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TITLE: Reverse hybrid and concomitant therapies are equivalent in efficacy for the first-line treatment of *H. pylori* infection

ABSTRACT

Background: Concomitant therapy is a recommended first-line treatment for *H. pylori* infection in most national or international consensuses. Reverse hybrid therapy is a modified 14-day concomitant therapy without clarithromycin and metronidazole in the final 7 days.

Aim: To test whether 14-day reverse hybrid therapy is non-inferior to 14-day concomitant therapy in the first-line treatment of *H. pylori* infection.

Methods: *H. pylori*-infected adult patients were randomly assigned to receive either reverse hybrid therapy (dexlansoprazole 60 mg o.d. plus amoxicillin 1 g, b.d. for 14 days, and clarithromycin 500 mg plus metronidazole 500 mg b.d. for initial 7 days) or concomitant therapy (dexlansoprazole 60 mg once o.d. plus amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg b.d. for 14 days). *H. pylori* status was assessed 6 weeks after the end of treatment.

Results: *H. pylori*-infected participants (n = 248) were randomized to receive either 14-day reverse hybrid therapy (n = 124) or 14-day concomitant therapy (n = 124). Intention-to-treat analysis demonstrated that the two therapies had comparable eradication rate (95.2% *vs* 93.5%; 95% confidence interval, -4.0% ~ 7.4%; P = 0.582). However, reverse hybrid therapy had a much lower frequency of adverse events than concomitant therapy (20.2 % *vs.* 38.7%, P = 0.001). The two therapies exhibited comparable drug adherence (93.5% *vs* 87.9%, P = 0.125).

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Conclusions: 14-day reverse hybrid therapy and 14-day concomitant therapy are equivalent in efficacy for the first-line treatment of *H pylori* infection. However, reverse hybrid therapy has fewer adverse events compared to concomitant therapy.

INTRODUCTION

With the rising prevalence of antimicrobial resistance, the eradication rates of standard triple therapy for *Helicobacter pylori* (*H. pylori*) infection have declined to less than 80% in most countries.[1,2] Several strategies including bismuth-containing quadruple therapy and non-bismuth- containing quadruple therapy (i.e., sequential therapy, concomitant therapy and hybrid therapy) have been proposed to increase the eradication rates.[3-6]

Concomitant therapy is an effective regimen with proven success regardless of clarithromycin resistance in several studies.[7,8] It is a 4-drug regimen containing proton pump inhibitor (PPI), clarithromycin, amoxicillin and metronidazole, which are all given for the entire duration of therapy. A meta-analysis demonstrated that concomitant therapy is more effective than standard triple therapy.[9] We recently developed hybrid therapy consisting of a dual therapy with a PPI and amoxicillin for 7 days followed by a quadruple regimen with a PPI, amoxicillin, clarithromycin and metronidazole for 7 days.[10] A pilot study of hybrid therapy showed that it achieved an eradication rate of 97.4% by intention-to-treat (ITT) analysis and 99.1% by per-protocol (PP) analysis in Taiwan.[10] A subsequent randomized controlled trial from Iran, an area with high clarithromycin resistance, demonstrated that 14-day hybrid therapy achieved a higher eradication rate than 14-day standard triple therapy.[11] Several randomized controlled trials demonstrated that 14-day hybrid therapies were comparable or more effective than 10-day sequential therapies.[12-16] A recent large multicentre randomized controlled trial documented that 14-day hybrid and 14-day bismuth quadruple therapies had comparable efficacy in the treatment of

H. pylori infection, and both could cure more than 90% of patients with *H. pylori* infections in areas of moderate clarithromycin resistance (17%).[17] Currently, it is a recommended first-line treatment in the ACG guideline on the treatment of *H. pylori* infection.[18] Additionally, it is also a recommended first-line treatment option on the Bangkok Consensus Report on *H. pylori* management in ASEAN.[19] In the Taiwan *H. pylori* Consensus Report, it is the treatment of choice in areas with either high or low clarithromycin resistance.[20]

Nonetheless, hybrid therapy requires additional two antibiotics in the last 7 days of therapy, which may confuse patients and may dampen enthusiasm for its use in clinical practice. Reversing the sequence of drug administration (a quadruple regimen followed by a dual regimen) can simplify hybrid therapy so that it is not necessary for patients to take additional medications during the course of treatment. A pilot randomized trial demonstrated that 12-day reverse hybrid therapy was more effective than 12-day standard triple therapy in the first-line treatment of *H. pylori* infection.[21] A subsequent multicentre randomized controlled trial showed that 14-day reverse hybrid and bismuth quadruple therapies had comparable efficacy in the treatment of *H. pylori* infection, and both could cure more than 90% of patients with *H. pylori* infections in a population with a clarithromycin resistance rate of 14%.[22]

Basically, 14-day reverse hybrid therapy is a 14-day concomitant therapy without clarithromycin and metronidazole in the final 7 days. Current evidences showed that 7-day concomitant quadruple therapy achieves a high eradication rate for clarithromycin-sensitive strains.[7,8] It remains unclear whether extending the treatment durations of clarithromycin and metronidazole of concomitant therapy from 7 days to

14 days can improve the eradication rate for *H. pylori* strains with clarithromycin resistance or clarithromycin-metronidazol dual resistance. We therefore conducted the randomized controlled trial to prove our hypothesis that 14-day reverse hybrid therapy is non-inferior to 14-day concomitant therapy in the first-line treatment of *H. pylori* infection. Additionally, we also compared the side effect profiles of the two treatment strategies in this trial.

METHODS

Study population

For this randomized, open-label trial, non-inferiority phase 3 trial, we recruited *H. pylori*-infected adult patients (age > 20 years) who underwent an esophagogastroduodenoscopy for the investigation of gastrointestinal symptoms in the Kaohsiung Veterans General Hospital and Kaohsiung Medical University Hospital. *H. pylori* infection was documented by at least two positive results of rapid urease test, histology, urea breath test and culture. Additionally, individuals who underwent *H. pylori* screening with a positive result of both ^{13}C-urea breath test and *H. pylori* serological testing were also included for the study. Subjects with any of the following criteria were excluded from this trial: (a) previous eradication therapy, (b) allergy to any antibiotic of our study, (c) previous gastrectomy, (d) the coexistence of severe concomitant illness, (f) pregnancy or lactating women and (g) the use of antibiotics within the previous 4 weeks.[23]

Written informed consent was obtained for all patients before enrollment. This trial was approved by the Institutional Review Boards of the Kaohsiung Veterans

General Hospital and Kaohsiung Medical University Hospital. It is registered as a standard randomized Clinical Trial (ClinicalTrials.gov.identifier: NCT02646332). All authors had access to the study data and had approved the final manuscript.

Study Protocol

Randomization

Using a permuted block randomization with a block size of four, we randomly allocated eligible patients to receive one of the two regimens (1:1): 14-day reverse hybrid or 14-day concomitant therapy. An independent research assistant generated the computerized random number sequence. The sequence was concealed in an opaque envelope until the intervention was assigned. All clinical investigators were masked to the randomization sequence. After the written informed consents were obtained from eligible subjects, study nurses telephoned independent research assistant who then informed the patient's treatment allocation.

Procedures

The recruited patients received either a 14-day reverse hybrid therapy (dexlansoprazole MR [Dexilant delayed release®; Takeda, Osaka, Japan] 60 mg once daily plus amoxicillin 1 g twice daily for 14 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for initial 7 days) or a 14-day concomitant therapy (dexlansoprazole MR 60 mg once daily plus amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg twice daily for 14 days). All drugs were taken one hour before breakfast or dinner. Alcohol consumption during treatment was prohibited as it

may impact metronidazole-related side effects.

A complete medical history and demographic were obtained from each patient, including age, sex, medical history, history of smoking, alcohol, coffee and tea consumption at enrollment. Additionally, blood sampling for genotyping of *CYP2C19* and *IL-1β-511* was performed using the polymerase chain reaction-restriction fragment length polymorphism as previous description.[24,25] Genotypes of *CYP2C19* were classified into three groups: homogeneous extensive metabolizer (homEM; *CYP2C19**1/*CYP2C19**1); heterogeneous extensive metabolizer (hetEM; *CYP2C19**1/*CYP2C19**2 and *CYP2C19**1/*CYP2C19**3); poor metabolizer (PM; *CYP2C19**2/*CYP2C19**2, *CYP2C19**2/*CYP2C19**3, and *CYP2C19**3/*CYP2C19**3). *IL-1β-511* polymorphisms were classified as C/C, C/T, and T/T genotypes. The biopsy specimens were cultured on Brucella chocolate agar with 7% sheep blood and incubated for 7 days under microaerobic condition. The antibiotic susceptibility of *H. pylori* strains was determined by E-test (AB Biodisk, Solna, Sweden) in the central laboratory in the Kaohsiung Medical University Hospital. *H. pylori* strains with a minimal inhibitory concentration value >0.5 μg/mL, >1 μg/mL and >8 μg/mL were considered to be resistant to clarithromycin, amoxicillin and metronidazole, respectively.[22,25]

Drug adherence and adverse events were recorded at week 2 of therapy. All participants were informed of the common side effects of the study drugs before treatment and were asked to record these symptoms in the provided diaries. Participants with gastric ulcer on enrollment received a follow-up endoscopy with rapid urease test, histological examination and bacterial culture to assess ulcer healing

and post-treatment *H. pylori* status 6 weeks after the end of eradication therapy. The other subjects underwent a urea breath test to assess *H. pylori* eradication 6 weeks following therapy ending. *H. pylori* eradication was defined as (1) a negative result of urea breath test, or (2) negative results of all histology, rapid urease test and bacterial culture.[25,26] All participants were asked to discontinue PPI and histamine-2 blocker for at least 2 weeks before follow-up endoscopy and urea breath testing. ^{13}C-urea breath test was performed after an overnight fast using the Proto Pylori kit (Isodiagnostika, Montreal, Canada). The 75-mg ^{13}C-urea was dissolved in water. Baseline and 30 min breath samples were assayed with an infrared spectrometer that produced computer-generated results in the Kaohsiung Veterans General Hospital and Kaohsiung Medical University Hospital. Positive results were defined as a computer-generated $\delta^{13}CO_2$ value $\geq$ 4 units and negative results as < 2.5 units.[25] The subjects with inconclusive results underwent another ^{13}C-urea breath test at least 4 weeks later until the results became conclusive. The technicians carrying out urea breath test were blinded to the eradication regimens received by patients.

End points

The primary outcome was *H. pylori* eradication. The secondary outcomes were the frequencies of adverse events and drug adherence. Adverse events were prospectively assessed according to a 4-point scale system: none; mild (discomfort annoying but not interfering with daily life); moderate (discomfort sufficient to interfere with daily life); and severe (discomfort resulting in discontinuation of eradication therapy).[27] Drug adherence was checked by counting unused medication

at the completion of treatment. Poor adherence was defined as taking less than 80% of pills in the concomitant group. In the hybrid group, poor compliance was defined as taking less than 80% of pills in either initial 7 days or the last 7 days.[28]

Statistical analysis

Our study was designed as a non-inferiority trial. The hypothesis for sample size calculations was based on 94% reverse hybrid therapy eradication rate and 95% concomitant therapy eradication rate.[16,17,22,28] Δ(defining equivalent range or non-inferiority margin) of -10%, expected power of 90%, and α of 0.05 (one-sided). 110 patients per group (completers) were needed to show non-inferiority of the experimental therapy versus active control treatment. An estimated 10% of patients would not be included in the PP analysis because one or more major protocol deviations; therefore, at least 124 patients randomly assigned treatment per group were planned to protect the trial's power. Eradication rate was assessed was by ITT, modified ITT and PP. The ITT population included all randomized patients who receive at least one dose of study drugs. Patients whose infection status was unknown following treatment were considered treatment failures for the purposes of ITT analysis. Modified ITT included all those receiving at least one dose of drugs and completing post-treatment *H. pylori* testing. The PP analysis excludes the patients with unknown *H. pylori* status following therapy and those with poor drug adherence. The 95% confidence interval (CI) of the eradication rate of each therapy was calculated. The $\chi 2$ test or Fisher's exact test was used to analyze categorical data. Student's *t* test was used to analyze continuous variables and give results as mean ±

standard deviation (SD). A *P* value less than 0.05 was considered statistically significant. Statistic Package for the Social Science (SPSS) (version 12.0 for Microsoft Windows) was used for all statistical analyses.

RESULTS

Characteristics of the study groups

From July 2016 to August 2108, 1091 patients were screened for eligibility. Among them, 248 *H. pylori*-infected patients were eligible and randomly allocated to receive either reverse hybrid (*n* = 124) or concomitant (*n* = 124) therapy (**Figure 1**). Data regarding the clinical characteristics of patients upon entry are summarized in **Table 1**. The two groups had comparable age, gender, history of smoking, alcohol drinking, coffee and tea consumption, presence of peptic ulcers, and *CYP2C19* and *IL-1β-511* genotypes. The two study groups also had a similar prevalence of antibiotic resistant strains (**Table 1**). Among the subjects, 8 patients in the reverse hybrid group and 18 in the concomitant group were excluded from PP analysis due to incomplete follow-up or poor adherence (**Figure 1**).

Eradication of H. pylori

Table 2 lists the eradication rates of the two therapies. ITT analysis showed that the eradication rates were 95.2% (95% CI, 91.4% ~ 99.0%) for reverse hybrid therapy and 93.5% (95% CI, 89.2% ~ 97.8%) for concomitant therapy. We recorded no statistically significant differences in treatment efficacy between the two therapies (difference, 1.7%; 95% CI, -4.0% ~ 7.4%; *P* = 0.582). Modified ITT (95.2% *vs* 95.0%)

and PP analyses (95.7% *vs* 93.6%) yielded similar results (P = 0.965 and 0.481, respectively). Among the subjects with drug susceptibility data, the eradication rates of hybrid therapy for *H. pylori* strains with non-resistance, single clarithromycin resistance, single metronidazole resistance and dual resistances were 100% (20/20), 100% (4/4), 100% (9/9), and 100% (1/1), respectively. In the concomitant therapy group, the eradication rates for *H. pylori* strains with non-resistance, single clarithromycin resistance, single metronidazole resistance and dual resistances were 100% (18/18), 80% (4/5), 100% (12/12), and 100% (4/4), respectively. No differences in eradication rates between reverse hybrid therapy and concomitant therapy existed in the four subgroups of *H. pylori* strains.

Adverse events and adherences

All the patients were included in the ITT analysis for adverse events and drug adherences. The frequencies of adverse events in the participants receiving 14-day reverse hybrid and 14-day concomitant therapies were 20.2% (95% CI, 14.9% ~ 27.3%) and 38.7% (95% CI, 30.1% ~ 47.3%), respectively. The former had fewer adverse events than the latter (difference, 16.7%; 95% CI, -27.8% ~ -5.6%; P = 0.001). **Table 3** lists the profiles of adverse events of 14-day reverse hybrid and 14-day concomitant therapies. The reverse hybrid group had lower frequencies of abdominal pain (4.0% *vs* 18.5%) and taste perversion (2.4% *vs* 11.3%) than the concomitant group (P < 0.001 and = 0.010, respectively). In the reverse hybrid group, eight patients discontinued treatment owing to adverse events (diarrhea: three patients; nausea: one patient; abdominal pain: one patient; headache: one patient; fever: one

patient; skin rash: one patient). Fifteen patients in the concomitant group stopped the anti-*H. pylori* medication because of adverse events (diarrhea: three patients; nausea: one patient; abdominal pain: four patients; taste perversion: one patient; cold sweating: one patient; skin rash: five patients). The two treatment groups displayed similar adherence (93.5% *vs* 87.9% (difference 5.6%; 95% CI: -1.6% ~ 12.7%; *P* = 0.125).

Factors affecting the efficacy of anti-*H. pylori* therapy

Table 4 lists the factors affecting the eradication rates of anti-*H. pylori* therapies. In the 14-day reverse hybrid group, there were no clinical, genetic or bacterial factors significantly related to eradication efficacy. In the concomitant group, all factors including *CYP2C19* genotype, *IL-1β-511* genotype, smoking, alcohol drinking, drug adherence and antibiotic resistance also did not affect eradication efficacy (**Table 4**).

DISCUSSION

In the current study, we conducted the first, head-to-head, randomized, controlled trial to compare the efficacies of 14-day reverse hybrid and 14-day concomitant therapies for the first-line treatment of *H. pylori* infection. The results demonstrated several novel findings. First, the two therapies were equivalent in efficacy, curing most *H. pylori*-infected patients in an area of moderate clarithromycin resistance (19.2%). Second, 14-day reverse hybrid therapy exhibited a lower frequency of adverse events than 14-day concomitant therapy (20.2% *vs* 38.7%; *P* = 0.001). Third, the two therapies had comparable drug adherence (93.5% *vs* 87.9%; *P* = 0.125).

Recent studies showed that 7-day concomitant quadruple therapy achieved a high

eradication rate for *H. pylori* strains with non-resistance, single clarithromycin resistance or single metronidazole resistance), but had a low eradication efficacy for clarithromycin-metronidazol dual resistance (50%).[8,9,29] Theoretically, it is ineffective to extend the duration of clarithromycin or metronidazole to 14 days to improve eradication efficacy of concomitant regimen for clarithromycin-metronidazole dual resistant strains. Therefore, 14-day reverse hybrid therapy applies amoxicillin, clarithromycin and metronidazole in the initial 7 days of the regimen and only contains amoxicillin in the final 7 days of treatment. The current study proved our hypothesis that 14-day reverse hybrid and 14-day concomitant therapies have comparable eradication efficacy in the first-line treatment of *H. pylori* infection.

Antibiotic resistance is the key factor in predicting eradication outcome of anti-*H. pylori* therapy with standard triple therapy and sequential therapy.[30-32] In this study, antibiotic susceptibility data were only available in 73 *H. pylori* stains. Nonetheless, one of our previous studies provided large data assessing the impacts of antibiotic resistances on the eradication rates of 14-day reverse hybrid therapy (n = 107). According to the combination data of the two studies, the eradication rates of reverse hybrid therapy for *H. pylori* strains with non-resistance, single clarithromycin resistance, single metronidazole resistance and dual resistances were 98.8% (85/86), 92.9% (14/15), 100% (33/33), and 85.7% (6/7), respectively. The results indicated that 14-day reverse hybrid therapy also can be recommended in areas with high clarithromycin or metronidazole resistance.

An ideal treatment for *H. pylori* infection should be highly effective, well tolerated, simple and inexpensive. 14-day revere hybrid therapy is a simplified hybrid

therapy with a quadruple regimen in initial 7 days followed by a dual regimen in final 7 days. The altered drug sequence of reverse hybrid regimen renders the treatment simpler to standard hybrid therapy. A recent study showed that reverse hybrid therapy achieved a similar eradication rate as hybrid therapy for *H pylori* infection.[32] While both reverse hybrid therapy and concomitant therapy were simple to administer, reverse hybrid therapy has lower frequencies of abdominal pain and taste perversion than concomitant therapy, probably due to different durations of clarithromycin and metronidazole exposure. With regard to the cost of therapies, 14-day reverse hybrid therapy was less expensive than 14-day concomitant therapy (US Dollars: 31.9 *vs* 45.2; Euros: 28.9 *vs* 41.6). The data suggest that 14-day reverse hybrid therapy is more cost-effective than 14-day concomitant therapy in the first-line treatment of *H. pylori* infection.

Because false-negative results can occur in patients taking antibiotics and PPI, we performed post-treatment evaluation for *H. pylori* status 6 weeks after the end of eradication therapy in the current study. This study has some limitations. First, current work was not a double-blind placebo-controlled trial in which the selection bias would be minimized. However, the application of rapid urease test, histology, culture and ^{13}C-urea breath test to assess the primary outcome was objective, and the staffs who performed the tests were blind to the treatment groups. Second, the number of *H pylori* strains with antibiotic susceptibility data in the reverse hybrid and concomitant groups were too small to make a robust conclusion for the impacts of antibiotic resistances on the eradication rates of each therapy. Nonetheless, this study is the first trial comparing reverse hybrid therapy and concomitant therapy in the treatment of *H.*

pylori infection.

In conclusion, 14-day reverse hybrid therapy has comparable eradication efficacy as 14-day concomitant therapy in the first-line treatment of *H. pylori* infection. The former has fewer adverse events and is cheaper than the latter.

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Table 1. Demographic data and antibiotic resistance of 14-day reverse hybrid and 14-day concomitant therapies

Characteristics	Reverse hybrid Therapy (n = 124)	Concomitant therapy (n = 124)	*P* value
Age (yr) (mean ± SD)	56.1±12.3	54.7 ±11.2	0.368
Gender (male / female)	58/66	60/64	0.799
Smoking	18 (14.5%)	26 (21.0%)	0.184
Alcohol consumption	7 (5.6%)	5 (4.0%)	0.554
Ingestion of coffee	29 (23.4%)	35 (28.2%)	0.384
Ingestion of tea	32 (25.8%)	33 (26.6%)	0.885
Peptic ulcer disease	62 (50.0%)	56 (45.2%)	0.446
CYP2C19 genotype			0.753
Homo EM	40/111 (36.0%)	36/115 (31.3%)	
Het EM	43/111 (38.7%)	48/115 (41.7%)	
PM	28/111 (25.2%)	31/115 (27.0%)	
IL1-β genotype			0.570
CC	33/111 (29.7%)	33/115 (28.7%)	
CT	51/111 (45.9%)	47/115 (40.0%)	
TT	27/111 (24.3%)	35/115 (30.0%)	
Prevalence of antibiotic resistance			
Clarithromycin resistance	5/34 (14.7%)	9/39 (23.1%)	0.365

Metronidazole resistance	10/34 (29.4%)	16/39 (41.0%)	0.301
Amoxicillin resistance	0/34 (0%)	0/39 (0%)	—

Table 2. The major outcomes of 14-day reverse hybrid and 14-day concomitant therapies

Eradication rate	Reverse hybrid Therapy (n = 124)	Concomitant therapy (n = 124)	*P* value
Intention-to-treat analysis	95.2% (118/124) (91.4% - 99.0%)*	93.5% (116/124) (89.2% - 97.8%)	0.582
Modified intention-to-treat analysis	95.2% (118/124) (91.4% - 99.0%)*	95.0% (115/121) (91.1% - 98.9%)	0.965
Per-protocol analysis	95.7% (111/116) (92.0% - 99.4%)	93.6% (102/109) (89.0% - 98.2%)	0.481

* 95% confidence interval

Table 3. Adverse events of 14-day reverse hybrid and 14-day concomitant therapies

Adverse Events	Reverse hybrid Therapy (*n* = 124)	Concomitant therapy (*n* = 124)	*P* value
Any adverse events	25 (20.2%)	48 (38.7%)	0.001*
Abdominal pain	5 (4.0%)	23 (18.5%)	< 0.001*
Constipation	0 (%)	0 (0%)	—
Diarrhea	6 (4.8%)	6 (4.8%)	0.989
Dizziness	2 (1.6%)	5 (4.0%)	0.446
Taste perversion	3 (2.4%)	14 (11.3%)	0.010*
Headache	1 (0.8%)	1 (0.8%)	1.000
Nausea	11 (8.9%)	13 (10.5%)	0.668
Vomiting	1 (0.8%)	1 (0.8%)	1.000
Skin rash	3 (2.4%)	6 (4.8%)	0.500

Fatigue	2 (1.6%)	5 (4.0%)	0.446
Others	3 (2.4%)	9 (7.3%)	0.136
Discontinued drugs because of adverse events	8 (6.5%)	15 (12.1%)	0.214
Adherence	116 (93.5%)	109 (87.9%)	0.125

Table 4. Factors affecting modified intention-to-treat eradication rates of 14-day reverse hybrid therapy and 14-day concomitant therapies

Variables	Reverse hybrid Therapy	Concomitant Therapy
Cyp2C19 genotype		
HomoEM	40/40 (100%)	33/36 (91.7%)
HetEM	41/43 (95.3%)	45/48 (93.8%)
PM	27/28 (96.4%)	30/31 (96.8%)
P value	0.404	0.683
IL1-β-511 genotype		
CC	33/33 (100%)	30/33 (90.9%)
CT	50/51 (98.0%)	44/47 (93.6%)
TT	25/27 (92.6%)	34/35 (100%)
P value	0.192	0.226
Smoking		
Yes	16/18 (88.9%)	24/26 (92.3%)
No	102/106 (96.2%)	92/98 (93.9%)
P value	0.209	0.673
Compliance		
Good	111/116 (95.7%)	102/109 (93.6%)

Poor	7/8 (87.5%)	14/15 (93.3%)
P value	0.336	1.000
Clarithromycin resistance		
No	29/29(100%)	30/30(100%)
Yes	5/5(100%)	8/9(88.9%)
P value	—	0.231
Metronidazole resistance		
No	24/24(100%)	22/23(95.7%)
Yes	10/10(100%)	16/16(100%)
P value	—	1.000
Amoxicillin resistance		
No	34/34 (100.0%)	38/39 (97.4%)
Yes	—	—
P value	—	—

Figure legend

Figure 1. Disposition of patients.