



WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Current progress toward eradicating *Helicobacter pylori* in East Asian countries: Differences in the 2013 revised guidelines between China, Japan, and South Korea

Sun-Young Lee

Sun-Young Lee, Department of Internal Medicine, Konkuk University School of Medicine, Seoul 143-729, South Korea

Author contributions: Lee SY solely contributed to this paper.

Supported by Konkuk University

Correspondence to: Sun-Young Lee, MD, PhD, Department of Internal Medicine, Konkuk University School of Medicine, 4-12 Hwayang-dong, Gwangjin-gu, Seoul 143-729,

South Korea. sunyoung@kuh.ac.kr

Telephone: +82-2-20307505 Fax: +82-2-20307505

Received: September 13, 2013 Revised: November 3, 2013

Accepted: January 6, 2014

Published online: February 14, 2014

Abstract

New 2013 guidelines on *Helicobacter pylori* (*H. pylori*) infection have been published in China, Japan, and South Korea. Like the previous ones, these new guidelines differ between the three countries with regard to the indications for *H. pylori* eradication, diagnostic methods, and treatment regimens. The most profound change among all of the guidelines is that the Japanese national health insurance system now covers the expenses for all infected subjects up to second-line treatment. This makes the Japanese indications for eradication much wider than those in China and South Korea. With regard to the diagnosis, a serum *H. pylori* antibody test is not recommended in China, whereas it is considered to be the most reliable method in Japan. A decrease relative to the initial antibody titer of more than 50% after 6-12 mo is considered to be the most accurate method for determining successful eradication in Japan. In contrast, only the urea breath test is recommended after eradication in China, while either noninvasive or invasive methods (except the bacterial culture) are recommended in South Korea. Due to the increased rate of antibiotics resistance, first-line treatment is omitted in China and South Korea in cases of

clarithromycin resistance. Notably, the Japanese regimen consists of a lower dose of antibiotics for a shorter duration (7 d) than in the other countries. There is neither 14 d nor bismuth-based regimen in the first-line and second-line treatment in Japan. Such differences among countries might be due to differences in the approvals granted by the governments and national health insurance system in each country. Further studies are required to achieve the best results in the diagnosis and treatment of *H. pylori* infection based on cost-effectiveness in East Asian countries.

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Key words: *Helicobacter pylori*; Eradication; Guideline; Diagnosis; Treatment

Core tip: Considerable advances in shifting from secondary prevention to primary prevention of gastric cancer are notable in the new 2013 guidelines from China, Japan, and South Korea. Compared to the previous guidelines, indications for *Helicobacter pylori* (*H. pylori*) eradication have expanded to include younger populations with acute gastric lesions, who will show markedly greater improvements than older populations with chronic gastric lesions. The indications of eradication, diagnostic methods, and treatment regimens for *H. pylori* infection differ between the countries due to differences in the approvals granted by the governments and national health insurance system in each country.

Lee SY. Current progress toward eradicating *Helicobacter pylori* in East Asian countries: Differences in the 2013 revised guidelines between China, Japan, and South Korea. *World J Gastroenterol* 2014; 20(6): 1493-1502 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i6/1493.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i6.1493>

INTRODUCTION

East Asian countries such as China, Japan, and South Korea are the high risk countries of *Helicobacter pylori* (*H. pylori*) infection and gastric cancer. Debates have been continued on whether to eliminate *H. pylori* in all infected East Asians by revising the guidelines, because everyone with *H. pylori* infection would be better eradicated at a reversible stage before the development of precancerous conditions^[1]. *H. pylori* tend to be more virulent East-Asian type cagA strain in these countries, and thus concerns were raised with regard to the previous guidelines that indicate to eliminate *H. pylori* only for some, leaving many infected East Asians untreated^[2-4].

The new revised 2013 guidelines from China, Japan, and South Korea show expanded indications for *H. pylori* eradication^[5-7]. These new guidelines started to include more recent infections at the acute stage that has not yet progressed to the irreversible stage leading to gastric cancer. Based on these guidelines, it is believed that strategy for the prevention of gastric cancer will shift from secondary prevention using esophagogastroduodenoscopy (EGD) to primary prevention using *H. pylori* eradication in East Asians. In this review, recent trends on *H. pylori* eradication in the East Asian countries will be discussed in terms of (1) indications; (2) diagnostic methods; (3) therapeutic regimens; and (4) issues after eradication based on the new 2013 guidelines.

INDICATIONS FOR *H. PYLORI* ERADICATION

Revised guidelines published in 2013 include more of the *H. pylori*-infected stomachs than the previous ones (Table 1)^[5-7]. Previous East Asian guidelines on *H. pylori* eradication were mainly focus low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, peptic ulcer disease (PUD), after the resection of early gastric cancer (EGC), idiopathic thrombocytopenic purpura (ITP), iron deficiency anemia of uncertain origin, and long-term use of certain drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or proton pump inhibitor (PPI)^[2-4]. However, new indications include even the asymptomatic *H. pylori*-infected subjects based on the concept that the benefits of eradication for gastric cancer prevention outweigh the risks.

China

The Fourth National Consensus Conference on the management of *H. pylori* infection consists of 3 categories: (1) detection; (2) indication; and (3) regimen for eradication^[6]. Indications for *H. pylori* eradication consist of 2 strongly recommended diseases (PUD and gastric MALT lymphoma) and 10 recommended diseases as summarized in Table 1. It is notable that *H. pylori*-related diseases consist of lymphocytic gastritis, Ménétrier disease, and gastric hyperplastic polyps^[8]. Intestinal metaplasia (IM) is not included based on the concept that it is hard to reverse

Table 1 Indications for *Helicobacter pylori* eradication in 2013 guidelines

	Indications
China	Strongly recommended
	Peptic ulcer (regardless of activeness or complications)
	Gastric MALT lymphoma
	Recommended
	Chronic gastritis with dyspepsia
	Chronic gastritis with mucosal atrophy/erosion
	Early gastric cancer resected endoscopically or by subtotal gastrectomy
	Long-term use of proton pump inhibitor
	Family history of gastric cancer
	Planning to take long-term NSAIDs (including low-dose aspirin)
	Iron deficiency anemia of unknown causes
	Idiopathic thrombocytopenic purpura
	Other <i>H. pylori</i> -related diseases (lymphocytic gastritis, gastric hyperplastic polyps, Ménétrier disease, etc.)
Japan	Requested by individual patient
	Approved by the Japanese national health insurance system
	Peptic ulcer disease
	After resection of early gastric cancer
	Gastric MALT lymphoma
	Idiopathic thrombocytopenic purpura
South Korea	<i>H. pylori</i> -related gastritis
	Strongly recommended
	Peptic ulcer disease
	Low-grade gastric MALT lymphoma
	After resection of early gastric cancer
	Recommended
	Chronic atrophic gastritis or intestinal metaplasia
	Family history of gastric cancer
	Functional dyspepsia
	Long-term aspirin/NSAIDs medication with history of peptic ulcer disease
Idiopathic thrombocytopenic purpura	

H. pylori: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue; NSAIDs: Nonsteroidal anti-inflammatory drugs.

IM^[9]. Their analysis also revealed that *H. pylori* eradication improves chronic atrophy gastritis (CAG) only in the gastric body.

Japan

The Ministry of Health, Labour and Welfare of Japan announced that the Japanese national health insurance system started to cover the expenses for *H. pylori* eradication in all of the infected subjects from February 2013. The current indications consist of five categories: (1) PUD; (2) after resection of EGC; (3) Gastric MALT lymphoma; (4) ITP; and (5) *H. pylori*-related gastritis (http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryuu/iryuuhoken). These expanded indications are not only for the prevention of *H. pylori*-related diseases such as gastric cancer but also for the prevention of dissemination. Since infection seems to disseminate from the parents to a child during the childhood period, dissemination of *H. pylori* can be prevented by eradicating all infected adults^[7].

Japanese cohort studies and randomized control trial on the effect of *H. pylori* eradication in preventing gastric

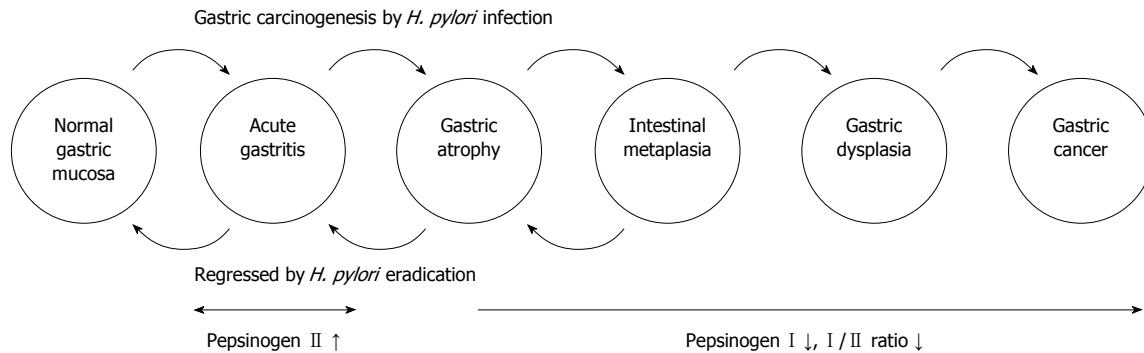


Figure 1 Changes in serum pepsinogen levels according to the progress of gastric carcinogenesis. The pepsinogen II level is increased in the acute stage of *Helicobacter pylori* (*H. pylori*) infection. A pepsinogen II level exceeding 30 ng/dL indicates that the subject has a high risk of diffuse-type gastric cancer. The pepsinogen I level then decreases as the infection progresses to the chronic stage. These features altogether results in the pepsinogen I / II ratio decreasing with the progress of gastric carcinogenesis. A pepsinogen I level below 70 ng/dL and a pepsinogen I / II ratio below 3.0 indicate that the subject has a high risk of intestinal-type gastric cancer. Since the pepsinogen II level is decreased after *H. pylori* eradication to a variable degree, a combination test for serum *H. pylori* antibody and the pepsinogen I / II ratio is not recommended for gastric cancer screening after eradication.

cancers have shown that it would more benefit in earlier ages and even in subjects with CAG and/or metaplastic gastritis (MG) before it progress further^[10-15]. Although open-type CAG and MG seem to be more progressed toward gastric carcinogenesis than closed-type CAG and nonatrophic/nonmetaplastic cases^[16], there is still a chance for incomplete-type IM to changed to a milder complete-type IM after eradication^[17]. When *H. pylori* eradication therapy is performed before the 30 years-old, the effect on gastric cancer prevention is near 100%, but it decreases to 41% in men and 71% in women when the eradication is performed after 70 years-old^[7,18,19].

Of various “*H. pylori*-related gastritis”, CAG, MG, hypertrophic gastritis (HG), and nodular gastritis (NG) are considered significant with regard to gastric carcinogenesis. CAG and MG are endoscopic findings of chronic *H. pylori* infection, while NG and HG are those of recent infection^[20]. In NG, inflammatory cytokines and *H. pylori*-infection-induced prostaglandins are normalized after eradication^[21]. Without eradication, some progress to a diffuse-type nodular gastritis, MALT lymphoma, or adenocarcinoma with poor differentiation^[22]. Besides, the odds ratio for gastric carcinoma is increases up to 35.5 in HG due to the increased levels of 8-Hydroxy-2-deoxy guanosine and interleukin-1 beta in the gastric mucosa^[23]. Similar to NG, *H. pylori* eradication is highly recommended for HG because the mutagenicity of gastric juice and the methylation of E-cadherin in gastric mucosa decrease significantly after eradication^[23,24].

In May 2013, the “Kyoto Guideline on the Endoscopic Gastritis” was announced at the Annual conference of Japanese Society of Gastrointestinal Endoscopy. According to this guideline, scores for these 4 types of endoscopic gastritis reported as “A M H N (total score)”. For CAG, the scores range from 0-3 according to the extent of the atrophic border. For MG, score 2 is given when metaplastic changes are observed during EGD. When an image-enhanced endoscopy was used for the diagnosis of MG, “(IM)” should be added. For HG, score 1 is given when there is a gastric fold width

greater than 7 mm. For NG, score 2 is given when there is a chicken-skin-like nodularity. If there is a history of *H. pylori* eradication, score -1 is subtracted from the total score and recorded as “E-1” after “A M H N”. For example, A3M2(IM2)H0N0E-1(4 scores) means that the subject has an opened-type CAG of severe-degree (3 scores), MG observed by image enhancing endoscopy (2 scores), and underwent a successful *H. pylori* eradication (-1 score). Therefore, score for the risk of gastric cancer is 4, indicating that there is a high risk of intestinal-type gastric cancer in this subject.

South Korea

The new South Korean guideline consists of 11 statements for the indication of *H. pylori* eradication, 4 statements for the diagnosis, and 4 statements for the treatment^[5]. Highly recommended indications for *H. pylori* eradication are (1) PUD including scar; (2) low-grade gastric MALT lymphoma; (3) after the resection of EGC. Although the level of evidence is lower than these indications, *H. pylori* eradication may be considered for the prevention of gastric cancer in the subjects with (4) CAG or IM; and (5) a family history of gastric cancer. South Korean studies have shown the importance of a family history of gastric cancer especially for those before 40 years-old^[25-27]. *H. pylori* eradication is reported to improve severe CAG and IM^[28]. Improvement by *H. pylori* eradication seems to be more definite in patients with body-predominant gastritis, severe IM, or low pepsinogen I / II ratio (Figure 1). Although the *H. pylori* infection rate in South Korea is decreasing^[29], care should be taken to prevent gastric carcinogenesis, because most of *H. pylori* isolated in South Koreans possesses virulent East-Asian cagA type as observed in our previous study^[30].

According to this new guideline^[5], EGD followed by *H. pylori* eradication is recommended for functional dyspepsia (FD) subjects, because eliminating *H. pylori* improves not only the gastritis but also the FD symptoms suggesting that *H. pylori*-induced inflammation mediates FD in the East Asians^[31]. There is a view point that FD-

Table 2 Diagnostic methods for *Helicobacter pylori* infection in 2013 guidelines

		China	Japan	South Korea
For initial diagnosis	Non-invasive methods	Urea breath test Stool antigen test	Serum antibody test Urea breath test Stool antigen test	Serum antibody test Urea breath test Stool antigen test
	Invasive methods	Rapid urease test Histology Culture	Rapid urease test Histology Culture	Rapid urease test Histology
Follow-up test after eradication	Non-invasive methods	Urea breath test Stool antigen test	Serum antibody test ¹ Urea breath test Stool antigen test	Urea breath test Stool antigen test
	Invasive methods	Rapid urease test	Rapid urease test Histology Culture	Rapid urease test Histology

¹In Japan, a decrease relative to the initial antibody titer of more than 50% after 6-12 mo is considered to be the most accurate method for determining successful eradication. Since the Japanese national health insurance system covers 2 of 3 non-invasive tests at the same time, either "serology with the urea breath test" or "serology with the stool antigen test" is usually performed before and after *Helicobacter pylori* eradication.

related symptoms in the East Asian population should be considered as an organic disease due to *H. pylori* infection which is different from those in the West^[32]. Besides, *H. pylori* eradication should be considered in case of long-term aspirin medication to prevent the recurrence of PUD for those who have a history of PUD. Asians are considered to be more prone to bleeding than Caucasians^[33], and therefore eradication should be performed in East Asia where the prevalence of *H. pylori* infection is higher^[34]. Furthermore, the risk of PUD recurrence cannot be blocked by *H. pylori* eradication alone in case of long-term NSAIDs/aspirin medication, and thus PPI could be considered. Since acid suppressants accelerate body gastritis in the presence of *H. pylori* infection, it should be eradicated before the long-term use of PPI^[35]. In South Korea, eradicating *H. pylori* infection is less expensive and more effective than no-screening strategy in case of NSAIDs and/or aspirin medication^[36].

For the extraintestinal diseases, *H. pylori* eradication is indicated for the subjects with ITP^[5]. Other extragastric disease is not mentioned in the guideline, but there are several cardiovascular, hepatobiliary, dermatological, immunological, hematological, ophthalmological, and neurologic diseases improve after *H. pylori* eradication^[1].

DIAGNOSTIC METHODS FOR *H. PYLORI* INFECTION

Diagnosis of *H. pylori* infection in East Asians countries consists of invasive and non-invasive methods like those of the Western countries, but guidelines differ between China, Japan, and South Korea (Table 2). Noninvasive methods are serum *H. pylori* immunoglobulin G (IgG) antibody test, urine antibody test, stool antigen test, and 13C- or 14C-urea breath test (UBT). Invasive methods are those based on the gastric biopsy specimen using EGD. These include rapid urease test (RUT), bacterial culture, histology (Hematoxylin and Eosin stain, modified Giemsa stain, Genta stain, Warthin-Starry silver stain, toluidine blue stain, etc.), and gene detection method such

as Fluorescence *in situ* hybridization or polymerase chain reaction for testing resistance to the antibiotics. Due to the low cost of EGD in East Asian countries, invasive tests are frequently performed as noninvasive tests.

China

H. pylori infection can be diagnosed when there is a positive finding on the: (1) stool antigen test; (2) UBT; or (3) one of the invasive tests among RUT, histology, and culture^[6]. Positive serum *H. pylori* antibody is not included in the diagnostic criteria. Serology is used mainly for epidemiological survey and for certain conditions such as PUD bleeding and gastric MALT lymphoma in China. Different from Japan where the decreased antibody titer after 6 to 12 mo is considered as a reliable method in diagnosing successful eradication, serology is not recommended for both pre- and post-treatment re-examination in China.

UBT is recommended as the first choice for post-treatment evaluation of eradication of *H. pylori* infection at least 4 weeks after eradication^[6]. The new guideline indicates that *H. pylori* eradication can be diagnosed when there is a negative finding on the: (1) UBT; (2) stool antigen test; or (3) RUT of both samples taken from the gastric body and antrum. At least 4 wk before UBT, bismuth agents, antibiotics, or herbal medicines with antibiotic activity should be stopped. Acid suppressants should be stopped at least 2 wk before UBT, if any. Urease-dependent tests are not recommended for bleeding PUD, severe CAG, after gastrectomy, and gastric malignancy. For histology, the guideline denotes that *H. pylori* infection is highly suggestive even in the absence of organism when there is an active inflammation in IM.

Japan

The most reliable method for the confirmation of *H. pylori* infection is considered as the titer of serum *H. pylori* IgG antibody in Japan^[7,18,19]. Either 1 of 3 invasive methods (RUT, culture, or histology with either Giemsa, Warthin-Starry, Genta stain, etc.) or 2 of 3 noninvasive methods (serum *H. pylori* antibody, UBT, and stool an-

Table 3 Regimens for *Helicobacter pylori* eradication in 2013 guidelines

	China	Japan	South Korea
First-line treatment ¹	Amoxicillin 1 g (or metronidazole 400 mg), clarithromycin 500 mg, and PPI twice daily for 7-14 d	Amoxicillin 750 mg, clarithromycin 200 mg (or 400 mg), and PPI twice daily for 7 d	Amoxicillin 1 g, clarithromycin 500 mg, and PPI twice daily for 7-14 d
Second-line treatment	Bismuth 220 mg, tetracycline 750 mg, metronidazole 400 mg twice, and PPI twice daily for 10 or 14 d	Amoxicillin 750 mg, metronidazole 250 mg, and PPI twice daily for 7 d	Bismuth 120 mg four times, tetracycline 500 mg four times, metronidazole 500 mg thrice, and PPI twice daily for 7-14 d

¹In China and South Korea, first-line treatment can be passed directly to second-line treatment using bismuth-based quadruple therapy in cases with a high clarithromycin resistance rate (> 15%-20%). PPI: Proton pump inhibitor.

tigen test) are covered by the Japanese national health insurance system. For the initial diagnosis, both RUT and histology can be covered at the same time, but not thereafter. A combination of 2 noninvasive methods is preferred than 1 invasive test, because the accuracies of invasive tests are lower than those of noninvasive tests. After the first-line and second-line eradication therapy, the Japanese national health insurance system covers either 1 of 3 invasive methods or 2 of 3 noninvasive methods, respectively. Successful eradication is considered as more than 50% reduction of serum IgG antibody titer than its initial level after 6-12 mo of eradication.

South Korea

Recommendations for the diagnosis includes either one of the noninvasive methods (UBT, stool antigen test, or serum *H. pylori* IgG antibody test) or invasive methods (RUT or gastric biopsy for histology) as noninvasive methods^[5]. For invasive methods, it is recommended to take both samples at the antrum and body, and to biopsy the sites that show the least atrophic and metaplastic findings. Follow-up tests after eradication include UBT, stool antigen test, RUT, or histology after 4 wk. Acid suppressants are asked to be stopped at least 2 wk before UBT.

THERAPEUTIC REGIMENS FOR *H. PYLORI* ERADICATION

Increased use of antibiotics for various infections since childhood has resulted in increasing drug resistance and decreasing in *H. pylori* eradication rate using clarithromycin or metronidazole. The increased primary and secondary antibiotic resistance of *H. pylori* is different according to the region, and therefore the current recommended first-line therapy and second-line therapy are different between China, Japan, and South Korea (Table 3). There is no standard for third-line therapy in these guidelines, and thus (1) regimens including levofloxacin, moxifloxacin, or rifabutin; (2) sequential therapy; (3) concomitant therapy; (4) dual therapy; or (5) tailored therapy might be considered as alternatives.

China

Standard triple therapy using amoxicillin (or metronidazole), clarithromycin, and PPI twice a day for 7 to 14 d

are recommended for first-line treatment^[6]. However, the eradication rate of this triple therapy in China is below 80%. Some studies showed that individualized therapy should be done based on the region of the China indicating the antibiotic resistance, patient occupation, gender, and compliance^[37,38]. The resistance rates to metronidazole (60%-70%), clarithromycin (20%-38%), and levofloxacin (30%-38%) are higher than amoxicillin, furazolidone, and tetracycline (1%-5%)^[39]. As an alternative regimen, levofloxacin triple therapy (PPI, levofloxacin, and amoxicillin) or sequential therapy (5 d of PPI and amoxicillin followed by 5 d of PPI, clarithromycin, and metronidazole) is recommended. However, concomitant therapy (PPI, clarithromycin, amoxicillin, and metronidazole) is used only if the patients have the contraindication for bismuth.

In regions with high clarithromycin resistance rate over 15%-20%, bismuth quadruple therapy (bismuth, tetracycline, metronidazole, and PPI for 10 or 14 d) is recommended as a first-line treatment^[6]. In such cases, second-line treatments are used from the beginning without using first-line treatment. To overcome the resistance to metronidazole and clarithromycin, combined use of bismuth and PPI are usually recommended. Other quadruple regimens consist of a standard dose of PPI, bismuth potassium citrate 220 mg, and 2 different antibiotics twice daily for 10 or 14 d: (1) amoxicillin 1000 mg and clarithromycin 500 mg twice daily; (2) amoxicillin 1000 mg and levofloxacin 200 mg twice daily (or 500 mg once daily); (3) amoxicillin 1000 mg and furazolidone 100 mg twice daily; (4) tetracycline 750 mg and metronidazole 400 mg twice daily (or thrice daily); and (5) tetracycline 750 mg and furazolidone 100 mg twice daily^[6,40]. A recent Chinese study showed the efficacy and safety of traditional Chinese medicine for *H. pylori* eradication by reviewing 16 clinical trials^[41]. However, there was no significant effect of traditional Chinese medicine for *H. pylori* treatment as triple regimen, and therefore it is not recommended alone for *H. pylori* eradication.

Japan

Japanese treatment regimen consists of lower dose of antibiotics than other countries^[7,42]. For first-line treatment, a standard dose of PPI, amoxicillin 750 mg, and clarithromycin 200 mg (or 400 mg) are recommended twice daily for 7 d. For second-line treatment, PPI, amoxicillin

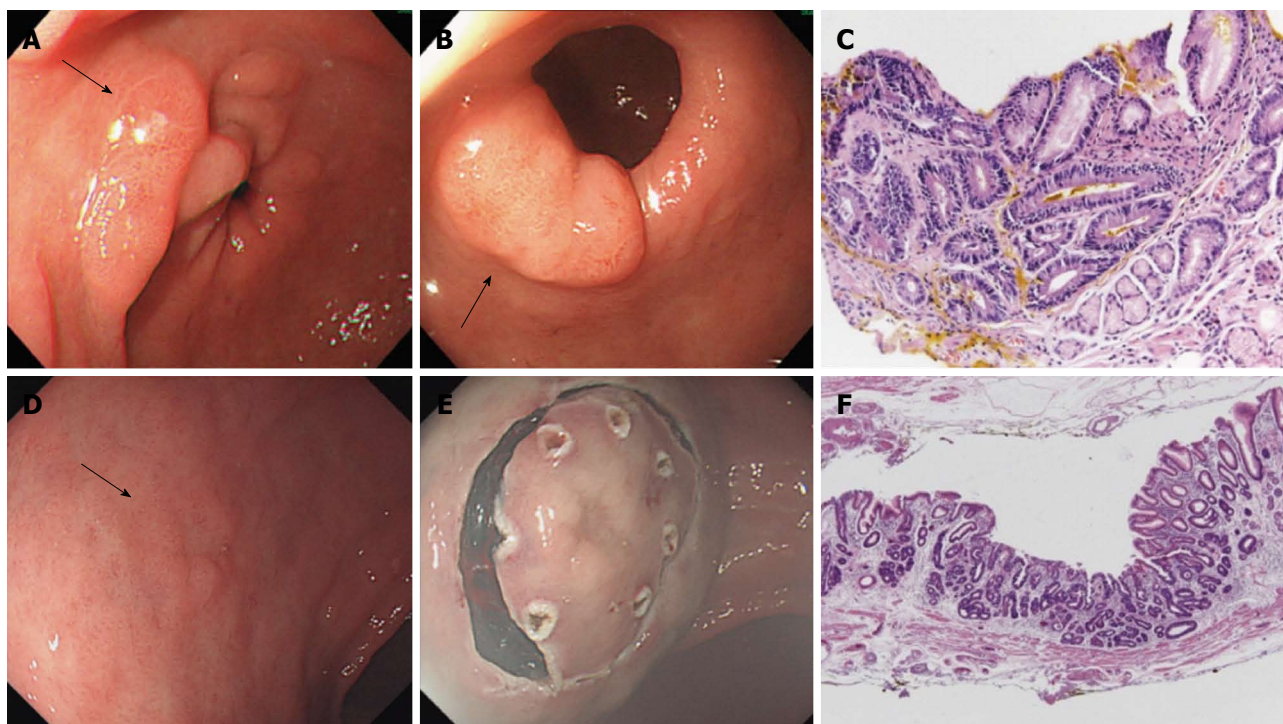


Figure 2 Metachronous gastric cancer that developed after 6 years of *Helicobacter pylori* eradication. A 61 year-old South Korean man visited because of epigastric discomfort in March 2007. A: Initial endoscopic finding. Several raised erosions with central ulceration (arrow) were evident. Since *H. pylori* infection was found by gastric biopsy, eradication was achieved using amoxicillin (1 g), clarithromycin (500 mg), and a standard dose of proton pump inhibitor twice daily for 7 d; B: Endoscopic finding after 2 years. In June 2009, a gastric adenoma near the pylorus (arrow) was diagnosed by endoscopic biopsy. Complete endoscopic resection was performed; C: Immunohistochemical staining of the resected specimen. Ki-67 staining was positive in the adenoma (Ki-67 stain, x 400); D: Endoscopic finding after 6 years. In January 2013, a slightly depressed lesion was evident on the lesser curvature side of the mid-antrum (arrow); E: Endoscopic submucosal dissection. The lesion was resected since the endoscopic biopsy revealed an adenocarcinoma; F: Pathological finding of the resected specimen. Early gastric cancer type II c of Lauren's intestinal-type, moderately-differentiated, tubular adenocarcinoma was diagnosed. The tumor size was 8.0 mm x 6.0 mm x 1.0 mm, and the depth of invasion was limited to the lamina propria (pT1a). Resection margins were free from carcinoma.

750 mg, and metronidazole 250 mg are recommended twice daily for 7 d. Neither 14 d nor bismuth-based quadruple treatment has been recommended as first-line or second-line treatment in Japan.

The eradication rate of the first-line regimen is 70% and that of the second-line regimen is 90% in Japan, and thus the eradication rate exceeds 95% with these two regimens^[42,43]. There is no standard recommendation for the third-line treatment in Japan. Moreover, the Japanese national health insurance system does not cover after second-line treatment. Regimens such as (1) high-dose amoxicillin with PPI; or (2) quinolone with amoxicillin and PPI are often used for the third-line treatment^[44]. Third-line treatment regimens preferred by the Japanese doctors are (1) amoxicillin 500 mg 3 or 4 times daily, ciprofloxacin 100 mg twice daily, and PPI 2-4 times daily for 1-2 wk; (2) metronidazole 250 mg twice daily, ciprofloxacin 100 mg twice daily, and PPI 2-4 times daily for 1-2 wk; and (3) amoxicillin 500 mg 4 times daily and PPI 4 times daily (with ecarbet sodium 1 g) 4 times daily for 2-4 wk as mentioned in page 36 of the Japanese supplement published in April 18th, 2013 by the Japanese Society of *Helicobacter* Research (unpublished data in English).

South Korea

For first-line treatment, recommended regimens are a standard dose of PPI, amoxicillin 1 g, and clarithromycin

500 mg twice daily for 7 to 14 d^[5]. In cases of treatment failure and with clarithromycin resistance, a standard dose of PPI twice a day, metronidazole 500 mg thrice a day, bismuth 120 mg 4 times a day, and tetracycline 500 mg 4 times a day are recommended for 7 to 14 d. In case of treatment failure with the quadruple therapy, more than two antibiotics that differ from previous regimens are recommended. Phytochemicals such as South Korean red ginseng, green tea, red wine, flavonoids, broccoli sprouts, garlic, probiotics, and flavonoids are known to inhibit *H. pylori* colonization *H. pylori*-related inflammatory process^[45]. However, phytochemicals are not recommended as a standard treatment in East Asian countries.

The guideline denotes the duration of medication from 7 to 14 d^[5]. Notably, the eradication rate second-line treatment differs according to the duration of the treatment. The eradication rate of 2 wk of bismuth-containing quadruple therapy is significantly higher (93.6%) than that of the 1 wk-treatment (77.2%)^[46]. In South Korea, the eradication rates of first-line and second-line regimen are decreasing because of the antibiotic resistance rates on amoxicillin (6.3%-14.9%), clarithromycin (17.2%-23.7%), and synchronous levofloxacin and moxifloxacin (4.7%-28.1%)^[47]. In addition, continuing genomic diversities in the same *H. pylori* strain may result in the presence of simultaneous antibiotic-susceptible and -resistant *H. pylori* in the same host, and modulate

Table 4 Different characteristics of 2013 guidelines in three countries

	Country	Notable differences in characteristics
Indication for eradication	China	Strong recommendations do not include after resection of EGC. Intestinal metaplasia is not included in the indications
	Japan	All infected subjects are included as “ <i>H. pylori</i> -related gastritis” Focus is on preventing dissemination
Diagnostic method	South Korea	Strong recommendations include only peptic ulcer disease, gastric MALT lymphoma, and after resection of EGC
	China	Serology is not recommended Only the urea breath test is recommended after eradication Invasive tests are not recommended after eradication
	Japan	Either two noninvasive tests or one invasive test is recommended
Treatment regimen		A decrease relative to the initial serum antibody level of more than 50% after 6-12 mo is considered the most reliable method
	South Korea	Bacterial culture is not included
	China	Due to the high resistance to the antibiotics metronidazole, clarithromycin, and tetracycline, an alternative regimen is recommended First-line treatment can be omitted in cases of clarithromycin resistance
	Japan	Lower dose of antibiotics for shorter duration (7 d) than other countries There is neither 14 d nor bismuth-based regimen in the first-line and second-line treatment
	South Korea	First-line treatment can be omitted in cases of clarithromycin resistance

EGC: Early gastric cancer; *H. pylori*: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue.

heteroresistant antibacterial phenotypes in South Korean adults^[48]. Such an isogenic variation of *H. pylori* strain in a single host would be one of the reasons of treatment failure.

ISSUES AFTER THE SUCCESSFUL ERADICATION

After the eradication, it is important to inform the patients that there is a risk of false-negative finding, gastric cancer, GERD, and reinfection. The rates of reinfection are decreasing in East Asian countries due to the improved sanitization and socioeconomic status. Recent studies showed that reinfection rate is lower in Japan (0.22% per year) than China (2.82%) and South Korea (2.94%)^[49-51]. Male gender (HR = 2.28) and low monthly family income (HR = 3.54) are known as main factors associated with *H. pylori* reinfection^[52].

Gastric cancer after eradication

H. pylori eradication will have the greatest impact on reducing the burden of gastric cancer in the East Asian countries. Based on previous studies and hypotheses that eradication therapy not only inhibits the new occurrence of gastric cancer but also regresses the growth of gastric cancer^[10-15], prophylactic eradication is recommended after EGC resection to prevent metachronous gastric carcinoma. However, some will continue to progress toward a gastric cancer even after the eradication because the benefit differs according to the degree of CAG and type of IM (Figure 2). A Japanese study showed that *H. pylori* eradication prior to development of incomplete-type IM improves gastritis in the gastric body^[7,18,53]. Eradication seem to be most effective before the significant atrophy develops, but eradication cannot completely prevent EGC even some mild CAG cases^[14]. Taken altogether, *H. pylori* eradication should be recommended even in high-risk populations with CAG and IM, although it cannot

completely abolish the risk of gastric cancer.

The incidence of gastric cancer after a successful eradication is higher in the subjects after gastric cancer resection (10.1%) than gastric ulcer (2.4%), gastric MALT lymphoma (2.2%), chronic gastritis (1.6%), and duodenal ulcer (0.3%)^[18,19]. Therefore, regular EGD follow-up is usually recommended after eradication. In South Korea, most of the physicians recommend annual EGD follow-up to the subjects with CAG and IM regardless of their career, position, and degree of the hospital^[54].

Gastroesophageal reflux disease after eradication

There is still a controversy on the link between *H. pylori* and GERD. Although some GERDs are improved by *H. pylori* eradication^[55], some develop after eradication^[56,57]. Care should be taken because hyperacidity-related diseases such as GERD and erosive gastroduodenitis after *H. pylori* eradication seem to occur more often in Eastern countries due to increased gastric acid secretion in body-dominant gastritis. In a prospective post-eradication study on 1195 *H. pylori*-positive BGU patients, GERD developed in 279 of 1000 successfully eradicated cases after a mean follow-up period of 3.6 years^[57]. Most of newly developed GERD was mild (Los Angeles grade A) and transient, and most did not require long-term treatment in their study. Different from Japanese studies, large-sized study from South Korea and meta-analysis on 11 papers from China show that there is no link between *H. pylori* eradication and GERD^[58,59]. Taken as a whole, *H. pylori* eradication therapy should not be withheld for fear of GERD development in the East Asia.

The prevalence of GERD might be increased due to obesity after the physiological changes that happen after eradication. *H. pylori* infection increases gastric leptin by reducing ghrelin-producing cells in the gastric mucosa^[60]. As a result, *H. pylori* influences body weight, hunger, and satiety, and thus affect the pathophysiology of obesity^[61]. After eradication, subjects show increased gastric emptying and increased appetite due to increased ghrelin

level^[62].

CONCLUSION

The new 2013 guidelines from China, Japan, and South Korea reflect the current progress toward eradicating *H. pylori* among East Asians. Compared to the previous guidelines, indications for *H. pylori* eradication have expanded to include younger populations with acute gastric lesions, who will show markedly greater improvements than older populations with chronic gastric lesions. Considerable advances in shifting from secondary prevention to primary prevention of gastric cancer are notable in these new guidelines. It is also notable that the indications of eradication, diagnostic methods, and treatment regimens for *H. pylori* infection differ between the countries (Table 4), despite similarities in the prevalence rates of *H. pylori* infection and gastric cancer. Such differences among countries might be due to differences in the approvals granted by the governments and national health insurance system in each country. Further studies are required to provide directions for identifying the optimal (1) diagnostic method with low false-negative rates; (2) treatment regimen to overcome antibiotic resistance, and (3) follow-up strategy after *H. pylori* eradication based on cost-effectiveness in East Asian countries.

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P- Reviewers: Buzas GM, D'Elios MM, Kim BW, Pimanov SI
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ISSN 1007-9327



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