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**Efficacy of tailored *Helicobacter pylori* eradication therapy based on antibiotic susceptibility and *CYP2C19* genotype**

Sugimot M *et al*Tailored *H. pylori* eradication

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**Abstract**

The cure rates of *Helicobacter pylori* (*H. pylori*) eradication therapy using a proton pump inhibitor (PPI) and antimicrobial agents such as amoxicillin, clarithromycin, and metronidazole are mainly influenced by bacterial susceptibility to antimicrobial agents and the magnitude of the inhibition of acid secretion. Annual cure rates have gradually decreased because of the increased prevalence of *H. pylori* strains resistant to antimicrobial agents, especially in clarithromycin. Alternative regimens have therefore been developed incorporating different antimicrobial agents. Further, standard PPI therapy (twice-daily dosing) often fails to induce a long-term increase in intragastric pH to values > 4.0. Increasing the eradication rate requires more frequent and higher doses of PPIs. Therapeutic efficacy related to acid secretion is influenced by genetic factors such as variants of the genes encoding drug-metabolizing enzymes (*e.g.*, cytochrome P450 2C19, CyP2C19), drug transporters (*e.g.*, multidrug resistance protein-1; ABCB1), and inflammatory cytokines (*e.g.*, interleukin-1β). For example, quadruple daily administration of PPI therapy potently inhibits acid secretion within 24 h, irrespective of *CYP2C19* genotype. Therefore, tailored *H. pylori* eradication regimens that address acid secretion and employ optimal antimicrobial agents based on results of antimicrobial agent-susceptibility testing may prove effective in attaining higher eradication rates.

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**Key words:** *Helicobacter pylori*; Tailored eradication therapy; Proton pomp inhibitor; Cytochrome P450 2C19; Clarithromycin

**Core tip:** The eradication for *Helicobacter pylori* (*H. pylori*) infection is mainly influenced by antibiotic susceptibility and insufficient acid inhibition [*e.g.*, cytochrome P450 2C19 (*CyP2C19*) genotype, proton pump inhibitor (PPI) dose, and PPI treatment schedule]. When a PPI is administered to *CYP2C19* rapid metabolizers and intermediate metabolizers, plasma levels of PPIs cannot be maintained between once-daily doses. The intragastric pH attained with four-times-daily-dosing of PPI is significantly higher than those observed when PPI is administered as once-daily-dosing of four-fold doses or twice-daily-dosing of two-fold doses. We describe a tailored treatment that was designed according to pharmacogenomics and antimicrobial susceptibility to achieve an eradication rate exceeding 95%, irrespective of different C*YP2C19* genotypes.

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**INTRODUCTION**

The Maastricht IV/Florence Consensus Report issued by the European *Helicobacter* Study Group in 2012[[1](#_ENREF_1)] recommends *Helicobacter pylori* (*H. pylori)* eradication therapy as first-line treatment for patients with upper gastrointestinal disorders such as peptic ulcer disease, gastric mucosa associated-lymphoid tissue (MALT) lymphoma {Evidence level in support of the recommendations formulated in the Maastricht IV / Florence Consensus Report: 1a [Systematic review of randomized controlled trial (RCT)], Grade of recommendation: A}, atrophic gastritis [2a (Systematic review of cohort studies) and B], intestinal metaplasia (2a and B), and functional dyspepsia (1a and A) as well as for patients with extra-gastrointestinal disorders such as idiopathic thrombocytopenic purpura (ITP) [1b (Individual RCT with narrow CI) and A], vitamin B12 deficiency [3b (Individual case-control study) and B], and iron-deficiency anemia (1a and A)[[2-11](#_ENREF_2)].

“Test and treat” is a strategy involving a noninvasive test (*e.g.,* serum anti-*H. pylori* IgG or urea breath test) given to patients with dyspepsia to diagnose *H. pylori* infection of the gastric mucosa, with treatment initiated upon detection[[1](#_ENREF_1" \o "Malfertheiner, 2012 #619)]. In Japan, first-line *H. pylori* eradication therapy is limited to a regimen that employs a proton pump inhibitor (PPI) administered twice-daily (*bid*) using a standard dose (*e.g.,* omeprazole, rabeprazole, lansoprazole, and esomeprazole), amoxicillin (AMPC) 750 mg *bid*, and clarithromycin (CAM) 200 mg or 400 mg *bid* for 1 wk. Unfortunately, the prevalence of CAM-resistant *H. pylori* strains in Japan is increasing (> 30%)[[12](#_ENREF_12),[13](#_ENREF_13)]. Therefore, alternative regimens are designed to consist of different antimicrobial agents with susceptibility to *H. pylori* strain, increased dosing dosages of antimicrobial agents and PPIs, increased dosing times of drugs and prolonged treatment periods[[14-17](#_ENREF_14)].

In this review article, we consider first the factors that influence the cure rate of *H. pylori* eradication therapy and the importance of inhibiting acid secretion. We then propose optimal treatment strategies based on the most effective antimicrobial agents and the patient’s genotype.

**FACTORS CONTRIBUTING TO THE SUCCESS OF *H. PYLORI* ERADICATION THERAPY**

The cure rates of *H. pylori* infection are influenced by several factors such as antibiotic susceptibility[[12](#_ENREF_12),[13](#_ENREF_13),[18](#_ENREF_18)], insufficient inhibition of acid secretion [*e.g.,* cytochrome P450 2C19 (*CYP2C19*) genotype, PPI dose, and PPI treatment schedule][[19](#_ENREF_19)], bacterial genotypes that reduce virulence (*e.g.*, *cagA*-negative strains and the *vacA* s2 genotype), the environment (*e.g.,* smoking), and compliance (Table 1).

Antibiotics targeted to *H. pylori* strains with known drug sensitivities will likely increase the eradiation rate[[20](#_ENREF_20" \o "Furuta, 2007 #130),[21](#_ENREF_21)].When patients are treated with antibiotics that are targeted specifically to the infecting *H. pylori* strain, increased eradication rates are achieved. Therefore, determining the antibiotic susceptibility of *H. pylori* using either or both culture or genetic testing is of great import, particularly in a population with a high rate of infection with drug-resistant strains. These tests should be conducted before treatment, particularly with second- and third-line treatment[[1](#_ENREF_1" \o "Malfertheiner, 2012 #619)]. The Maastricht IV Consensus Report[[1](#_ENREF_1" \o "Malfertheiner, 2012 #619)] recommends that, after a second failure, if culture and susceptibility testing is not possible, molecular genetic tests should be conducted to detect *H pylori*. Recently, a novel fully-automated rapid genetic analyzer was developed which was capable of determining CAM resistance (*e.g.,* 23S rRNA gene point mutations of A2143G and A2144G) within 60-120 min[[20](#_ENREF_20)], whereas culture tests required 7-10 d. Note that the treatment strategy should take into account the drug resistance of *H. pylori* in different patient populations in different localities.

The optimal intragastric pH condition with potent acid inhibition in the stomach makes selected antibacterial agents more stable and bioavailable[[21](#_ENREF_21),[22](#_ENREF_22)]. Controlling intragastric pH with PPIs depends on dosing schedules, dose, and combination of acid inhibitors[[23-27](#_ENREF_23)], and polymorphisms in the genes encoding drug-metabolizing enzymes and drug transporter genes such as CYP2C19 and multidrug resistance protein-1 (ABCB1)influence pH during treatment[[23-29](#_ENREF_23)]. In the gastrointestinal tract, ABCB1 is expressed on the apical surfaces of superficialcolumnar epithelial cells of distal small bowel and the pharmacokinetics of PPIs are influenced by the activity of ABCB1. Polymorphism of *ABCB1* is one of the determinants of successful eradication of *H. pylori* by the triple therapy with lansoprazole, amoxicillin and clarithromycin, and eradication rates for *H. pylori* infection are 82%, 81%, and 67% in patients with the *ABCB1* 3435 C/C, C/T and T/T genotype, respectively (*P* = 0.001)[[30](#_ENREF_30)]. In particular, patients’ pharmacogenetic characteristics [*e.g.,* CYP2C19 rapid metabolizer (RM), interleukin (IL)*-1*β-511 C/C, and *ABCB1* 3435 T/T genotype] require a modified treatment regimen to effectively inhibit acid secretion for 24 h[[23-29](#_ENREF_23)].

The increased levels of IL-1β induced by *H. pylori* infection potently inhibit acid production, and IL-1β is one hundred times more potent an inhibitor than PPIs on a molar basis[[31](#_ENREF_31)]. Polymorphisms in the gene encoding IL-1βare associated with individual differences in IL-1β levels[[32](#_ENREF_32" \o "El-Omar, 2000 #99)], and presence of the *IL-1B*-511 polymorphism has been shown to be related to eradication rate[[33-35](#_ENREF_33)]. Indeed, the eradication rate achieved for patients with the low IL-1β-producer genotype *IL-1B*-511 C/C (77.4%) is lower than that of the C/T and T/T genotypes (87.2%; odds ratio for failure: 1.98, 95%CI: 1.38-2.84, *P* = 0.0002)[[35](#_ENREF_35" \o "Sugimoto, 2009 #436)]. Further, *H. pylori* virulence factors (*e.g., cagA* and *vacA*), which play critical roles in gastric mucosal injury and inflammation, determine cure rates[[19](#_ENREF_19)]. In a meta-analysis, individuals infected with strains with the *cagA-*negative 69.9%(95%CI: 65.7%-73.9%) *vs* 83.1% (80.7%-85.3%) for *cagA-*positive genotypes and *vacA* s2 genotype [72.1% (64.8%-78.7%) *vs* *vacA* s1 genotype 79.2%(75.1%-83.0%] are at increased risk of failure of eradication therapy[[19](#_ENREF_19)]. The presence of *dupA,* which is associated with the development of duodenal ulcers, influences the cure rate of eradication therapy[[36](#_ENREF_36),[37](#_ENREF_37)].

**CAM RESISTANCE AND ERADICATION TREATMENT**

CAM is a key component of *H. pylori* eradication therapy, exerting its antimicrobial effects by binding to the subunit 50S of the bacterial ribosome, which inhibits protein synthesis. In general, although the cut-off concentration used to define resistance to CAM is higher than 1.0 mg/mL[[38](#_ENREF_38)], bacterial susceptibility to CAM in most strains is conferred by a single nucleotide polymorphism at either position 2142 or 2143 of the *H. pylori* 23S rRNA gene (A2142G or A2143G). The most frequent mutation is A2143G (69.8%), followed by A2142G (11.7%) and A2142C (2.6%)[[39](#_ENREF_39),[40](#_ENREF_40)].

From 1990 to 2000, the eradication rates achieved in Japan using CAM-based triple therapy ranged from approximately 85%-91%[[12](#_ENREF_12)]; in contrast, eradication rates for patients infected with CAM-resistant strains were markedly low (10%-30%)[[41](#_ENREF_41),[42](#_ENREF_42)]. The frequencies of resistance of *H. pylori* strains to CAM in Japan and Europe exceed 35% and 20%, respectively, and account for the relatively low eradication rates with the CAM-based regimen[[12](#_ENREF_12),[13](#_ENREF_13),[42](#_ENREF_42),[43](#_ENREF_43)].

The Maastricht IV consensus report recommends first-line eradication treatment using a CAM-based regimen [PPI-CAM-AMPC or -metronidazole (MNZ)] and an alternative eradication using a bismuth-containing quadruple treatment in areas where prevalence of CAM-resistant strains is low, and a bismuth-containing quadruple treatment in areas of high resistance[[1](#_ENREF_1)]. Extending the duration of CAM-based triple treatment from 7 to 10-14 d improves the eradication success rate by approximately 5%[[44](#_ENREF_44),[45](#_ENREF_45)]. When CAM-based treatment fails, either bismuth-containing quadruple therapy or levofloxacin-based therapy is recommended. In areas of high CAM resistance, levofloxacin-based treatment is recommended after quadruple therapy fails.

**IMPORTANCE OF INHIBITING GASTRIC ACID SECRETION DURING ERADICATION THERAPY**

Rapid and potent neutralization of intragastric pH after treatment with drugs that inhibit acid secretion is required to cure acid-related diseases. Thus, intragastric pH during treatment is associated with the cure rates of peptic ulcers[[46](#_ENREF_46)], gastroesophageal reflux disease[[47](#_ENREF_47)], and aspirin-induced gastroduodenal mucosal injury[[48](#_ENREF_48)]. Further, eradication treatment fails if acid secretion is not sufficiently inhibited[[49-51](#_ENREF_49" \o "Yang, 2011 #670)].

Whereas *H. pylori* survives with a periplasmic pH of 4.0-8.0, it only grows between pH 6.0-8.0[[52](#_ENREF_52)]. When bacterial urease activity elevates the pH to 4.0-6.0, *H. pylori* survives but does not divide[[52](#_ENREF_52)]. The consistent and potent action of drugs that inhibit acid secretion increases the stability and bioavailability of acid-sensitive antimicrobial agents such as CAM and AMPC by preventing their degradation in the stomach. Further, these inhibitors increase the concentration of antimicrobial agents in the gastric mucosa[[21](#_ENREF_21),[52](#_ENREF_52),[53](#_ENREF_53)]. Raising pH from 3.5 to 5.5 increases the *in vitro* effectiveness of AMPC more than 10-fold[[21](#_ENREF_21)]. Ampicillin is bactericidal at pH 4.5-7.4 but not at pH 3.0, as this pH inhibits the expression of genes encoding cell envelope components and proteins required for cell division[[54](#_ENREF_54)]. The activity of CAM is higher at pH 7.4 than at pH 5.0, and activity is intermediate at pH 6.8[[55](#_ENREF_55)]. Inhibiting acid secretion also allows *H. pylori* to grow and become more sensitive to antimicrobial agents[[52](#_ENREF_52)].

In a previous study, the 24-h intragastric pH level in patients treated successfully with eradication therapy (omeprazole 20 mg *bid* and AMPC 1 g *bid*) was found to be higher than in patients that failed 7-d treatment[[51](#_ENREF_51)]. When 24-h pH exceeds 5.5, *H. pylori* can be eradicated using dual PPI/AMPC therapy without a second antimicrobial agent such as CAM, MNZ, or both[[51](#_ENREF_51" \o "Labenz, 1995 #267)]. Eradication using PPI/AMPC therapyis preferred for patients with pH > 4.0 for 75% of total treatment duration and above 5.5 in 4-h pH[[49](#_ENREF_49" \o "Yang, 2011 #670)]. Univariate analysis shows that pH values depend on the dose of omeprazole (*P* = 0.003), *CYP2C19* genotype (*P* = 0.001), and *H. pylori* density (*P* = 0.044)[[49](#_ENREF_49" \o "Yang, 2011 #670)]. We demonstrate further that the median 24-h pH was 6.4 (range, 5.0-7.6) for successful eradication therapy compared with that for failed therapy [pH 5.2 (2.2-6.2), *P* = 0.0131] and that median percentage time at pH < 4.0 for successful cures [0.5% (0.0%-31.6%)] is significantly shorter compared with failures [26.7% (6.0%-72.2%), *P* = 0.0017; Figure 1A and B][[50](#_ENREF_50" \o "Sugimoto, 2007 #429)]. Therefore, the degree and duration of acid suppression arerelated to cure rate, and we may conclude that pH > 4 should be maintained for 24 h and 24-h pH higher than 6.0 (Figure 1C). Unfortunately, the PPI standard-dose *bid* treatment does not maintain pH values > 4.0 long enough to satisfy the above criteria in all of patients[[23](#_ENREF_23)].

***CYP2C19* POLYMORPHISMS AND *H. PYLORI* ERADICATION THERAPY**

*P****harmacokinetics and pharmacodynamics of PPIs according to CYP2C19 genotype***

PPIs delivered through the circulatory system are absorbed in the small intestine and reach gastric parietal cells where they bind irreversibly to and alter the function of H+/K+-ATPase, which potently inhibits acid secretion[[56](#_ENREF_56),[57](#_ENREF_57)]. Therefore, PPIs are currently used as the first-line treatment of acid-related diseases[[33](#_ENREF_33),[50](#_ENREF_50),[58](#_ENREF_58),[59](#_ENREF_59)].

PPIs undergo extensive hepatic metabolism by the CYP system, which includes CYP2C19 and CYP3A4 (Figure 2)[[60](#_ENREF_60)]. *CYP2C19* polymorphisms therefore influence both pharmacokinetics [*i.e.,* peak plasma concentration (Cmax) and area under the curve (AUC) of the plasma concentration] and pharmacodynamics (*i.e.,* intragastric pH) of PPIs (Figure 3A and B). At least 20 *CYP2C19* variants (Figure 4) have been identified, with the majority classified into three genotypes: rapid metabolizers (RMs), intermediate metabolizers (IMs), and poor metabolizers (PMs)[[60-63](#_ENREF_60" \o "Ishizaki, 1999 #215)]. The inhibition of acid secretion achieved using PPIs (*e.g.,* omeprazole and lansoprazole) to treat PMs is enhanced compared with IMs or RMs because of the different pharmacokinetics among the three *CYP2C19* genotypes[[26](#_ENREF_26),[27](#_ENREF_27),[29](#_ENREF_29),[64](#_ENREF_64)]. In contrast, rabeprazole reduces acid secretion mainly *via* a non-enzymatic reaction, with minor involvement of CYP2C19 (Figure 2)[[60](#_ENREF_60),[65](#_ENREF_65)], and its acid inhibitory effect is less influenced by *CYP2C19* genotypes than that of omeprazole or lansoprazole. Esomeprazole, which is the S-isomer of omeprazole, more effectively inhibits acid secretion than omeprazole[[66](#_ENREF_66),[67](#_ENREF_67)], and this relatively high activity can be attributed to its less extensive metabolism during first-pass hepatic metabolism compared with omeprazole. The increased systemic bioavailability of esomeprazole offers the prospect of improved clinical efficacy and more effective management of acid-related diseases[[68](#_ENREF_68)]. A 2006 study shows that the *CYP2C19\*17* variant is an ultrarapid metabolizer genotype[[69](#_ENREF_69" \o "Sim, 2006 #413)]. Interethnic differences have been reported in the frequencies of genotypes[[63](#_ENREF_63),[70](#_ENREF_70),[71](#_ENREF_71)], with frequency of the \*17 allele approximately 20% among Caucasian, African-American, Swedish, and Ethiopian populations but only 4% among Asians.

Several studies have compared the level of acid inhibition attained among CYP2C19 genotypes on PPI *bid* administration[[23](#_ENREF_23),[33](#_ENREF_33),[68](#_ENREF_68),[72](#_ENREF_72),[73](#_ENREF_73)]. Effects of lansoprazole (30 mg, *bid*) have been found to vary markedly with *CYP2C19* genotype[[33](#_ENREF_33),[68](#_ENREF_68)], whereas little or no differences in efficacy were observed in patients treated with rabeprazole (10 mg) or esomeprazole (20 mg) *bid*, regardless of *CYP2C19* genotype[[68](#_ENREF_68),[72](#_ENREF_72),[73](#_ENREF_73)]. Further, *CYP2C19* genotype-dependent differences in intragastric pH attained using esomeprazole and rabeprazole are smaller than those noted with lansoprazole and omeprazole[[68](#_ENREF_68)]. As such, twice-daily dosing with a second-generation PPI may attenuate the influence of *CYP2C19* genotype, but not completely remove it.

We reported that the median 24-h pH [5.4 (3.5–6.8)] of *H. pylori*-negative *CYP2C19* RMs administered esomeprazole 20 mg *bid* was significantly higher than that achieved with omeprazole [5.0 (2.4-5.9), *P* = 0.018], rabeprazole [4.8 (2.5-6.4), *P* = 0.002], or (check) lansoprazole [4.7 (3.7-5.5), *P* = 0.017][[68](#_ENREF_68)]. However, these findings suggest that although esomeprazole inhibits acid secretion in CYP2C19 RMs, twice-daily dosing of omeprazole, lansoprazole, and rabeprazole as well as with esomeprazole does not sustain high pH for 24 h for all patients.

***Influence of CYP2C19 polymorphisms on PPI-based eradication of H. pylori***

The rates for eradicating *H. pylori* infection using triple therapy (omeprazole 20 mg *bid* or lansoprazole 30 mg *bid*, AMPC 250 mg *tid*, and CAM 200 mg *tid* for 1 wk) vary with *CYP2C19* genotype as follows: 72.7%, RMs; 92.1% IMs; and 97.8%, PMs[[18](#_ENREF_18)]. The frequency of *CYP2C19* RMs is relatively high among patients that experience eradication failure (58.6%, *vs* 2.9% for PMs). Schwab *et al*[[74](#_ENREF_74" \o "Schwab, 2004 #396)] also noted significant differences in eradication rates among RMs (80.2%), IMs (97.8%), and PMs (100%) (*P* < 0.01), which were associated with corresponding changes in median serum lansoprazole levels (753 ng/mL, PMs; 59 ng/mL, IMs; and 21 ng/mL, RMs; *P* < 0.001). A meta-analysis performed by those authors[[74](#_ENREF_74" \o "Schwab, 2004 #396)] further revealed that failure to eradicate *H. pylori* infection using PPI-based regimens is strongly influenced by the *CYP2C19* genotype.

A more recent meta-analysis performed by Tang *et al*[[75](#_ENREF_75)] on the effects of *CYP2C19* loss-of-function variants revealed significant differences in rates between RMs and IMs (OR = 0.72; 95%CI: 0.59-0.88), between RMs and PMs (0.51; 0.38-0.68), and between IMs and PMs (0.69; 0.52-0.92) regardless of the PPI administered. Although other studies have reported significant differences in eradication rates using other PPI-based eradication therapies (*e.g.,* rabeprazole, esomeprazole, or pantoprazole) among the different *CYP2C19* genotypes[[76](#_ENREF_76),[77](#_ENREF_77)], Tang *et al*[[75](#_ENREF_75)] found no significant differences in efficacy between rabeprazole or esomeprazole for loss-of-function *CYP2C19* variants. Therefore, *CYP2C19* loss-of-function variants such as *CYP2C19* PMs are associated with increased *H. pylori* eradication rates in patients taking PPI-based triple therapies with either omeprazole or lansoprazole[[75](#_ENREF_75)].

**EFFICACY OF DIVIDED DOSING WITH PPIS**

When PPIs are administered to *CYP2C19* RMs and IMs, plasma levels of PPIs cannot be maintained between once-daily doses[[23](#_ENREF_23),[26](#_ENREF_26),[29](#_ENREF_29),[78](#_ENREF_78)]. RMs rapidly eliminate PPIs from the systemic circulation, and plasma levels of PPIs before dosing and 3 h later are often below detectable levels (plasma half-life, 2-3 h). Following rapid elimination of PPIs, activated or newly synthesized H+, K+-ATPase expressed in gastric parietal cells secretes gastric acid[[23](#_ENREF_23),[26](#_ENREF_26),[29](#_ENREF_29),[78](#_ENREF_78)]. Although the Cmax for multiple-dosing PPI regimens (*e.g., bid* or *qid*) does not increase compared with *oid* administration, plasma levels of PPIs reached using multiple doses can be sustained throughout the 24-h period and continue to inactivate H+, K+-ATPase consistently for 24 h, achieving sufficient inhibition of acid secretion.

We reported that when rabeprazole (40 mg *oid* or 20 mg *bid*) is administered to *CYP2C19* RMs, the levels of plasma rabeprazole are often below the limit of detection. However, when rabeprazole (20 mg *bid* or 10 mg *qid*) is administered to IMs and RMs, respectively, plasma levels are sustained above 10 ng/mL throughout the 24-h period, and sufficient suppression of acid secretion is achieved[[23](#_ENREF_23)]. When rabeprazole is administered once, twice, or four times to achieve a daily dose of 40 mg, the median pH values are 4.8 (3.6-6.4), 5.7 (4.1-7.4), and 6.6 (4.9-8.4), respectively (Figure 5A)[[25](#_ENREF_25)]. Administering 10 mg rabeprazole, 30 mg lansoprazole, and 10 mg esomeprazole *qid* to RMs achieves sufficient inhibition of acid secretion[[23](#_ENREF_23),[64](#_ENREF_64),[73](#_ENREF_73)].

However, when patients with the same *CYP2C19* genotype were treated with different doses of rabeprazole on different dosing schedules, the median pH attained with 10 mg *qid* was significantly higher than those observed when the drug was administered as 40 mg *oid* or 20 mg *bid* (Figure 5A). Further, multiple doses of a PPI decreased the influence of *CYP2C19* genotype on pH (Figure 5B)[[25](#_ENREF_25)]. Fischbach *et al*[41] reported that inhibition of acid secretion attained using esomeprazole 20 mg *bid* or 10 mg *qid* was similar among *CYP2C19* genotypes but differed markedly from that achieved with 40 mg *oid*. We may therefore reasonably assume that, in order to maintain plasma PPI levels above a certain threshold level throughout the 24 h period, a multiple-dosing regimen would be more effective in inhibiting acid secretion by increasing the dose than by increasing either or both the Cmax or the AUC value.

Previously, sufficient eradication rates were achieved for RM patients treated with either lansoprazole 30 mg *qid* or rabeprazole 10 mg *qid* plus AMPC 500 mg *qid* for 2 weeks. These findings suggest that potent inhibition of acid secretion using more frequent dosing intervals than at present *bid* may help to improve the eradication rate[[18](#_ENREF_18),[43](#_ENREF_43),[79-81](#_ENREF_79)]. In addition, interestingly, rabeprazole 20 mg *bid* plus AMPC 1000 mg *bid* attains a 59.6% cure rate irrespective of administration of high daily doses of a PPI and AMPC[[82](#_ENREF_82)]. This observation may be explained by findings that inhibition of acid secretion is insufficient when RMs are treated with rabeprazole 20 mg *bid.*

**EFFICACY OF DIVIDED DOSING WITH AMPC**

Similarly, AMPC should have been administered at 500 mg *qid*, not 1000 mg *bid* We therefore believe that administering AMPC using a regimen of 750-1000 mg *bid* is theoretically inappropriate according to pharmacological considerations, as antibiotics with a beta-lactam ring, such as AMPC, exert little post-antibiotic effects on gram-negative rods[[83](#_ENREF_83)]. Their antibacterial effect depends largely on the duration for which their concentration is maintained at levels above the MIC and not the AUC or Cmax. The regimens reported to achieve high re-eradication rates (96.8%-100%) using dual therapy use a PPI *qid* plus AMPC *qid*[[18](#_ENREF_18),[43](#_ENREF_43),[79](#_ENREF_79),[84](#_ENREF_84)].

**EFFICACY OF TAILORED ERADICATION TREATMENT FOR *H****. PYLORI* **INFECTIONS BASED ON SUSCEPTIBILITY TO ANTIBIOTICS AND *CYP2C19* GENOTYPE**

Tailored eradication therapy shows promise for delivering significantly more successful outcomes than the standard therapies described above. For example, in their preliminary trial, Kawai *et al*[[85](#_ENREF_85" \o "Kawai, 2008 #618)] determined the efficacy of a regimen based on bacterial drug susceptibility to CAM that included 70 *H. pylori*-positive patients administered the following drugs: PPI/AMPC/CAM for patients with CAM-sensitive strains and PPI/AMPC/MNZ for CAM-resistant strains. The tailored treatment regimen achieved a 94.3% eradication rate, which is significantly higher than that achieved with standard treatment (71.4%, PPI/AMPC/CAM)[[85](#_ENREF_85)], suggesting that treatment based on susceptibility to CAM will be effective, particularly in areas such as Japan with a high prevalence of CAM-resistant strains.

A second example of the increased efficacy of a tailored therapy comes from our own studies in which we administered PPIs according to *CYP2C19* genotype and sequence analysis of the gene encoding *H. pylori* 23S rRNA[[86](#_ENREF_86" \o "Furuta, 2007 #130)]. Patients infected with a CAM-sensitive strain were treated with CAM 200 mg *tid*, AMPC 500 mg *tid*, and personalized doses of lansoprazole (*e.g.,* RMs, 30 mg *tid*; IMs, 15 mg *tid*; and PMs, 15 mg *bid*) for 1 wk. Patients infected with a resistant strain were treated with AMPC 500 mg *qid* and a personalized dose of lansoprazole (*e.g.,* RMs, 30 mg *qid*; IMs, 15 mg *qid*; and PMs, 15 mg *bid* for 2 wk) [[86](#_ENREF_86)]. The ITT analyses of eradication rates for standard triple regimen (PPI/AMPC/CAM) are 70.0% compared with 96.0% (*P* < 0.0001) for tailored treatment (graded A, excellent)[[86](#_ENREF_86" \o "Furuta, 2007 #130)].

Although this tailored treatment may be optimal with high eradication rate, a setting of drug selection and dosing doses of PPI and antimicrobial agents may be complicated. We therefore propose that a regimen based on administering rabeprazole *qid* for all patients, irrespective of their *CYP2C19* genotype, may achieve higher eradication rates than using a regimen employing a PPI *bid*, in particular in RMs. We assessed the efficacy of the tailored eradication regimens that control acid secretion using a PPI *qid* and selected antimicrobial agents based on the CAM-susceptibility of the patient’s *H. pylori* strain (Figure 6A). Patients infected with CAM-sensitive strains were treated with a tailored regimen of rabeprazole (RPZ) *qid*, AMPC 500 mg *qid*, and CAM 200 mg *bid* for 1 wk, while those infected with resistant strains were given RPZ *qid*, AMPC 500 mg *qid*, and MNZ 250 mg *bid* for 1 wk, irrespective of *CYP2C19* genotype. The overall eradication rate achieved using the standard regimen was 77.8% (95%CI: 72.0%-85.5%) according to ITT analysis and that of the tailored regimen was 98.0% (94.3%-99.6%) (Figure 6B). The eradication rates using CAM-based and MNZ-based treatment were similar (96.5% and 98.4%, respectively, *P* = 0.469), and the eradication rates using the tailored regimen were similar among different CYP2C19 genotypes (RM, 94.3%; IM, 98.3%; and PM, 100%). In contrast, the outcomes achieved using the standard regimen were as follows: RM, 75.7%; IM, 81.7%; and PM, 87.0%) (Figure 6C). A tailored *H. pylori* eradication regimen based on CAM susceptibility that inhibits acid secretion for 24 h using RPZ 10 mg *qid* is more effective than the standard therapy used in Japan, as its eradication rate exceeds 95% irrespective of *CYP2C19* genotype. Benefits of this tailored treatment are to save a cost of genotyping test and to prevent increased CAM-resistant *H. pylori* strain. We added limitation of this treatment in revised version. However, because not all patients are CYP2C19 RM and more frequent dosing with the PPI forIMs and PMs is more costly, this tailored treatment may be applicable third-line treatment. To identify efficacy of this tailored treatment for first- and second-line treatment (*i.e.,* eradication rate and cost benefit), further study will be required.

**CONCLUSION**

This review focuses on *H. pylori* eradication therapy in relation to pharmacogenomics and susceptibility to antimicrobial agents. We highlight the many genetic factors that influence therapeutic outcomes of *H. pylori* eradication therapy using a PPI and antimicrobial agents. We describe a tailored treatment that was designed according to pharmacogenomics and antimicrobial susceptibility to achieve an eradication rate exceeding 95%, irrespective of eradication history, that overcomes differences among *CYP2C19* genotypes. Although a tailored regimen based on an individual’s *CYP2C19* genotype is a valid therapeutic consideration, our strategy saves the cost of *CYP2C19* genotyping. However, using increased doses of PPIs may not be universally welcomed and may not be tolerated by some patients. In addition, because there are other genetic factors to influence in eradication rate as listed in Table 1, it may be better to consider effects of genetic factors for optimal tailored treatment.

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**Figure 1 Success of *Helicobacter pylori* eradication treatment as a function of pH.** A, B: Median 24-h pH values (A) and the percentage of the times when pH < 4.0 during eradication therapy according to successful and failed treatment (B); C: Variation of pH and the percentage of time at pH < 4.0[[51](#_ENREF_51)]. The median pH of successfully treated patients was significantly higher than compared with patients that failed treatment (A). The median percentage of the time when pH < 4.0 in successfully treated patients was significantly shorter compared with unsuccessfully treated patients (B). The majority of patients were cured using triple therapy when the percentage of time at pH < 4.0 during the 24-h post-dose period was < 10% and the 24-h pH was > 6.0 (shaded area) (C). CAM: Clarithromycin.

**Figure 2 Metabolism of omeprazole, lansoprazole, rabeprazole, and esomeprazole by cytochrome P450 isoenzymes.** Reproduced from Chang *et al*[[61](#_ENREF_61)]. The thickness of the arrows indicates the relative contribution of the different reactions.

**Figure 3 Median 24-h intragastric pH profiles (A) and median 24-h pH values after administering a standard dose of a proton pump inhibitor to patients with the three *CYP2C19* genotypes (B).** Proton pump inhibitor (PPI) treatment of poor metabolizers (PMs) inhibited gastric acid secretion more effectively than that of rapid metabolizers (RMs) and intermediate metabolizers (IMs).

**Figure 4 Genetic polymorphisms of *CYP2C19*.** More than 20 variants have been discovered.

**Figure 5 Median 24-h pH values as a function of dosing frequency using 40 mg of rabeprazole (A), and the pH attained using three different dosing regimens as a function of *CYP2C19* genotype (B).** Reproduced from Shirai *et al*[[27](#_ENREF_27)]. PMs: Poor metabolizers; RMs: Rapid metabolizers; IMs: Intermediate metabolizers.

**Figure 6 Study design and outcomes.** A: Patients were classified into two treatment regimens: standard treatment group (first- or second-line standard Japanese regimen) and tailored treatment group (based on clarithromycin-susceptibility); B: Eradication rates for the standard and tailored regimens for eradication of *H. pylori*; C: eradication rates for the standard and tailored regimens among different *CYP2C19* genotypes. CAM: Clarithromycin; PPI: Proton pump inhibitor; AMPC: Amoxicillin; MNZ: Metronidazole; RPZ: Rabeprazole.

**Table 1 Major factors preventing eradication of *Helicobacter pylori* infection**

|  |  |  |
| --- | --- | --- |
|  | Factor |  |
| Antibiotics | Resistance to antibiotics | Clarithromycin |
|  |  | Metronidazole |
|  |  | Levofloxacin |
|  |  | Amoxicillin |
| Inhibition of acid secretion | *CYP2C19* | Rapid metabolizer |
|  | *CYP2C19*\*17 | \*17 carrier |
|  | *ABCB1* 3435 | C/C genotype (Caucasian) |
|  | *IL-1B*-511 | C/C genotype |
|  | *IL-1B*-31 | T/T genotype |
|  | Acid inhibitory drug dosing time | Low frequency (*oid* ) |
|  | Acid inhibitory drug dosing dose | Insufficient dose |
| *H. pylori* phenotype | *H. pylori* virulence factors | *cagA*-negative |
|  |  | *vacA* s2 genotype |
|  | volume | much |
| Environment | Smoking | Many |
|  | Compliance | Poor |

CYP2C19: Cytochrome P450 2C19; IL: Interleukin; ABCB1: Multidrug resistance protein-1; *H. pylori*: *Helicobacter pylori.*