**Review article**

# Treatment for *Helicobacter pylori* infection, an overview

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**Abstract**

**The best treatment schedule for eradication of *Helicobacter pylori* in Iran is a type of quadruple therapy for a minimum duration of two weeks. Since, clarithromycin and furazolidone based quadruple regimen has the highest eradication rate, it can be considered as the first line therapy. Metronidazole based quadruple therapy may be used as an alternative choice of first line therapy. It is also important to note that furazolidone based regimens could induce side effects and are highly contraindicated in patients with G6PD deficiency. We recommend triple therapy with a proton pump inhibitor (PPI) (eg, lansoprazole 30mg twice daily, omeprazole 20mg twice daily, pantoprazole 40mg twice daily, rabeprazole 20mg twice daily, or esomeprazole 40mg once daily), amoxicillin (1g twice daily), and clarithromycin (500mg twice daily) for 10 days to two weeks. We suggest substitution of amoxicillin with metronidazole (500mg twice daily) only in penicillin-allergic individuals since metronidazole resistance is common and can reduce the efficacy of treatment. An initial attempt at eradicating *H. pylori* fails in as many as 20 percent of patients. For patients failing one course of *H. pylori* treatment, we suggest either an alternate regimen using a different combination of medications, or preferably quadruple therapy consisting of a PPI twice daily and bismuth-based triple therapy preferably given with meals and an evening snack for 14 days. For those failing two attempts at treatment, it is especially important to reinforce compliance with medications. Culture with antibiotic sensitivity testing can be done to guide subsequent treatments but generally we forgo culture in favor of "rescue" therapy. We suggest levofloxacin (250mg), amoxicillin (1g) and a PPI each given twice daily for two weeks. Alternative dosing regimens have also been suggested.**

**Keywords:** *Helicobacter pylori*, Eradication, Resistance**,** Iran

## Introduction

For many years, the human stomach was considered to be an inhospitable acidic environment in which bacteria could not grow. This view changed following the discovery of *Helicobacter pylori*, from the human stomach in the early 1980s [1]. Human host is the only known reservoir for the infection. Transmission occurs by person-to-person contact, oral-oral, and fecal-oral routes. Infection is most commonly acquired in childhood. In the absence of antimicrobial therapy, *H. pylori* can persist in the human stomach for many decades or potentially for the entire lifetime of the host.

*Helicobacter pylori* is a Gram negative spiral bacillus causing peptic ulcer, low-grade gastric mucosa-associated lymphoid tissue lymphoma (maltoma), carcinoma and other disorders [2-5]. While the prevalence is decreasing in developed countries, it is very common in developing countries, which includes most of the world's population. The incidence rate of *H. pylori* infection in the developed countries may be as low as 30% [6]. While, in different parts of Iran has been reported more than 80% prevalence of *H. pylori* infection in adults older than 35 years [6,7]. A recent study in Ardabil, northwestern of Iran, also revealed near 90% *H. pylori* infection in the normal population, older than 40 years, by histopathology [8].

Although the available antimicrobial therapy is effective, it is still evolving. Antibiotic resistance, patient's poor compliance and intolerance to therapeutic regimens are said to be the major problems with eradication of *H. pylori* [9]. In recent years, resistance to antibiotic therapy has increased, and multiple drug therapies have decreased the patient's compliance [10]. The aim of *H. pylori* treatment is the complete elimination of the organism.

Once this has been achieved, re-infection rates are low; thus, the benefit of treatment is durable. Clinically relevant *H. pylori* eradication regimens must have cure rates of at least 80 percent (according to intention-to-treat analysis) without major side effects and with minimal induction of bacterial resistance. Such goals have not been achieved with antibiotics alone. Because luminal acidity influences the effectiveness of some antimicrobial agents that are active against *H. pylori*, antibiotics are combined with proton-pump inhibitors (PPI) or ranitidine bismuth citrate. The so-called triple therapy, combinations of one anti-secretory agent with two antimicrobial agents for 7 to 14 days has been extensively evaluated, and several regimens have been approved by the Food and Drug Administration (FDA). This review surveys scientific knowledge concerning *H. pylori* treatment and focuses on the many aspects of this infection that are relevant to the clinician.

**First line therapies, proton pump inhibitor based triple therapies**

Following the success of initial trials of proton pump-inhibitor–based triple therapy in Italy and France, large randomized trials confirmed the effectiveness of treatment twice daily for seven days with 20mg of omeprazole, given either with 1g of amoxicillin and 500mg of clarithromycin, or with 400 mg of metronidazole and 250mg of clarithromycin [11]. Several comparative trials have demonstrated the equivalence of 30mg of lansoprazole twice daily, 40mg of pantoprazole twice daily, 20mg of rabeprazole daily, and 20mg of esomeprazole twice daily with omeprazole in these triple therapies [12]. The *H. pylori* eradication rate of metronidazole based on triple drug regimen was 80-90% in western countries, whereas in Iran this rate was lower, possibly due to increasing rate of drug resistance [13].

In a recent study, the approximate rates of drug resistant of *H. pylori* isolates were 70% to metronidazole, 10% to clarithromycin and furazolidone, 20% to amoxicillin, and 5% to tetracycline and ciprofloxacin whereas the *H. pylori* isolated from patients with peptic ulcer disease and dyspepsia were not resistant to amoxicillin plus clavulanic acid [14]. High rate of metronidazole resistance (62.7%) was also reported from other Asian countries too [15]. The rate of adverse effects was more frequent with furazolidone based regimen. Malekzadeh *et al.* [16] reported that in two groups of patients who were receiving the same doses of omeprazole, furazolidone and tetracycline with the durations of four and seven days, the adverse effects of the drugs was very low and the eradication rate of *H. pylori* in both groups were 17% and 23.8%, respectively.

In this study they concluded that in Iran the use of these regimens with duration less than two weeks are ineffective and a minimum of two weeks are needed to have an acceptable outcome.

Roughani *et al*. [17] reported that in the triple therapy consisting of bismuth subcitrate, metronidazole and tetracycline, the eradication rate was 80.7% in metronidazole sensitive strains *H. pylori* and 64% in metronidazole resistant strains. Triple therapy including clarithromycin resulted in an acceptable eradication rate, whereas when the combination of amoxicillin, clarithromycin, and omeprazole used for a duration of 7 and 14 days, the *H. pylori* eradication rate was about 86% and the intent-to-treat eradication rates were 73.1% and 65% respectively [18]. The duration of therapy remains controversial. In Europe, 7-day treatment is recommended, whereas in the United States, 14-day courses have been found to be better than shorter courses and are approved by the FDA [19]. We suggest treatment for two weeks.

**Sequential therapy**

Sequential triple therapy using three antibiotics may improve eradication rates, especially with clarithromycin resistant stains. An illustrative trial included 300 individuals with dyspepsia or peptic ulcer disease who were *H. pylori* positive and were randomly assigned to either a 10-day sequential regimen (40mg of pantoprazole, 1g of amoxicillin, and placebo, each administered twice daily for the first five days, followed by 40mg of pantoprazole, 500mg of clarithromycin, and 500mg of tinidazole, each administered twice daily for the remaining five days) or standard 10-day therapy (40mg of pantoprazole, 500mg of clarithromycin, and 1g of amoxicillin, each administered twice daily) [20]. Both treatments were well tolerated but eradication was significantly greater with the sequential regimen than with standard treatment (89 versus 77%). These differences were even more pronounced in a subset with clarithromycin resistant *H. pylori* strains (89 versus 29%). Two pooled analyses confirmed the efficacy of sequential therapy, especially in those infected with macrolide resistant organisms [21,22]. The role of sequential therapy is still being debated [23,24]. As further published studies become available, the role of sequential therapy in initial treatment of infection will be better defined.

**Quadruple drug therapy**

A proton pump inhibitor can be combined with bismuth (525mg four times daily) and two antibiotics (e.g. metronidazole 500mg four times daily and tetracycline 500mg four times daily) for two weeks. A combination capsule containing bismuth subcitrate 140mg, metronidazole 125mg, and tetracycline 125mg (Pylera (Axcan ScandiPharma) has been approved by the FDA. In 137 patients treated with three combination capsules dosed four times daily for 10 days along with omeprazole 20mg twice daily, *H. pylori* infection was cured in 88% compared to 83% of 137 patients receiving 10 days of omeprazole 20 mg, amoxicillin 1g, and clarithromycin 500mg (OAC) twice daily (not significantly different) [25]. One week of bismuth based treatment may be sufficient as long as it is given with a PPI [26]. A one day course of bismuth based treatment has also been evaluated but long term efficacy has not been established and thus it cannot yet be recommended [27]. Furazolidone a nitrofuran derivative has also been proposed for use in quadruple therapies. However, furazolidone, particularly when combined with bismuth for two weeks is associated with substantial side effects [28].

**Treatment failures**

An initial attempt at eradicating *H. pylori* fails in as many as 20% of patients. A systematic review that included 16 studies and 24 abstracts estimated that eradication rates were 46, 70, 80, and 76 percent for PPI-based dual therapy, PPI-based triple

therapy, ranitidine bismuth citrate-based triple therapy, and quadruple therapy, respectively [29]. For patients failing one course of *H. pylori* treatment, we recommend either an alternate regimen using a different combination of medications, or quadruple therapy consisting of a PPI twice daily and bismuth-based triple therapy (pepto bismol two tablets, tetracycline 500mg, and high dose metronidazole 500mg all four times daily) preferably given with meals for 14 days [30].

A meta-analysis that included four trials concluded that 10-day course of levofloxacin triple therapy appeared to be more effective and better tolerated than seven-day bismuth-based quadruple therapy [31]. In one report, for example, a 70 percent eradication rate was achieved with a 10-day course of pantoprazole (40mg), amoxicillin (1g), and levofloxacin (250mg), all given twice daily [32]. One study evaluated a new combination of antibiotics as "rescue" therapy following treatment failure with "PPI-based triple therapy" [33]. Treatment consisted of pantoprazole (40mg twice daily), rifabutin (either 150mg or 300mg once daily), and amoxicillin (1g twice daily) for 10 days. The higher dose rifabutin combination was significantly more effective than the lower dose combination or quadruple therapy with pantoprazole, bismuth, metronidazole, and tetracycline (eradication rate 87%).

**Antibiotic resistance**

*Helicobacter pylori* is naturally resistant to several commonly used antibiotics, including vancomycin, trimethoprim, and sulfonamides. Primary resistance to antibiotics used in a number of eradication regimens also occurs. At least two studies have estimated the rates of antibiotic resistance in Iran [34,35]. Routine culture for *H. pylori* is not currently recommended. However, patients with refractory disease may require culture and sensitivity testing since the incidence of resistance is dramatically high in this subgroup. Biopsies for culture and testing for antibiotic resistance should be obtained before the forceps are contaminated with formalin. The tissue should be placed into a container and moistened with a single drop of saline; if too much solution is added to the biopsy, the *H. pylori* is likely to be diluted. This sort of preparation will allow culture and sensitivity testing on-site or transport for processing at a central facility. A culture can be obtained on the biopsy used for a CLO® test if the specimen is removed from the gel within one hour and sent immediately to the laboratory.

**Salvage therapy**

In patients with persistent *H. pylori* infection, every effort should be made to avoid antibiotics that have been previously taken by the patient. Bismuth-based quadruple therapy for 7 to 14 days is an accepted salvage therapy. Levofloxacin-based triple therapy for 10 days is another option in patients with persistent infection, which requires validation.

**Conclusion**

High prevalence of *H. pylori* infection warrants further studies to identify the best treatment options. Several good trials of *H. pylori* eradication have been performed in our country; Iranian physicians should be familiar with the best treatment regimen. As a first line treatment, a two weeks quadruple therapy is recommended. Culture and antibiotic susceptibility testing is not advised unless after failure of the second line treatment.

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