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High-dose Dual Therapy is Superior to Standard First-line or Rescue Therapy for *Helicobacter pylori* Infection

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Disclosures

All authors have no conflicts of interest to disclose

Author Contributions

J-C Yang and C-J Lin had the study concept. J-C Yang, C-J Lin, and H-L Wang contributed to the study design and wrote the protocol and the draft of paper. H-L Wang, J-C Yang, and C-W Lu did the statistical analyses. C-T Shun and J-C Yang provided central histological and microbiological assessment. JY Kao revised the draft critically for important intellectual content. J-C Yang and JY Kao obtained funding. J-C Yang, J-D Chen, B-R Lin, M-J Shieh, M-C Chang, Y-T Chang, S-C Wei, L-C Lin, W-C Yeh, J-S Kuo, C-C Tung, Y-L Leong, T-H Wang, and J-M Wong enrolled and treated the patients and collected data. All authors contributed to the comment and interpretation of results and approved the final version of manuscript.

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Abstract

Background & Aims—The efficacy of treatment of *Helicobacter pylori* infection has decreased steadily due to increasing resistance to clarithromycin, metronidazole, and levofloxacin. Resistance to amoxicillin is generally low, and high intragastric pH increases the efficacy of amoxicillin, so we investigated whether a combination of a high-dose proton-pump inhibitor and amoxicillin (dual therapy) was more effective than standard first-line or rescue therapies in eradicating *H pylori*.

Methods—We performed a large-scale, multi-hospital trial to compare the efficacy of a high-dose dual therapy (HDDT) with that of standard therapies in treatment-naïve (n=450) or treatment-experienced (n=168) patients with *H pylori* infection. Treatment-naïve patients were randomly assigned to groups given HDDT (rabeprazole 20 mg and amoxicillin 750 mg, 4 times/day for 14 days; group A1), sequential therapy for 10 days (group B1), or clarithromycin-containing triple therapy for 7 days (group C1). Treatment-experienced patients were randomly assigned to groups given HDDT for 14 days (group A2), sequential therapy for 10 days (B2), or levofloxacin-containing triple therapy for 7 days (C2). *H pylori* infection was detected using the ^{13}C–urea breath test. We evaluated factors associated with treatment outcomes.

Results—In the intention-to-treat treat analysis, *H pylori* was eradicated in 95.3% of patients in group A1 (95% confidence interval [CI], 91.9%–98.8%), 85.3% in B1 (95% CI, 79.6%–91.1%), and 80.7% in group C1 (95% CI, 74.3%–87.1%). Infection was eradicated in 89.3% of patients in group A2 (95% CI, 80.9%–97.6%), 51.8% in group B2 (95% CI, 38.3%–65.3%), and 78.6% (95% CI, 67.5%–89.7%). The efficacy of HDDT was significantly higher than that of currently recommended regimens, irrespective of *CYP2C19* genotype. Bacterial resistance to drugs was associated with treatment failure. There were no significant differences between groups in adverse events or patient adherence.

Conclusions—HDDT is superior to standard regimens as empiric first-line or rescue therapy for *H pylori* infection, with similar safety profiles and tolerability. ClinicalTrials.gov no: NCT01163435.

Keywords

PPI; proton pump inhibitor; bacterial infection; stomach; microbe

Introduction

Helicobacter pylori (*H. pylori*) infection is common worldwide and is strongly associated with gastrointestinal diseases including peptic ulcer and gastric cancer.[1] Clarithromycin-containing triple therapy has been recommended in many guidelines as the first-line therapy for the treatment of *H. pylori* infection.[2–4] However, due to increasing antibiotic resistance, higher treatment failure rate for *H. pylori* is a growing global concern.[2,5] Sequential therapy, quadruple therapy with or without bismuth compounds, and levofloxacin-containing triple therapy have all been recommended as the first-line, alternative, or rescue therapies[2,5] but their eradication rates vary among studies and are usually below 90% by intention-to-treat

analysis.[6] Meanwhile, the failure of first-line therapy for *H. pylori* can significantly increase the development of secondary antibiotic resistance,[7,8] further limiting the efficacy of subsequent rescue therapies. Although antimicrobial susceptibility testing is recommended in regions of high antibiotic resistance and after treatment failure,[2,5] it is technique-dependent and not readily available in most areas. Therefore, it is important to design a treatment regimen of substantially high efficacy and can be used empirically without the need for susceptibility testing.

Unlike *H. pylori* resistance rates to clarithromycin (CLA), metronidazole (MTZ) or levofloxacin (LEV), *H. pylori* resistance to amoxicillin (AMO), both primary and acquired, have been reported to be uncommon.[7,9,10] AMO is also unique in that its bactericidal effect against *H. pylori* is time-and pH-dependent because AMO is more stable at a higher intragastric pH.[11–13] Thus, an optimized dual therapy consisting of high-dose PPI and AMO may have a selective advantage over currently recommended sequential, CLA-or LEV-containing therapy.

Except that quadruple therapy with bismuth compound is hardly used in Taiwan because bismuth subcitrate was not readily available, in this large-scale multi-hospital and randomized trial, we compared the efficacy and tolerability of high-dose dual therapy with those of currently recommended therapies (sequential therapy, CLA-containing triple therapy, and LEV-containing triple therapy) in treatment-naïve or treatment-experienced *H. pylori*-infected subjects. Potential factors influencing treatment outcomes were also examined.

Materials and Methods

Study design, settings, and participants

This prospective, randomized study was conducted at one medical center (National Taiwan University Hospital) and four community hospitals in the northern Taiwan region. The study was approved by the Research Ethics Committee of National Taiwan University Hospital and registered at ClinicalTrials.gov (number NCT01163435). All authors had access to the study data and had reviewed and approved the final manuscript. Patients (aged ≥ 20) having *H. pylori*-positive chronic gastritis with/without peptic ulcers (duodenal or gastric ulcers) were recruited. Exclusion criteria included pregnancy or nursing, serious concomitant illness, malignant tumors, history of hypersensitivity to study drugs, severe ulcer bleeding, previous gastric surgeries, taking PPIs or antibiotics in the previous month. Patients without previous anti-*H. pylori* treatment were invited to receive the first-line regimens, whereas patients who had previously received anti-*H. pylori* therapies were invited to receive rescue regimens.

A computer-generated random number sequence was blocked (1:1:1, block size: 6) into three subgroups: A1, B1 and C1 (or A2, B2, and C2). The assignment was recorded on a group assignment card and sealed in opaque envelops by an independent statistician. All investigators were masked to the randomization sequence. After giving their written informed consent, each patient was assigned a number by enrolling order and randomly allocated, according to group assignment card, to one of three treatment groups for first-line

or rescue therapies. For the first-line therapy, group A1 (high-dose dual therapy; HDDT) consisted of rabeprazole (20 mg, QID) and AMO (750 mg, QID) for 14 days; group B1 (sequential therapy; ST) consisted of rabeprazole (20 mg, BID) and AMO (1000 mg, BID) for 5 days, followed by rabeprazole (20 mg, BID), MTZ (500 mg, BID), and CLA (500 mg, BID) for 5 additional days; group C1 (CLA-containing triple therapy; CLA-TT) consisted of rabeprazole (20 mg, BID), AMO (1000 mg, BID), and CLA (500 mg, BID) for 7 days. For the rescue regimens, group A2 (HDDT) was the same as group A1; group B2 (ST) was the same as group B1; group C2 (LEV-containing triple therapy; LEV-TT) consisted of rabeprazole (20 mg, BID), AMO (1000 mg, BID), and LEV (250 mg, BID) for 7 days.

Procedures

All subjects underwent an upper endoscopy with gastric biopsy before the initiation of assigned treatment regimen. *H. pylori* status was determined by histology, culture, ^{13}C-urea breath test (^{13}C-UBT). During the treatment period, patients were instructed to avoid acidic foods (e.g., citrus fruits or juices) to minimize the impact of ingested foods on increasing intragastric acidity which can alter drug activity. Subjects also completed a standardized questionnaire and recorded symptoms and daily drug consumption during the treatment period in a diary card. After completing the course of the treatment, the patients were followed in outpatients clinic to investigate patient adherence and adverse effects of treatments. Patients taking rescue therapies were requested to obtain their previous medical records pertaining to *H. pylori* treatment. *CYP2C19* and *IL-1β-511* genetic polymorphism were identified by polymerase chain reaction-based restriction fragment length polymorphism.

Histology, bacterial culture, ^{13}C-urea breath test and genotyping of *CYP2C19* and *IL-1β-511*

See supplementary methods.

H. pylori status and susceptibility testing

The initial *H. pylori* status was considered positive based on (1) positive bacterial cultures or (2) positive histological examination with confirmation by ^{13}C-UBT testing.[14] Four to eight weeks after treatment completion, *H. pylori* eradication was determined by ^{13}C-UBT. A result of ≥ 5 units was considered a positive breath test. The E-test (AB Biodisk, Solna, Sweden) was used to evaluate the resistance to antibiotics according to MIC (minimum inhibitory concentration) values of > 0.5, ≥ 1, ≥ 8, and > 1 mg/L for AMO, CLA, MTZ, and LEV, respectively.[14]

Statistical analysis

The sample size in the first-line therapy was designed based on the assumption that there were about 93% and 81% cure rates in HDDT and CLA-TT groups, respectively.[6,13] Accordingly, 140 to 150 patients were required for each group to give the study a power of at least 80% at 5% statistical significance level with about 10% drop-out rate. For the rescue therapy, based on an assumption of about 90% and 75% cure rates in HDDT and LEV-TT groups, respectively,[13,15] 100 patients were required for each group. However, the trial for rescue treatment was prematurely terminated with 56 patients in each group because the cure

rate in ST group was significantly worse than the expected outcome. Nevertheless, this patient number provided the rescue regimens a power of 85% at 5% significant level.

Categorical variables are described by percentages and continuous variables by mean with standard deviation. The eradication rates and the 95% confidence intervals (95% CI) were calculated by intention-to-treat (ITT) and per-protocol (PP) analyses. Differences in demographic information, eradication rates, and adverse events among different groups were determined by the χ^2 test or one-way ANOVA, followed by both multiple comparisons with Bonferroni correction and the Tukey's method for all-pairwise comparisons. Univariate analysis was performed using χ^2 test, two-sample *t*-test, one-way ANOVA, or simple logistic regression to explore significant predictive variables, which were listed in Table 1, followed by a multiple logistic regression analysis. A backward/forward strategy and the Wald statistic were used for model comparisons. The impacts of factors were described by odds ratios and 95% CI. Two-side P values less than 0.05 were considered statistically significant. The Mann-Whitney test was used to compare the distributions of MIC. The SPSS statistical software, version 17 was used for analyses.

Results

From Aug 2010 to Jul 2013, 1567 patients were assessed for eligibility and 450 and 168 patients were enrolled and randomly allocated to the first-line and rescue therapies, respectively. Five patients in the first-line groups (2, 2, and 1 patients in HDDT, ST, and CLA-TT groups, respectively) and 2 patients in the rescue ST group were excluded due to consent withdrawal, loss to follow-up, or poor adherence (Supplementary Figures 1A and B). A total of 617 *H. pylori* strains (99.8%) were successfully cultured. The demographic data, including gender, age, body mass index, life-style, peptic ulcer disease, bacterial density, *CYP2C19* and *IL-1β-511* genotypes, and antibiotic susceptibility were similar among patients in different groups of first-line and rescue therapies (Table 1).

For the first-line therapies, the ITT eradication rates were 95.3% (95% C.I. 91.9–98.8), 85.3% (79.6–91.1), and 80.7% (74.3–87.1) for HDDT, ST, and CLA-TT groups, respectively. For the rescue treatments, the ITT eradication rates were 89.3% (80.9–97.6), 51.8% (38.3–65.3), and 78.6% (67.5–89.7) for HDDT, ST, and LEV-TT groups, respectively (Table 2). These data indicate that the efficacy of HDDT was superior to the efficacy of ST or CLA-TT in treatment-naïve patients and of ST in treatment-experienced patients. HDDT also appeared to be more efficacious than LEV-TT. For both first-line and rescue treatments, the occurrence of overall adverse events and protocol adherence were similar when compared across all groups except bad taste which was observed more frequently in ST and CLA-TT groups than in HDDT group (Table 3).

For factors that influence treatment outcomes, antibiotic resistance was the most important determinant for treatment failure in both treatment-naïve group (Table 4) and treatment-experienced group (Table 5), based on univariate and multiple logistic regression analyses. Resistance to CLA significantly reduced the eradication rates in treatment-naïve ST (by 40%) and CLA-TT groups (by 74%). MTZ resistance significantly reduced the eradication rates in both treatment-naïve (by 20%) and treatment-experienced ST groups (by 53%).

CLA/MTZ dual resistance significantly reduced the *H. pylori* eradication rates in treatment-naïve patients receiving ST (by 65%) or CLA-TT (by 84%) and in treatment-experienced patients receiving ST (by 63%). The resistance to LEV or AMO significantly reduced the eradication rate in LEV-TT group (71% and 82% drop, respectively). In addition to antibiotic resistance, age and the presence of peptic ulcer significantly reduced the eradication rates of CLA-TT and LEV-TT, respectively. Moreover, the frequency of previous treatment failure significantly affected the eradication rate of all rescue regimens. However, CYP2C19 genotype of patients did not affect the treatment outcome of these groups. Other factors that did not have a significant impact on eradication rates were listed in Supplementary Table 1.

For the previous regimens patients received in treatment-experienced groups, CLA-TT (97.6%) was the most commonly prescribed first-line therapy. MTZ-TT and LEV-TT were chosen only after one and two treatment failures, respectively (Supplementary Figure 2). Among the 617 strains that were successfully cultured, the resistant rates of *H. pylori* to AMO, MTZ, CLA, CLA/MTZ dual, and LEV were 0.4%, 34.9%, 16.4%, 7.6%, and 16.2%, respectively, in the first-line treatment groups, and were 3%, 52.1%, 82%, 43.7%, and 21%, respectively, in the rescue treatment groups. It is worth noting that CLA and CLA/MTZ dual resistance significantly increased from the first-line treatment groups to the rescue treatment groups (Supplementary Table 2).

A comparison of the MIC distribution between these treatment-naïve patients and patients who had exposed only once to AMO, CLA, MTZ or LEV for anti-*H. pylori* therapies in these treatment-experienced groups revealed a dramatic shift towards increased resistance in CLA, MTZ, and LEV recipient but not in AMO recipient (Figure 1). The resistance rates changed from 16.4%, 34.9% and 16.2% in treatment-naïve groups to 82.3%, 90.9% and 75.0% in CLA-recipient, MTZ-recipient, and LEV-recipient, respectively.

Discussion

To our best knowledge, this is the first large-scale prospective, randomized trial comparing the efficacy of HDDT to that of the currently recommended treatment for first-line or rescue therapies for *H. pylori* infection. We also successfully cultured almost all strains (617/618) of enrolled patients, which provided adequate sample size to analyze the impact of resistance patterns. Our results showed that HDDT cured more than 95% of treatment-naïve patients and about 90% of treatment-experienced patients, and was superior to standard first-line or rescue therapies, irrespective of the CYP2C19 genotype and antibiotic resistance patterns.

Current guidelines recommend CLA-TT, ST and (bismuth or non-bismuth) quadruple therapies for first-line treatment of *H. pylori* infection.[2,16] However, the high reported resistance rates of CLA and MTZ significantly reduces the efficacy of these regimens.[5,6,17] To improve the treatment outcome, it is therefore important to use antibiotics, such as AMO, that have low resistance rates to *H. pylori*.[7,9,10] AMO is usually used twice daily to compromise with other concentration-dependent antibiotics (e.g., CLA, MTZ and LEV) in the anti-*H. pylori* therapies.[2] However, dual therapies given PPI and AMO twice daily did

not achieve satisfactory treatment outcomes.[18] Instead, its effectiveness can be improved by giving both drugs at higher doses/frequencies.[19] It was observed that the eradication rate was generally higher when dual therapy was given four times daily compared to three times daily.[16] This is because it is critical to maintain steady plasma concentration of AMO above the MIC with more frequent dosing for its bactericidal effect against *H. pylori*.[11,12] Furthermore, to optimize AMO therapeutic efficacy, it depends on an intragastric pH of 5.5 or higher, achievable by higher doses and frequency of PPIs,[13] and avoidance of acidic foods.[20] High-dose PPIs may also exert direct antimicrobial activities against *H. pylori*.[21] Although PPIs are metabolized by CYP2C19 which is an important factor for suboptimal-dose dual therapy,[22] a regimen of four times daily dosing maintained the intragastric pH at a value higher than 6.5 regardless of *CYP2C19* genotype.[23] This is consistent with our finding that HDDT was able to achieve high therapeutic efficacy in CYP2C19 extensive metabolizers (Tables 4 and 5) and can be corroborated by the finding of Furuta et al.,[24] showing the eradication rate of *H. pylori* were 100% in extensive metabolizers. Thus, an optimized high-dose PPI and AMO dual therapy is likely to be superior to suboptimally dosed dual therapy and has the selective advantage over standard CLA-, MTZ-, or LEV-containing therapies in most regions of the world reporting increasing *H. pylori* resistance to CLA, MTZ, and/or LEV.

The prevalence of primary resistance to AMO, MTZ, and CLA were about 2%, 44%, and 29%, respectively, in America; 0.7%, 35%, and 18%, respectively, in Europe; 2%, 38%, and 21%, respectively, in Asia.[16,25] In Europe, the *H. pylori* resistance to CLA has increased from 9.8% to 17.5% over the past 10 years and a rapid emergence of LEV resistance (to 14.1%) is noted.[25] Comparable to these reports from different geographic regions, our results showed that the primary resistance to AMO, MTZ, CLA, and LEV were 0.4%, 34.9%, 16.4%, and 16.2%, respectively. In this regard, the treatment outcome shown by the present study may be also applicable to other geographic areas. Our findings also showed that the application of CLA-TT resulted in a significant increase of not only CLA resistance but also CLA/MTZ dual resistance.

Among the factors reported to affect the treatment outcome of *H. pylori* infection, our results showed that antibiotic resistance is the major determinant of treatment failure against *H. pylori*. In our study, the medical history of previous *H. pylori* therapies for each patient was documented. We found a rapid acquisition of *H. pylori* antibiotic resistance to CLA, MTZ, or LEV, but not AMO (Figure 1). The possible explanation for the difference in acquired antibiotic resistance is that single point mutation can lead to resistance to CLA, MTZ and LEV, while multiple site mutations are required to induce AMO resistance.[26] In this regard, the application of therapies containing CLA, MTZ, or LEV should be cautious although the resistant rates of *H. pylori* to these antibiotics vary among geographic areas.[16] HDDT may prove to be the empiric therapy of choice irrespective of local antibiotic resistance pattern.

Although prior meta-analysis showed limited impact of CLA-resistance on therapeutic efficacy of ST,[27] leading to recommending ST as the alternative first-line treatment in high CLA resistance area,[5] we found that the eradication rate of first-line ST was only 29% in patients with CLA/MTZ dual resistance. Likewise, while the use of ST as the second-line

treatment has never been previously verified, we showed that the increase of dual resistant rate from 8% in treatment-naïve patients to 44% in treatment-experienced patients causing a decrease of eradication rate from 85% in naïve ST to 52% in rescue ST. These findings show the significant impact of CLA/MTZ dual resistance on the treatment outcome of ST, and indicate that first-line regimens should be carefully chosen as it may significantly impact the efficacy of available rescue therapy. In addition, patient education regarding close adherence to prescribed dose of treatment is imperative to avoid the development of multi-resistant *H. pylori* strains.

The strengths of this study include large sample size, parallel comparisons of first-line and rescue regimens, clear records of previous regimens for *H. pylori* therapies, high successful culture rate of *H. pylori* strains, and extensive analyses of factors that may influence the success of *H. pylori* eradication. However, some limitations exist. First, varying treatment durations were adopted in different groups. However, a recent meta-analysis study shows that the extending duration of CLA-TT from 7 days to 14 days would only slightly increase its efficacy (5%),[28] and would provide only marginal clinical benefit.[1,29] This may be related to the fact that the CLA-resistance cannot be overcome by increasing the dose and duration.[5,30] Likewise, there was no significant difference in the efficacy between 14-day and 10-day ST.[31,32] For LEV-TT, one meta-analysis showed the 10-day regimen was more effective than the 7-day regimen.[15] However, our study along with a recent report indicate that the resistance rate of LEV may have already been high, limiting its use in the front-line treatment.[5] Second, HDDT is a regimen with higher dosing frequency (4 times daily). Although the present study showed high adherence in the enrolled patients, this needs to be confirmed by studies conducted in different regions of the world.

In summary, this study demonstrated that HDDT consisting of high-dose PPI and AMO given four times daily was superior to standard first-line or rescue therapy for *H. pylori* infection, irrespective of *CYP2C19* genotype. We found *H. pylori* rapidly acquired antibiotic resistance to CLA, MTZ, and LEV but not to AMO following a single course of anti-*H. pylori* therapy containing the respective antibiotics. Under these circumstances, empiric treatment with optimized HDDT, especially in regions with high rates of antibiotic resistance or when antimicrobial susceptibility testing is not readily available, would potentially achieve higher eradication rates, curb the emergence of multi-antibiotic resistant *H. pylori* strains, and fills a gap in clinical management of patients failing multiple courses of anti-*H. pylori* therapy given the overall low rate of amoxicillin resistance worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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role in the study design, data collection, analysis, data interpretation, or writing of the manuscript. C-J Lin and H-L Wang contributed equally to this article. We acknowledge the contribution of the study patients, their families, and study-site personnel.

Abbreviations

AMO	amoxicillin
^{13}C-UBT	^{13}C-urea breath test
CLA-TT	clarithromycin-containing triple therapy
HDDT	high-dose dual therapy
ITT	intention-to-treat
LEV-TT	levofloxacin-containing triple therapy
MTZ	metronidazole
PP	per-protocol
PPI	proton pump inhibitor
ST	sequential therapy

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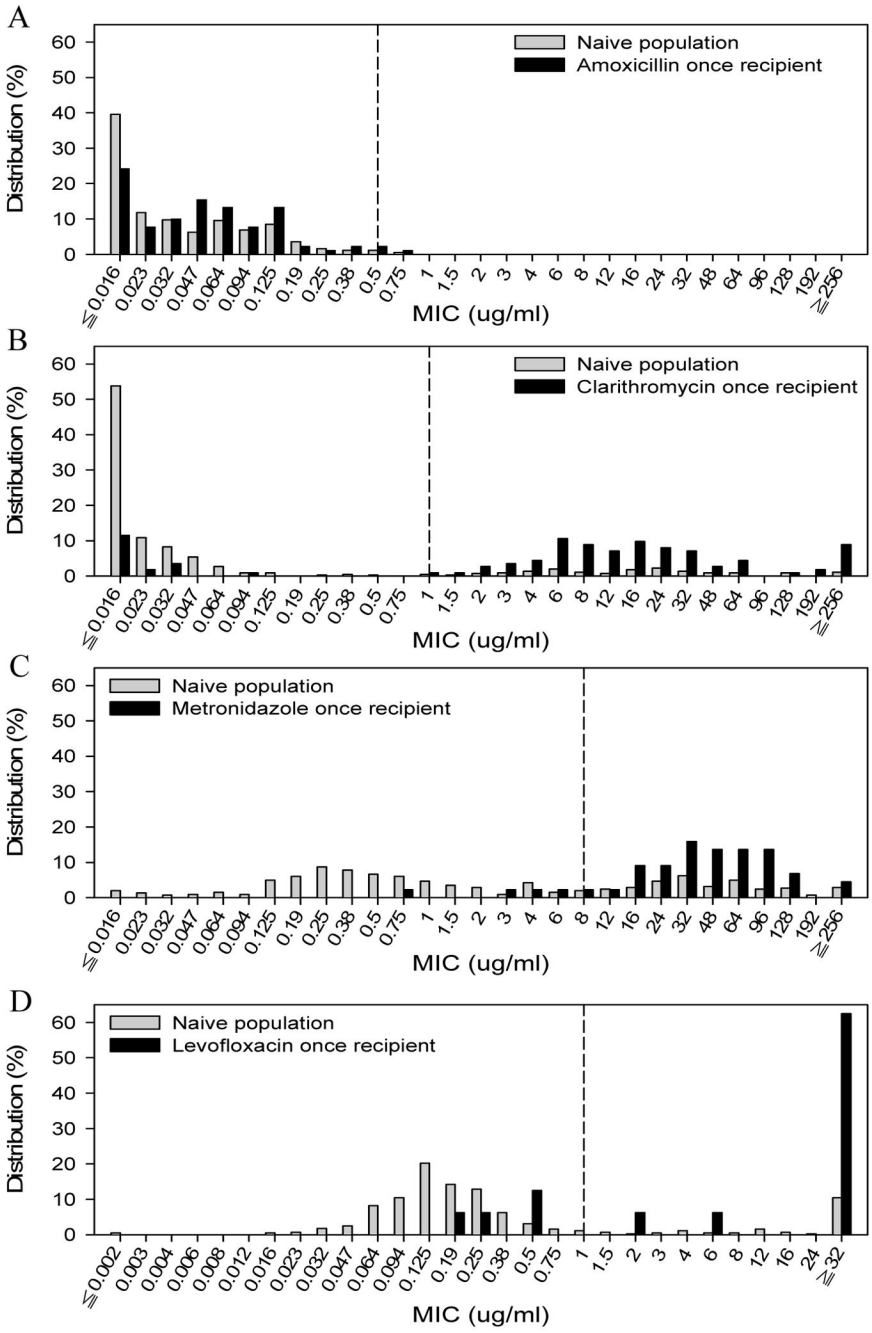

Figure 1. Distribution of MIC (minimum inhibitory concentrations) values of isolated *H. pylori* in response to (A) amoxicillin, (B) clarithromycin, (C) metronidazole, and (D) levofloxacin

H. pylori was isolated from patients enrolled for first-line therapies (naïve group) and, among rescue groups, patients who had previously received amoxicillin, clarithromycin, metronidazole or levofloxacin only once on anti-*H. pylori* therapies (antibiotic once recipient group). The breakpoint for resistance to each antibiotic was indicated by the vertical dash line.

Table 1

Demographics of patients receiving first-line and rescue regimens

First-line regimens	HDDT group	ST group	CLA-TT group	P-value
No. of patients	150	150	150	
Male	46.0 (69/150)	39.3 (59/150)	39.3 (59/150)	0.405
Age, years	53.4±10.4	53.4±13.0	54.3±12.3	0.798
BMI, kg/m^2	23.8±3.5	24.1±3.6	23.7±3.6	0.832
Life Style				
Regular Alcohol use	15.0 (22/147)	8.8 (13/148)	13.5 (20/148)	0.247
Smoking	25.9 (35/135)	22.7 (31/136)	25.9 (36/136)	0.984
Peptic ulcer disease	68.7 (103/150)	65.3 (98/150)	66.7 (100/150)	0.841
Bacterial density				
Mild	30.0 (45/150)	28.0 (42/150)	29.3 (44/150)	0.948
Moderate	32.7 (49/150)	34.0 (51/150)	40.7 (61/150)	0.317
Severe	37.3 (56/150)	38.0 (57/150)	30.0 (45/150)	0.285
CYP2C19 genotype				
EM	43.6 (65/150)	44.0 (66/150)	45.3 (68/150)	0.956
IM	43.6 (65/150)	42.7 (64/150)	42.0 (63/150)	0.993
PM	12.8 (19/150)	12.7 (19/150)	12.7 (19/150)	1.000
IL-1β-511 genotype				
C/C	28.7 (43/150)	25.3 (38/150)	24.0 (36/150)	0.665
C/T	52.0 (78/150)	54.0 (81/150)	63.3 (95/150)	0.112
T/T	18.7 (28/150)	20.0 (30/150)	12.7 (19/150)	0.204
Antibiotic sensitivity				
AMO-R	0.0 (0/150)	0.7 (1/150)	0.7 (1/150)	1.000
MTZ-R	34.7 (52/150)	36.7 (55/150)	33.3 (50/150)	0.844
CLA-R	15.3 (23/150)	16.7 (25/150)	17.3 (26/150)	0.924
CLA-S/MTZ-S	57.3 (86/150)	56.0 (84/150)	56.7 (85/150)	0.993
CLA-S/MTZ-R	27.3 (41/150)	27.3 (41/150)	26.0 (39/150)	0.972
CLA-R/MTZ-S	8.0 (12/150)	7.3 (11/150)	10.0 (15/150)	0.754
CLA-R/MTZ-R	7.3 (11/150)	9.3 (14/150)	7.3 (11/150)	0.841
LEV-R	16.0 (24/150)	16.7 (25/150)	16.0 (24/150)	1.000

Rescue regimens	HDDT group	ST group	LEV-TT group	P-value
No. of patients	56	56	56	
Male	41.1 (23/56)	37.5 (21/56)	37.5 (21/56)	0.940
Age, years	53.4±12.3	55.8±12.3	50.4±13.0	0.084
BMI, kg/m^2	24.2±3.4	23.7±4.5	23.9±4.0	0.850
Life Style				
Regular Alcohol use	14.3 (8/56)	10.9 (6/55)	10.7 (6/56)	0.871
Smoking	20.4 (11/54)	23.2 (13/56)	25.0 (14/56)	0.870
Peptic ulcer disease	57.1 (32/56)	66.1 (37/56)	66.1 (37/56)	0.567
Bacterial density				

Rescue regimens	HDDT group	ST group	LEV-TT group	P-value
Mild	44.6 (25/56)	41.1 (23/56)	41.1 (23/56)	0.942
Moderate	26.8 (15/56)	25.0 (14/56)	37.5 (21/56)	0.324
Severe	28.6 (16/56)	32.1 (18/56)	21.4 (12/56)	0.480
CYP2C19 genotype				
EM	46.4 (26/56)	41.1 (23/56)	44.6 (25/56)	0.888
IM	35.7 (20/56)	44.6 (25/56)	41.1 (23/56)	0.654
PM	17.9 (10/56)	14.3 (8/56)	14.3 (8/56)	0.895
IL-1β-511 genotype				
C/C	32.1 (18/56)	21.4 (12/56)	23.2 (13/56)	0.401
C/T	46.4 (26/56)	58.9 (33/56)	50.0 (28/56)	0.434
T/T	21.4 (12/56)	19.6 (11/56)	26.8 (15/56)	0.716
Antibiotic sensitivity				
AMO-R	3.6 (2/56)	1.8 (1/56)	3.6 (2/56)	1.000
MTZ-R	50.0 (28/56)	52.7 (29/56)	53.6 (30/56)	0.943
CLA-R	85.7 (48/56)	80.0 (44/56)	80.4 (45/56)	0.721
CLA-S/MTZ-S	7.1 (4/56)	9.1 (5/56)	12.5 (7/56)	0.647
CLA-S/MTZ-R	7.1 (4/56)	10.9 (6/56)	7.1 (4/56)	0.734
CLA-R/MTZ-S	42.9 (24/56)	38.2 (21/56)	33.9 (19/56)	0.634
CLA-R/MTZ-R	42.9 (24/56)	41.8 (23/56)	46.4 (26/56)	0.888
LEV-R	21.4 (12/56)	23.6 (13/56)	17.9 (10/56)	0.746
Treatment failure				
One failure	53.6 (30/56)	53.6 (30/56)	51.8 (29/56)	1.000
Two failure	30.4 (17/56)	32.1 (18/56)	30.4 (17/56)	1.000
Three failure	5.5 (3/56)	5.5 (3/56)	8.9 (5/56)	0.792
≥ four failure	10.7 (6/56)	8.9 (5/56)	8.9 (5/56)	1.000

Data are mean ± SD or % (n/N); HDDT: high-dose dual therapy; ST: sequential therapy; CLA-TT: clarithromycin-containing triple therapy; LEV-TT: levofloxacin-containing triple therapy; BMI: body mass index; AMO-R: amoxicillin resistant; CLA-S: clarithromycin susceptible; CLA-R: clarithromycin resistant; MTZ-S: metronidazole susceptible; MTZ-R: metronidazole resistant. LEV-R: levofloxacin resistant; EM: homozygous extensive metabolizer; IM: heterozygous extensive metabolizer; PM: poor metabolizer.

Table 2

Eradication rates by ITT analysis and PP analysis in the first-line and rescue regimens

First-line regimens	HDDT group	ST group	CLA-TT group	P-value
ITT analysis				
Eradication rate	95.3 (143/150)	85.3 (128/150)	80.7 (121/150)	<0.001
95% C.I.	91.9–98.8	79.6–91.1	74.3–87.1	
P-value*				
HDDT group	-	0.025	<0.001	
ST group	0.025	-	0.440	
CLA-TT group	<0.001	0.440	-	
PP analysis				
Eradication rate	96.6 (143/148)	86.5 (128/148)	81.2 (121/149)	<0.001
95% C.I.	93.7–99.6	80.9–92.1	74.9–87.6	
P-value*				
HDDT group	-	0.018	<0.001	
ST group	0.018	-	0.328	
CLA-TT group	<0.001	0.328	-	

Rescue regimens	HDDT group	ST group	LEV-TT group	P-value
ITT analysis				
Eradication rate	89.3 (50/56)	51.8 (29/56)	78.6 (44/56)	<0.001
95% C.I.	80.9–97.6	38.3–65.3	67.5–89.7	
P-value*				
HDDT group	-	<0.001	0.363	
ST group	<0.001	-	0.002	
LEV-TT group	0.366	0.002	-	
PP analysis				
Eradication rate	89.3 (50/56)	53.7 (29/54)	78.6 (44/56)	<0.001
95% C.I.	80.9–97.6	40.0–67.4	67.8–89.7	
P-value*				
HDDT group	-	<0.001	0.363	
ST group	<0.001	-	0.006	
LEV-TT group	0.363	0.006	-	

Data are % (n/N); HDDT: high-dose dual therapy; ST: sequential therapy; CLA-TT: clarithromycin-containing triple therapy; LEV-TT: levofloxacin-containing triple therapy; ITT: intention-to-treat; PP: per-protocol; C.I.: confidence interval.

* P values from pairwise comparison made by Tukey's all-pairwise test.

Table 3

Adverse events and protocol adherence in patients receiving first-line or rescue regimens

First-line regimens	HDDT group (N=148)	ST group (N=148)	CLA-TT group (N=149)	P-value
Adverse event				
No. of patients	23.0 (34/148)	33.2 (49/148)	26.8 (40/149)	0.149
Total No. of events	39	78	53	
Abdominal distress	4.7 (7/148)	6.1 (9/148)	3.4 (5/149)	0.503
Dysgeusia (bad taste)	0.7 (1/148)	10.8 (16/148)	10.1 (15/149)	0.001
Nausea	2.0 (3/148)	6.1 (9/148)	2.1 (4/149)	0.136
Diarrhea	4.7 (7/148)	8.8 (13/148)	8.1 (12/149)	0.351
Dizziness	7.4 (11/148)	10.8 (16/148)	4.7 (7/149)	0.145
Pruritus (itching)	2.7 (4/148)	2.0 (3/148)	2.0 (3/149)	0.927
Others	4.1 (6/148)	6.8 (10/148)	3.4 (5/149)	0.339
Adherence	95.3 (142/149)	98.0 (146/149)	98.7 (147/149)	0.258

Rescue regimens	HDDT group (N=56)	ST group (N=54)	LEV-TT group (N=56)	P-value
Adverse event				
No. of patients	28.6 (16/56)	35.2 (19/54)	32.1 (18/56)	0.798
Total No. of events	20	25	22	
Abdominal distress	1.8 (1/56)	9.3 (5/54)	5.4 (3/56)	0.197
Dysgeusia (bad taste)	1.8 (1/56)	7.4 (4/54)	1.8 (1/56)	0.205
Nausea	7.1 (4/56)	3.7 (2/54)	3.6 (2/56)	0.733
Diarrhea	8.9 (5/56)	11.1 (6/54)	8.9 (5/56)	0.896
Dizziness	5.4 (3/56)	3.7 (2/54)	5.4 (3/56)	1.000
Pruritus (itching)	5.4 (3/56)	1.9 (1/54)	1.8 (1/56)	0.621
Others	3.6 (2/56)	5.6 (3/54)	10.7 (6/56)	0.205
Adherence	96.4 (53/55)	96.3 (52/54)	100.0 (56/56)	0.397

Data are % (n/N). HDDT: high-dose dual therapy; ST: sequential therapy; CLA-TT: clarithromycin-containing triple therapy; LEV-TT: levofloxacin-containing triple therapy. Adherence: took at least 80% of drugs.

Table 4

Univariate and multiple logistic regression analyses of factors that may influence *H. pylori* eradication in patients receiving first-line regimens.

First-line regimens	HDDT group	ST group	CLA-TT group
Univariate analysis			
Amoxicillin Resistance			
Yes	-	100.0 (1/1)	0.0 (0/1)
No	95.3 (143/150)	85.2 (127/149)	81.2 (121/149)
P-value	-	1	0.193
Clarithromycin Resistance			
Yes	95.7 (22/23)	52.0 (13/25)	19.2 (5/26)
No	95.3 (121/127)	92.0 (115/125)	93.5 (116/124)
P-value	1	<0.001	<0.001
Metronidazole Resistance			
Yes	92.3 (48/52)	72.7 (40/55)	76.0 (38/50)
No	96.9 (95/98)	92.6 (88/95)	83.0 (83/100)
P-value	0.236	0.001	0.381
Clarithromycin and Metronidazole Resistance			
CLA-S/MTZ-S	97.7 (84/86)	94.0 (79/84)	92.9 (79/85)
CLA-S/MTZ-R	90.2 (37/41)	87.8 (36/41)	94.9 (37/39)
CLA-R/MTZ-S	91.7 (11/12)	81.8 (9/11)	26.7 (4/15)
CLA-R/MTZ-R	100.0 (11/11)	28.6 (4/14)	9.1 (1/11)
P-value	0.245	<0.001	<0.001
Levofloxacin Resistance			
Yes	95.8 (23/24)	72.0 (18/25)	66.7 (16/24)
No	95.2 (120/126)	88.0 (110/125)	83.3 (105/126)
P-value	1	0.059	0.087
CYP2C19 genotype			
EM	92.3 (60/65)	89.4 (59/66)	76.5 (52/68)
IM	96.9 (63/65)	87.5 (56/64)	85.7 (54/63)
PM	100.0 (19/19)	84.2 (16/19)	78.9 (15/19)
P-value	0.358	0.949	0.441
Age, years			
not eradicated	58.29 ± 8.361 (7)	57.09 ± 12.405 (22)	49.34 ± 12.941(29)
eradicated	53.17 ± 10.413 (143)	53.38 ± 13.09 (128)	55.53 ± 11.929 (121)
P-value	0.203	0.217	0.015
Multiple logistic regression			
Dual resistance		0.015(0.003–0.085)	
P-value		<0.001	
Clarithromycin resistance			0.008(0.002–0.039)
P-value			<0.001
Age, years			1.086(1.029–1.145)

First-line regimens	HDDT group	ST group	CLA-TT group
P-value			0.003

Data for univariate analysis are % (n/N) or mean ± S.D. (n) and data for multiple logistic regression are odds ratio (95% C.I.); HDDT: high-dose dual therapy; ST: sequential therapy; CLA-TT: clarithromycin-containing triple therapy; CLA: clarithromycin; MTZ: metronidazole; S: susceptible; R: resistant. Dual resistance: clarithromycin and metronidazole resistance; EM: homozygous extensive metabolizer; IM: heterozygous extensive metabolizer; PM: poor metabolizer.

Table 5

Univariate and multiple logistic regression analyses of factors that may influence *H. pylori* eradication in patients receiving rescue regimens.

Rescue regimens	HDDT group	ST group	LEV-TT group
Univariate analysis			
Amoxicillin Resistance			
Yes	50.0 (1/2)	0.0 (0/1)	0.0 (0/2)
No	90.7 (49/54)	53.7 (29/54)	81.5 (44/54)
P-value	0.205	0.473	0.043
Clarithromycin Resistance			
Yes	89.6 (43/48)	47.7 (21/44)	77.8 (35/45)
No	87.5 (7/8)	72.7 (8/11)	81.8 (9/11)
P-value	1	0.185	1
Metronidazole Resistance			
Yes	82.1 (23/28)	27.6 (8/29)	70.0 (21/30)
No	96.4 (27/28)	80.8 (21/26)	88.5 (23/26)
P-value	0.193	<0.001	0.114
Clarithromycin and Metronidazole Resistance			
CLA-S/MTZ-S	75.0 (3/4)	80.0 (4/5)	85.7 (6/7)
CLA-S/MTZ-R	100.0 (4/4)	66.7 (4/6)	75.0 (3/4)
CLA-R/MTZ-S	100.0 (24/24)	81.0 (17/21)	89.5 (17/19)
CLA-R/MTZ-R	79.2 (19/24)	17.4 (4/23)	69.2 (18/26)
P-value	0.133	<0.001	0.433
Levofloxacin Resistance			
Yes	83.3 (10/12)	38.5 (5/13)	20.0 (2/10)
No	90.9 (40/44)	57.1 (24/42)	91.3 (42/46)
P-value	0.599	0.343	<0.001
CYP2C19 genotype			
EM	84.6 (22/26)	34.8 (8/23)	76.0 (19/25)
IM	90.0 (18/20)	60.0 (15/25)	82.6 (19/23)
PM	100.0 (10/10)	75.0 (6/8)	75.0 (6/8)
P-value	0.393	0.084	0.910
Peptic ulcer disease			
Yes	90.6 (29/32)	45.9 (17/37)	89.2 (33/37)
No	87.5 (21/24)	63.2 (12/19)	57.9 (11/19)
P-value	1	0.267	0.014
Previous treatment failure			
not eradicated	3.500 ± 2.588 (6)	2.185 ± 1.178 (27)	3.000 ± 1.954 (12)
eradicated	1.640 ± 0.964 (50)	1.276 ± 0.455 (29)	1.546 ± 0.875 (44)
P-value	0.139	0.001	0.027
Multiple logistic regression			
Dual resistance		0.033(0.005–0.204)	

Rescue regimens	HDDT group	ST group	LEV-TT group
P-value		<0.001	
levofloxacin resistance			0.005(0.000–0.115)
P-value			0.001
Peptic ulcer disease			11.084(1.171–104.919)
P-value			0.036
Previous treatment failure	0.482(0.266–0.874)	0.158(0.029–0.852)	0.302(0.118–0.773)
P-value	0.016	0.032	0.013

Data for univariate analysis are % (n/N) or mean ± S.D. (n) and data for multiple logistic regression are odds ratio (95% C.I.); HDDT: high-dose dual therapy; ST: sequential therapy; LEV-TT: levofloxacin-containing triple therapy; CLA: clarithromycin; MTZ: metronidazole; S: susceptible; R: resistant. Dual resistance: clarithromycin and metronidazole resistance; EM: homozygous extensive metabolizer; IM: heterozygous extensive metabolizer; PM: poor metabolizer.