



Quadruple therapy for **H. pylori** eradication

PYLERÀ®
CAPSULES

(bismuth subcitrate potassium,
metronidazole, tetracycline HCl)



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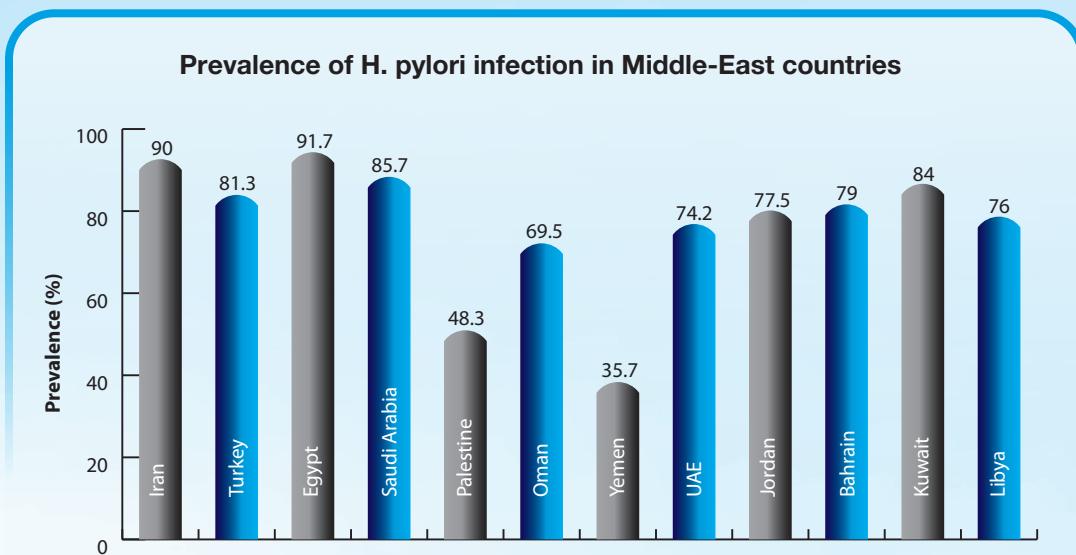
Helicobacter pylori: The Middle East scenario

Helicobacter pylori infection is ubiquitous, and infects about half of the world's population.¹

H. pylori is notorious for causing gastritis and peptic ulceration, and is cited as a significant risk factor for gastric adenocarcinoma, the second highest cause of mortality due to cancer worldwide.²

The rates of H. pylori infection in the Middle East region are reported to be high and warrant attention.³ Epidemiological data from some of these countries show the incidence of H. pylori infection in children to be 40-70%, which increases with age to 85-90%.⁴

The following figure shows the prevalence of H. pylori infections in various Middle East countries.^{2,3,5}



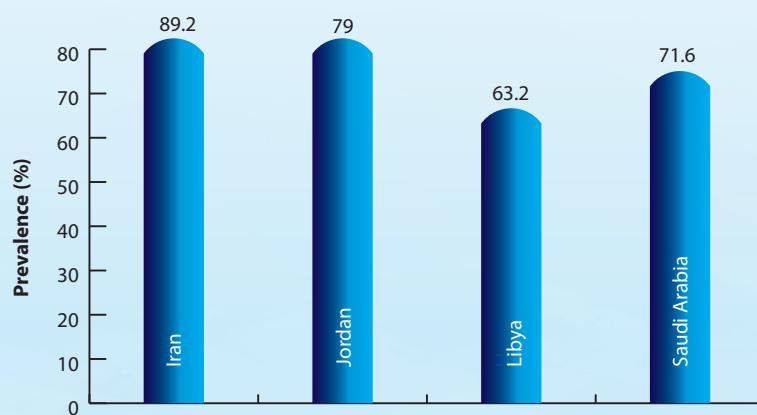
Gastric cancer due to H. pylori

The association of H. pylori infection with benign and malignant diseases of the gastrointestinal tract is well-recognized.⁶ In fact, H. pylori has been deemed as the strongest risk factor for gastric cancer.⁷

In the Middle Eastern countries, gastric adenocarcinoma occurring as a consequence of chronic H. pylori infection, is a significant cause disability adjusted life-years, and imposes a high health-care burden.⁸

In an Iranian study⁹, 89.2% of adults with gastric cancer aged 40 years or above had evidence of H. pylori. Similarly, the microbiological/serological tests in 79% and 71.6% patients with gastric carcinoma in Jordan and Saudi Arabia, respectively were positive for the organism.¹⁰ Libyan studies¹¹ have further suggested H. pylori infection to be the most probable causal factor of gastric cancer, particularly in the Eastern territory. In patients with histologically proven gastric adenocarcinoma and malignant lymphoma, residing in Eastern Libya, the overall frequency of H. pylori infection was 63.2%.

High rates of H. pylori infection in Middle-Eastern patients with gastric cancer

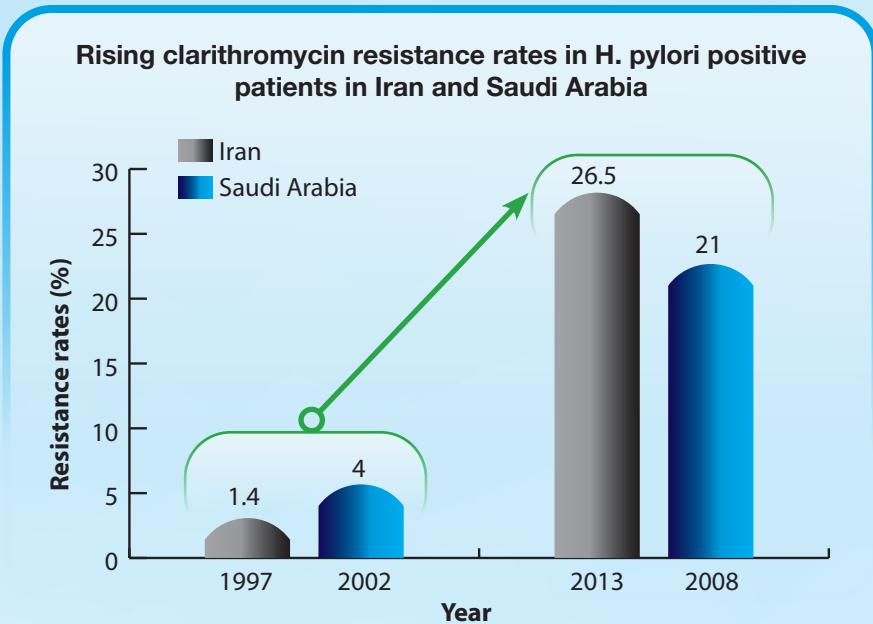


Growing threat of clarithromycin resistance

Eradication of *H. pylori* infection is a promising preventive strategy for gastric cancer, particularly in high risk regions of the world.⁹

Historically, clarithromycin-based triple therapy was considered a standard empiric treatment for *H. pylori* infections. However, rising rates of bacterial resistance to clarithromycin have compromised its efficacy.¹²

The resistance rates of *H. pylori* to clarithromycin have been increasing over the last 20 years in some Middle-East countries as shown in the figure.¹³



Recent studies showing high rates of clarithromycin resistance in Middle-Eastern countries

Study	Country	Clarithromycin resistance (%)
Alsohaibani et al ¹⁴ 2015	Saudi Arabia	23.3
Khademi et al ¹⁵ 2015	Iran	22.4
Kocazeybek et al ¹⁶ 2015	Turkey	24.8
John et al ¹⁷ 2015	Qatar	21.2



Is clarithromycin-based triple therapy against H. pylori failing?¹⁷

H. pylori eradication rates have demonstrated a steady decline over the past decade in many regions due to antibiotic resistance. Maastricht 4 guidelines recommend tracing the local antibiotic resistance patterns and to avoid empirical standard triple therapy when clarithromycin resistance is more than 20%. A study was conducted to evaluate the H. pylori eradication rates with standard triple therapy and assess the local antibiotic resistance pattern.

A total of 789 patients were subjected to gastroscopy during the study period, of which 279 (35.35%) were rapid urease test positive. Among these, 268 patients were administered standard triple therapy and eradication rates were studied using urea breath test. H. pylori strains by culture at a reference laboratory were isolated and the antibiotic resistance pattern was studied.

Among the patients receiving standard triple therapy, 115 returned for urea breath test 4 weeks after discontinuing treatment. Only 81 patients had a negative test, indicating 70% eradication rates. Clarithromycin resistance was reported in 21.2%, contributing to the suboptimal eradication rates. Resistance rates of H. pylori to other antibiotics studied are tabulated below.

Antibiotic	Resistant isolates (%)
Amoxycillin	2.9
Clarithromycin	21.2
Metronidazole	78.1
Levofloxacin	15.4
Tetracycline	0
Rifabutin	4.8

The investigators concluded that standard triple therapy leads to low eradication rates, due to high rates of clarithromycin resistance. Hence, indiscriminate and empirical use of this regimen as first-line therapy for H. pylori treatment in regions of high clarithromycin resistance must be avoided.

Quadruple therapy for H. pylori eradication

Although, an ideal antibiotic for H. pylori should achieve eradication rates of approximately 90%, the World Gastroenterology Organization states that eradication rates by standard triple therapy have dropped to 70% due to increasing clarithromycin resistance.¹⁸

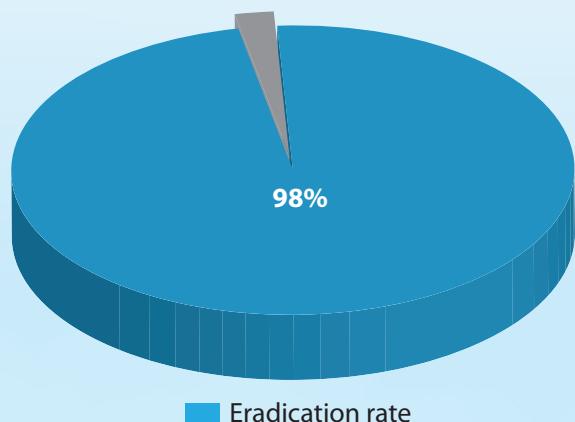
A study¹⁸ from Kuwait suggested the efficacy of standard triple therapy for H. pylori eradication to be suboptimal. Similarly, a 14-day triple therapy was not considered an ideal empiric first-line treatment in Saudi Arabia.¹²

The American college of gastroenterology (ACG) therefore recommends bismuth-based quadruple therapy, which combines bismuth, PPI, tetracycline, and metronidazole, as an alternate first-line treatment option for H. pylori treatment, especially in areas of high rate of clarithromycin resistance (>20%).¹⁸

Up to 98% of H. pylori eradication rate, leading to cure in patients with peptic ulcer disease has been reported by using a bismuth-based quadruple regimen.¹⁹

Bismuth-based quadruple therapy has proven more effective than clarithromycin-based triple therapy for eradicating H. pylori in Kuwaiti patients with chronic gastritis.¹⁸ Similarly, Saudi Arabian researchers have suggested that eradication rates over 90% can be achieved with this regimen even in the presence of high clarithromycin and metronidazole resistance.¹²

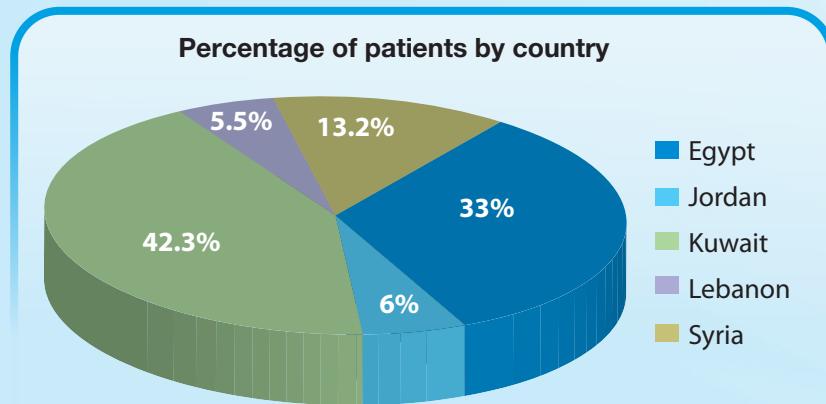
H. pylori eradication rate in patients with peptic ulcer disease on treatment with bismuth-based quadruple regimen¹⁹



Quadruple therapy is superior to standard triple therapy for eradication of H. pylori in Kuwaiti patients¹⁸

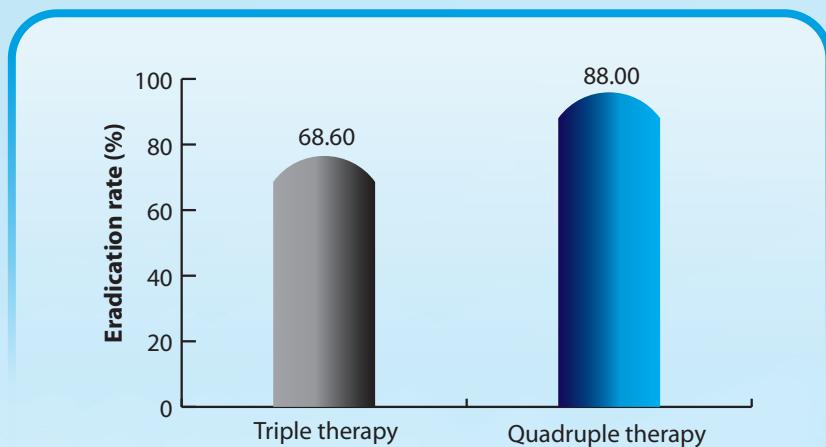
The prevalence of H. pylori among Kuwaitis is estimated to be 42.6%. Adopting H. pylori eradication strategies reduces morbidity due to chronic gastritis and incidence of gastric cancer in high-risk population.

This study compared the efficacy of clarithromycin-based triple therapy and bismuth-based quadruple therapy for eradicating H. pylori in chronic gastritis patients. A total of 218 treatment-naïve dyspeptic patients with gastric biopsy-proven chronic gastritis were recruited. Although the study was performed on patient with 19 nationalities, for the purpose of statistical analysis, they were categorized into top five dominant groups, i.e, Kuwaitis, Egyptians, Syrians, Lebanese, and Jordanians.



They were randomized to receive either triple therapy (omeprazole, amoxicillin, and clarithromycin), or quadruple therapy (omeprazole, bismuth subcitrate potassium, tetracycline, and metronidazole) for 10 days. All patients were tested for eradication of H. pylori by carbon-13 urea breath test 4 weeks after treatment. Assessment was based on variables including age, gender, nationality, and eradication rates.

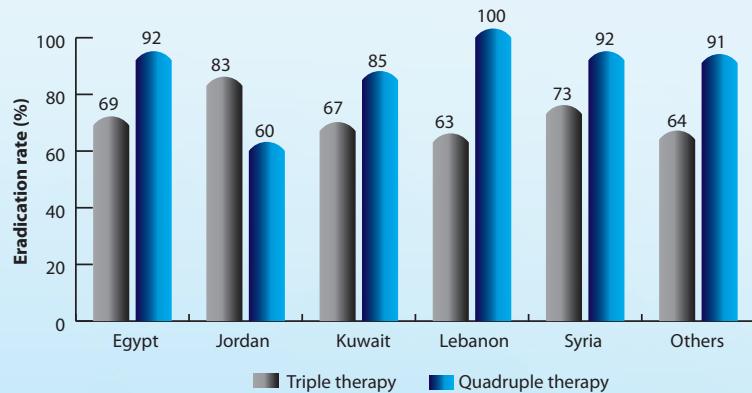
The results demonstrated the response rate to eradication therapy in both groups to be 77.5% ($n = 169$). However, there was a significant difference between the overall eradication rate in the two groups. Patients in the quadruple therapy group achieved a higher eradication rate (88%) than those in the triple therapy group (68.6%).



Median ages of responsive and nonresponsive participants were 42.89 and 44.49 years, respectively. There was no noteworthy difference in the *H. pylori* eradication rates in terms of median age.

However, the response rates to *H. pylori* treatment differed remarkably between males (84.21%, $n = 96$) and females (70.19%, $n = 73$). Likewise, *H. pylori* eradication rate was much higher in males (84.2%) than females (70.2%) in both groups.

Eradication rates varied in patients with different nationalities in both groups, but there was no statistical difference between Kuwaitis and non-Kuwaitis, Egyptians and non-Egyptians, Egyptians and Kuwaitis, or between all studied nationalities, as shown in figure.



The investigators concluded that bismuth-based quadruple therapy was more effective as a first-line therapy than clarithromycin-based triple therapy for eradicating *H. pylori* in patients with chronic gastritis. Males were demonstrated higher response rates to *H. pylori* eradication therapy than females. There were no statistical differences in eradication rates of *H. pylori* between different age groups or ethnic groups.

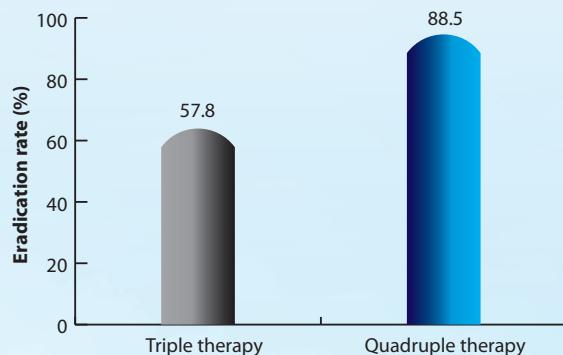
Quadruple therapy provides better eradication rates than triple therapy in H. pylori positive Iraqi patients with peptic ulcer²⁰

Resistance to clarithromycin, the key antibiotic in H. pylori treatment appears to have decreased the efficacy of standard triple therapy worldwide during the last decade. Therefore, quadruple therapy has been recommended as an alternate treatment option. A prospective case controlled study was conducted to compare the eradication of H. pylori using triple and quadruple therapy in Iraqi patients with peptic ulcer disease and to treat the patients who relapsed after triple therapy. The overall response to both the therapies was also evaluated based on Body Mass Index (BMI).

A total of 60 H. pylori positive patients who had established peptic ulcer disease were enrolled and divided into 3 groups. The first group had 38 patients treated with triple therapy (500 mg clarithromycin capsules; 1 g amoxicillin capsules; and 20 mg esomeprazole capsules) for 14 days. The second group had 22 patients who received quadruple therapy (140 mg bismuth sub citrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride) for 10 days, while third group involved patients not responding to triple therapy treated with second-line quadruple therapy for 10 days.

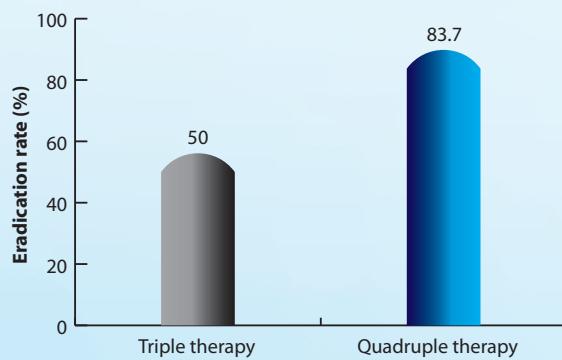
The results demonstrated that the eradication rate of the per-protocol and intention-to-treat for quadruple therapy was 88.57%, 83.78% respectively which was remarkably higher than 57.89% per-protocol and 50% intention-to-treat for standard triple therapy.

Comparative H. pylori eradication rate with standard triple therapy and quadruple therapy based on per-protocol analysis





Comparative H. pylori eradication rate with standard triple therapy and quadruple therapy based on intention-to-treat analysis



The eradication efficacy in patients also differed significantly in terms of BMI, as shown in the following table.

Body mass index	Triple regimen		Quadruple regimen	
	Number of patients	Eradication efficacy	Number of patients	Eradication efficacy (%)
BMI<25	13	53.85%	14	87.5%
BMI 25-30	16	56.25%	11	100%
BMI ≥30	9	66.67%	6	75%

Greater number of eradication failures with the first-line triple regimen occurred in patients aged less than 50 years. Eradication efficacies of the two regimens did not significantly differ between males and females. Patient compliance with quadruple and triple therapy was good for both the therapies.

It was concluded that a 10 day-treatment with quadruple therapy leads to higher eradication rates for H. pylori and is therefore more effective than a 14-day triple therapy in the Iraqi population. Higher eradication rates in this study were obtained for normal, overweight and obese patients.

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- ✓ High efficacy up to 90% eradication rates in patients of Clarithromycin Resistance³
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- ✓ Well-established tolerability profile^{9,10}
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Abbreviated prescribing information.

INDICATIONS AND USAGE: PYLERA® is a combination antibacterial indicated for the treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. **DOSAGE FORMS AND ADMINISTRATION:** Each dose of PYLERA® includes 3 capsules and should be taken 4 times a day, after meals and at bedtime for 10 day. Administer PYLERA with omeprazole 20 mg twice daily, after morning and evening meals **DOSAGE FORMS AND STRENGTH:** Each capsule of PYLERA® contains (140mg of bismuth subcitrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride) **CONTRAINDICATIONS:** Patients with renal impairment and Patients with known hypersensitivity to product components. **USE IN SPECIFIC POPULATIONS:** Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. Pediatric Use: Tetracycline may cause permanent discoloration of the teeth. Enamel hypoplasia has also been reported. Do not use in children less than 8 years of age. **WARNINGS AND PRECAUTIONS:** Fetal Toxicity, Maternal Toxicity, Central and Peripheral Nervous System Effects, Development of superinfection and photosensitivity. **ADVERSE REACTIONS:** The most frequently reported adverse reactions ($\geq 5\%$) during clinical trials were abnormal feces, Diarrhea, Nausea and Headache. **DRUG INTERACTION:** Methoxyflurane: Risk of fatal renal toxicity, Disulfiram: Psychotic reactions can occur, Alcohol: Abdominal cramps, nausea, vomiting, headaches, and flushing can occur, Oral Contraceptives: Decreased efficacy possibly resulting in pregnancy, Anticoagulants: Potentiation of the anticoagulant effect, Lithium: Increased lithium serum concentrations Antacids, Multivitamins or Dairy Products: Decreased absorption of PYLERA®. **Package quantities:** supplied in bottles of 120 capsules

Full prescribing information is available upon request.

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