



Management of *Helicobacter pylori* Infection: A Comparison between Korea and the United States

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Helicobacter pylori has been well known to cause gastritis, peptic ulcers, mucosa-associated lymphoid tissue, and gastric cancer. The importance of *H. pylori* eradication has been emphasized; however, the management of *H. pylori* infection is difficult in clinical practice. In both Eastern and Western countries, there has been a constant interest in confirming individuals who should be tested and treated for *H. pylori* infection and developing methods to diagnose *H. pylori* infection. Many studies have been implemented to successfully eradicate *H. pylori*, and various combinations of eradication regimens for *H. pylori* infection have been suggested worldwide. Based on the findings of previous studies, a few countries have published their own guidelines that are appropriate for their country; however, these country-specific guidelines may differ depending on the circumstances in each country. Evidence-based guidelines and clinical practice updates for the treatment of *H. pylori* infection have been published in Korea and the United States in 2021. This review will summarize the similarities and differences in the management of *H. pylori* infection in Korea and the United States, focusing on indications, diagnosis, and treatments based on recent guidelines and recommendations in both countries. ([Gut Liver 2022;16:503-514](#))

Key Words: *Helicobacter pylori*; Disease management; Republic of Korea; United States

INTRODUCTION

Helicobacter pylori infection is a cause of certain gastrointestinal disorders, including gastritis, peptic ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. The International Agency for Research on Cancer, an agency of the World Health Organization (WHO), has proclaimed that *H. pylori* is a definite risk factor for gastric cancer (group I) in 1994 and 2009;¹ however, successful treatment of *H. pylori* infection is as difficult as preventing *H. pylori* infection in the clinical setting due to increased antibiotic resistance in *H. pylori*.

Regarding antibiotic resistance, clarithromycin resistance in *H. pylori* is the most important factor determining the success or failure of eradication therapy. Clarithromycin-containing regimens have revealed eradication rates of <80% worldwide, indicating that they are unsuitable for empirical use.² The WHO has announced that clarithromycin-resistant *H. pylori* is a high-priority pathogen (pri-

ority 2) for the research and development of new antibiotics and has been assigned the same grade as vancomycin-resistant *Enterococcus faecium* and methicillin-resistant, vancomycin-intermediated, and vancomycin-resistant *Staphylococcus aureus*.³

The third edition of the Korean guidelines on the treatment of *H. pylori* infection was recently published.⁴ In addition, clinical practice update of the American Gastroenterological Association (AGA) on the treatment of refractory *H. pylori*, especially salvage or rescue therapies for *H. pylori* infection, was published in 2021.⁵ Nonetheless, the existing American College of Gastroenterology (ACG) clinical guidelines and recommendations of the Houston Consensus Conference (HCC) are important references for the diagnosis and treatment of *H. pylori* infection in the United States (US).^{6,7} Therefore, this review aimed to investigate the current recommendations concerning the indications, diagnosis, and treatments of *H. pylori* infection in Korea and the US based on the abovementioned



reference guidelines.

H. pylori ERADICATION IN KOREA

The Korean College of *Helicobacter* and Upper Gastrointestinal Research group proposed guidelines for the diagnosis and treatment of *H. pylori* infection for the first time in Korea in 1998, and the revised edition was published in 2013.^{8,9} The third edition of guidelines for the treatment of *H. pylori* infection in Korea was published in 2021.⁴ The difference between the current and previous guidelines is that the third edition of guidelines is based on evidence-based medicine and *de novo* meta-analysis.⁴

1. Indication

The previous revised edition of the Korean guidelines describes 11 statements on the indications for *H. pylori* eradication,^{9,10} and the third edition of the Korean guidelines newly added two statements⁴ to include unexplained iron deficiency anemia (IDA) and after endoscopic resection of gastric adenoma. All statements were either strong or weak recommendations.

The five strong recommended indications for *H. pylori* eradication include the following: (1) peptic ulcer diseases,

including scar stage, (2) MALT lymphoma of the stomach, (3) after endoscopic resection of early gastric cancer (EGC), (4) long-term low-dose aspirin user with a history of peptic ulcer diseases, and (5) idiopathic thrombocytopenic purpura (ITP).^{4,9} Although the level of evidence for weak recommended indications is lower than that for strong recommended indications, they include the following: (1) family history of gastric cancer, (2) functional dyspepsia, (3) unexplained IDA, and (4) after endoscopic resection of gastric adenoma (Table 1).⁴ Atrophic gastritis and/or intestinal metaplasia, a previous indication, dismissed owing to a lack of evidence and expert agreement.⁴ However, the controversy over atrophic gastritis and/or intestinal metaplasia seems to be discussed again when setting up the next Korean guidelines.

The insurance coverage policy is another issue in Korea. Until 2017, the Korean Health Insurance Review and Assessment Service allowed *H. pylori* eradication treatment in patients with peptic ulcer diseases, including scar stage; low-grade gastric MALT lymphoma; and after endoscopic resection of EGC. However, since January 1, 2018, the range of diseases that can be treated for *H. pylori* eradication was expanded. The newly added indications were as follows: ITP, after endoscopic resection of gastric adenoma, first-degree relatives of gastric cancer, atrophic gastritis,

Table 1. Indications for *Helicobacter pylori* Eradication in Korea and the United States

Strength of recommendations	Korea	United States	
		ACG	Houston Consensus Conference
Strong recommendations	Peptic ulcer disease	All patients with active <i>H. pylori</i> infection	All patients with active <i>H. pylori</i> infection
	Gastric MALT lymphoma	Active peptic ulcer disease	Peptic ulcer disease
	History of endoscopic resection of early gastric cancer	Low-grade gastric MALT lymphoma	Gastric MALT lymphoma
	Idiopathic thrombocytopenic purpura	History of endoscopic resection of early gastric cancer	Uninvestigated dyspepsia
	Long-term low-dose aspirin user with a history of peptic ulcer	Functional dyspepsia	Patients with reflux symptoms (only if they have high risk for <i>H. pylori</i> -related disease)
Weak recommendations	Family history of gastric cancer	Patients with typical GERD symptoms who do not have a peptic ulcer disease history*	Idiopathic thrombocytopenic purpura
	Functional dyspepsia	Patients starting chronic treatment with a NSAID	Family history of gastric cancer
	Unexplained iron deficiency anemia		Family history of peptic ulcer disease
	History of endoscopic resection of gastric adenoma		First-generation immigrants from high prevalence areas
			Family members residing in the same household of patients with proven active <i>H. pylori</i> infections
Weak recommendations	Family history of gastric cancer	Uninvestigated dyspepsia	Latino and African American racial or ethnic groups
	Functional dyspepsia	Long-term low-dose aspirin user	Long-term PPI user (>1 month)
	Unexplained iron deficiency anemia	Unexplained iron deficiency anemia	Long-term aspirin/NSAID user (>1 month)
	History of endoscopic resection of gastric adenoma	Idiopathic thrombocytopenic purpura	Patients treated with medications whose absorption is known to be impacted by infection (e.g., levodopa, thyroxin)

ACG, American College of Gastroenterology; MALT, mucosa-associated lymphoid tissue; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

*The ACG guidelines strongly recommend that these patients do not need to be tested for *H. pylori* infection.

and when medical judgment requires eradication therapy and the patient agrees to administer the treatment. These changes may be possible based on the broad clinical and epidemiological research on *H. pylori* in Korea.

In 2013, the insurance coverage policy for *H. pylori* eradication was expanded to cover all patients with *H. pylori*-positive gastritis in Japan. The number of patients with successful *H. pylori* eradication almost doubled to 1,380,000 per year in 2013 compared to 650,000 per year between 2001 and 2012.¹¹ The indications for *H. pylori* eradication have reorganized recently in Korea, and the proportion of *H. pylori* eradication treatment is predicted to increase in the near future, similar to that seen in Japan.

2. Diagnosis

The third edition of the Korean guidelines did not fully cover the diagnostic aspect of *H. pylori* infection. Nevertheless, the third edition of the Korean guidelines covered polymerase chain reaction (PCR) or sequencing tests for the identification of clarithromycin-resistant *H. pylori*.⁴ Since the 2010s, the diagnosis of clarithromycin-resistant *H. pylori* infection using PCR or sequencing tests has been gradually and widely implemented in Korea. According to the results of several studies, the eradication rates of tailored therapy using PCR results were higher than those of control treatment, and similar results were observed for 7-day tailored therapy.¹²⁻¹⁴ Therefore, the third edition of Korean guidelines recommend clarithromycin resistance test using PCR or sequencing tests when prescribing standard triple therapy for 7 days as a first-line treatment.⁴ Except for the above change, the diagnosis for *H. pylori* infection is almost identical to the previous Korean guidelines. The Korean guidelines recommended either noninvasive or invasive diagnostic methods (Table 2).⁹ Noninvasive diagnostic methods comprise urea breath, stool antigen, and serology tests, including blood agglutination, complement

fixation, indirect immunofluorescence tests, and enzyme-linked immunosorbent assays.⁹ Rapid urease test (RUT) and histology are the recommended invasive diagnostic methods for *H. pylori* infection.⁹ A clarithromycin resistance test using PCR or sequencing tests, another invasive method, can be performed under the aforementioned circumstances.⁴ However, before the urea breath test (UBT), acid suppressants and antibiotics should be discontinued at least 2 weeks.⁹ Additionally, gastric biopsy specimens are collected both the antrum and corpus. When performing gastric biopsy on only one site, the specimens should be collected from an area with no or minimal mucosal atrophy and intestinal metaplasia to reduce false-negative results of invasive diagnostic methods.⁹ After treatment, the UBT, the stool antigen test, the RUT, or histological analysis are recommended to ascertain *H. pylori* eradication (Table 2).⁹ All tests should be implemented at least 4 weeks after termination of eradication therapy.⁹

As proposed in other guidelines, the antibiotic susceptibility test (AST) using culture is an ideal method for ascertaining *H. pylori* eradication therapy.¹⁵ However, only a few centers have a culture-based AST system in Korea, and it is difficult to implement an AST in most cases even if *H. pylori* eradication therapy fails. Although PCR or sequencing tests has a relatively high probability of false-positive results,¹⁵ they have the advantages of good accessibility and simplicity. Reflecting actual medical practice in Korea, the third edition of the Korean guidelines contained PCR or sequencing tests, and further research is needed to demonstrate the usefulness of PCR or sequencing tests.

3. *H. pylori* antimicrobial resistance

Successful *H. pylori* eradication has been difficult owing to the increase in antibiotic resistance in *H. pylori*. Recently, a nationwide prospective multicenter study evaluating the antibiotic resistance rates of *H. pylori* was conducted

Table 2. Diagnosis of *Helicobacter pylori* Infection in Korea and the United States

	Methods	Korea	United States
			Houston Consensus Conference
Initial diagnosis	Noninvasive	Serology	Urea breath test Stool antigen test
		Urea breath test Stool antigen test	
	Invasive	Rapid urease test	Histology [†]
		Histology	
		Polymerase chain reaction or sequencing for clarithromycin resistance test*	
Follow-up test after eradication therapy	Noninvasive	Urea breath test	Urea breath test Stool antigen test
		Stool antigen test	
	Invasive	Rapid urease test	Histology [†]
		Histology	

*When 7 days of standard triple therapy is considered first-line treatment; [†]If endoscopy is performed.

between 2017 and 2018 in Korea. A total of 580 patients were enrolled, and the resistance rates to clarithromycin, metronidazole, levofloxacin, ciprofloxacin, amoxicillin, and tetracycline were 17.8%, 29.5%, 37.0%, 37.0%, 9.5%, and 0%, respectively (Table 3).¹⁶ Another recent Korean study reported that the resistance rates to clarithromycin, metronidazole, and levofloxacin were high and increased from 2003 to 2018. Although the study was performed at a single tertiary hospital, and the number of patients was relatively small, they investigated the antibiotic resistance rates of *H. pylori* as primary and secondary. The primary resistance rates to clarithromycin, metronidazole, levofloxacin, amoxicillin, tetracycline, and rifabutin during 2015 to 2018 were 43.7%–45.9%, 36.6%–43.2%, 40.8%–62.2%, 5.6%–8.1%, 12.7%–16.2%, and 0%–3%, respectively.¹⁷ In addition, the secondary resistance rates to clarithromycin, metronidazole, levofloxacin, amoxicillin, and tetracycline between 2015 and 2018 were 78.0%, 51.2%, 70.7%, 17.1%, and 12.2%, respectively (Table 3). There were some differences in antibiotic resistance rates of *H. pylori* between the two studies; however, the results showed that the primary and secondary resistance rates to salient antibiotics were high in Korea.

Recently, Lee *et al.*¹⁸ reported the therapeutic effect of potassium-competitive acid blocker (PCAB), a potent gastric acid suppressant agents compared to proton pump inhibitor (PPI), on *H. pylori* using cultures and AST. After PCAB administration, the minimum inhibitory concentrations were improved by 46.3% for clarithromycin, 55.6% for metronidazole, 46.7% for fluoroquinolone, and 34.5% for amoxicillin in a total of 220 resistant *H. pylori* isolates from Korean patients.¹⁸ It is presumed that administration of PCAB might increase the susceptibility of *H. pylori* to antimicrobial resistance, and further studies on *H. pylori* eradication therapy with PCAB should be conducted in Korea.

4. Treatment

The primary *H. pylori* eradication regimens recom-

mended by the Korean College of *Helicobacter* and Upper Gastrointestinal Research group have barely changed from 1998. However, recommendations regarding *H. pylori* eradication regimens have substantially changed in the third edition of the Korean guidelines compared to those in the previous guidelines. Briefly, the duration of regimens has been extended, and the types of recommended first-line therapies have been added.

The duration of the standard triple therapy of 1 to 2 weeks was changed to 2 weeks in the third edition guidelines. Therefore, the Korean guidelines recommend primary treatment with 2 weeks of standard triple therapy comprising of a standard dose of PPI (1 g), amoxicillin (1 g), and clarithromycin (500 mg) twice a day (Table 4).⁴ If physicians consider 7-day standard triple therapy as the first-line treatment, the third edition Korean guidelines recommend performing a PCR or sequencing test for the confirmation of clarithromycin-resistant *H. pylori*.⁴

Sequential therapy and concomitant therapy, which were second-line treatments in the previous guidelines, are recommended as first-line treatments in the third edition.⁴ Sequential therapy consisted of 5-day standard dose of PPI and 1 g amoxicillin twice daily, followed by another 5-day standard dose of PPI, 500 mg clarithromycin, and 500 mg metronidazole twice daily.⁴ Concomitant therapy included 500 mg metronidazole twice daily in standard triple therapy.⁴ Further, bismuth-containing quadruple therapy was also discussed as one of the first-line eradication therapies; however, it was recommended when other therapies were unfeasible because of its high adverse effects and the possibility of use as salvage therapy.⁴

Two-week bismuth-containing quadruple therapy, which consisted of a standard dose of PPI two times daily, 500 mg metronidazole three times daily, 120 mg bismuth four times daily, and 500 mg tetracycline four times daily, was recommended as salvage regimen in patients with failure of standard triple therapy or non-bismuth quadruple therapy (sequential or concomitant therapy) (Table 4).⁴ If bismuth-containing quadruple therapy failed, several

Table 3. Antibiotic Resistance Rates of *Helicobacter pylori* in Korea and the United States since 2015

Antibiotic	Korea		United States	
	Primary, %	Secondary, %	Primary, %	Secondary, %*
Clarithromycin	17.8–45.9	78.0	30.0	70.6
Metronidazole	29.5–43.2	51.2	33.3	79.4
Levofloxacin	37.0–62.2	70.7	29.6	42.9 [†]
Tetracycline	12.7–16.2	12.2	0.5	0.0
Amoxicillin	5.6–9.5	17.1	1.1	0.0
Rifabutin	0–3	-	0.5	-

*Antibiotic susceptibility test (AST) results in patients who failed two or more *H. pylori* eradication therapies between 2010 and 2017; [†]AST result for ciprofloxacin.

Table 4. Treatment Recommendations for *Helicobacter pylori* Eradication in Korea and the United States

	United States				
	Korea	AGA			
First-line treatment		ACG			
	Standard triple	Clarithromycin 500 mg bid for 14 days + amoxicillin 1 g bid for 14 days	PPI (standard or double dose) bid + clarithromycin 500 mg bid + amoxicillin 1 g bid or metronidazole 500 mg tid for 14 days	Not covered	
	Sequential	PPI (standard dose) bid + amoxicillin 1 g bid for 5 days + PPI (standard dose) bid + clarithromycin 500 mg bid + metronidazole 500 mg bid for 5 days	Bismuth quadruple	PPI (standard dose) bid + bismuth subcitrate (120–300 mg) or subsalicylate (300 mg) qid + metronidazole 500 mg tid to qid or metronidazole 250 mg qid + tetracycline 500 mg qid for 10–14 days	
	Concomitant	PPI (standard dose) bid + clarithromycin 500 mg bid + amoxicillin 1 g bid + metronidazole 500 mg bid for 10 days	Sequential	PPI (standard dose) bid + amoxicillin 1 g bid for 5–7 days + PPI (standard dose) bid + clarithromycin 500 mg bid + nitroimidazole [†] 500 mg bid for 5–7 days	
	Bismuth quadruple*	PPI (standard dose) bid + bismuth 120 mg qid + metronidazole 500 mg tid + tetracycline 500 mg qid for 10–14 days	Concomitant	PPI (standard dose) bid + clarithromycin 500 mg bid + amoxicillin 1 g bid + nitroimidazole [†] 500 mg bid for 10–14 days	
			Hybrid	PPI (standard dose) bid + amoxicillin 1 g bid for 7 days + PPI (standard dose) bid + clarithromycin 500 mg bid + amoxicillin 1 g bid + nitroimidazole [†] 500 mg bid for 7 days	
			Levofloxacin triple	PPI (standard dose) bid + levofloxacin 500 mg qd + amoxicillin 1 g bid for 10–14 days	
			Levofloxacin sequential	PPI (standard or double dose) bid + amoxicillin 1 g bid for 5–7 days + PPI (standard dose) bid + levofloxacin 500 mg qd + nitroimidazole [†] 500 mg bid for 5–7 days	
			LOAD	PPI (double dose) qd + levofloxacin 250 mg qd + nitazoxanide 500 mg bid + doxycycline 100 mg qd for 7–10 days	

Table 4. Continued

	Korea		United States	
	ACG	AGA	ACG	AGA
Second-line treatment				
1. After failure of standard (or clarithromycin) triple therapy	Bismuth quadruple PPI (standard dose) bid + bismuth 120 mg qid + metronidazole 500 mg tid + tetracycline 500 mg qid for 14 days	Bismuth quadruple	PPI (standard dose) bid + bismuth sub-citrate (120–300 mg) or subsalicylate (300 mg) qid + metronidazole 500 mg tid to qid + tetracycline 500 mg qid for 14 days	Not mentioned
2. After failure of non-bismuth quadruple therapy	Bismuth quadruple PPI (standard dose) bid + bismuth 120 mg qid + metronidazole 500 mg tid + tetracycline 500 mg qid for 14 days	Not mentioned	Levofloxacin triple PPI (standard dose) bid + levofloxacin 500 mg qd + amoxicillin 1 g bid for 14 days	Not mentioned
3. After failure of bismuth quadruple therapy	Levofloxacin triple PPI (standard dose) bid + levofloxacin 500 mg qd or 250 mg bid + amoxicillin 1 g bid for 14 days	Levofloxacin triple [§]	PPI (standard dose) bid + levofloxacin 500 mg qd + amoxicillin 1 g bid for 14 days	Levofloxacin triple Levofloxacin + high-dose or high-potency PPI tid + amoxicillin 750 mg tid
Additional regimens to consider	Triple therapy containing other fluoroquinolone Fluoroquinolone quadruple Rifabutin-containing therapy High-dose dual Concomitant	Concomitant Rifabutin triple High-dose dual	PPI (standard dose) bid + clarithromycin 500 mg bid + amoxicillin 1 g bid + nitroimidazole [‡] 500 mg bid for 10–14 days PPI (standard dose) bid + rifabutin 300 mg qd + amoxicillin 1 g bid for 10 days PPI (standard to double dose) tid to qid + amoxicillin 1 g tid or 750 mg qid for 14 days	Rifabutin triple High-dose dual Levofloxacin quadruple (PBLT or PBLM) Repeat PPI + bismuth + metronidazole + tetracycline
			Clarithromycin-containing therapy [§] (except clarithromycin triple therapy)	Rifabutin triple Alternative bismuth-containing quadruple PBLA (PPI + bismuth + levofloxacin + amoxicillin) PBLT (PPI + bismuth + levofloxacin + tetracycline) PBLM (PPI + bismuth + levofloxacin + metronidazole) PBMT (PPI + bismuth + metronidazole + tetracycline) PBCT (PPI + bismuth + clarithromycin [†] + tetracycline)

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; PPI, proton pump inhibitor; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day.

*Bismuth-containing quadruple therapy is recommended as the first-line treatment regimen if other first-line therapy regimens are not available; [†]Clarithromycin triple therapy is recommended for patients in areas with low rates of clarithromycin-resistant *H. pylori* (<15%) and for patients without a history of macrolide exposure; [‡]Metronidazole or tinidazole; [§]Choice is based on local antibiotic resistance data and patients' antibiotic history; ^{||}Metronidazole dose is 1.5–2 g daily in split doses; ^{††}This regimen applies only to the clarithromycin-sensitive strain.

salvage therapies were suggested. Among them, the first suggested regimen was levofloxacin triple therapy, which consisted of a standard dose of PPI twice daily, 500 mg levofloxacin once daily, or 250 mg levofloxacin twice daily, and 1 g amoxicillin twice daily.⁴ The other suggested regimens included triple therapy containing other fluoroquinolones, fluoroquinolone quadruple therapy, rifabutin containing therapy, high-dose dual therapy, or concomitant therapy (Table 4).⁴

In the past decades, the eradication rate of standard triple therapy has sustainably declined in Korea. A recent study using data from an online nationwide database registry revealed that the *H. pylori* eradication rate of 7- to 14-day standard triple therapy was 71.5% in 6,188 patients between 2010 and 2015.¹⁹ For sequential and concomitant therapies, a recent meta-analysis of six studies including 1,897 Korean patients from 2010 to 2015 reported that the pooled eradication rate of sequential therapy was 77.5% (95% confidence interval [CI], 64.8% to 90.2%) and 85.5% (95% CI, 78.6% to 92.4%) in intention-to-treat (ITT) and per-protocol (PP) analyses, respectively, and the pooled eradication rate of concomitant therapy was 82.5% (95% CI, 71.0% to 94.1%) and 91.5% (95% CI, 83.8% to 99.2%) in ITT and PP analyses, respectively.²⁰

The Korean College of *Helicobacter* and Upper Gastrointestinal Research group conducted a nationwide multicenter prospective randomized trial to evaluate the efficacy of 10-day sequential, 10-day concomitant, and 7-day standard triple therapies in Korea from 2016 to 2018.²¹ A total of 1,141 patients were enrolled from 15 hospitals, and the eradication rate of 10-day sequential therapy was 76.3% and 85.0% in ITT and PP analyses, respectively, and the eradication rate of 10-day concomitant therapy was 81.2% and 90.6% in ITT and PP analyses, respectively.²¹ However, the eradication rate of 7-day standard triple therapy was 63.9% in ITT analysis and 71.4% in PP analysis, and the eradication rates of 10-day sequential and concomitant therapies were statistically higher than those of 7-day standard triple therapy.²¹ Although there are limitations of different treatment durations in the three therapies, this study showed that 7-day standard triple therapy was insufficient in Korea. In accordance with the results of other studies, including this study,^{19,22} the use of 7-day standard triple therapy was discarded, and the third edition of the Korean guidelines has added sequential and concomitant therapies as new first-line eradication therapy.

Bismuth-containing quadruple therapy is valuable for *H. pylori* eradication. However, 10- to 14-day bismuth-containing quadruple therapy did not show a superior eradication rate compared to 14-day standard triple, 10-day sequential, and 10-day concomitant therapies.⁴ Instead, 10-

to 14-day bismuth-containing quadruple therapy revealed higher adverse effects than other regimens.⁴ Furthermore, because of the possibility of using it as salvage therapy, the third edition of the Korean guidelines did not recommend bismuth-containing quadruple therapy first.⁴

H. pylori ERADICATION IN THE UNITED STATES

Although the prevalence of *H. pylori* infection is relatively low in the US, the management of *H. pylori* infection is an area of medical interest. The last ACG clinical guidelines for *H. pylori* management were reported in 2007.²³ Subsequently, the revised clinical guidelines from the ACG were published in 2017,⁶ and there have been significant changes over the last decade. Among them, the most significant development has been made in medical treatment of *H. pylori* infection, and clinicians have been able to test various regimens for *H. pylori* eradication.

In 2018, recommendations of the HCC, which was comprised of experts on the management of *H. pylori* infection in the US, were published for indications for *H. pylori* eradication and diagnosis of *H. pylori* infection.⁷ There are some discrepancies between the ACG guidelines and the HCC recommendations. Overall, the HCC recommendations appear to be more specific and extend indications for *H. pylori* eradication.

The AGA clinical practice update was published in 2021. The updated review accentuated the importance of sufficient acid suppression, addition of bismuth, and use of a sufficient dose of metronidazole.⁵ Although the AGA update review only covered the management of refractory *H. pylori* infection, which is the same as salvage therapy, it is the first review associated to *H. pylori* infection proposed by the AGA.

1. Indication

The ACG clinical guidelines for the US divided the indications into two broad categories—indications to test and indications to treat. The strength of statements was also comprised of strong and conditional recommendations, depending on the quality of the evidence.⁶

A prerequisite of *H. pylori* management, which is strongly recommended, is that all patients with a positive result for active *H. pylori* infection should be treated, and patients with the crucial problem should be tested for *H. pylori* infection.⁶ The four established and recommended indications for diagnosis and eradication of *H. pylori* infection include the following: (1) active gastric or duodenal peptic ulcer diseases, (2) proven history of peptic ulcer

diseases, which are not previously treated for *H. pylori*, (3) low-grade gastric MALT lymphoma, and (4) after endoscopic resection of EGC.⁶ Additionally, treatment with chronic nonsteroidal anti-inflammatory drug was also a strongly recommended indication for testing and treating *H. pylori* infection.⁶ Further, dyspeptic symptoms along with a history of endoscopy with confirmed *H. pylori* infection and *H. pylori* infection with typical gastroesophageal reflux diseases symptoms are the strongly recommended indications for *H. pylori* eradication. However, the indications to test for *H. pylori* in these patients were slightly different from those to treat.⁶ For patients aged <60 years with uninvestigated dyspepsia and no alarming symptoms, a non-endoscopic *H. pylori* test should be considered; this is a conditional recommendation.⁶ With regard to patients with typical gastroesophageal reflux diseases symptoms, patients without a history of peptic ulcer diseases do not need to test for *H. pylori* infection, which is strongly recommended (Table 1).⁶

The conditional recommended indications for diagnosing and treating *H. pylori* infection are as follows: (1) long-term, low-dose aspirin use, (2) unexplained IDA, and (3) ITP.⁶ Additionally, there are no recommendations for routine diagnosis and treatment of *H. pylori* infection in patients with lymphocytic gastritis, hyperplastic gastric polyps, and hyperemesis gravidarum or asymptomatic patients with a family history of gastric cancer (Table 1).⁶

However, the HCC published 14 statements to ascertain appropriate patients for testing. Most indications are similar to those described in the ACG guidelines; however, the additional indications in the HCC recommendations are as follows: (1) patients with a family history of gastric cancer, (2) first-generation immigrants from high-prevalence areas of gastric cancer and *H. pylori* infection, (3) Latino and African American racial or ethnic group patients, (4) patients with a family history of peptic ulcer disease, (5) family members living with patients with confirmed active *H. pylori* infection, (6) long-term PPI (>1 month) users, and (7) patients receiving medications whose *H. pylori* infection influences drug absorption (Table 1).⁷

There are some differences in the indications for *H. pylori* eradication between the US and Korea, and there may also be discrepancies between strong and weak recommendations for *H. pylori* eradication indications. Among them, it is necessary to mention how patients with a family history of gastric cancer are considered indications for *H. pylori* eradication depending on the country. Although it is a weak recommendation, individuals with a family history of gastric cancer are one of the indications for *H. pylori* eradication in the Korean guidelines. However, patients with a family history of gastric cancer are not recommended for

the treatment of *H. pylori* infection in the ACG guidelines. This may be owing to differences in the prevalence of *H. pylori* infection and the incidence of gastric cancer between the two countries. The GLOBOCAN 2018 updates reported that Korea had the highest incidence rates of gastric cancer worldwide for both sexes.²⁴ A recent double-blind, placebo-controlled study from Korea reported that *H. pylori* eradication therapy declined the gastric cancer risk in *H. pylori*-infected patients with a family history of gastric cancer in first-degree relatives (hazard ratio, 0.45; 95% CI, 0.21 to 0.94; p=0.03).²⁵ Thus, the HCC strongly recommends testing and treating *H. pylori* in patients with a family history of gastric cancer.

2. Diagnosis

There were concise recommendations for diagnostic methods before and after eradication therapies in 2017 the ACG guidelines.⁶ However, the HCC proposed nine statements regarding testing methods and identification of *H. pylori* infection (Table 2).

For initial diagnosis, the UBT and stool antigen immunoassay are recommended for evaluating *H. pylori* infection, and serology is not recommended for the investigation of active *H. pylori* infection.⁷ If patients underwent endoscopy, two gastric biopsy samples were obtained from both the antrum and corpus (with or without the incisura).⁷ Cessation of PPIs, antibiotics, and bismuth before diagnosing *H. pylori* infection is similar between the guidelines; however, the duration of discontinuation of drugs is different depending on the guidelines. The HCC recommends that these drugs should be discontinued at least 4 weeks before performing the UBT, stool antigen immunoassay, and histological analysis, while the ACG guidelines recommend that acid suppressants and antibiotics should be discontinued at least 2 weeks before performing the UBT.^{7,9} There was no description in the ACG guidelines for histamine (H₂) receptor blockers and antacids; however, the HCC recommended that these drugs can be used continuously before performing the UBT and stool antigen immunoassay.^{7,9}

Stool antigen immunoassay is widely used for the detection of *H. pylori* infection in the US; however, the RUT is more widely used for diagnosing *H. pylori* infection in Korea. In terms of expense, the cost of stool antigen immunoassay is \$19.62 in the US and that of the RUT is approximately \$45 in Korea.²⁶ Nonetheless, the RUT is more popular in Korea owing to the Korean National Cancer Screening Program. Since 2002, biennial screening using upper endoscopy has been conducted every 2 years for adults aged ≥40 years in Korea according to the National Cancer Screening Program.²⁷ Therefore, accessibility to

upper endoscopy, including the RUT, is relatively easier in Korea than in the US.

Recently, real-time PCR testing to detect clarithromycin-resistant *H. pylori* from stool specimens has been reported in the US.²⁸ With the PCR assay, the eradication rate of *H. pylori* without clarithromycin resistance was significantly higher than that of clarithromycin-resistant *H. pylori* with clarithromycin triple therapy ($p=0.03$).²⁸ Moreover, a recent study from the US performed next-generation sequencing to confirm *H. pylori* infection and resistance rates using formalin-fixed paraffin-embedded gastric biopsy samples.²⁹ Further studies on the usefulness of PCR or sequencing tests may be needed in the US.

3. *H. pylori* antimicrobial resistance

The US is considered a country with low antibiotic resistance rates of *H. pylori* compared to Asian or European countries generally. However, studies verifying *H. pylori* antibiotic resistance in the US are scarce, and since the 2010s, there have been only two or three studies in a relatively large number of patients. According to the Veterans Affairs data in the US, *H. pylori* resistance to clarithromycin was 16.4%, to metronidazole was 20.3%, to levofloxacin was 31.3%, to tetracycline was 0.8%, and to amoxicillin was 0% in 2009 to 2013.³⁰ Recently, Argueta *et al.*²⁹ demonstrated antimicrobial resistance rates of *H. pylori* in the US using next-generation sequencing methods. Between 2018 and 2019, the *H. pylori* resistance rates for clarithromycin, metronidazole, levofloxacin, tetracycline, amoxicillin, and rifabutin were 30.0%, 33.3%, 29.6%, 0.5%, 1.1%, and 0.5%, respectively (Table 3). A notable aspect in the study is that 65.6% of *H. pylori* strains were resistant to one or more frequently used antimicrobials, and 9.7% of those strains were resistant to all three antimicrobials, including clarithromycin, metronidazole, and levofloxacin. Although more research needs to be supported, this result suggests the antibiotic resistance rates in the US is increasing in recent years.

Information of the secondary resistance rates of *H. pylori* is important to overcome *H. pylori* eradication failure. Tan *et al.*³¹ reported that the prevalence of antibiotic resistance to clarithromycin, metronidazole, and ciprofloxacin was 70.6%, 79.4%, and 42.9%, respectively, in 34 *H. pylori*-positive patients who failed more than two regimens of *H. pylori* eradication therapy from 2010 to 2017 in the US (Table 3). Although the number of *H. pylori* strains was relatively small, the study showed higher antibiotic resistance rates than that expected in the US. There are few studies on antibiotic resistance in the US, and it is practically difficult to be equipped with facilities for *H. pylori* culture and ASTs. Therefore, the ACG guidelines and AGA

clinical practice updates tend to emphasize on patient information with respect to previous antibiotic exposures, particularly macrolides and fluoroquinolones.

4. Treatment

The ACG guidelines recommend various *H. pylori* treatment options compared to the Korean guidelines for first-line eradication therapy. Fourteen-day clarithromycin triple therapy containing PPI, clarithromycin, and amoxicillin or metronidazole was recommended in areas with low rates of clarithromycin-resistant *H. pylori* infection (<15%) and patients without a previous history of macrolide exposure.⁶ Additionally, the following regimens were recommended for first-line therapy: (1) 10- to 14-day bismuth-containing quadruple therapy, (2) 10- to 14-day sequential therapy, (3) 10- to 14-day concomitant therapy, (4) 14-day hybrid therapy, (5) 10- to 14-day levofloxacin triple therapy, (6) 10- to 14-day fluoroquinolone sequential therapy, and (7) 7- to 10-day "LOAD" regimen (Table 4).⁶ The regimens of clarithromycin triple, bismuth quadruple, sequential, concomitant, and levofloxacin triple therapies are identical to those in the Korean guidelines. Additionally, hybrid therapy consisted of a standard PPI dose and 1 g amoxicillin for 7 days twice a day, followed by an additional 7-day standard PPI dose, 1 g amoxicillin, 500 mg clarithromycin, and 500 mg nitroimidazole twice a day.⁶ Levofloxacin sequential therapy was similar to the sequential therapy, with the drug changed from 500 mg clarithromycin twice a day to 500 mg levofloxacin once a day, and the duration was extended from 10 days to 10–14 days.⁶ An open-label, randomized study using the LOAD regimen was implemented in the US consisted of 250 mg levofloxacin, 40 mg omeprazole, and 100 mg doxycycline once a day with 500 mg nitazoxanide twice a day for 7–10 days.³²

For salvage therapy, the ACG guidelines proposed the following five regimens for use: (1) 14-day bismuth-containing quadruple therapy, (2) 14-day levofloxacin triple therapy, (3) 10- to 14-day concomitant therapy, (4) 10-day rifabutin triple therapy, and (5) 14-day high-dose dual therapy (Table 4).⁶ When a patient was treated with first-line clarithromycin-containing therapy, bismuth-containing quadruple and levofloxacin-containing regimens were the preferred therapeutic options.⁶ When a patient was treated with first-line bismuth-containing therapy, clarithromycin-containing or levofloxacin-containing regimens were the preferred therapeutic options.⁶ However, the AGC guidelines recommended that clarithromycin triple therapy should not be prescribed as salvage therapy.⁶

When bismuth-containing quadruple therapy failed as a first-line treatment, the AGA clinical practice update

proposed the following treatments: (1) levofloxacin triple therapy with high-dose dual PPI and amoxicillin, (2) rifabutin triple therapy with high-dose dual PPI and amoxicillin, and (3) an alternative bismuth-containing quadruple therapy, such as PBLA (PPI, bismuth, levofloxacin, amoxicillin), PBLT (PPI, bismuth, levofloxacin, tetracycline), PBLM (PPI, bismuth, levofloxacin, metronidazole), or PBCT (PPI, bismuth, clarithromycin, tetracycline).⁵ If second-line treatment with these regimens failed, the following regimens were proposed: (1) high-dose dual therapy, (2) levofloxacin quadruple therapy, such as PBLT or PBLM, and (3) repeat PBMT (PPI, bismuth, metronidazole, tetracycline) with high-dose metronidazole (1.5–2 g divided a day) (Table 4).⁵

Regarding the specific dose of regimens, rifabutin triple therapy consisted of a standard PPI dose, 1 g amoxicillin twice a day, and 300 mg rifabutin once a day for 10 days owing to rare complications of rifabutin, including myelotoxicity.³³ High-dose dual therapy, defined as a total dose of amoxicillin of >3 g per day, and amoxicillin should be administered at least three times a day to avoid low drug levels.³⁴ According to the ACG guidelines, a standard PPI dose and 750 mg amoxicillin four times a day for 14 days were components of high-dose dual therapy.⁶ However, according to the AGA updated review, when high-dose dual therapy is not used alone but used in addition to other therapies, a lower dose of antibiotics (750 mg amoxicillin three times a day) may be used.⁵ Additionally, the updated review recommended high-dose and/or high-potency PPIs in high-dose dual therapy.⁵

With regard to eradication therapy, several randomized controlled trials (RCTs) have identified the efficacy of various *H. pylori* eradication regimens in the US.^{35–37} However, most RCTs have evaluated the efficacy of first-line clarithromycin triple therapy containing a PPI, and a few RCTs have assessed the efficacy of first-line bismuth-containing quadruple therapy and sequential therapy.²³ However, no RCTs have investigated the efficacy of first-line concomitant, hybrid, levofloxacin triple, and fluoroquinolone sequential therapies in the US.²³ Similarly, one RCT has compared the efficacy of bismuth-containing quadruple therapy and clarithromycin triple therapy with a PPI,³⁸ and no RCT has been conducted in the US. There are various therapeutic options for *H. pylori* management in the ACG guidelines and AGA clinical practice updates; however, it is currently difficult to suggest evidence-based recommendations concerning the efficacy of these regimens. Further nationwide studies are needed to verify the efficacy of *H. pylori* eradication regimens in the US.

CONCLUSION

In summary, we compared the management of *H. pylori* infection between Korea and the US based on the guidelines and recommendations. Initially, it was predicted that there would be many similarities. However, in addition to similarities, there were many differences in the management of *H. pylori* infection in both countries. In the case of indications, the prevalence of *H. pylori* infection and gastric cancer varies by country; therefore, the Korean guidelines have emphasized on risk factors for gastric cancers compared with the US guidelines. Additionally, depending on the circumstances of the country, the differences in cost-effectiveness or accessibility of diagnostic tests may influence the type of test preferred in the clinical setting. In the treatment setting, both countries understand the seriousness of antibiotic-resistant *H. pylori* and have investigated various therapies to overcome this problem. Despite the higher prevalence of *H. pylori* infection and gastric cancer in Korea than in the US, the US guidelines recommend more progressive and liberal treatment regimens.

The primary and secondary antibiotic resistance rates of *H. pylori* are high in Korea and the US, and the management of *H. pylori* infection is difficult for many physicians. Fortunately, antibiotic resistance to tetracycline, amoxicillin, and rifabutin is not relatively high in both countries, therefore it is necessary to consider these factors when selecting antibiotics for *H. pylori* eradication therapy. Also, if PCAB can be used instead of PPI in the future, it is expected that the eradication rate of *H. pylori* eradication rate between Korea and the US will increase. Although limited centers conduct these tests in both countries, several additional tests such as PCR, culture and AST will need to be activated. A comprehensive understanding of the situation and problem-solving efforts is required at a national level.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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