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REVIEW ARTICLE

Helicobacter Pylori infection: A review

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INTRODUCTION

Helicobacter pylori (*H. pylori*) a spiral-shaped, Gram negative bacterium found on the luminal surface of the gastric epithelium, was first isolated in 1983 (1). *H. pylori* infection is the most common chronic human bacterial infection (2). Its prevalence increases with lower socioeconomic class and older age, so its geographic distribution is markedly variable (3). *H. pylori* infects more than 50% of the world's adult population. In Iran, 80% of adult population are infected by *H. pylori*, however, only 5-10% have developed peptic ulcer disease (PUD) or much more rarely gastric mucosa – associated lymphoid tissue (MALT) lymphoma (4). In contrast to developed countries, *H. pylori* infection usually acquired during childhood, by the age of 5 years, in developing countries (5). *H. pylori* has the ability to survive within acid environment of stomach (6). Its infection recurrence is a common problem after eradication, which may be due to an infectious source in gastrointestinal tract (7).

Who should test for *H. pylori* infection?

Since majority of *H. pylori* infected patients do not have any obvious clinical disease, routine evaluation is not necessary. Definite indications for diagnosing and treating *H. pylori* infection are endoscopically proven duodenal and gastric ulcer and MALT lymphoma (8,9). Testing for *H. pylori* infection and subsequent eradication is also reasonable after resection of gastric cancer (10). European guidelines recommend to eradicate *H. pylori* infection in patients with family history of gastric cancer in the first-degree relatives and in those with atrophic gastritis, unexplained iron deficiency anemia or chronic idiopathic thrombocytopenic purpura (chronic ITP), but there are scant evidences to support these recommendations. Patients with uninvestigated, uncomplicated dyspepsia should undergo noninvasive testing for *H. pylori* infection and receive eradication treatment if test results were positive (particularly in the area of young populations with *H. pylori* infection prevalence of >10%) (9,11). Non-endoscopic methods are not appropriate for patients with alarm signs (weight loss, persistent vomiting, gastrointestinal bleeding) or for patients older than 45 (in Iran) (12) and 55 years (in developed countries), hence endoscopy should be performed. Generally, noninvasive methods are not recommended for patients with NSAID-associated dyspepsia, since NSAIDs can induce ulcers in the absence of *H. pylori* infection (13).

Test- and- treat strategy avoids the discomfort and costs of endoscopy. However, since only a

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minority of patients with dyspepsia who have positive test result for *H. pylori*, have underlying ulcer disease, almost all patients treated with this strategy are at risk of inconvenience, costs and potential side effects of therapy without a benefit (14). In a placebo controlled clinical trial including 294 patients with uninvestigated dyspepsia and a positive urea breath test for *H. pylori* infection, the 1-year rate of symptom improvement was 50% in patients receiving eradication therapy, compared with 36% symptom improvement in the placebo group (p= 0.02)(15).

In randomized clinical trials which compare test- and- treat strategy with early endoscopy(16) or with proton- pump- inhibitor therapy (17), the three strategies have similar degree of symptom relief, but early endoscopy was more expensive than the other two strategies (18). It seems that the test- and- treat strategy is not cost-effective in populations with low prevalence of *H. pylori* infection (less than 20%) (19) (Table 1).

Table 1. Tests for *H.pylori* infection

Test	Advantages	Disadvantages
Nonendoscopic Serologic test[1]	Widely available; the least expensive test sensitivity (88-89%), specificity(86-95%)	Not recommended for eradication confirmation
Urea breath test[2]	High NPV & PPV values; useful before and after treatment; sensitivity (90-97%), specificity (90-100%)	False negative results possible with use of PPI, antibiotics or bismuth.[3]
Fecal antigen Test	High NPV & PPV with monoclonal antibody test; useful before & after treatment; sensitivity (90%), specificity (98%)	False negative results with recent use of PPI, antibiotic or bismuth.[3]
Endoscopic Urease–based Tests	Rapid, inexpensive and accurate; sensitivity (89-98%), specificity (93-98%)	False negative results with recent use of PPI, antibiotic and bismuth.[3]
Histology	Good sensitivity and specificity; sensitivity (93-99%), specificity (95-99%)	Need expert personnel
Culture	Excellent specificity; sensitivity (77-92%), specificity (100%)	Variable sensitivity

[1] With respect to low sensitivity and remaining positive after H.pylori eradication, serologic test is not recommended in Iran for confirmation of eradication and also diagnosis of H.pylori infection.

[2] Urea breath test with ^{14}C is contraindicated in pregnant women and in nursery period and children. In these patients we can use ^{13}C urea breath test.

[3] In order to confirm the test PPI, H_2- receptor antagonist, bismuth and antibiotics should discontinued at least 14 days ago. (one month period is also mentioned for antibiotics)

There are two clinical guidelines for diagnosing and treating *H. pylori* infection (American College of Gastroenterology and Maastricht III guidelines) which are somehow different (Table 2).

Table 2. Guidelines for evaluation and management of *H.pylori* infection

	American College of Gastroenterology	Maastricht III Consensus Report
Criteria for testing	Active gastric or duodenal ulcer, history of active GU or DU not previously treated for H.pylori infection, gastric MALToma, history of endoscopic resection of early gastric cancer, uninvestigated dyspepsia	Same as ACG criteria with some other criteria: gastric cancer in first-degree relatives, atrophic gastritis, unexplained iron deficiency anemia, chronic ITP
Criteria for test-treat strategy	Age <55 yr; dyspepsia without alarm signs	Age <45yr; dyspepsia without alarm signs
Duration of therapy	10-14 days	7 days

Treatment of *H. pylori* infection

A decade ago, it seemed that *H. pylori* infection treatment would have the same high rate of cure success of other common infections (20). Unfortunately, nowadays successful treatment of *H. pylori* infection is a challenge. The success rate of eradication therapy for *H. pylori* infection has been decreasing, largely due to development of resistance to clarithromycin (21-24). Antimicrobial resistance is not the only cause of dropping eradication rates. In a recent trial, resistance was present in one-third of patients with treatment failure (25). Lack of compliance to treatment is a major factor in eradication failure, but it is difficult to assess in clinical trials.

The latest Maastricht III guideline for *H. pylori* infection treatment emphasizes on regimens containing clarithromycin (500 mg/BD), a PPI (standard dosing) and amoxicillin (1 gr/BD) or alternative regimen including metronidazole (400 or 500 mg/BD) substituting for amoxicillin (24). American College of Gastroenterology (ACG) guideline for *H. pylori* infection treatment also focuses on mentioned regimens, despite only 70-85% success rate (26). In penicillin-allergic patients amoxicillin can be replaced by metronidazole (500 mg/BD).

Table 3. Recommended regimens for treatment of *H.pylori* infection

Regimen	Dosing, duration and drugs
14-day concomitant Treatment	Amoxicillin 1gr/ BD Metronidazole or tinidazole 500mg/BD Clarithromycin 500mg/BD PPI (standard dose)/ BD
10-day sequential Treatment	Amoxicillin 1gr/BD on days 1-5 Metronidazole 500mg/TDS on days 5-10 Clarithromycin 500mg/BD on days 5-10 PPI (standard dose)/ BD on days 1-10
14-day bismuth quadruple therapy	Bismuth subcitrate or subsalicylate two tablet Tetracycline 500mg with meals and HS Metronidazole or tinidazole 500mg/QID PPI (standard dose)/ BD

In order to treat *H. pylori* infection we should consider these issues:

- The golden rule is that to use the treatment regimen which is effective locally (>90-95% success rate)
- Monitor treatment effectiveness over time.
- The success rate for each treatment regimen should be ≥ 95%.
- Assess cured patients for expected outcome. (≥95%)

Several meta-analyses have demonstrated that the effectiveness of clarithromycin containing regimens has been declined due to increasing clarithromycin resistance (27).

Table 4. Recommended *H.pylori* eradication regimens in Iran

Regimen A (2 weeks)
Omeprazole (20mg/BD), **bismuth subcitrate** (240mg/BD), **amoxicillin** (1gr/BD), **furazolidone** (200mg/BD) after breakfast and dinner
Regimen B (2 weeks)
Omeprazole (20 mg/BD), **bismuth subcitrate** (240mg /BD), **amoxicillin** (1gr/BD), **metronidazole** (500mg/BD)after breakfast or dinner
Regimen C (10 days)
Omeprazole (20mg/BD), **bismuth subcitrate** (240mg/BD), **amoxicillin** (1gr/BD), **metronidazole** (500mg/BD) on the first 5 days, followed by **furazolidone** (200mg/BD) on the second 5 days
Regimen D (2 weeks)
Omeprazole (20 mg/BD), **bismuth subcitrate** (240mg/BD), **amoxicillin** (1gr/BD), **clarithromycin** (500mg/BD)
Regimen E (2 weeks) second line treatment
Omeprazole(20mg/BD),**tetracycline**(500mg/BD), **metronidazole** (500mg/BD),**bismuth subcitrate** (240 mg/BD)

There are many reasons to explain why *H. pylori* infection treatment remains a challenge:

- Nature of the microorganism
- Those related to intragastric environment
- Those related to the eradication regimens
- Those related to reactions of the host

The strongest predictor of *H. pylori* eradication failure is antimicrobial resistance (28). To overcome antimicrobial resistance, we can increase the dose, duration or number of antibiotics in the regimen. The underlying disorder condition is also play a role in treatment failure. Some studies have indicated that *H. pylori* treatment in patients with NUD has lower success rate compared with PUD. However, other trials have not demonstrated this effect (23,29).

Table 5. Recommended rescue treatments for H.pylori infection

Regimen	Dosing , duration and drugs
14-day rescue triple therapy	Amoxicillin 1gr/BD on days 1-5 Third drug (fluoroquinolone or rifabutin)[1] PPI (standard dose)/ BD for all 10 days
14-day bismuth quadruple rescue treatment	Bismuth subcitrate or subsalicylate 2 tablets/QID Tetracycline 500 mg with meals and HS New drug (furazolidone 100mg/ TDS) PPI (standard dose)/ BD
14-day high dose PPI-amoxicillin dual therapy	PPI (full dose)/ QID Amoxicillin 500mg/QID

Fluoroquinolons resistance is rapidly rising and should not be used prior to susceptibility testing

Clarithromycin resistance is more frequent in southern European countries such as Italy, Spain, Portugal and France as well as Mexico, Japan and Iran (22,30). Many studies concluded that clarithromycin resistance was more common in women (44 upt), and was associated with older age and the presence of inactive PUD (31,32). Levofloxacin-based triple therapy is another alternative, but increasing worldwide resistance to fluoroquinolones results in that in most regions fluoroquinolones would not be a good choice for the first line therapy (33). A recent study concluded that levofloxacin-based regimen had high eradication rate as the second line treatment, but it was inferior as the first line treatment compared with clarithromycin-based therapy. This study

indicates that in the era of clarithromycin resistance, levofloxacine- based triple therapy cannot be effectively replaced up to the first line treatment and quadruple strategies should be considered as the first line therapy (34). Rifabutin-based triple therapy is prescribed as a salvage regimen when other treatment options have failed, but side effects of rifabutin such as bone marrow suppression limit its widespread use (35).

Global guidelines recommend that first line therapies for *H. pylori* infection should have at least 90% success rate (36). According to meta-analyses, a four-drug regimen (either sequential, concomitant or bismuth containing) is recommended. Concomitant treatment is a quadruple regimen containing a PPI, amoxicillin, clarithromycin and a nitroimidazole (like metronidazole or tinidazole); sequential therapy include a PPI plus amoxicillin (1 gr), each administered twice daily for the first 5 days, followed by a PPI, clarithromycin (500 mg) and metronidazole (500 mg) each administered twice daily for additional 5 days (36,37). Both concomitant and sequential therapies are designed to overcome clarithromycin resistance. The results of a recent meta-analysis suggest that sequential therapy is superior to PPI-based triple therapy in adults .This study have also showed that sequential therapy is preferred in patients with NUD and in persons with clarithromycin-resistant strains, but the results may not be better in patients with PUD (38). In another study, the eradication rate of sequential therapy was 84% compared with the triple therapy rate of 90% (39). Therefore, there are conflicting results about the efficacy of sequential therapy and the role of this regimen is still being debated.

In a recent study, sequential and concomitant therapies were compared and demonstrated that dual resistance to clarithromycin and metronidazole declined the efficacy of the sequential therapy but not the concomitant treatment (40). Nowadays, prescription of concomitant therapy for 2 weeks is recommended to improve eradication rate (41). Theoretically, success rate of sequential therapy can be improved by increasing the doses, duration or the number of drugs in each phase (eg, by continuing amoxicillin in the second phase) (42). A recent study reported on a new sequential-concomitant hybrid regimen with 7 days PPI plus amoxicillin, followed by amoxicillin, clarithromycin, metronidazole and PPI for additional 7 days. This therapy has a success rate of more than >95% (41).

In many countries including Iran, standard quadruple therapy containing a bismuth compound, metronidazole (250 mg/QID), tetracycline (500 mg/QID) and a PPI (standard dose/BD) for 14 days has a success rate of >90% and is superior to standard triple therapy as initial treatment (36). Table 3 summarizes the various treatment modalities for *H. pylori* infection.

In a recent prospective Chinese study, a bismuth compound was added to the legacy PPI-based triple therapy and concluded that the *H. pylori* eradication rate became >90%. Increased treatment duration was also essential. A therapeutic gain of 13% was achieved if the regimen was administered for 14 days instead of 7 days. Clarithromycin resistance can also overcome by the prolonged bismuth containing quadruple therapy (43).

Metronidazole resistant *H. pylori* strains are considered to be the most common cause of treatment failure in developing countries. Approximately 40-70% of *H. pylori* isolates from developing countries are resistant to metronidazole (44-46).

In one study, the resistance rates of *H. pylori* strains isolated from dyspeptic Iranian patients to metronidazole, tetracycline, clarithromycin, furazolidone and amoxicillin were 55.6%, 38.1%, 7.3%, 7.3% and 4.5%, respectively (47). Similar to clarithromycin , metronidazole resistance is more common among women (44upt).

Low resistance rate of *H. pylori* strains in Iranian patients to furazolodone, inspired many

investigators to assess furazolidone-based regimens in Iranian dyspeptic patients.

A study including 278 Iranian *H. pylori*-infected patients with PUD concluded that furazolidone-based regimens are superior to metronidazole-based treatments for Iranian patients. (per-protocol eradication rate of 95.2% in furazolidone-based group vs 83.1% in metronidazole-based group). However, treatment-associated side effects were more common in furazolidone-based regimen (48).

The efficacy of furazolidone-based therapy for eradication of *H. pylori* infection was assessed in a study including 90 Iranian patients with a past history of *H. pylori* infection who had failed to respond to a 14-day course of metronidazole-based quadruple therapy. The total eradication rate of furazolidone-based regimen (consisting furazolidone, bismuth subcitrate, amoxicillin and omeprazole for 14 days) was 78.8%. Based on this study we can conclude that furazolidone can replace metronidazole in areas with high resistance rate to metronidazole (49).

In a prospective randomized controlled trial in Iran, the safety and efficacy of furazolidone was compared with metronidazole. In this study, 106 patients with endoscopically proven duodenal ulcer and positive urease test were assigned to receive ranitidine 300mg, amoxicillin 1gr and bismuth subcitrate 240mg/BD with either furazolidone 200mg/B (RABF), or metronidazole 500mg/BD (RABM) for 14 days. Intention-to-treat eradication rates in the RABF and RABM groups were 75% and 55%, respectively (p=0.03). Per-protocol eradication rates were 82% and 56% in the RABF and RABM groups, respectively (p=0.006) (50).

In another study, quadruple therapy on the basis of metronidazole and amoxicillin was examined as a first line treatment of *H. pylori* infection in Iranian patients. In this study, patients received a 2-week quadruple therapy consisting of metronidazole, bismuth subcitrate, amoxicillin and omeprazole followed by an additional two weeks of omeprazole. Intention-to-treat and per-protocol eradication rates were 34.9% and 35.9%, respectively (51).

There are several surveys which assessed *H. pylori* eradication regimens in Iranian population. Due to high prevalence of metronidazole- and clarithromycin- resistant *H. pylori* strains in Iranian population, it seems that the most effective first line treatment is standard quadruple therapy with either metronidazole or furazolidone for 14 days. (48,52-59). These therapies are shown in table 4.

Follow up after treatment

The eradication of *H. pylori* infection should be confirmed particularly in patients with *H. pylori* associated ulcer or gastric MALT lymphoma. In dyspeptic patients whose symptoms do not improve after *H. pylori* eradication treatment, urea breath test or stool antigen assay should be performed 4 weeks or longer after completion of treatment to confirm eradication. Because of the malignant potential of gastric ulcer, multiple biopsies of a gastric ulcer should be taken at first endoscopy and even if these are negative for malignancy, repeat endoscopy at 8-12 weeks should be performed.

A gastric ulcer that fails to heal after 12 weeks should be considered refractory and malignancy must be excluded (60).

Management of treatment failure

When treatment failure has been occurred, an appropriate second-line therapy should be chosen. For selecting rescue treatment we should consider following issues:

-Which antimicrobial agent is the infection likely to be resistant to?

-Which agent can not be prescribed due to allergy or side effects?

-Which drugs are available locally?

Thus, experts recommend that second-line regimen should include at least one antibiotic the patient has not previously taken (41). Furthermore, we should expect the same success rate for first, second and even third therapies if the organisms are susceptible (41). If a patient used a

clarithromycin-containing concomitant or sequential therapy at first, the best second-line treatment would be 14-day bismuth quadruple regimen (61). If this regimen was not effective, we can replace metronidazole by furazolidone (100mg).

In a study, efficacy of a quadruple furazolidone-based therapy as a second-line treatment in metronidazole-resistant patients, had been examined. Total eradication rate in 89 Iranian patients was 75.6%. Eradication rates were 11/19 and 57/75 among smokers and non-smokers, respectively ($p<0.05$). Eradication rates were 55/70, 6/10 and 7/9 in patients with DU, GU and NUD, respectively ($p>0.05$). Thus, in Iran where clarithromycin is expensive and not available easily, furazolidone could be a good choice (62).

In a study from Ireland including 3280 *H. pylori* infected patients showed that furazolidone-based rescue treatment had high rates of eradication after failure of the standard first-line, second-line and rifabutin-based therapies (63).

These rescue treatments are summarized in table 5.

Side effects of anti-*H. pylori* antibiotics

Metronidazole, tinidazole and furazolidone have carcinogenic effect.

Furazolidone is a monoamine oxidase inhibitor and patients who received this agent should avoid eating all cheeses (except cottage and cream cheeses), bologna, salami and pepperoni, lima beans, lentils, snow bees and soy beans, beer and wines. Other side effects of furazolidone are fever, malaise and nausea. One of the major side effects of furazolidone is flushing.

Fluoroquinolones are associated with increased risk of tendinitis and tendon rupture. This risk is more in patients older than 60 years, in kidney, heart and lung transplant recipients and with concomitant use of corticosteroids (41).

Conclusions

Due to increasing antimicrobial resistance, *H. pylori* treatment success rates decreased over time. The most commonly prescribed regimen of *H. pylori* infection treatment (clarithromycin-based triple therapy) is no longer effective in most populations.

We should choose a treatment regimen which has success rate more than 90%. We should consider following notes for eradicating *H. pylori* infection:

-Do not use the conventional regimen consist of amoxicillin, a PPI and clarithromycin, unless it has been proven to have high eradication rate (≥90%) in per-protocol analyses.

-Prescribe antibiotics for 14 days, unless shorter courses of treatment has been proven locally to be similarly effective.

-Do not use fluoroquinolones if a fluoroquinolone had been previously prescribed.

-After treatment failure, do not reuse drugs for which resistance is likely to have developed. (i.e., clarithromycin, flouroquinolone and metronidazole)

Treatments which need more evaluation are: furazolidone- or nitazoxanide- containing regimens, amoxicillin-PPI dual treatment and hybrids of sequential- concomitant treatments.

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