BRIEF REPORT

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Antibiotic Resistance and *Helicobacter pylori* Eradication Therapy

Younghee Choe

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

There are various reasons why *Helicobacter pylori* eradication treatment fails, but the most important is antibiotic resistance. Over the past 20 years, the antibiotic resistance of clarithromycin (CLR), metronidazole, and levofloxacin has steadily increased. In particular, the eradication rate of the CLR-containing triple therapy has dropped by about 20%.[1] Antibiotic resistance is shared within antibiotic classes, which is, of course, related to the degree of antibiotic use of the background population for all indications, not just *H. pylori*. In order to achieve a high eradication rate again, it is necessary to recognize *H. pylori* as an infectious disease and apply the concept of antibiotic management like an infectious disease doctor.[2] Ideally, antibiotics in a population, sometimes in an individual consideration should be given to using a targeted regimen based on knowledge of tolerance. This improves eradication rates, minimizes antibiotic overuse, and aids resistance in organisms other than *H. pylori*.

Ideally, therapies that have been demonstrated to be effective with an eradication success rate of at least 90% should be used. To achieve high eradication rates, three things must be done. First, the eradication rate of currently used regimens must be accurately measured. Second, it is necessary to identify the regional resistance rate and utilize it. Third, if it is unclear which regimen to choose, antibiotic susceptibility testing should be used.

The European Registry has registered about 60,000 patients, and as a result of tracking antibiotic resistance and providing feedback to doctors, it is said that it has been able to increase the eradication rate from 85 to 93% over the past ten years.[3]

There are two main methods for testing antibiotic resistance. The classical method is culture and molecular testing for antibiotic resistance. While the success rate of culture is about 50 to 60%, molecular testing gives about 90% results, and recently, it can be relatively easily performed for six antibiotics through next-generation sequencing. There are studies on antibiotic resistance published in the last five years in Korea (Table 1).[4-7] In a study conducted in 2019 on 590 people nationwide, the resistance rates of CLR, amoxicillin, and metronidazole were 18, 10, and 30%, respectively.[8] In addition, resistance rate studies conducted in Seoul in 2020 and 2021 showed, 25~30%, 7~20%, and 24~35%, respectively.[4-6] Further studies on regional resistance are needed.

The most important principle in *H. pylori* eradication is that initial treatment is the most important. This is because the highest chance of success lies in early treatment. In order to optimize initial treatment, the first requirement is to determine the patient's prior antibiotic exposure. CLR and quinolones should be avoided in areas with high *Helicobacter* resistance. Second, it is better to avoid antibiotics that have been previously used or have a resistance rate of 15% or higher. However, bismuth quadruple therapy (BQT) is known to be resistant to metronidazole but can be overcome by increasing the dose or duration of administration.[9] Ideally, a sensitivity test should determine the treatment method. Since patient compliance is one of the major causes of treatment failure, optimizing dosage and frequency is also important. In addition, intragastric acid suppression should be maintained at a pH of 6 or higher.

So far, most studies on treatment outcomes have been

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Corresponding author: Younghee Choe
Division of Gastroenterology and Hepatology, 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
Tel: +82-32-280-7497, **Fax:** +82-32-280-5342, **E-mail:** cyh1129@catholic.ac.kr

conducted in East Asia and Europe. In the first-line treatment of *H. pylori*, there was a recent meta-analysis that tailored therapy was more favorable than empirical therapy (odds ratio 1.14; 95% confidence interval 1.08–2.20).[10,11] However, the difference in the efficacy was not very large. There was heterogeneity for each treatment regimen and treatment period. In the randomized controlled trial (RCT) comparing tailored therapy and empirical therapy in Korea, all recent studies showed similar eradication success rates, and the difference was not significant (Table 2).[12-14]

As a first-line treatment not only in Korea but also in Europe and the United States, CLR triple therapy has a very low success rate of less than 60%.[3,15] BQT is recommended as first-line treatment, and concomitant therapy was recommended only when there was qualification at the guidelines.[16,17] Proton pump inhibitor (PPI)-based CLR triple therapy is recommended only when the regional CLR resistance is less than 15%, the local eradication success rate is high, the CLR susceptible strain is known, and there is no previous macrolide exposure.

BQT consistently showed an eradication success rate of over 85%, even including metronidazole-resistant areas, but there was no correlation between in vitro metronidazole resistance and actual results. Of course, there is a downside to poor compliance. Concomitant therapy has proven effective in Europe, but has the disadvantage of taking at least one antibiotic unnecessarily. In addition, high-dose PPI dual (PPI+amoxicillin) has low potency, and Rifabutin triple (PPI+amoxicillin+rifabutin) has low tolerance and has some side effects, making both of them not favored as first-line therapy.

A preferred method for the future is a potassium-competitive acid blocker (PCAB)-based therapy. PCAB has a higher acid secretion inhibitory effect than PPI and acts quickly. It also has the advantage of having a long half-life, no relation to CYP2C19 metabolism, and no relation to meal time. The results of the "Lansoprazole triple vs. Vonoprazan triple vs. Vonoprazan dual" study conducted in the US and Europe last year were less impressive than those in Japan. In particular, patients with CLR resistance strains showed more significant results (32% vs 66% vs 70%, $P<0.001$).[18] Korean RCT on the efficacy of PCAB-based regimen, showed some predominant efficacy. With tego-

Table 1. Studies on Antibiotic Resistance Performed in Korea over the Past 5 Years

Author	Publication year	Region	Subject (n)	CLR-R (%)	AMX-R (%)	MDZ-R (%)	LVF-R (%)
Kang et al.[6]	2021	Seoul	257	24.9	7.0	34.6	-
Park et al.[5]	2020	Seoul	174	28.6	20.0	27.1	42.9
Kim et al.[4]	2020	Seoul	247	29.6	10.0	23.9	36.0
Lee et al.[7]	2019	Nationwide	590	17.8	9.5	29.5	37.0

AMX-R, amoxicillin resistance; CLR-R, clarithromycin resistance; LVF-R, levofloxacin resistance; MDZ-R, metronidazole resistance.

Table 2. Randomized Controlled Trials Performed in Korea over the Past 5 Years to Compare Tailored and Empirical Therapy for *Helicobacter pylori*

Author	Publication year	Tailored therapy			Empirical therapy		
		Regimens[a]	Eradication rate (ITT)	Eradication rate (PP)	Regimens[a]	Eradication rate (ITT)	Eradication rate (PP)
Kim et al.[14]	2022	PAC-14 or PBMT-14	145 (85.5)	129 (94.6)	PACM-14	145 (82.8)	132 (88.6)
Cho et al.[13]	2022	PAC-14 or PBMT-14	141 (80.9)	127 (89.0)	PBAM-14	141 (85.8)	124 (93.5)
Choi et al.[12]	2021	PAC-14 or PBMT-14	110 (82.7)	101 (90.1)	PACM-14	107 (82.2)	95 (91.6)

Values are presented as number (%).
ITT, intention-to-treat; PP, per-protocol; PPI, proton pump inhibitor.
[a]PAC=PPI+amoxicillin+metronidazole; PACM=PPI+amoxicillin+clarithromycin+metronidazole; PBAM=PPI+busmuth+amoxicillin+metronidazole; PBMT=PPI+bismuth+metronidazole+tetracyclin.
All three studies used a PPI.
All three studies had no significant difference in eradication rates between tailored and empirical therapy.

prazan and lansoprazole as the base, respectively, standard triple therapy showed intention-to-treat (ITT, 63% vs. 61%, $P<0.05$) and per-protocol (PP, 69% vs. 67%, $P<0.05$),[19] and BQT showed ITT (80% vs. 77%, $P<0.05$) and PP (90% vs. 82%, $P<0.05$).[20]

The goal of refractory *H. pylori* infection is to avoid unnecessary antibiotics and to optimize the patient's experience in terms of costs and side effects. As with first-line therapy, the key principle is to avoid antibiotics already used. However, in case of BQT failure, the duration of administration may be increased, or the dose of metronidazole may be increased. Korean literature on salvage therapy is relatively small, with few RCTs. The most important thing is to increase the success rate of primary treatment. If salvage therapy is required, molecular antibiotics sensitivity or a PCAB-based regimen may be an important option.[17]

The major cause of eradication failure for *H. pylori* infection is antibiotic resistance. Antibiotic resistance testing should allow for personalized treatment that improves eradication rates. More studies comparing susceptibility-based therapy with empirical therapy should be conducted. In addition, PCAB-based therapy may be a good option to eradication therapy in the future.

AVAILABILITY OF DATA AND MATERIAL

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

CONFLICT OF INTEREST

There is no potential conflict of interest related to this work.

ORCID

Younghee Choe https://orcid.org/0000-0002-9443-2108

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