Original Article

A Randomized Clinical Trial Comparing Triple Therapy versus Non-bismuth based Quadruple Therapy for the Eradication of *Helicobacter Pylori* in Kuwait

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Abstract

Introduction: *Helicobacter pylori*-induced chronic infection is associated with peptic ulcer, chronic gastritis, gastric cancer, and increasing antibiotic resistance. We aimed to evaluate the efficacy of clarithromycin-based triple therapy and non-bismuth based quadruple therapy for eradicating *H. pylori* in patients with chronic gastritis in Kuwait. **Methods:** We enrolled a total of 603 treatment-naive dyspeptic patients with gastric biopsy-proven chronic gastritis secondary to *H. pylori* in a prospective, open-label, randomized study. Patients were randomized into two groups: a group received the standard triple therapy (omeprazole, amoxicillin, and clarithromycin) for 14 days and a group received quadruple therapy (omeprazole, amoxicillin, clarithromycin, and metronidazole) for 14 days. All patients were tested for the eradication of *H. pylori* by carbon-13 urea breath test 1 month after eradication therapy. **Results:** The overall eradication rate was 63.2%. The eradication rates in intention-to-treat (ITT) and per protocol (PP) population were 58.4% and 64.6%, respectively, in triple therapy group. In the quadruple therapy group, the eradication rates in ITT and PP population were 68.0% and 78.5%, respectively, with a statistically significant higher eradication rate in patients treated by quadruple therapy than the triple therapy ($P < 0.01$). Multivariate logistic regression analysis revealed that treatment regimen was the only significant predictor for successful *H. pylori* eradication. The most common adverse events were abnormal taste, headache, dizziness, and abdominal pain. **Conclusion:** Non-bismuth based quadruple therapy is more effective than standard clarithromycin-based triple therapy for eradicating *H. pylori* in patients with chronic gastritis.
ClinicalTrials.gov Identifier: NCT04617613

Keywords: Amoxicillin, clarithromycin, *Helicobacter pylori*, metronidazole, omeprazole, quadruple therapy, triple therapy

Introduction

Helicobacter pylori infection is a common public health problem that affects 7%–87% of adults.[1,2] Its prevalence varies significantly among countries and population groups within the same country due to a strong correlation with factors including geography, culture, age, and socioeconomic status.[3] *H. pylori* infects approximately 50% of the worldwide adult population and is more common in developing countries.[4] The increased prevalence of *H. pylori* in developing countries is attributed to polluted drinking water, basic hygiene, poor diet, and overcrowded living conditions. The prevalence of *H. pylori* in Kuwait is estimated to be 42.6% among Kuwaitis and 57.6% among expatriates (non-Kuwaitis). In addition, males tend to be affected more (51.3%) than their female counterparts (48.6%).[5]

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_13_22

H. pylori infection is associated with a number of digestive diseases including chronic gastritis, peptic ulcer disease, and gastric malignancies such as mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma.[6] However, eradication of the organism effectively prevents relapses of gastroduodenal ulcers and associated gastric

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How to cite this article: Alfadhli A, Alboraie M, Afifi M, Dangi A. A randomized clinical trial comparing triple therapy versus non-bismuth based quadruple therapy for the eradication of *Helicobacter pylori* in Kuwait. J Global Infect Dis 2022;14:99-105.

Received: 20 January 2022 **Revised:** 01 March 2022
Accepted: 09 March 2022 **Published:** 26 August 2022

malignancies.[7] In addition, the latest Maastricht V Consensus has reconfirmed the strong recommendation for *H. pylori* eradication in infected patients with peptic ulcer and MALT lymphoma and for those with functional dyspepsia.[8-10]

Treatment strategies for the eradication of *H. pylori* continue to evolve and is still a major challenge. The standard triple therapy for *H. pylori* utilizes proton-pump inhibitors (PPIs) in combination with several antibiotics such as clarithromycin plus amoxicillin or metronidazole. The triple therapy has been considered the preferred first-line treatment for *H. pylori* infection until recently.[11] Previous studies suggested that the efficacy of standard triple therapy for *H. pylori* eradication in Kuwaitis was suboptimal.[5] Hence, the bacterium's resistance to clarithromycin is increasing rapidly. However, the eradication rate of standard triple therapy has declined to <80% in most countries worldwide due to increasing resistance rate to antibiotics.[12-15] The Kyoto Consensus Report on *H. pylori* recommends that, within any region, only regimens which reliably produce eradication rates of ≥90% in that population should be used.[16] Therefore, continued use of standard triple therapy has recently been interrogated, and alternative approaches with minimal bacterial resistance have been recommended. A good alternative in areas with high clarithromycin resistance could be nitazoxanide–levofloxacin-containing triple therapy that showed eradication rates of ≥90% in a recent study.[17]

Several attempts to implement new first-line treatments resurfaced. Trials of increasing the duration of triple therapy, thus prolonging exposure to antibiotics, were conducted but achieved controversial results and have not generally resulted in noteworthy benefits.[18,19]

Sequential treatment which involves a simple dual regimen including a PPI plus amoxicillin for the first 5 days followed by a triple regimen including a PPI, clarithromycin, and tinidazole for the following 5 days was another promising approach. Several randomized clinical trials have concluded that a sequential regimen is more effective than standard triple therapy.[20-24] Therefore, sequential therapy was proposed to be an alternative to standard triple therapy for the eradication of *H. pylori*.[25] However, a recently updated meta-analysis performed by a Cochrane collaboration group found that the results obtained with the sequential regimen were heterogeneous and the sequential therapy cannot be presented as a valid alternative to standard triple therapy. Furthermore, neither sequential therapy nor standard triple therapy regimens achieved optimal efficacy (≥90% eradication rate).[26]

From this perspective, the triple combination of clarithromycin plus amoxicillin and metronidazole with a PPI (without bismuth) has previously been examined as a nonsequential regimen, which proved its efficacy. Thus, the concept of a non-bismuth quadruple regimen (or concomitant treatment) has recently emerged as an effective regimen for eradicating *H. pylori*.[27-29] Traditional standard triple therapy (PPI, clarithromycin, and amoxicillin) can easily be converted to concomitant therapy by adding 500 mg of metronidazole or tinidazole twice daily.[30] A meta-analysis of 19 studies revealed a mean *H. pylori* cure rate of about 90% for concomitant therapy. A trend toward better outcomes with longer treatment durations with the concomitant regimen has been observed.[31] Experience with the quadruple therapy in patients with metronidazole-resistant strains is still very limited. Although susceptibility guided treatment would be the best first-line option, it is clinically applicable in different parts of the world. Guidelines still recommend empirical approach for 14-day treatment for the eradication of *H. pylori* to provide simplicity for clinicians.[29] Evidence supporting these conclusions is insufficient because no studies with an appropriate design have been performed. With these considerations in mind, we designed the present randomized controlled trial to compare the efficacy of clarithromycin-based triple therapy (omeprazole, amoxicillin, and clarithromycin) and no-nbismuth based quadruple therapy (omeprazole, amoxicillin, clarithromycin, and metronidazole) for the eradication of *H. pylori* in treatment-naïve patients with *H. pylori*-related chronic gastritis in Kuwait.

Methods

We followed the Consolidated Standards of Reporting Trials statement guidelines[32] when reporting this manuscript. This study was approved by the Ethics Committee of the Ministry of Health in Kuwait and all enrolled patients signed informed consent to participate in the study.

Study design, study setting, and study participants

We conducted a prospective, open-label, randomized controlled trial in the gastroenterology outpatient clinics of Haya Al-Habeeb Gastroenterology Center, Mubarak AL-Kabeer Hospital in Kuwait. We included patients meeting the following criteria: (1) male and female dyspeptic subjects aged ≥18 years with any nationality; (2) patients with gastric biopsy-proven *H. pylori*-related chronic gastritis and no other abnormalities in the upper gastrointestinal tract upon endoscopy, and (3) patients who were naive to treatment for *H. pylori* infection.

We excluded cases in the following conditions: (1) pregnant or breastfeeding females, (2) patients who were previously treated for *H. pylori* infection, and (3) patients who received any antibiotics, bismuth, or acid-suppressant drugs within the last month.

Study treatments

Patients were randomized in a 1:1 ratio using a SAS-based computer-generated randomization scheme into two groups. The first group (standard triple therapy group) received omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg. The second group (quadruple therapy group) received omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg. Patients in both groups received omeprazole capsule twice daily before meals and the rest of the drugs twice daily after meals for 14 days.

Study assessments

For each eligible patient, we reported the following data: (1) demographic data including age, gender, and nationality; (2) the main patient's complaint; (3) the results of physical examination; (4) *H. pylori* eradication rate defined as negative 13-carbon urea breath test (^{13}C-UBT) 1 month after treatment; and (5) the reported adverse events during the study period.

Study endpoints

The primary endpoint was the *H. pylori* eradication rate defined as the frequency of patients who have negative UBT (at least 1 month after treatment) in both treatment arms divided by the total number of patients (intention-to-treat [ITT]) or divided by those completed the treatment course (as per protocol [PP]). The secondary endpoints included compliance and adverse events defined as an event not present prior to exposure to the study medication or any event already present that worsens following exposure to study medication up to 2 months after study discontinuation.

Sample size

The sample size was calculated using power and sample size calculator (PS version 3.0.34). A dropout rate of 20% was considered, and the sample size was chosen to detect a 12% difference in proportions of participants who achieved *H. pylori* eradication in both treatment arms using the Chi-squared test assuming *H. pylori* eradication rate of 78% among standard triple therapy group versus 90% among quadruple therapy group. These calculations were made based on the assumption that study power is 95% and type I error probability is 0.05.

Statistical analysis

Data were summarized as frequencies and percentages for categorical variables. For continuous variables, data were summarized as mean and standard deviation if normally distributed or as median and interquartile ranges if not normally distributed. Comparison of quantitative variables was performed using the two-sample *t*-test or the MannWhitney *U*-test. Comparison of qualitative variables was carried out by the Chi-squared test. Multivariate logistic regression analyses were performed to identify factors affecting the eradication rate. A *P* value level smaller than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the study population

The present study included 603 patients. Of them, 303 patients with mean (± standard deviation [SD]) age of 44.4 (±15.4) were assigned to receive the standard triple therapy, and 300 patients with mean (SD) age of 42.4 (±13.4) were assigned to receive the quadruple therapy. Figure 1 shows the flow diagram of the included patients throughout the study period. The characteristics of the study population are shown in Table 1. Male-to-female ratio was comparable in the two groups. There were no differences between the two groups with regard to age, gender, or nationalities ($P > 0.05$).

Table 1: Baseline characteristics in the treated population

Variable	Standard triple therapy (*n*=303)	Quadruple therapy (*n*=300)
Age (year)		
Mean (±SD)	44.4 (±15.42)	42.4 (±13.4)
Median (minimum–maximum)	44 (14-89)	41 (15-83)
Gender, *n* (%)		
Male	147 (48.5)	160 (53.3)
Female	156 (51.5)	140 (46.7)
Ethnic origin, *n* (%)		
Kuwaitis		
Yes	93 (30.8)	95 (31.7)
No	209 (69.2)	205 (68.3)
Egyptian		
Yes	92 (30.5)	76 (25.3)
No	210 (69.5)	224 (74.7)
Arab		
Yes	264 (87.4)	243 (81.0)
No	38 (12.6)	57 (19.0)
Asian	206 (68.2)	216 (72.0)
African	94 (31.1)	83 (27.7)
Others	2 (0.7)	1 (0.3)
Complain, *n* (%)		
Abdominal pain	68 (22.52)	69 (23)
Bloating	11 (3.60	11 (3.7)
Constipation	1 (0.3)	1 (0.3)
Constipation alt with diarrhea	8 (2.6)	8 (2.7)
Diarrhea	1 (0.3)	1 (0.3)
Dyspepsia	68 (22.5)	67 (22.3)
GB stones	11 (3.6)	11 (3.7)
Heartburn	48 (15.9)	47 (15.7)
Iron deficiency anemia	13 (4.3)	13 (4.3)
Nausea and vomiting	68 (22.5)	67 (22.3)
Peptic ulcer disease	5 (1.7)	5 (1.7)
Physical examination		
Normal	265 (95.67)	251 (93.66)
Epigastric tenderness	4 (1.44)	4 (1.49)
Others	8 (2.89)	13 (4.85)

In the standard triple therapy group, abdominal pain, dyspepsia, nausea, and vomiting were the most common complaints (22.5%), followed by heartburn (15.9%). The same results were observed in the quadruple therapy group. Most of the patients were normal during the physical examination, and only four patients in each group had epigastric tenderness. The study population included 23 nationalities. The most common nationalities were Kuwaitis (31.2%), Egyptians (27.9%), Jordanians (7.8%), Indian (7.5%), and Syrian (6.6%) [Figure 2].

Safety analysis

Adverse events were described for 119 patients (39.3%) in the triple therapy group, while in the quadruple therapy group, the adverse events were described for 185 patients (61.7%). The

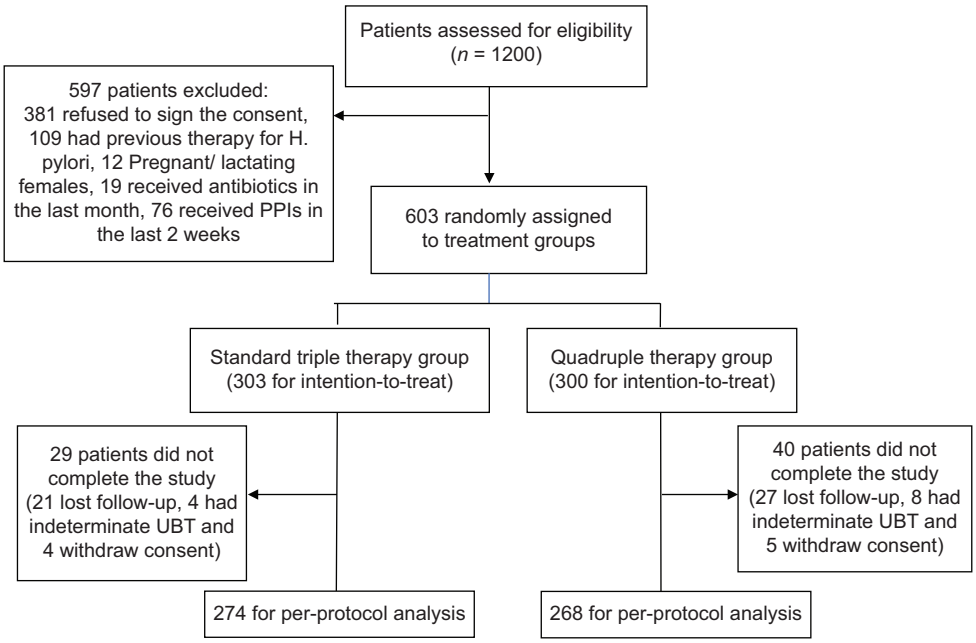

Figure 1: Flow chart of enrolled patients

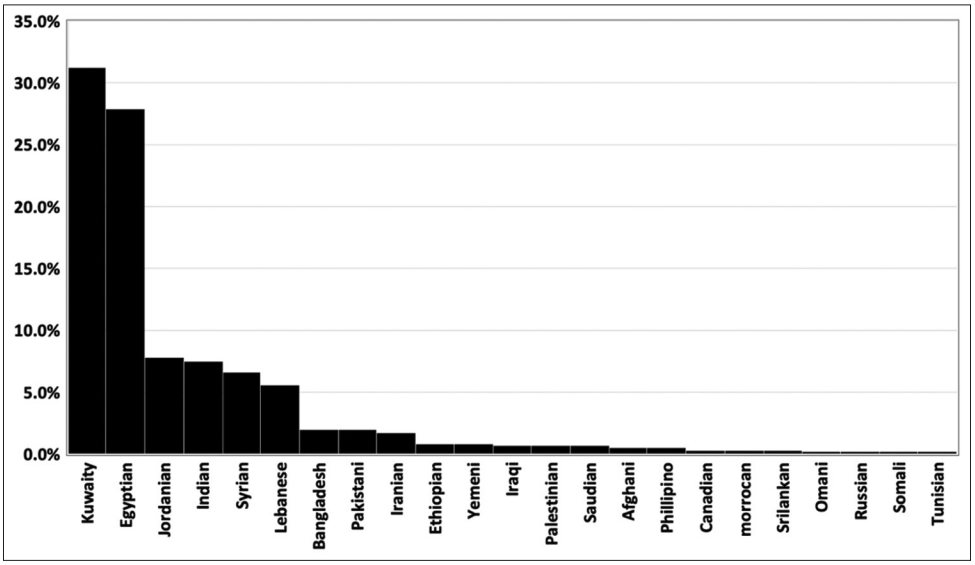

Figure 2: Nationality of included patients in the study

most common adverse events were abnormal taste, headache, diarrhea, dizziness, and abdominal pain.

Efficacy analysis

The overall eradication rate was 63.2% (381/603). Regarding the triple therapy group, eradication rates as PP and ITT analysis were 64.6% and 58.4%, respectively, while in the quadruple therapy group, the eradication rates in ITT and PP were 68.0% and 78.5%, respectively [Table 2]. Pearson's Chi-Square test revealed a statistically significant higher eradication rate in patients treated with quadruple therapy than with the triple therapy ($P < 0.01$).

In the triple therapy group, the eradication rates in males and females were 67.4% and 62.0%, respectively. While in the quadruple therapy group, the eradication rates were 81.1% in males and 75.2% in females. In Kuwaitis patients, the eradication rate was 60.5% in the triple therapy group, while in the quadruple therapy group, the eradication rate was 77.0%. In non-Kuwaitis, the eradication rate was 66.8% in the triple therapy group, while in the quadruple therapy group, the eradication rate was 79.2%. In Egyptian patients, the eradication rate was 65.1% in the triple therapy group, while in the quadruple therapy group, the eradication rate was 86.7%. In non-Egyptian, the eradication rate was 64.7% in the triple therapy group, while in the quadruple therapy group, the eradication rate was 76% [Figure 3]. In both treatment groups, the number of patients with symptoms improvement was significantly increased throughout the study period as shown in Figure 4. Furthermore, in both treatment groups, the number

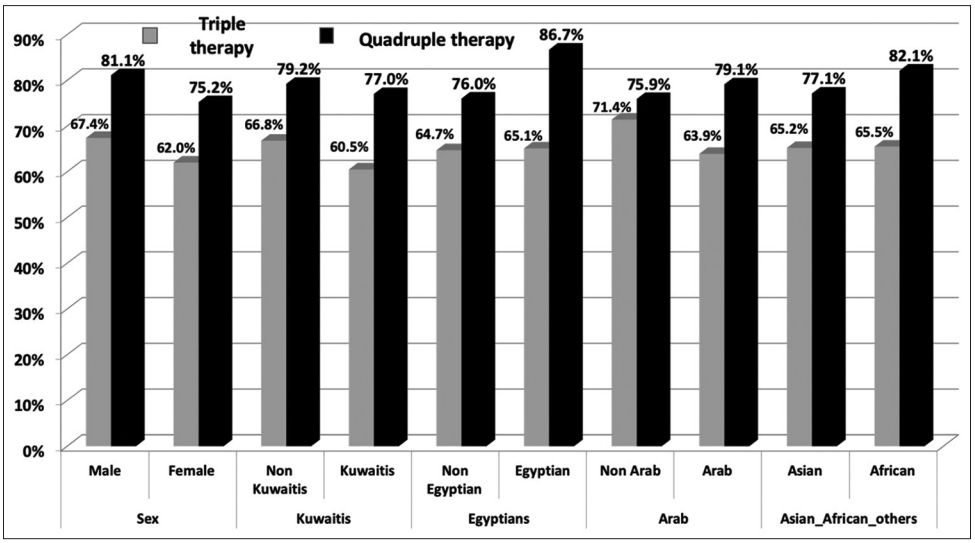

Figure 3: *Helicobacter pylori* Eradication rates based on different baseline characteristics

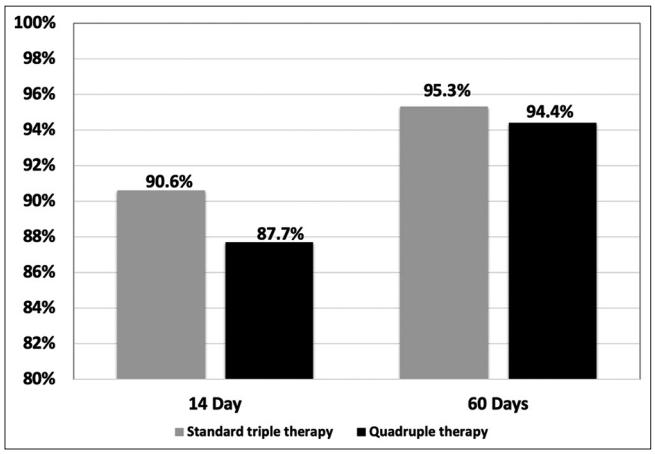

Figure 4: Percentage of symptoms improvement after eradication therapy. Pearson Chi-Square test did not reveal any difference in the percentage of patients who had symptoms improvement between the two groups all over the study period ($P > 0.05$)

of epigastric tenderness was significantly decreased throughout the study visits as shown in Supplementary Figure 1.

In both treatment groups, eradication rates were somewhat higher in males (67.4% and 81.1%) than in females (62.0% and 75.2%) and in non-Kuwaitis (66.8% and 79.2%) than in Kuwaitis (60.5% and 77.0%) [Supplementary Table 1]. In the quadruple group, the eradication rate in Egyptians was 86.7%, compared to 76.0% in non-Egyptians; the eradication rate in Africans was 82.1%, compared to 77.1% in Asians. In the standard triple group, the eradication rate in non-Arabs (71.4%) was higher than in Arabs (63.9%). However, in the multivariate logistic regression analysis, none of the above factors was a significant predictor of the eradication rate.

Discussion

Many of antibiotic regimens have been evaluated for the treatment of *H. pylori*.[33-36] However, there are limited data about the antibiotic resistance rates to guide the treatment of *H. pylori*.[37] The most common regimens are the clarithromycin-based triple therapy, the non-bismuth sequential or the concomitant quadruple therapy, and the bismuth-based quadruple therapies.[38] The choice of initial antibiotic regimen for the treatment of *H. pylori* should be supported by the presence of risk factors for macrolide resistance.[39] In patients with risk factors for macrolide resistance, clarithromycin-based therapy should be avoided. In the United States, it is assumed that clarithromycin resistance rates are more than 15%, leading to eradication rates with clarithromycin triple therapy <85%.[40] In Kuwait, there is no sufficient data about clarithromycin resistance.[41] Consequently, high eradication rate of clarithromycin-containing therapy cannot be guaranteed.

Therefore, we conducted our study to delineate the efficacy of two clarithromycin-containing regimens for eradicating *H. pylori* infection in patients with chronic gastritis in Kuwait. Most of the included patients were Kuwaitis (31.2%) and Egyptian (27.9%). The baseline and demographic characteristics were comparable between the two groups with no differences in age, gender, or nationalities ($P > 0.05$).

Table 2: Eradication rate in the per protocol and intention-to-treat populations

UBT results	Standard triple therapy (%)	Quadruple therapy (%)
UBT results (ITT)		
Negative	177/303 (58.4)	204/300 (68.0)
Positive	97/303 (32.0)	56/300 (18.7)
Lost follow up	21/303 (6.9)	27/300 (9.0)
Indeterminate	4/303 (1.3)	8/300 (2.7)
Consent refused	4/303 (1.3)	5/300 (1.7)
UBT results (PP)		
Negative	177/274 (64.6)	204/260 (78.5)
Positive	97/274 (35.4)	56/260 (21.5)

ITT: Intention-to-treat, PP: Per protocol, UBT: Urea breath test

These characters were comparable with the previously published articles by Alazmi *et al*.[42] The study population included 23 nationalities: Kuwaitis, Egyptians, Jordanians, Indian, Syrian, Canadian, Afghani, Ethiopian, Lebanese, and others. Differences in treatment outcomes between the studied nationalities may be explained by differences in baseline clarithromycin resistance, different socioeconomic and environmental factors, or because of the presence of multiple different strains of *H. pylori*. Epidemiological studies revealed that the occurrence of different strains of the bacteria varies between geographical areas and response to treatment varices due to variable efficacy of PPIs and resistance to antibiotics.[4]

Kyoto global consensus report confirmed that treatment regimen is considered effective when it achieves more than 90% eradication rate.[16] However, the eradication rates for the most commonly used regimens in clinical practice have fallen below 80%. This is generally because of poor compliance with medication and the rising rates of antibiotic resistance. [12,15,30,14]

Our study reported an overall eradication rate of 63.18% in both groups with clarithromycin-containing therapy, which was less than the overall eradication rate of 77.5% in the previous report by Alboraie *et al*. in Kuwait, where the eradication rates were 64.6% in the 10 days triple therapy group and 78.5% in the bismuth quadruple therapy group as PP analysis.[43] Results of a recent meta-analysis by Gatta *et al*. showed that global eradication rates for the 14-day standard triple therapy range between 79.5% and 84.7%.[44]

We presented that the efficacy of 14-day clarithromycin-based triple therapy for eradicating *H. pylori* (63.2%) is lower than that reported earlier from Kuwait (68.6%),[4] although there was a single report indicating 0% resistance to clarithromycin among patients in Kuwait.[41] This discrepancy may be explained by the fact that the previous study was performed 13 years ago, and the macrolides resistance could be developed during this time interval.

The frequency of primary clarithromycin resistance to *H. pylori* strains is increasing worldwide. A meta-analysis of 31 studies revealed that the overall *H. pylori* antibiotic resistance rates were 17.2% for clarithromycin, 26.7% for metronidazole, 11.2% for amoxicillin, 16.2% for levofloxacin, 5.9% for tetracycline, and 1.4% for rifabutin. The prevalence rate of clarithromycin, metronidazole, and levofloxacin resistance significantly increased from Europe to Asia, America, and Africa.[45]

It is generally accepted that clinical factors influencing the eradication rate have been unclear. Several studies proposed the possibility that age was one of the main factors affecting the eradication rate among treatment groups.[46-48] In our study, the treatment group either triple or quadruple therapy was the only significant predictor for the eradication rate in a multivariate logistic regression analysis and there were no significance differences in the eradication rate regarding age, sex, or nationality. Studies with larger sample size are recommended for identifying other predictors of eradication rate in both regimens.

Limitations of our study are we did not evaluate the antibiotics resistance in our study which is recommended to be done in subsequent studies. No comparison was done with other antibiotics that may have higher eradication rates like levofloxacin and nitazoxanide.[17] On the other hand, we have many strength points including (1) large representative sample size and (2) it is the first comparative study to assess the efficacy and safety of standard tripe therapy versus the non-bismuth based quadruple therapy for the eradication of *H. pylori* in a large multinational patient population in Kuwait.

Conclusion

Our study demonstrated the superiority of the 14-day non-bismuth based quadruple therapy over the clarithromycin-based triple therapy for *H. pylori* eradication. This is most likely due to an increasing rate of resistance to clarithromycin in Kuwait over the past 13 years, leading to reduced efficacy of the standard triple therapy. Further studies are recommended to identify local resistance to guide the choice of appropriate therapy.

Research quality and ethics statement

This study was approved by the Ethics Committee (Kuwait Ministry of health Ethics Committee Approval #2016-367). The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the conduct of this research project.

Acknowledgment

This work was supported by Abbott Laboratories GmbH.

Declaration for all articles: We also certify that none of the authors is a member of the Editorial board of the JGID.

Financial support and sponsorship

This study was supported by Abbott.

Conflicts of interest

There are no conflicts of interest.

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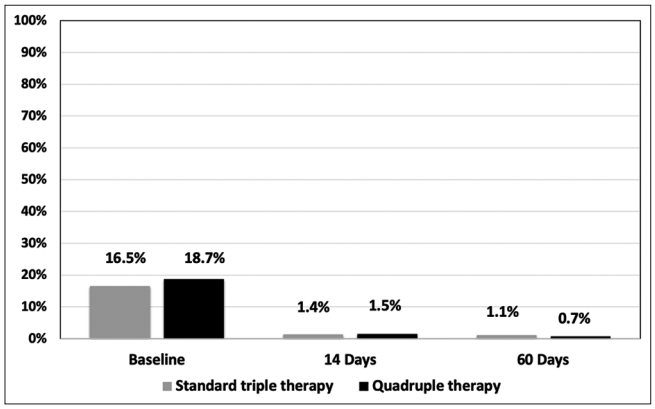
Supplementary Table 1: Stratification of the per protocol eradication rate according the baseline characteristics

Variable	Standard triple therapy (*n*=303)		Quadruple therapy (*n*=300)	
	Negative UBT (*n*=177), *n* (%)	Positive UBT (*n*=97), *n* (%)	Negative UBT (*n*=204), *n* (%)	Positive UBT (*n*=56), *n* (%)
Gender				
Male	89 (67.42)	43 (32.58)	116 (81.11)	27 (18.89)
Female	88 (61.97)	54 (38.02)	88 (75.21)	29 (24.79)
Kuwaitis				
Non-Kuwaitis	125 (66.84)	62 (33.16)	137 (79.19)	36 (20.81)
Kuwaitis	52 (60.47)	34 (39.53)	67 (77.01)	20 (22.99)
Egyptians				
Non-Egyptian	123 (64.73)	67 (35.27)	152 (76.00)	48 (24.00)
Egyptian	54 (65.06)	29 (34.94)	52 (86.67)	8 (13.33)
Arab				
Non-Arab	25 (71.43)	10 (28.57)	41 (75.93)	13 (24.07)
Arab	152 (63.87)	86 (36.13)	163 (79.13)	43 (20.87)
Asian, African and others				
Asian	122 (65.24)	65 (34.76)	148 (77.08)	44 (22.92)
African	55 (65.48)	29 (34.52)	55 (82.09)	12 (17.91)
Others	0	2 (100)	1 (100)	0

UBT: Urea breath test



Supplementary Figure 1: Frequency of epigastric tenderness throughout the study visits. Pearson Chi-Square test did not reveal any difference in the adverse frequency of epigastric tenderness between the two groups allover the study period ($p > 0.05$)