess treatment effectiveness: V
***H. pylori* culture**	1. High accuracy and specificity 2. The culture is recommended before the third-line therapy	1. Gastroduodenoscopy and biopsy are required 2. Sampling location and number of specimens can affect accuracy 3. Transportation of specimen and culture require special equipment 4. Time-consuming and difficult 5. Avoid using proton pump blockers for 2 weeks and antibiotics for more than 4 weeks before the test	Sensitivity: 90% Specificity: 98% Accuracy: 95%	Screening: V Decide whether to treat or not: V Assess treatment effectiveness: V

9

Clinical question **How accurate is the *H. pylori* stool antigen test?**

Statement The *H. pylori* stool antigen test can accurately detect the presence of *H. pylori* infection and can be used to confirm the treatment response after eradication therapy.

Evidence level moderate

Grade of recommendation recommend

Comments:

Non-invasive tests for diagnosis of *H. pylori* infection include ^{13}C-UBT, *H. pylori* stool antigen (HpSA) and serology tests, can be used in the mass screening in the community. A meta-analysis showed that the sensitivity and specificity of monoclonal HpSA were 94% versus 97% for confirming *H. pylori* infection before treatment, and 93% versus 96% for confirming eradication effect after treatment, respectively[64].

In the Cochrane meta-analysis study, ^{13}C-UBT was more accurate than HpSA by the indirect comparisons (OR: 3.4, 95% CI: 1.3-8.8)[61]. On the other hand, HpSA is cheaper, and when the accuracies of the two tests are similar, HpSA is a substitute for ^{13}C-UBT. In addition to primary screening of *H. pylori* infection, HpSA can also be used to confirm efficacy after eradication therapy[65, 66].

The adherence rate of HpSA was lower than UBT (48% versus 86%) [67] and the delayed defecation may result in the degradation of antigen in stool samples resulting false negative. The ^{13}C-UBT remained cost-effective if the prevalence rate of *H. pylori* infection is more than 25%. However, the HpSA remained more cost-effective if the adherence rate is more than 63%[67].

HPSA can accurately identify the *H. pylori* status before and after eradication therapies. When using HpSA in the mass screening for *H. pylori* infection, the patient' s adherence, medical accessibility, and the collection and delivery of stool samples should be ameliorated to increase the completion rates and avoid false-negative results.

10 Clinical question How accurate is the *H. pylori* serology test?

Statement The serology test can detect previous and current *H. pylori* infection. It can be used in epidemiological studies but is not recommended to guide the decision for eradication therapy or to confirm the treatment response.

Evidence level moderate

Grade of recommendation recommend

Comments:

The seven head-to-head studies in the Cochrane meta-analysis showed that the ratios of diagnostic odds ratios (DOR) were 0.68 (95% CI: 0.12-3.70, p=0.56) for ^{13}C-UBT versus serology, and 0.88 (95% CI: 0.14-5.56, p=0.84) for ^{13}C-UBT versus HpSA[61]. A multi-center screening program for *H. pylori* infection conducted by the National Taiwan University Hospital included a total of 9014 adults who received serology, histology, culture and rapid urase test. If any two or more of the other tests are positive as positive for *H. pylori* infection, the accuracy, sensitivity and specificity of the serology test are 88%, 94% and 84%, respectively.

Since the serology test does not require any special equipment, it can be easily performed [68], and previous studies found that the serology test for screening of gastric cancer and precancerous lesions is cost-effective[53]. Boklage et al. showed that the patient′ s adherence to serology test and ^{13}C-UBT was higher than that of HPSA[67]. However, whether it is active *H. pylori* infection, or previous infection, the serological test may be positive[69].

Based on the above evidence, the serology test can correctly detect the status of *H. pylori* infection, but its accuracy is slightly lower than ^{13}C-UBT. The serology test is inexpensive and convenient, but can′ t distinguish between active and past *H. pylori* infections. For those with a positive serology test, the *H. pylori* eradication should be provided only after confirmation of 13C-UBT or HPSA.

11 Clinical question: Screening strategy for subjects at intermediate or high risk of gastric cancer in community

Statement Screening and eradication of *H. pylori* for subjects at intermediate or high risk of gastric cancer can be integrated or included in the routine screening programs to optimize the national resources for health care.

Evidence level moderate

Grade of recommendation strong

Comments:

We search the literatures addressing the following issues:

- P (Patient): subjects with high risk of gastric cancer
- I (Intervention): *H. pylori* screening and treatment
- C (Comparison): no *H. pylori* screening
- O (Outcome): gastric cancer incidence

H. pylori screening strategy for subjects at intermediate or high risk of gastric cancer in community is shown in Figure 1. *H. pylori* screening and eradication strategy for population at intermediate or high risk of gastric can be used as health care policy. When implementing in community, it is necessary to consider how to invite, participate rate, diagnostic test accuracy, referral rate, and eradication rate. For example, Matsu Islands has the highest incidence of gastric cancer in Taiwan, Mass *H. pylori* eradication program has been implemented in this community since 2004[48], the prevalence rates of *H. pylori* fall from nearly 70% to about 10%, the effectiveness in reducing incidence and mortality of gastric cancer is 53% and 25%, respectively; when extrapolating the decreasing trend, a greater reduction of incidence rate up to 70% would be expected by 2025[47]. In 2018, the Taiwanese government started a pilot program for the prevention and treatment of gastric cancer in remote villages, and proposed a household screening method to improve the eradication effect and avoid cross-infection[70]. Starting in 2014, with the support of the Ministry of Health and Welfare of Taiwan and using the platform of the National Colorectal Cancer Screening Program, a two-in-one method combining fecal occult blood test and *H. pylori* stool antigen (HPSA) test is proposed and provided *H. pylori* eradication; the preliminary results show the incidence rate of gastric cancer has been reduced by about 10%, besides, providing an additional HPSA test not only increased participation but also improved the effect of colorectal cancer prevention simultaneously[71]. The non-invasive methods for *H. pylori* detection, including UBT, HPSA test, and serology, can be used for large-scale screening in community[1, 72]; however, a direct comparison of the accuracy and compliance between these three tests in large-scale screening is still lacking.

12 Clinical question What is the recommended screening strategy for high risk subjects in the hospitals?

Statement The ^{13}C-urea breath test (^{13}C-UBT), stool antigen test, or the serology test can be used for screening of *H. pylori* infection for subjects at moderate or high risk of gastric cancer in the hospital setting. However, the positive result of a serology test should be confirmed by tests that can detect active infection, in order to guide the decision for antibiotic treatment.

Evidence level low

Grade of recommendation recommended

Discussion:

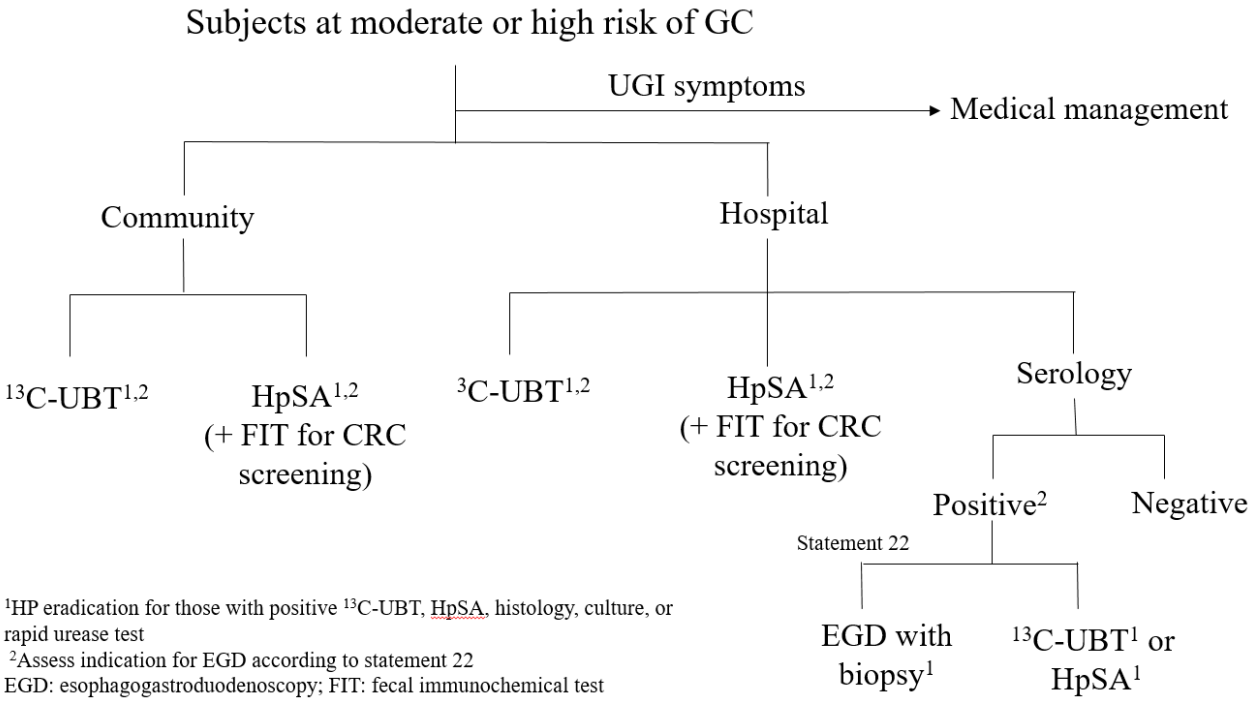
We searched the studies addressing the following issue in the literature

- P (Patient): Asymptomatic subjects aged 50 years or greater
- I (Intervention): *H. pylori* stool antigen test
- C (Comparison): ^{13}C-urea breath test
- O (Outcome): accuracy, compliance, cost-effectiveness

Non-invasive tests, including ^{13}C-urea breath test, *H. pylori* stool antigen (HpSA) testing, and serology testing are available for large-scale community-based screening for *H. pylori*[1, 72]. But a direct comparison of the accuracy and compliance of these three tests in large-scale screening programs are still lacking. In a meta-analysis based on hospital studies, the results of indirect comparisons showed that ^{13}C-UBT appeared to be more effective than serology (diagnostic odds ratio 3.2, 95% CI 1.2 to 8.4) and HpSA testing (diagnostic odds ratio 3.4, 95% CI 1.3) is more accurate 8.8)[61]. Factors that may influence the cost-effectiveness of mass screening include rates of *H. pylori* infection, patient compliance, costs of testing and gastric cancer treatment, additional benefits of testing, incidence of gastric cancer, and estimated cancer reductions[53, 67]. The ^{13}C-UBT method is accurate, but it is more expensive. The *H. pylori* stool antigen test is as accurate as the ^{13}C-UBT, but less expensive than the ^{13}C-UBT. However, the acceptability of *H. pylori* fecal antigen testing may be lower when used for mass screening, and delayed delivery of fecal samples may also result in antigen degradation, leading to false-negative results. Model estimates suggest that ^{13}C-UBT is more cost-effective than stool antigen testing if the prevalence of pylori is higher than 25%, but stool antigen testing is more cost-effective if compliance is higher than 63%. In a large-scale screening program in Changhua County, Taiwan, for subjects aged 50-69 years, a two-in-one approach was used to simultaneously

detect fecal occult blood for colorectal cancer screening and *H. pylori* antigen detection for gastric cancer prevention, thereby increasing the beneficial effects of mass screening[73]. Serological testing is the cheapest and most convenient test, but it cannot distinguish active infection from past infection. Therefore, a locally validated high-sensitivity serological test can be used for large-scale screening of *H. pylori*. The sensitivity of the test is 94% and the specificity is 84% in Taiwan, so it can be used for the first stage screening. However, for those who are seropositive, it is recommended that the ^{13}C-UBT or *H. pylori* stool antigen test be used to confirm the positive result before prescription of *H. pylori* eradication therapy (Figure 1) [1].

Figure 1. Algorithm for screening and eradication of *H. pylori* for gastric cancer prevention



[1]HP eradication for those with positive ^{13}C-UBT, HpSA, histology, culture, or rapid urease test
[2]Assess indication for EGD according to statement 22
EGD: esophagogastroduodenoscopy; FIT: fecal immunochemical test

13 Clinical question How to improve the screening efficiency in population? (family unit)

Statement Family-based screening and eradication of *H. pylori* may detect higher proportion of infected subjects, increase the compliance to therapy, and reduce the risk of reinfection after eradication therapy.

Evidence level moderate

Grade of recommendation weak

Comments:

We search the literatures, including cohort studies and meta-analysis, addressing the following issues:

- P (Patient): subjects with *H. pylori* infection
- I (Intervention): family-based screening and treatment
- C (Comparison): single-infected screening and treatment
- O (Outcome): screening efficiency

H. pylori is transmitted by oral route, and most *H. pylori* infections occur by infected family members during childhood or adolescents. According to the meta-analysis, the risks (odds ratio [OR]) of transmission to other children were 13.0 (95% CI: 3.0-55.2), 3.0 (95% CI: 0.8-11.2), and 3.7 (95% CI: 0.5-26.2) if maternal infected, paternal infected, and at least one family member infected, respectively[30]. *H. pylori* infection, even in childhood or adolescence, may still cause atrophic gastritis or intestinal metaplasia due to inflammation and damage to the gastric mucosa[74, 75]. According to the meta-analysis, compared with single-infected treatment, whole family-based screening and treatment can achieve higher eradication rate (OR: 2.9; 95% CI: 1.7- 5.1) and lower recurrence rate (OR: 0.3; 95% CI: 0.2-0.5)[76] China has also reported a consensus on family-based *H. pylori* infection control and management, which is expected to effectively improve the efficiency of infection control and to reduce the subsequent related diseases burden[77]. Therefore, family-based screening and eradication of *H. pylori* may detect higher proportion of infected subjects to receive treatment[70], avoid cross-transmission among family members, avoid transmission to children, protect uninfected family members, and reduce the risk of reinfection.

14 Clinical question Consideration of *H. pylori* infection and reinfection rate

Statement *H. pylori* is transmitted through the per-oral route. Improvement of sanitation, hygiene, dietary habits, and lifestyles can reduce the risk of *H. pylori* infection.

Evidence level low

Grade of recommendation weak

Comments:

We search the literatures, including cohort studies and meta-analysis, addressing the following issues:

- P (Patient): subjects with *H. pylori* infection
- I (Intervention): *H. pylori* treatment
- C (Comparison): no *H. pylori* treatment
- O (Outcome): *H. pylori* infection and reinfection rate

The current global prevalence of *H. pylori* infection is estimated at 42.8% for adults and 34.0% for children, but there are significant geographic differences[78]. According to Taiwan report, the prevalence rate in Changhua community is about 38%[71], and up to 44% in indigenous townships[70] *H. pylori* reinfection rate is also affected by the prevalence of local population. According to meta-analysis, the annual recurrence rate is approximately 3%[79], and it could be also affected by the environmental sanitation and prevalence of local population. In Matsu community, after the implementation of mass screening and eradication of *H. pylori*, the current reinfection rate is less than 1%[47]. That is, if the majority of those infected population in the community receive eradication treatment, the reinfection rate will be very low in the future. *H. pylori* is transmitted through the per-oral route; in addition to personal lifestyle and environmental hygiene are factors causing reinfection, cross-infection in the family members is also one of the reasons for reinfection[76]. Therefore, for those who have tested negative or have been successfully eradicated, they also must pay attention to the improvement of personal sanitation, hygiene, dietary habits, and lifestyles; besides, family members living with the *H. pylori* carrier may also consider to receive screening in order to reduce their risk of new infection or reinfection[77].

15 Clinical question: Which regimens are recommended for the first-line therapy in subjects with *H. pylori* infection?

Statement The quadruple therapy, including the bismuth quadruple therapy for 10-14 days or the non-bismuth quadruple therapy for 14 days, is recommended as the first-line therapy. The triple therapy for 14 days is acceptable as an alternative in regions with the lower clarithromycin resistance.

Evidence level moderate

Grade of recommendation strong

Discussion:

We searched the randomized trials addressing the following issue in the literature

- P (Patient): *H. pylori* infected subjects
- I (Intervention): bismuth or non-bismuth quadruple therapy
- C (Comparison): triple therapy
- O (Outcome): eradication rates

The commonly used prescriptions for first-line treatment of *H. pylori* are shown in Table 7. Currently, the resistance to clarithromycin in most parts of Taiwan is between 15% and 20% [80, 81]. Our previous randomized controlled trial with a crossover design confirmed that clarithromycin-containing triple therapy is more effective than levofloxacin-containing triple therapy in first-line treatment of *H. pylori* infection, so levofloxacin is not suitable for first-line eradication treatment of *H. pylori* infection[62, 82]. At present, several studies have shown that when the number of treatment days is the same, the eradication rate of bismuth or non-bismuth quadruple therapy is better than triple therapy. 14 days of non-bismuth sequential quadruple therapy is more effective than 14-day triple therapy[83-86]. Several large randomized trials in Taiwan also showed that 10-14 days of bismuth quadruple therapy was superior to 14 days of triple therapy, and 14 days of non-bismuth combined quadruple therapy was also superior to 14 days of triple therapy[83-88].

Adequate treatment length is also important, and systematic reviews and meta-analyses of randomized trials have shown that 14 days of clarithromycin-containing triple therapy is more effective than 10 or 7 days of triple therapy[89]. Studies have also shown that non-bismuth quadruple therapy containing clarithromycin can achieve better efficacy for 14 days[83-88, 90-92], so the recommended treatment length of triple therapy containing clarithromycin and non-bismuth quadruple therapy is 14 days. The recommended treatment

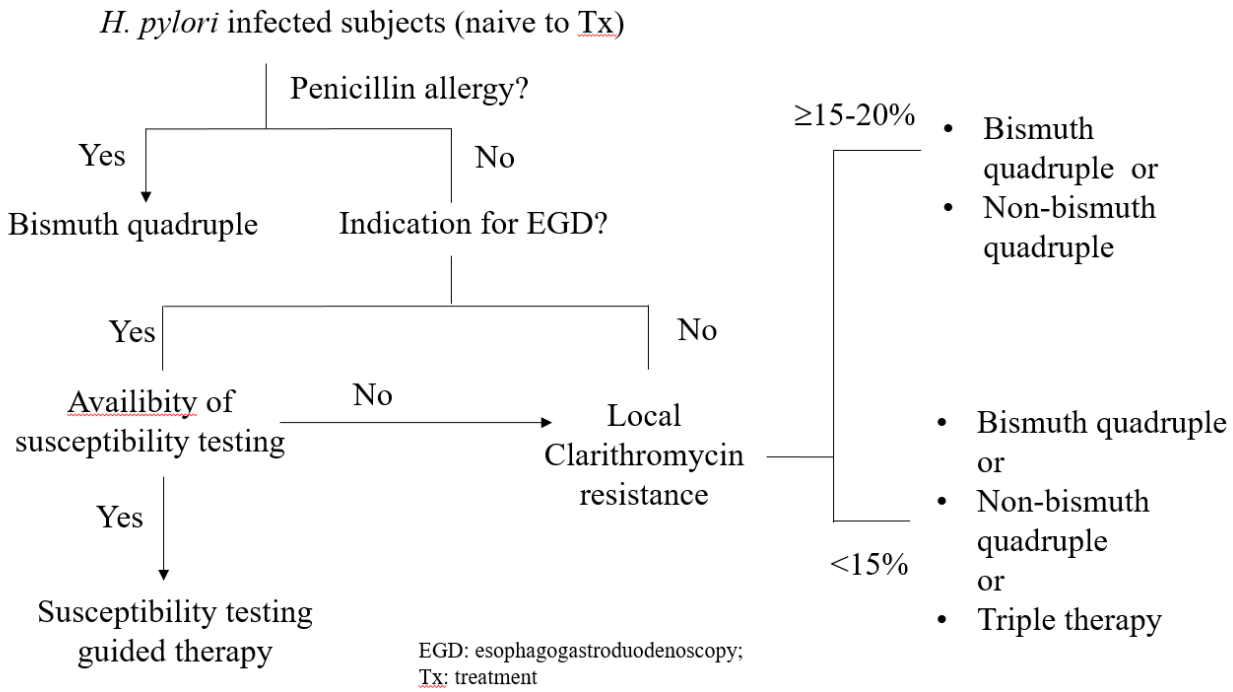
length of bismuth quadruple therapy is also 14 days. However, research in Taiwan showed that if all drugs are used in standard doses (Table 7), the eradication rate of bismuth quadruple therapy for 10 days can reach 90%[84, 87, 91]. Therefore, the treatment length of standard dose of bismuth quadruple therapy in Taiwan can be 10 days. However, when the standard dose is used, some patients may experience moderate to severe adverse effects. Therefore, it is necessary to evaluate the reduction of dosing frequency of tetracycline and metronidazole for 14 days can achieve similar eradication rates with reduced adverse events. Although bismuth and non-bismuth quadruple therapy has higher efficacy, its administration method is more complicated than triple therapy. Therefore, for those who are less able to take with quadruple therapy, such as some older people, 14-day triple therapy is an acceptable alternative treatment in regions with low clarithromycin resistance.

Table 7. Commonly used regimens for first-line treatment of *H. pylori*

Regimen	Drugs, dosage, frequency and treatment length
Clarithromycin triple therapy	A PPI bid, clarithromycin 500mg bid, and amoxicillin 1gm bid or metronidazole 500mg bid for 14 days
Bismuth quadruple therapy	A PPI bid, bismuth qid, tetracycline 500mg qid, and metronidazole 500mg tid for 10-14 days (standard dosage and frequency)
Sequential therapy	A PPI bid plus amoxicillin 1gm bid for7 days, followed by a PPI bid plus clarithromycin 500mg bid and metronidazole 500mg bid for another 7 days
Concomitant therapy	A PPI bid plus amoxicillin 1gm bid, clarithromycin 500mg bid and metronidazole 500mg bid for 14 days
Hybrid therapy	A PPI bid plus amoxicillin 1gm bid for 7 days, followed by a PPI bid plus amoxicillin 1gm bid, clarithromycin 500mg bid and metronidazole 500mg bid for another 7 days

PPI: proton pump inhibitor; bid: twice daily; tid: three times a day; qid: four times a day.

Figure 2. Algorithm for the first-line treatment of *H. pylori* infection



16 Clinical question: What is the first line treatment of *H. pylori* infection in penicillin allergic individuals?

Statement The bismuth quadruple therapy for 10-14 days is suggested as the first-line therapy for patients who report penicillin allergy. Antibiotic susceptibility testing guided therapy can be an alternative choice.

Evidence level low

Grade of recommendation recommended

Comments:

There are 9 non-randomized prospective studies and 3 retrospective studies after literature research (Table 8). In patients with penicillin allergy, first line therapies with ITT or mITT over 90% were considered in the following discussion. A study using PPI + clarithromycin + metronidazole + bismuth reached a 90.3% of eradication rate but subject number were small, and the treatment contains clarithromycin[93]. Another study using PPI + metronidazole + sitafloxacin with a eradication rate of 100% were earlier (before 2015) study and includes floroquinolone as one of the medications[94-96]. On the other hand, vonoprazan based combination including vonoprazan + clarithromycin + metronidazole and vonoprazan + metronidazole + sitafloxacin were also effective in Japan[94, 97]. Susceptibility-guided first line treatment is also a reasonable and effective option[98]. However, considering the country specific issue including health insurance reimbursement, treatment of resistant tuberculosis, resistance of clarithromycin and low availability of *H. pylori* culture and susceptibility testing, the combinations were not practical in the first hand. The suggested first line treatment in Penicillin allergic patients were bismuth-based quadruple therapy (BQT, containing PPI + bismuth + tetracyclin + metronidazole). In Taiwan, with a medium clarithromycin resistant rate, the efficacy of BQT in general population with a treatment duration of 10-14 days reached a good efficacy of 90.4%-96.0%[84, 91, 99].

Table 8. Studies regarding first-line treatment of *H. pylori* in penicillin-allergic patients

Author date	Study	Conduct Year	Country	Center	Regimen	Duration	Total n.	ITT ER	mITT ER	PP ER	AE
O. P. Nyssen 2020	P	2013-2019	Multiple (Eur)	M	P+B+T+M	NA	233		207/228 (91%)	203/221 (92%)	68/233 (29%)
J. P. Gisbert 2015	P	NA	Spain	M	P+B+T+M	10	50	37/50 (74%)		37/49 (75%)	14%
O. P. Nyssen 2020	P	2013-2019	Multiple (Eur)	M	P+C+L	NA	52		40/50 (80%)	40/49 (82%)	10/52 (19%)
O. P. Nyssen 2020	P	2013-2019	Multiple (Eur)	M	P+C+M	NA	243		158/228 (69%)	157/227 (69%)	55/243 (23%)
X. Long 2018	P	2016-2017	China	S	P+C+M	14	33	21/33 (63.6%)	21/31 (67.7%)	21/30 (70%)	15/33 (45.5%)
S. Sue 2017	P	2015-2016	Japan	S	P+C+M	7	30	25/30 (83.3%)		24/29 (82.7%)	NA
S. Ono 2017	R	2009-2016	Japan	S	P+C+M	7	10	5/10 (50.0%)		5/9 (55.6%)	NA
J. P. Gisbert 2015	P	NA	Spain	M	P+C+M	7	112	64/112 (57%)		62/105 (59%)	14%
J. P. Gisbert 2010	P	NA	Spain	M	P+C+M	7	50	27/50 (54%)		27/49 (55%)	5/50 (10%)
J. P. Gisbert 2005	P	NA	Spain	S	P+C+M	7	12	7/12 (58%)		7/11 (64%)	2/12 (17%)
X. Long 2018	P	2016-2017	China	S	P+C+M+B	14	33	28/33 (84.8%)	28/31 (90.3%)	24/25 (96%)	16/33 (48.5%)
Z. Song 2019	P	2015-2017	China	S	P+L+B+Ce	14	152	130/152 (85.5%)	130/147 (88.4%)	128/142 (90.1%)	32/150 (21.3%)
S. Ono 2017	R	2009-2016	Japan	S	P+M+S	7	20	20/20 (100%)		20/20 (100%)	NA
H. Mori 2017	P	2014-2015	Japan	S	P+M+S	10	33	33/33 (100%)		33/33 (100%)	NA
T. Furuta 2014	R	2008-2013	Japan	NA	P+M+S	7~14	11	11/11 (100%)		11/11 (100%)	7/11 (63.6%)
M. Rodríguez-Torres 2005	R	NA	Puerto Rico	NA	P+T+M	10	17	14/17 (85%)			NA
L. Luo 2020	P	2018-2019	China	S	Susceptibility-guided	14	37	32/37 (86.5%)	32/33 (97%)	30/31(96.8%)	21/37 (56.8%)
S. Sue 2017	P	2015-2016	Japan	S	V+C+M	7	20	20/20 (100%)		20/20 (100%)	NA
S. Ono 2017	R	2009-2016	Japan	S	V+C+M	7	13	12/13 (92.3%)		12/13 (92.3%)	NA
S. Ono 2017	R	2009-2016	Japan	S	V+M+S	7	14	13/14 (92.9%)		13/13 (100%)	NA

17 Clinical question Is confirmation test needed after *H. pylori* eradication?

Statement Confirmation of treatment response is suggested after eradication therapy for *H. pylori* infection.

Evidence level low

Grade of recommendation strong

Comments:

Current guidelines suggest a confirmatory test, ^{13}C-Urea Breath Test (UBT) or stool antigen test, after symptomatic *H. pylori* eradication[1, 100]. Ideally all eradication treatments should be evaluated for their efficacy considering the geographical and temporal differences in the prevalence or antibiotic resistance of *H. pylori*. Moreover, the treatment itself, and its cost for sequela of chronic *H. pylori* infection vary among different countries. There is only one cost-effective analysis based on earlier data collected in the United States[101]. The study suggested a better cost-effectiveness noted in ^{13}C -UBT than in stool antigen test.

However, variable *H. pylori* prevalence, antibiotic stress, and resistance were noted in different area in Taiwan with a trend of gradual increase[102]. A 7-day-course of non-bismuth concomitant therapy reached a 90.1% of eradication rate in Kaohsiung but only 85.9% in Taipei with a 10-day-course of the same treatment[103, 104]. Considering the difficulties of culture and generalized antibiotic sensitivity test before treatment, a post-treatment ^{13}C -UBT is suggested to monitor the change in treatment effect.

18-1 Clinical question

Which regimens are recommended for the second-line therapy in subjects with *H. pylori* infection?

Statement The bismuth quadruple therapy, levofloxacin based triple therapy, or levofloxacin based quadruple therapy can be used as the second-line treatment for *H. pylori* infection.

Evidence level moderate

Grade of recommendation strong

Comments:

We searched the randomized trials addressing the following issue in the literature

- P (Patient): *H. pylori* infected subjects who fail from first-line clarithromycin based regimens
- I (Intervention): levofloxacin-containing triple or quadruple therapy
- C (Comparison): bismuth quadruple therapy
- O (Outcome): eradication rates

The commonly used drug prescriptions for second-line treatment of *H. pylori* include bismuth quadruple therapy, levofloxacin-containing triple or quadruple therapy, as shown in Table 9[62, 81]. The resistance rate of *H. pylori* to levofloxacin was lower than 10% in most countries before 2010. Therefore, earlier meta-analysis of randomized trials conducte before 2010 showed that levofloxacin-containing triple therapy was superior to bismuth-based quadruple therapy[105]. However, levofloxacin resistance has risen to between 15-20% after 2015[80]. Therefore, recent randomized trials have shown that the efficacy of levofloxacin-containing triple therapy in second-line treatment of *H. pylori* has declined to 80% or below[106]. A randomized trial conducted in Taiwan showed that levofloxacin sequential quadruple therapy was superior to triple therapy with levofloxacin in second-line therapy[107]. Sequential quadruple therapy is as effective as bismuth-based quadruple therapy[108]J. M. </author></authors></contributors><titles><title>Levofloxacin sequential therapy versus bismuth quadruple therapy in the second-line and third-line treatment of Helicobacter pylori infection- a multicenter randomized trial</title><secondary-title>Gastroenterology</secondary-title></titles><periodical><full-title>Gastroenterology</full-title></periodical><pages>S570 (Su1377. Adequate treatment length is also important. Systematic reviews and meta-analyses of randomized trials showed that levofloxacin-containing triple therapy for 14 days was more effective than that of 10-day or 7-day triple therapy[106]. Therefore, the recommended treatment length for levofloxacin triple or quadruple therapy is 14 days. The recommended treatment length for second-line therapy bismuth quadruple therapy is 10-14 days.

Table 9. Commonly used regimens for second-line treatment of *H. pylori*

Regimens	Drug names, dosage, frequency and treatment length
Bismuth quadruple therapy	A PPI bid, bismuth qid, tetracycline 500mg qid, and metronidazole 500mg tid for 10-14 days
Levofloxacin triple therapy	A PPI bid, levofloxacin 500mg qd (or 250mg bid), and amoxicillin 1gm bid for 14 days
Levofloxacin sequential therapy	A PPI bid plus amoxicillin 1gm bid for7 days, followed by a PPI bid plus levofloxacin 500mg qd (or 250mg bid) and metronidazole 500mg bid for another 7 days
Levofloxacin concomitant therapy	A PPI bid plus amoxicillin 1gm bid, levofloxacin 500mg qd (or 250mg bid) and metronidazole 500mg bid for 14 days

PPI: proton pump inhibitor; bid: twice daily; tid: three times a day; qid: four times a day.

18-2 Clinical question

What is the treatment suggestion after first line *H. pylori* treatment failure in penicillin allergic individuals?

Statement The susceptibility testing guided therapy or the empirical levofloxacin-based therapy is suggested for patients with penicillin allergy after failure from bismuth quadruple therapy in the first-line treatment.

Evidence level low

Grade of recommendation recommended

Comments:

In patients with penicillin allergy, second line treatment and beyond using fluoroquinolone after first line non-fluoroquinolone treatment reached a 64-100% eradication rate[109, 110]. Hence, PPI + clarithromycin + levofloxacin (in patient not previously receiving clarithromycin based therapy) or PPI + metronidazole + Levofloxacin [109] are reasonable empirical choices. Using vonoprazan to replace PPI in second line treatment needs more evidence for its efficacy[94, 111]. If culture and susceptibility tests are available, susceptibility guided therapy in a trial of 75 people achieved good efficacy (96%, with CI 91.6%-100%) [98].

19 Clinical question How to treat patients who fail after two or more eradication therapies?

Statement The susceptibility testing guided therapy is recommended after two or more treatment failures. Bismuth or non-bismuth quadruple therapies containing the high dose of proton pump inhibitors for 14 days are recommended.

Evidence level moderate

Grade of recommendation strong

Comments:

We searched the randomized trials addressing the following issue in the literature

- P (Patient): *H. pylori* infected subjects who fail from two or more eradication therapies
- I (Intervention): susceptibility testing guided therapy
- C (Comparison): empirical therapy according to medication history
- O (Outcome): eradication rates

Treatment of refractory pylori is usually defined as patients with *H. pylori* infection who have not been successfully eradicated after two or more eradication treatments. Factors that should be considered in the treatment of refractory pylori infection include: 1. Provide adequate treatment days; 2. Use adequate antibiotic and proton pump inhibitor (PPI) doses; 3. Use four drug (quadruple) therapy; and 4. Select appropriate of antibiotics[62, 112]. Extending bismuth or non-bismuth quadruple therapy to 14 days resulted in higher sterilization rates compared to shorter periods (7 or 10 days)[83, 92]. The use of higher doses of PPI or metronidazole can also improve eradication rates[113, 114]. The use of quadruple therapy, including bismuth or non-bismuth quadruple therapy, generally achieves higher eradication rates than triple therapy[86]. The addition of bismuth or metronidazole to levofloxacin-amoxicillin-proton-pump inhibitor triple therapy also improved eradication rates[115]. Therefore, for patients with refractory *H. pylori* infection, four drug (quadruple) therapy with a higher dose of a proton pump inhibitor (PPI) for 14 days is recommended[112]. In the selection of antibiotics, susceptibility tests or medication history can be used to guide the selection of appropriate antibiotics. However, there is only one randomized clinical trial in the literature that compared the differences in efficacy between the two methods of choosing antibiotics. The results show that the eradication rate of antibiotics selected according to the results of drug resistance gene testing can reach 78% in the treatment of refractory *H. pylori*, and the eradication rate of empirical therapy according to the

medication history is 72%, but there was no statistically significant difference[116]. Therefore, it is recommended that antibiotics should be selected according to susceptibility testings whenever possible. However, empiric therapy based on past medication history, ie avoiding repeated use of clarithromycin or levofloxacin, is an acceptable alternativ after considering test accessibility, cost, and patient preference [116].

20 **Clinical question** **Does *H. pylori* eradication increase the risk of long-term antibiotic resistance of gut microbiota?**

Statement The short-term increase of antibiotic resistance of the gut microbiota may be restored months after eradication therapies.

Evidence level low

Grade of recommendation recommended

Comments:

With the widespread use of antibiotics, antibiotic resistance rate has increased significantly globally, which is also one of the concerns for large-scale screening and eradication of *H. pylori* for gastric cancer prevention[117]. In a systematic review, we found five studies assessing short-term changes in gut microbiota and gut microbial phenotypic resistance before and after *H. pylori* eradication, and three studies exploring the clarithromycin resistance gene erm(B) [118-123]. The results of these studies showed a significant increase in the antibiotic resistance of gut bacteria shortly after *H. pylori* eradication. We also found three studies investigating the long-term changes in the gut microbiota and phenotypic resistance of gut microbes after *H. pylori* eradication[118, 121, 122]. A prospective clinical trial in Taiwan showed a significant increase in antibiotic resistance in E. coli two weeks after triple therapy or concomitant therapy, but no significant increase in E. coli antibiotic resistance after bismuth quadruple therapy. Interestingly, antibiotic resistance had returned to its pre-treatment state after both two months and one year. Another study in Taiwan also showed that the increased abundance of the erm(B) gene in stool samples at the eighth week of sterilization returned to the pre-treatment state at the forty-eighth week. Limitations of the above studies include small sample sizes, susceptibility testing tested in only a few representative bacteria, and only a few studies evaluating long-term changes in resistance after *H. pylori* eradication. However, the emergence of antibiotic resistance is multifactorial, and it is not appropriate to exclude the use of antibiotics for the treatment of *H. pylori* infection and the prevention of gastric cancer because of concerns about the increase of drug resistance in the short term after *H. pylori* eradication. In addition, overuse of antibiotics in agriculture animal husbandry, environmental pollution, and insufficient antibiotic doses are also important reasons for the increase of antibiotic resistance in the environment and human bacteria[124, 125]. Overall, there is still insufficient evidence to determine the long-term impact of large-scale eradication therapy on antibiotic resistance in the community, and more large-scale prospective studies and clinical trials are urgently needed to explore this important issue.

21 Clinical question

How is the accuracy of methods for *H. pylori* detection which requiring gastric biopsies obtained during an endoscopy?

Statement Accuracies of the rapid urease test, histology, and the culture are 90% or higher but may be affected by the site and number of endoscopic sampling. The accuracy of the rapid urease test is reduced by the recent use of antibiotics, bismuth, and proton pump inhibitors. The accuracy of histology is associated with the inter-observer variations. The successful rate of culture is affected by the endoscopic sampling and the laboratory quality.

Evidence level moderate

Grade of recommendation strong

Comments:

We search the literatures addressing the following issues:

- P (Patient): subjects with *H. pylori* infection
- I (Intervention): rapid urease test, histology, culture
- C (Comparison): ^{13}C-urea breath test
- O (Outcome): diagnostic accuracy

The invasive methods for *H. pylori* detection which requiring gastric biopsies obtained during an endoscopy include rapid urease test, histology, and culture. Theoretically, the accuracy of the rapid urease test is equivalent to ^{13}C-urea breath test; besides, before tissue sampling for with rapid urease test, proton pump inhibitor should be discontinued at least 2 weeks, antibiotics and bismuth compounds also should be discontinued at least 4 weeks[62, 63]. The acquisition of at least two biopsy specimens or more from antrum and corpus, essentially following the Sydney System recommendations, could increase the sensitivity of rapid urease test[126]. Histology allows for direct visualization of *H. pylori*; but it is affected by many factors, including size of tissue, frequency of the biopsy, applied staining varieties, use of antibiotics, and the interpretation of different pathologists[127]. The specificity of bacterial culture is very high; it means that there is *H. pylori* infection when it is cultured, but the sensitivity is not high, and leads to false-negative results. Besides, the successful rates of culture are affected by sample quality, delayed transport, exposure to an aerobic environment, and the laboratory quality[128].

22 Clinical question For those with *H. pylori* screening positive, who need additional endoscopy?

Statement Endoscopic examinations are indicated for those with the first degree relatives of gastric cancer, abnormal results of pepsinogen testing, and those with alarm symptoms, in order to exclude the presence of gastric cancer.

Evidence level high

Grade of recommendation strong

Comments:

We search the literatures, including randomized controlled trials, cohort studies and meta-analysis, addressing the following issues:

- P (Patient): subjects with *H. pylori* infection
- I (Intervention): serum pepsinogen test, inquiry of clinical symptoms and family history of gastric cancer
- C (Comparison): no serum pepsinogen test, no inquiry of clinical symptoms and family history of gastric cancer
- O (Outcome): prediction of the incidence of gastric cancer or precancerous lesions

According to the randomized controlled trial in Korea, eradicate *H. pylori* can reduce 55% risk of gastric cancer in persons with a family history of gastric cancer in first-degree relatives during 14-year follow-up[45]. According to the meta-analysis, compared with no family history of gastric cancer, the relative risk for the development of gastric cancer in association with a positive family history was 2.35 (95% CI: 1.96-2.81)[31] Besides, serum pepsinogen (PG) is secreted by gastric mucosa and released into the systematic circulation; its serum concentration can indirectly reflect the function and morphological state of gastric mucosa to evaluate whether gastric mucosa is atrophic or not. A lower serum PG-I level or lower serum PG-I/II ratio would have a higher risk of gastric cancer in the future[129, 130]. In the current free-market system, different brands of PG testing may be chosen; although tests from different manufacturers, even using different analytical methods and cutoff criteria, can perform equivalently in the prediction of premalignant gastric lesions[131]. For those with clinical alarm symptoms, such as body weight loss, dysphagia, and evidence of gastrointestinal bleeding, it is also recommended to arrange endoscopy to exclude the presence of gastric cancer.[132]

Table 10. Diagnostic cult-off values of serological pepsinogen tests

Brand	Method	Diagnostic cult-off values
GastroPanel® (Biohit HealthCare, Helsinki, Finland)	Enzyme-linked immunosorbent assay	PG-I <30 ng/mL or PG-I/II ratio <3
LZ-Test® (Eiken Chemical Co., Ltd, Tokyo, Japan)	Latex-enhanced turbidimetric immunoassay	PG-I ≤70 ng/mL and PG-I/II ratio ≤3

23 Clinical question Who needs surveillance endoscopy after successful *H. pylori* eradication?

Statement After *H. pylori* eradication, endoscopic surveillance is indicated for patients with advanced precancerous conditions, such as the operative link for gastritis assessment (*OLGA*) and/or operative link on gastric intestinal metaplasia assessment (*OLGIM*) stages III-IV on histology, severe or open-type gastric atrophy by endoscopy, abnormal results of pepsinogen testing by serology, and for those with dysplasia or gastric cancer following surgical or endoscopic resection.

Evidence level low

Grade of recommendation recommended

Comments:

We searched the literature on the following issues

- P (Patient): *H. pylori* eradication, atrophic gastritis, intestinal metaplasia, dysplasia
- I (Intervention): surveillance endoscopy
- C (Comparison): not *H. pylori* eradication
- O (Outcome): gastric cancer, gastric tumor, gastric neoplasm

There were eight systemic review and meta-analyses, six case-control studies, eight cohort studies for this clinical question. The severity of gastric precancerous conditions could be evaluated by pathology, endoscopy, or serum pepsinogen tests.

According to pathology, a systematic review and meta-analysis published in 2021 showed that the incidence rates of gastric cancer in gastric precancerous conditions, including atrophic gastritis and intestinal metaplasia were 2.25 (95% CI, 1.67~2.90) and 7.58 (95% CI, 4.10~11.91) per 1000 person-years in East Asia[133]. Furthermore, the severity of such precancerous conditions could be classified based on operative link for gastritis assessment (OLGA) and operative link on gastric intestinal metaplasia assessment (OLGIM) staging system to predict gastric cancer risk more accurately. A meta-analysis showed that the Odds ratio was 2.64 (95% CI, 1.84~3.79, P<0.001) and the risk ratio was 27.70 (95% CI, 3.75~204.87, P<0.001) for gastric cancer while OLGA stages III-IV *vs*. stages 0-II; the Odds ratio was 3.99 (95% CI, 3.05~5.21, P<0.001) for gastric cancer and the risk ratio was 16.67 (95% CI, 0.80~327.53) for high-grade dysplasia while OLGIM stages III-IV *vs*. stages 0-II [134]. In Europe, the risk of low- or high-grade intraepithelial neoplasia and gastric cancer in OLGA stage I, II, III, and IV were 0.34 (0.09~1.36), 1.48 (0.48~4.58), 19.1 (11.9~30.7),

41.2 (17.2~99.3) per 1000 person-years[135]. In Singapore Chinese, the risk of early gastric cancer in OLGIM stage I, II, and III-IV were 0.22, 1.09, and 5.44 per 1000 person-years[136]. In Taiwan, the risk of gastric cancer in stage 0, I-II, and III-IV of combined OLGA and OLGIM and dysplasia were 0, 4.61, 11.13, and 76.41 per 1000 person-years, respectively [137].

The gastric mucosal lesions could be examined by endoscopic recognition to diagnose gastric atrophy and intestinal metaplasia. Accordingly, the severity of gastric atrophy could be evaluated by the Kimura-Takemoto classification, which consisted of the closed-type and open-type. The closed-type is divided into three subtypes, C-1, C-2, and C-3, and the open-type is also divided into three subtypes, O-1, O-1, and O-3. The open-type had more severe atrophy than the close-type; thus, C-1 and C-2 are classified as mild, C-3 and O-1 as moderate, and O-2 and O-3 as severe. A meta-analysis showed that the pooled risk ratio of gastric cancer or neoplasms was 8.02 (95% CI 2.39~26.88) in the open-type as compared with the close-type based on the Kimura-Takemoto classification, and 3.84 (95% CI 2.47~5.97) in severe as compared with mild-to-moderate for subjects after *H. pylori* eradication based on the severity classification [138].

Additionally, serum pepsinogen (PG) I ≤70 ng/mL and PG I/II ratio ≤3 had the sensitivity, specificity, odds ratio, and area under the curve were 0.59 (95% CI 0.38~0.78), 0.89 (95% CI 0.70~0.97), 12 (6~25), 0.81 (0.77~0.84) to diagnose chronic atrophic gastritis, 0.59 (95% CI 0.50~0.67), 0.73(95% CI 0.64~0.81), 4 (3~6), 0.7 (0.66~0.74) to diagnose gastric cancer [139]. Moreover, serum PG I < 45 ng/mL and PG I/II ratio <6 had the sensitivity, specificity, and area under the curve of to diagnose OLGA or OLGIM stages III-IV or gastric cancer 0.60 (95% CI 0.36~0.80), 0.71 (95% CI 0.65~0.76), 0.68 (0.62~0.73) [130].

Because patients with atrophic gastritis or gastric intestinal metaplasia were at risk of gastric cancer, regular surveillance endoscopy after *H. pylori* eradication is suggested. However, there were not well-designed studies yet till now to show the exact interval to arrange surveillance endoscopy. Nevertheless, it was cost-effective to arrange surveillance endoscopy once per 2 to 3 years for patients with extensive gastric atrophy or intestinal metaplasia[140-142]. Surveillance endoscopy were suggested once per 5 years for subjects with OLGIM stage II and on demand for OLGIM stage 0-I if symptomatic[136].

The risk of gastric cancer in low- and high-grade gastric dysplasia was higher than atrophy and intestinal metaplasia. About 2.9% and 44% of subjects with initial low- and high-grade dysplasia were diagnosed to have gastric cancer within one-year follow-up, respectively [143-145], and the incidence rates of gastric cancer risk per 1000 person-years were 14.4 for low-grade dysplasia and 18.4~29.9 for high-grade dysplasia, respectively,

after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [146-148]. It was cost-effective to arrange surveillance endoscopy once per year for such patients after endoscopic removal of gastric lesions [149].

Gastric cancer may develop in the stump or the remnant stomach after distal gastrectomy, namely gastric stump cancer or remnant gastric cancer. The prognosis of remnant gastric cancer was poor because the stage at diagnosis was too advanced to receive curative resection as compared with the primary gastric cancer [150]. Therefore, regular follow-up is suggested, including surveillance endoscopy, to detect remnant cancer or recurrence early on. However, there is still the lack of evidences to show such follow-up improved the overall survival of patients with gastric cancer after distal gastrectomy [151].

Additionally, as compared with subjects without family history of gastric cancer, those with family history had increased risk to have gastric cancer. The possible causes were they had higher prevalence of *H. pylori* infection (Odds ratio 1.93 [95% CI, 1.42~2.61], *P*<0.001), atrophic gastritis (2.20 [95% CI, 1.27~3.82], *P*=0.005), or intestinal metaplasia (1.98 [95% CI, 1.36~2.88], P<0.001) [152]. The subjects with family history of gastric cancer also had increased prevalence of pyloric/pseudopyloric metaplasia of corpus, namely spasmolytic polypeptide-expressing metaplasia, which was also a precancerous condition [153]; therefore, they were suggested to receive surveillance endoscopy [154]. Moreover, there was familial clustering of gastric cancer, namely familial gastric cancer. The criteria to diagnose familial gastric cancer include (1) one relative with gastric cancer and diagnosed before the age of 40 years, (2) two first- or second-degree relatives with gastric cancer and one of them diagnosed before the age of 50 years, (3) three first- or second-degree relatives with gastric cancer independent of age. The first- or second-degree relatives were at the same father or mother side. Because the mutation of tumor suppressor gene or DNA base-excision repair gene was inheritable, the subject was at increased risk of gastric cancer and may need to receive surveillance endoscopy [155].

Figure 3. The clinical course of chronic gastritis after *H. pylori* infection

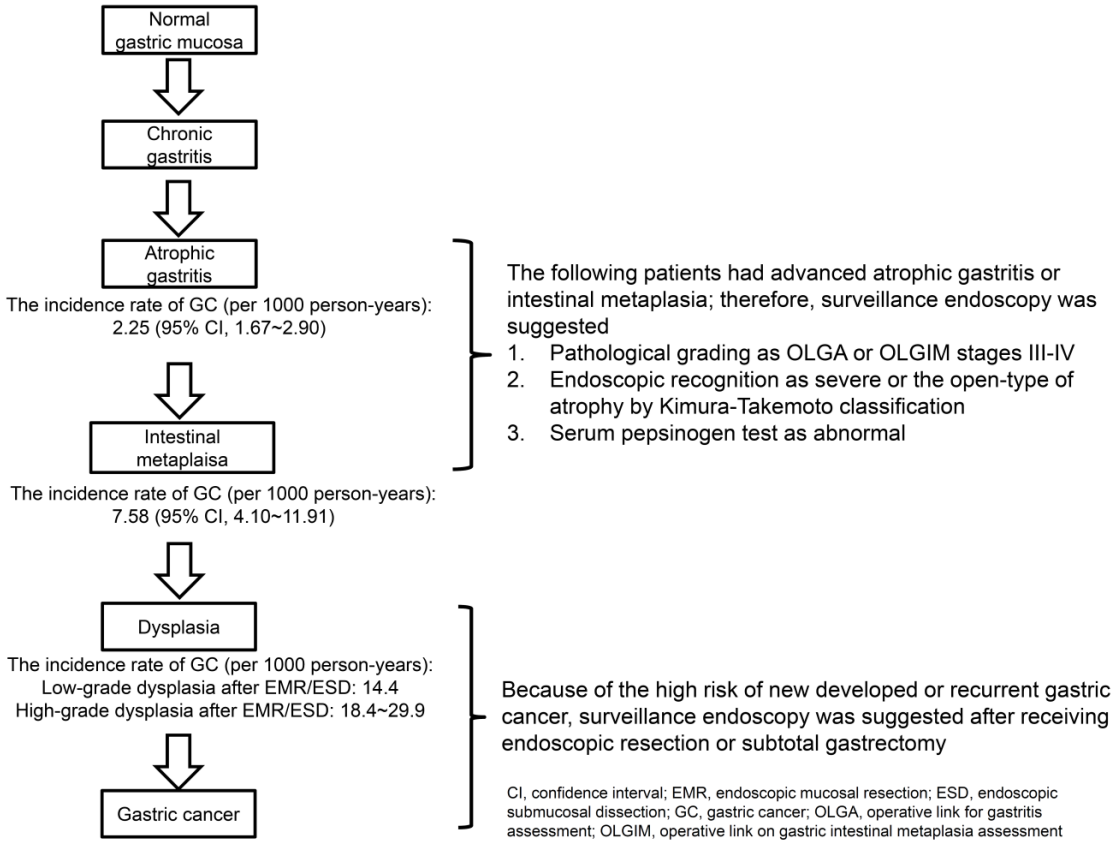


Table 11. The operative link for gastritis assessment (OLGA) and operative link on gastric intestinal metaplasia assessment (*OLGIM*) staging system for reporting gastric atrophy and intestinal metaplasia, respectively, in terms of stage

Score	Corpus				
Antrum (including incisura angularis)	Grading	Normal (score 0)	Mild (score 1)	Moderate (score 2)	Severe (score 3)
	Normal (score 0)	0	I	II	II
	Mild (score 1)	I	I	II	III
	Moderate (score 2)	II	II	III	IV
	Severe (score 3)	III	III	IV	IV

The grading of the atrophy and intestinal metaplasia of gastric mucosa according to updated Sydney System for gastritis [156]. The score for normal, mild, moderate, and severe was 0, 1, 2, and 3, respectively. Combining the scores from the antrum and corpus, the stage of OLGA or OLGIM is reported.

Conclusion

Due to the increase in the elderly population, gastric cancer will remain an important health problem globally and in Taiwan. Nearly 90% of non-cardia gastric cancers are attributable to *H. pylori* infection. Eradication therapy reduces the risk of gastric cancer, and is therefore recommended in all infected subjects unless there are other competing considerations, such as those with terminal stage cancer or severe comorbidities. The strategy of screening and eradication of *H. pylori* for gastric cancer prevention is most cost-effective in populations in areas with a high incidence of gastric cancer, especially when provided before the development of atrophic gastritis and intestinal metaplasia. However, when the limited national health care resources is taken into account, the priority of screening can be given to populations at higher risk of gastric cancer, such as those with family history of gastric cancer in first-degree relatives, older subjects (aged 50 years or older), and people living in regions with high incidence of gastric cancer. The program can be integrated with existing health care priorities to optimize resources. Screening can be carried out by ^{13}C-UBT or stool antigen test, or serology test. However, those with positive serology should be confirmed by ^{13}C-UBT or stool antigen test before eradication therapy. Endoscopy is recommended in subjects at high risk of gastric cancer or those with clinical warning symptoms of gastric cancer to assess the severity of gastritis and to exclude gastric cancer. In the face of increasing resistance rates of clarithromycin and levofloxacin in *H. pylori*, we recommend choosing appropriate eradication regimens according to the prevalence of local antibiotic resistance. People at higher risk of gastric cancer, such as those with more severe gastric mucosal atrophy or intestinal metaplasia, should undergo regular endoscopic surveillance after eradication of *H. pylori*.

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