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Current guidelines for *Helicobacter pylori* treatment in East Asia 2022: Differences among China, Japan, and South Korea

Cho JH *et al.* *H. pylori* treatment in East Asia

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Abstract

Helicobacter pylori (*H. pylori*) infection is highly prevalent in East Asia. The overall seroprevalence rate of *H. pylori* infection is 44.2% in China, 37.6%-43.2% in Japan, and 51.0% in South Korea. *H. pylori* can cause peptic ulcer disease and gastric cancer. East Asian countries have high rates of gastric cancer (age-standardized incidence rate: 20-30 per 100000). The Kyoto global consensus report emphasized that *H. pylori* gastritis should be considered the main cause for the development of gastric cancer. *H. pylori* treatment guidelines in China, Japan, and South Korea have recently been revised according to data from each of those countries. However, emerging antibiotic resistance is an important barrier to *H. pylori* eradication. The recommended *H. pylori* treatment regimens differ among those three East Asian countries. In this review, recent guidelines and up-to-date research on *H. pylori* treatment regimens from China, Japan, and South Korea are discussed.

Key Words: *Helicobacter pylori*; Treatment; Antibiotic resistance; China; Japan; South Korea

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Core Tip: Since 2000, the standard triple regimen containing clarithromycin (CAM) has been used as a legacy therapy to eradicate *Helicobacter pylori*. Resistance to CAM by *Helicobacter pylori* (*H. pylori*) has increased to > 15% in East Asia. First-line eradication rates below 80% are strongly associated with CAM-resistant *H. pylori* strain emergence. *H. pylori* treatment guidelines in China, Japan, and South Korea were revised according to new data. In China, adding bismuth to *H. pylori* regimens was recommended as an empirical first-line treatment. In Japan, *H. pylori* treatment success increased when the potassium-competitive acid blocker (P-CAB) was introduced. In South Korea, tailored *H. pylori* eradication based on molecular testing for CAM resistance is used as the first-line

treatment option. Dual therapy involving frequent administration of high-dose amoxicillin has shown good efficacy for *H. pylori* eradication in clinical trials. Furthermore, P-CABs, with their rapid and strong acid-suppressing activity, may contribute to successful *H. pylori* treatment in future.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) can cause peptic ulcer disease and gastric cancer^[1]. In *H. pylori*-infected stomachs, gastric atrophy and intestinal metaplasia are linked to gastric cancer development^[2]. *H. pylori* is present in more than half of the world's population^[3]. The overall seroprevalence rate of *H. pylori* infection is 44.2% in China, 37.6%–43.2% in Japan, and 51.0% in South Korea^[4–6]. Gastric cancer is the fourth most common cause of cancer-related mortality worldwide^[7]. Almost half of the incident cases and deaths occur in East Asia. In 2019, the age-standardized incidence rate of gastric cancer per 100000 was 30.64 in China, 28.29 in Japan, and 28.67 in South Korea^[8].

The Kyoto Global Consensus recommends *H. pylori* treatment to prevent gastric cancer in countries with a high incidence thereof^[9]. In Japan, eradication therapy for all *H. pylori*-positive subjects has been covered by the national insurance system since 2013^[10]. In China, *H. pylori* treatment was strongly recommended for preventing primary gastric cancer in a recent consensus report^[11]. In 2018, the South Korean government insurance system started to cover eradication therapy for *H. pylori* gastritis. However, primary antibiotic resistance of *H. pylori* has increased in East Asia, so obtaining successful therapeutic outcomes using antibiotic regimens is challenging^[12]. To prevent primary gastric cancer, *H. pylori* should be successfully eradicated. Based on a comparison of recent guidelines, this review focuses on the current status of *H. pylori* treatment in China, Japan, and South Korea in terms of *H. pylori* resistance to antibiotics, recommended *H. pylori* treatment regimens, and up-to-date results of *H. pylori* therapy in the three countries.

H. PYLORI RESISTANCE TO ANTIBIOTICS IN EAST ASIA

Since 2000, the standard triple regimen containing clarithromycin (CAM) has been used as a legacy therapy to eradicate *H. pylori*^[13]. Macrolides have been widely used to treat other infectious diseases. Accordingly, the number of CAM-resistant *H. pylori* strains has increased rapidly in many countries over the past decade^[14]. In East Asia, CAM resistance of *H. pylori* has increased by > 15%. Therefore, first-line *H. pylori* eradication rates using triple therapy have decreased to < 80%^[15]. *H. pylori* resistance rates to metronidazole (MDZ) and fluoroquinolone are also high in East Asia (Figure 1). In China, primary resistance of *H. pylori* to CAM, MDZ, and levofloxacin (LVFX) is high and has increased over time (28.9%, 63.8%, and 28.0%, respectively)^[16]. These patterns of *H. pylori* resistance are similar to those in South Korea. A recent nationwide study reported *H. pylori* resistance rates to CAM, MDZ, and LVFX of 17.8%, 29.5%, and 37.0%, respectively^[17]. In Japan, the CAM resistance rate has increased gradually from 7% in 2000 to 38.5% in 2014^[18]. The resistance rate of *H. pylori* to LVFX is relatively high at approximately 15%^[19]. In Japan, MDZ resistance is lower (< 10%) than in other Asian countries. Low MDZ resistance against *H. pylori* is thought to be correlated with antibiotic consumption in the community. The use of MDZ is strictly regulated in Japan, where it has been approved for the treatment of only selected diseases, such as trichomoniasis^[20]. In contrast, the *H. pylori* resistance rates to amoxicillin (AMX) and tetracycline (TET) are equally low among the three countries (3.1% and 3.9% in China, 3.0% and 2.0% in Japan, and 9.5% and 0% in South Korea, respectively)^[21].

RECOMMENDED *H. PYLORI* REGIMENS

Some differences in *H. pylori* treatment regimens exist among the guidelines of China, Japan, and South Korea. Bismuth-based *H. pylori* regimens are strongly recommended in China. In Japan, potassium-competitive acid blockers (P-CABs) are widely used to eradicate *H. pylori*. The current South Korean guidelines are similar to those of Western countries. Notably, molecular testing to detect CAM resistance is recommended as the initial treatment option.

CHINA

According to the Fifth Chinese Consensus for *H. pylori* Management of 2016, seven *H. pylori* therapies containing bismuth salt are recommended as empirical regimens^[11]. The various antibiotic combinations include two of the following six antimicrobial agents: AMX, CAM, MDZ, TET, LVFX, and furazolidone (FZD). The recommended eradication regimens for *H. pylori* include AMX and CAM, AMX and MDZ, AMX and LVFX, AMX and FZD, AMX and TET, MDZ and TET, and FZD and TET (Table 1). The standard dose of a proton pump inhibitor (PPI) and 220 mg of bismuth are prescribed twice daily with the two antibiotics. Bismuth has long been used to treat peptic ulcer disease, dyspepsia, parasite infections, and infectious diarrhea^[22]. The antibacterial effects of bismuth include inhibition of protein and cell wall synthesis in *H. pylori*. The main role of bismuth is to increase the eradication rate by 30%-40% in resistant *H. pylori* strains^[23].

Zhang *et al*^[24] reported on a 14-d modified bismuth quadruple therapy (BQT) containing CAM or MDZ that was effective against *H. pylori* in a region with high resistance to CAM (26.5%) and MDZ (45.5%). CAM- and MDZ-containing regimens displayed high eradication rates of 88.8% and 88.9% in the intention-to-treat (ITT) analysis, and 94.9% and 96.9% in the per-protocol (PP) analysis, respectively. In an MDZ-containing regimen, 1 g of AMX twice daily was used as a substitute for 500 mg of TET four times daily. Notably, a modified BQT containing AMX and MDZ was demonstrated to be effective (> 90%) in MDZ-resistant *H. pylori* strains. A high dosage (1500 mg/d) of MDZ for 14 d can overcome *H. pylori* resistance^[25]. Chen *et al*^[26] performed a comparative study between the classic BQT and a modified one containing AMX and MDZ as a rescue *H. pylori* therapy. In comparison with the classic BQT, the modified BQT achieved a similar eradication rate (87.2%-95.3% vs 88.5%-93.7%). Adverse events occurred less frequently with the modified than the classic BQT regimen (34.0% vs 51.9%, $P = 0.001$).

FZD is a nitrofurantoin antibiotic effective against gram-negative and -positive bacteria^[27]. Qiao *et al*^[28] reported that an FZD-based BQT showed a similar first-line *H. pylori* eradication rate in PP analysis to a CAM-based BQT (95.8% vs 93.4%). The resistance rates of *H. pylori* to AMX, TET, and FZD remain low in China at < 5%^[29]. Accordingly, a

modified BQT containing FZD/AMX and FZD/TET achieved a > 90% *H. pylori* eradication rate in patients who did not respond to the previous treatment^[30]. Compared to the classic BQT, two FZD-containing regimens resulted in less frequent adverse events. The *H. pylori* eradication efficacy of regimens employing AMX and TET may not be inferior to other regimens^[31]. However, TET and FZD have limited availability^[32].

Interestingly, the recommended *H. pylori* therapies were not categorized into first- and second-line regimens. This strategy is markedly different from Japanese and South Korean guidelines, in which the first- and second-line regimens are divided. Any of the seven regimens can be prescribed to patients to eradicate *H. pylori*. After failed initial therapy, a second-line regimen is selected from among the remaining regimens. Among the antibiotic combinations, the LVFX-containing regimen is not recommended as an initial treatment due to a high resistance rate^[33]. It can be considered an alternative to rescue therapy in combination with bismuth salt. AMX, TET, and FZD ²can be reused after treatment failure because these drugs rarely produce secondary resistance. Repeat MDZ prescription requires an optimized dose (at least 1500-1600 mg/d). In contrast, reuse of CAM and LVFX should be avoided after failed eradication.

JAPAN

Since *H. pylori* treatment for chronic gastritis was approved by the Japanese national health insurance system in 2013, prescriptions for eradication therapy have markedly increased. Approximately 8.5 million *H. pylori*-positive patients received eradication regimens from 2013 to 2019^[34]. The revised 2016 guidelines were similar to previous ones^[35]. As a first-line regimen, standard triple therapy was still recommended to eradicate *H. pylori* (Table 1). The AMX and CAM dosages were lower than those of China and South Korea. The recommended AMX and CAM doses are 750 and 200 mg twice daily, respectively. The 200 mg dose of CAM twice daily has similar efficacy to 400 mg twice daily, and no significant difference was found between 7- and 14-d treatment durations. However, adverse drug events, such as dysgeusia, occurred more frequently during the 14-d therapy.

In Japan, the successful eradication rates for all types of *H. pylori* therapy decreased to < 80% in 2014. Since the P-CAB was launched in February 2015, the eradication rates of triple therapy, including AMX and CAM with P-CAB, have been significantly higher than those with conventional PPIs^[36]. The novel P-CAB vonoprazan (VPZ) exerts a rapid and sustained suppressive effect on gastric acid for optimal *H. pylori* treatment^[37]. The proportion of regimens including VPZ has increased rapidly, and is now 80%^[34]. As first-line treatment, standard triple therapy containing 20 mg VPZ twice daily resulted in higher *H. pylori* eradication rates than those of a PPI-based regimen (86.4%-91.2% vs 71.7%-79.4%)^[38,39]. There was no significant difference between the VPZ- and PPI-based triple regimens for eradicating CAM-susceptible *H. pylori* strains. *H. pylori* eradication rates were 87.3% and 76.5% ($P = 0.21$) in the ITT analysis, and 88.9% and 86.7% ($P = 0.77$) in the PP analysis, respectively^[40]. However, VPZ was superior to the PPI-based triple regimen for CAM-resistant *H. pylori* strains (73.2%-87.5% vs 40.0%-53.8%)^[41].

CAM resistance is a strong contributor to *H. pylori* eradication failure after first-line treatment^[42]. Therefore, MDZ-based triple therapy with PPI/VPZ is recommended as the second-line eradication therapy. MDZ (250 mg) is prescribed twice daily for 7 d. The MDZ-based *H. pylori* treatment results in a higher eradication rate (> 90%) than CAM-based triple therapy because of the low MDZ resistance in Japan^[43,44]. In a meta-analysis by Shinozaki *et al*^[45], VPZ was more efficacious for second-line *H. pylori* eradication compared to conventional PPIs. Seven-day VPZ, AMX, and MDZ triple therapy can be a strong candidate as an empirical *H. pylori* regimen. Sitafloxacin (STFX)-based triple therapy has been recommended as a third-line therapy in combination with AMX or MDZ^[46]. STFX is a new quinolone antibacterial agent expected to be efficacious due to its low minimum inhibitory concentration (MIC) for *H. pylori*, even for LVFX-resistant strains^[47]. STFX has a good *H. pylori* eradication effect in combination with AMX or MDZ, even for third-line treatment^[48].

SOUTH KOREA

First-line *H. pylori* therapies consist of three empirical regimens and one tailored eradication regimen (Table 1)^[49]. One of the following empirical regimens can be chosen: standard triple therapy for 14 d, non-BQT for 10 d, or classic BQT for 10-14 d. Standard triple therapy consists of a standard PPI dose, 1000 mg of AMX, and 500 mg of CAM, twice daily for 14 d. The eradication rate of 14-d standard triple therapy is superior to those of the 7- and 10-d therapeutic regimens. The pooled eradication rate of 14-d therapy was 78.1%, which is unacceptable for successful *H. pylori* eradication.

Non-BQT has been divided into concomitant and sequential therapy. A PPI, 500 mg of CAM, 1 g of AMX, and 500 mg of MDZ are prescribed twice daily for 10 d for the concomitant therapy. The sequential therapy consists of a PPI and 1 g of AMX twice daily for 5 d, followed by the PPI, 500 mg of CAM, and 500 mg of MDZ twice daily for 5 d. Concomitant and sequential therapy resulted in good *H. pylori* eradication rates of 94.2% and 91.7% in a modified ITT analysis, and 95.6% and 91.4% in the PP analysis, respectively^[50]. Sequential therapy was superior to 7- and 10-d standard triple therapy as a first-line treatment^[51]. However, the role of sequential therapy in *H. pylori* eradication is diminishing according to Western guidelines^[52]. Lee *et al*^[53] reported a higher eradication rate for concomitant than sequential therapy (94.4% vs 84.4%, $P = 0.018$). A recent nationwide study demonstrated that the *H. pylori* eradication rate of concomitant therapy is significantly higher than that of sequential therapy (91.8% vs 86.1%, $P < 0.001$)^[54]. Antibiotic overuse and the emergence of multidrug-resistant *H. pylori* may be problematic for concomitant therapy^[55].

As the last of the empirical first-line therapies, the classic BQT (standard dose PPI twice a day, MDZ 500 mg three times a day, TET 500 mg, and bismuth 120 mg four times a day) is administered for 10-14 d. However, the guidelines report high rates of adverse drug events. The relatively high rates of adverse events and high pill burden are problematic^[56]. According to the South Korean nationwide registry database, the prescription rate of the classic BQT as a first-line therapy is currently low (2.63%)^[57]. Thus, the classic BQT can be considered as a rescue therapy for other regimens.

Tailored *H. pylori* eradication shows promise for achieving more successful outcomes before treatment, compared to conventional therapies^[58]. Antimicrobial susceptibility testing using a culture method has been recommended for effective first-line *H. pylori* eradication in regions with a high rate of antibiotic resistance^[14]. However, susceptibility-guided therapy is time-consuming and requires specific expertise in clinical practice^[59]. As an alternative, molecular methods for detecting CAM resistance are available for tailored *H. pylori* eradication in South Korea^[60]. *H. pylori* resistance against CAM is mediated by point mutations in 23S ribosomal RNA^[61]. The treatment regimen is selected based on the presence of the A2142G and A2143G point mutations that cause CAM resistance^[62]. *H. pylori*-infected subjects without point mutations are treated with the 7-d standard triple regimen. Lee *et al*^[63] demonstrated that the 7-d triple therapy was as effective as the 14-d therapy in patients without a point mutation. The classic BQT is recommended when A2142G and/or A2143G point mutations are detected. In contrast, MDZ-based triple therapy has an unacceptably low eradication rate in CAM-resistant *H. pylori* strains^[64]. Tailored *H. pylori* eradication using molecular testing was more efficacious as a first-line treatment than standard CAM-based triple therapy (97.0% *vs* 81.8%)^[65]. A recent study showed that the *H. pylori* eradication rate was similar between tailored eradication using DPO-PCR and the classic BQT (96.0% *vs* 95.7%, $P = 0.9$)^[66]. Adverse drug events occurred less frequently with tailored eradication than BQT (12.0% *vs* 43.7%, $P < 0.001$).

UP-TO-DATE RESEARCH ON *H. PYLORI* THERAPY

H. pylori is an infectious disease; as such, the general principles regarding the treatment of infectious diseases, such as antimicrobial stewardship, are relevant to *H. pylori*^[67]. Accordingly, recent research has focused on the optimal drug regimen in terms of dose, treatment duration, and minimal adverse events^[68]. AMX, a beta-lactam antibiotic, has a half-life of approximately one hour, exhibiting time-dependent killing^[69]. Therefore, frequent dosing has clinical advantages which help to maintain the plasma concentration higher than the MIC. The time above the MIC can reach 24 hours if 500 mg of AMX is

dosed four times a day^[70]. Along with efficacious antibiotics, sufficient and continuous acid suppression is required for successful eradication^[71]. When *H. pylori* enters a replicative state between pH 6 and 8, the pathogen becomes highly susceptible to antibiotics, such as AMX. Recently, P-CABs have been found to increase the intragastric pH to 6 or more, which improves antibiotic stability and bioavailability^[72].

DUAL THERAPY

The primary and secondary *H. pylori* resistance rates to AMX are low. In 1989, PPI-AMX dual therapy (DT) was first used to eradicate *H. pylori*^[73]. However, the dosage of AMX, dosing intervals, and duration of therapy differed among previous investigators. Thereafter, a satisfactory *H. pylori* eradication using DT has not been achieved consistently^[74]. DT has good *H. pylori* eradication efficacy, and is gaining increasing attention worldwide. In 2015, Yang *et al*^[75] introduced a modified 14-d DT by increasing the dosage and frequency of administration (second-generation PPI and 750 mg of AMX four times daily). In a meta-analysis by Gao *et al*^[76], DT and other commonly used regimens achieved similar efficacies in the ITT analysis (83.2% *vs* 85.3%, $P = 0.87$) and PP analysis (87.5% *vs* 90.1%, $P = 0.33$). In the DT group, drug-related adverse events occurred less frequently compared to the current mainstream therapy recommended by guidelines (12.9% *vs* 28.0%, $P < 0.001$).

In a meta-analysis, Li *et al*^[77] included randomized controlled studies in which both a PPI and AMX were administered four times daily. As a first-line *H. pylori* treatment, administering high-dose DT resulted in a higher eradication rate than other regimens in ITT analysis (89.8% *vs* 84.2%, $P = 0.04$) and PP analysis (92.9% *vs* 88.3%, $P = 0.06$). Zou *et al*^[78] reported that 14-d DT had a higher *H. pylori* eradication rate than 10-d DT in ITT (89.7% *vs* 78.4%, $P = 0.039$) and PP (92.9% *vs* 80.0%, $P = 0.014$) analyses. The dosage and treatment duration of AMX were recommended as 3 g/d for 14 d to optimize the DT, respectively. As a first-line treatment, high-dose, high-frequency DT was effective and safe for treating *H. pylori* infections in elderly patients and those with multiple

comorbidities^[79]. Successful *H. pylori* eradication was achieved in 90.9% of patients, and adverse events (11.1%) were mainly mild.

P-CABS

P-CABs are highly active drugs targeting H⁺, K⁺-ATPase in the gastric acid secretion of parietal cells. The mechanism of action is different from that of PPIs. Conventional PPIs require 3-5 d to achieve maximal and steady-state gastric acid inhibition, whereas P-CABs increase the intragastric pH to nearly 7 within four hours^[80].

As an alternative to a PPI, VPZ was efficacious when combined with DT. Furuta *et al*^[81] compared the first-line *H. pylori* eradication rate of VA-DT (20 mg of VPZ twice daily and 500 mg of AMX three times daily for 7 d) and CAM-based triple therapy using VPZ. The eradication rates using the VPZ-based dual and triple therapies were 92.9% and 91.9% ($P = 0.728$) in the ITT analysis and 94.4% and 92.7% ($P = 0.715$) in the PP analysis, respectively. VA-DT showed a comparable *H. pylori* eradication rate without the need for CAM. In a randomized trial by Suzuki *et al*^[82], the eradication rate of VA-DT (20 mg of VPZ and 750 mg of AMX twice daily for 7 d) was similar to that for VPZ-based triple therapy (84.5% *vs* 89.2%, $P = 0.203$ in the ITT analysis; 87.1% *vs* 90.2%, $P = 0.372$ in the PP analysis). In the subgroup analysis, the eradication rates of VA-DT in CAM-resistant *H. pylori* strains were significantly higher than those of VPZ-based triple therapy (92.3% *vs* 76.2%, $P = 0.048$). When CAM-resistant *H. pylori* infection was treated with VPZ and AMX, CAM was not beneficial. Thus, extending the treatment duration of VA-DT to 14 d may be a promising alternative *H. pylori* treatment.

CONCLUSION

At present, the availability of specific drugs and reagents differs among China, Japan, and South Korea. Bismuth is not licensed for use in Japan, whereas classic and modified BQTs are recommended in China and South Korea. Since 2015, VPZ was introduced to eradicate *H. pylori* in Japan. In contrast, few studies have focused on VPZ outside of Japan. In South Korea, molecular tests for CAM-resistant *H. pylori* are commercially

available. In Japan, a low rate of MDZ resistance results from the limited use of MDZ by the national health insurance system. Unlike in the other two countries, MDZ has not been approved as a component of first-line *H. pylori* regimens in Japan. Therefore, the strategy for the treatment of *H. pylori* infection might be selected based on the antibiotic resistance rate and medical policy in each country.

In China, adding bismuth to all *H. pylori* regimens is recommended as the empirical first-line treatment. Clinical trials with DT involving frequent administration of high-dose AMX have been widely performed in the Chinese population. In Japan, *H. pylori* treatment success has increased since VPZ was launched. Furthermore, VPZ may play an important role in DT by optimizing the intragastric environment for AMX action. PPIs may be replaced by VPZ due to its rapid and strong acid suppression. In South Korea, tailored eradication can be used as a first-line *H. pylori* treatment option based on the presence of a point mutation. The advantages of the *H. pylori* regimens used in China, Japan, and South Korea need to be combined in future research.

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