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Treatment of *Helicobacter pylori* Infection in Korea: An Evidence-Based Analysis of the Upcoming 2025 Guideline

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The efficacy of clarithromycin-containing triple therapy (TT) against *Helicobacter pylori* has declined in Korea, with recent first-line eradication rates falling below 70%. Clarithromycin resistance exceeded 30%, undermining the standard regimen for *H. pylori*. These trends necessitate a change in the treatment strategy. This review analyzed the shift proposed in the draft of the 2025 Korean *H. pylori* guidelines. We examined the rationale for abandoning TT as a first-line empirical therapy and the establishment of a new dual-pillar strategy: 1) the declining role of clarithromycin-containing TT as a first-line treatment and 2) polymerase chain reaction (PCR)-based tailored therapy as the recommended precision approach. We explored the 1) emergence of new empirical regimen options, 2) application of tailored therapy, and 3) adoption of potassium-competitive acid blockers (P-CABs). Empirical regimens have shifted toward four-drug combinations to achieve higher cure rates. Concomitant therapy (proton-pump inhibitor [PPI] or P-CAB+amoxicillin+clarithromycin+metronidazole) offers high efficacy but raises concerns about antibiotic overuse. As a compromise, bismuth-augmented triple regimens (adding bismuth to TT) are now recommended; these modified quadruple therapies (e.g., PACB: PPI+amoxicillin+clarithromycin+bismuth, or PAMB: PPI+amoxicillin+metronidazole+bismuth) significantly improve eradication rates without requiring a third antibiotic class. Regarding tailored therapy, PCR-based domestic clinical research data consistently achieves ≥90% cure rates in first-line treatment—markedly higher than empirical TT in Korea. Economic analyses supported the cost-effectiveness of this approach. The guideline algorithm for salvage therapy was clarified. Bismuth quadruple therapy has been confirmed as the standard second-line treatment. For third-line therapy, we analyzed the efficacy of levofloxacin-based regimens, rifabutin-based therapy, and bismuth add-on therapy with two previously unused antibiotics. The 2025 Korean guidelines

establish quadruple therapies as the new standard through a dual strategy: pragmatic empirical treatment and PCR-guided tailored therapy, with P-CABs and bismuth-based regimens as key components.

Keywords *Helicobacter pylori*; Tailored therapy; Antibiotic resistance; Bismuth; Clarithromycin.

INTRODUCTION

Helicobacter pylori infection remains one of the most prevalent chronic bacterial infections worldwide, affecting approximately 50% of the Korean population¹⁻³ and contributing to chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.⁴ Successful eradication of *H. pylori* significantly reduces the risk of these sequelae, making effective therapy a critical component of gastric cancer prevention and peptic ulcer management.⁵⁻⁷ However, the efficacy of traditional regimens has decreased in recent years, posing a therapeutic challenge for clinicians.⁸

Previous Korean guidelines recommended 14-day clarithromycin-containing triple therapy (TT), consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin, as the primary empirical treatment. However, it now achieves an eradication success rate of only about 66.9% by intention-to-treat (ITT) analysis, falling below the internationally accepted 80% threshold.^{9,10} This decline stems primarily from increasing antibiotic resistance among *H. pylori* isolates: clarithromycin resistance rates from 17.8% in 2018 to 33.3% in 2021–2023,^{9,11} levofloxacin resistance has reached 37%–62.2%,^{12,13} and multi-drug-resistant (MDR); resistant to at least two key antibiotics, strains now account for 37.1% of isolates.¹⁴ These trends make traditional treatments ineffective, requiring guideline updates.

In response, the 2025 Korean clinical practice guidelines for *H. pylori* management will represent a shift in treatment philosophy. The new approach moves away from multiple empirical regimen choices (which traditionally include TT, bismuth quadruple therapy [BQT], sequential therapy [ST], and concomitant therapy [CT])^{15,16} toward a more stratified strategy that emphasizes precision medicine and efficacy. The revised guidelines prioritize antibiotic susceptibility testing (AST) when feasible, adoption of potassium-competitive acid blockers (P-CABs) as potent alternatives to PPIs, appropriate empirical options, introduction of salvage therapy options, and deliberate elimination of regimens with unacceptably low success from the recommended use.^{15,16} This review highlights the evidence underpinning these changes and provides an analysis of how the dual strategy of empirical quadruple vs. tailored

therapy can be applied in clinical practice to optimize *H. pylori* eradication in Korea. A summary comparison of the key recommendations of the 2020 and 2025 guidelines is presented in Table 1.

DECLINING EFFICACY OF CLARITHROMYCIN-CONTAINING TT

Clarithromycin-containing TT has been the most widely used first-line eradication therapy since the publication of the 1998 Korean *H. pylori* guidelines.¹⁷ Its advantages include being the most familiar regimen to clinicians, having a simple drug composition, and imposing a relatively low-cost burden. Unfortunately, accumulating evidence shows that the efficacy of this regimen has fallen below acceptable levels in the Korean population.^{9,18} The 2020 Korean guidelines have attempted to salvage this regimen by extending the treatment duration from 7 to 14 days, hoping that prolonged antibiotic exposure might compensate for the rising resistance.^{15,16} This strategy proved insufficient. In a multicenter registry study from 2021–2023, the overall first-line eradication rate in routine practice was only about 70.5% in ITT analyses despite most patients receiving 14-day therapy, below acceptable thresholds.⁹ When a strain is clarithromycin-resistant, TT success drops dramatically (often <50% success against resistant strains). Given that one-third or more Korean patients harbor clarithromycin-resistant *H. pylori*, it is unsurprising that the overall cure rates with TT are now unacceptably low.

We performed a systematic review using an established search strategy by experts in this field and found nine Korean randomized controlled trials (RCTs)¹⁹⁻²⁷ relevant to 14 days clarithromycin-containing TT efficacy. Eradication rates were analyzed using three RCTs published after 2018,²⁵⁻²⁷ and six studies¹⁹⁻²⁴ from the previous guidelines (Table 2). Specifically, the eradication rates for the three studies prior to 2009¹⁹⁻²¹ were ITT 79.8% (95% confidence interval [CI], 75.9%–83.2%) and per-protocol (PP) 87.6% (95% CI, 84.1%–90.5%). For the three studies conducted between 2010 and 2019,²²⁻²⁴ rates were ITT 76.1% (95% CI, 71.8%–79.9%) and PP 84.3% (95% CI, 80.3%–87.6%). For the three studies after 2018,²⁵⁻²⁷ rates dropped to ITT 66.9% (95% CI, 63.1%–70.5%) and PP 76.2% (95% CI,

Table 1. Summary of key changes: 2020 vs. 2025 Korean *H. pylori* treatment guidelines

Category	2020 guideline	2025 guideline
Treatment philosophy	Multiple empirical regimen choices (TT, BQT, sequential therapy, CT)	Dual-pillar strategy: precision (PCR-guided)+ pragmatic empirical quadruple therapy
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	Deemphasized (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	Emphasized: BQT+new mQTs (PACB, PAMB) as preferred empirical options
PCR-based tailored therapy	Mentioned as optional approach	Primary recommended strategy; core pillar of dual-pillar framework
Acid suppressant	PPI-based regimens	P-CAB formally incorporated as alternative/ preferred option
Second-line therapy	BQT (10–14 days)	BQT reaffirmed; PAMB as alternative if tetracycline unavailable
Third-line therapy	Limited guidance	Clarified algorithm: rifabutin TT, mQTs with unused antibiotics, levofloxacin TT (limited); AST-guided therapy strongly recommended

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

Table 2. Evidence table about the eradication rate of 14-day clarithromycin-containing TT in *H. pylori* infection

Study	Indication	Number of enrolled subjects	Eradication rate (ITT)	Eradication rate (PP)
Kim et al. ¹⁹ (2007)	PUD	261	75.5% (197/261)	86.6% (194/224)
Kim et al. ²⁰ (2008)	PUD	112	80.4% (90/112)	85.9% (79/92)
Kim et al. ²¹ (2008)	PUD	93	91.4% (85/93)	92.1% (82/89)
Kim et al. ²² (2011)	HP infected patients	204	75.0% (153/204)	85.0% (153/180)
Choi et al. ²³ (2012)	PUD	115	80.0% (92/115)	84.4% (92/109)
Kim et al. ²⁴ (2012)	PUD	104	74.0% (77/104)	82.8% (77/93)
Kim et al. ²⁵ (2020)	HP infected patients	191	66.0% (126/191)	79.7% (114/143)
Lim et al. ²⁶ (2023)	HP infected patients	270	66.7% (180/270)	74.6% (179/240)
Kim et al. ²⁷ (2024)	HP infected patients	153	68.6% (105/153)	75.5% (105/139)

TT, triple therapy; HP, *Helicobacter pylori*; PUD, peptic ulcer disease; ITT, intention-to-treat; PP, per protocol.

72.4%–79.7%), showing a significant difference in eradication rates over time ($p<0.001$).

Because it fails to meet the criterion that the ITT eradication rate should be at least 80% to be recommended as a primary therapy, it is difficult to consider TT as a first-choice option for empirical first-line treatment without AST.¹⁰ Furthermore, as the use of TT has recently decreased, recent regional data on eradication rates according to antibiotic resistance rates are lacking. International guidelines also do not recommend TT as a first-line treatment in regions such as Korea, where clar-

ithromycin resistance exceeds 15%.^{28,29} The implementation of TT mandates AST-guided selection of appropriate regimens.²⁹

TAILORED THERAPY BASED ON MOLECULAR TESTING: A NEW FIRST-LINE STRATEGY

In response to the limited efficacy of empirical approaches, molecular testing using polymerase chain reaction (PCR) or sequencing has facilitated the adoption of tailored therapy.³⁰ Tai-

lored therapy refers to selecting a treatment regimen based on the patient's specific *H. pylori* antibiotic susceptibility profile, rather than using a one-size-fits-all regimen.³¹ In practice, this often involves PCR-based testing of gastric biopsy specimens for known resistance mutations, particularly the 23S rRNA mutations conferring clarithromycin resistance.³² Dual-priming oligonucleotide (DPO)-based multiplex PCR assays have been developed in Korea to rapidly determine clarithromycin susceptibility from biopsy or even stool samples.^{9,27}

PCR-based testing accurately detects 23S rRNA point mutations (e.g., A2142G and A2143G) associated with clarithromycin resistance, demonstrating a concordance rate of over 95% with phenotypic tests such as the E-test.^{33–35} Tailored therapy based on resistance detection has been shown to improve eradication rates. Additionally, this method allows for the partial analysis of levofloxacin resistance by detecting *gyrA* mutations with a sensitivity of over 90%.³⁶ Compared to culture tests, PCR offers superior rapidity and high sensitivity. In terms of cost-effectiveness, economic benefits are generally observed when the eradication rate is below 80% or when the clarithromycin resistance rate exceeds 20%.³⁷

In regions with high clarithromycin resistance, implementing tailored therapy yields results superior to or comparable to those of empirical therapy. However, the universal application of this approach in routine practice requires careful consideration of the regional medical environments and economic factors. The overall eradication success of tailored therapies in previous studies was influenced by the therapeutic potency of the control regimen. We conducted a systematic review of 5 Korean RCTs and 16 prospective or retrospective studies (published up to August 2024). In most studies, clarithromycin-resistant patients received BQT and clarithromycin-susceptible patients received TT. The control group included regimens that were previously recommended as first-line therapies (clarithromycin-based TT, BQT, CT, or metronidazole-based TT). A meta-analysis was performed on four of these RCTs that specifically utilized BQT for clarithromycin-resistant cases and clarithromycin-containing TT for susceptible cases.^{27,38–40} The meta-analysis revealed that in the ITT analysis, the eradication rate for tailored therapy was 84.3% (95% CI, 78.5%–90.1%), whereas the rate for empirical therapy was 77.3% (95% CI, 63.0%–91.6%), with a risk ratio (RR) of 1.11 (95% CI, 1.05–1.17). In the PP analysis, the eradication rate for tailored therapy was 91.6% (95% CI, 83.4%–99.7%) compared to 84.8% (95% CI, 71.9%–97.6%) for empirical therapy, with an RR of 1.08 (95% CI, 1.03–1.13). Both the ITT and PP analyses demonstrated that the eradication rate of tailored therapy was significantly higher than that of empirical therapy. The pooled eradication rate across all included 21 studies also showed ITT 80.9% (95%

CI, 77.4%–84.4%) and PP 90.0% (95% CI, 88.2%–91.7%) of eradication success in tailored therapy, which is an acceptable level for first-line therapy.

More recent nationwide RCTs conducted in Korea have also confirmed this result and demonstrated that tailored therapy—comprising BQT or clarithromycin-containing TT (based on clarithromycin resistance)—yielded superior therapeutic outcomes compared to a CT control group. These regimens achieved eradication success rates exceeding 80% in the ITT analysis and 90% in the PP analysis.⁴¹ Similarly, another nationwide study reported that such tailored therapy demonstrated superior efficacy compared to a TT control group.²⁷

As an alternative strategy, a prospective study was conducted in Korea using the Drug Utilization Review system to screen antibiotic medication history and assign treatment (BQT or clarithromycin-containing TT) accordingly.⁴² This study demonstrated that strategically designed empirical treatment based on medication history is a feasible alternative to genotypic resistance-guided therapy.^{43,44}

However, despite these advantages, tailored therapies do not always guarantee complete eradication. Potential reasons for reduced success rates include: 1) mixed infection and heteroresistance: the coexistence of *H. pylori* strains with different resistance profiles can lead to treatment failure.^{45–47} 2) Diagnostic limitations (sensitivity and resistance variants): rare atypical mutations (e.g., A2142C) may be missed. Furthermore, there is a risk of misidentifying resistant strains as susceptible owing to sampling errors caused by variations in bacterial density across different gastric regions. 3) Lack of adherence: poor medication adherence remains a significant cause of treatment failure independent of antibiotic resistance patterns. 4) Resistance to other antibiotics: tailored regimens often focus solely on clarithromycin resistance, potentially overlooking resistance to the other antibiotics included in the regimen.

Overall, in regions with high clarithromycin resistance, tailored strategies have resulted in significant improvements in eradication rates, particularly when clarithromycin-containing TT is used as the control.⁴⁸ It is also a cost-effective strategy for *H. pylori* eradication in Korea, particularly in the context of high clarithromycin resistance rates.⁴⁸ Conversely, in studies where reinforced empirical therapies (e.g., BQT) served as the control, or in studies with small sample sizes, the statistical superiority of tailored therapy may not be clearly established.

We recommend performing a DPO-PCR or a similar genotypic test for clarithromycin resistance in all patients before starting therapy, whenever feasible. This approach discourages the previous concept of multiple empirical first-line options^{15,16} in favor of precision medicine guided by the molecular detection of genotypic resistance to clarithromycin (23S rRNA

A2142G or A2143G). If a clarithromycin-resistant mutation is detected, BQT is recommended as the first-line treatment; if no mutation is found (i.e., a susceptible strain), a clarithromycin-containing TT can be used with careful monitoring.

OPTIMIZING EMPIRICAL FIRST-LINE THERAPY: FROM TT TO QUADRUPLE-AND STEWARDSHIP CONSIDERATIONS

For cases where AST is not performed (or results are awaiting), the guidelines recommend empirical regimens that cover likely resistance. As noted above, clarithromycin resistance now exceeds 30%, indicating that a large proportion of patients harbor clarithromycin-resistant strains. When clarithromycin is ineffective, the efficacy of TT decreases (amoxicillin rarely encounters resistance, but resistance to clarithromycin is sufficient to cause failure). In cases where tailored therapy is not used, the 2025 guidelines recommend empirical regimens that can achieve the highest possible eradication rates in the face of prevalent resistance. Given the shortcomings of TT, this necessitates a shift toward four-drug regimens (quadruple therapies) for empirical treatment in most patients. Two main strategies have been highlighted: CT and BQT, including newer “modified” combinations (modified quadruple therapies [mQTs] [e.g., PACB: PPI+amoxicillin+clarithromycin+bismuth, or PAMB: PPI+amoxicillin+metronidazole+bismuth]) adapted for Korean practice. These regimens have high intrinsic cure rates despite prevalent resistance. Notably, 10-day CT has gained popularity in Korea; its usage as a first-line therapy increased sharply after 2019,⁴⁹ and the 2025 guidelines list CT as an effective empiric option alongside BQT. The role of ST has been deemphasized. This is attributed to poor medication adherence, difficulties in selecting salvage regimens due to multiple antibiotic exposure upon treatment failure, and lower eradication rates compared to CT and BQT.⁴⁹ Similarly, metronidazole-based TT (PAM: PPI+amoxicillin+metronidazole), which was recommended by the 2020 Korean guidelines as an alternative for clarithromycin-resistant strains, is no longer endorsed as a first-line empirical option. This decision reflects the high domestic metronidazole resistance rate (29.5%)¹¹ and concerns that prior metronidazole exposure may compromise the efficacy of BQT, a standard second-line salvage regimen. Instead, bismuth-augmented regimens (e.g., PAMB), which can overcome metronidazole resistance through intensified dosing, are preferred. Overall, the main message was that the 14-day clarithromycin-containing TT should only be used in low-risk or confirmed susceptible cases, whereas quadruple therapies should be used upfront in most Korean patients to ensure

higher success, given the resistance landscape.⁵⁰

Continuing clarithromycin use when over one-third of strains are resistant is against antibiotic stewardship and has been a major driver of rising resistance. Paradoxically, previous Korean guidelines (and some practitioners) still recommended clarithromycin-based TT despite high resistance levels, due to inertia and limited alternatives.⁵⁰ The 2025 revision breaks from this position: it emphasizes that we are at a “critical juncture where it may be necessary to discontinue empirical clarithromycin-containing TT in Korea.” In other words, unless there is evidence that a patient is susceptible (via AST), a clarithromycin-based regimen should not be chosen empirically.

CT refers to a non-bismuth quadruple regimen consisting of a PPI (or P-CAB), amoxicillin, clarithromycin, and nitroimidazole (typically metronidazole or tinidazole) administered simultaneously for 10–14 days. This regimen essentially adds nitroimidazole to TT, thereby attacking *H. pylori* with three antibiotics simultaneously. CT has demonstrated high eradication rates (>90% in many studies), even in populations with significant clarithromycin or metronidazole resistance because the likelihood of a strain being resistant to all components is low. Indeed, CT’s efficacy in Korea has far surpassed that of TT alone. Our meta-analysis of 58 studies showed no significant difference in CT success rates between studies published before 2018 and those after 2018.^{51–53} Notably, 10-day CT achieved over 80% ITT and over 90% PP eradication (Table 3), with no higher incidence of adverse events than other regimens. CT was also marginally more effective than ST, likely owing to its superior performance against single-drug resistance. Specifically, CT outperformed ST in clarithromycin-resistant strains^{51,52} and in strains resistant to metronidazole but susceptible to clarithromycin.^{51,53} Nonetheless, the guideline authors urge caution in using CT because of stewardship concerns; deploying three antibiotics upfront could broaden antimicrobial resistance and increase the risk of adverse events. We acknowledge that while CT is highly effective, it should be reserved for cases of truly high resistance risk (e.g., when tailored therapy is unavailable) and used for as long as necessary.

To ensure a balance between efficacy and antibiotic stewardship, the updated guidelines place particular emphasis on bismuth-containing quadruple regimens as the empirical regimens of choice. Bismuth-based regimens typically include a bismuth salt plus two antibiotics and an acid suppressor, meaning that they use only two antibiotics rather than three. BQT uses PPI, bismuth, tetracycline, and metronidazole. However, tetracycline is not always easily available or well tolerated by patients. Evidence supports that the addition of bismuth substantially improves eradication rates. A recent systematic review and meta-analysis examined randomized trials comparing

Table 3. Evidence table about the eradication rate of CT in *H. pylori* infection (meta-analysis)

Study	Eradication rate (ITT) (before 2018)	Eradication rate (PP) (before 2018)	Eradication rate (ITT) (after 2018)	Eradication rate (PP) (after 2018)
10-day CT, overall (n=23 before 2018) (n=10 after 2018)	85% (82%–88%)	91% (88%–93%)	85% (85%–85%)	93% (91%–95%)
10-day CT, Korean studies (n=7 before 2018) (n=4 after 2018)	84% (77%–89%)	92% (88%–94%)	82% (79%–85%)	93% (91%–95%)
14-day CT, overall (n=6 before 2018) (n=19 after 2018)	86% (76%–92%)	94% (88%–97%)	86% (84%–87%)	91% (89%–92%)
14-day CT, Korean studies (n=2 before 2018) (n=3 after 2018)	79% (72%–85%)	94% (50%–99%)	84% (80%–87%)	90% (87%–93%)

Data are presented as effect size (95% CI).

CT, concomitant therapy; ITT, intention-to-treat; PP, per protocol; CI, confidence interval.

bismuth-containing regimens to comparable regimens without bismuth as a first-line therapy.⁵⁴ The meta-analysis included 13 studies (over 2500 patients), and found that overall, bismuth supplementation led to significantly higher cure rates. The odds of successful eradication were 1.63 times higher with bismuth (95% CI 1.33–2.00) in ITT analysis. When considering only patients who were fully compliant with the therapy (PP analysis), the benefit was even greater (OR highest 2.05, 95% CI 1.58–2.68). There were no significant differences in adverse event rates or compliance between the bismuth and non-bismuth regimens. The benefits of bismuth are particularly pronounced in populations with high clarithromycin resistance. In trials conducted in high-resistance areas, the addition of bismuth increased the odds of eradication by approximately 1.66-fold (ITT) to 2.22-fold (PP) compared to non-bismuth regimens. These findings validate the recommendations of the guidelines to augment empirical therapy with bismuth in Korea.

The modified regimens proposed in Korea add bismuth to the standard TT backbone, creating hybrid regimens that are effective quadruple therapies with familiar components. The two mQT regimens highlighted in the guidelines are PACB (PPI or P-CAB+amoxicillin+clarithromycin+bismuth) and PAMB (PPI or P-CAB+amoxicillin+metronidazole+bismuth).

In PACB, bismuth is added to a PAC (PPI-amoxicillin-clarithromycin) clarithromycin-containing TT. This may be suitable in regions or patients where clarithromycin resistance is not exceedingly high as long as bismuth is present to boost efficacy. In PAMB, clarithromycin is omitted (replaced by metronidazole) and bismuth is added, which resembles a metronidazole TT with bismuth and is useful if clarithromycin resistance is known or strongly suspected. Both regimens leverage bismuth's ability to enhance antibiotic effectiveness. Bismuth

compounds have multimodal antibacterial actions against *H. pylori* and help overcome resistance by synergizing with antibiotics and perhaps mildly suppressing *H. pylori* on their own.⁵⁵

PAMB (14-day in particular) achieved high eradication rates (87%–93% ITT, highest 95% PP) in diverse populations^{56–59} and was statistically non-inferior or superior to the standard first-line regimens (including CT and BQT). PACB also yielded high cure rates (77.8%–93% ITT, highest 95% PP), although its efficacy decreases in clarithromycin-resistant cases.^{58,60} PAMB is effective despite high clarithromycin and/or metronidazole resistance, essentially bypassing clarithromycin resistance and overcoming metronidazole resistance with aggressive dosing.⁵⁸ PACB improves outcomes over clarithromycin-containing TT empirically and can partly overcome low-level clarithromycin resistance,⁵⁸ but is still significantly compromised by high-level clarithromycin resistance. Neither regimen is affected by fluoroquinolone or tetracycline resistance because these drugs are not used, and bismuth has no resistance.^{61,62}

P-CAB: OPTIMIZING ACID SUPPRESSION

Another advancement in empirical therapy is the introduction of P-CABs as the preferred acid-suppressive agents. Achieving a high intragastric pH is crucial for *H. pylori* treatment efficacy, as it enhances antibiotic stability and activity (especially for acid-labile drugs such as clarithromycin) and promotes the replicative state of *H. pylori* (making bacteria more susceptible to antibiotics).^{55,63} Since P-CABs provide faster and more stable acid suppression than PPIs, they may enhance antibiotic efficacy, potentially allowing for reduced anti-

biotic dosages or shorter treatment durations. Given reports that P-CAB-based eradication is more effective against clarithromycin-resistant strains, effective regimens that reduce the number, dose, or duration of antibiotics based on resistance profiles in tailored therapy can be anticipated.^{64,65} However, the primary barriers to using P-CABs for *H. pylori* eradication are the limited number of studies on various P-CAB agents and the restricted scope of insurance coverage in Korea. P-CABs may have a higher initial cost than PPIs and the financial burden on patients varies depending on insurance coverage. However, if high eradication rates are confirmed, as seen with vonoprazan, there is the potential to reduce long-term medical resource consumption by decreasing the need for retreatment. Moreover, P-CAB efficacy is not influenced by the CYP2C19 genotype, and higher eradication rates can be expected even against resistant strains.⁶⁶

We systematically searched for RCTs that compared the eradication rates of P-CAB- and PPI-containing regimens. A meta-analysis was conducted on 19 studies^{65,67-84} that compared the same antibiotic combinations (Table 4). These included 14 studies^{65,67-70,72-74,76-79,83,84} on vonoprazan, four on tegoprazan, and one on keverprazan. Most studies were designed to test the non-inferiority of P-CABs to PPIs, while four vonoprazan studies tested for superiority. P-CAB-based eradication therapies were more effective than PPI-based therapies (86.3% vs. 78.8%; RR 1.08, 95% CI 1.04–1.12). Specifically, vonoprazan demonstrated superior eradication outcomes compared with PPIs (88.4% vs. 79.0%; RR 1.10, 95% CI 1.05–1.15). When analyzing only four studies testing for superiority, the efficacy was even more pronounced (86.1% vs. 72.0%; RR 1.19, 95% CI 1.09–1.30). In contrast, the meta-analysis of tegoprazan (all non-inferiority trials) showed that it was not significantly more effective than PPIs for eradication (79.3% vs. 76.8%; RR 1.03, 95% CI 0.98–1.09). In a meta-analysis of 16 studies that reported adverse events with P-CAB- or PPI-containing regimens, the incidence of adverse events was 32.8% for P-CABs and 31.8% for PPIs. No significant difference was observed between the groups (RR 1.01, 95% CI 0.93–1.11).

In summary, while P-CAB regimens showed superior overall eradication efficacy compared to PPI-based regimens, tegoprazan (which is available in Korea) did not demonstrate superiority, indicating that its eradication rate was comparable to that of PPIs. Based on these findings, the guideline will conclude that P-CAB-based therapy can be used as an alternative to traditional PPI-based regimens for first-line *H. pylori* eradication. Korean guidelines encourage the use of P-CABs in both tailored and empirical regimens, whenever available, to maximize the probability of success. This is especially relevant in rescue regimens or patients who rapidly metabolize PPIs. By

combining P-CAB-enhanced acid suppression with either four-drug combinations or bismuth-supplemented therapy, empirical treatment can achieve efficacy on par with tailored approaches, while mitigating resistance development by avoiding ineffective clarithromycin use.

SALVAGE THERAPY AFTER TREATMENT FAILURE

With more effective first-line treatment, the overall proportion of patients requiring salvage therapy should decrease. Nonetheless, the guidelines have updated and clarified the recommended second- and third-line options for cases in which the initial treatment (whether tailored or empirical) fails. The overarching principle is to avoid repeating any antibiotic to which the strain has already been exposed and to use the most effective available regimen for salvage, taking into account cumulative resistance (Fig. 1).

Second-line therapy

BQT, consisting of a PPI, bismuth, metronidazole, and tetracycline (PBMT), has been reaffirmed as the standard second-line regimen in Korea for patients in whom first-line therapies (e.g., 10-day CT or tailored therapy) have failed. This recommendation is supported by robust evidence demonstrating that BQT is largely unaffected by clarithromycin resistance and maintains consistently high eradication rates (>85%) as second-line treatment in Korea.^{18,85,86} Korean data indicate that successful second-line BQT improves the cumulative eradication rate to approximately 95%.^{18,85-87}

Regarding treatment duration, a course of 10–14 days is recommended over 7 days. In previous guidelines analyzing nine RCTs, 10–14-day regimens showed a significantly higher pooled eradication rate (81.6%) compared to 7-day regimens (68.4%).^{15,16} This finding is supported by a recent network meta-analysis where 10–14 day BQT demonstrated a pooled eradication rate of 78.8% and a significantly higher odds ratio (OR) for eradication (OR 2.02; 95% CI, 1.32–3.07) compared to 7-day regimens, with no significant difference in dropout rates (OR 1.11; 95% CI, 0.78–1.59).⁸⁸

In a recent study of 10-day BQT after the failure of first-line clarithromycin-containing TT or CT, the regimen achieved high eradication rates (ITT, 87.5%; PP, 92.8%). Adverse events were reported in 77% of the patients, but the vast majority were mild, and adherence remained high (95.6%). This finding indicates that BQT is a highly effective and tolerable rescue regimen for patients receiving appropriate support.⁸⁹

In terms of antibiotic resistance, while a recent nationwide survey in Korea reported a high metronidazole resistance rate

Table 4. Evidence table about the comparative efficacy between P-CAB-based- vs. PPI-based regimens in *H. pylori* eradication

Study	Country	Regimen	P-CAB regimen			PPI regimen		
			P-CAB	Duration (day)	ITT	PP	ITT	PP
Murakami et al. ⁶⁷ (2016)	Japan	PAC	Vonoprazan	7	92.6% (300/324)		75.9% (243/320)	
Maruyama et al. ⁶⁸ (2017)*	Japan	PAC	Vonoprazan	7	95.8% (69/72)	95.7% (67/70)	69.6% (48/69)	71.4% (45/63)
Bunchornritavakul and Buranathawornsom ⁶⁹ (2021)*	Thailand	PAC	Vonoprazan	7	96.7% (59/61)	98.3% (59/60)	88.5% (54/61)	93.1% (54/58)
Ang et al. ⁷⁰ (2022)	Singapore	PAC	Vonoprazan	7	87.4% (104/119)	96.3% (104/108)	88.0% (110/125)	94.0% (110/117)
Chey et al. ⁶⁵ (2022)*	USA, Europe	PAC	Vonoprazan	14	80.8% (273/338)	85.7% (240/280)	68.5% (226/330)	70.0% (194/277)
Choi et al. ⁷¹ (2022)	Korea	PAC	Tegoprazan	7	62.9% (110/175)	69.3% (104/150)	60.6% (106/175)	67.3% (101/150)
Chen et al. ⁷² (2023)	China	PACB	Vonoprazan	14	77.0% (77/100)	86.5% (77/89)	69.0% (69/100)	78.4% (69/88)
Han et al. ⁷³ (2023)	China	Dual	Vonoprazan	10	89.3% (308/345)	91.4% (308/337)	84.9% (293/345)	86.6% (291/336)
Huang and Lin ⁷⁴ (2023)*	China	PBAF	Vonoprazan	14	97.5% (39/40)		80.0% (32/40)	
Kim et al. ⁷⁵ (2023)	Korea	PBMT	Tegoprazan	14	80.0% (84/105)	90.2% (74/82)	77.4% (82/106)	82.4% (70/85)
Lu et al. ⁷⁶ (2023)	China	PBAF	Vonoprazan	10 or 14	96.8% (151/156)	98.0% (147/150)	93.6% (73/78)	94.8% (73/77)
Su et al. ⁷⁷ (2023)	China	Dual	Vonoprazan	14	89.0% (65/73)	94.1% (64/68)	87.7% (64/73)	92.8% (64/69)
Chen et al. ⁷⁸ (2024)	China	PBAF	Vonoprazan	14	84.4% (38/45)	92.7% (38/41)	84.4% (38/45)	88.4% (38/43)
Hou et al. ⁷⁹ (2024)	China	PACB	Vonoprazan	14	90.6% (259/286)			85.2% (236/277)
Kong et al. ⁸⁰ (2024)	China	Dual	Tegoprazan	14	85.9% (158/184)	88.2% (157/178)	84.2% (155/184)	88.5% (154/174)
Lee et al. ⁸¹ (2024)	Korea	Sequential therapy	Tegoprazan	10	83.8% (171/204)	83.8% (171/204)	87.1% (176/202)	87.1% (176/202)
Tan et al. ⁸² (2024)	China	PACB	Keverprazan	14	87.8% (252/287)	93.5% (244/261)	82.5% (236/286)	88.2% (225/255)
Waqar et al. ⁸³ (2024)	Iran	PAL	Vonoprazan	14	95.1% (58/61)			
Zhou et al. ⁸⁴ (2024)	China	Dual	Vonoprazan	10	85.4% (245/287)	91.1% (245/269)	76.7% (217/283)	85.5% (212/248)

*These studies were superiority trials directly testing whether P-CAB regimens were superior to PPI regimens.
P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; ITT, intention-to-treat; PP, per-protocol; PAC, PPI+amoxicillin+clarithromycin; PACB, PPI+amoxicillin+clarithromycin+bismuth; PBAF, PPI+bismuth+amoxicillin+furazolidone; Dual, PPI or PACB+amoxicillin; PBMT, PPI+bismuth+metronidazole+tetracycline; PAL, PPI+amoxicillin+levofloxacin.

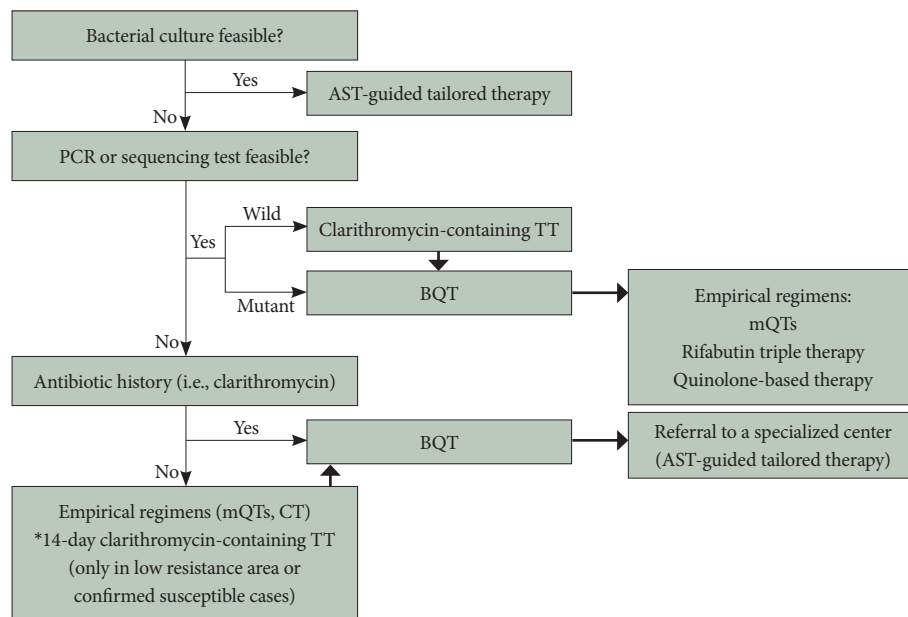


Fig. 1. Flowchart summarizing the *H. pylori* treatment algorithm, from first-line AST-guided or empirical therapy to second- and third-line salvage options. AST, antibiotic susceptibility test; PCR, polymerase chain reaction; TT, triple therapy; BQT, bismuth quadruple therapy; mQTs, modified quadruple therapy; CT, concomitant therapy.

of 29.5%,¹¹ reviews suggested that this does not significantly impact the clinical efficacy of BQT, as resistance can often be overcome by increasing the dosage and duration of treatment.⁹⁰ Consequently, BQT remains an appropriate rescue therapy in the Korean context. In cases where tetracycline is unavailable or not tolerated, a PAMB regimen (PPI, amoxicillin, metronidazole, and bismuth) may be considered as an alternative second-line option, provided that amoxicillin is being reused (amoxicillin resistance in *H. pylori* is rare, so reusing it is acceptable).

Third-line rescue therapy

If both the first- and second-line treatments fail, the *H. pylori* strain is likely to be MDR. At this stage, expert consultation and susceptibility testing are strongly advised. The 2025 guidelines outline several options for third-line therapy, emphasizing regimens involving antibiotics that have not been previously used. It is considered inappropriate to reuse clarithromycin-containing regimens after failure of second-line BQT (following failure of first-line clarithromycin-containing TT or CT) or after failure of first-line BQT. Failure of these regimens implies that clarithromycin resistance is either confirmed via molecular diagnosis or strongly suspected due to prior exposure. Generally, reusing clarithromycin, levofloxacin, or rifabutin is not recommended if resistance is present or suspected; however, amoxicillin and metronidazole can be reused.⁹¹ Studies indicate that empirical therapy based on a carefully reviewed history of failed antibiotics can achieve efficacy comparable to sus-

ceptibility-guided therapy in second- or third-line settings.⁹² Based on these principles, the preferred rescue regimens include rifabutin TT, modified BQT (incorporating previously unused antibiotics), or, in restricted cases, levofloxacin-based therapy.

Rifabutin is an antibiotic primarily used for tuberculosis, but possesses activity against *H. pylori* with no cross-resistance to other antibiotic classes. A typical regimen consists of PPI, amoxicillin, and rifabutin (150 mg twice daily or 300 mg once daily) for 10–14 days. Clinical evidence supports its use as rescue therapy. A Chinese study comparing 14-day rifabutin TT versus 14-day BQT as third-line treatment found no significant difference in ITT eradication rates (89.0% vs. 89.6%).⁹³ However, the rifabutin group demonstrated significantly fewer moderate-to-severe adverse events (14.3% vs. 28.6%) and higher adherence (96.2% vs. 85.4%) compared to the BQT group. Although this study targeted patients naïve to BQT, a Korean RCT specifically investigated patients who failed BQT.¹⁴ Although efficacy depends on resistance, the rifabutin resistance rate in Korea is estimated to be extremely low, recently reported to be 0.8%.¹⁴ Thus, rifabutin TT remains a viable salvage option, achieving success rates in the 60%–80% range for refractory cases.¹⁴ However, caution is required due to cost, rare but serious myelotoxicity (necessitating monitoring), and the potential for inducing resistance in *Mycobacterium tuberculosis*.⁹⁴

Another third-line strategy involves designing a regimen that includes two antibiotics to which the patient has not been previously exposed, combined with bismuth and a strong acid

suppressant. This is referred to as the mQT. For example, if a patient fails to respond to regimens containing clarithromycin, metronidazole, and tetracycline, the third-line mQT might utilize levofloxacin or amoxicillin. While no RCTs have specifically addressed the efficacy after BQT failure, studies in third-line settings have demonstrated non-inferiority to traditional BQT. A Chinese study comparing a regimen of PPI, bismuth, amoxicillin, and levofloxacin against traditional BQT showed similar ITT eradication rates (83.0% vs. 88.1%) but significantly fewer adverse events (5% vs. 22.4%).⁹⁵ Another RCT replacing tetracycline with amoxicillin found no significant difference in eradication rates (ITT: 88.5% vs. 87.2%) but noted significantly higher adverse events in the traditional BQT group.⁹⁶ These findings suggest that mQTs offer a flexible and effective alternative, although further research is needed to confirm its effectiveness, specifically in patients who have already failed traditional BQT.

Levofloxacin TT (PPI+amoxicillin+levofloxacin) has been used as a salvage regimen in Korea, but its utility is increasingly limited by resistance rates exceeding 30%.⁹ Recent registry findings indicate that levofloxacin-based therapy achieves sub-

optimal success rates (around 70%–80%) as a third-line treatment in Korea.⁹ A Korean study analyzing efficacy by treatment duration in patients who failed both first-line clarithromycin-containing TT and second-line BQT reported ITT eradication rates of 58.3% (7-day), 62.5% (10-day), and 73.7% (14-day).⁹⁷ Even when restricting analysis to 10–14-day regimens, the rate was only 67.4%, which is lower than other rescue options. Therefore, levofloxacin TT should be attempted only on a limited basis, considering prior antibiotic history and regional resistance patterns or if susceptibility is confirmed. While some international reports suggest that levofloxacin quadruple or sequential therapies offer superior efficacy compared to levofloxacin TT in rescue settings,⁸⁸ domestic data regarding these regimens are lacking in Korea. The resistance rate of *H. pylori* to levofloxacin in Korea has steadily increased over the past 20 years, reaching 36.0%–42.9% in recent studies conducted between 2019 and 2020.⁹⁸ Consequently, eradication success cannot be guaranteed even in second- or third-line settings because of high resistance rates. Furthermore, following the failure of standard therapy, selection pressure for levofloxacin resistance occurs, and cross-resistance between clarithromycin

Table 5. Summary comparison of empirical versus tailored treatment strategies for *H. pylori* eradication

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

PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker; A, amoxicillin; C, clarithromycin; M, metronidazole; B, bismuth; T, tetracycline; L, levofloxacin; CT, concomitant therapy; BQT, bismuth quadruple therapy; mQTs, modified quadruple therapies; TT, triple therapy; AST, antibiotic susceptibility testing; PCR, polymerase chain reaction; FQ, fluoroquinolone; ITT, intention-to-treat; Tbc, tuberculosis.

and fluoroquinolones—leading to increased secondary resistance—has been confirmed.⁹⁹ Regarding other therapeutic options, sitafloxacin, which is widely used even as a first-line agent in Japan, is currently unavailable in Korea. Moxifloxacin TT lacks sufficient study numbers to allow for generalization.^{100,101} Similarly, high-dose dual therapy, utilized in other countries, currently lacks sufficient evidence for recommendation owing to the absence of domestic studies.¹⁰²

In cases where two or more eradication therapies fail, referral to a specialized center capable of performing susceptibility-based tailored therapies is strongly recommended. If second-line rifabutin- or levofloxacin-based therapies or mQTs fail after first-line BQT, expert judgment is required. Even in refractory cases, susceptibility-guided therapy can achieve relatively high eradication rates of over 80%–90% in ITT analysis.^{43,92} Through this stepped approach (Table 5), first-line tailored or empirical quadruple, second-line BQT, and third-line individualized rescue, the goal is to achieve eradication while minimizing unstructured retrials that drive further resistance.

CONCLUSION

The 2025 revisions of the Korean *H. pylori* treatment guidelines have replaced clarithromycin-containing TT with a strategy that prioritizes efficacy and precision. To address high antibiotic resistance, the guidelines establish a robust “dual-pillar” framework: pragmatic empirical treatment using high-efficacy quadruple regimens (CT or bismuth-based) and precision medicine utilizing PCR-guided tailored therapy. Both pathways, reinforced by extended treatment durations (10–14 days), aim to maximize first-line cure rates. In particular, the guidelines highlight mQTs (e.g., PACB or PAMB) as the preferred empirical first-line option in Korea’s high-resistance setting. This approach balances high efficacy with prudent antibiotic use, and aligns with the principles of antibiotic stewardship.

A significant update is the formal incorporation of P-CABs. P-CABs are recognized as valuable tools that offer potent acid suppression comparable or superior to that of PPIs, and serve as integral components to counteract resistance. For rescue therapy, the guidelines provide a clear stepwise algorithm. BQT is reaffirmed as the standard second-line regimen, whereas fluoroquinolone- or rifabutin-based therapies are reserved for third-line salvage, ideally guided by antimicrobial susceptibility testing.

These guidelines address the resistance patterns in Korea. The framework targets eradication rates of >9%, thereby minimizing the development of secondary resistance. The successful implementation of these recommendations is expected to reduce treatment failures and significantly lower the burden

of *H. pylori*-related diseases, including gastric cancer, across the population. Future efforts should focus on ongoing resistance surveillance and real-world research to sustain these clinical gains.

Authors’ Contribution

Conceptualization: Chang Seok Bang, Byung-Wook Kim. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Resources: all authors. Supervision: Chang Seok Bang, Hye-Kyung Jung, Byung-Wook Kim. Writing—original draft: Chang Seok Bang. Writing—review & editing: Chang Seok Bang. Approval of final manuscript: all authors.

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