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***Helicobacter pylori* eradication in West Asia: A review**

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Malekzadeh R *et al*. *Helicobacter pylori* eradication in Western Asia

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**Abstract**

The efficacy of first- and second-line *Helicobacter pylori* (*H. pylori*) eradication regimens varies considerably in West Asian countries, mainly due to the variable prevalence of resistant organisms. However, no review article has yet evaluated and compared the efficacy of different regimens among different countries of this region. Therefore, we conducted a review to select the best options and provide recommendations for *H. pylori* treatment in this geographic region. A search through PubMed was carried out to obtain relevant randomized clinical trials published in English language up to June 2013. According to the results, among different therapeutic regimens used as the first-line protocols, 10-d Bismuth-Furazolidone/Metronidazole quadruple therapy, 14-d Clarithromycin-containing hybrid therapy and 14-d quadruple therapy including a proton pump inhibitor (PPI) + Bismuth + Tetracycline (500 mg QID) + Metronidazole (500 mg TDS) seemed to be appropriate options. Among second-line therapeutic regimens, Bismuth-based quadruple therapies containing Tetracycline and Furazolidone/Metronidazole, triple therapy containing Amoxicillin and Gatifloxacin and Quadruple therapy including Bismuth + Azithromycin and Ofloxacin seemed to be effective options. Third-line therapies were not evaluated in West Asia; most guidelines, however, recommend choosing optimal eradication regimen according to the pattern of antibiotic susceptibility of *H. pylori*. Although we limited our investigation to *H. pylori* eradication regimens in West Asia, the clinical significance of the results goes beyond the countries situated in this geographic region. In fact, the results are transferrable to any region as long as the patterns of resistance are the same.

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**Key words:** *Helicobacter pylori*; Eradication; West Asia; Resistance; Recurrence

**Core tip:** The efficacy of first- and second-line *Helicobacter pylori* (*H. pylori*) eradication regimens varies considerably in West Asian countries, mainly due to the variable prevalence of resistant organisms. The present study evaluates and compares the efficacy of different regimens among different countries of this region.

Although we limited our investigation to *H. pylori* eradication regimens in West Asia, the clinical significance of the results goes beyond the countries situated in this geographic region. In fact, the results are transferrable to any region as long as the patterns of resistance are the same.

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**Introduction**

*Helicobacter pylori* (*H. pylori*) is among the most common bacterial infections, affecting almost half the world population[[1](#_ENREF_1)]. It is a known cause of chronic gastritis which may be complicated by peptic ulcer disease (PUD), gastric adenocarcinoma and lymphoma. While the prevalence of *H. pylori* infection is decreasing in developed countries, it still occurs commonly in developing countries, beginning in early childhood[[1](#_ENREF_1)]. This suggests the possible role of socio-economic status and living standards in the distribution of the infection.

There is little detailed data on the prevalence of *H. pylori* infection in West Asia; nevertheless, the available data is almost similar among different countries in this region. In Iran, almost 90% of the adult population is infected with the bacterium[[2](#_ENREF_2),[3](#_ENREF_3)]. The prevalence has been reported to be about 82% in Jordan[[4](#_ENREF_4)] and 78.4% among industrial workers and 64.3% among referent workers in the United Arab Emirates[[5](#_ENREF_5)]. At the same time, a significant fraction of children are also infected. According to a report from Turkey, 17.4% of children younger than 1 year were infected with the bacterium and the rate exceeded 70% in adults[[6](#_ENREF_6)]. Al-Moagel *et al*[[7](#_ENREF_7)] reported the prevalence of *H. pylori* infection to range from 40% in individuals aged 5-10 years to more than 70% in those aged 20 years or older in Saudi Arabia. Also, 2 different studies in Kuwait and Yemen reported the prevalence of *H. pylori* infection to be 27% in children younger than 13 years and 12.5% in children 9-10 years old, respectively[[8](#_ENREF_8),[9](#_ENREF_9)] (Figure 1).

The high prevalence of *H. pylori* infection in West Asia highlights the need for identifying definite *H. pylori* eradication regimens for the countries situated in this geographic region.

**Indications for *H. pylori* eradication**

Indications for *H. pylori* eradication vary by geographic regions. In countries with high *H. pylori* prevalence rates, it is not cost-effective to treat every person positive for *H. pylori* infection. Furthermore, *H. pylori* treatment would often constitute a temporary solution due to high recurrence rates. Therefore, guidelines categorize indications for *H. pylori* treatment by the geographic region and *H. pylori* prevalence rates[[10](#_ENREF_10)].

According to Maastricht IV Consensus Report, eradication of *H. pylori* is highly recommended in the following situations[[11](#_ENREF_11)].

Functional dyspepsia, Gastro-esophageal reflux disease, complicated or uncomplicated PUD, mucous-associated lymphoid tissue lymphoma (MALT), before starting and during long term NSAID therapy in patients with a history of PUD, patients receiving long term proton pump inhibitors (PPIs), unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura, gastric cancer prevention in special situations (including first degree relatives, previous history of gastric neoplasia, severe pan-/corpus dominant gastritis, severe gastric atrophy, more than 1 year acid suppression therapy, strong environmental risk factors such as heavy smoking and those who fear gastric cancer) and gastric atrophy.

In addition, advisable indications include presence of intestinal metaplasia and vitamin B12 deficiency.

**Resistance patterns in West Asia**

The prevalence of *H. pylori* resistance to antibiotics is increasing worldwide, mainly correlated with consumption of antibiotics by the general population[[12](#_ENREF_12)].

In West Asia, the resistance rates have been increasing over the last 20 years. In Iran, Clarithromycin resistance has increased from 1.4% in 1997[[13](#_ENREF_13)] to 26.5% in 2013[[14](#_ENREF_14)]. The rate is even reported higher in Turkey and Bahrain[[15-17](#_ENREF_15)]. Resistance to other antibiotics, including Metronidazole, Amoxicillin and Tetracycline, has been on the rise, as well. Table 1 demonstrates primary *H. pylori* resistance to different antibiotics in some West Asian countries. The data highlights the importance of surveillance of antibiotic resistance in clinical practice.

**Data Collection Method**

The present article is a narrative review to critically appraise randomized controlled trials in terms of the efficacy of different treatments for *H. pylori* eradication conducted in West Asian countries.

To find relevant papers, a search was carried out on PubMed website for studies published in English language up to June 2013. The following keywords were used: (“*Helicobacter pylori*” or “*H. pylori*”) and (therapy or treatment or eradication) and country name (Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Iran, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, Yemen). Relevant randomized clinical trials were selected after their abstracts were reviewed by two gastroenterologists. Since the number of second-line therapeutic regimens was very small, non-randomized trials were also included for evaluating second-line therapeutic options for *H. pylori* eradication in this region. Data on type of patients and therapy regimens in each arm and eradication rate based on intention-to-treat (ITT) and per-protocol (PP) analyses were extracted from the selected studies and recorded in data extraction forms.

**First-line treatment regimens**

The optimal first-line regimen for treatment of *H. pylori* infection should be considered the one that can achieve > 90% PP eradication rate[[18](#_ENREF_18)].

According to the Maastricht IV consensus report, the regimen is influenced by the resistance rate to Clarithromycin: thus, standard triple therapy including a PPI + Clarithromycin + Amoxicillin or Metronidazole is recommended for countries with less than 20% resistance to Clarithromycin, while Bismuth-containing quadruple therapies are recommended for those countries with high Clarithromycin resistance[[11](#_ENREF_11)].

**standard triple therapy**

In Iran, a total of 9 studies have investigated the efficacy of standard triple therapy on *H. pylori* eradication (table 2). Out of three 7-d regimens, 1 study showed acceptable eradication rates[[19-21](#_ENREF_19)]. Also, out of three 10-d regimens, 2 were successful in achieving > 90% PP eradication rate[[22-24](#_ENREF_22)] and out of three 14-d regimens, 1 yielded optimal results[[25-27](#_ENREF_25)].

However, out of 12 studies conducted in Turkey to evaluate the effects of 7-, 10- and 14-d standard triple therapies on *H. pylori* eradication, only one of the 14-d regimens could achieve an acceptable eradication rate[[28-39](#_ENREF_28)] (table 3).

Overall, it seems that Clarithromycin-containing triple therapies were not successful in studies performed in West Asian countries. This pattern of response is in concordance with the pattern of resistance to Clarithromycin in these countries. As previously reported by Graham *et al*[[40](#_ENREF_40)], the success rate with standard triple therapy falls below 90% when the level of resistance to Clarithromycin is above 10%and therefore, should not be used unless proven to be locally effective.

In most studies, resistance to Clarithromycin has been reported to be above 10% in Iran[[41-44](#_ENREF_41)] and above 20% in Turkey[[16](#_ENREF_16),[17](#_ENREF_17),[45](#_ENREF_45)] (table 1). Furthermore, Clarithromycin is not routinely administered in Iran due to its high cost.

**Bismuth-containing quadruple therapy**

Venerito *et al*[[46](#_ENREF_46)] conducted a meta-analysis on 12 randomized clinical trials to compare the efficacy of Bismuth-containing quadruple therapy with standard triple therapy. Per-protocol eradication rates were 77.6% and 68.9%, respectively, and both regimens had suboptimal eradication rates.

Out of nine 7-, 10- and 14-d Bismuth plus Metronidazole-containing quadruple regimens in Iran, none had acceptable eradication rates[[20](#_ENREF_20),[22](#_ENREF_22),[26](#_ENREF_26),[47-52](#_ENREF_47)] (table 2). Besides, only one of the 9 studies conducted in Turkey had 90.1% PP eradication rate (table 3)[[30](#_ENREF_30),[34-36](#_ENREF_34),[53-57](#_ENREF_53)].

The efficacy of Bismuth-containing quadruple therapies depends on the pattern of resistance to Metronidazole. In Iran, the resistance rate has been increasing, from 33% in 1997 to 76.8% in 2012[[13](#_ENREF_13),[14](#_ENREF_14),[41-44](#_ENREF_41),[58](#_ENREF_58)]. The rate has also been rising from 38% to 78.5% over the past 20 years in Saudi Arabia[[59-62](#_ENREF_59)]. Moreover, in 2 different studies, 42.6% and 63% of *H. pylori* strains were resistant to Metronidazole in 2012 in Turkey and United Arabia Emirates, respectively[[63](#_ENREF_63),[64](#_ENREF_64)].

Furthermore, the dose and duration of Bismuth therapy are also important variables, especially in case of resistance to Metronidazole[[65](#_ENREF_65)]. In most previous studies, suboptimal dose and duration have been used and, as expected, unsatisfactory results were achieved[[66](#_ENREF_66)]. But when administering higher doses, some studies have reported optimal results even in case of high resistance to Metronidazole. [Salazar](http://www.ncbi.nlm.nih.gov/pubmed?term=Salazar%20CO%5BAuthor%5D&cauthor=true&cauthor_uid=22967122) *et al*[[67](#_ENREF_67)] reported 97.1% PP eradication rate with 2 wk of Omeprazole (20 mg BD), Bismuth subsalicilate (240 mg QID), Tetracycline (500 mg QID) and Metronidazole (500 mg TDS). Also, Bismuth, if given in sufficient duration and doses, may revert metronidazole resistance, and render Metronidazole resistant *H. pylori* sensitive to metronidazole.

**Novel Therapies**

Recently, some studies have shown promising results with the novel sequential therapy. Nevertheless, a meta-analysis performed by Gatta *et al*[[68](#_ENREF_68)] on 46 randomized controlled trials including 5666 patients receiving sequential therapy and 7866 patients receiving non-sequential therapies, indicated the overall PP eradication rate with sequential therapy to be 84.3%. According to the result of the mentioned study, sequential therapy was superior to 7-day triple therapy and yielded a marginally higher eradication rate compared to 10-d triple therapy. However, all the three regimens had suboptimal eradication rates.

In Iran, 3 studies evaluated the efficacy of sequential therapy, none of which showed promising results[[22](#_ENREF_22),[69](#_ENREF_69),[70](#_ENREF_70)]. Also, 4 studies were performed in Turkey (one 10-d and tree 14-d regimens)[[37](#_ENREF_37),[56](#_ENREF_56),[71](#_ENREF_71),[72](#_ENREF_72)]. They all contained Metronidazole and Tetracycline in the second half of therapy, but none could achieve optimal eradication rates (table 3). Another sequential study was conducted in Turkey which contained levofloxacin instead of Clarithromycin. The PP eradication rate was 90%[[38](#_ENREF_38)].

Concomitant therapy is another therapeutic regimen that has been proposed for areas with high resistance to Clarithromycin. It consists of a PPI plus Amoxicillin, Clarithromycin and Metronidazole prescribed simultaneously during the entire duration of therapy. A meta-analysis comprising of 481 patients showed 90% PP eradication rate with concomitant therapy[[73](#_ENREF_73)]. An advantage of this regimen over sequential therapy is its simplicity.

One study evaluated the effects of concomitant therapy in Turkey, with less than satisfactory results. In this study, Tetracycline was used instead of Clarithromycin[[36](#_ENREF_36)].

Hybrid therapy is another novel regimen consisting of dual therapy with a PPI and Amoxicillin over the first 7 days and a concomitant quadruple therapy containing a PPI plus Amoxicillin, Clarithromycin and Metronidazole over the second 7 d. This regimen seems to be effective in areas with dual resistance to Metronidazole and Clarithromycin. A study by Hsu *et al*[[74](#_ENREF_74)] reported 99% PP eradication rate with hybrid therapy.

In an Iranian study, 420 patients were randomized to receive either hybrid or sequential therapy[[69](#_ENREF_69)]. The eradication rates with hybrid therapy were 92.9% and 89.5% on PP and ITT analyses, respectively, while sequential regimen had 79.9% PP eradication and 76.7% ITT eradication rates.

Cetinkaya *et al*[[71](#_ENREF_71)] compared the efficacy of a hybrid regimen with sequential therapy in Turkey. They used Tetracycline instead of Clarithromycin in both regimens. The PP eradication rates were 81.4% and 83.6% in hybrid and sequential therapy groups, respectively.

**Other treatments**

***Quinolones***

Many clinical trials have shown the efficacy of quinolone-based triple therapies in *H. pylori* eradication, ranging from 72% to 96% as the first-line therapy[[75](#_ENREF_75)]. Two studies from Turkey investigated the efficacy of levofloxacin-based triple therapies, but both yielded suboptimal results[[76](#_ENREF_76),[77](#_ENREF_77)]. However, Gatifloxacin-containing triple therapy conferred 92% PP eradication rate in a study performed by Sharara *et al*[[78](#_ENREF_78)] in Lebanon (table 4).

***Furazolidone***

Furazolidone has been used in nine quadruple therapies in Iran[[23](#_ENREF_23),[27](#_ENREF_27),[47-49](#_ENREF_47),[79-82](#_ENREF_79)], four of which showed optimal efficacy, although severe side effects were reported in 14-day regimens. Low dose Furazolidone was used in a further study, which led to significant decline in eradication rate[[81](#_ENREF_81)]. Therefore, another study was conducted in which Furazolidone was administered only over the first 7 days of therapy, Yielding suboptimal eradication rates[[70](#_ENREF_70)]. Consequently, 2 other Bismuth-based quadruple therapies were conducted in 10- and 14-d regimens in which Metronidazole was administered over the first half of therapy and was then replaced by Furazolidone over the second half. Both protocols had ideal results with fewer side effects[[23](#_ENREF_23),[48](#_ENREF_48)].

Furazolidone has also been used in triple therapies in Iran[[21](#_ENREF_21),[81-84](#_ENREF_81)]. Five studies have investigated the effects of 4-, 7- and 14-d Furazolidone-containing triple therapies, but only a 7-d protocol, in which a probiotic had been added to the regimen, could achieve > 90% PP eradication rate[[83](#_ENREF_83)].

In Iran, the resistance of *H. pylori* to Furazolidone increased from 2003 to 2010, although the rise was not significant (0% to 4.5%) (table 1). Furazolidone has low cost and is readily available in developing countries. When it was administered in low doses (50 mg BD), the efficacy of regimen was shown to be very low[[84](#_ENREF_84)]. On the other hand, when administered in high doses (200 mg BD), if tolerated, the efficacy of regimen was comparable to that of Clarithromycin-containing regimens[[80](#_ENREF_80)]. In order to lower the incidence of adverse effects, it is recommended to eliminate foods high in tyramine and also decrease the duration of Furazolidone administration to 5 or 7 d and replace it with Metronidazole for the remaining days or vice versa. It is obvious that the duration of therapy should not be less than 10 d. Four- or seven-day regimens have not been successful even if the bacteria are susceptible to Furazolidone[[21](#_ENREF_21)].

**Bismuth-Clarithromycin quadruple therapy**

Three Iranian studies have investigated the efficacy of 14-d Bismuth- and Clarithromycin-containing quadruple regimens. Only one of the studies could achieve 90% PP eradication rate[[52](#_ENREF_52),[80](#_ENREF_80),[85](#_ENREF_85)]. However, if a Clarithromycin-containing 4-drug regimen is to be tried, hybrid therapy may be a better option since it has higher success rates.

**Treatment failure**

Failure of *H. pylori* treatment depends on multiple factors related to both the bacterium and the host. In fact, the effects of antibiotics *in vivo* are not the same as those observed *in vitro*, since the antibiotics must diffuse to the gastric mucosal layer where the bacteria reside. Moreover, low gastric pH may compromise antibiotic activity. Most antibiotics have greatest activity at neutral pH; nevertheless, Clarithromycin especially has greatest activity at high pH (around 8) and metronidazole has greatest activity at lower pH (around 6). Thus, Clarithromycin is the only antibiotic that benefits from a high pH caused by PPI[[86](#_ENREF_86)]. Furthermore, sometimes *H. pylori* transforms into coccoid shape, which keeps it from the effects of antibiotics[[87](#_ENREF_87)]. Also, some strains, including Cag A-negative strains and those carrying Vac As2m2 allele, show resistance to antibiotics[[88](#_ENREF_88)]. However, the most important factor influencing response to treatment is primary resistance to antibiotics which is increasing all over the world due to extensive use of antibiotics[[12](#_ENREF_12)].

Among host factors, compliance to treatment plays an important role. Patients may not completely adhere to treatment due to adverse effects or combination of multiple drugs in multiple daily doses.

Besides, the patient’s underlying disease also affects the *H. pylori* eradication rate. Many studies have shown that patients with non ulcer dyspepsia have lower eradication rates compared to those with PUD[[88](#_ENREF_88),[89](#_ENREF_89)].

Since low gastric pH lowers the effects of antibiotics, PPIs are administered to increase gastric pH. Most PPIs are metabolized by cytochrome P450 in the liver. Therefore, extensive metabolizer patients do not attain sufficient PPI levels to achieve optimal pH level for antibiotic effects[[90](#_ENREF_90)].

Smoking is also another factor influencing the response to treatment[[91](#_ENREF_91)]; it reduces gastric mucosal blood flow and increases gastric acid secretion; therefore lowering antibiotics activity.

All the mentioned factors should be kept in mind in patients with failure of treatment,

**Second-line treatment regimens**

A second-line *H. pylori* therapy regimen may be considered optimal that can achieve > 80% PP eradication rate[[18](#_ENREF_18)]. Few studies have addressed second-line therapeutic regimens in West Asia.

In a study by Minakari *et al*[[92](#_ENREF_92)], 220 patients who had failed treatment with OABM were randomized to receive either OABC (C: Clarithromycin) or OBAzOf (Az: Azithromycin, Of: Ofloxacin). Per-protocol eradication rates were 74.7% and 86.7%, respectively.

In a study by Sotoudehmanesh *et al*[[93](#_ENREF_93)], 80 patients who had failed treatment with 2 weeks of Omeprazole + Amoxicillin + Bismuth + Metronidazole (OABM) received 2 weeks of OTBF (F: Furazolidone, T: Tetracycline). Per-protocol eradication rate was 90%.

Fakheri *et al*[[94](#_ENREF_94)] investigated the effects of a modified Bismuth- and Furazolidone-containing 14-d quadruple therapy on patients who had failed treatment with classic sequential therapy. The regimen contained Furazolidone only for the first 7 d. The per-protocol eradication rate was optimal (82.9 %).

***Four other studies investigated second-line therapies in Turkey***

In a study by Sezikli *et al*[[31](#_ENREF_31)] 30 patients who had failed treatment with standard triple therapy received Tetracycline instead of Clarithromycin. The per-protocol eradication rate was suboptimal (48.3%).

Another study investigated the effects of 7-d Omeprazole-Amoxicillin-Levofoxacin on 37 patients who had failed treatment with 14-d standard triple therapy. The per-protocol eradication rate was 58.2%[[95](#_ENREF_95)].

In a study by Koksal *et al*[[96](#_ENREF_96)], 56 patients who had failed treatment with 10-d standard triple therapy were randomized to receive either 10-day Ranitidine-Bismuth-Amoxicillin-Clarithromycin (RBAC) or 10-d Ranitidine-Bismuth-Metronidazole-Tetracycline (RBMT). The per-protocol eradication rates were 60.7% and 85.7%, respectively.

Another study investigated the efficacy of 14-d RBMT and 7-d RBAz (Az: Azithromycin) on 52 patients who had failed treatment with 14-d standard triple therapy[[97](#_ENREF_97)]. The results were unsatisfactory (44.4% and 13% PP eradication rates, respectively).

Second-line therapy was also investigated by Sharara *et al*[[98](#_ENREF_98)] in Lebanon. Forty five patients with failed standard triple therapy received Rabeprazole-Amoxicillin-Gatifloxacin for only 7 d. The per-protocol eradication rate was 84.4%.

**Third-line treatment regimens**

No study in West Asia had dealt with patients who have failed second-line *H. pylori* eradication therapy.

According to Maastricht IV Consensus Report, the best therapeutic approach is to obtain gastric biopsy in order to identify suitable antibiotics by culture and antibiogram. However, there are some limitations. The results obtained *in vitro* are not reproduced exactly *in vivo* and vice versa. Furthermore, the sensitivity of *H. pylori* cultures has been reported to be less than 60%[[99](#_ENREF_99)].

Some regimens have been proposed as third-line therapy. Bismuth-based quadruple therapies including quinolones or Furazolidone + Tetracycline are among the candidates[[100](#_ENREF_100)]. Rifabutin is another drug introduced to be effective in third-line regimens[[101](#_ENREF_101),[102](#_ENREF_102)]. However, its risks include myelotoxicity and severe ocular adverse effects, and if used extensively, may lead to resistant Mycobacterium tuberculosis strains in the future.

Therefore, it seems that the best option is still to treat based on antibiotic resistance patterns.

**Cost-effectiveness of therapy**

The studies evaluating the cost-effectiveness of *H. pylori* eradication regimens in West Asia are very scarce. In 2006, Sancar *et al*[[103](#_ENREF_103)] reported 7-d Lansoprazole-Amoxicillin-Clarithromycin and 14-d Ranitidine-Bismuth-Amoxicillin-Metronidazole regimens as the most cost-effective regimens among 8 therapeutic options in Turkey. That study, however, was conducted in 2001 and therefore reflects the expenses of that time. We could not find a newer study on the pharmaco-economics of *H. pylori* eradication regimens in Turkey.

In 2013, Sardarian *et al*[[69](#_ENREF_69)] compared the effects of hybrid vs. sequential regimens in Iran. The PP eradication rates were 92.9% and 79.9%, respectively. The cost of therapy was 30.3$ for the hybrid and 20.5$ for the sequential regimen and Clarithromycin accounted for about 70% of the total price in each arm.

In Iran, Furazolidone, Bismuth, Metronidazole and Tetracycline are very cheap and readily available. A 10-d Pantoprazole-Amoxicillin-Bismuth-Furazolidone therapy costs 8.96$ and a 14-d Omeprazole-Bismuth-Tetracycline-Metronidazole costs 9.85$. Therefore, regarding the results of the present review, the latter 2 regimens seem more cost-effective in Iran.

We found no data about the pharmaco-economics of *H. pylori* treatment from other countries in West Asia.

Nonetheless, it is logical to assume that the cost-effectiveness of different *H. pylori* eradication regimens depends largely on the efficacy of the first-line option, since failure of the initial therapy leads to prescription of more expensive drugs with lower success rates and also additional costs of confirming *H. pylori* eradication.

**Recurrence after successful treatment**

Treatment of peptic ulcer disease, mucus-associated lymphoid tissue lymphoma and also prevention of peptic ulcer complications and even gastric cancer depends on definite *H. pylori* eradication. Recurrence of *H. pylori* infection 1 year after successful treatment is rare in developed countries but goes as high as 41% in developing countries[[104](#_ENREF_104)]. Investigations have shown that recrudescence mostly accounts for the recurrences during the first year after treatment, while re-infection is responsible for those that occur after one year from the treatment.

Recurrence of *H. pylori* infection after successful eradication has been investigated in some countries in West Asia. The recurrence rate after 1 year of treatment has been reported to be 34% in Yemen[[105](#_ENREF_105)], 41.6% in Turkey[[106](#_ENREF_106)] and 5%-19.1% in Iranian adults and 14.7% in Iranian children[[107](#_ENREF_107),[108](#_ENREF_108)].

Also, 2 other studies from Iran reported 2-year and 3-year recurrence rates to be 13.7% and 20.4%, respectively[[109](#_ENREF_109),[110](#_ENREF_110)].

In conclusion, a significant number of successful *H. pylori* treatments result in recurrence after 1 year or more in West Asia. This should influence follow up strategies for patients in these countries.

**Limitations**

The main limitation of the present narrative review is the unavailability of data about *H. pylori* culture results in each study.

Furthermore, heterogeneity was present and the studies differed in many aspects, including the underlying peptic disorder, dose of antibiotics, kinds of PPIs and duration of therapy. This could lead to discrepancy in eradication rates, since increased dose and duration of therapy would change eradication rates and the underlying peptic disorder would influence the results. Also, a significant number of studies had less than 100 patients in each therapeutic arm.

Language was another limitation of the present study and our research was restricted to English reports.

**Conclusion**

Considering the diverse effectiveness of different regimens in West Asian countries, it seems that the ideal therapeutic option must be chosen based on the individual pattern of antibiotic resistance of *H. pylori* in each single country.According to the results of studies conducted in West Asia, most of which were from Iran, 10-d Bismuth-Furazolidone/Metronidazole quadruple therapy, 14-d Clarithromycin-containing hybrid therapy and 14-d quadruple therapy including a proton pump inhibitor (PPI) + Bismuth + Tetracycline (500 mg QID) + Metronidazole (500 mg TDS) seem to be appropriate options among different therapeutic regimens used as the first-line protocols (table 5).Among second-line therapeutic regimens, Bismuth-based quadruple therapies containing Tetracycline and Furazolidone/Metronidazole, triple therapy containing Amoxicillin and Gatifloxacin and Quadruple therapy including Bismuth + Azithromycin and Ofloxacin seem to be effective options (table 5).Third-line therapies have not been evaluated in West Asia, but most guidelines recommend choosing optimal eradication regimen based on the pattern of antibiotic susceptibility of *H. pylori*. Rifabutin-containing triple therapy may also be a suitable option (table 5).Although we investigated *H. pylori* eradication regimens in West Asia only, the clinical significance of the results is not limited to those countries situated in this geographic region. In fact, the results are transferrable to any region provided the patterns of resistance are the same.

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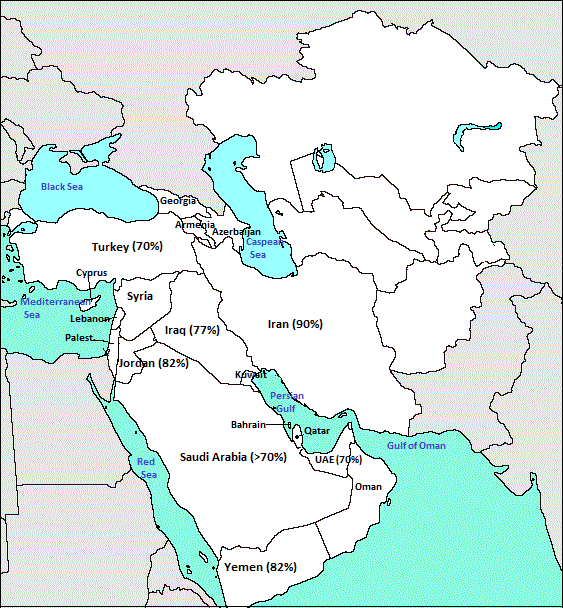
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**Figure 1 map of the prevalence of *Helicobacter pylori* infection (%) in West Asian countries.**

**Table 1 primary *Helicobacter pylori* resistance to different antibiotics in West Asia**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Country(R)** | **Year** | **Number of Patients** | **Testing method** | **Amoxicillin** | **Metronidazole**  **(%)** | **Tetracycline**  **(%)** | **Clarithromycin**  **(%)** | **Other drugs**  **(%)** |
| Iran[[13](#_ENREF_13)] | 1997-2000 | 70 | DDM | 1.4 | 33 | 0 | 1.4 |  |
| Iran[[14](#_ENREF_14)] | 2001-2004 | 135 | DDM | 3.7 | 36.3 | 0.7 | 3.7 |  |
| Iran[[42](#_ENREF_42)] | 2005 | 120 | DDM | 1.6 | 57.5 | 0 | 16.7 |  |
| Iran[[58](#_ENREF_58)] | 2005-2008 | 160 | DDM | 7.3 | 55.6 | 38.1 | 7.3 | Furazolidone: 4.5 |
| Iran[[44](#_ENREF_44)] | 2008 | 124 | DDM | 9.8 | 64.6 | 0 | 17.1 |  |
| Iran[[43](#_ENREF_43)] | 2010 | 42 | DDM | 2.4 | 40.5 | 4.8 | 14.3 | Ciprofloxacin: 2.4 |
| Iran[[41](#_ENREF_41)] | 2012 | 112 | DDM | 28 | 76.8 | 18.6 | 14.3 | Ciprofloxacin: 33  Rifampin: 28.6 |
| Iran[[111](#_ENREF_111)] | 2013 | 153 | DDM | 7.2 | 63.8 | - | 26.5 | - |
| Turkey[[45](#_ENREF_45)] | 2003 | 87 | DDM | - | - | - | 27.5 |  |
| Turkey[[16](#_ENREF_16)] | 2004 | 110 | DDM | - | - | - | 48.2 |  |
| Turkey[[17](#_ENREF_17)] | 2006 | 92 | DDM | - | - | - | 40.5 |  |
| Turkey[[112](#_ENREF_112)] | 2007 | 61 | DDM | - | - | - | 16.4 |  |
| Turkey[[63](#_ENREF_63)] | 2012 | 61 | DDM | 0 | 42.6 | 0 | 21.3 | Levofloxain: 3.3 |
| Lebanon[[113](#_ENREF_113)] | 2002 | 54 | DDM | 0 | 29.5 | 2 | 4 |  |
| Bahrain[[15](#_ENREF_15)] | 1999 | 83 | Epsilometer test | - | 57 | - | 33 |  |
| Saudi Arabia[[59](#_ENREF_59),[61](#_ENREF_61)] | 1988 | 71 | DDM | - | 38 | 1.4 | - |  |
| Saudi Arabia[[59](#_ENREF_59),[61](#_ENREF_61)] | 1996 | 62 | DDM | - | 85.5 | 0 | - |  |
| Saudi Arabia[[59](#_ENREF_59)] | 1998 | 63 | DDM | - | 78.5 | - | - |  |
| Saudi Arabia[[60](#_ENREF_60)] | 2002 | 223 | DDM | 1.3 | 80 | 0.4 | 4 |  |
| Saudi Arabia[[62](#_ENREF_62)] | 2008 | 46 | DDM | 0 | 69.5 | - | 21 |  |
| UAE[[114](#_ENREF_114)] | 2010 | 26 | E- test | - | - | - | 19.2 |  |
| UAE[[64](#_ENREF_64)] | 2013 | 16 | ? | - | 63 | - | - |  |
| Syria[[115](#_ENREF_115)] | 2012 | 130 | FH | - | - | - | 12.3 |  |

DDM: Disk diffusion method; FH: Fluorescence *in situ* hybridization; UAE: United Arab Emirates.

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| --- | --- | --- | --- | --- | --- |
| **Table 2 Randomized controlled trials for *Helicobacter pylori* eradication in Iran** | | | | | |
| **Ref.** | **Type of patients** | **Type of triple therapy regimens** | **Number of patients in each study arm** | **Eradication rate (%)** | |
| **Per-protocol** | **Intention-to-treat** |
| Mirzaee *et al*[[21](#_ENREF_21)], 2012 | NA | PAC-7, PAC-7 with yoghourt, PAC-7 with probiotic | 34-34-34 | 61.3-73.1-64.5 | NA |
| Sarkeshikian *et al*[2[4](#_ENREF_21)], 2013 | PUD + NUD | OAC-10, OAAz-10 | 76-89 | 83-75 | NA |
| Keshavarz *et al*[[25](#_ENREF_21)], 2007 | NUD | OAC-14, OAC[half dose]-14 | 80-80 | 89-88 | 83.7-85 |
| Malekzadeh *et al*[[19](#_ENREF_21)], 2003 | Cancer Screening | OAC-7, OFT-4, OFT-7 | 45-41-42 | 42.1-20.6-29.4 | 35.5-17.1-23.8 |
| Ahmad *et al*[[83](#_ENREF_21)], 2013 | PUD + NUD | OAF-7, OAF-7 with probiotic | 33-33 | 70-90 | 70-90 |
| Roghani *et al*[[84](#_ENREF_21)], 2003 | DU | OAF-14, OAF-14 [half dose] | 63-61 | 88.9-67.9 | 76.2-62.3 |
| Seyedmajidi *et al*[[26](#_ENREF_21)], 2013 | PUD | OAC-14, OABM-14, OCPen-14 | 110-110-110 | 90.8-56-87 | 80.9-50.9-79 |
| Ghadir *et al*[[82](#_ENREF_21)], 2011 | PUD | OAF-14, OABF-14 | 43-43 | 61.1-85.3 | 51.2-67.4 |
| Taghavi *et al*[[27](#_ENREF_21)], 2009 | NUD | OAC-14, O.Co.Dox.-14, OABF-14 | 53-67-69 | 70-63-56 | 66-61-49 |
| Sotudehmanesh *et al*[[52](#_ENREF_21)], 2001 | DU | RBTM-14, RBTM-21, OBCT-14 | 74-73-76 | 73-71-88 | 68-68-80 |
| Malekzadeh *et al*[[49](#_ENREF_21)], 2000 | DU | RABM-14, RABF-14 | 53-53 | 56-82 | 55-75 |
| Khatibian *et al*[[48](#_ENREF_21)], 2007 | PUD | OABM-14, OABF-14, OABF (first week) M (second week) | 107-104,103 | 83.1-95.2,95.3 | 74.5-87,86.6 |
| Shidfar *et al*[[51](#_ENREF_21)], 2012 | NS | OABM-14, OABM-14 + Lycopen | 27-27 | 68-77.8 | 62.9-77.8 |
| Mousavi S. (2006)[[50](#_ENREF_50)] | PUD, NUD | OABM-14, OAzBM-7 | 65-64 | 75.7-78.1 | 70.4-74.1 |
| Agah *et al*[[47](#_ENREF_21)], 2009 | NUD | OABM-14, OABAz[first 7 days]-14 | 30-30 | 69-68 | NA |
| Mirbagheri *et al*[[20](#_ENREF_21)], 2006 | NUD | OAC-7, OABM-10, O.Am.BM-10 | 120-120-120 | 91.1-85.5-92.8 | 84.1-86.6-80.8 |
| Shavakhi *et al*[[85](#_ENREF_21)], 2013 | PUD | OABC-14, OABC-14 with probiotic | 90-90 | 84.4-82.1 | 81.1-76.6 |
| Fakheri *et al*[[80](#_ENREF_21)], 2001 | DU | OABC-14, OABF-14 | 55-63 | 90-90 | 85-84 |
| Daghaghizadeh *et al*[[79](#_ENREF_21)], 2007 | PUD, NUD | OABF-7, OABF-14 | 78-78 | 84.8-82.6 | 71.8-73.1 |
| Fakheri *et al*[[81](#_ENREF_21)], 2004 | DU | OAF-14, OABF(low dose F)-14 , OABF-14 | 50-50-50 | 54-72-92 | 54-72-92 |
| Aminian *et al*[[22](#_ENREF_21)], 2010 | Dyspepsia | OA-MC-10, OABM-14, OAC-10, OCCip[first 7 days]-14 | 107-107-107 | 81.1-85.7-90.7-70 | 80.4-84-90.7-65 |
| Fakheri *et al*[[70](#_ENREF_21)], 2012 | DU | PA-CT-10, PA-BF[7]-14 | 148-148 | 89.1-88.7 | 83.7-80.4 |
| Sardarian *et al*[[69](#_ENREF_21)], 2013 | DU | PA-CT-10, PA-CT-14 (HYBRID) | 210-210 | 79.9-92.9 | 76.7-89.5 |
| Riahizadeh *et al*[[23](#_ENREF_21)], 2010 | PUD, NUD | OAB-MF-10, OAC-10, OAB-CF-10 | 107-106-106 | 91.3-90.4-88.7 | 78.5-81.1-82 |
| O: Omeprazole; R: Rabeprazole; A: Amoxicillin; C: Clarithromycine; Az: Azithrmycine; Cip: Ciprofluxacin; Pen: Penbactam; Of: Ofloxaciline; Co: Co-amoxicalv; Dox: Doxycylcine; F: Furazolidone; T: Tetracycline; M: Metronidazole; B: Bismuth subcitrate; NA: not available; PUD: Peptic ulcer disease; NUD: Non-ulcer dyspepsia. | | | | | |

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| **Table 3 Randomized controlled trials for *Helicobacter pylori* eradication in Turkey** | | | | | |
| **Ref.** | **Type of patients** | **Type of triple therapy regimens** | **Number of patients in each study arm** | **Eradication rate (%)** | |
| **Per-protocol** | **Intention-to-treat** |
| Aydin *et al*[[29](#_ENREF_29)], 2007 | PUD + NUD | PAC-14, PAC-7 | 40-40 | 73.5-47.1 | 67.6-44.4 |
| Yasar *et al*[[33](#_ENREF_29)], 2010 | Dyspepsia | PAC-14, PAC-14 with probiotic | 38-38 | 53-66 | 53-66 |
| Uygun *et al*[[32](#_ENREF_29)], 2004 | Dyspepsia | LAC-14, PAC-14 | 45-45 | 69.2-70 | 62.2-60 |
| Sezikli *et al*[[31](#_ENREF_29)], 2012 | NUD | LAC-14, LAT-14 | 40-40 | 47.4-39.3 | 45-37.5 |
| Aladag *et al*[[28](#_ENREF_29)], 2005 | DU | OAC-14, PAC-14 | 64-62 | 90.6-93.5 | 90.6-93.5 |
| Ericin *et al*[[76](#_ENREF_29)], 2011 | DU | LALevo-7, LALevo-14 | 51-40 | 34.1-72.7 | 27-65 |
| Seven *et al*[[77](#_ENREF_29)], 2004 | PUD-NUD | OALevo-10, OALevo-10 [half dose] | 50-60 | 72.7-60 | 72.7-60 |
| Gumurdulu *et al*[[30](#_ENREF_29)], 2004 | PUD | OAC-7 , OAC-14, OBTM-10 | 53- 59- 52 | NA | 24.5- 40.6-61.5 |
| Alkim *et al*[[34](#_ENREF_29)], 2011 | PUD + NUD | OAC-14, LAC-14, RAC-14, PAC-14, EAC-14, RBAC-14 | 66-66-66-66-66-66 | 65.6- 72.1-84.4- 62.5-60.3- 85.7 | 63.6- 66.7-81.8- 60.6-57.6- 81.8 |
| Songur *et al*[[35](#_ENREF_29)], 2009 | PUD, NUD | LAC-14, LMT-10, LBMT-10, RLBMT-10 | 113-115-119-117 | 35.6- 64.4-54.9- 64.6 | 32.7- 60-47.1- 57.3 |
| Uygun *et al*[[36](#_ENREF_29)], 2007 | NUD | LAC-14, LBMT-14 | 120-120 | 62.7 – 82.3 | 57.5 – 70 |
| Uygan *et al*[[56](#_ENREF_29)], 2012 | NUD | EABT-14, EAMT-14 | 100-100 | 89.7-80.4 | 79-74 |
| Sezgin *et al*[[55](#_ENREF_29)], 2006 | PUD + NUD | RBMT-14, PBMT-14 | 42-40 | 61.9-55 | 61.9-55 |
| Uygun *et al*[[57](#_ENREF_29)], 2007 | NUD | RBAT-14, RBAC-14, RBMT-14 | 100-100-100 | 64.4-66.2-58.9 | 58-59-56 |
| Akyldiz *et al*[[53](#_ENREF_29)], 2009 | PUD + NUD | RBAT-14, RBADox-14 | 58-57 | 40.8-45.7 | 34.5-36.8 |
| Koksal *et al*[[54](#_ENREF_29)], 2013 | Dyspepsia | OBTM-14 ,  OBTM-14[Optimal dose] | 45 - 45 | 86.8 – 90.1 | 73.3 – 89.9 |
| Nadir *et al*[[37](#_ENREF_29)], 2011 | Dyspepsia | LA-MT-14, LAC-14, | 144-138 | 77.6-53.6 | 72.2-52.5 |
| Yakut *et al*[[72](#_ENREF_29)], 2010 | Dyspepsia | PA-MT-10, RaBAC-14 | 108-75 | 88-95 | 88-95 |
| Uygun *et al*[[39](#_ENREF_29)], 2008 | NUD | PA-MT-14, PAC-14 | 150-150 | 80.1-63 | 72.6-58 |
| Cetinkaya *et al*[[71](#_ENREF_29)], 2010 | NUD | PA-MT-14, PA-TM-14 (HYBRID) | 56-56 | 83.6-81.4 | 82.1-78.5 |
| Polat *et al*[[38](#_ENREF_29)], 2011 | NUD | E-A-[first 7 d]-LevoM-[last 7 d]-14, EAC-14 | 75-75 | 90-57 | 86.6-50.6 |
| O: Omeprazole; E: Esomeprazole; B: Bismuth; Ra: Ranitidine; A: Amoxicillin; C: Clarithromycine; L: Lansoprazole; P: Pantoprazole; T: Tetracycline; M: Metronidazole; R: Rabeprazole; Levo: Levofloxacine; NA: not available; PUD: Peptic ulcer disease; NUD: Non-ulcer dyspepsia. | | | | | |

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| --- | --- | --- | --- | --- | --- |
| **Table 4 Randomized controlled trials for *Helicobacter pylori* eradication in other West Asian countries** | | | | | |
| **Ref.** | **Type of patients** | **Type of triple therapy regimens** | **Number of patients in each study arm** | **Eradication rate (%)** | |
| **Per-protocol** | **Intention-to-treat** |
| Sharara *et al*[[78](#_ENREF_78)], 2004 | Dyspepsia | RAG-7, R[half dose]AG-7 | 52-52 | 92-83 | 92-83 |
| A: Amoxicillin; C: Clarithromycine; R: Rabeprazole; G: Gatifloxacine; Tin: Tinidazole; R: Rabeprazole; E: Esomeprazole; T: Tetracycline; PUD: Peptic ulcer disease; NUD: Non-ulcer dyspepsia. | | | | | |

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| --- |
| **Table 5 Recommended treatment regimens for *Helicobacter pylori* eradication in West Asia** |
| **First-line therapeutic options:**  **10-d Bismuth-Furazolidone Quadruple therapy:**  Pantoprazole 40 mg BD + Amoxicillin 1 g BD + Bismuth 240 mg BD for 10 d; Metronidazole 500 mg BD just over the first 5 d and Furazolidone 200 mg BD over the second 5 d.  **14-d Clarithromycin-containing Hybrid therapy:**  Pantoprazole 40 mg BD + Amoxicillin 1 g BD for 14 d and Clarithromycin 500 mg BD + Tinidazole 500 mg BD just over the last 7 d.  **14-d Omeprazole-Bismuth-Tetracycline-Metronidazole, if:**  Omeprazole 20 mg BD + Bismuth 240 mg BD + Tetracycline 500 mg QID + Metronidazole 500 mg TDS for 14 d. |
| **Second-line therapeutic options:**  **14-d Omeprazole-Bismuth-Tetracycline-Furazolidone:**  Omeprazole 20 mg BD + Bismuth 240 mg BD + Tetracycline 500 mg BD + Furazolidone 200 mg BD (if Furazolidone is not used as first-line)  **14-d Ranitidine-Bismuth-Tetracycline-Metronidazole:**  Ranitidine-Bismuth 400 mg BD + Tetracycline 500 mg BD + Metroidazole 500 mg BD  **7-d Rabeprazole-Amoxicillin-Gatifloxacin:**  Rabeprazole 20 mg BD + Amoxicillin 1 g BD + Gatifloxacin 400 mg Daily  **14-d Omeprazole-Bismuth-Azithromycin-Ofloxacin:**  Omeprazole 20 mg BD + Bismuth 240 mg BD + Azithromycin 250 mg BD + Ofloxacin 200 mg BD |
| **Third-line therapeutic options:**  The optimal regimen must be chosen according to the pattern of antibiotic susceptibility of *H. pylori*1. |

1Rifabutin-containg triple therapy may also be a suitable option[[101](#_ENREF_101),[102](#_ENREF_102)]. BD: Twice a day; TDS: Three times a day; QID: Four times a day.