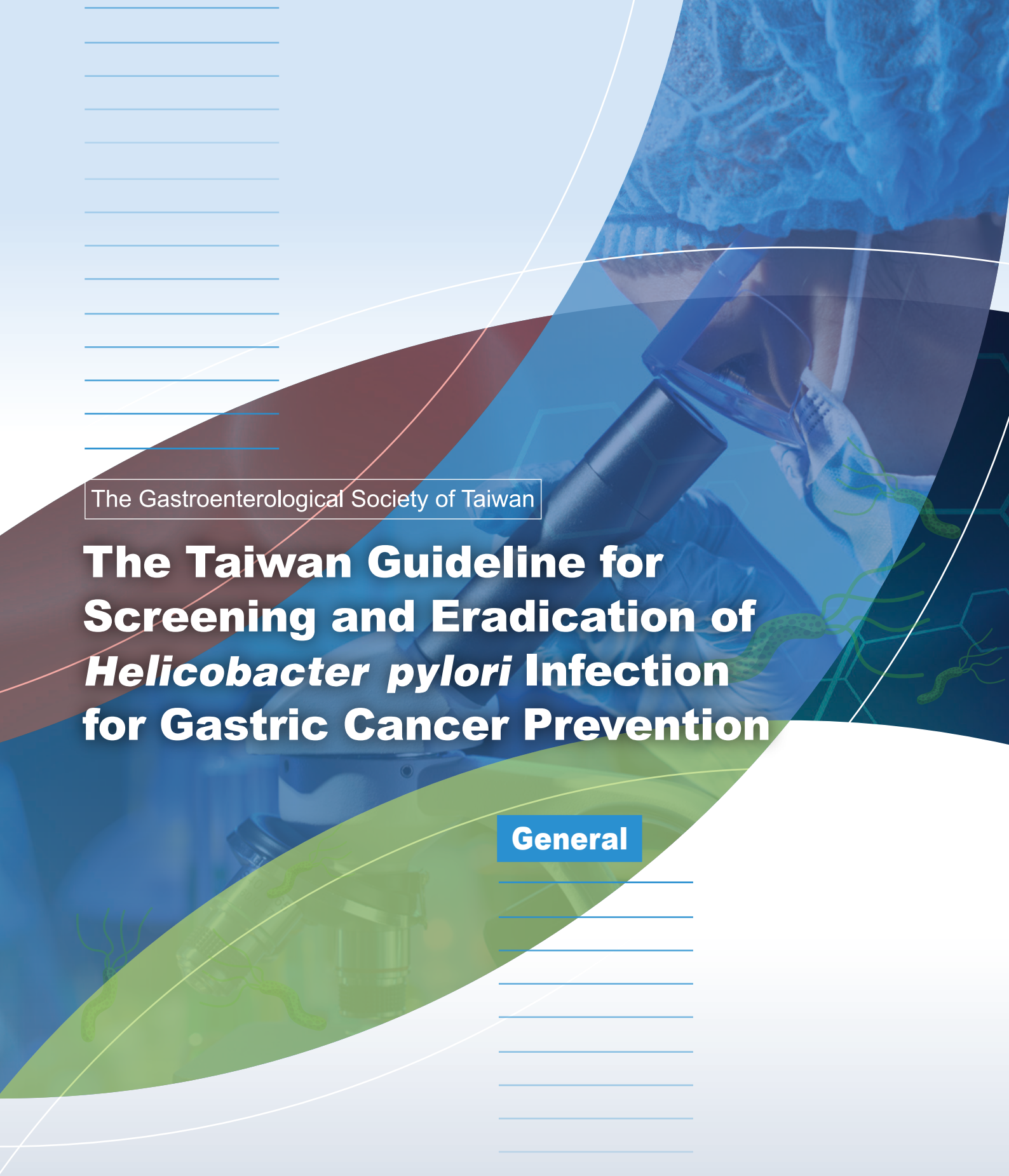

The Gastroenterological Society of Taiwan

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

General

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Introduction

Cancer remains the most common cause of death in Taiwan, and gastric cancer ranks among the top ten causes of cancer deaths in Taiwan. *Helicobacter pylori* (*H. pylori)* infection is an important causal factor for the development of gastric cancer. About 80 to 90% of gastric cancers are attributable to *H. pylori* infection. Therefore, eradication of *H. pylori* is an effective method for the prevention of gastric cancer.

In order to let people understand the causal relationship between *H. pylori* and gastric cancer, as well as the various problems that may be faced in the process of screening and eradication of *H. pylori* for gastric cancer prevention, the Health Promotion Administration commissioned the Gastroenterological Society of Taiwan to develop this guideline based on the most up-to-date research evidence. This guideline will help you to further understand the impact of *H. pylori* on gastric cancer and understand relevant information, so as to provide you with the most appropriate decision.

Prevention of Gastric Cancer - Start with *H. pylori* screening

Helicobacter pylori (H. pylori) is one of the few bacteria that can survive in the stomach. In addition to causing chronic gastritis and peptic ulcer, the most serious outcome is the development of gastric cancer. According to epidemiological studies, up to 90% of gastric cancers are attributable to *H. pylori* infection. The incidence of gastric cancer can be reduced and gastric cancer can be prevented through screening and eradication of *H. pylori.*

» What is *H. pylori*

H. pylori is a causal factor of several upper gastrointestinal diseases. *H. pylori* infection causes chronic gastritis and may lead to peptic ulcer disease, atrophic gastritis, intestinal metaplasia, or gastric cancer if left untreated. The lifetime risks of peptic ulcer disease and gastric cancer are 15-20% and 1-4% among those with *H. pylori* infection. *H. pylori* was classified as a class I carcinogen by the consensus group of the World Health Organization and the International Agency for Research on Cancer in 1994. Meta-analysis of cohort studies showed that *H. pylori* infection is a major risk factor of gastric cancer. *H. pylori* infected subjects have a six-fold increased risk of gastric cancer than those without infection. Epidemiological studies showed that about 90% of non-cardia gastric cancers are attributable to *H. pylori* infection. A prospective cohort study from Japan showed that of the 1246 people with *H. pylori* infection, gastric cancer developed in 3% of them during the 8-year follow-up period. It is worth noting that none of the 280 people without *H. pylori* developed gastric cancer during the follow-up period. Meta-analysis of randomized controlled trials further showed that eradication of *H. pylori* infection reduces the risk of gastric cancer. These collectively provide strong evidence that gastric cancer can be prevented through screening and eradication of *H. pylori* infection.

» The route of transmission of *H. pylori* infection

The most important route of transmission for *H. pylori* is through oral ingestion. Epidemiological studies suggest that intra-familial transmission is an important source of infection, and most infected persons are infected by infected family members during childhood or adolescence, especially mothers with *H. pylori* infection. Therefore, screening of *H. pylori* may protect not only the health of individual subjects but also their family. In the 1990s, the prevalence of *H. pylori* was about 55% among adults in Taiwan. With the improvement of the economic situation and public health, the prevalence of *H. pylori* is now 30% among adults over the age of 20 in Taiwan. The prevalence among children and adolescents is 10%. It is expected that screening and eradication of *H. pylori* may further speed the reduction in the prevalence rate of *H. pylori* infection, although further evidence is required.

» Effectiveness of screening and eradication of *H. pylori* for gastric cancer prevention in Taiwan

In the past, some regions in Taiwan have piloted the screening and treatment of *H. pylori*, with remarkable results. The Matsu Islands used to be the place with the highest incidence of gastric cancer in Taiwan. After the implementation of mass screening and eradication of *H. pylori* infection since 2004, the prevalence of *H. pylori* has been reduced from nearly 70% to about 10%. The incidence of gastric cancer in Matsu Islands was significantly reduced by 53%, and it is predicted that the incidence of Matsu gastric cancer will be reduced by 68% by 2025. In Changhua County, the two-in-one detection method of fecal occult blood and fecal antigen of *H. pylori* was implemented in 2014. Preliminary results show that the incidence of gastric cancer has been reduced by about 10%, and the effect of colorectal cancer prevention and treatment has also been improved simultaneously. Based on the characteristics of oral transmission of *H. pylori*, current research points out that screening and eradication of *H. pylori* in families can reduce reinfection rate, avoid transmission among family members to children, and protect families. In 2018, high-risk areas in China started a pilot program for gastric cancer prevention adopting the household screening method.

» Who should be prioritized for screening of *H. pylori*?

Meta-analysis showed that people with a history of gastric cancer in the first-degree relatives have an overall risk of developing gastric cancer 2.4 times that of people without a family history of gastric cancer. According to the Taiwan Cancer Registry, the incidence of gastric cancer in men is about twice as high as in women. The elderly is also at a high risk of gastric cancer. The incidence of gastric cancer in men aged 55 to 59 has increased to 27.7 per 100,000 populations. Therefore, it is recommended that groups at higher risk of gastric cancer, including first-degree relatives with a history of gastric cancer, people aged over 50 years old, and people living in areas with a high incidence of gastric cancer, should be prioritized for screening of *H. pylori*.

» Early detection and early treatment

The effectiveness of screening and eradication of *H. pylori* infection for gastric cancer prevention is high, because eradication of *H. pylori* can reduce the risk of peptic ulcer and gastric cancer. Cost-effectiveness analysis showed that screening of *H. pylori* in high-risk populations for gastric cancer can reduce medical costs and improve health outcomes. In Taiwan, gastric cancer causes a loss of life expectancy of 12.3 years for women and 9.3 years for men, while a gastric cancer patient from the initial diagnosis and treatment to death costs about NT$500,000 in medical expenses. Based on cost-benefit calculation, it is cost-effective to provide eradication therapy for *H. pylori* infected people who are age 30 years or greater. Younger people benefit most from screening and eradication of *H. pylori* infection for gastric cancer prevention.

» How to screen *H. pylori* infection?

Non-invasive detection methods for *H. pylori* include carbon-13 urea breath test (^{13}C-UBT), *H. pylori* stool antigen test (HpSA) and serology. The ^{13}C-UBT is very accurate and it can be used to assess the effect of eradication therapy. However, the test subject must stop proton pump inhibitor (PPI) for at least 2 weeks and stop antibiotics or bismuth drugs for at least 4 weeks. ^{13}C-UBT is more expensive than the other two tests. HpSA is also accurate for detection of *H. pylori* infection and can be used to assess the treatment response of eradication therapy and is also less expensive than ^{13}C-UBT. The sensitivity of serology test for *H. pylori* is high and is least expensive. However, it cannot distinguish past infection from active infection. Therefore, subjects with positive serology test should be confirmed by ^{13}C-UBT or HpSA for therapy decision. Cost-effectiveness analysis showed that serology test or HpSA is more cost-effective than the ^{13}C-UBT for large-scale *H. pylori* screening programs.

» Invasive tests for detection of *H. pylori* infection during endoscopy

Endoscopic biopsy can also detect *H. pylori* infection by rapid urease test, histology, and culture. These tests are accurate but are subject to the number and site of sampling. The accuracy of the rapid urease test is comparable to the ^{13}C-UBT, and the results can be obtained in about half an hour, but it is necessary to stop proton pump inhibitors for at least 2 weeks, and to stop antibiotics or bismuth for at least 4 weeks before the test. Histology is subject to inter-observer variations. The specificity of culture is high but the sensitivity is affected by the number and site of sampling.

» How to treat *H. pylori* if the screening test is positive?

Once screening is positive for pylori, it is recommended to receive eradication therapy. The physician will decide the optimal regimen according to history of drug allergy, the local prevalence of antibiotic resistance, and the compliance with medication. At present, the recommended first-line treatment is quadruple therapy (including 10-14 days of bismuth quadruple therapy or 14 days of non-bismuth quadruple therapy). In areas with low clarithromycin resistance, 14-day triple therapy is an acceptable alternative. If the first-line treatment is unsuccessful, the second-line treatment can be taken. Bismuth quadruple therapy or levofloxacin triple or quadruple therapy can be used as the second-line rescue therapy.

Some people will experience mild to moderate side effects during eradication therapy, including nausea, vomiting, dizziness, abdominal discomfort, diarrhea, poor appetite, etc. People taking bismuth will have darker stool color or even black stool. In addition, drug-drug interactions should be taken into consideration in patients taking medication for chronic illness, such as cholesterol-lowering drugs (statins), as well as alcohol, grapefruit, etc. During the medication, you must follow the doctor′ s instructions to stop or avoid taking certain drugs. If two or more eradication therapies are still unsuccessful, susceptibility testing guided therapy is recommended. However, after considering the accessibility of testing, cost, and patient preference, empirical therapy based on medication history can be an alternative strategy.

» Endoscopic surveillance is indicated for people with gastric precancerous lesions

It is noteworthy that the efficacy of eradication therapy should be confirmed after eradication therapy. ^{13}C-UBT or HpSA are currently recommended tests to confirm the treatment response after eradication therapy. For those with atrophic gastritis or intestinal metaplasia, surveillance endoscopy is recommended because these people still have residual risk of gastric cancer even *H. pylori* eradication is successful. There are three methods to assess the severity of precancerous lesions, including

1. Histological examination through endoscopic biopsy to assess whether more advanced (stage 3 or 4) atrophic gastritis or intestinal metaplasia is present.
2. Endoscopic features suggestive of more extensive or severe atrophic gastritis or intestinal metaplasia of the stomach.
3. Abnormal serum pepsinogen I, II levels or ratio also indicates more severe atrophic gastritis.

For patients with atrophic gastritis and intestinal metaplasia, these lesions may still progress into gastric cancer after *H. pylori* eradication in some patients. Regular surveillance endoscopy is recommended in those with advanced atrophic gastritis or intestinal metaplasia. Surveillance endoscopy is also recommended for people with a family history of gastric cancer.

» How to avoid reinfection after eradication therapy

H. pylori is transmitted via oral route. Improvement in the public health and hygiene status can reduce the risk of reinfection. Since intra-familial transmission is an important source of re-infection, screening is recommended for their family members. If most of the *H. pylori* infected people in the community received eradication therapy, it is expected that the chance of *H. pylori* transmission will be greatly reduced, and the reinfection rate in the future will be very low, but further evidence is required.

Gastric Cancer Can be Prevented Through Screening and Eradication of *H. pylori*

» Features of Gastric Cancer

- 90% attributable to H. pylori
- Incidence higher in male than female by 1.5-2 fold
- Rising incidence after the age of 50 years

» Main Risk Factors of Gastric Cancer

- *H. pylori* infection
- High salt food
- Smoking
- Gastric cancer in first degree relatives
- Post subtotal gastrectomy

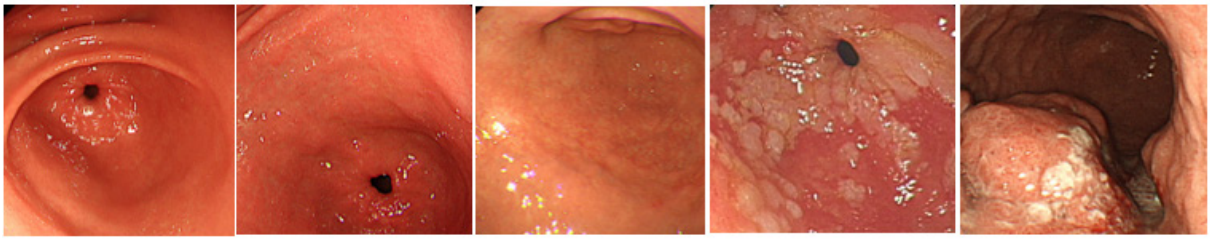
» *H. pylori* and Upper GI Diseases

- Increased risk of gastric cancer by 6-fold
- Among *H. pylori* infected people
  - ✓ Chronic gastritis in 90%
  - ✓ Gastric ulcer in 10%
  - ✓ Duodenal ulcer in 10%
  - ✓ Gastric cancer in 1-4%

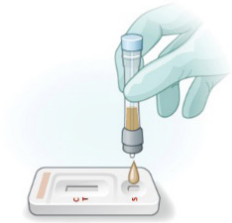
» *H. pylori* Negative Gastric Cancer

- 10% of gastric cancer are not related to *H. pylori* infection
- Etiology
  - ✓ Hereditary gastric cancer (1-5%)
  - ✓ EB virus
  - ✓ Severe gastroesophageal reflux disease

» Carcinogenesis processes after *H. pylori* infection



Normal mucosa | Chronic gastritis | Atrophic gastritis | Intestinal metaplasia | Gastric Cancer

Type of test	13C-UBT	HpSA	Serology
			
Price	More expensive	Intermediate	Less expensive
Sensitivity	≥95%	90%	90%
What should I do if the test is positive	Active infection. Eradication therapy is indicated.	Active infection. Eradication therapy is indicated.	Detects both past or active infection. Should be confirmed by 13C-UBT or HpSA for therapy decision.
Used to confirm treatment response?	Yes	Yes	No

» Early Detection and Early Treatment

- The risk of gastric cancer can be reduced by 50% after *H. pylori* eradication in infected subjects aged 50 years or above
- Better protective effect of eradication therapy for younger subjects
- The eradication rate of quadruple therapy is 90% in the first-line treatment
- The eradication rate of triple therapy for 14 days is 85% and can be an alternative therapy in regions with low clarithromycin resistance
- 13C-UBT or HpSA can be used to confirm eradication status 4-6 weeks after eradication therapy
- The reinfection or recrudescence rate is 1-2% after successful eradication therapy

MEMO

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