Two Different 1-Week Quadruple Therapies Given Back-to-Back Consecutive Therapy for Difficult-to-Treat Helicobacter pylori Infection: A Pilot Study

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INTRODUCTION: We aim to evaluate the efficacy of 2 different 1-week quadruple therapies given back-to-back consecutive therapy in patients with difficult-to-treat Helicobacter pylori infection.

METHODS: Patients with proven H. pylori infection were recruited after >3 failed standard quadruple eradication. They received consecutive therapy consisting of esomeprazole 40 mg or rabeprazole 20 mg twice daily, amoxicillin 1,000 mg twice daily, tetracycline 500 mg 4 times daily, and furazolidone 100 mg 3 times daily for the first 7 days, followed by colloidal bismuth pectin 200 mg twice daily in place of furazolidone 100 mg for another 7 days. Eradication rates, treatment-emergent adverse events (TEAEs), and compliance were assessed.

RESULTS: Sixty-five patients were enrolled. The mean number of previous eradication was 3.6 (range: 3–7). The intention-to-treat and per-protocol eradication rates were 90.8% (59/65) and 95.1% (58/61). In total, 23.4% (15/64) of patients experienced drug-related TEAEs. No serious adverse events were observed. None of the patients required treatment for TEAEs, and 95.3% (61/64) showed good compliance. Overall, 51 patients (78.5%) were with the available antimicrobial susceptibility testing results. The resistance rates to clarithromycin, metronidazole, levofloxacin, and amoxicillin were 60.8% (31/51), 100% (51/51), 70.6% (36/51), and 2.0% (1/51), respectively. No resistance was detected to either furazolidone or tetracycline. However, in 54.9% of patients (28/51), H. pylori was resistant to 3 antibiotics (metronidazole, levofloxacin, and clarithromycin).

DISCUSSION: Consecutive therapy, including amoxicillin, tetracycline, and furazolidone, achieved a good eradication rate (>90%), with desirable compliance and tolerability in difficult-to-treat H. pylori infection.

INTRODUCTION

The global prevalence of Helicobacter pylori is approximately 40% (1). As a common pathogen leading to various gastrointestinal diseases, H. pylori eradication alleviates gastric atrophy and prevents metachronous gastric cancer (2–5). However, with increasing antibiotic resistance, H. pylori eradication has become a therapeutic challenge (6,7).

Currently, 14-day bismuth-containing quadruple therapies (BQTs) are recommended as the first-line therapeutic regimen in areas where antibiotic resistance is high (8–10). After BQT failure, fewer options of subsequent rescue regimens are available. Currently, traditional treatment regimens fail to achieve satisfactory cure rates (11). The posttreatment resistance rates of H. pylori to clarithromycin (58.3%), metronidazole (99.2%), and levofloxacin (52.3%) have increased significantly in China (12), reducing the efficacy of all non-BQTs. For this reason, in a certain proportion of patients, the infection cannot be eliminated after multiple rounds of treatment, and they are often left untreated because there are no other conventional options (13).

In clinical trials involving patients with refractory H. pylori infection, antimicrobial susceptibility-guided therapies failed to achieve satisfactory efficacies. We conducted a randomized controlled trial (RCT) for the second-line or third-line therapy of H. pylori to compare the efficacy of antimicrobial susceptibility-
guided with empirical BQTs. The eradication rates in both groups were <80% in intention-to-treat (ITT) analysis (14). However, antimicrobial susceptibility testing is time-consuming, expensive, and has certain technical prerequisites.

A novel rescue regimen is urgently required to solve this therapeutic dilemma in China. The aim of this pilot study was to evaluate the efficacy and tolerability of 2 different 1-week quadruple therapies given back-to-back consecutive therapy in Chinese patients with difficult-to-treat H. pylori infection.

METHODS

Study design and participants

This pilot study was approved by the Ethics Committee of Qilu Hospital of Shandong University (number 2019186), and the Declaration of Helsinki was followed. All patients provided written informed consent before recruitment (Clinical Trials.gov, number NCT03658733).

Consecutive patients aged 18–70 years were eligible for this study if they were confirmed to have persistent H. pylori infection and had failed >3 rounds of standard quadruple regimens in previous eradication attempts. Before enrollment, H. pylori infection was diagnosed using at least 2 of the following tests: 13C-urea breath test (13C-UBT), histology, and rapid urease test. Exclusion criteria were as follows: (i) history of gastrectomy, acute gastrointestinal bleeding, or gastric malignancy; (ii) unclear previous eradication regimens; (iii) contraindication or allergy to any study drugs administered in the regimens; (iv) pregnancy or lactation; (v) severe concurrent diseases; (vi) alcohol abuse or drug addiction; (vii) use of proton pump inhibitors (PPIs), histamine-2 receptor antagonists, bismuth-containing drugs, or antibiotics in the preceding 4 weeks; (viii) unwillingness or intolerance to gastroscopy or H. pylori culture; (ix) compliance of <90% during any previous eradication; and (x) inability to sign informed consent.

Procedures

Patient demographics, characteristics, and previous eradication regimens were recorded at entry. Previous antibiotic use was defined as the continuous use of antibiotics whether oral or intravenous for >14 days for any reason besides H. pylori eradication. In addition, physical examinations, vital signs, hematology, serum chemistry, and electrocardiography were performed before gastroscopy. All patients underwent gastroscopy, H. pylori culture, and antimicrobial susceptibility testing before treatment.

H. pylori culture and antimicrobial susceptibility testing

At gastroscopy, 2 biopsy specimens were obtained from antrum and corpus for H. pylori culture. The specimens were maintained at −80 °C in brain-heart infusion broth (Oxoid, Basingstoke, UK) and then immediately sent to Zhiyuan Medical Inspection Institute (Hangzhou, Zhejiang, China). Specimens were fully ground and then cultured on brain-heart infusion agar medium (Oxoid, Basingstoke, UK) with 5% sheep blood at 37 °C under microaerophilic conditions (85% N2, 10% CO2, 5% O2) for 3–7 days. The H. pylori colonies were identified by Gram-negative staining and positivity for urease, cytochrome oxidase, and catalase activity.

Susceptibility to commonly used antibiotics against H. pylori was evaluated using the standard agar plate dilution method. After 72 hours of cultivation at 37 °C under microaerophilic conditions, the minimal inhibitory concentration was determined based on the lowest antibiotic concentration that inhibited visible bacterial growth. The reference strain ATCC43504 (NCTC11637) was included as a quality control. The minimal inhibitory concentrations of clarithromycin (1 μg/mL), metronidazole (8 μg/mL), amoxicillin (1 μg/mL), levofloxacin (1 μg/mL), furazolidone (1 μg/mL), and tetracycline (1 μg/mL) were in accordance with the criteria of the US Clinical and Laboratory Standards Institute.

Eradication therapy and follow-up

Patients were randomly assigned to receive either esomeprazole or rabeprazole in a ratio of 1:1 according to a predetermined random number sequence generated by a computer. All patients were administered consecutive therapy containing esomeprazole 40 mg/rabeprazole 20 mg, amoxicillin 1,000 mg, furazolidone 100 mg, and tetracycline 500 mg for the first 7 days, followed by colloidal bismuth pectin 200 mg in place of furazolidone for another 7 days. PPIs and colloidal bismuth pectin were administrated 30 minutes before breakfast and dinner; amoxicillin was administrated 30 minutes after breakfast and dinner; tetracycline was given 4 times daily (30 minutes after breakfast/lunch/dinner and before bed); and furazolidone 3 times daily (30 minutes after breakfast/lunch/dinner).

Before treatment, patients received both oral and written medical instructions, including detailed therapy regimens, possible treatment-emergent adverse events (TEAEs), and the importance of rational medication use. Patients who experienced discomforts were instructed to contact the investigators immediately. All patients were asked to return within 3 days of the end of treatment. Adherence and adverse symptoms were evaluated using their medication diaries and laboratory tests.

Outcomes

Eight weeks after completion of the regimen, H. pylori infection status was evaluated using 13C-UBT, whereas of histamine-2 blocker, PPIs, antimicrobials, and bismuth-containing drugs for at least 4 weeks. Successful H. pylori eradication was defined as a negative 13C-UBT result with a delta-over-baseline value of <0.4%. The primary endpoint was the H. pylori cure rate. The secondary outcomes were the rates of drug-related TEAEs, compliance, and resistance to antibiotics. Physical examinations, vital signs, hematology, and serum chemistry were performed after the treatment. TEAEs and concomitant medications were observed synchronously during therapeutic sessions. All TEAEs were coded and categorized (MedDRA v.19.0) for system organ class and preferred term among patients who received a minimum of 1 dose of the study drug. The relationships of the TEAEs to the study drugs were also recorded, as were their severity and the necessity of early treatment discontinuation. Low compliance was identified when <90% of the pills had been taken.

Statistical analysis

We assumed that the eradication rate of consecutive therapy was 88% (15). Given a 95% confidence interval of 79.8%–96.2%, a sample size of 61 patients was required. Assuming that 5% would be lost to follow-up, a minimum of 65 patients was required. Continuous variables were described as mean ± SD, and percentages were calculated for categorical variables. The H. pylori eradication rates were calculated on an ITT basis and a per-protocol (PP) basis. All eligible patients were included in the ITT analysis. All protocol violators, for whom a posttreatment 13C-UBT was unavailable, were excluded from PP analysis, as were those with low compliance. Data were analyzed using R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).
This pilot study was approved by the Ethics Committee of Qilu Hospital of Shandong University (number 2019186).

RESULTS

Patients

The study flow is shown in Figure 1. From December 2018 to August 2020, 102 patients were screened for eligibility. Of these, 65 met the selection criteria and received consecutive treatments at Qilu Hospital of Shandong University. The demographic and clinical characteristics of the study population in the ITT analysis are listed in Table 1. On average, patients had undergone 3.6 previous H. pylori treatment courses (range 3–7). Among their medication histories, multiple antibiotics had previously been administered, including clarithromycin, amoxicillin, metronidazole, and levofloxacin. In total, 87.7% of the enrolled patients reported a previous history of furazolidone medication and 43.1% had a history of tetracycline medication. One patient withdrew from this study, and 2 patients discontinued treatment. One patient with poor compliance was excluded from PP analysis, despite a negative follow-up 13C-UBT.

Eradication rates

Successful H. pylori eradication was confirmed in 59 patients. The overall eradication rates of consecutive therapy using ITT and PP analyses were 90.8% (59/65) and 95.1% (58/61), respectively. The eradication rates of esomeprazole-based and rabeprazole-based regimens were 90.6% (29/32) and 90.9% (30/33), respectively, using ITT analysis and 96.7% (29/30) and 93.6% (29/31) using PP analysis. The eradication rate was 92.2% (47/51) in H. pylori-isolated participants. The eradication rates based on the number of previous failed regimens are listed in Table 2. Notably, H. pylori strains from 28 patients were resistant to at least 3 commonly used antibiotics, and 92.9% of these patients achieved successful eradication. The eradication rates were similar between the fourth- and fifth-line attempts, and they were not decreased when the regimen was prescribed after 5 or more eradication failures.

Adverse effects and compliance

In the safety analysis, the incidence of TEAEs was 39.1% (25/64), with 35.9% of patients (23/64) reporting only mild TEAEs and 3.1% (2/64) reporting TEAEs of moderate severity. No serious adverse events (SAEs) were observed. None of the patients received drug or nonpharmaceutical treatment for TEAEs. Two patients experienced TEAEs that led to study drug discontinuation, and they refused to undergo follow-up UBT; 1 patient had drug-related headache, dizziness, nausea, and vomiting on the ninth day of medications. The others reported headache, arthralgia, pyrexia, abdominal pain, nausea, and vomiting on day 2 after eating expired food and then was diagnosed with acute gastroenteritis by investigators, which was unrelated to the eradication therapy.

Overall, 23.4% (15/64) of patients reported drug-related TEAEs judged by investigators as having a reasonable suspected causal relationship to the study drug. Gastrointestinal disorders (nausea and abdominal pain) were the most common drug-related SOCs with an incidence of 14.1% (9/64). The incidences of drug-related TEAEs for the first week (furazolidone-based) and second week (bismuth-based) quadruple therapy were 15.6% (10/64) and 10.9% (7/64), respectively. All drug-related symptoms resolved spontaneously after treatment completion or premature drug cessation.

Regarding laboratory abnormalities, 2 patients showed mild liver function abnormality, which was caused by nonalcoholic fatty liver disease in 1 patient. A 46-year-old man had mild leukopenia (white cell count 2.1 × 10^9/L and neutrophils 1.3 × 10^9/L), which was considered to be related to esomeprazole. All TEAEs disappeared at the posttreatment week 4 visit, and no drug intervention was conducted. No clinically relevant changes were observed in electrocardiogram or vital signs.

Patients with good compliance accounted for 95.3% (61/64). An overview of TEAEs and compliance with consecutive therapy is listed in Table 3.

Susceptibility results

Overall, H. pylori were successfully isolated in 78.5% (51/65) of the patients. The resistance rates of H. pylori isolates toward clarithromycin, metronidazole, levofloxacin, and amoxicillin were 60.8% (31/51), 100% (51/51), 70.6% (36/51), and 2.0% (1/51), respectively. No resistance was detected to furazolidone or tetracycline (Table 1). The overall triple drug resistance rate (clarithromycin, metronidazole, and levofloxacin) was 54.9% (28/51) and further increased to 71.4% (5/7) among patients with 5 previous therapy failures.

DISCUSSION

Failure to cure H. pylori infection presents a difficult clinical therapeutic problem, especially in patients with precancerous lesions who have experienced several failed attempts with combined common antibiotics. In this pilot study, consecutive eradication therapy containing 3 antibiotics known to have the highest resistance barrier was developed to treat those who had experienced >3 previous eradication failures; the results showed that the regimen achieved good therapeutic efficacy (95.1% by PP and 90.8% by ITT), it was tolerable by most patients, and compliance was good in China. The incidence of drug-related TEAEs was similar to that of previously reported TEAEs (15,16).

Factors that may cause treatment failure include presence of multiple antibiotic resistance, inadequate suppression of gastric
acid secretion, poor compliance, and inadequate therapy duration. The enrolled patients had already failed multiple quadruple eradication regimens involving key antibiotics. Moreover, 96.9% of patients (63/65) had received failed quadruple eradication with at least 2 low-resistance antibiotics, such as amoxicillin, furazolidone, and tetracycline. Of these, 14 patients (21.5%) have experienced failed regimens containing amoxicillin, tetracycline, and a PPI. In China, the resistant rates of *H. pylori* to amoxicillin, tetracycline, and furazolidone are lower than 5% (14,17), and reuse of these antibiotics rarely results in subsequent resistance. The consecutive regimen includes 3 antibiotics known to have the highest resistance barrier to achieve satisfactory efficacy in a difficult-to-treat group. In addition, 57 patients (87.7%) had received at least 1 failed eradication attempt containing amoxicillin 1,000 mg and furazolidone 100 mg twice daily. Regimens containing an increased dose of furazolidone (100 mg 3 or 4 times daily), based on previous data (18–20), could achieve satisfactory efficiency. This should be taken into account because the short duration of these treatments did not increase SAEs (21,22). Without increasing the total dose (<2.8 g), the daily dose of furazolidone was increased to 300 mg for 7 days in this study. Finally, amoxicillin 500 mg 4 times daily may further increase the eradication rate, although it may also lower patient compliance because it involves complex regimens. Consecutive therapy achieved a cure rate of 95.1% in the PP population, an encouraging result when considering that almost every patient received the same 2 low-resistance antibiotics previously used. This may be because no drug resistance was noted for these 3 antimicrobials. Moreover, the efficacy did not decrease with an increasing number of previous failures.

Previous studies have shown that double-dose esomeprazole regimens increase the efficacy of *H. pylori* eradication therapy (23,24). Esomeprazole-based and rabeprazole-based regimens have shown little difference in efficacy among different CYP2C19 genotypes and are recommended for rescue therapies in Asian populations (25–28). Thus, in this preliminary study, we selected esomeprazole 40 mg and rabeprazole 20 mg twice daily to obtain adequate acid suppression. However, as a novel potassium-competitive acid blocker, vonoprazan exhibits a more rapid, sustained, and profound acid-inhibitory effect compared with esomeprazole and rabeprazole in Japanese individuals, regardless of CYP2C19 polymorphisms. Further studies will undertake vonoprazan because of the established importance of acid suppression in improving the efficacy of amoxicillin against *H. pylori*.

The furazolidone-containing regimen showed no increased risk of drug-related TEAEs or SAEs compared with other antibiotic regimens, despite variable daily doses, medication duration, and regimen forms (29,30). Liang et al. (19) showed that the regimens containing 300 mg of furazolidone per day were well tolerated and achieved ≥90% cure rates. Severe TEAEs are more common in regimens containing high doses (≥200 mg twice daily) or long durations (>7 days). Tetracycline-containing and furazolidone-containing regimens may have good efficacy with only occasionally SAEs (31,32). The incidence of SAEs is rare (0.4%), and penicillin allergy cannot be completely ruled out (30). Meanwhile, amoxicillin-based and furazolidone-based therapies have also demonstrated high cure rates with a

### Table 1. Demographic and clinical characteristics of the enrolled patients

| Characteristic | Consecutive therapy (N = 65) |
|----------------|-------------------------------|
| Age (yr; mean ± SD) | 49.7 ± 8.8 |
| Male | 41 (63.1%) |
| Smoking<sup>a</sup> | 5 (7.7%) |
| Drinking<sup>b</sup> | 9 (13.9%) |
| BMI, kg/m², mean ± SD | 23.3 ± 3.4 |
| NSAID user | 3 (4.6%) |
| Complication | 7 (10.8%) |
| Diabetes mellitus | 4 (6.2%) |
| Hypertension | 5 (7.7%) |
| Endoscopic finding | |
| Atrophy gastritis | 42 (64.6%) |
| Peptic ulcer | 4 (6.2%) |
| Gastric intraepithelial neoplasia | 3 (4.6%) |
| Familial history of gastric cancer | 12 (18.5%) |
| Times of eradication failure | |
| 3 | 37 (56.9%) |
| 4 | 18 (27.7%) |
| ≥5 | 10 (15.4%) |
| Previous clarithromycin use<sup>c</sup> | 65 (100%) |
| Previous amoxicillin use<sup>c</sup> | 65 (100%) |
| Previous metronidazole use<sup>c</sup> | 65 (100%) |
| Previous levofloxacin use<sup>c</sup> | 65 (100%) |
| Previous furazolidone use<sup>c</sup> | 57 (87.7%) |
| Previous tetracycline use<sup>c</sup> | 28 (43.1%) |
| Clarithromycin resistance<sup>d</sup> | 31 (60.8%) |
| Amoxicillin resistance<sup>d</sup> | 1 (2.0%) |
| Metronidazole resistance<sup>d</sup> | 51 (100%) |
| Levofloxacin resistance<sup>d</sup> | 36 (70.6%) |
| Furazolidone resistance<sup>d</sup> | 0 |
| Tetracycline resistance<sup>d</sup> | 0 |

<sup>a</sup>An individual who smoked more than 1 cigarette every day for more than 1 yr was considered a smoker.

<sup>b</sup>An individual who drank alcohol more than once per week for at least 12 mo was defined as a drinker.

<sup>c</sup>Previous antibiotic use was identified in patients who had continuous antibiotics (oral or intravenous agents for ≥14 d) for any reason besides *H. pylori* eradication.

<sup>d</sup>Strains were isolated from 51 patients.

### Table 2. Eradication rates of consecutive therapy according to previous regimen failures

| Variable | Overall eradication rates | 4th-line | ≥5th-line |
|----------|--------------------------|---------|----------|
| ITT analysis | 90.8% (59/65) | 86.5% (32/37) | 96.4% (27/28) |
| PP analysis | 95.1% (58/61) | 91.4% (32/35) | 100% (26/26) |

ITT, intention-to-treat; PP, per-protocol.
favorable safety profile (19,33). Significantly, dual therapies including high doses of PPIs and amoxicillin have proven to be safe and effective (34,35). Our current findings showed that consecutive therapy was well tolerated in the study population. A similar incidence of drug-related TEAEs has been observed previously (15,31). One-week furazolidone quadruple therapy has a higher incidence of drug-related TEAEs probably because of the increased daily dose of furazolidone 300 mg. Notably, all adverse events were mild-to-moderate with a low occurrence of drug-related discontinuation. The most common drug-related TEAEs were nausea (6.3%), and similar results have been reported in previous studies.

Good compliance with treatment could improve the H. pylori cure rate (36,37). Despite the slightly complex regimen, good compliance was achieved in 95.3% of the patients, probably attributed to the detailed education by investigators, high motivation of patients, and exclusion of patients with poor compliance during previous therapies.

The success rate of H. pylori isolation (78.5%, 51/65) was not ideal. Previous studies found that patients with autoimmune gastritis are often misdiagnosed with false-positive results in ¹³C-UBT and rapid urease test because of the presence of other urease-containing bacteria (38–40). Furthermore, bacteria with structural similarity to H. pylori may lead to the false-positive histology result (41). No patients with pernicious anemia were found in our study population. Antiparietal cell antibody and anti-intrinsic factor antibody tests were not performed, and prolonged transport may influence the optimal recovery of the organisms from gastric biopsy specimens. Finally, among patients with good compliance, the eradication rates were similar in the positive-culture and negative-culture groups (95.8% vs 92.3%).

There were some methodological weaknesses that may restrict the validity of our results. First, as this study was a single-arm pilot study, it was not possible to compare the eradication efficacy. The occurrence of drug-related TEAEs was similar between consecutive therapy in this study and bismuth-containing quadruple therapy in a previous study (15). Large-scale, multicenter RCTs must be conducted to confirm these results in regions with different patterns of resistance. Second, CYP2C19 polymorphisms were not tested before initiating treatment. Nevertheless, esomeprazole 40 mg or rabeprazole 20 mg was selected to ensure sufficient acid suppression because CYP2C19 has a minimal significant effect on the esomeprazole-based or rabeprazole-based therapies. However, it remains a major weakness of our study because both esomeprazole and rabeprazole were used simultaneously. Third, although drug-related TEAEs were carefully assessed, the dynamic changes of gut microbiota were not monitored while the relatively broad-spectrum antibiotics were used. It is still unknown whether this regimen affects the antimicrobial resistance of Escherichia coli and its metabolic parameters. Finally, tetracycline, furazolidone, and bismuth compounds are not always available in many areas. Considering the relatively low cost of these drugs, reasonable application of these drugs could effectively reduce the cost of eradication.

This pilot study showed that even after >previous H. pylori eradication failures in a specific population with high levels of multiple antimicrobial resistance, consecutive therapy including amoxicillin, tetracycline, and furazolidone, was feasible to achieve a good eradication rate (>90%) with acceptable tolerability and good compliance, regardless of a medication history of these 3 antibiotics. These findings should be further elucidated using multicenter RCTs for clinical application in Chinese patients.

TABLE 3. TEAEs and patient compliance with 14-day consecutive therapy

| Variable | Consecutive therapy |
|----------|---------------------|
| Total no. of TEAEs | 41 |
| No. of drug-related TEAEs | 46.3% (19/41) |
| Mild | 84.2% (16/19) |
| Moderate | 15.8% (3/19) |
| Severe | 0 |
| Serious adverse events | 0 |
| No. of patients with TEAEs | 39.1% (25/64) |
| No. of patients with drug-related TEAEs | 23.4% (15/64) |
| Headache | 3.1% (2/64) |
| Dizziness | 1.6% (1/64) |
| Nausea | 6.3% (4/64) |
| Abdominal pain | 3.1% (2/64) |
| Dyspepsia | 3.1% (2/64) |
| Vomiting | 1.6% (1/64) |
| Fatigue | 1.6% (1/64) |
| Leukopenia | 1.6% (1/64) |
| Eyelid edema | 1.6% (1/64) |
| Vision blurred | 1.6% (1/64) |
| AST increased | 1.6% (1/64) |
| Dropout because of TEAEs | 3.1% (2/64) |
| Drug-related dropout | 1.6% (1/64) |
| Compliance | 95.3% (61/64) |
| Compliance was indicative of patients taking at least 90% of the pills. AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event. |

CONFLICTS OF INTEREST
Guarantor of the article: Xiu-Li Zuo, MD, PhD.
Specific author contributions: Jing Liu, MD, and Chao-Ran Ji, MD, contributed equally to this work. J.L., C-R.J., and Y-Y.L.: research design and drafting of the article. C.Q., J-N.H., M.W., B-S.L., M-J.L., J.W., and J.Z.: data collection. J.L. and C-R.J.: analysis and interpretation of data. X-L.Z. provided critical revision of the article. All authors read and approved the final article.

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Potential competing interests: None to report.

Institutions participating in the study: The endoscopy unit, Qilu Hospital of Shandong University, Jinan, China; Laboratory of Translational Gastroenterology, Qilu Hospital of Shandong University, Jinan, China.

Trial identification number: ClinicalTrials.gov ID: NCT03658733, https://clinicaltrials.gov/ct2/show/NCT03658733
Study Highlights

WHAT IS KNOWN

✓ The posttreatment resistance rates of Helicobacter pylori are increasing.
✓ Traditional fourth-line regimens fail to achieve satisfactory cure rates of H. pylori infection.

WHAT IS NEW HERE

✓ Consecutive therapy achieves a good cure rate in difficult-to-treat H. pylori infections.

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