KJHUGR REVIEW
pISSN 1738-3331 / eISSN 2671-826X https://doi.org/10.7704/kjhugr.2026.0029 Korean J Helicobacter Up Gastrointest Res 2026;26(2):164-188

https://www.helicojournal.org

Received April 13, 2026
Revised May 11, 2026
Accepted May 20, 2026

Corresponding author
Byung-Wook Kim, MD, PhD
Division of Gastroenterology,
Department of Internal Medicine,
Incheon St. Mary's Hospital,
College of Medicine,
The Catholic University of Korea,
56 Dongsu-ro, Bupyeong-gu,
Incheon 21431, Korea
E-mail: gastro@catholic.ac.kr

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest
Sung Eun Kim and Beom Jin Kim, contributing editors of the *Korean Journal of Helicobacter and Upper Gastrointestinal Research*, were not involved in the editorial evaluation or decision to publish this article.
All Development Committee members submitted conflicts of interest prior to participation. Members with identified conflicts were excluded from voting on the relevant recommendations.
The funding source had no influence on the content of the guidelines.

Funding Statement
This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2025-02304642).

Acknowledgements
None

This article is being published jointly in the *Korean Journal of Helicobacter and Upper Gastrointestinal Research*, the *Korean Journal of Gastroenterology*, and *Helicobacter*.

Evidence-Based Guidelines for the Diagnosis and Treatment of *Helicobacter pylori* Infection in Korea: 2025 Revised Edition

Chang Seok Bang[1], Seung Joo Kang[2], Hyunchul Lim[3], Seung Han Kim[4], Moon Won Lee[5], Su Youn Nam[6], Chung Hyun Tae[7], Sung Eun Kim[8], Seung Young Kim[9], Hye-Kyung Jung[7], Beom Jin Kim[10], Miyoung Choi[11], Hwoon-Yong Jung[12], Byung-Wook Kim[13]; Korean College of *Helicobacter* and Upper Gastrointestinal Research

[1]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea
[2]Department of Internal Medicine, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Korea
[3]Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea
[4]Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[5]Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea
[6]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea
[7]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea
[8]Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea
[9]Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Seoul, Korea
[10]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea
[11]Division of Healthcare Technology Assessment Research, National Evidence-based Healthcare Collaborating Agency, Seoul, Korea
[12]Department of Gastroenterology, Asan Medical Center, Asan Digestive Disease Research Institute, University of Ulsan College of Medicine, Seoul, Korea
[13]Division of Gastroenterology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Since the 2020 Korean guidelines for *Helicobacter pylori* treatment, clarithromycin resistance rates have risen from 17.8% to 33.3%, dual-priming oligonucleotide-based polymerase chain reaction-guided tailored therapy has been adopted, and potassium-competitive acid blockers (P-CABs) have become available. This fourth revision addressed these changes. Nine key questions were addressed through systematic review and meta-analysis. Thirteen recommendations were evaluated using a modified Delphi process involving 64 experts. Twelve recommendations achieved a first-round consensus; one required revision and achieved 73.9% agreement. Key changes included: 1) a dual-pillar strategy of tailored therapy and empirical quadruple therapy; 2) restricted use of empirical clarithromycin-based triple therapy under specific conditions; 3) removal of sequential therapy; 4) use of P-CABs as alternatives to proton pump inhibitors; 5) expansion of eradication indications to include gastric cancer prevention in *H. pylori* gastritis and regression of hyperplastic polyps ≤10 mm; and 6) positioning of bismuth quadruple therapy as a conditionally recommended first-line empirical option, with preference for reservation as salvage therapy, and introduction of modified bismuth quadruple therapy (addition of bismuth to conventional regimens) as an additional first-line empirical option. The revised guidelines provide updated evidence-based recommendations for the diagnosis and treatment of *H. pylori* infection, reflecting the rapidly changing antibiotic resistance landscape and the introduction of new diagnostic and therapeutic tools in Korea. These guidelines aim to assist clinicians, patients,

policymakers, and medical educators in optimizing *H. pylori* management. They may differ from the current medical insurance standards and will be further revised based on emerging evidence.

Keywords *Helicobacter pylori*; Clinical practice guideline; Antibiotic resistance; Tailored therapy; Potassium-competitive acid blockers.

INTRODUCTION

Helicobacter pylori infection is a common chronic bacterial infection that affects approximately 50% of the Korean population,[1-3] and is the causative agent of chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.[4] According to a nationwide multicenter serological study, the prevalence of *H. pylori* in Korea declined from 66.9% in 1998 to 51.0% in 2015–2016,[1,2] with a dual-priming oligonucleotide polymerase chain reaction (DPO-PCR)-based multicenter study (DPO-PCR) showing a similar rate of 50.5% between 2015 and 2018.[3] However, this prevalence remains substantially higher than that in Western countries. *H. pylori* eradication therapy reduces the risk of gastric cancer and plays a critical role in gastric cancer prevention and peptic ulcer management.[5-7] However, the efficacy of conventional treatment regimens has declined significantly in recent years.[8]

Previous Korean guidelines recommended 14-day clarithromycin-based triple therapy (TT) (proton pump inhibitor [PPI], clarithromycin, and amoxicillin [PAC]) as the first-line empirical treatment.[9,10] However, the current eradication rate of this regimen is only 66.9% (95% confidence interval [CI], 63.1%–70.5%) by intention-to-treat (ITT) analysis, falling below the 80% ITT threshold generally required for first-line therapy.[11] A temporal trend analysis of 34139 patients across 20 Korean institutions confirmed a significant decline in eradication rates: 79.8% before 2009, 76.1% during 2010–2019, and 67.0% after 2020 (p<0.001).[11]

The primary driver of the declining eradication rates is an increase in antibiotic resistance. A nationwide culture-based survey from 2017 to 2018 reported a clarithromycin resistance rate of 17.8%,[12] whereas a concurrent DPO-PCR-based analysis across 138 institutions documented a rate of 28.3%.[3] Data from the Korean Registry on the Current Management of *H. pylori* (K-Hp-Reg), a society-led registry encompassing 66 hospitals and 7451 patients (2021–2023), further increased to 33.3% using culture-based methods and 31.3% using PCR-based methods.[13] A single-center, 20-year longitudinal study (2003–2022) documented increases in clarithromycin resistance from 16.1% to 31.0%, levofloxacin resistance from 4.5% to 37.0%–62.2%, and multidrug resistance (resistance to ≥2 antibiotics) from 1.4% to 37.1%.[14] These resistance rates substantially exceed the 15% threshold above which international guidelines no longer recommend empirical TT.[15,16]

The Korean College of *Helicobacter* and Upper Gastrointestinal Research (KCHUGR) has published *H. pylori* treatment guidelines since 1998,[7,17] with revisions in 2013[8] and 2020.[9,10] The 2020 guidelines presented multiple empirical regimens in parallel, including TT, bismuth quadruple therapy (BQT), sequential therapy (ST), concomitant therapy (CT), and metronidazole-based TT (PAM). However, since then, eradication rates with TT have continued to decline, DPO-PCR-based tailored therapy has been introduced into clinical practice,[18,19] and potassium-competitive acid blockers (P-CABs) have become available as alternatives to PPIs.[20,21] Therefore, this revision shifted from a parallel presentation of multiple empirical regimens to a dual-pillar strategy centered on tailored therapy and pragmatic empirical quadruple therapy.

Specifically, ST and PAM, which were included as first-line options in the 2020 guidelines, were excluded from this revision. ST was excluded based on its lower compliance due to complex dosing schedules, difficulty in selecting salvage regimens after exposure to both clarithromycin and metronidazole upon treatment failure, and inferior eradication rates compared with CT and BQT in a nationwide randomized controlled trial (RCT).[11] PAM was excluded because its high domestic metronidazole resistance rate of 29.5%[12] precludes adequate eradication rates with empirical use, and first-line metronidazole exposure may compromise the efficacy of BQT as a standard second-line salvage therapy.[13]

This revision focuses on four key areas: 1) PCR-based antibiotic susceptibility testing (AST) tailored therapy, 2) introduction of P-CABs, 3) strengthening of bismuth-based regimens, and 4) expansion of eradication indications to include gastric cancer prevention and hyperplastic polyps.

METHODS

These guidelines were developed by a multidisciplinary Development Committee of 10 gastroenterologists under the auspices of the KCHUGR with participation from the Korean

Society of Gastroenterology (KSG), Korean Association of Internal Medicine (KAIM), Korean Society of Gastrointestinal Endoscopy (KSGE), and Korean Society of Neurogastroenterology and Motility (KSNM). A methodology expert from the National Evidence-based Healthcare Collaborating Agency (NECA) provided guidance on the systematic literature search, quality assessment, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The target population comprised adults aged ≥18 years with confirmed or suspected *H. pylori* infection. The guidelines were developed according to the Korean Academy of Medical Sciences (KAMS) Patient-Centered Clinical Research Coordinating Center (PACEN) guideline development protocol version 1.0.

Key questions and literature search

Nine key questions (KQs) were formulated using the PICO (population, intervention, comparison, and outcome) frameworks (Table 1). For the KQs previously addressed in the 2020 guidelines (KQs 1, 5, 6, 7, and 9), an updated approach was employed by searching for literature published after the previous search endpoint (2019). Newly introduced KQs (KQs 2, 3, 4, and 8) were subjected to a de novo systematic review. Literature searches were conducted using the Ovid-MEDLINE, Embase, Cochrane Library, KoreaMed, and KMbase databases for studies published until May 2025.

Quality assessment and evidence synthesis

Selected RCTs were assessed for risk of bias using the Co-

Table 1. Key questions and PICO framework

KQ	Key question	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	Method
1	Does *H. pylori* eradication in patients with *H. pylori* gastritis help prevent gastric cancer?	Patients with *H. pylori* gastritis	Eradication therapy	No treatment/ placebo	Gastric cancer incidence, gastric cancer mortality, all-cause mortality	Update
2	Does *H. pylori* eradication in patients with *H. pylori* gastritis and hyperplastic polyps help treat or prevent polyp recurrence?	*H. pylori* gastritis + hyperplastic polyps	Eradication therapy	No treatment	Polyp regression rate, recurrence rate	De novo
3	Is PCR an appropriate method for *H. pylori* diagnosis and antibiotic susceptibility testing?	Patients with suspected *H. pylori* infection	DPO-PCR	Culture/ susceptibility testing	Diagnostic accuracy, resistance prediction accuracy	De novo
4	Is tailored therapy based on clarithromycin resistance testing effective as first-line *H. pylori* eradication?	Patients with *H. pylori* infection	Tailored therapy	Empirical therapy	Eradication rate, adverse events	De novo
5	Is concomitant therapy effective as first-line empirical treatment for *H. pylori* infection?	Patients with *H. pylori* infection	Concomitant therapy	Sequential therapy/ clarithromycin-containing TT	Eradication rate, adverse events	Update
6	Can bismuth quadruple therapy be used as first-line empirical treatment for *H. pylori* infection?	Patients with *H. pylori* infection	Bismuth quadruple therapy	Sequential therapy/ concomitant therapy	Eradication rate, adverse events, adherence	Update
7	Is 14-day clarithromycin-containing triple therapy effective as first-line *H. pylori* eradication?	Patients with *H. pylori* infection	14-day clarithromycin-containing TT	Other first-line regimens	Eradication rate, adverse events	Update
8	Can P-CAB-based antibiotic combination therapy replace PPI-based therapy?	Patients with *H. pylori* infection	P-CAB-based regimen	PPI-based regimen	Eradication rate, adverse events	De novo
9	What is the effective salvage therapy after *H. pylori* eradication failure?	Patients who failed first-line eradication	Salvage therapy	Other salvage regimens	Eradication rate, adverse events	Update

KQ, key question; P, population; I, intervention; C, comparison; O, outcome; DPO-PCR, dual-priming oligonucleotide-based multiplex polymerase chain reaction; TT, triple therapy; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

 https://doi.org/10.7704/kjhugr.2026.0029

chrane Risk of Bias (RoB 2.0) tool,[22] and nonrandomized studies were assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.[23] Two independent reviewers evaluated each study, and discrepancies were resolved through discussion with a committee chair. Meta-analyses were performed using RevMan 5 (Version 5.3. Copenhagen: The Cochrane Collaboration, 2020) or R software (version 4.2.1, R Foundation for Statistical Computing) where applicable. Dichotomous outcomes were expressed as risk ratios (RRs) or odds ratios (ORs) with 95% CIs. Heterogeneity was assessed using the I^2 statistic, with random effects models applied when I^2 exceeded 50%.

Evidence grading and recommendation strength

The GRADE methodology was applied to determine the evidence levels and recommendation strengths for each KQ.[24] Evidence profiles and Summary of Findings tables were generated using the GRADEpro Guideline Development Tool (GDT) software (McMaster University and Evidence Prime, 2023; https://www.gradepro.org/). The evidence levels were classified into four categories: high, moderate, low, and very low. The recommendation strength (strong or weak) was determined by considering the balance of benefits and harms, patient values and preferences, and resource utilization (Tables 2 and 3).

Expert consensus

The draft recommendations were evaluated using the modified Delphi process. In the first round, an online vote was conducted among a panel of 64 multidisciplinary experts using a 6-point Likert scale. Consensus was defined as ≥66.7% (2/3) of respondents selecting "completely agree" or "mostly agree." An in-person public hearing was held on December 20, 2025, during which first-round results were reviewed, and recommendations that did not achieve consensus were revised and submitted for a second vote. Eight external experts from six related medical societies participated in the public hearing, and 10 members of the general public were invited to provide patient perspectives.

RESULTS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist. The PRISMA flowchart and study characteristics for each KQ are shown in Supplementary Fig. 1 and Supplementary Table 1 (in the online-only Data Supplement). The results of the methodological quality and GRADE assessments are in Supplementary Tables 2 and 3 (in the online-only Data Supplement).

Twelve of the thirteen recommendations achieved consensus in the first Delphi round. One recommendation regarding clarithromycin-based TT required revision after a public hearing, and achieved 73.9% agreement in the second round. A summary of these recommendations is presented in Table 4.

Indications for eradication therapy

Statement 1. H. pylori eradication therapy is suggested for the prevention of gastric cancer in patients with H. pylori gastritis.

Strength of recommendation: weak; level of evidence: moderate

Expert agreement: 95.3% (61/64)

Table 2. Level of evidence

Level of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Table 3. Strength of recommendation

Strength of recommendation	Definition	Phrasing
Strong	Benefits clearly outweigh harms; recommended in most clinical situations	"...is recommended"
Weak	Benefits and harms are closely balanced or may vary by clinical situation or patient/societal values	"...is suggested" or "...may be considered"
Strong against	Harms clearly outweigh benefits; use is not recommended	"...is not recommended"
Weak against	Harms may outweigh benefits but may vary by situation	"...is suggested not to be performed"

We conducted a systematic review and meta-analysis to assess the effects of eradication therapy on the incidence of gastric cancer in patients with *H. pylori* gastritis. Including seven RCTs from previous gastritis guidelines[5,25-32] and two additional studies[6,33] (studies by Leung et al.[30] and Zhou et al.[34] represent 5-year and 10-year follow-up from the same cohort; see also[35]), eight RCTs were analyzed. Meta-analysis of the eight RCTs demonstrated that the eradication group (56232 patients) had a significantly lower gastric cancer incidence compared with controls (54421 patients) (RR 0.65, 95% CI 0.48–0.88; I^2=46%; p=0.006) (Fig. 1A). All-cause mortality did not differ significantly between groups across five studies (RR 0.98, 95% CI 0.87–1.11; I^2=0%; p=0.77) (Fig. 1B). Gastric cancer-related mortality was significantly lower in the eradication group across five studies (RR 0.81, 95% CI 0.68–0.98; I^2=0%; p=0.03) (Fig. 1C). Notably, two studies enrolling patients with pre-existing atrophic gastritis or intestinal metaplasia[26,29] did not show a reduction in gastric cancer, suggesting that eradication

Table 4. Summary of recommendations

Statement	Recommendation	Strength of recommendation	Level of evidence	Expert agreement
1	*H. pylori* eradication therapy is suggested for the prevention of gastric cancer in patients with *H. pylori* gastritis.	Weak	Moderate	95.3% (61/64)
2	*H. pylori* eradication therapy is suggested for patients with confirmed *H. pylori* infection and gastric hyperplastic polyps ≤10 mm, to achieve polyp regression or size reduction.	Weak	Low	81.3% (52/64)
3	PCR or sequencing-based testing is suggested for *H. pylori* infection diagnosis and antibiotic resistance detection to guide first-line treatment selection.	Weak	Very low	95.3% (61/64)
4-1	Tailored therapy based on clarithromycin resistance testing (antibiotic susceptibility testing) is recommended as first-line eradication therapy for *H. pylori* infection.	Strong	Moderate	96.9% (62/64)
4-2	Based on clarithromycin resistance testing, 10-day BQT is recommended for resistant strains, and 7-day clarithromycin-based triple therapy for susceptible strains.	Strong	Moderate	84.4% (54/64)
5	Ten-day concomitant therapy is recommended as first-line empirical eradication therapy for *H. pylori* infection.	Strong	High	68.8% (44/64)
6-1	Ten to 14-day BQT may be used as first-line empirical eradication therapy for *H. pylori* infection.	Weak	Moderate	71.9% (46/64)
6-2	BQT is associated with higher adverse event rates and potential utility as salvage therapy; its use as first-line therapy is suggested when other eradication regimens cannot be used.	Weak	Expert consensus	84.4% (54/64)
7	Clarithromycin-based triple therapy may be used in a limited fashion when antibiotic susceptibility testing is unavailable and regional clarithromycin resistance is expected to be below 15%.	Weak	Moderate	Revised consensus 73.9% (34/46)
8	P-CAB-based antibiotic combination therapy may substitute for PPI-based antibiotic combination therapy as first-line eradication treatment for *H. pylori* infection.	Strong	Moderate	98.4% (63/64)
9-1	Ten to 14-day BQT is recommended as second-line eradication therapy when clarithromycin-based triple therapy or concomitant therapy has failed.	Strong	Moderate	100% (64/64)
9-2	When BQT has failed as first-line or second-line therapy, rifabutin-based triple therapy or modified BQT incorporating previously unused antibiotics may be considered. Levofloxacin-based therapy may be attempted in a limited fashion, considering regional resistance patterns.	Weak	Very low	89.1% (57/64)
9-3	Referral to a specialized *H. pylori* center capable of antibiotic susceptibility testing-guided tailored therapy is suggested when two or more lines of eradication therapy have failed.	Weak	Expert consensus	81.3% (52/64)

P-CAB, potassium-competitive acid blocker; PCR, polymerase chain reaction; BQT, bismuth-based quadruple therapy; PPI, proton pump inhibitor.

 https://doi.org/10.7704/kjhugr.2026.0029

therapy is most beneficial before the development of preneoplastic mucosal changes. Eradication-related adverse events were relatively common but mostly mild, with serious adverse events reported in approximately 0.08% and treatment discontinuation due to adverse events in approximately 1.3% of patients in a European multicenter registry of 22000 patients.[36]

Given that Korea has one of the highest gastric cancer incidence rates globally, and endoscopic screening reduces gastric cancer mortality (RR 0.60, 95% CI 0.49–0.73)[37] but does not substitute for preventive eradication, the benefits of eradication therapy for gastric cancer prevention in *H. pylori*-positive patients with gastritis are considered substantial.

Statement 2. H. pylori eradication therapy is suggested for patients with confirmed H. pylori infection and gastric hyperplastic polyps ≤10 mm, to achieve polyp regression or size reduction.

Strength of recommendation: weak; level of evidence: low
Expert agreement: 81.3% (52/64)

Gastric hyperplastic polyps are found in approximately 2%–3% of endoscopic examinations[38] and in up to 10% of national cancer screening programs.[39] Although predominantly inflammatory regenerative lesions, they harbor neoplastic potential, with dysplasia rates of 1.5%–4.4% and adenocarcinoma prevalence of 1.1%–2.1%.[40,41] Japanese guidelines strongly recommend eradication of hyperplastic polyps,[42] and the Kyoto Global Consensus also acknowledges this indication.[43] The risk of neoplastic transformation increased substantially with polyp size: 8.4% for polyps ≥10 mm versus 1.6% for those <10 mm.[40,41]

Eight studies were included in the systematic review: three RCTs,[44-46] two prospective studies,[47,48] two retrospective cohort studies,[39,49] and one uncontrolled prospective study.[50] Regression rates following successful eradication ranged from 70.5% to 100% across the studies. ITT analysis of the three RCTs comparing eradication with no treatment showed significant polyp regression in the eradication group (Fig. 2). The evidence level was graded as low because of the small sample sizes of the included studies.

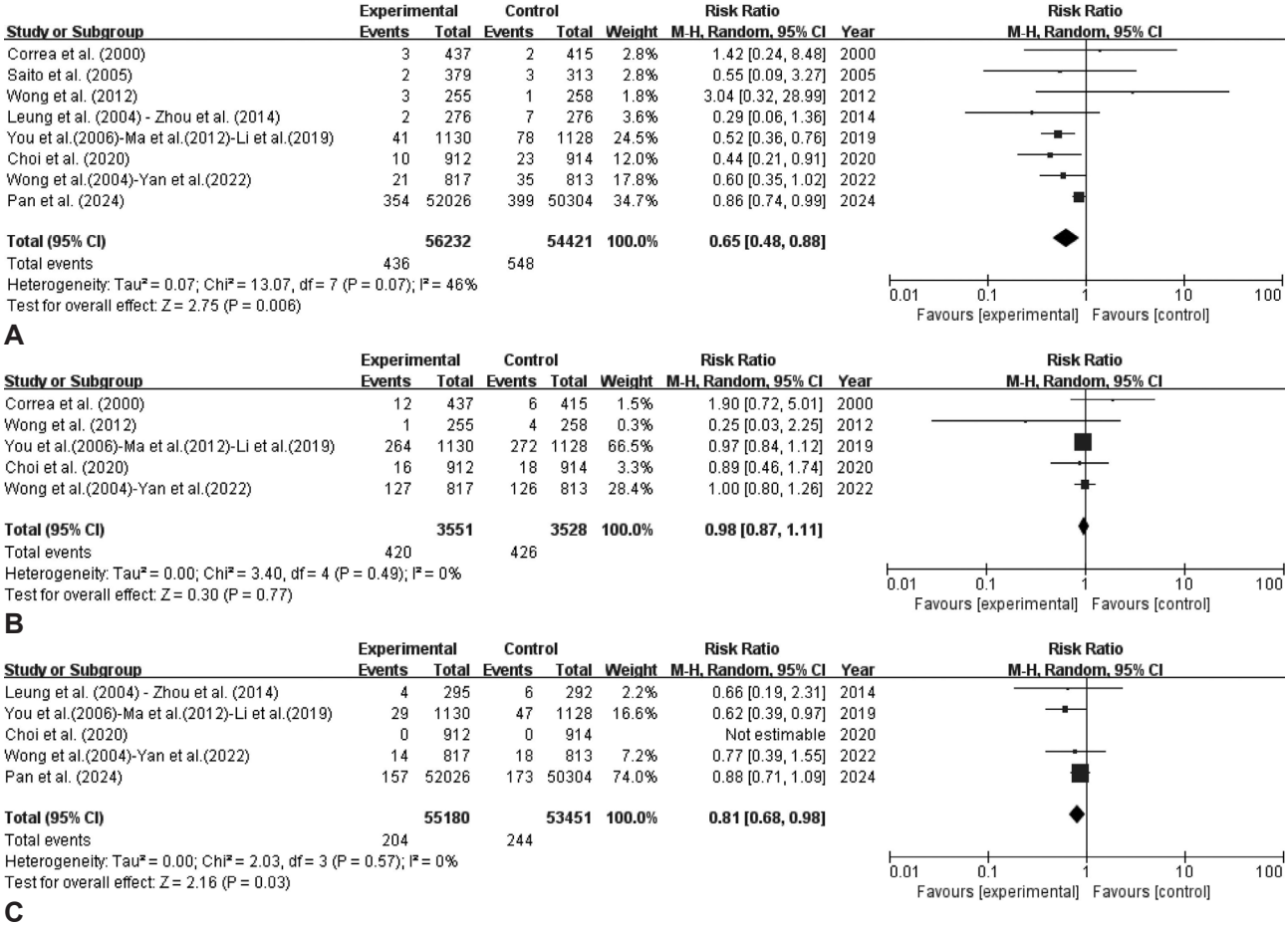

Fig. 1. A: Meta-analysis for the incidence of gastric cancer between the *H. pylori* eradication and control groups. B: Meta-analysis of all-cause mortality between the *H. pylori* eradication and control groups. C: Meta-analysis of gastric cancer-related mortality between the *H. pylori* eradication and control groups. CI, confidence interval; M-H, Mantel–Haenszel method.

For polyps <10 mm, where the malignancy risk is very low (<1%), eradication therapy offers a noninvasive management approach, potentially avoiding unnecessary endoscopic polypectomy. For polyps ≥10 mm, endoscopic resection is recommended because of the higher malignancy risk associated with concurrent eradication therapy for background mucosal inflammation management and recurrence prevention. International guidelines, including those of the British Society of Gastroenterology[51] and Maastricht VI,[15] also recommend *H. pylori* testing and eradication in patients with hyperplastic polyps.

Diagnosis of *H. pylori* infection

Statement 3. PCR or sequencing-based testing is suggested for H. pylori infection diagnosis and antibiotic resistance detection to guide first-line treatment selection.

Strength of recommendation: weak; level of evidence: very low

Expert agreement: 95.3% (61/64)

Conventional diagnostic methods for *H. pylori*, including histology, rapid urease test (RUT), urea breath test (UBT), and stool antigen test, do not provide information on antibiotic resistance. Culture-based AST, although considered the reference standard, has low success rates and is time-consuming and impractical for routine clinical use.[15]

DPO-PCR, a molecular-based test, shows a diagnostic accuracy comparable to or exceeding that of conventional methods, with sensitivity and specificity consistently reported to be approximately 95% in prospective studies, including in patients with bleeding ulcers and RUT-processed specimens.[52-54] Recent evidence also supports fecal PCR testing for clarithromycin resistance detection, with a sensitivity of 97% and specificity of 98%, suggesting its potential as a noninvasive alternative.[55]

Eight diagnostic and six resistance studies using DPO-PCR were reviewed (Supplementary Table 1 in the online-only Data Supplement). Diagnostic studies have reported a sensitivity of 95.9%–100% and a specificity of 42.7%–100% compared to culture, histology, RUT, and gene sequencing.[56-60] Resistance studies have demonstrated concordance rates of approximately 94%–95% with phenotypic testing (E-test).[56,60-62] Next-generation sequencing studies have shown a sensitivity of 96.0% and specificity of 100%.[57] Clinically, AST-guided tailored therapy achieved higher eradication rates than empirical therapy, and DPO-PCR-based treatment was non-inferior to culture-based treatment.[18,19]

Regarding practical implementation, susceptibility-guided strategies are most readily implemented in tertiary referral and academic centers. Although uniform access to primary care has not yet been achieved, the KCHUGR has established five regional AST reference hospitals (see Discussion), and DPO-PCR is reimbursed under the Korean National Health Insurance and increasingly available through commercial laboratory networks. DPO-PCR typically yields results within several working hours, supporting same-week or same-day prescriptions. When PCR-based testing is unavailable, three pragmatic alternatives are recommended: prior antibiotic exposure review through the Korean Drug Utilization Review (DUR) system (see Statement 5), empirical BQT, or empirical clarithromycin-based TT in which regional resistance is documented below 15% (Statement 7). Multiple Korean economic analyses have demonstrated the cost-effectiveness of DPO-

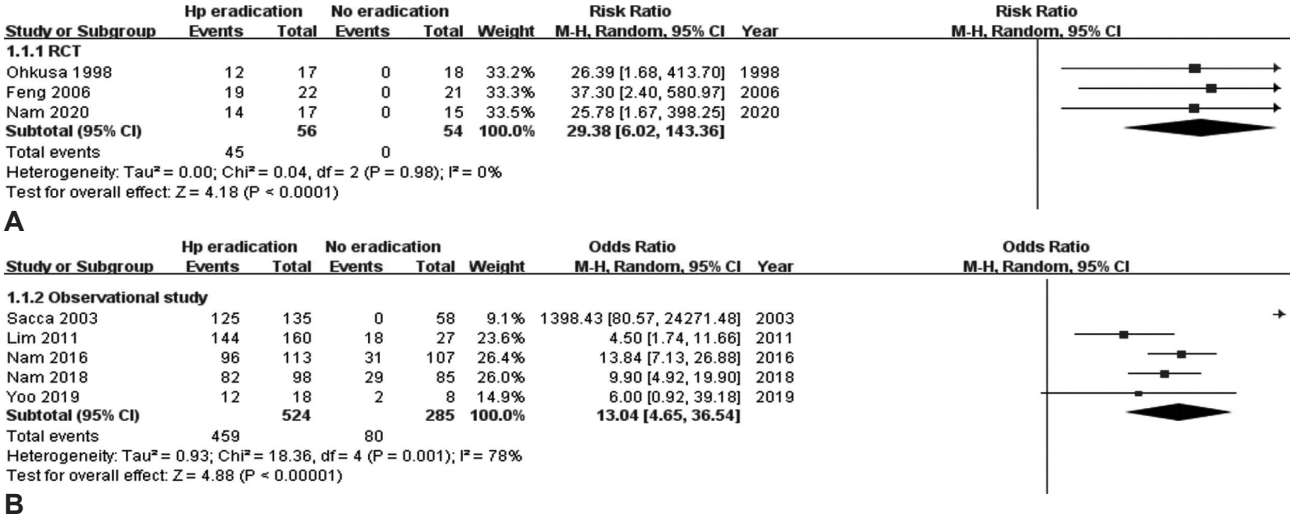

Fig. 2. A: Meta-analysis of the regression rate of gastric hyperplastic polyps between the *H. pylori* eradication and control groups (randomized controlled trials). B: Meta-analysis of the regression rate of gastric hyperplastic polyps between the *H. pylori* eradication and control groups (non-randomized controlled trials). Hp, *Helicobacter pylori*; RCT, randomized controlled trial; CI, confidence interval; M-H, Mantel–Haenszel method.

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PCR-based tailored therapy in the current resistant environment, comparable to empirical BQT; detailed evidence is presented in the Discussion section. In primary care or less specialized settings, where institutional adoption may be more limited, the same framework can be operationalized through specimen referral to network laboratories or, where this is not feasible, by defaulting on the empirical BQT (see also Limitations subsection).

First-line eradication therapy

Statement 4-1. Tailored therapy is recommended based on clarithromycin resistance testing (antibiotic susceptibility testing) as first-line eradication therapy for H. pylori infection.

Strength of recommendation: strong; level of evidence: moderate

Expert agreement: 96.9% (62/64)

Statement 4-2. Based on clarithromycin resistance testing, 10-day BQT is recommended (standard-dose PPI twice daily, metronidazole 500 mg three times daily, bismuth 120 mg and tetracycline 500 mg four times daily) for resistant strains, and 7-day clarithromycin-based triple therapy (standard-dose PPI, amoxicillin 1 g, and clarithromycin 500 mg, all twice daily) for susceptible strains.

Strength of recommendation: strong; level of evidence: moderate

Expert agreement: 84.4% (54/64)

The eradication rates of clarithromycin-based TT have continuously decreased. Analysis of 26 Korean RCTs from 2007 to 2016 showed ITT and per-protocol (PP) eradication rates of 71.6% (95% CI 69.9%–73.3%) and 79.6% (95% CI 76.6%–82.2%), respectively.[10] More recent Korean RCTs (post-2018) showed further declines to ITT 66.9% (95% CI 63.1%–70.5%) and PP 76.2% (95% CI 72.4%–79.7%).[11,18] To overcome resistance-driven treatment failure, tailored therapy based on individual AST has been proposed (hereafter used interchangeably with the term "susceptibility-guided therapy").[63-65] DPO-PCR detects A2142G and A2143G mutations in 23S rRNA that confer clarithromycin resistance and provides a rapid, cost-effective, and clinically practical testing method.[66]

Twenty-one studies on DPO-PCR-based tailored therapies were analyzed (Supplementary Table 1 in the online-only Data Supplement).[18,19,63,64,67-83] The pooled eradication rates were 90.0% (95% CI 88.2%–91.7%) for tailored therapy and 84.9% (95% CI, 80.1%–89.7%) for empirical therapy. The adverse event rates were similar between the groups (32.0% vs. 31.3%). In the K-Hp-Reg interim analysis of 7261 patients across 66 hospitals, tailored therapy achieved a modified ITT (mITT) eradication rate of 88.4% (n=1342), which was significantly higher than those of 14-day TT (77.9%) and 10-day CT (83.9%). In multivariate logistic regression, tailored therapy was an independent predictor of eradication success compared with 14-day TT (OR 2.41; 95% CI 1.97–2.95; $p<0.001$).[13,84]

Meta-analysis of four RCTs showed that tailored therapy was significantly superior to empirical therapy in both ITT (RR 1.11, 95% CI 1.05–1.17) and PP analyses (RR 1.08, 95% CI

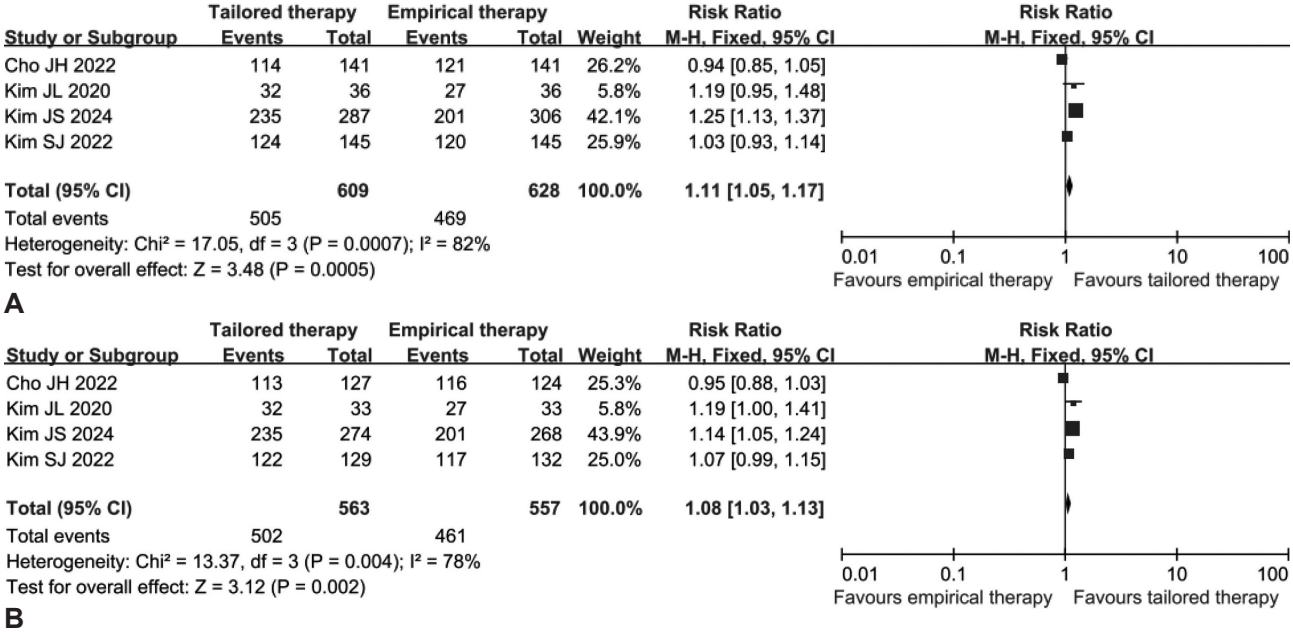


Fig. 3. Meta-analysis of eradication rates between tailored therapy and empirical therapy in randomized controlled trials. A: Intention-to-treat analysis. B: Per-protocol analysis. CI, confidence interval; M-H, Mantel–Haenszel method.

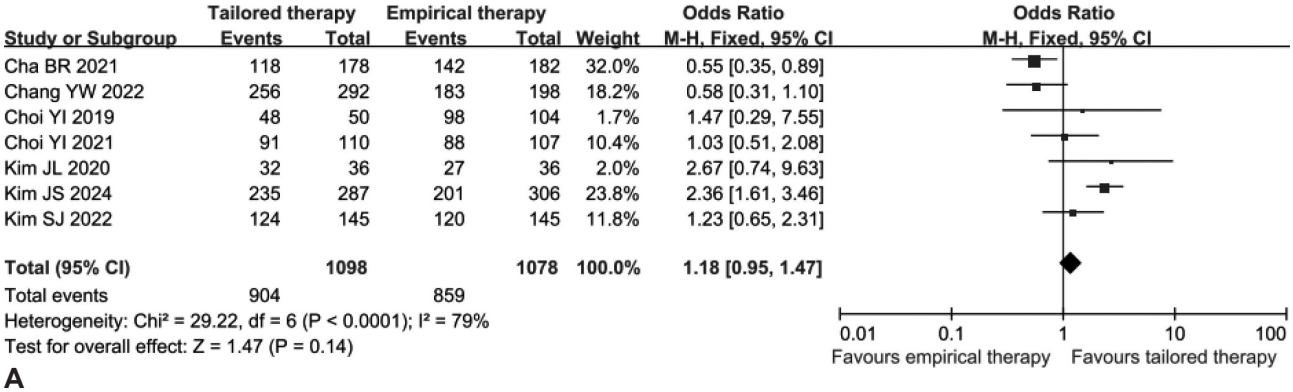
1.03–1.13) (Fig. 3).[18,63,64,72] In a subgroup analysis restricted to studies using BQT for clarithromycin-resistant patients and clarithromycin-based TT for susceptible patients, the ITT analysis of 7 studies showed no significant difference between tailored therapy (84.1%, 95% CI 75.7%–92.6%) and empirical therapy (81.5%, 95% CI 72.3%–90.6%), with an RR of 1.18 (95% CI 0.95–1.47) (Fig. 4A). However, the PP analysis of 9 studies demonstrated significantly higher eradication rates with tailored therapy (90.4%, 95% CI 86.3%–94.6%) than with empirical therapy (85.3%, 95% CI 78.1%–92.4%), yielding an RR of 1.50 (95% CI 1.18–1.91) (Fig. 4B). Although no statistically significant difference in antibiotic consumption was observed between the tailored and empirical therapies, tailored therapy was considered to reduce the number of antibiotics used compared with CT. Regarding the treatment duration for Statement 4-2, BQT for clarithromycin-resistant strains showed the highest eradication rates with 10-day regimens (ITT 86.4%, PP 92.9%), whereas clarithromycin-based TT for susceptible strains showed comparable rates between 7-day (ITT 80.2%, PP 89.7%) and 14-day regimens. Based on the highest eradication rates observed, a 10-day BQT for resistant strains and 7-day TT for susceptible strains are recommended.

However, eradication failure can still occur with clarithromycin PCR-based tailored therapy owing to mixed infections and heteroresistance, atypical mutations not detected by standard PCR (e.g., A2142C), poor medication adherence, and undetected resistance to non-clarithromycin antibiotics. Accordingly, while tailored therapy clearly outperforms empirical TT, the advantage narrows when compared with enhanced empirical regimens such as CT or BQT and should be regarded as an incremental improvement rather than a complete solution.

Statement 5. Ten-day concomitant therapy is recommended (standard-dose PPI, clarithromycin 500 mg, amoxicillin 1 g, and metronidazole 500 mg, all twice daily) as first-line empirical eradication therapy for H. pylori infection.

Strength of recommendation: strong; level of evidence: high
Expert agreement: 68.8% (44/64)

Sixteen RCTs involving CT were systematically analyzed[85-100] (Supplementary Table 1 in the online-only Data Supplement). Ten-day CT showed marginally higher eradication rates than 10-day ST (approximately 4% difference in ITT and PP analyses) (Fig. 5A), whereas 14-day CT demonstrated an 18% higher



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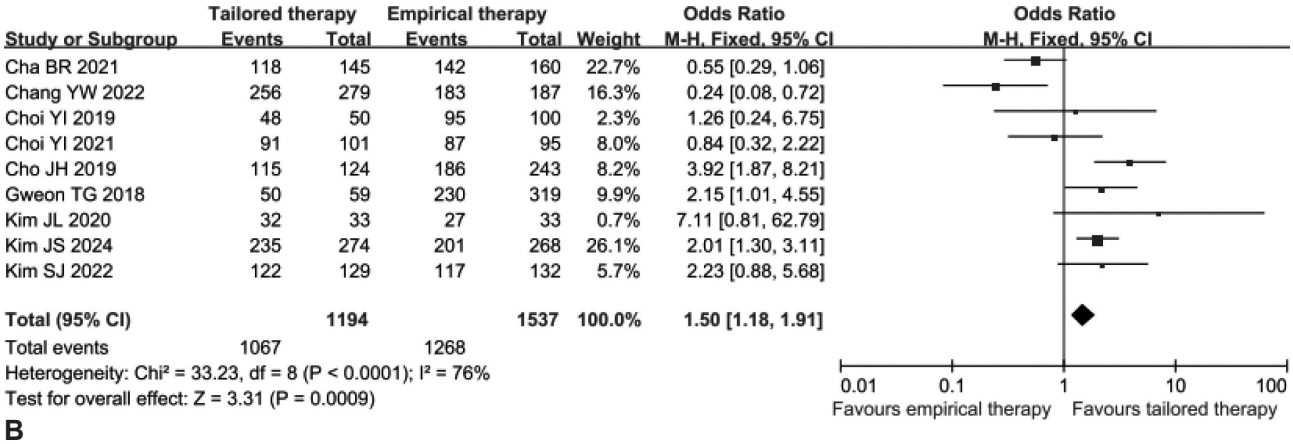

B

Fig. 4. Subgroup analysis of eradication rates between tailored therapy and empirical therapy (including clarithromycin-containing triple therapy, bismuth quadruple therapy, and concomitant therapy). A: Intention-to-treat analysis. B: Per-protocol analysis. CI, confidence interval; M-H, Mantel–Haenszel method.

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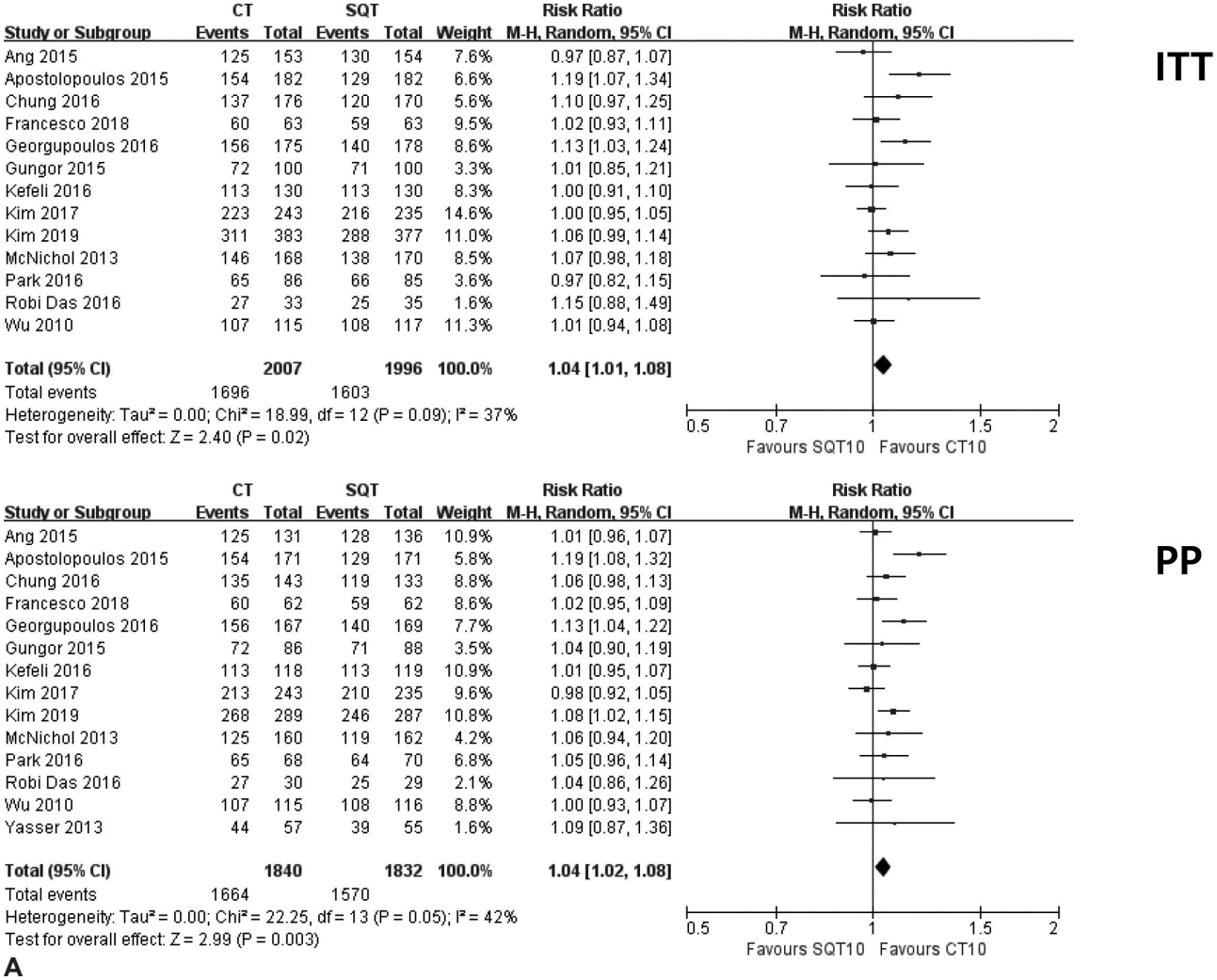
PP eradication rate than 14-day clarithromycin-based TT[85,88,93] and an 11% higher PP eradication rate than 14-day high-dose dual therapy.[86,96] No significant differences have been observed between CT and hybrid or reverse hybrid therapy.[90,91,99,100]

The pooled eradication rates for the 10-day CT were ITT 85.1% and PP 90.6%, whereas the 14-day CT achieved ITT 85.5% and PP 93.8%.[85-100] An analysis restricted to Korean studies showed no significant difference between the 10-day and 14-day regimens[94] (Fig. 5B and C). CT did not demonstrate higher adverse event rates than other regimens,[85-100] and its simpler dosing and shorter duration compared to hybrid therapy (14 days) offered advantages in patient convenience. Ten-



A

	ITT	PP
	Effect size (95% CI)	Effect size (95% CI)
10D CT, overall (n=23)	0.85 (0.82-0.88)	0.91 (0.88-0.93)
10D CT, Korea (n=7)	0.84 (0.77-0.89)	0.92 (0.88-0.94)
14D CT, overall (n=6)	0.86 (0.76-0.92)	0.94 (0.88-0.97)
14D CT, Korea (n=2)	0.79 (0.72-0.85)	0.94 (0.50-0.99)

B

	ITT	PP
	Effect size (95% CI)	Effect size (95% CI)
10D CT, overall (n=10)	84.97%	93.0% (937/1008)
10D CT, Korea (n=4)	81.9% (576/703)	92.9% (526/566)
14D CT, overall (n=19)	85.5% (1543/1806)	90.7% (1309/1443)
14D CT, Korea (n=3)	83.9% (343/409)	90.1% (328/364)

C

Fig. 5. A: Meta-analysis of eradication rates between 10-day concomitant therapy and 10-day sequential therapy in randomized controlled trials. B: Meta-analysis summary for the eradication rate of 10-day and 14-day concomitant therapy in randomized controlled trials before 2018. C: Meta-analysis summary of eradication rates with 10-day and 14-day concomitant therapy in randomized controlled trials after 2018. ITT, intention-to-treat analysis; PP, per-protocol analysis; CT, concomitant therapy; SQT, sequential therapy; CI, confidence interval; M-H, Mantel–Haenszel method.

day CT is recommended as the preferred empirical first-line treatment option when AST is unavailable.

Statement 6-1. Ten to 14-day BQT may be used as first-line empirical eradication therapy for H. pylori infection.

Strength of recommendation: weak; level of evidence: moderate

Expert agreement: 71.9% (46/64)

Statement 6-2. BQT is associated with higher adverse event rates and potential utility as salvage therapy; therefore, its use as first-line therapy is suggested when other eradication regimens cannot be used.

Strength of recommendation: weak; level of evidence: expert consensus

Expert agreement: 84.4% (54/64)

Unless otherwise specified, BQT throughout these guidelines refers to the regimen detailed in Statement 4-2 (standard-dose PPI twice daily; metronidazole 500 mg three times daily; bismuth 120 mg; and tetracycline 500 mg four times daily), and the standard clarithromycin-based TT regimen is similar to that specified in Statement 4-2 (standard-dose PPI, amoxicillin 1 g, and clarithromycin 500 mg, all twice daily). BQT is internationally recognized as a first-line strategy capable of maintaining high eradication rates despite increasing clarithromycin resistance. The Maastricht VI/Florence Consensus, Toronto Consensus, and American College of Gastroenterology (ACG) 2024 guidelines recommend 10–14-day BQT as the empirical standard in regions with >15% antibiotic resistance.[15,16,101] A meta-analysis of 13 RCTs comparing BQT with ST (5 RCTs) and CT (8 RCTs) showed no significant differences in eradication rates: 81.3% for BQT versus 83.5% for ST (RR 0.98; p=0.61) and 81.8% for BQT versus 81.4% for CT (RR 0.98; p=0.54) (Fig. 6).[94,95,102-109]

In the K-HP-Reg interim analysis, 10–14-day BQT achieved an mITT eradication rate of 92.1%, the highest among all first-line regimens, yet constituted only 4.4% of the first-line prescriptions.[13] The limited first-line utilization is likely attributable to concerns about adverse events and the perception that BQT should be reserved for salvage therapy. Approximately 40% of patients experience adverse events with BQT, with 6.5% experiencing moderate-to-severe events.[110,111] The four-times-daily dosing schedule may reduce compliance, particularly in elderly patients and those on polypharmacy. Given its essential role as salvage therapy, selective use as first-line therapy in

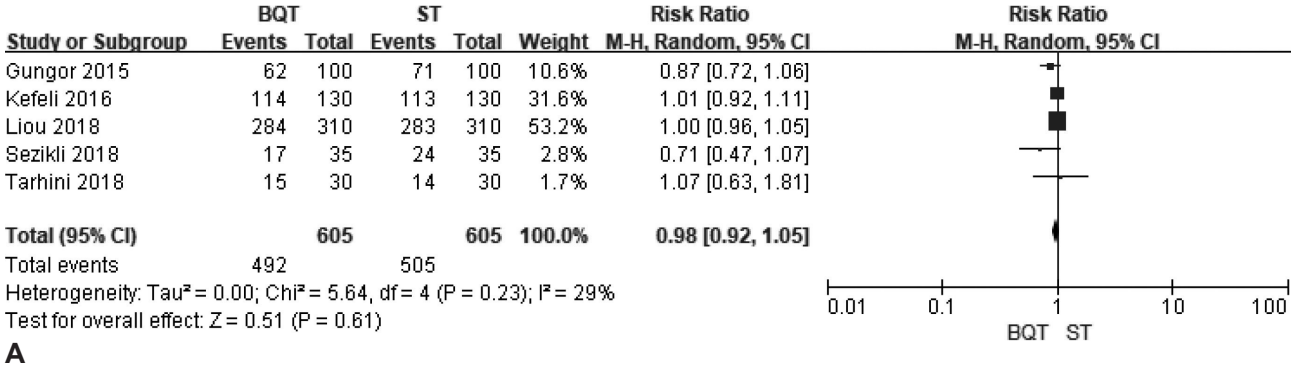


Fig. 6. A: Meta-analysis of *H. pylori* eradication rates between bismuth quadruple therapy and sequential therapy. B: Meta-analysis of *H. pylori* eradication rates between bismuth quadruple therapy and concomitant therapy. BQT, bismuth-based quadruple therapy; ST, sequential therapy; CT, concomitant therapy; CI, confidence interval; M-H, Mantel–Haenszel method.

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specific clinical situations (e.g., penicillin allergy and inability to use other first-line regimens) is recommended. For comparative context, BQT carries the highest adverse-event burden among currently recommended first-line regimens, whereas clarithromycin-based TT and CT show substantially lower rates (≈32% in tailored-therapy trials), P-CAB- and PPI-based combinations show comparable adverse-event profiles (≈32% in both groups), modified BQT (mBQT) regimens reduce the BQT burden, and rifabutin-based TT (in salvage settings) further reduces moderate-to-severe events compared with traditional BQT (detailed comparison and supporting references in Statements 9-1 and 9-2).

Statement 7. Clarithromycin-based triple therapy may be used in a limited fashion when antibiotic susceptibility testing is unavailable and regional clarithromycin resistance is expected to be below 15%.

Strength of recommendation: weak; level of evidence: moderate

Expert agreement: 73.9% (34/46) [second-round vote after first-round non-consensus at 53.1%]

Nine studies evaluating the 14-day clarithromycin-based TT were analyzed[18,112-119] (Supplementary Table 1 in the online-only Data Supplement). The pooled ITT eradication rate was 73.5% (95% CI 71.2%–75.7%) and the PP rate was 82.1% (80.0%–84.1%). Temporal analysis showed a significant decline: ITT rates were 79.8% (pre-2009), 76.1% (2010–2019), and 66.9% (post-2020) (p<0.001) (Fig. 7). K-Hp-Reg confirmed these trends, with mITT eradication rates of 77.9% after 14-day and 71.1% after 7-day TT.[13] Notably, the proportion of 7-day TT prescriptions decreased significantly from 29.0% in 2021 to 5.2% in 2023 (p<0.001), reflecting the clinical impact of guideline dissemination.[13]

As the ITT eradication rate fell below the 80% threshold for first-line empirical therapy,[120] the initial recommendation against empirical clarithromycin-based TT did not achieve consensus in the first Delphi round (53.1% agreement). This reflects the long-standing clinical practice of using this regimen and the recognition that some regions may have relatively low rates of clarithromycin resistance. Following public hearing deliberation, a revised conditional recommendation permitting limited use when susceptibility testing is unavailable and regional resistance is expected to be below 15% achieved 73.9% agreement.

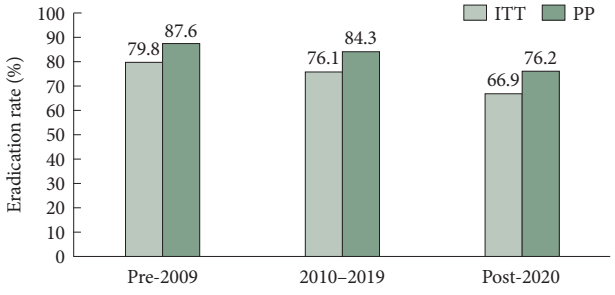


Fig. 7. *H. pylori* eradication rates with 14-day standard triple therapy by study period (Korean randomized controlled trials). ITT, intention-to-treat analysis; PP, per-protocol analysis.

While first-line therapies are ideally expected to achieve ≥90% eradication by mITT or PP analyses, this benchmark is rarely attained in high-resistance environments such as Korea, and the 80% ITT threshold widely cited as the minimum acceptable performance criterion[120] applies to ITT—the most conservative estimator, counting all dropouts and protocol violations as failures—and is intended as a minimum performance floor rather than an optimization target. The recommended regimens consistently met or approach ≥90% in the mITT or PP analyses; tailored therapy achieved an mITT rate of 88.4% in the K-Hp-Reg cohort and a PP rate of 90.4% in the pooled meta-analysis (Fig. 4B), and the 10-day BQT achieved a PP rate of 92.9%, supporting clinical acceptability despite ITT point estimates in the 80%–85% range.

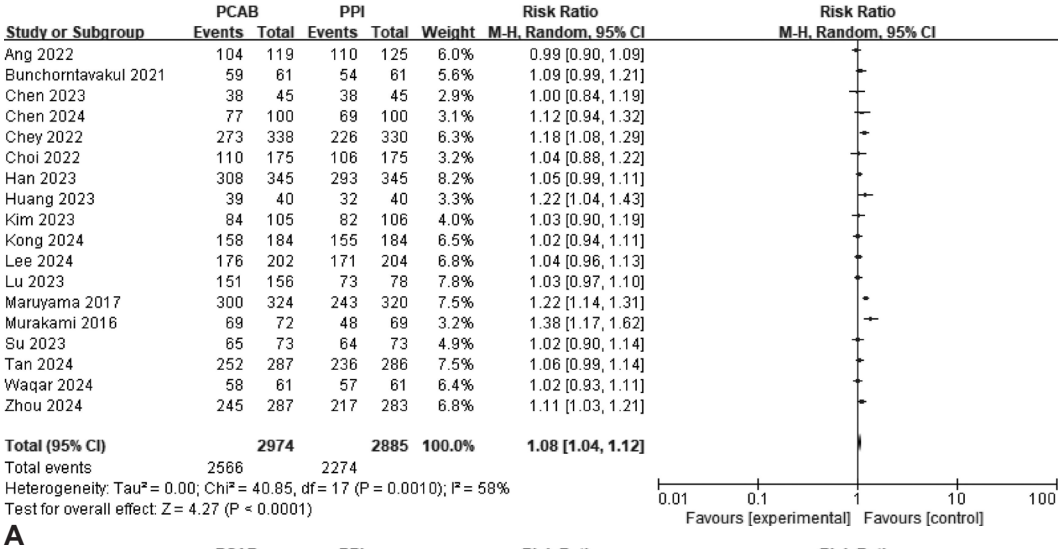
Statement 8. P-CAB-based antibiotic combination therapy may substitute for PPI-based antibiotic combination therapy as first-line eradication treatment for H. pylori infection.

Strength of recommendation: strong; level of evidence: moderate

Expert agreement: 98.4% (63/64)

P-CABs offer more rapid and potent acid suppression than PPIs, and are increasingly used in eradication therapies.[20,21] Nineteen RCTs directly comparing PPI-based and P-CAB-based regimens with identical antibiotic combinations were analyzed[121-139] (Supplementary Table 1 in the online-only Data Supplement). Fourteen studies evaluated vonoprazan, four evaluated tegoprazan, and one evaluated keverprazan.

P-CAB-based regimens were more effective than PPI-based regimens overall (86.3% vs. 78.8%; RR 1.08, 95% CI 1.04–1.12) (Fig. 8A), and this superiority was maintained when restricting to studies with identical treatment durations (84.7% vs. 76.6%; RR 1.09, 95% CI 1.04–1.15). Vonoprazan showed significant superiority over PPIs (88.4% vs. 79.0%; RR 1.10, 95% CI 1.05–1.15), and analysis of four superiority trials confirmed this advantage (86.1% vs. 72.0%; RR 1.19, 95% CI 1.09–1.30) (Fig. 8B). Tegoprazan showed numerically but not statistically significantly higher eradication rates than PPIs (79.3% vs. 76.8%; RR 1.03, 95% CI 0.98–1.09) (Fig. 8C). Adverse event rates did not differ between the P-CAB and PPI groups (32.8% vs. 31.8%; RR 1.01, 95% CI 0.93–1.11) (Fig. 8D). Mechanistically, this superiority reflects the more profound and sustained in-



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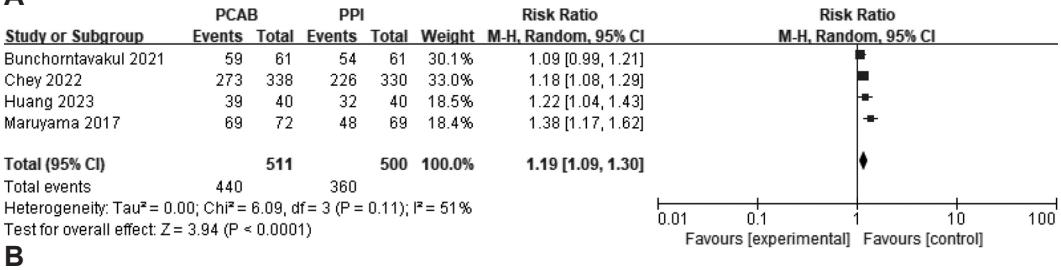

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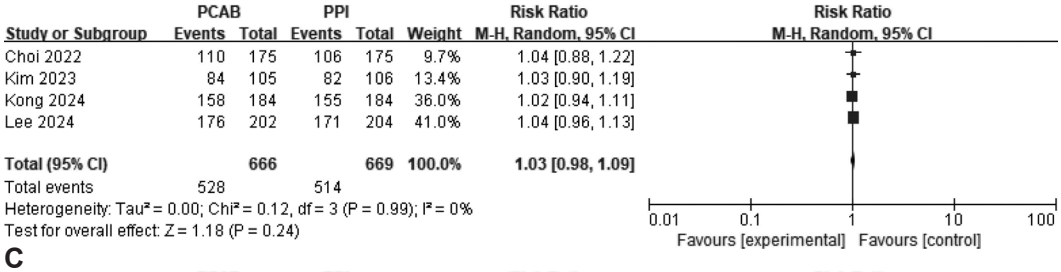

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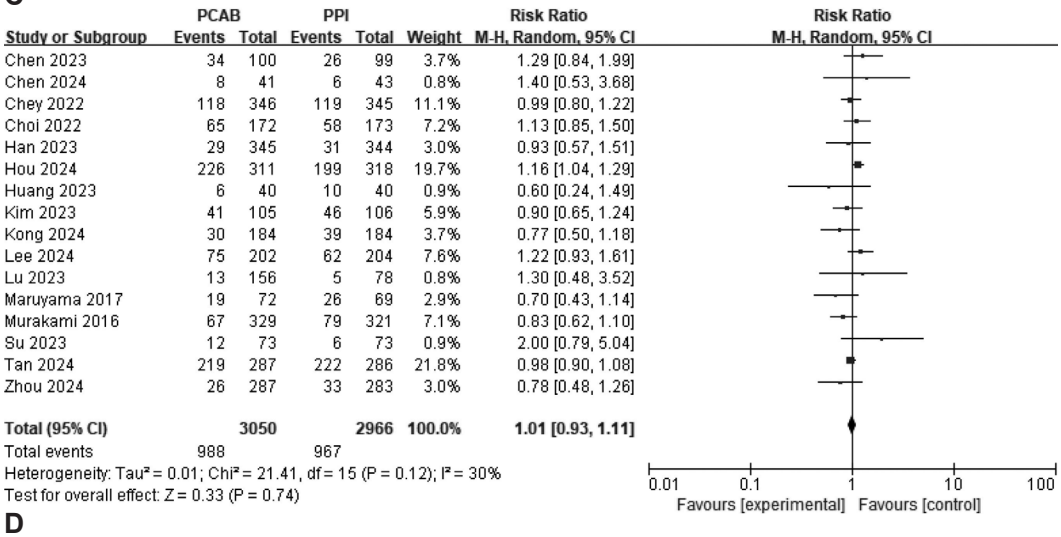

D

Fig. 8. A: Meta-analysis comparing potassium-competitive acid blocker and proton pump inhibitor regimens for *H. pylori* eradication (intention-to-treat analysis). B: Meta-analysis of 4 superiority trials evaluating vonoprazan versus proton pump inhibitor in *H. pylori* eradication therapy. C: Meta-analysis evaluating tegoprazan versus proton pump inhibitor in *H. pylori* eradication therapy. D: Meta-analysis of adverse event rates comparing potassium-competitive acid blocker and proton pump inhibitor regimens for *H. pylori* eradication. P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; CI, confidence interval; M-H, Mantel–Haenszel method.

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tragastric acid suppression provided by P-CABs, which enhances antibiotic stability and bioavailability, and supports the actively replicating bacterial state required for eradication (see further mechanistic discussion below).

Notably, P-CABs are not affected by CYP2C19 genetic polymorphisms, which is particularly advantageous in East Asian populations where the prevalence of CYP2C19 rapid metabolizers is high, allowing more consistent acid suppression compared to PPIs. P-CAB-based regimens are at least as effective as PPI-based regimens and are viable alternatives. Although vonoprazan has shown superiority in some settings, the evidence for other P-CABs remains limited.[125,140] In Korea, where vonoprazan is not yet available, the evidence is primarily based on tegoprazan. Optimal antibiotic combinations and treatment durations for P-CAB-based regimens warrant further investigation. In particular, adequately powered head-to-head Korean RCTs of tegoprazan, fexuprazan, and zastaprazan are needed to consolidate the evidence base for non-vonoprazan P-CABs and to clarify their relative efficacy, optimal dosing, and combination partners (see "Future research priorities").

The differential efficacy between vonoprazan- and tegoprazan-based regimens likely reflects differences in acid-suppressive potency among individual P-CABs rather than a class-level distinction. Vonoprazan provides among the most profound and sustained gastric acid inhibition reported, with intragastric pH ≥4 holding times exceeding those of standard-dose PPIs and reportedly greater than those of tegoprazan.[20,21] Because clarithromycin and amoxicillin require sustained near-neutral gastric pH both for antibiotic stability and to permit *H. pylori* transition into the actively replicating phase, even modest potency differences can translate into measurable efficacy differences. The numerical but non-significant advantage of tegoprazan over PPIs (79.3% vs. 76.8%; RR 1.03, 95% CI 0.98–1.09) is therefore consistent with both its lower potency relative to vonoprazan and the smaller number of available trials (4 vs. 14). Whether higher-dose tegoprazan or other newer P-CABs can close this gap is a question for future Korean RCTs (see "Future research priorities").

Salvage therapy

A systematic literature search restricted to publications after the previous guidelines identified 12 RCTs on salvage therapy, which were integrated with 36 previously selected studies to formulate salvage therapy recommendations.

Statement 9-1. Ten to 14-day BQT is recommended as second-line eradication therapy when clarithromycin-based triple therapy or concomitant therapy has failed.

Strength of recommendation: strong; level of evidence: moderate

Expert agreement: 100% (64/64)

In previous guidelines, nine RCTs reported a pooled second-line BQT eradication rate of 75.5% (95% CI 71.6%–79.1%).[9] Subgroup analysis by duration showed that the 10/14-day therapy (81.6%) was significantly superior to the 7-day therapy (68.4%). A newly identified RCT reported an ITT eradication rate of 87.5% (245/280) and a PP rate of 92.8% (245/264) for 10-day BQT as a second-line therapy.[141] Adverse events occurred in 77% of patients, but were mostly mild, with 95.6% achieving ≥80% medication adherence. A network meta-analysis confirmed that 10/14-day BQT was significantly superior to 7-day BQT (OR 2.02, 95% CI 1.32–3.07) without significant differences in dropout rates.[142] Metronidazole resistance can be largely overcome by increasing the dose and duration of bismuth-containing regimens.[143]

Regarding levofloxacin-based salvage therapy, a previous guideline reported pooled second-line eradication rates of 73.1% across eight RCTs.[9] However, levofloxacin resistance significantly compromises efficacy, with eradication rates of 81.1% and 36.3% for the susceptible and resistant strains, respectively.[144] Given the domestic levofloxacin resistance rate of 37.0%,[12] the estimated eradication rate of levofloxacin-based TT is approximately 64.5%. Regional data have reported levofloxacin resistance rates as high as 70.7% among candidates for salvage therapy.[145] Early Korean data also reported limited second-line eradication rates of approximately 52%–72% for levofloxacin-based therapy.[146] Therefore, levofloxacin-based regimens should be used cautiously and restricted to patients without prior levofloxacin exposure or with confirmed susceptibility, consistent with the principles of rational evidence-based therapy.[147] Of particular concern, cross-resistance between clarithromycin and fluoroquinolones has been reported,[14] raising the possibility that patients who fail clarithromycin-containing first-line therapy may harbor concomitant levofloxacin resistance.

Statement 9-2. When BQT has failed as first-line or second-line therapy, rifabutin-based triple therapy or modified BQT incorporating previously unused antibiotics may be considered.

Levofloxacin-based triple or quadruple therapy may be attempted in a limited fashion, considering regional antibiotic resistance patterns.

Strength of recommendation: weak; level of evidence: very low

Expert agreement: 89.1% (57/64)

When BQT fails, reusing clarithromycin-containing regimens is inappropriate. A Chinese multicenter RCT comparing 14-day rifabutin-based TT with 14-day BQT in third-line

treatment patients showed comparable ITT eradication rates (89.0% vs. 89.6%), significantly fewer moderate-to-severe adverse events (14.3% vs. 28.6%), and higher compliance (96.2% vs. 85.4%) in the rifabutin group.[148] This rationale aligns with broader systematic review evidence demonstrating that susceptibility-guided treatment achieves higher eradication rates than empirical approaches,[149] underscoring the central role of AST in optimizing rescue therapy. A Korean RCT in patients with BQT failure demonstrated that high-dose PPI rifabutin-based TT achieved an ITT eradication rate of 96.3% (26/27).[150] Rifabutin resistance in Korea remains extremely low (0.8%),[151] making it a promising option, although its rare myelotoxicity and potential for mycobacterial resistance warrant monitoring.[152]

mBQT, in which tetracycline is replaced with amoxicillin, levofloxacin, or minocycline, has shown efficacy comparable to that of traditional BQT in salvage settings. RCTs have shown that amoxicillin-based (PAMB), levofloxacin-based (PALB), and minocycline-based modified regimens achieved ITT eradication rates of 83.0%–88.5%, similar to traditional BQT, but with significantly fewer adverse events in several studies.[153-155] Levofloxacin-based TT after BQT failure showed limited efficacy in Korean data (67.4% for 10/14-day regimens)[156] and should be guided by prior antibiotic exposure history and regional resistance patterns.

Several considerations regarding levofloxacin in third-line and refractory settings warrant summary. First, third-line efficacy: 10- to 14-day levofloxacin-based TT achieves only ~67.4% ITT after BQT failure in Korean data,[156] below the 80% threshold, while levofloxacin-based mBQT (PALB) shows better but inadequate third-line results (83.0%–88.5% in mixed first/second-line[153-155]). Second, in refractory disease, the guideline restricts empirical levofloxacin to highly selected cases (no prior fluoroquinolone exposure, DUR-verifiable [Statement 5]; ideally with confirmed susceptibility) and favors specialist referral when ≥2 lines have failed (Statement 9-3); empirical levofloxacin is not a default rescue option. Third, fluoroquinolone resistance is a major limitation, with rates of 37.0% nationwide[12] and 70.7% among regional salvage candidates,[145] while clarithromycin–quinolone dual resistance increased from 2.8% to 41.7% and triple resistance from 1.4% to 28.2% over 20 years[14]; documented cross-resistance with clarithromycin[14] further reduces empirical utility. Long-term refractory management in Korea will therefore rely increasingly on susceptibility-guided rifabutin-based or individualized regimens (see "Future research priorities").

Statement 9-3. Referral to a specialized H. pylori center capable of antibiotic susceptibility testing-guided tailored therapy is suggested when two or more lines of eradication therapy have failed.

Strength of recommendation: weak; level of evidence: expert consensus

Expert agreement: 81.3% (52/64)

The KCHUGR has established five regional AST reference hospitals (Asan Medical Centre, Incheon St. Mary's Hospital, Chuncheon Sacred Heart Hospital, Kyungpook National University Hospital, and Kosin University Hospital), with plans for further expansion. After multiple eradication failures, further treatment selection requires expert judgment and AST-guided tailored therapy. Even after second-line BQT failure, susceptibility-guided therapy can achieve ITT eradication rates of 80%–90%.[149,157] The overall treatment algorithm that integrates the first-line and salvage therapies is presented in Fig. 9.

DISCUSSION

This fourth revision of the Korean *H. pylori* guidelines, published five years after the third revision in 2020, updates evidence-based clinical recommendations in response to the rapidly changing antibiotic resistance environment and the introduction of new diagnostic and therapeutic tools. The key changes, clinical implications, limitations, and future directions are discussed below.

Changes in the treatment environment since 2020

Since 2020, several fundamental changes have been observed in Korean *H. pylori* treatment environments. First, antibiotic resistance has dramatically increased. The K-Hp-Reg (2021–2023, 66 hospitals, 7261 patients) documented a culture-based clarithromycin resistance rate of 33.3%, a sharp increase from 17.8% reported in a 2019 nationwide survey.[12,13] A single-center, 20-year longitudinal study showed that dual resistance to clarithromycin and metronidazole increased from 9.2% to 37.9%, clarithromycin and quinolone dual resistance increased from 2.8% to 41.7%, and triple resistance increased from 1.4% to 28.2% (p<0.001).[14] Levofloxacin resistance increased from 7.3% to 35.7% (p<0.001).[14] In contrast, resistance rates against amoxicillin and tetracycline remain low.[12,14]

Second, the clinical adoption of PCR-based tailored therapies has expanded substantially. In the K-Hp-Reg, the proportion of tailored therapy increased significantly from 10.7% in early 2021 to 28.8% in mid-2023 (p<0.001), which was attributed to the DPO-PCR test dissemination and National Health Insurance coverage since 2018 (with expanded indications from 2021).[13] An estimated 40000 DPO-PCR tests are performed annually nationwide, supported by a network of major reference laboratories enabling specimen referral from any health-

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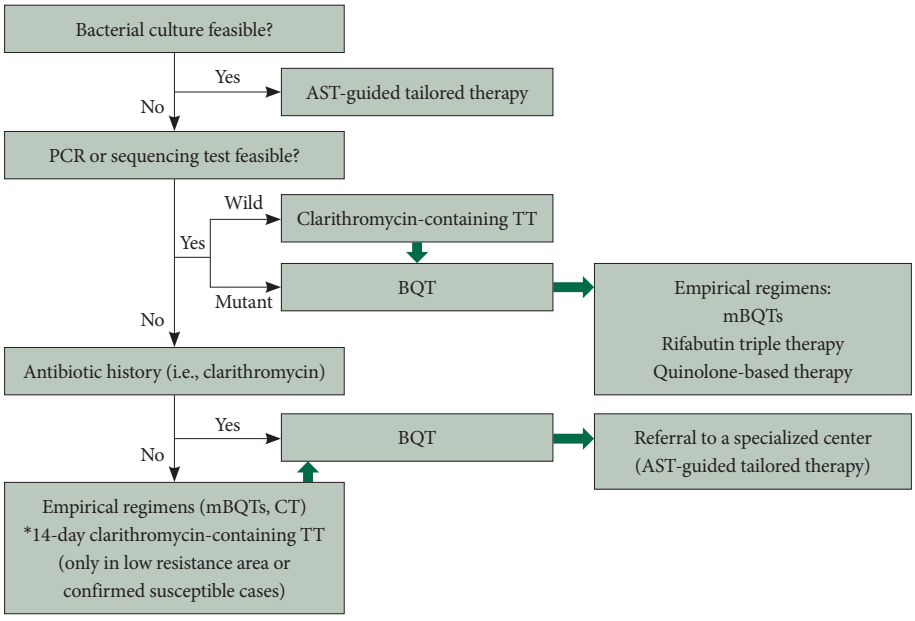

Fig. 9. Proposed treatment algorithm. AST, antibiotic susceptibility testing; PCR, polymerase chain reaction; TT, triple therapy; BQT, bismuth-based quadruple therapy; mBQT, modified BQT; CT, concomitant therapy.

care facility, although institutional-level adoption in primary care settings remains limited. The K-CREATE study, a nationwide multicenter RCT, demonstrated that PCR-based tailored therapy achieved an ITT eradication rate of 81.9%, which was significantly higher than that achieved with empirical therapy (65.7%, $p<0.001$).[18]

Third, multiple P-CABs, including tegoprazan (approved in 2018), fexuprazan (approved in 2021), and zastaprazan (approved in 2024), have been approved in Korea, diversifying acid suppressant options. A Phase III trial showed the non-inferiority of tegoprazan-based TT to PPI-based therapy,[126] and tegoprazan-based CT has also shown high eradication rates.[158] However, vonoprazan remains unavailable in Korea, distinguishing Korean P-CAB evidence from vonoprazan-centric data from Japan and the United States.[159]

These trends have direct implications for regimen selection. The increase in clarithromycin–metronidazole dual resistance to 37.9% and clarithromycin–quinolone dual resistance to 41.7%[14] indicates that several previously effective empirical regimens are now compromised by resistance to multiple agents. Empirical CT is particularly effective, as clarithromycin–metronidazole dual resistance can simultaneously inactivate two of its three antibiotics, and empirical clarithromycin-based TT is even more vulnerable. In contrast, BQT remains relatively robust because amoxicillin and tetracycline resistance is consistently low in Korea,[12,14] and bismuth partially overcomes metronidazole resistance through cell wall destabilization. These considerations underpin the guidelines' preference for BQT (or mBQT) as the empirical backbone when susceptibility data are unavailable, reinforce the importance of molecular tailored therapy where feasible, and strengthen the rationale for DUR-based prescriptions (see Statement 5). Future guidelines may need to expand molecular testing beyond clarithromycin to additional resistance markers (see "Future research priorities").

Key changes and their rationale

The most significant change in this revision is the reorganization of first-line treatment into a dual-pillar strategy (Table 5): tailored therapy when PCR-based clarithromycin resistance testing is available and empirical quadruple therapy (CT or BQT) when it is not. This strategy aligns with the Maastricht VI recommendation against empirical clarithromycin-based TT in regions with >15% resistance,[15] and the ACG 2024 recommendation to avoid empirical clarithromycin or levofloxacin without confirmed susceptibility,[16] while uniquely using Korea's DPO-PCR infrastructure.

In clinical settings where DPO-PCR is unavailable, the DUR system, a national electronic database that tracks individual prescription histories, may serve as a supplementary tool for antibiotic selection. A recent prospective study demonstrated that the clarithromycin resistance rate was 66.7% among patients with prior macrolide exposure, compared to 7.5% among unexposed patients ($p<0.001$), suggesting that DUR-based prescribing decisions may offer a practical alternative in PCR-inaccessible environments.[13]

The Delphi process for clarithromycin-based TT has revealed a notable gap between evidence and clinical practice. The ini-

tial recommendation against empirical use failed to achieve consensus (53.1%) in the first round, reflecting deeply entrenched clinical practice and the possibility that clarithromycin resistance may be lower in certain regions.[13] After public hearing deliberation, a conditional recommendation permitting limited use under specific conditions (unavailable susceptibility testing and expected regional resistance <15%) achieved 73.9% agreement. This stepwise approach acknowledges the gap between the evidence and clinical reality while guiding directional shifts.

ST, recommended as a first-line option in the 2020 guidelines, was removed from this revision based on evidence of inferior eradication rates compared to CT in a nationwide RCT,[11] poor compliance due to complex dosing, and difficulty in selecting salvage regimens after dual antibiotic exposure.[13]

P-CABs were newly incorporated, with evidence from 19 RCTs demonstrating non-inferiority or superiority over PPIs.[121-139] However, evidence that P-CABs can overcome clarithromycin resistance remains insufficient[126] and evaluation from an antibiotic stewardship perspective is needed.[160] Accordingly, these guidelines recommend P-CABs as alternatives that "may substitute for" PPIs.

Regarding the resource implications, multiple Korean cost-effectiveness analyses have consistently reported that tailored therapy is more cost-effective than empirical therapy. Economic modeling by Gweon et al.[78] showed that DPO-PCR-based tailored therapy demonstrated economic superiority over empirical TT when eradication rates fell below 80%, with the advantages becoming more pronounced at clarithromycin resistance rates exceeding 20%. Recent decision-tree analyses have confirmed the cost-effectiveness of tailored therapy compared to empirical TT, with cost-effectiveness comparable to empirical BQT in the current Korean resistance environment.[161]

Modified bismuth quadruple therapy

This revision introduced BQT (mBQT) as an empirical first-line option (Table 6). In mBQT, tetracycline in traditional BQT is replaced with amoxicillin to yield formulations such as PAMB (PPI+amoxicillin+metronidazole+bismuth) or PACB (PPI+amoxicillin+clarithromycin+bismuth). A Korean multicenter non-inferiority RCT showed that 14-day PAMB was non-inferior to 14-day traditional BQT (ITT 87.2% vs. 82.8%, p=0.37; PP 96.2% vs. 96.9%, p>0.99), and antibiotic resistance (clarithromycin 31.7%, metronidazole 40%, and levofloxacin 42.2%) did not significantly affect either regimen's efficacy.[162] A systematic review and meta-analysis of 43 RCTs (9162 patients)

Table 5. Comparison of the main components between the 2025 and 2020 guidelines

Category	2020 guideline	2025 guideline
Treatment philosophy	Multiple empirical regimen choices (TT, BQT, ST, CT)	Dual-pillar strategy: precision (PCR-guided)+pragmatic empirical quadruple therapy
Tailored therapy (PCR-based)	Mentioned as optional approach	Primary recommended strategy; core pillar of dual-pillar framework
Clarithromycin-containing TT	Primary empirical first-line (14 days recommended over 7 days)	Not recommended empirically; only with confirmed clarithromycin susceptibility (tailored therapy)
Sequential therapy	Recommended first-line option	Excluded (poor adherence, salvage selection difficulty, inferior to CT/BQT)
Metronidazole TT (PAM)	Alternative for clarithromycin-resistant strains (7 days)	Not recommended (high metronidazole resistance 29.5%; may compromise future BQT efficacy)
CT	Recommended first-line option (10 days)	Effective empirical option (10–14 days); stewardship concerns noted
Bismuth-based regimens	BQT as first-line alternative	Emphasised: BQT+new mBQTs (PACB, PAMB) as preferred empirical options
Acid suppressant	PPI-based regimens	P-CAB formally incorporated as alternative/preferred option
Second-line therapy (salvage)	BQT (10–14 days)	BQT reaffirmed; PAMB as alternative if tetracycline unavailable
Third-line therapy	Limited guidance (levofloxacin TT)	Clarified algorithm: rifabutin TT, mBQTs with unused antibiotics, levofloxacin TT (limited); AST-guided therapy strongly recommended
Gastric cancer prevention indication	Atrophic gastritis/intestinal metaplasia did not reach expert consensus	*H. pylori* gastritis patients: eradication suggested for gastric cancer prevention (weak; moderate)
Hyperplastic polyps	Not included	Eradication suggested for hyperplastic polyps ≤10 mm (weak; low)

PCR, polymerase chain reaction; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker; PAM, PPI+amoxicillin+metronidazole; PACB, PPI+amoxicillin+clarithromycin+bismuth; PAMB, PPI+amoxicillin+metronidazole+bismuth; TT, triple therapy; BQT, bismuth-quadruple therapy; mBQT, modified BQT; CT, concomitant therapy; ST, sequential therapy; AST, antibiotic susceptibility testing.

 https://doi.org/10.7704/kjhugr.2026.0029

confirmed that mBQT achieved significantly higher eradication rates than non-bismuth TT and comparable rates to traditional BQT, with 14-day PACB achieving ITT rates of 87.9%–93.7%.[163] Network meta-analysis ranked PAMB as the highest overall (surface under the cumulative ranking curve=0.866).[164]

Notably, bismuth addition improved eradication rates by 40% for clarithromycin-resistant strains and 26% for metronidazole-resistant strains.[163] The high eradication rates of mBQT are attributable to the unique multimodal antimicrobial mechanisms of bismuth, which operate independently of conventional antibiotic resistance pathways, including direct disruption of bacterial cell walls and membranes, biofilm inhibition and dissolution, inhibition of bacterial enzymes (urease and catalase), interference with DNA/RNA synthesis, ATP production blockade, and efflux pump inhibition.[152,163] From an antibiotic stewardship perspective, PAMB avoids clarithromycin exposure while achieving comparable eradication rates through bismuth's resistance-independent bactericidal effects, potentially reducing unnecessary clarithromycin exposure and mitigating resistance propagation, a consideration aligned with the WHO antibiotic stewardship principles and particularly relevant given Korea's current clarithromycin resistance rates exceeding 30%.

Comparison with international guidelines

The Maastricht VI (2022),[15] ACG 2024,[16] Chinese 2022,[165] and World Gastroenterology Organization (WGO) 2023[166] guidelines reveal several commonalities: departure from empirical TT in high-resistance regions, emphasis on susceptibility-guided tailored therapy, recognition of BQT as a first-line option, and recommendations for post-eradication confirmation testing. Key differences include: 1) Korea uniquely recommends PCR-based tailored therapy as one of two pillars of first-line therapy, using its DPO-PCR infrastructure—whereas the ACG 2024 encourages but acknowledges infrastructure limitations,[16] and Maastricht VI considers susceptibility testing "reasonable" without issuing a strong recommendation[15]; 2) Korea maintains CT as a primary empirical option (whereas ACG 2024 prioritizes quadruple therapy)[16]; and 3) Korea bases P-CAB recommendations on tegoprazan-centric evidence,

Table 6. Summary of recommended first-line, second-line, and third-line *H. pylori* treatments in the 2025 guidelines

Treatment line	Approach	Regimen components	Duration (day)	Key restrictions/considerations
First-line	Tailored (PCR-guided)	C-susceptible: PPI/P-CAB+A+C	14	Requires PCR/AST confirmation of susceptibility
		C-resistant: BQT (PPI/P-CAB+B+M+T)	10–14	Recommended precision approach; ITT ≥90%
First-line	Empirical	CT: PPI/P-CAB+A+M+C	10	Stewardship concern (3 antibiotics); reserve for high resistance risk
		BQT: PPI/P-CAB+B+M+T	10–14	Tetracycline availability/tolerability issues possible
		mBQT-PACB: PPI/P-CAB+A+C+B	14	Efficacy reduced in high-level clarithromycin resistance
		mBQT-PAMB: PPI/P-CAB+A+M+B	14	Preferred mBQT; bypasses clarithromycin resistance
Second-line	Empirical	BQT: PPI/P-CAB+B+M+T	10–14	Standard salvage; metronidazole resistance overcome by higher dose/duration
		Alternative: PAMB (PPI/P-CAB+A+M+B)	14	If tetracycline unavailable or not tolerated
Third-line	Empirical/ AST-guided	Rifabutin TT: PPI/P-CAB+A+rifabutin	10–14	Low resistance (0.8%); monitor for myelotoxicity; Tbc resistance concern
		mBQT with unused antibiotics: PPI/P-CAB+B+(A or L)+ (unused antibiotics)	14	Avoid previously used antibiotics except A/M
		Levofloxacin TT: PPI/P-CAB+A+L	10–14	Limited use; resistance 36%–43%; only if susceptible or no prior fluoroquinolone exposure
	AST-guided	Susceptibility-guided regimen	Per AST	Strongly recommended; referral to specialised centre; ITT ≥80%–90%

PCR, polymerase chain reaction; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker; PACB, PPI+amoxicillin+clarithromycin+bismuth; PAMB, PPI+amoxicillin+metronidazole+bismuth; TT, triple therapy; BQT, bismuth-quadruple therapy; mBQT, modified BQT; CT, concomitant therapy; AST, antibiotic susceptibility test; ITT, intention-to-treat; A, amoxicillin; C, clarithromycin; B, bismuth; M, metronidazole; T, tetracycline; L, levofloxacin.

distinct from the vonoprazan-centric evidence in the ACG 2024[16] and American Gastroenterological Association (AGA) guidelines.[167,168] Among East Asian guidelines, Japan primarily recommends vonoprazan-based TT as first-line therapy, whereas China centers its approach on BQT[169]; Korea integrates the strengths of both through its dual-pillar strategy. A further distinction is that, whereas the Maastricht VI[15] and ACG 2024[16] guidelines position BQT as the preferred empirical first-line option in high-resistance regions, the present guidelines place BQT in a conditional first-line role alongside CT, reflecting the substantial adverse-event burden (~40% of patients[111]), four-times daily dosing, and adherence concerns documented in Korean real-world data, while preserving BQT's full potency for salvage therapy.

Of note, the ACG 2024 guideline includes P-CAB-based high-dose amoxicillin dual therapy as a first-line option; however, the only Korean study evaluating dual therapy used amoxicillin at 1 g twice daily (2 g/day), which falls below the internationally accepted high-dose threshold of ≥3 g/day. Consequently, robust Korean evidence supporting appropriate high-dose P-CAB-based dual therapy is lacking, which is the primary reason why these guidelines do not issue separate recommendations for high-dose dual therapy.

Mono-antibiotic strategies and antimicrobial stewardship considerations

Mono-antibiotic strategies, particularly high-dose amoxicillin-based dual therapy, have gained international attention as part of antimicrobial stewardship efforts: amoxicillin resistance in *H. pylori* remains consistently low worldwide and below 10% in Korea,[12,13] dual regimens reduce selective pressure on commensal microbiota, and these regimens have favorable adverse-event profiles. Recent multicenter RCTs have reported eradication rates approaching 90% with vonoprazan- or tegoprazan-based high-dose amoxicillin dual therapy,[125,128,132,135,139] and the ACG 2024 guideline includes P-CAB-based high-dose dual therapy as a first-line option.[16] The present guidelines do not yet recommend dual therapy as first-line treatment in Korea because the only Korean study used 2 g/day amoxicillin (below the ≥3 g/day high-dose threshold), the optimal dose, duration, and acid suppressant remain unsettled across trials, and head-to-head Korean comparisons with BQT or tailored therapy in the current >30% clarithromycin resistance environment are unavailable. High-dose P-CAB-based dual therapy is therefore identified as a priority research area (see "Future research priorities"); this position will be reassessed as Korean evidence accumulates.

Gastric cancer prevention

This revision recommends eradication therapy for gastric cancer prevention in *H. pylori* gastritis patients (weak recommendation; moderate evidence), advancing the 2020 guidelines, which failed to achieve expert consensus (63.3% agreement in the second vote).[9,10] This evolution is supported by recent evidence from Choi et al.[5] in patients with a family history, and Pan et al.[6] in a large-cluster RCT. Korea's National Cancer Screening Program provides biennial upper gastrointestinal endoscopy for adults ≥40 years, but *H. pylori* testing has not yet been formally integrated.[170] However, the Fourth National Cancer Control Plan (2021–2025) identified *H. pylori* treatment as an early intervention strategy for preventable cancers,[171] and a cost-effectiveness study evaluating the addition of *H. pylori* screening to the National Cancer Screening Program is ongoing.[172] The ongoing International Agency for Research on Cancer (IARC) HELPER study (NCT02112214)[173] is expected to provide critical evidence for policy decisions regarding population-based screening and treatment strategies.

Limitations

However, this guideline has several limitations. First, the recommendations are based on Korean antibiotic resistance patterns and healthcare infrastructure, limiting direct applicability to other settings, although referring to East Asian countries with similar resistance profiles is feasible. Second, the evidence levels for some recommendations were low or moderate, particularly for salvage therapy, for which Korean RCT evidence is limited. Third, a temporal gap between published guidelines and actual resistance rates is inevitable in rapidly changing environments. Fourth, although multiple cost-effectiveness analyses support tailored therapy,[73,76,78,161] comprehensive economic evaluations of all recommended regimens were not conducted. Fifth, accessibility of PCR testing varies across healthcare institutions, particularly in primary care settings.[174] Sixth, the recommendations are most directly applicable in settings with comparable molecular diagnostic infrastructure. In environments where DPO-PCR is unavailable, BQT (or mBQT) can serve as a robust empirical backbone, culture-based AST may substitute where feasible, and structured clinical interviews can partially substitute for prescription-history databases such as the Korean DUR system, although specific regimens and durations may require adaptation to local resistance epidemiology.[175]

Finally, this revision focused on evidence-based updates to the nine KQs and did not formulate separate recommendations for established clinical principles that remained unchanged from the previous guidelines.[7-10] These include general *H. pylori* diagnostic methods (UBT, stool antigen test, RUT,

 https://doi.org/10.7704/kjhugr.2026.0029

histology, and serology) and their interpretation; timing of diagnostic testing after discontinuation of PPIs or antibiotics; the requirement for post-eradication confirmation testing at least four weeks after treatment completion using a UBT or stool antigen test; established eradication indications such as peptic ulcer disease, post-endoscopic resection of early gastric cancer, and MALT lymphoma; and management of patients with penicillin allergy, for whom amoxicillin-free regimens such as BQT or clarithromycin-metronidazole-based therapy should be prioritized after careful allergy history verification. These principles should continue to be observed in clinical practice, as outlined in preceding Korean guidelines[7-10] and recent Korean gastritis clinical practice guidelines.[35]

Future research priorities

Priority research areas include establishment of a nationwide antibiotic resistance surveillance system building on K-Hp-Reg[13,16]; large-scale Korean RCTs evaluating optimal P-CAB-based regimen dosing, duration, and combinations, particularly high-dose tegoprazan[176] and amoxicillin-based dual therapy; head-to-head comparisons of tailored therapy versus empirical CT; cost-effectiveness evidence for integrating *H. pylori* screening into the National Cancer Screening Program; evaluation of new therapeutic strategies for multidrug-resistant *H. pylori* in the Korean resistance environment; and monitoring of post-eradication gut microbiota changes and long-term P-CAB safety.[141] A detailed evidence-based analysis of the key evidence underpinning this revision is published separately.[177]

CONCLUSION

The fourth revised guideline for *H. pylori* management in Korea addresses the rapidly changing antibiotic resistance patterns with the following key changes. First, a dual-pillar strategy was established comprising PCR-based tailored therapy and empirical quadruple therapy (CT or bismuth-based regimens), effectively excluding empirical clarithromycin-based TT from routine first-line use. Second, ST- and metronidazole-based TT (PAM) were removed from the first-line recommendations. Third, P-CABs have been formally included as PPI alternatives. Fourth, a stepped salvage therapy algorithm was systematized with strong recommendations for referral to specialized centers capable of susceptibility-guided therapy after two or more treatment failures. Fifth, eradication therapy for gastric cancer prevention in *H. pylori* gastritis and hyperplastic polyp regression were introduced as new indications. Sixth, a mBQT (the addition of bismuth to clarithromycin-based TT) was introduced as an empirical first-line option.

These guidelines aim to achieve first-line eradication rates exceeding 85%, minimize unnecessary antibiotic exposure, and implement antibiotic stewardship principles in a Korean high-resistance environment. Continuous monitoring through the K-Hp-Reg registry and periodic updates at 3- to 5-year intervals will ensure responsiveness to evolving resistance patterns. In the K-Hp-Reg interim analysis, guideline adherence was an independent predictor of eradication success (OR 2.03; 95% CI 1.61–2.56),[13] underscoring both the clinical utility and the need for continuous monitoring. This direction is further reinforced by international alignment, including the recently published Taipei Global Consensus 2025,[178] which converges on the same core recommendations of BQT as the preferred first-line option, P-CAB integration, and restriction of empirical clarithromycin-containing TT in high-resistance regions.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.7704/kjhugr.2026.0029.

Authors' Contribution

Conceptualization: Byung-Wook Kim. Data curation: Chang Seok Bang, Seung Joo Kang, Hyunchul Lim, Seung Han Kim, Moon Won Lee, Su Youn Nam, Chung Hyun Tae, Sung Eun Kim, Seung Young Kim, Beom Jin Kim. Formal analysis: Chang Seok Bang, Seung Joo Kang, Hyunchul Lim, Seung Han Kim, Moon Won Lee, Su Youn Nam, Chung Hyun Tae, Sung Eun Kim, Seung Young Kim, Beom Jin Kim, Miyoung Choi. Funding acquisition: Byung-Wook Kim. Investigation: Chang Seok Bang, Seung Joo Kang, Hyunchul Lim, Seung Han Kim, Moon Won Lee, Su Youn Nam, Chung Hyun Tae, Sung Eun Kim, Seung Young Kim, Beom Jin Kim, Miyoung Choi, Hwoon-Yong Jung, Byung-Wook Kim, Hye-Kyung Jung. Methodology: Miyoung Choi. Project administration: Chang Seok Bang, Byung-Wook Kim. Resources: Chang Seok Bang, Byung-Wook Kim. Writing—original draft: Chang Seok Bang. Writing—review & editing: Chang Seok Bang, Byung-Wook Kim. Approval of final manuscript: all authors.

ORCID iDs

Chang Seok Bang https://orcid.org/0000-0003-4908-5431
Seung Joo Kang https://orcid.org/0000-0002-7401-8356
Hyunchul Lim https://orcid.org/0000-0003-4912-7136
Seung Han Kim https://orcid.org/0000-0001-9247-9175
Moon Won Lee https://orcid.org/0000-0002-8411-6398
Su Youn Nam https://orcid.org/0000-0002-5568-7714
Chung Hyun Tae https://orcid.org/0000-0002-0764-7793
Sung Eun Kim https://orcid.org/0000-0002-1835-4830
Seung Young Kim https://orcid.org/0000-0001-8933-7715
Hye-Kyung Jung https://orcid.org/0000-0002-6653-5214
Beom Jin Kim https://orcid.org/0000-0002-0938-6697
Miyoung Choi https://orcid.org/0000-0002-2424-9965
Hwoon-Yong Jung https://orcid.org/0000-0003-1281-5859
Byung-Wook Kim https://orcid.org/0000-0002-2290-4954

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