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A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy regimen achieves a high eradication rate as first-line anti-*Helicobacter pylori* treatment in Taiwan: a prospective randomized trial

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Background: The first-line eradication rate of standard triple therapy for *Helicobacter pylori* infection has declined to <80%, and alternative therapies with >90% success rates are needed. Inconsistent eradication rates were reported for proton pump inhibitor- and amoxicillin-containing high-dose dual therapy.

Objectives: We performed a prospective, randomized controlled study to assess the efficacy of esomeprazole- and amoxicillin-containing high-dose dual therapy and investigated the influencing clinical factors.

Patients and methods: We recruited 240/278 eligible *H. pylori*-infected patients after exclusion. They were randomly assigned to 14 day high-dose dual therapy (esomeprazole 40 mg three times daily and amoxicillin 750 mg four times daily for 14 days; EA group) or 7 day non-bismuth quadruple therapy (esomeprazole 40 mg twice daily, clarithromycin 500 mg twice daily, amoxicillin 1 g twice daily and metronidazole 500 mg twice daily for 7 days; EACM group). Urea breath tests were followed up 8 weeks later.

Results: The eradication rates for the EA and EACM groups were 91.7% (95% CI = 85.3%–96.0%) and 86.7% (95% CI = 79.3%–92.2%) ($P = 0.21$) in ITT analysis; and 95.7% (95% CI = 90.2%–98.6%) and 92.0% (95% CI = 85.4%–96.3%) ($P = 0.26$) in PP analysis. The adverse event rates were 9.6% versus 23.0% in the two groups ($P = 0.01$). The *H. pylori* culture positivity rate was 91.8%. The antibiotic resistance rates were amoxicillin, 0%; clarithromycin, 14.6%; and metronidazole, 33.7%.

Conclusions: A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy achieves a high eradication rate as first-line anti-*H. pylori* therapy, comparable to that with 7 day non-bismuth quadruple therapy but with fewer adverse events.

Introduction

The previously recommended first-choice treatment for *Helicobacter pylori* infection of a proton pump inhibitor (PPI)/clarithromycin/amoxicillin or metronidazole treatment for 7–14 days has been abandoned as the eradication rate of this standard triple therapy has generally declined to unacceptable levels (≤80%) recently.[1–8] The reasons for this fall in efficacy with time may relate to the increasing incidence of clarithromycin-resistant strains of *H. pylori*.[3,4,9] The main reasons for eradication failure for *H. pylori* infection include antibiotic resistance, poor compliance and rapid metabolism of PPIs.[3,4] Clarithromycin resistance is the major cause of eradication failure for standard triple therapy.[9] The rate of clarithromycin-resistant strains ranged from 49% (Spain) to 1% (The Netherlands) worldwide.[10] It has been recommended that standard triple therapies should be abandoned in the areas with clarithromycin resistance ≥20% because the PP eradication rates of standard therapies are often <85% and the ITT eradication

rates are usually <80%.[2–9,11] Other treatment regimens have high proven eradication success in various parts of the world in the presence of clarithromycin resistance. These treatment regimens include 7–14 day non-bismuth quadruple therapy, 10–14 day sequential therapies and 14 day hybrid therapy.[5,12–14] Another treatment with 14 day PPI- and amoxicillin-containing high-dose dual therapy also attained high eradication rates in studies reported by Ren *et al.*[15] and Yang *et al.*[16] This treatment regimen is simple, involving only two drugs, and (most importantly) amoxicillin resistance is still very low globally and is 0% in Taiwan.[5,12] The key point to success for this therapy is that a high-dose PPI has been used in several studies for *H. pylori* eradication in order to increase the intragastric pH for optimal eradication.[15–18]

So far, it is still unclear which is the best first-line *H. pylori* eradication regimen with the highest eradication rate and least adverse effects. We therefore designed a randomized controlled trial to assess simultaneously the efficacy of a 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy through comparison with the 7 day non-bismuth quadruple therapy and to investigate the host and bacterial factors predicting the treatment outcomes of eradication therapies.

Patients and methods

Ethics

This open-label trial was conducted in Kaohsiung Chang Gung Memorial Hospital (outpatient department) in Taiwan. This protocol was approved by the institutional review board and the Ethics Committee of Chang Gung Memorial Hospital (IRB104-2643A3). All patients provided their written informed consent before enrolment. None of our patients was a minor/child. The ClinicalTrials.gov registration identifier is NCT03383003.

Trial design and setting

Participants

We invited 278 eligible *H. pylori*-infected outpatients ≥18 years old with endoscopically proven peptic ulcer disease or gastritis to join the study. We enrolled 240 patients after excluding those who had taken antibiotics, bismuth, PPIs or non-steroidal anti-inflammatory drugs within the previous 4 weeks, were allergic to the medications used, had a history of previous gastric surgery or serious concomitant illness, were currently pregnant or those who refused to participate.

Study design

Figure 1 shows the schematic flow chart of the study design. Endoscopy was performed for all patients on recruitment. During endoscopy, gastric specimens were taken from the antrum and corpus for rapid urease test (with one specimen from the antrum and one from the corpus) and culture (with one specimen from the antrum and one from the corpus). Patients were requested to complete a standard questionnaire for a complete medical history and demographic data. Using a computer-generated number sequence, the eligible *H. pylori*-infected patients were randomly assigned to each of two participant groups at a ratio of 1:1: (i) 14 day high-dose dual therapy (esomeprazole 40 mg three times daily and amoxicillin 750 mg four times daily; EA group) or (ii) 7 day non-bismuth quadruple therapy (esomeprazole 40 mg twice daily, clarithromycin 500 mg twice daily, amoxicillin 1 g twice daily and metronidazole 500 mg twice daily; EACM group). The 7 day non-bismuth quadruple therapy was chosen instead of a 14 day regimen because 7 day non-bismuth-containing quadruple therapy achieved a grade 'A' report card (>95% eradication rate) in our previous study.[5] Esomeprazole and amoxicillin were taken 1 h before meals, while clarithromycin and metronidazole were taken with food. Patients were also instructed to avoid spicy food during the treatment period.

Patients were asked to return to assess drug compliance and adverse events after they finished all the medications (at day 15 for the EA group and day 8 for the EACM group). Patients with peptic ulcers on initial endoscopy received an additional 3 weeks of monotherapy with esomeprazole 40 mg orally once daily, while patients with gastritis only took 3 weeks of antacid following eradication therapy. Follow-up urea breath tests were conducted to assess *H. pylori* status 8 weeks and 12 weeks later. The second urea breath test at 12 weeks was performed on the participants deemed to have achieved eradication to minimize misdiagnoses. Eradication was defined as a negative result of the urea breath test. Finally, the rates of eradication, adverse events and compliance were compared between groups by χ^2 test, and the host and bacterial factors influencing the efficacy of the eradication therapy were assessed by multivariate analysis.

Objectives

The current study aimed to assess the efficacy of 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy by comparing this with 7 day non-bismuth-containing quadruple therapy for *H. pylori* infection in Taiwan and to investigate the host and bacterial factors predicting the treatment outcomes.

Outcomes

The primary endpoint of our study was the successful eradication of *H. pylori*. We also conducted additional analyses on adverse events during the therapies.

Questionnaire

A complete medical history and demographic data were obtained from the participants, including age, sex and medical history, history of smoking, alcohol, and coffee and tea consumption. Smoking was defined as consumption of cigarettes (one pack or more per week). Coffee or tea consumption was defined as drinking one cup or more per day. Adverse events were prospectively evaluated. The adverse events were 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).[5] Compliance was checked by counting unused medication at the completion of treatment. Poor compliance was defined as taking <80% of the total medication.[5,19]

Diagnosis of H. pylori infection

Rapid urease test

The rapid urease test was performed according to our previous studies[5–8,20,21] Biopsy specimens taken from the antrum and corpus were placed immediately in 1 mL of a 10% solution of urea in deionized water (pH 6.8) to which two drops of 1% phenol red solution were added and then incubated at 37°C for up to 24 h. If the yellowish colour around the area of the inserted specimen changed to bright pink within the 24 h limit, the urease test was considered positive.

Urea breath test

The urea breath test was performed according to our previous studies.[22] The cut-off value was set at 4.8% of $\delta^{13}CO_2$. Staff who were blind to the *H. pylori* status performed the tests.

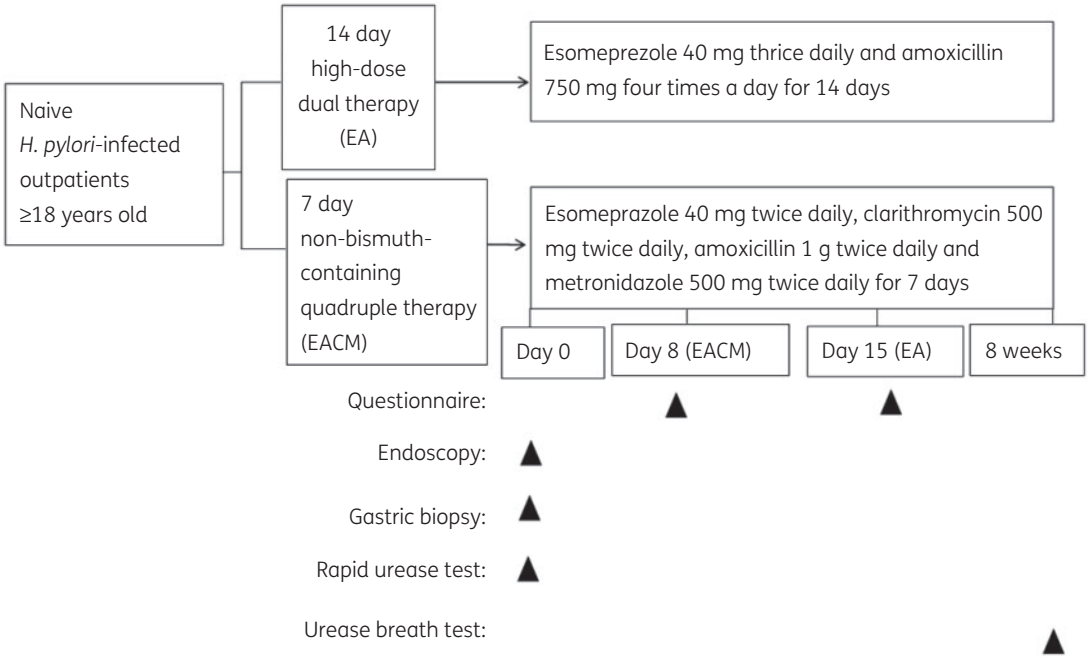

Figure 1. Schematic flow chart of study design.

Culture and antimicrobial resistance

One antral gastric and one corpus biopsy specimen were obtained for *H. pylori* isolation using previously described culture methods.[20] All stock cultures were maintained at −80°C in Brucella broth (Difco, Detroit, MI, USA) supplemented with 20% glycerol (Sigma Chemical Co., St Louis, MO, USA). The organisms were identified as *H. pylori* by Gram staining, colony morphology and positive oxidase, catalase and urease reactions. As previously described in more detail,[22] antibiotic susceptibility was determined by Etest (AB Biodisk, Solna, Sweden). The MIC was determined by the agar dilution test. *H. pylori* strains with MIC values ≥0.5, ≥1, ≥1, ≥4 and ≥8 mg/L were considered to be resistant to amoxicillin, clarithromycin, levofloxacin, tetracycline and metronidazole, respectively.

Randomization

Our statistician generated randomization lists by computer to obtain 'random sequences' which combine blocking and stratified randomization.[23] We used separate randomization procedures within each of the two participant groups at a ratio of 1:1. We then set a block for every six participants. The statistician generated a randomization list, and the doctors determined the patients who were suitable for this study and sorted the sequence order, which was provided by a research assistant. The sequence was concealed in an opaque envelope until the intervention was assigned. After written informed consent was obtained from the participants, the research assistant assigned the therapies according to the treatment allocations kept in the envelopes. Each patient collected the medications on the same day from the pharmacy department in our hospital.

Statistical analysis

Assuming that the conventional eradication rate in the EA group was 80% and that the EACM group achieved a 90% eradication rate (a 10% difference), our statistical power in this study will be 80% with sample sizes of ∼119 subjects in each group and have a two-sided *P* value of 0.05 if 95% of patients completed the follow-up. The primary outcome variables were the rates of eradication, adverse events and compliance. χ^2 test with or without Yates correction for continuity and Fisher's exact test were used when appropriate to compare the major outcomes between groups. A *P* value <0.05 was considered statistically significant. Eradication rates were evaluated by ITT and PP analyses. ITT was defined as the analysis of all participants in the groups to which they were randomized, regardless of whether they received or adhered to the allocated intervention. For instance, ITT analysis in this study included all randomized patients who had taken at least one dose of study medication. Patients whose infection status was unknown following treatment were considered treatment failures for the purposes of ITT analysis. PP was defined as the analysis limited to the participants who fulfilled the protocol in terms of the eligibility, adherence to the intervention and outcome assessment. In this study, the PP analysis excluded the patients with unknown *H. pylori* status following therapy and those with major protocol violations.

To determine the independent factors affecting the treatment response, clinical, endoscopic, histological, and bacterial factors were analysed by univariate analysis. These variables included the following: age (<60 or ≥60 years), gender, history of smoking, history of alcohol consumption (<80 g/day or ≥80 g/day), ingestion of coffee (<1 cup/day or ≥1 cup/day), ingestion of tea (<1 cup/day or ≥1 cup/day), coexistence of a systemic disease (yes or no), previous history of peptic ulcer disease, endoscopic appearance (ulcer or gastritis), drug compliance (good or poor) and antibiotic resistance of *H. pylori*. Those variables found to be significant by univariate analysis were subsequently assessed by a stepwise logistic regression method to identify independent factors for eradication outcome.

Results

Characteristics of the study groups

As shown in Figure 2, a total of 278 eligible *H. pylori*-infected patients with endoscopically proven peptic ulcer diseases or gastritis were invited; 240 patients were enrolled ($n = 120$ per group) in the ITT analysis. Ultimately, five patients were lost during follow-up

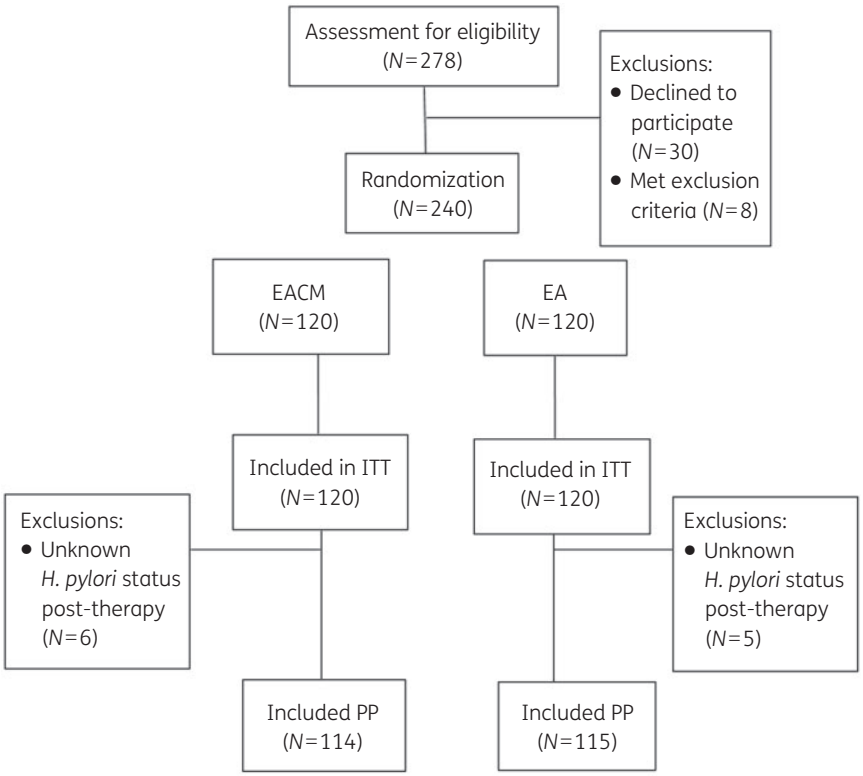

Figure 2. Patient disposition. EA, 14 day high-dose dual therapy; EACM, 7 day non-bismuth quadruple therapy.

Table 1. Demographic data and endoscopic appearance of the two groups of patients

Characteristics	EA ($n = 115$)	EACM ($n = 114$)	*P* value
Age (year) (mean ± SD)	55.0 ± 11.5	54.7 ± 13.2	0.82
Gender (male/female)	58/57	60/54	0.74
Previous history of peptic ulcer	14	12	0.69
Endoscopic findings			
gastritis	50	56	0.37
gastric ulcer	45	33	
duodenal ulcer	16	18	
gastric and duodenal ulcer	4	7	

Table 2. The major outcomes of the two groups of patients

	Eradication rate		
Characteristic	EA ($n = 115$)	EACM ($n = 114$)	*P* value
Intention-to-treat[a]	91.7% (110/120)	87.5% (105/120)	0.29
Per-protocol	95.7% (110/115)	92.1% (105/114)	0.26
Adverse events	9.6% (11/115)	22.8% (26/114)	0.01
Compliance	100% (115/115)	100% (114/114)	–

[a]Patients with unknown outcome are counted as treatment failures.

in the EA group and six patients in the EACM group, resulting in 115 for the EA group and 114 in the EACM group. The demographic data of the two groups were similar (Table 1).

Eradication of H. pylori

Table 2 lists the eradication rates of the EA and EACM groups. ITT analysis demonstrates similar eradication rates in the two study groups (EA 91.7%, 95% CI 85.3%–96.0%; and EACM 87.5%, 95% CI 79.3%–92.2%) ($P = 0.21$). According to the PP analysis, the success rates of eradication of *H. pylori* infection were EA 95.7% (95% CI 90.2%–98.6%) and EACM 92.1% (95% CI 85.4%–96.3%) ($P = 0.26$).

Adverse events and clinical factors influencing the efficacy of H. pylori eradication therapy

The adverse event rates were 9.6% in the EA group and 22.8% in the EACM group, $P = 0.01$ (Table 2). These adverse events included abdominal pain, constipation, diarrhoea, dizziness, headache, nausea/vomiting and skin rash (Table 3); however, these were mild and did not markedly disturb the patients' daily activities. Therefore, both groups had good drug compliances (100%). As shown in Table 4, univariate analysis showed that there was no significant clinical factor influencing the efficacy of *H. pylori* eradication therapy.

Antibiotic resistance

Samples from 97 patients were cultured for *H. pylori*, and the positive culture rate was 91.8% (89/97). Hence, the antibiotic

Table 3. Adverse events in the two groups of patients

Adverse event	No. of adverse events (%)		*P* value
	EA ($n = 115$)	EACM ($n = 114$)	
Abdominal pain	4 (3.5)	11 (9.6)	0.06
Constipation	0	1 (0.9)	0.31
Diarrhoea	1 (0.9)	1 (0.9)	1
Dizziness	1 (0.9)	3 (2.6)	0.31
Headache	1 (0.9)	4 (3.5)	0.17
Nausea/vomiting	4 (3.5)	11 (9.6)	0.06
Skin rash	0	0	–

resistance rates were 0% (0/89) for amoxicillin, 14.6% (13/89) for clarithromycin and 33.7% (30/89) for metronidazole. The *H. pylori* eradication rates for the amoxicillin- and clarithromycin-susceptible strains were EA 92.3%, 95% CI 75.3%–99.0%; and EACM 92.0%, 95% CI 74.0%–99.0%. The *H. pylori* eradication rates for the clarithromycin-susceptible but metronidazole-resistant strains were EA 91.7%, 95% CI 61.6%–99.8%; and EACM 83.3%, 95% CI 51.6%–97.9%.

Discussion

The globally increasing antibiotic resistance in recent decades is an important cause of first-line *H. pylori* eradication failures, especially those with clarithromycin resistance or dual resistance to clarithromycin and metronidazole.[2–8] The emergence of novel therapies such as sequential therapy, non-bismuth quadruple therapy and hybrid therapy has achieved high eradication rates in first-line *H. pylori* eradication.[5,12–14] As all these regimens included a PPI and multiple antibiotics, the potential for adverse events is greater. For instance, both the high-dose dual therapy and non-bismuth quadruple therapy groups achieved comparable high eradication rates in this study, but 23% of our patients in the non-bismuth quadruple therapy (which included one PPI and three antibiotics) encountered adverse events.

Although the antibiotic resistance has increased globally in recent decades, primary and acquired amoxicillin resistance remains low. Zullo *et al.*[23] showed that a 10 day high-dose dual therapy (esomeprazole 40 mg three times daily and amoxicillin 1 g three times daily) was effective and safe as a first-line treatment for *H. pylori* infection in Italy but did not achieve 90% eradication. These authors suggested a 14 day regimen to be a better option. Consequently, our 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy achieved a 95.7% eradication rate in the PP analysis for first-line anti-*H. pylori* therapy, comparable to the 92.0% in the 7 day non-bismuth quadruple therapy, but with fewer adverse events. In our study, the antibiotic resistance rates were 0% for amoxicillin, 14.6% for clarithromycin and 33.7% for metronidazole. Obviously, amoxicillin was one of the key reasons for the success of *H. pylori* eradication given that the intragastric environment was probably kept at a constant intragastric pH >6 by esomeprazole 40 mg three times daily to optimize the antibiotic susceptibility and also by lengthening the treatment duration from 10 to 14 days.

Table 4. Univariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication therapy

Principal parameters	Patients (*n*)	Eradication rate (%)	*P* value
Age			
<60 years	141	95.7	0.14
≥60 years	88	90.9	
Sex			
female	111	93.7	0.91
male	118	94.1	
Previous history of peptic ulcer			
no	203	93.6	0.61
yes	26	96.2	
H. pylori eradication (per-protocol)			
EA	115	95.7	0.26
EACM	114	92.1	
Compliance			
good	229	100	–
poor	0		
Resistance of *H. pylori* in culture ($n = 89$)			
amoxicillin	0	–	–
clarithromycin	12/13	92.3	0.85
metronidazole	26/30	86.7	0.32
clarithromycin and metronidazole	5/6	83.3	0.5

It was interesting to trace the history around when dual therapies with PPI and amoxicillin were introduced to eradicate *H. pylori* but failed to attain an acceptable eradication rate three decades ago.[24,25] Since then, there have been other reports on high-dose dual therapies but the results varied. For instance, Kwack *et al.*[26] reported an unacceptable cure rate of *H. pylori* by using high-dose dual therapy with ilaprazole 40 mg tablets given twice daily and amoxicillin 750 mg tablets given four times daily in Korea (79.3% in the ITT analysis and 82.1% in the PP analysis). In contrast, a high-dose dual therapy (rabeprazole 20 mg four times daily and amoxicillin 750 mg four times daily) for 14 days achieved a 95.3% success rate as a first-line treatment for *H. pylori* eradication and 89.3% as second-line rescue therapy.[16] Interestingly, Goh *et al.*[27] proved that a good success rate of rescue therapy after first-line *H. pylori* eradication can be attained with a 14 day high-dose PPI/amoxicillin dual therapy (rabeprazole 20 mg three times daily and amoxicillin 1 g three times daily) followed by a PPI/amoxicillin/levofloxacin triple therapy.

Possibly, the success of the regimens in the EA group was because it was studied here in a Taiwanese population. Although a high dose of PPI and antimicrobial agents was required to acheive successful eradication, high frequency (three or four times daily) was more important. The effect of amoxicillin was dependent on time and intragastric pH. It was absorbed and then excreted very quickly within 6–8 h once ingested by patients.[28] Therefore, it was rational that administration of amoxicillin at high dose and every 6–8 h was found to be more efficient than administration every 12 h. At intragastric pH < 6, amoxicillin is less stable.[29,30] The use of esomeprazole three times daily in the current study might have contributed to the good result because it is the *S*-isomer of

omeprazole, with a stronger acid-suppressive effect than other PPIs in terms of percentage of time with intragastric pH >4.[31,32] In addition, Asians have an advantage in that their average body weight is less than that of Caucasians, with significantly lower acid secretion capacity.[33,34] Regarding the issue of increasing intragastric pH, a novel gastric acid suppressant, vonoprazan, which can reliably maintain a higher intragastric pH than a traditional PPI, is very likely to become the first option for future eradication therapy.[35] Systematic reviews with meta-analyses reported that the eradication rate of vonoprazan-based triple therapy was higher compared with PPI-based triple therapy.[36,37]

Consideration of antimicrobial resistance is crucial in the success of *H. pylori* eradication. A high PP eradication in the EA group might have been expected given zero resistance for amoxicillin in our study. The patients in both the EA and EACM groups attained good eradication rates if their *H. pylori* was susceptible to both clarithromycin and metronidazole. This suggested that non-bismuth quadruple therapy was also an effective option for first-line eradication in Taiwan but might encounter difficulties in patients with dual clarithromycin- and metronidazole-resistant strains. Unfortunately, the number of patients infected with clarithromycin-resistant/metronidazole-resistant strains was small in this study and therefore we were unable to evaluate the influence of dual clarithromycin-resistant/metronidazole-resistant strains.

Nevertheless, antimicrobial resistance was not the sole explanation for failing eradication in real-world practice. Non-adherence to treatment also may have contributed. Side effects of any medications were the likely main reasons for poor compliance and might lead to failure to eradicate *H. pylori* and the risk of developing resistant bacterial strains if patients failed to finish all the prescribed drugs. In the current study, the adverse event rates were 22.8% in the EACM group and 9.6% in the EA group, but the compliance was 100% in both groups. In our experience, explanation (together with provision of a consultation phone number) to patients of possible treatment side effects and including mention of the importance of treatment compliance was helpful in increasing their compliance.

This study has some limitations. First, culture of *H. pylori* was done in only a subset of patients (97 patients were cultured for *H. pylori*) although the positive culture rate was 91.8% (89/97). For *H. pylori* infection, multiple drugs were used. However, since drug susceptibility testing was done in only 97 patients, there was a possibility of type II error due to small sample size with culture reports. Second, in this study, which ended in February 2018, the MIC values for clarithromycin and metronidazole resistance were indicated at ≥1 mg/L and ≥8 mg/L, respectively, which differ from the new MIC values for clarithromycin and metronidazole resistance indicated at >5 mg/L and >8 mg/L by an international committee (EUCAST; Breakpoint tables for interpretation of MICs and Zone Diameters. Version 8.1; May 2018).

In conclusion, a 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy achieves a high eradication rate for the first-line anti-*H. pylori* therapy, comparable with that with 7 day non-bismuth quadruple therapy, but with fewer adverse events.

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Transparency declarations

None to declare.

Author contributions

W.-C. T. performed the research, C.-M. L., C.-M. K., P.-Y. H., C.-K. W., S.-C. Y., Y.-H. K., M.-T. L., C.-H. L., C.-N. H., K.-L. W., T.-H. H. and S.-K. C. collected and analysed the data, W.-C. T. designed the research study and wrote the paper, and S.-K. C. contributed to the design of the study. All authors approved the final version of the manuscript.

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