

Helicobacter pylori treatment in Turkey: Current status and rational treatment options

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ABSTRACT

According to the TURHEP study, the prevalence of *Helicobacter pylori* in Turkey is 82.5%. After FDA approval in 1995, many countries have used standard triple therapy (proton pump inhibitor 40 mg b.i.d clarithromycin 500 mg b.i.d and amoxicillin 1 gr b.i.d) for *Helicobacter pylori* treatment. In the beginning, eradication rates were above 90% in many countries; however, current studies have demonstrated a prominent decrease in successful treatment rates, even down to 60%. This unfavorable reduction stimulated searches for new treatment protocols. Treatment protocols differ according to country, prevalence, cost-effectiveness, antibiotic resistance, CYP2C19 polymorphism and eradication rates. Thus, each country/region needs to revise its own therapeutic results and the efficacy of various eradication regimens in the treatment of *Helicobacter pylori*. This report aims to review the current status of *Helicobacter pylori* treatment in Turkey and to provide recommendations for rational therapeutic considerations for the eradication of the bacterium.

Keywords: Eradication; *Helicobacter pylori*; proton pump inhibitors; Turkey.

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Helicobacter pylori (Hp) is a frequently encountered gram-negative pathogenic bacterium that affects almost half of the world population [1]. This worldwide common agent discovered by J.R. Warren and B. Marshall in 1982 has been linked to gastric cancer and many other malignant and non-malignant diseases [2, 3]. Hp prevalence is 10–50% in developed countries and 80% in developing countries, the annual incidence being 1% and 5–10%, respectively. The epidemiology of Hp varies widely according to age, socioeconomic status and geographic area [1, 4]. The age-related prevalence in developing countries ranges between 5% for the 0–5 age group and up to 60% for the 5–17 age group, yet Hp infection is markedly more prevalent at younger ages in developing countries than in developed countries [2–4].

This high prevalence of Hp and the burden of associated diseases has made its eradication a challenging issue. Since conventional triple therapy used for Hp eradication has shown decreasing success, other options have come into question. In recent years, treatment regimens have included sequential therapies, concomitant therapies, and hybrid therapies used in various combinations [2, 4]. The main point is that eradication rates of Hp differ between countries, particularly due to differences in antibiotic resistance [4–6]. Thus, each country/region needs to revise its own therapeutic results and the efficacy of various eradication regimens in the treatment of Hp. This report aims to review the current status of Hp treatment in Turkey and to provide recommendations for rational therapeutic considerations for its eradication.

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Epidemiology

According to the TURHEP study, the prevalence of Hp in Turkey is 82.5% [2]. Bor et al. demonstrated that Hp prevalence is inversely proportional to reflux prevalence [7]. *H. pylori* is most prevalent in the Southeastern Anatolia region at a rate of 88.7%, where the reflux prevalence is around 17%. However, in the Marmara region, the Hp prevalence is low at 71.8%, while the reflux prevalence is 27.3% [7]. In a multi-centered study consisting of biopsies taken during routine endoscopy procedures, the prevalence of Hp was 65% [8]. In another study from the Erzurum region, it was reported to be 71% [9].

In addition to its high prevalence in children from families with low socioeconomic status, other risk factors for Hp are unclean water and food, being raised in a crowded family with an infected mother or father, and contact with infected devices or stomach contents [10–12]. Chronic infection usually takes place during infancy through intra-familial transmission from mother to baby by direct contact or contamination of saliva or feces transmitted by food, water, or medical devices [10–11]. Also, endogenous infection by the the colonization of the teeth is important. Anand et al. showed that dental stones and plaques are an important source of re-infection after Hp treatment. Hence, it should not be forgotten that these plaques constitute an important target for the eradication of Hp [13].

The prevalence of Hp infection in the adult population does not decrease with the improvement of sanitation conditions in the country, although childhood Hp diminishes by resolving the sanitation problems and development of healthier living conditions. A reduction in the prevalence of adults can be achieved by effective eradication of Hp [13–15]. For rapidly developed economies, such as Japan, the prevalence of Hp is expected to decline in all age groups, even to become a rare disease in the future [16]. Eradication is successful if Hp cannot be shown at least 4 weeks –or 3–6 months, according to some experts - after the end of the treatment [10, 11, 13]. Infection by another Hp strain after absolute eradication is true re-infection, which is rare in adults. Recurrence of Hp at six months is 1.7% when the ER exceeds 80% and 20% if the ER is <80% [16].

After acute infection in childhood, the disease may progress to gastric and duodenal ulcers, MALT lymphoma, atrophic gastritis, dysplasia, or carcinoma in adulthood or may continue to be asymptomatic [14–16]. In accordance with this, The Kyoto global consensus re-

port by the Japanese Society of Gastroenterology recommends treating all patients with Hp gastritis [15].

Diagnosis

Hp diagnostic tests consist of invasive and non-invasive tests. The most common non-invasive tests are serology, urea breath test and stool antigen tests, whereas invasive tests are the rapid urease test, histopathology, culture and PCR [1, 2, 4]. After an effective eradication treatment, control using the urea breath test is commonly used following discontinuation of antibiotics for one month and proton pump inhibitors for 7–14 days. If the urea breath test is not available, a stool antigen test is appropriate [1, 4].

Treatment

After FDA approval in 1995, many countries have used standard triple therapy (PPI b.i.d, clarithromycin 500 mg tb b.i.d and amoxicillin 1 gr tb b.i.d) for Hp treatment [5]. Although treatment success rates at the beginning were above 90% in many countries, studies demonstrated a gradual decline in the eradication rates in the subsequent years, even down to 60% [14–15]. This reduction stimulated searches for new treatment protocols. In Turkey, this rate was found to have decreased to 55.7% [9, 17].

The eradication rate for sequential treatment (PPI 40 mg b.i.d and amoxicillin 1 gr b.i.d for the first five days and PPI b.i.d, clarithromycin 500 mg b.i.d and metronidazole 500 mg t.i.d for the next five days) was higher at the beginning but decreased to 80% in the following years whereas concomitant therapy (PPI 40 mg b.i.d and amoxicillin 1 gr b.i.d, clarithromycin 500 mg b.i.d and metronidazole 500 mg t.i.d) showed a success greater than 90% in the first years, but decreased to 80% subsequently [5, 8]. The rates of eradication for levofloxacin-based treatments (PPI 40 mg b.i.d, levofloxacin 500 mg b.i.d, amoxicillin 1 gr b.i.d) used as first-line treatment were around 80–85% [8, 17]. In the literature, it has been proposed that clarithromycin resistance rates have now reached ~40% in Turkey. Moreover, increasing levofloxacin resistance is another important concern since the restriction of macrolides use. And of course, increased prevalence of primary levofloxacin resistance may easily and negatively affect the efficacy of levofloxacin-based regimens [18].

The indications for Hp treatment and the drugs which are used are shown in Table 1 and Table 2, respectively. European Medicines Agency recommendation for an-

TABLE 1. Indications for *H. Pylori* treatment

Conditions requiring treatment:
1. Duodenal or gastric ulcer (without activity or complication)
2. MALT-lymphoma (gastric)
3. Atrophic gastritis
4. Story of previous gastric surgery
5. Gastric cancer in first-degree relatives
6. If the patient him/herself wants Hp eradication therapy
Conditions where treatment can be recommended:
1. Dyspepsia patients
2. Gastroesophageal reflux disease patients
3. NSAID users
4. Idiopathic thrombocytopenia
5. Unexplained anemia of iron deficiency
6. Other controversial extragastric conditions (such as IHD, DM)

TABLE 2. Drugs which are used in Hp treatment

Antibiotics
Amoxicillin (A) 2X1000 mg
Clarithromycin (K) 2X500 mg
Metranidazole (M) 3X500 mg
Tetracycline (T) 4X500 mg
Levofloxacin (L) 1X500 mg
Tinidazole (Ti)
Doxycycline (D)
Furazolidone (F)
Rifabutin (R)
PPIs
Omeprazole (O)
Lansaprazole (L)
Pantoprazole (P)
Esomeprazole (E)
Rabeprazole (R)
Bismuth salts (4X1)
Ranitidine bismuth citrate
Colloid bismuth citrate
Bismuth subsalicylate

PPIs: Proton pump inhibitors.

tibiotic sensitivity and resistance rates in Hp treatment are displayed in Table 3.

Current drugs used in the treatment of Hp are rather limited. Several combinations of regimens have been

TABLE 3. European Medicines Agency recommendation for antibiotic sensitivity and Hp resistance rates (%)

European Medicines Agency recommendation for antibiotic sensitivity:	
Generally sensitive	<10
Rarely sensitive	10–50
Usually resistant	>50
Clarithromycin is important for areas with the resistance of less than 20%; primary treatment can still be applied as a classical 3-drug therapy.	
Resistance rates in Hp treatment:	
Clarithromycin	Approximately 40–50
Levofloxacin	41
Metronidazole	50–76
Amoxicillin	0.5–1.1

used and recently updated. Furthermore, the emergence of antibiotic-resistant bacteria in countries where antimicrobials are extensively used and the paucity of centres providing culture and antibiogram facilities for Hp makes the management of this fastidious bacterium even more challenging. The duration of treatment should be at least 14 days. PPIs should be taken half an hour before meals and all other medications after meals. Bismuth salts, tetracycline and metronidazole are not affected by pH changes. Gastric pH affects amoxicillin and clarithromycin [1].

H. Pylori Treatment in Turkey

Eradication rates of bismuth-containing quadruple regimen in Turkey vary between 77% and 96.4%, and sequential treatment varies between 39% and 82% [1, 5]. For bismuth-containing sequential treatments or levofloxacin containing treatments, the ER range from 82% to 95% [5, 8]. With concomitant treatment, 75% and 90% ER were reported and eradication with hybrid treatment is around 83%. In levofloxacin-based treatment protocols (PPI 40 mg b.i.d., levofloxacin 500 mg b.i.d and amoxicillin 1 gr b.i.d), ER range from 56% to 84% [8, 17, 19].

In their study Erdoğan et al. demonstrated eradication rates of 52.6% to 72.4% with classical triple treatment, concomitant treatment and bismuth-containing quadruple protocols. Overall, eradication rates with these treatment protocols are low in our country, Turkey [20].

One of the important issues in designing the treatment protocol is the drug interactions, which are too often overlooked when combining antibiotics, and as a result, random protocols might be generated. When antibiotics are combined, quinolones, nitroimidazoles and rifampicin should not be in the same group. Otherwise, they will all affect bacterial RNA/DNA. Likewise, tetracyclines and macrolides should not be combined since they both disrupt bacterial ribosomal function. Tetracycline antagonizes the antibacterial effects of penicillin [14, 16, 17]. Calhan et al. used levofloxacin based sequential and bismuth-containing quadruple therapy protocols and reported eradication rates of 85.7% and 93.1%, and there was no statistically significant difference between the two groups. Thus, levofloxacin-based therapies are recommended for second-line treatment in Turkey [17].

The sequential HP eradication protocol consists of: PPI + amoxicillin for the first seven days and PPI + metronidazole + tetracycline for the second seven days. The ER in patients with clarithromycin resistance was 90% in Italy and 88% in Turkey [1, 5, 8]. The eradication rate of 300 patients treated for 10 days with levofloxacin-based protocols was 77% [19]. Levofloxacin can be used as the second choice with penicillin allergy [19]. Aydin et al. used rabeprazole + amoxicillin for seven days and rabeprazole + levofloxacin + metronidazole for the next seven days and indicated an eradication rate of 80% [21]. In 2006, Gisbert reported a 66% eradication rate with levofloxacin [22]. In a multicentre study by Basyigit et al., they applied hybrid treatment protocols based on levofloxacin and the eradication rate was 79.3%. Eventually, they did not suggest this treatment regimen because of ineffectual-cost effectiveness [23].

The last option is rifabutin-based treatments, but they cannot be recommended in our country. Antibacterial activity is not affected by gastric acid in rifampicin containing therapies. Though rifabutin resistant Hp strains have not been isolated, it can only be applied in patients who have received twice but failed Hp treatment. The eradication rate with PPI + amoxicillin + rifabutin for 14 days is 79%. Reported side effects are serious neutropenia and thrombocytopenia [1, 5, 8].

Recommendations of classical treatment protocols in case of high clarithromycin resistant patients are exhibited in Table 4. Studies about new and experimental approaches for the treatment of HP is still going on. However, no worldwide accepted eradication option has been emerged yet (see some examples in Table 5).

TABLE 4. Recommendations of classical treatment protocols in case of high clarithromycin resistant patients

First-line treatment	Quadruple treatment containing bismuth* If not possible, sequential or quadruple (without bismuth) therapy
Second-line treatment	Levofloxacin triple therapy (attention to increasing levofloxacin resistance)
Third-line treatment/ rescue treatments Penicillin allergy	Treatment according to antimicrobial susceptibility and culture results Bismuth quadruple therapy

*Tetracycline resistance is rare, metronidazole resistance is widespread but can be overcome by prolonging the treatment duration.

TABLE 5. New and experimental approaches for the treatment of HP

Liposomal Linoleic Acid (Lipo LLA)
Synthetic antimicrobial peptide; Pexiganan
Probiotics
Phytomedicine (thyme oil, cinnamon, clove oil)
N-Acetyl cysteine, capsaicin, red ginseng
Green tea, red wine
Photodynamic therapy
Vaccination (preventive vaccination against urease → efficacy 71.8%) (China)
Re-immunization of suppressed T cell response (Germany)

Role of PPI's in Hp Eradication Therapy

Most of the PPIs used in Turkey are metabolized via the CYP2C19 enzyme of the cytochrome P450 system (omeprazole, lansoprazole and pantoprazole prominently, and rabeprazole and esomeprazole to a lesser degree) [11]. The important point here is that the enzyme does not metabolize these drugs at the same rates for everyone because of regional differences. Individuals are divided into three groups according to their metabolism:

1. Fast metabolizers
2. Moderate metabolizers
3. Slow metabolizers

In trials of triple therapy containing PPIs, the CYP2C19 polymorphism appears to be 20–25% effective in Hp eradication. In 2003, Miehle et al. studied Omeprazole 4 x 40 mg + Amoxicillin 4 x 750 mg for 14 days and the rate of eradication was reported as 76% [24].

TABLE 6. Hp eradication rates in different CYP2C19 genotypes

Treatment	Eradication rate		
	Fast metabolizing (%)	Moderate metabolizing (%)	Slow metabolizing (%)
Dual therapy; PPI + Amoxicillin	50	64	97
Triple therapy; PPI + Amoxicillin + Clarithromycin	76	89	90
Quadruple therapy; PPI + Amoxicillin + Clarithromycin + Metronidazole	80	98	100

In a study by Furuta et al. investigating the CYP2C19 polymorphism, they used amoxicillin 1 gr 2x1 with omeprazole 4x1 in all groups (rapid, moderate and slow metabolizing) for two weeks [25]. Eradication rates were 28.6% in the fast metabolizing group and 60% in the moderate group, while in the slow metabolizing group, it was 100%. This study demonstrates the importance of CYP2C19 polymorphism in eradication therapies [25]. Intra-gastric pH after PPI treatment was analyzed according to the CYP2C19 gene polymorphism. The fast metabolizing group had a pH of 3–4. In the moderate group, it was between 4 and 5 and the pH in the slow metabolizing group was over 5.4. Hp eradication rate in different CYP2C19 genotypes is shown in Table 6.

Ormeci et al. investigated the effects of high-dose proton pump inhibitors on the eradication of the rapid metabolizing group. They added different PPIs (pantoprazole and rabeprazole) to the classical triple clarithromycin-based treatment. They found that ER exceeded 80% with high-dose PPI [26]. Moreover, the ER for fast, moderate and slow metabolisers in our country was 78%, 19.5% and 2.5%, respectively. Studies of the CYP2C19 polymorphism in Turkey pointed out that the percentage of ‘poor’ metabolizers was 1–5% and ‘homozygous extensive’ metabolizers were 75–84% [26]. Thus, proton pump inhibitors were recommended to be prescribed at higher doses for Hp treatment in our country compared to the rest of the world. PPIs should also be administered at certain intervals - usually as 4x1. This approach can also facilitate control of night acidity. Thus, “nocturnal acid breakthrough” could be avoided.

The duration of treatment should not be fewer than 14 days unless 10 days of treatment is proven to be sufficient. It is also suggested that esomeprazole and rabeprazole should be the preferred PPIs in Europe and North America due to the high rate of rapid metabolizers [26, 27].

Celebi et al. administered proton pump inhibitors to different groups and examined gastric pH on day 1 and day 5 [28]. On the first day, PPIs had increased the gastric pH to above 4: with pantoprazole 35%, esomeprazole 67%, lansoprazole 68% and rabeprazole 60%, respectively. And on the fifth day, the results were pantoprazole 59%, esomeprazole 67%, lansoprazole 68% and rabeprazole 60%. Esomeprazole was the fastest proton pump inhibitor that increased gastric pH above 4 [28].

Other Different Treatment Modalities Regarding Eradication

In the Maastricht V/Florence consensus report, triple or quadruple treatment protocols containing fluoroquinolone are recommended as second-line when eradication cannot be achieved with bismuth quadruple therapy. If eradication cannot be achieved with second-line treatment, culture and antibiotics are recommended in the third step. In the case of fluoroquinolone resistance, different antibiotics, or rifabutin-containing treatment protocols may be used [18]. The Toronto Consensus report also recommends a quadruple therapy protocol containing bismuth as first-line treatment [29]. Treatment success has gradually decreased over the years in bismuth-free regimens, yet there was no reduction in bismuth-containing regimens [29].

In the last 10 years, the success rate of triple therapy has fallen below 80% (50–79%) due to resistance to metronidazole and clarithromycin [5, 8]. Thus, triple treatment is recommended as the first option only in communities with resistance lower than 15–20% for clarithromycin and 40% for metronidazole [26, 28]. Bismuth + PPI + two antibiotics are recommended in populations with high resistance, and if bismuth is not possible, quadruple treatments, such as PPI + three antibiotics, can be used.

TABLE 7. Recommendations for HP eradication

1) Bismuth quadruple therapy (PPI + Bismuth + Two antibiotics)*

2) Bismuth-out quadruple therapy (PPI + Three antibiotics)

3) High dose PPI (4X1) + Amoxicillin 500 mg (4x1) + Tetracycline 500 mg (3 x 1) + Metronidazole 500 mg (3 x 1)

First-line therapy:	Bismuth containing quadruple therapy Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Colloidal bismuth subcitrate 300 mg tb 4x1 Tetracycline 500 mg tb 4x1 Metronidazole 500 mg tb 3x1	OR Sequential treatment without bismuth 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1, 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Tetracycline 500 mg tb 4x1 Metronidazole 500 mg tb 3x1
Second-line therapy:	Concomitant (without bismuth) quadruple therapy: Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Metronidazole 500 mg tb 3x1 Clarithromycin 500 mg tb 2x1	OR Hybrid therapy: 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Clarithromycin 500 mg tb 2x1 Metronidazole 500 mg tb 3x1
Third-line therapy	Levofloxacin Bismuth containing quadruple therapy: Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Colloidal bismuth subcitrate 300 mg tb 4x1 Amoxicillin 750 mg tb 3x1 Levofloxacin 500 mg tb 2x1	OR Sequential treatment with levofloxacin: 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Levofloxacin 500 mg tb 2x1
Fourth-line therapy	Culture + Treatment should be arranged according to antibiogram result	OR 14 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Amoxicillin 750 mg tb 3x1 Rifabutin 150 mg tb 2x1 OR 7 days; Esomeprazole 40 mg or rabeprazole 20 mg tb 3x1 Colloidal bismuth subcitrate 300 mg tb 4x1 Tetracycline 500 mg tb 4x1 Furazolidone 200 mg tb 2x1

Sezikli M. et al. used vitamin C and E supplementation in addition to standard triple therapy and the result was an increase in HP eradication from 60% to 91.25% [30]. A similar study was performed by Demirci H. et al. and they found no difference in eradication rates (76%) [31].

The effects of smoking on treatment success are conflicting in the literature, but a recent large study has sug-

gested that smoking increases the likelihood of unsuccessful first-line treatment for *H. pylori* infection [32].

Cekin et al. added probiotics to the standard triple treatment and they found no difference in eradication rates. There were also fewer side effects in the standard treatment group [33]. Probiotics are proposed to reduce antibiotic side effects with the current treatment proto-

cols. In cases of penicillin allergy, bismuth-containing quadruple therapy protocols may be applied [33]. Recommendations for HP eradication are shown in Table 7.

Conclusion

There are many studies about treatment options for Hp in the literature. Treatment protocols vary according to country, prevalence, cost-effectiveness, antibiotic resistance, CYP2C19 polymorphism and eradication rates. As a high prevalence country, we recommend bismuth-containing quadruple therapy or sequential therapies (without bismuth) for the first-line treatment [16, 34, 35]. For the second line, concomitant (without bismuth) quadruple therapy or hybrid therapy, and for the third line, levofloxacin containing regimens can be administered [16, 34, 35]. As the last step, treatment should be arranged according to antibiogram results. Above all, the importance of patient compliance must be remembered for successful treatment. For the future, an increase in antibiotic resistance looks inevitable; however, effective treatment protocols can still be delivered by combining several agents.

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