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Review Article

Optimizing *Helicobacter pylori* Treatment: An Updated Review of Empirical and Susceptibility Test-Based Treatments

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As the rate of discovery of drug-resistant *Helicobacter pylori* cases increases worldwide, the relevant societies have updated their guidelines for primary eradication regimens. A promising strategy against drug-resistant *H. pylori* is tailored therapy based on the results of an antibiotic susceptibility test; however, it is difficult to apply this strategy to all cases. Although culture-based antibiotic susceptibility tests can assess resistance to any antimicrobial agent, their greatest disadvantage is the time required to draw a conclusion. In contrast, molecular-based methods, such as polymerase chain reaction, can rapidly determine the presence of resistance, although a single test can only test for one type of antimicrobial agent. Additionally, the limited availability of facilities for molecular-based methods has hindered their widespread use. Therefore, low-cost, minimally invasive, simple, and effective primary regimens are needed. Several studies have compared the efficacy of the latest primary eradication regimens against that of tailored therapies, and their results have shaped guidelines. This article reviews the latest research on empirical and tailored treatments for *H. pylori* infections. Evidence for the superiority of tailored therapy over empirical therapy is still limited and varies by region and treatment regimen. A network meta-analysis comparing different empirical treatment regimens showed that vonoprazan triple therapy provides a superior eradication effect. Recently, favorable results towards vonoprazan dual therapy have been reported, as it reached eradication levels similar to those of vonoprazan triple therapy. Both vonoprazan dual therapy and tailored therapy based on antibiotic susceptibility tests could contribute to future treatment strategies. **(Gut Liver 2023;17:684-697)**

Key Words: *Helicobacter pylori*; Antibiotics; Drug resistance; Bacterial susceptibility test; Vonoprazan

INTRODUCTION

Helicobacter pylori is a cause of gastritis and peptic ulcers, as well as a major cause of gastric carcinogenesis.[1,2] Eradication of *H. pylori* has been shown to reduce metachronous carcinogenesis.[3] Over the past 25 years, the number of infected patients[4,5] and new cases of gastric cancer[6] had decreased worldwide owing to the widespread adoption of eradication therapy and improved sanitation. In the 1990s, triple therapy (which combined a proton pump inhibitor [PPI] with clarithromycin, amoxicillin, or metronidazole) showed a high eradication success rate and became popular worldwide. This led to a growth in the number of clarithromycin-resistant strains and more frequent failures of empirical primary treatment. In Asia, the prevalence of clarithromycin-resistant strains has been reported to be 30% in Japan, 50% in China, 40% in Korea, and approximately 15% in Taiwan.[7] The gold standard eradication therapy for *H. pylori* infection is tailored therapy, which is based on the selection of antimicrobial agents according to antibiotic susceptibility test (AST) results[8] as well as other common bacterial infectious diseases. However, AST has several disadvantages and is not widely used.[9] This review presents the latest results of empirical and AST-based therapies for *H. pylori* to inform future treatment strategies.

STANDARD TREATMENT REGIMENS BASED ON CURRENT GUIDELINES

The primary treatment regimens recommended by current guidelines are listed in Table 1. For areas where clarithromycin-resistant strain rate is 15% to 20% or higher, the Maastricht VI/Florence Consensus Report recommends bismuth-containing quadruple therapy (BQT), consisting of a PPI and two antimicrobial agents plus bismuth, or quadruple concomitant therapy using a PPI and three antimicrobial agents (amoxicillin, clarithromycin, and nitroimidazole) for the same duration as the primary treatment.[10] In contrast, PPI-based standard triple therapy (STT) is recommended only in areas with a clarithromycin-resistant strain rate of ≤15%. In addition, for both treatment options, a 14-day duration of eradication was reported to increase the eradication success rate when compared to that of a shorter duration.[11,12] This supports the 14-day duration of eradication recommended by the guidelines.[10] Similarly, the Toronto consensus guidelines recommend selecting empirical primary eradication according to local clarithromycin resistance rates.[13]

Studies have shown that a patient's history of macrolide or fluoroquinolone use is associated with the prevalence of resistant strains.[14-16] A history of macrolide use for more than two weeks has also been shown to decrease the success rate of eradication with STT, including that of clarithromycin.[17] Therefore, the American College of Gastroenterology guidelines suggest that when estimating of the proportion of clarithromycin-resistant strains in a region is difficult, treatment should be selected based on the patient's history of macrolide use.[18] Specifically, 14-day triple therapy, including clarithromycin, should be limited to patients in areas with less than 15% clarithromycin-resistant strains and no history of macrolide use, while BQT or quadruple concomitant therapy for 10 to 14 days is recommended for other patients. As first-line treatments, the guidelines also allow quadruple sequential therapy (PPI+amoxicillin for 5 days, followed by PPI+clarithromycin+metronidazole for 5 days), quadruple hybrid therapy (PPI+amoxicillin for 7 days, followed by PPI+amoxicillin+clarithromycin+metron idazole for 7 days), and levofloxacin triple therapy.

Furthermore, the Fifth Chinese National Consensus Report also states that STT should be selected after confirming antimicrobial susceptibility, and BQT for 10 to 14 days is recommended as empirical treatment.[19] However Japanese[20] and Korean[21] guidelines contain regimens that include clarithromycin for primary eradication, despite expressing concerns about the increase in clarithromycin-resistant strains.

The availability of the potassium-competitive acid block-

Table 1. Comparison of Recommended Eradication Regimens Based on Guidelines

Guideline	First-line therapy	Salvage therapy
Maastricht VI/Florence Consensus Report (2022)[10]	Area of clarithromycin resistance <15%: PPI-based triple therapy for 14 days Area of clarithromycin resistance ≥15%: Bismuth-containing quadruple therapy for 14 days Quadruple concomitant therapy for 14 days	Bismuth-containing quadruple therapy for 14 days Fluoroquinolone-containing quadruple or triple therapy for 14 days Tailored therapy based on the result of AST (third line)
Toronto Consensus (2016)[13]	Area of clarithromycin resistance <15%: PPI-based triple therapy for 14 days Area of clarithromycin resistance ≥15%: Bismuth-containing quadruple therapy for 14 days Quadruple concomitant therapy for 14 days	Bismuth-containing quadruple therapy for 14 days Fluoroquinolone-containing triple therapy for 14 days
ACG Clinical Guideline (2016)[18]	Area of clarithromycin resistance <15%, and no history of clarithromycin use: PPI-based triple therapy for 14 days Area of clarithromycin resistance ≥15%, or history of clarithromycin use: Bismuth-containing quadruple therapy for 10–14 days Quadruple concomitant therapy for 10–14 days	Bismuth-containing quadruple therapy for 14 days Fluoroquinolone-containing quadruple or triple therapy for 14 days Quadruple concomitant therapy for 10 days Rifabutin-containing triple therapy for 10 days High-dose dual therapy for 14 days
Fifth Chinese National Consensus Report (2018)[19]	Bismuth-containing quadruple therapy for 10–14 days	No statement
Guideline in Korea (2021)[21]	PPI-based triple therapy for 14 days Quadruple sequential therapy for 10 days Quadruple concomitant therapy for 10 days PPI-based triple therapy for 7 days (after clarithromycin resistance testing)	Bismuth-containing quadruple therapy for 10–14 days Fluoroquinolone-containing triple therapy for 14 days
Guideline in Japan (2019)[20]	PPI-based triple therapy for 7 days Vonoprazan-based triple therapy for 7 days	PPI-based triple therapy for 7 days Vonoprazan-based triple therapy for 7 days

PPI, proton pump inhibitor; AST, antibiotic susceptibility test.

er (P-cab) vonoprazan in Japan since 2015 has led to changes in the Japanese guideline.[20] Vonoprazan has more potent and longer-lasting antacid effects than PPIs[22,23] and can achieve 24 hours with pH >4 ratio of 100%,[24] which is important in the eradication of *H. pylori* and is expected to have greater eradication success than that of conventional PPI-based triple therapy. In the eradication therapy of *H. pylori*, antimicrobial agents are active mainly when the intragastric pH exceeds 4.[25] Because vonoprazan can achieve intragastric pH >4 earlier than PPI after oral administration, it is suggested that the time for the antimicrobial agent to act on *H. pylori* can be prolonged, which leads to a higher eradication success rate.[25] The vonoprazan-based triple therapy (vonoprazan+clarithromycin+amoxicillin for 7 days) is also expected to be effective against clarithromycin-resistant strains.[26-28] A meta-analysis integrating eight randomized controlled trials (RCTs) showed that vonoprazan-based triple therapy had a higher eradication success rate than that of PPI-based triple therapy (pooled eradication rates 79.2% vs 45.8%: risk ratio [RR], 1.66; 95% confidence interval [CI], 1.08 to 2.54; p=0.02).[29] For first-line therapies, the Japanese guidelines recommend vonoprazan-based triple therapy or PPI-based triple therapy, which have the highest eradication success rate among the regimens covered by the Japanese insurance system. Most reports of vonoprazan efficacy have originated in Japan (Table 2), since it was first launched there; however, recently Singapore and Thailand have also conducted RCTs comparing 7-day vonoprazan-based triple therapy to 14-day conventional PPI-based triple therapy (Table 2).[30,31] In these studies, eradication success rates were comparable; 87.4% to 96.7% success rate was recorded for 7-day vonoprazan-based triple therapy and 88.0% to 88.5% for 14-day PPI-based triple therapy.

In Korea, clarithromycin-resistant strains have also risen in frequency over the past decade, although the success rate of eradication with STT has been declining; as of 2016, the success rate was approximately 70%.[32,33] In light of this situation, the Korean guidelines issued in 2020[21] proposed the following first-line therapies: (1) PPI-based triple therapy for 14 days; (2) quadruple sequential therapy; (3) quadruple concomitant therapy; and (4) STT after clarithromycin resistance testing. However, BQT, which is positioned as first-line therapy in Europe, the United States, and China, is not listed because of its rate of side effects and its potential as a second-line therapy option. The guidelines issued by the Korean College of *Helicobacter* and Upper Gastrointestinal Research in 2022 make similar recommendations.[34] Tegoprazan, the other P-cab product, was launched in Korea in 2018 and is now available for *H. pylori* treatment. Tegoprazan has been shown to achieve pH >4 in the stomach 2 hours after administration, with a

Table 2. Randomized Controlled Trials Comparing P-cab-Based Regimen and PPI-Based Regimen as First-Line Therapy

Author (year)	Country	CLA-resistant strain, %	P-cab-based regimen					PPI-based regimen				
			Regimen	ITT analysis		PP analysis		Regimen	ITT analysis		PP analysis	
				No.	Eradication rate, % (95% CI)	No.	Eradication rate, % (95% CI)		No.	Eradication rate, % (95% CI)	No.	Eradication rate, % (95% CI)
Murakami *et al.* (2016)[26]	Japan	30.4	VPZ/AMO/CLA, 7 days	324	92.6 (89.2–95.2)	NA	NA	LPZ/AMO/CLA, 7 days	320	75.9 (70.9–80.5)	NA	NA
Maruyama *et al.* (2017)[27]	Japan	NA	VPZ/AMO/CLA, 7 days	72	95.8 (88.3–99.1)	70	95.7 (88.0–99.1)	LPZ or RPZ/AMO/CLA, 7 days	69	69.6 (57.3–80.1)	63	71.4 (58.7–82.1)
Ang *et al.* (2022)[30]	Singapore	12.7	VPZ/AMO/CLA, 7 days	119	87.4 (80.1–92.3)	108	96.3 (90.5–98.8)	RPZ or OPZ or EPZ/AMO/CLA, 14 days	125	88.0 (81.0–92.7)	117	94.0 (87.9–97.2)
Bunchorntavakul *et al.* (2021)[31]	Thailand	NA	VPZ/AMO/CLA, 7 days	61	96.7 (88.0–99.7)	60	98.3 (90.1–100)	OPZ/AMO/CLA, 14 days	61	88.5 (77.8–94.6)	58	93.1 (83.0–97.7)
Choi *et al.* (2022)[35]	Korea	30.3	TPZ/AMO/CLA, 7 days	175	62.9 (55.5–69.6)	175	69.3 (53.2–67.5)	LPZ/AMO/CLA, 7 days	175	60.6 (61.5–76.1)	150	67.3 (59.4–74.3)

P-cab, potassium-competing acid blocker; PPI, proton pump inhibitor; CLA, clarithromycin; ITT, intension-to-treat; PP, per-protocol; CI, confidence interval; VPZ, vonoprazan; AMO, amoxicillin; NA, not applicable; LPZ, lansoprazole; RPZ, rabeprazole; OPZ, omeprazole; EPZ, esomeprazole.

rapid onset of effect comparable to that of vonoprazan.[36] *In vitro*, tegoprazan has been shown to improve minimum inhibitory concentrations (MICs) of clarithromycin, fluoroquinolone, metronidazole, and amoxicillin by 46.3%, 46.7%, 55.6%, and 34.5%, respectively.[37] Thus far, few studies have examined the efficacy of tegoprazan in the treatment of *H. pylori*, but one recent RCT found that 7-day triple therapy combining tegoprazan with amoxicillin and clarithromycin was non-inferior to 7-day lansoprazole-based triple therapy (62.9% vs 60.1%, non-inferiority test, p=0.009) (Table 2).[35] The possible reasons why tegoprazan-based regimen was not superior to PPI in a first-line therapy are as follows: (1) insufficient dose of tegoprazan used in the trial; (2) differences in the MIC distributions for clarithromycin-resistant strains compared with those reported in the Japanese trials; (3) pharmacological differences between vonoprazan and tegoprazan; and (4) insufficient eradication treatment period compared to 14 days of treatment.[38] In fact, in a retrospective case-controlled study, tegoprazan-based triple therapy was reported to be more effective in a 14-day regimen compared to a 7-day regimen (eradication rate: 78.6% vs 63.9%).[39] The efficacy of tegoprazan as first-line therapy will need to be validated in the future.

IMPACT OF ANTIMICROBIAL RESISTANCE ON *H. pylori* TREATMENT OUTCOME

1. Clarithromycin resistance

The acquisition of drug resistance in *H. pylori* is accelerated mainly by chromosomal mutations, physiological changes (such as impaired regulation of drug uptake and/or efflux), biofilms, coccoid formation, and other factors.[40] Clarithromycin resistance has a particularly large impact on eradication success. When STT was used as a primary regimen, a 90% success rate against clarithromycin-susceptible strains and a 22% success rate against clarithromycin-resistant strains were reported.[41] Accurate prediction and diagnosis of this clarithromycin-resistant strain are key to successful primary eradication. *H. pylori* is known to form cross-resistance to macrolide antimicrobial agents,[42,43] and a history of macrolide use is closely associated with the prevalence of clarithromycin-resistant strains. In fact, as reported in Taiwan, the rate of clarithromycin-resistant strains decreases when macrolide antimicrobial use is restricted.[44] The proportion of clarithromycin-resistant strains is increasing worldwide, but varies by region (Fig. 1).[45-54]

2. Metronidazole resistance

In addition, metronidazole-resistant *H. pylori* strains cannot be ignored. A meta-analysis calculated the proportion of *H. pylori* strains with potential drug resistance, het-

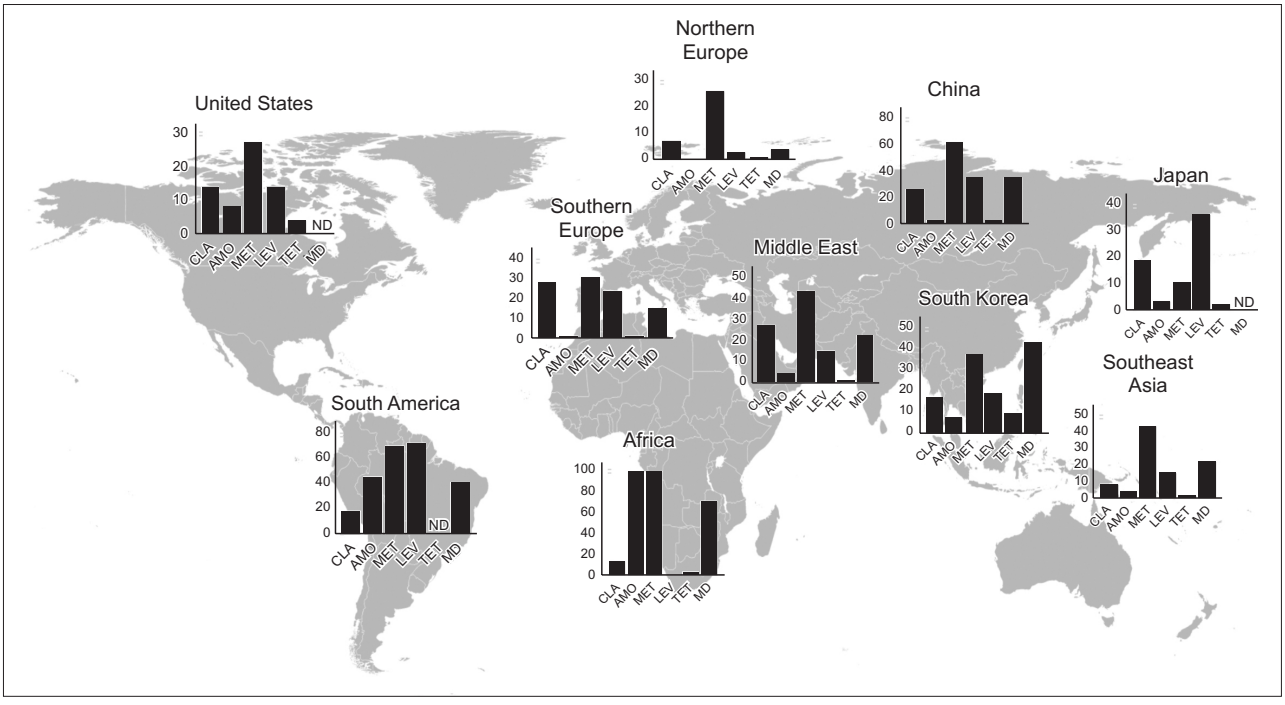

Fig. 1. Global comparison of the proportion of antimicrobial-resistant *Helicobacter pylori* strains. Data were obtained from reports published since 2012.[45-54] Multidrug-resistant strains were defined as those resistant to at least two antimicrobial agents.
CLA, clarithromycin; AMO, amoxicillin; MET, metronidazole; LEV, levofloxacin; TET, tetracycline; MD, multidrug resistance; ND, no data.

eroresistance,[55] by integrating and analyzing 22 studies.[56] In this study, heteroresistance to clarithromycin had a weighted pooled prevalence of 6.8% (95% CI, 5.1% to 8.6%), whereas heteroresistance to metronidazole was more common, with a weighted pooled prevalence of 13.8% (95% CI, 8.9% to 18.6%). Heteroresistance cannot be ignored, as it has been shown that subpopulations of strains confirmed to be heteroresistant *in vitro* are also clinically resistant to antimicrobial agents.[57] Although most drug-resistant *H. pylori* strains that pose clinical challenges are presently clarithromycin-resistant strains, there is a concern that metronidazole-resistant strains may become more common as metronidazole use increases owing to changing guidelines.

3. Resistances to other antimicrobials

In the context of eradication regimens, *H. pylori* strains resistant to levofloxacin, amoxicillin, and tetracycline can also be problematic. Emerging multidrug resistance to various types of antimicrobials has become a serious problem. The acquisition of multidrug resistance mainly occurs from biofilm formation and the expression of efflux pumps.[49,58] Special attention should be paid to multidrug resistance, as it can cause the failure of multiple rounds of empirical therapy. The emergence of multidrug-resistant *H. pylori strains* in more than 20% of cases has been noted in Southeast Asia (Fig. 1),[59] with inadequate durations of treatment with multiple antimicrobial agents noted as a cause of multidrug resistance.[16]

DETECTION METHODS FOR *H. pylori* ANTIMICROBIAL RESISTANCE

For AST, there are two main methods to detect antimicrobial resistance: MIC measurement using culture-based methods and molecular tests using polymerase chain reaction (PCR). Each method has their own advantages and disadvantages (Table 3).

1. Culture-based AST

The measurement of MIC by culturing gastric biopsy samples has a long history as an AST.[60] These methods are further classified as agar dilution, E-test, disk diffusion, and broth microdilution. Among these, agar dilution is the gold standard for AST, despite being labor-intensive and time-consuming.[61] Although the E-test is widely used in clinical practice because of its simplicity, it is limited by difficulties in assessing susceptibility to metronidazole.[62] The disk diffusion technique, by contrast, is as simple as the E-test but can evaluate susceptibility to a wide range of antimicrobial agents, including levofloxacin, clarithromycin, and metronidazole.[63] The broth microdilution technique is reported to be accurate and easy to perform.[64] Although both culture-based tests have the disadvantage of being labor- and time-intensive in the laboratory, their greatest advantage is that they can reliably assess resistance to all antimicrobial agents present.

2. Molecular-based methods

When drug susceptibility testing in culture is unavailable owing to time constraints, real-time PCR,[65,66] multiplex PCR,[67,68] fluorescence *in situ* hybridization,[69] and

Table 3. Comparison of Culture-Based and Molecular-Based Methods

	Culture-based method	Molecular-based method
Method details	Agar dilution E-test Disk diffusion Broth microdilution	Clarithromycin-resistance PCR-based method: real-time PCR, multiplex PCR, PCR-restriction fragment length polymorphism Fluorescence *in situ* hybridization Fluoroquinolone-resistance PCR-based method: real-time PCR, allele-specific PCR Metronidazole PCR-based method: real-time PCR, multiplex allele-specific PCR Amoxicillin PCR-based method: real-time PCR
Type of sample required	Gastric biopsy sample	Gastric biopsy sample Stool sample
Determinable resistance of antimicrobial agent	All antimicrobial agents	Clarithromycin Metronidazole Fluoroquinolone Amoxicillin
Time required to determine	Long (7–14 days)	Short (1–2 days)
Cost	Low	High

PCR, polymerase chain reaction.

PCR-restriction fragment length polymorphism (PCR-RFLP) using gastric biopsy samples,[70,71] or PCR using stool samples[72,73] can be used to evaluate drug resistance to specific antimicrobial agents.

Clarithromycin exerts its antibacterial activity by binding to the peptidyl transferase region of the 23S rRNA of *H. pylori*.[74] Point mutations of the *rrl* gene, which encodes the binding region of 23S rRNA (especially A2142G, A2143G, or A2144G point mutation), contribute to clarithromycin resistance,[75,76] and these point mutations are detected by PCR or other methods. Molecular tests, including PCR, can detect drug resistance faster than culture methods and have been found to be valid.[77] A report compared the detection rate of A2144 or A2143 from PCR-RFLP with that of MIC measurement by the agar culture method, and they found that the diagnostic performance was nearly equivalent.[78] Another study compared the diagnostic accuracy of real-time PCR against MIC measurements by culture test, and it showed a high concordance rate; 84.6% of subjects diagnosed with clarithromycin-resistant infections by the culture method also had point mutations in 23S rRNA.[79]

DNA gyrase, which is used to break the DNA double helix structure during DNA replication, is required for *H. pylori* to proliferate. DNA gyrase exists as a tetramer formed by the subunits encoded by the *gyrA* and *gyrB* genes. Fluoroquinolones exert antimicrobial activity by selectively inhibiting this tetramer. Point mutations in the quinolone resistance-determining region (QRDR) of *gyrA* and *gyrB* have been associated with fluoroquinolone resistance.[76,80] The strength of quinolone resistance varies by the number of mutated codons encoding the QRDR;[80,81] therefore, it is important to identify the mutated region. Allele-specific PCR[82] and fluorescence resonance energy transfer-based real-time PCR[66] have been developed to rapidly detect *gyrA* mutations.

Because the mechanism of resistance acquisition differs among antimicrobial agents, a single molecular test can usually evaluate only a single antimicrobial resistance. To overcome this disadvantage, GenoType HelicoDR® was developed, a revolutionary genotyping test that can simultaneously detect QRDR mutations and 23S rRNA mutations within 6 hours.[83] The sensitivity and specificity of the HelicoDR® test were reported to be 98.2% and 80.0% for *gyrA* and 94.9% and 87.1% for 23S rRNA mutations, respectively.[84] However, the types of molecular tests that can be used in real clinical practice are limited, and it is difficult to evaluate more than three types of drug resistance simultaneously. Limited access to molecular-based AST is a major limitation at this stage.

3. Next-generation sequencing

Genetic mutations associated with specific antimicrobial resistance do not coincide with the acquisition of other antimicrobial resistance.[74] Therefore, to examine mutations in multiple regions, a comprehensive study of the drug resistance profile of infectious *H. pylori* strains is required. Next-generation sequencing (NGS) of DNA was devised to address this shortcoming.[85] NGS can comprehensively examine mutations for specific antimicrobials, such as in genes for clarithromycin resistance,[86,87] amoxicillin resistance,[88] metronidazole resistance,[89] and levofloxacin resistance.[90] Furthermore, it can also simultaneously detect mutations associated with multiple antimicrobial resistance. In fact, reports have documented the use of NGS for increasing eradication success rates. A study comprehensively investigated mutations in *gyrA*, 23S rRNA, and 16S rRNA genes using NGS in gastric mucosal specimens from 126 *H. pylori*-infected patients. It showed a strong association between the eradication success rate and the number of mutations.[91] While some studies have shown the efficacy of NGS, a study found that this approach was inapplicable to some antimicrobials. This study compared the concordance rates of antimicrobial resistance to clarithromycin, amoxicillin, metronidazole, levofloxacin, rifabutin, and tetracycline using NGS and agar dilution, and the authors found that NGS accurately assessed resistance to clarithromycin, levofloxacin, rifabutin, and tetracycline; however, NGS results were in poor agreement with those of culture-based methods for amoxicillin and metronidazole resistance.[92] A major disadvantage of NGS is the higher cost compared with culture-based methods and molecular-based tests. Yet, as the cost of NGS decreases, it is expected to become easier to apply in clinical practice.

H. pylori ERADICATION OUTCOMES OF TAILORED THERAPY VERSUS THOSE OF EMPIRICAL THERAPY

To summarize, the main challenges in evaluating drug resistance are the time-consuming nature of the culture-based method, the inability to investigate specific drug resistances, and the high cost of molecular-based tests. We will explore whether tailored therapy can sufficiently compensate for these shortcomings.

1. Clinical outcomes of tailored therapy

Based on the results of AST, the possibility of clinically applying tailored therapy with individually-selected susceptible antimicrobial agents is being explored.[93] Several RCTs showed the superiority of tailored therapy over

Table 4. Randomized Controlled Trial Comparing the Efficacy of Empirical Therapy versus Tailored Therapy

Author (year)	Country	Empirical therapy			Tailored therapy			
		No.	Regimen	Eradication rate, % (95% CI)*	No.	Method	Target antimicrobials	Eradication rate, % (95% CI)*
First-line								
Furuta *et al.* (2007)[95]	Japan	150	PPI/AMO/CLA, 7 days	70.0 (69.5–76.7)	150	SISAR	CLA	96.0 (91.3–98.3)
Kawai *et al.* (2008)[73]	Japan	35	PPI/AMO/CLA, 7 days	71.4 (54.7–83.7)	35	Nested PCR (stool)	CLA	94.3 (80.2–99.3)
Lee *et al.* (2013)[94]	Korea	308 308	PPI/AMO/CLA, 7 days PPI/AMO/MET, 7 days	75.9 (70.5–80.5) 79.1 (73.9–83.4)	616	DPO-PCR	CLA	91.2 (86.2–94.5)
Ong *et al.* (2019)[104]	Korea	196	PPI/AMO/CLA/MET, 14 days	86.2 (80.6–90.4)	201	DPO-PCR	CLA	81.6 (75.6–86.3)
Delchier *et al.* (2019)[96]	France	208	PPI/AMO/CLA, 7 days	73.1 (66.6–78.6)	207	PCR/reverse hybridization	CLA/LEV	85.5 (80.0–89.7)
Choi *et al.* (2021)[105]	Korea	107	PPI/AMO/CLA/MET, 10 days	82.2 (73.8–88.4)	110	DPO-PCR	CLA	82.7 (74.5–88.7)
Cha *et al.* (2021)[106]	Korea	161	PPI/BIS/TET/MET, 7 days	88.2 (82.2–92.4)	147	DPO-PCR	CLA	80.3 (73.0–85.9)
Kim *et al.* (2022)[107]	Korea	145	PPI/AMO/CLA/MET, 14 days	82.8 (75.7–88.1)	145	DPO-PCR	CLA	85.8 (78.8–90.4)
Cho *et al.* (2022)[108]	Korea	141	PPI/BIS/AMO/CLA, 14 days	85.8 (79.0–90.7)	141	DPO-PCR	CLA	80.9 (73.5–86.5)
Hsieh *et al.* (2022)[97]	Taiwan	91	PPI/AMO/CLA, 7 days	75.8 (66.0–83.5)	91	PCR-RLFP (gastric juice)	CLA	89.0 (80.8–94.1)
Toracchio *et al.* (2000)[101]	Italy	56	PPI/CLA/TIN, 10 days	75.0 (62.1–84.5)	53	Agar dilution	CLA/TIN	90.6 (79.2–96.2)
Romano *et al.* (2000)[102]	Italy	40	PPI/CLA/MET, 7 days	77.5 (64.6–90.4)	40	E-test	CLA/AMO/MET/TET	95.0 (88.2–100)
Neri *et al.* (2003)[98]	Italy	116	PPI/AMO/CLA, 7 days	67.2 (58.2–75.1)	116	E-test	CLA/AMO/TIN	75.9 (67.3–82.7)
Romano *et al.* (2003)[103]	Italy	75	PPI/CLA/MET, 7 days	77.3 (66.9–85.7)	75	E-test	CLA/AMO/MET/TET	94.6 (87.6–98.3)
Marzio *et al.* (2006)[109]	Italy	39	PPI/AMO/LEV, 10 days	92.3 (78.8–98.0)	41	Agar dilution	CLA/AMO/LEV/RIF	95.1 (82.8–99.4)
Park *et al.* (2014)[99]	Korea	57	PPI/AMO/CLA, 7 days	71.9 (59.0–81.9)	57	Agar dilution	CLA	94.7 (84.9–98.7)
Martos *et al.* (2014)[100]	Spain	54	PPI/AMO/CLA, 10 days	66.7 (53.3–77.7)	55	E-test	CLA	94.5 (84.4–98.6)
Zhou *et al.* (2016)[110]	China	350 350	PPI/BIS/AMO/CLA, 10 days PPI/AMO/CLA/MET, 10 days	77.4 (73.1–82.0) 87.0 (83.0–90.7)	318	E-test	CLA	88.7 (85.2–92.1)
Chen *et al.* (2019)[111]	China	96	PPI/BIS/AMO/MET, 14 days	85.4 (78.4–92.5)	286	Agar dilution	CLA/MET/LEV	91.6 (88.4–94.8)
Pan *et al.* (2020)[112]	China	157	PPI/BIS/AMO/CLA, 14 days	63.7 (55.9–70.8)	310	Agar dilution	CLA/MET/LEV/AMO/FR	76.8 (71.7–81.1)
Li *et al.* (2022)[113]	China	67	PPI/AMO/FR, 10 days	85.1 (74.5–91.9)	134	E-test	CLA	80.6 (73.0–86.5)
Second-line								
Miwa *et al.* (2003)[118]	Japan	39	PPI/AMO/MET, 10 days	92.4 (79.0–98.0)	38	Dry plate	CLA/MET	81.6 (66.0–92.0)
Lamouliatte *et al.* (2003)[119]	France	57 58 57	PPI/AMO/CLA, 7 days PPI/AMO/CLA, 14 days PPI/AMO/MET, 14 days	47.4 (34.4–60.3) 34.5 (22.2–46.7) 63.2 (50.6–75.7)	113	E-test	CLA/AMO/MET	74.3 (65.0–82.4)
Marzio *et al.* (2006)[109]	Italy	32	PPI/AMO/LEV, 10 days	81.2 (63.5–92.7)	51	Agar dilution	CLA/AMO/TIN/RIF/LEV	98.0 (89.5–99.9)

CI, confidence interval; PPI, proton pump inhibitor; AMO, amoxicillin; CLA, clarithromycin; SISAR, serial invasive signal amplification reaction; PCR, polymerase chain reaction; MET, metronidazole; DPO-PCR, dual-priming oligonucleotide-based PCR; LEV, levofloxacin; TET, tetracycline; BIS, bismuth; PCR-RFLP, PCR-restriction fragment length polymorphism; TIN, tinidazole; RIF, rifabutin; FR, furazolidone.

*Eradication rate in intension-to-treat analysis.

STT, when comparing the efficacy of tailored therapy and empirical therapy in detecting clarithromycin-resistant strains using molecular-based methods[73,94-97] as well as using culture-based methods (Table 4).[98-103] However, RCTs that compared the efficacy of tailored therapy and empirical therapy using BQT, quadruple concomitant, or fluoroquinolone-containing regimens failed to show the superiority of tailored therapy (Table 4).[104-113] Whereas a meta-analysis integrating 16 RCTs compared the efficacy of empirical therapy and tailored therapy and concluded that tailored therapy was slightly more effective, this study found no difference in efficacy between tailored therapy and BQT (RR, 1.02; 95% CI, 0.92 to 1.13; p=0.759).[114] BQT, in fact, is recommended as an empirical first-line therapy in the United States[19] and European guidelines.[11] The efficacy of BQT was further supported by a meta-analysis that integrated five studies to compare its efficacy against that of tailored therapy. The pooled eradication rate of BQT was significantly higher (86% vs 78%, p<0.05).[115] A recent meta-analysis combined 54 clinical studies to examine the efficacy of tailored therapy as first- and second-line therapy.[116] In this study, tailored therapy had a significantly higher eradication success rate than that of empirical therapy in an integrated analysis that included all eradication regimens (86% vs 76%: RR, 1.12; 95% CI, 1.08 to 1.17). However, there were no differences within the group of primary treatments, and no differences within the group of secondary treatments. Furthermore, the efficacy of tailored therapy in second-line treatment and third-line treatment has been reported to vary in the range of 60% to 98% (Table 4).[109,117-119] Differences in resistance rates by region and time precluded easy comparisons; yet, they also suggested that tailored therapy may not be effective in all cases.

2. Cost-effectiveness of tailored therapy

For clinically applying tailored therapy, cost-effectiveness is very important for the allocation of facility resources. Tailored therapy methods have been mainly culture-based, but in recent years, molecular-based methods have been established for tailored therapy. The methods of AST targeted by cost-effectiveness analysis used to be dominated by culture-based methods, but in recent years there has been a shift to molecular-based methods; thus, we cannot compare old reports with recent ones. It is necessary to always keep abreast of the latest literature when considering cost-effectiveness; the recommended methods for first-line therapies have changed, which prevents meta-analyses from comparing studies conducted at different times. The first report evaluating the cost-effectiveness of tailored therapy was published in 1999, but it covered culture-based methods, such as AST.[120] Using molecular-based methods, a study compared the detection of clarithromycin resistance using dual-priming oligonucleotide-based PCR (DPO-PCR) between STT and tailored therapy. They found that tailored therapy was more effective, and cost-effectiveness was comparable or even slightly better.[121,122] This was supported by a recent study comparing the first-line regimens as recommended by U.S. and European guidelines (14-day triple therapy, sequential therapy, and BQT) with tailored therapy, for which clarithromycin resistance was detected by multiplex PCR. They also concluded that tailored therapy was more cost-effective.[123] In contrast, compared to 14-day pantoprazole, amoxicillin, metronidazole, and bismuth combination therapy, tailored therapy based on clarithromycin resistance detection by multiplex PCR was less cost-effective (average cost per patient: $340.70 vs $263.90).[108] When compared against BQT, tailored therapy based on clarithromycin resistance detection by DPO-PCR was less cost-effective (average cost per patient: $406.50 vs $503.50), while having comparable eradication success rates.[124] As this study suggests, the superiority of tailored therapy may remain unsupported if the control group is a regimen that is highly effective in eradicating *H. pylori*, even with mixed clarithromycin-resistant strains.

FUTURE ERADICATION STRATEGIES INCORPORATING TAILORED THERAPY

Finally, we discuss the potential position of tailored therapy when vonoprazan-based regimens are incorporated into future eradication strategies. Recently, the efficacy of a two-drug therapy combining vonoprazan and amoxicillin has been reported. Limiting the number of drugs used for eradication to two is expected to improve adherence to medication, and using only one antimicrobial agent is expected to avoid the acquisition of new drug resistance, including resistance to clarithromycin. Several reports from Japan showed that eradication rates of vonoprazan-based dual therapy were similar to vonoprazan-based triple therapy.[125-127] In a meta-analysis integrating these studies, the pooled eradication rate of vonoprazan-based dual therapy was similar to that of vonoprazan-based triple therapy (87.5% vs 89.6%: RR, 0.99; 95% CI, 0.93 to 1.05; p=0.65).[128] Vonoprazan-based dual therapy performed comparably to vonoprazan-based triple therapy, indicating application potential. Recently, an RCT of vonoprazan-based dual therapy versus STT was conducted in the United States and Europe.[129] Vonoprazan-based dual therapy eradicated *H. pylori* in 78.5% of cases, compared to 84.7% for vonoprazan-based triple therapy and 78.8% for lansoprazole-based triple therapy, demonstrating competitive

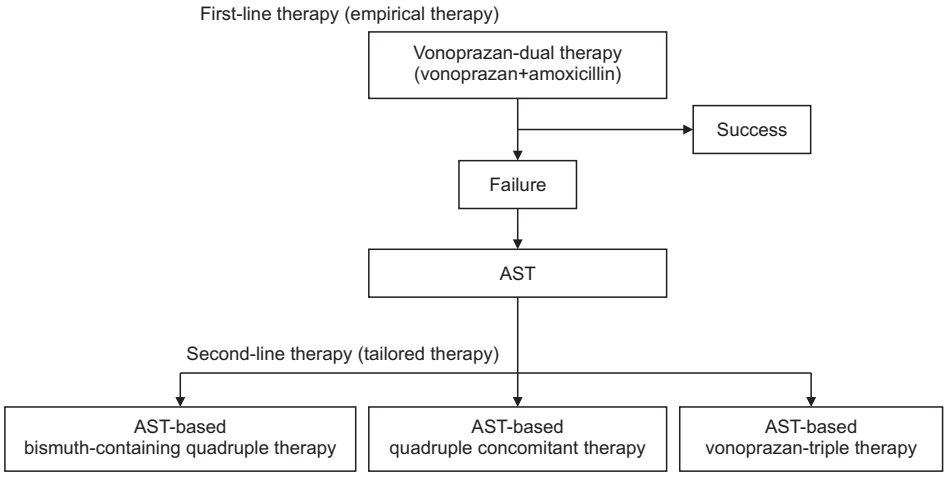

Fig. 2. Flowchart outlining future eradication strategies incorporating tailored therapy. The first-line therapy is vonoprazan-dual therapy, without considering clarithromycin-resistant strains. If eradication fails, an antibiotic susceptibility test (AST) is performed. A second-line therapy with a modified regimen of quadruple therapy may be needed depending on AST results.

efficacy. Furthermore, for vonoprazan-based triple therapy, the success rate of eradication against clarithromycin-resistant strains was also superior to that of lansoprazole-based triple therapy (69.6% vs 31.9%, p<0.001). Based on these results, vonoprazan-based triple therapy and dual therapy have been approved and are now available in the United States.[130] Since vonoprazan-based dual therapy can eradicate *H. pylori* while minimizing impact on *H. pylori* antimicrobial resistance, it may be acceptable to apply vonoprazan-based dual therapy as an empirical treatment for primary therapy. Subsequently, we propose the strategy of vonoprazan-based dual therapy as a primary treatment, followed by a tailored treatment based on AST. Our proposed strategy could reduce both the consumption of antimicrobials used in the overall *H. pylori* treatment and medical resources for AST, including cost, labor, and materials (Fig. 2). However, knowledge of vonoprazan-based dual therapy is insufficient in the field.[131] The specific duration of vonoprazan dual therapy and dosage of amoxicillin have not yet been determined. In fact, it has been reported that the effectiveness of vonoprazan dual therapy is higher in patients with smaller body surface area.[132] Further research is required to establish the new strategy.

CONCLUSION

This review describes the performance of empirical therapy within the current guidelines and the latest AST-based tailored therapies. Empirical therapy, recommended as the primary eradication regimen in current guidelines, is a reasonable strategy with outcomes comparable to those of tailored therapy. Tailored therapy is currently considered for secondary and tertiary eradication. An ideal treatment against *H. pylori* is, as stated in the first edition of the Maastricht Consensus Report,[133] "a simple, well-tolerated regimen with good compliance and cost-effectiveness." A potential candidate treatment consistent with this philosophy is a vonoprazan-based dual therapy and subsequent tailored therapy as first-line and second-line therapies, respectively. Further research is required to support this strategy.

CONFLICTS OF INTEREST

F.I. received honoraria for lectures from Takeda Pharmaceutical Co., Ltd., AstraZeneca PLC, Otsuka Pharmaceutical Co., Ltd., AbbVie GK, Zeria Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Inc., and EA Pharma Co., Ltd. S.S. received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. Except for that, no potential conflict of interest relevant to this article was reported.

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