

TREATMENT OF *HELICOBACTER PYLORI* INFECTION IN IRAN: LOW EFFICACY OF RECOMMENDED WESTERN REGIMENS

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Several consensus guidelines have been formulated to aid the medical practitioner for therapy of Helicobacter pylori infection. While triple therapy with a proton pump inhibitor (PPI), in combination with two antibiotics administered for one week, is the established treatment of choice in many parts of the world, this regimen is far from optimal in Iran. The best results of Helicobacter pylori eradication in this country are obtained with two weeks of furazolidone-based quadruple therapy or clarithromycin based quadruple therapy. Given the high cost of clarithromycin, the former regimen is preferable as a first line treatment. Although documentation of cure is certainly needed for high risk patients (e.g., patients with complicated peptic ulcer or gastric mucosa associated lymphoid tissue), but it is reasonable for any patient who undergoes Helicobacter pylori eradication. Urea breath test 3 months after treatment is the recommended post-eradication testing. For failed treatment, two weeks of quadruple therapy containing a PPI, bismuth and two antibiotics should be used. If a clarithromycin-based regimen was used initially, a furazolidone-based regimen can be used afterwards, and vice versa. Culture and antibiotic susceptibility testing is not recommended unless after failure of second line treatment. The low eradication and higher reinfection rate of H. pylori in Iranian patients in comparison with patients in western countries shows that our H. pylori strains are probably more resistant than those in western countries.

Keywords: *Helicobacter pylori*; Iran; eradication; antibiotics; quadruple therapy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common bacterial infections, affecting nearly half of the world's population. 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. While the prevalence is decreasing in developed countries, it is very common in developing countries, which includes most of the world's population.¹ Seroepidemiologic study in different parts of Iran revealed near 90% prevalence of *H. pylori* infection in adults older than 35 years;² a recent study in Ardabil, north-western part of Iran, also revealed near 90% *H. pylori* infection in the normal population, older than 40 years, by histopathology.³ Several drug regimens have been evaluated for *H. pylori* eradication in Europe,⁴ and in the United States.⁵

Clinical experience in Iran and many other developing countries have demonstrated that eradication rate of *H. pylori* is much lower than the rate reported from western countries, using the same treatment regimens; and the recrudescence or reinfection in short and long terms are much more than the rate reported in the western countries. Considering the high prevalence rate of the infection, high rate of metronidazole resistance (37%), and the resistance rate to clarithromycin in this country,⁶ the treatment regimens suggested in studies from the western world may not be ideal in Iran; treatment regimens and the duration of treatment should be based on local surveys. The optimal therapeutic regimen has not yet been defined. While the treatment has to be effective, considerations such as cost, side effects, and ease of

administration must also be taken into account.

During the last decade, *H. pylori* treatment learning curve has evolved in Iran using randomized double blind trial as our experimentation tool; we have abandoned multiple suboptimal therapies. We have increased the number of agents from monotherapy, to dual, triple, and recently, to quadruple therapy comprising a proton pump inhibitor (PPI), bismuth, and 2 antimicrobial agents. We have learned that treating *H. pylori* is more like treating tuberculosis than treating a urinary tract infection. We have also learned to avoid untested antimicrobial agents. This review discusses the current treatment of *H. pylori*, based on randomised controlled trials in Iran; or else on the best evidence available from a good clinical experience, from Iran or across the world.

HISTORY

Bizzozero, an Italian anatomist in 18th century, was the first to describe spiral bacteria in the stomach. He showed that the bacteria live in acid producing cells of the stomach. But thereafter, the role of *H. pylori* in peptic ulcer disease (PUD) remained in obscurity for nearly a century when Georg Ernst Konjetzny, a German surgeon of the early 20th century suggested the bacterial genesis of gastritis and its relationship to peptic ulcer and gastric cancer.⁷ In the 1970s the association of *H. pylori* and gastritis was described.⁸ Treatment of peptic ulcers specifically with antibiotics was first proposed by John Lykoudis.⁹ Since Lykoudis had no an academic position, he had difficulty publishing in recognized scientific literature. In 1960s, however Lykoudis became famous in Greece, for treating thousands of patients in a special clinic in Athens. He gave a combination, antibiotic therapy that included compounds such as nonabsorbable quinolones. Although Lykoudis presented his ideas to the drug companies and attempted publication in refereed journals, the concept of a bacterial cause of peptic ulcer was ignored and none of his work was ever published.

Interestingly, during the same period an Iranian surgeon, Dr. Emami-Ahari, proposed antibiotic therapy for PUD and gained a reputation in Iran, following successful treatment of thousands of patients in a private clinic in Tehran.¹⁰ Warren and Marshall in the early 1980s actually rediscovered *H. pylori* by successfully culturing the bacterium for the first time¹¹ and were able to show that eradication of *H. pylori* resulted in ulcer healing and dramatically reduced recurrence rate of PUD.¹² The

fact that eradication of the bacterium could result in cure of ulcer disease, attracted the attention of scientists around the globe so that, more than 11,000 papers have been published on *H. pylori* ever since. The first published clinical trial on eradication of *H. pylori* infection in Iran was in 1992, and worldwide; this trial was among the first few papers published up to that date.¹³

Indications for treatment

The recent consensus report of Maastricht 2 – 2000 strongly recommended the following situations for *H. pylori* treatment: PUD (complicated or uncomplicated), gastric mucosa-associated lymphoid tissue (MALT) lymphoma, atrophic gastritis, following gastric cancer resection, first degree relatives of gastric cancer patients, and request by patients.⁴ Advisable indications for treatment were recommended to include: erosive gastroduodenitis, functional dyspepsia, gastroesophageal reflux disease, and patients on nonsteroidal anti-inflammatory drugs. These indications remain controversial, as published data are often conflicting.^{4,14}

Antimicrobial susceptibility

According to published studies⁶ in Iran, about 37.5% of HP strains are resistant to metronidazoles (Tables 1 and 2), and 28% to clarithromycin. Among the 140 isolates tested for susceptibility to furazolidone, 7 (5%) were resistant. All 68 isolates tested were susceptible to tetracycline with a growth inhibition zone diameters of 20 – 60 mm. However, 5 isolates exhibited resistance to amoxicillin (7%) with growth inhibition zone diameters of 10 – 12 mm. Inhibition zone diameters for the remaining 63 isolates were 18 – 60 mm (Tables 1 and 2).

First line treatment regimens

Choice of a particular regimen will be influenced by several factors including efficacy, patient tolerance, existing antibiotic resistance, and cost of the drugs. The acceptable regimen for *H. pylori* eradication should lead to 85 – 90% eradication rate on intention-to-treat analysis. Marshall et al were first to treat *H. pylori* infection using bismuth compounds alone.¹⁵ But low eradication rate of this regimen prompted further studies and in the early 1990s a proton pump inhibitors (PPIs) were used in combination with amoxicillin as a dual therapy.¹⁶ But this therapy resulted in suboptimal eradication rates of < 60%. In an Iranian study which compared dual and triple therapies, eradication rate of dual therapy was only 30% compared to triple

Table 1. *H. pylori* sensitivity to antibiotics in Tehran,⁶ 1998.

| Antibiotics | Susceptibility | | |
|------------------------|----------------|-----------|---|
| | Sensitive | Resistant | % |
| Furazolidone (n = 140) | 133 | 7 | 5 |
| Amoxicillin (n = 68) | 63 | 5 | 7 |
| Tetracycline (n = 68) | 68 | 0 | 0 |

Table 2. *H. pylori* sensitivity to antibiotics in Tehran,⁶ 1998.

| Antibiotics | Susceptibility | | |
|-------------------------|----------------|--------------|-------------|
| | Sensitive | Intermediate | Resistant |
| Metronidazole (n = 195) | 95 (48.5%) | 27 (13.8 %) | 73 (37.5 %) |
| Tinidazole (n = 173) | 86 (50%) | 24 (13.8 %) | 63 (36 %) |
| Clarithromycin (n = 50) | 36 (72%) | — | 14 (28 %) |

therapy (bismuth and two antibiotics) with an eradication rate of 51%.¹⁷

PPI-based triple therapy consisting of one PPI with two antibiotics was first described in 1993,¹⁸ and its good efficacy (eradication rate of more than 80%) has been supported in several studies in Europe^{19,20} and in Canada.²¹ This regimen, however, had little efficacy (less than 60% eradication rate) in most of Iranian studies.^{22,23} There is only one study in Iran which shows relatively good results with triple therapy.²⁴ In that study, two weeks of omeprazole 20 mg BD, amoxicillin 1 g BD, and furazolidone 200 mg BD, had 76% eradication rate on intention-to-treat analysis. But reducing the dose of furazolidone,^{23,24} or removing furazolidone from the regimen²² reduced the eradication rate of triple therapy to less than 60% in the Iranian patients.

Another drug regimen for *H. pylori* eradication is quadruple therapy consisting of bismuth, a PPI, and two antibiotics. Although, in a recent meta-analysis this regimen was roughly equivalent to PPI-based triple therapy,²⁵ Iranian studies (Table 3) have shown that quadruple therapy is significantly more effective than triple therapy.²³

A quadruple regimen consisting of bismuth, a PPI, amoxicillin, and metronidazole had good efficacy (92% eradication rate) in a study from Netherlands.²⁶ However, this regimen had less than 70% intention-to-treat eradication rate in Iranian studies.²⁷

The high rate of resistance of *H. pylori* against metronidazole led to the replacement of

Table 3. Randomized, controlled trial for HP eradication in Iran.

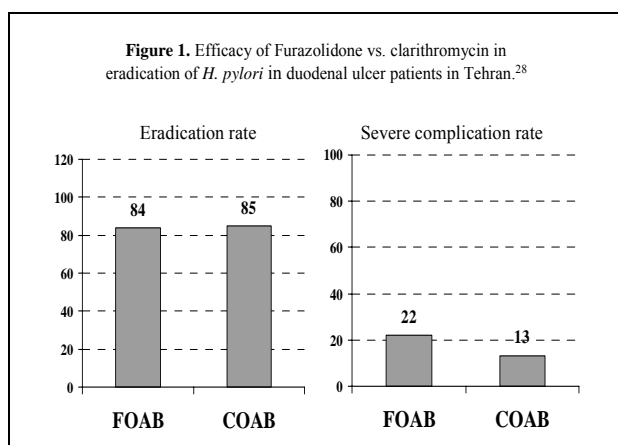
| Regimen | Eradication rate (%)* | Side effects (%) | Reference |
|-----------------|-----------------------|------------------|-----------|
| FOT(4 days) | 17.1 | Nil | 35 |
| AOC (7days) | 35.5 | Nil | 35 |
| FOT (7 days) | 23.8 | nil | 35 |
| RBMA (1 week) | 30 | 1.6 | 36 |
| OA (2 weeks) | 30.2 | 3 | 17 |
| AMB (2 weeks) | 36.3 | 5 | 36 |
| RAMB (2 weeks) | 55 | 10 | 29 |
| RAFB (2 weeks) | 77 | 27 | 29 |
| OAMB (2 weeks)† | 68 | 7 | 27 |
| OAFB (2 weeks) | 84 | 22 | 28 |
| OACB (2 weeks) | 85 | 13 | 28 |

O: Omeprazole; A: Amoxicillin; M: Metronidazole; B: Bismuth subcitrate; R: Ranitidine; F: Furazolidone; C: Clarithromycin
*Eradication rate by the intention to treat analysis; † These data are based on an uncontrolled trial.

metronidazole by clarithromycin in clinical trials conducted in this country. However, this drug is very expensive in the developing countries. Furazolidone, administered in China, for a long time especially in the patients with gastrointestinal disorders have been used in many clinical anti-*H. pylori* trials in Iran and proven to be as effective as clarithromycin (Figure 1). Furazolidone is available in developing countries at low cost. However, its side effects are relatively high.

The quadruple regimen comprising two weeks of omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, furazolidone 200 mg twice daily, and bismuth subcitrate 240 mg twice daily, had the eradication rate of 85% or more.^{23,28} Substitution of clarithromycin for furazolidone led to the same efficacy.²⁸ But substitution of ranitidine instead of omeprazole lowered the eradication rate.²⁹ Also, lowering the dose of furazolidone to 100 mg BD reduced the eradication rate to 70%.²³

In summary, the best results for *H. pylori* eradication in Iran were achieved with quadruple therapy using omeprazole, amoxicillin, bismuth with either furazolidone 200 mg twice daily or clarithromycin 500 mg twice daily. The major limitation of furazolidone is that the recommended adult dose (200 mg BD) of the drug is associated with side effects (e.g., dizziness, abdominal pain, fever, nausea, etc) in up to 20% of the patients;^{23,28} in some of the patients the side effects can be very severe. Since furazolidone inhibits monoamine oxidase (MAO), its side effects can be reduced with elimination of foods high in tyramine contents (e.g.,



O: Omeprazole; A: Amoxicillin; M: Metronidazole; B: Bismuth subcitrate; F: Furazolidone; C: Clarithromycine.

fermented cheese, overripe foods, smoked fish, banana, and beer) from the diet, during therapy.³⁰

Duration of treatment

The one-week course of PPI with two antibiotics had good efficacy (eradication rate of more than 80%) in several European studies.^{19,20} In head-to-head comparison of 7-day vs longer durations of treatment, some trials concluded that 7-day treatment was as effective as 14-day treatment.³¹ Others have shown a trend for higher eradication rate of 14-day treatment.³² In a meta-analysis, longer duration of treatment (10 – 14 days) was more effective than short course of therapy (7-day schedule).³³ In summary, while the European consensus panel has recommended 7-day course of therapy,⁴ many experts in US favour 10 – 14 days of treatment.³⁴ In Iranian studies, short course of triple therapy (4 or 7 days) had little efficacy (less than 40%) for *H. pylori* eradication.³⁵ Also, one week of quadruple therapy (ranitidine, bismuth, amoxicilline, and metronidazole) was unsuccessful.³⁶ However, one week of quadruple therapy including a PPI has not been studied in Iran. In general, 2 weeks of quadruple therapy had the best results in Iranian studies.^{23,28}

Confirmation of *H. pylori* eradication following treatment

Confirmation of cure is strongly recommended in complicated peptic ulcer disease as well as in low grade gastric MALT lymphoma. However, since the significant minority of patients may not be treated with the ideal regimens, confirmation of cure is reasonable in any patient who undergoes *H. pylori* treatment. This recommendation is in accordance with the recent consensus report of Maastricht 2-2000 on *H. pylori* infection.⁴ Confirmation of cure

reassures the patient and provides confidence that the risk of complications is removed provided the eradication is successful. Additionally, it facilitates the direction of any further management on individual basis, be it re-treatment following treatment failure, or a switch to symptomatic therapy.⁴ Urea breath test (UBT) is the recommended first line post-treatment diagnostic test.^{4,37} If urea breath testing is not available, stool antigen test would be the alternative.³⁸ In specific populations, *H. pylori* eradication can be confirmed by a biopsy-based test, as endoscopy is clinically indicated, in complicated duodenal ulcer, gastric ulcer, low-grade gastric MALT lymphoma, and local resection of early gastric cancer.⁴

Treatment failure

Poor adherence to eradication guidelines is an important factor in primary failure. For example, in a survey from community pharmacies in Ireland, several different combinations of antibiotics and acid suppressing agents were used for *H. pylori* eradication-many with undocumented efficacy. In comparison to specialist practices, prescriptions from primary care physicians were more likely to have undocumented efficacy.³⁹ Patient compliance is not regarded as a significant factor in eradication failure in clinical trials.⁴⁰ In Iranian clinical trials, compliance to treatment was good, even in patient treated with full dose of furazolidone which has high rate of side effects.²³ However, the importance of patient compliance has been emphasized in clinical practice, and the positive role of compliance-enhancing programs has been well demonstrated.⁴¹⁻⁴³

Bacterial resistance (especially resistance to metronidazole) is another cause of treatment failure.⁴⁰ Thus, prevalence of bacterial resistance in certain geographical areas can influence the selection of first line eradication regimens that region. Another cause of treatment failure is low gastric pH. The minimal bactericidal concentrations (MBCs) and minimal inhibitory concentrations (MICs) of most antibiotics against *H. pylori* (except metronidazole and tetracycline) are dependent on the pH of the environment;⁴⁴ at pH values lower than 7 or 7.4, the MIC increases. PPI increases the pH of the stomach, thus allowing better antimicrobial activity.⁴⁵ This is why proton pump inhibitors are used and are more effective in *H. pylori* eradication than ranitidine. In patients who are acid hyper secretors the pH remains low and the antimicrobial activity may be insufficient to eradicate the bacterium. Thus, in situations of

refractory *H. pylori* infection, increasing the dosage of PPI in the treatment regimen may have some beneficial effects for *H. pylori* eradication.

Second line treatment regimens

The utility of culture (with consequent antibiotic susceptibility testing) after eradication failure is controversial. *H. pylori* culture is expensive, time consuming, not always available on a routine basis, and requires the performance of endoscopic biopsy. Moreover, the sensitivity of bacterial culture is not 100%, and therefore the antimicrobial susceptibility cannot be obtained in all cases.⁴⁶ Furthermore, even when the susceptibility of *H. pylori* is known, eradication rates do not reach 100%, because the correlation between *in vivo* and *in vitro* susceptibility for anti-*H. pylori* antibiotics are often disappointing. Thus, a variable proportion of non-eradicated patients is made up of individuals who harbour strains sensitive to the administered drugs, and in these patients the reasons for treatment failure are unclear.^{46,47} Thus, it seems that the performance of culture after the first eradication failure is not necessary, therefore, the assessment of the sensitivity of *H. pylori* to antibiotics is suggested in clinical practice only after failure of the second treatment. Since the studies of the second line treatment regimens in Iran are scanty, most recommendations are based on evidences available from other countries.

Pretreatment antibiotic resistance is the most important factor, when there is no response to initial treatment.^{46,48} Thus, the choice of second line treatment depends on the type of treatment used initially. The impact of *in vitro* metronidazole resistance on clinical outcome of therapy is relatively modest, therefore the role of metronidazole resistance is somewhat different from other antibiotics. For example, when strains are metronidazole resistant, the rate of success with PPI-and metronidazole-based triple therapy is 20% lower than that observed with susceptible strains,⁴⁹ and even less with quadruple therapy.^{44,50} Thus, it is possible to overcome this resistance by increasing the duration or dose of treatment.

In a study in Iran, 2 weeks of quadruple therapy containing omeprazole 20 mg twice daily, furazolidone 200 mg twice daily, bismuth subcitrate 240 mg twice daily, and tetracycline 500 mg twice daily, had 90% eradication rate in patients who failed treatment with metronidazole based quadruple therapy.⁵¹ Thus, one option for the second line treatment is that if a clarithromycin-based regimen was used initially, a furazolidone-based regimen can be used afterwards, and vice versa (Table 4). Another option for the second line treatment is quadruple therapy containing omeprazole 20 mg/12 h, bismuth

subcitrate 120 mg/6 h, tetracycline 500 mg/6 h, and metronidazole 500 mg/8 h.⁵² As mentioned above, this regimen was also effective in metronidazole resistant strains of *H. pylori*.^{50,53} Also in a recent study, the use of a single capsule containing bismuth biscalcitate, metronidazole, and tetracycline given with omeprazole demonstrated a 93% eradication rate in patients with baseline metronidazole resistance.⁵⁴ However, it is notable that this regimen has not been tested in Iran.

Third line treatment regimens

Patients in whom the second line therapy fails and have definite indication for *H. pylori* eradication (e.g., patients with peptic ulcer, or gastric MALT lymphoma, etc) should be scheduled for third line treatment. Attempting for third line treatment in patients with less established indications for *H. pylori* treatment (e.g., patients with nonulcer dyspepsia) may not be justified (Table 4). For choosing the third line treatment regimen, results of culture and susceptibility testing are important. For

Table 4. Recommended treatment regimens for *Helicobacter pylori* eradication in Iran.

First line treatment options:

1. Furazolidone 200 mg BD, amoxicillin 1000 mg BD, Bismuth subcitrate 240 mg BD, omeprazole 20 mg BD (all two times per day) for 14 days (regimen A)
2. Clarithromycin 500 mg BD, amoxicillin 1000 mg BD, bismuth subcitrate 240 mg BD, omeprazole 20 mg BD for 14 days (regimen B)

Second line treatment options:

1. Furazolidone 200 mg BD, tetracycline 500 mg BD, bismuth subcitrate 240 mg BD, omeprazole 20 mg BD for 14 days (if furazolidone has not been used in the first line) (regimen C)
2. Regimen B (if clarithromycin has not been used in the first line)
3. Tetracycline 500 mg QID, metronidazole 500 mg TDS, bismuth subcitrate 120 mg QID, omeprazole 20 mg BD for 14 days (regimen D)*

Third line treatment:

Choose the antibiotic regimen according to *H. pylori* culture and drug susceptibility testing†

BD: Two times per day; TDS: Three times per day; QID: Four times per day.* Data are scanty for this regimen as a second line treatment in Iran. However, this regimen is recommended on the basis of treatment trials outside of the country. †Quadruple therapy containing higher doses of

omeprazole, bismuth subcitrate, and antibiotics such as furazolidone, clarithromycin, rifabutin, or tetracycline can be used.

example, one third of strains of *H. pylori* remain susceptible to clarithromycin after failure of previous therapy, including this drug.⁴⁴ In situations like these, clarithromycin can be repeated in the further treatment regimens. For third line treatment, quadruple therapy including bismuth compounds, high dose omeprazole, and two antibiotics (such as furazolidone, clarithromycin, rifabutin, or tetracycline) can be used if the *H. pylori* strain is susceptible to them.

Reinfection with *H. pylori*

It is important to mention that recurrent infection (reinfection) should be distinguished from recrudescence. The latter is due to re-emergence of previous strains of *H. pylori* which were inhibited but were not completely eradicated with treatment. Thus, on recrudescence, pre-treatment and recurrent strains have the same DNA profile. But on reinfection, pretreatment and recurrent strains have different DNA profiles. Late recrudescence can occur within 3 months post therapy, but only 50% of these cases can be detected using urease-based test, 4 weeks after the therapy is ceased⁵⁵ Thus, for documentation of the cure, it is better to defer UBT for 3 months after treatment.

In developed countries reinfection is a rare event.⁵⁴ But in countries with high prevalence of *H. pylori*, the annual reinfection rate is 13% or greater.^{55, 57} Studies in Iran indicate one and three year reinfection rate after successful eradication to be 19% and 20%, respectively.⁵⁸ These data suggest that the statement “cured once, cured for ever” does not hold true in many areas. In areas with high rate of reinfection (such as Iran), repeating UBT some years after successful *H. pylori* eradication may be justified in high risk patients (e.g., patients with complicated peptic ulcer, or gastric MALT lymphoma). Interestingly, an Iranian study has shown that yeasts of the oral cavity can be reservoirs for *H. pylori*.⁵⁹ Since yeasts, compared to bacteria, are more tolerant against environmental stresses such as heat, desiccation, acidic pH, and antibiotics, they may play a role for bacterial transmission and recurrent *H. pylori* infection. Thus, adding ketokonazole—an antifungal drug—in reducing recurrent infection is now under further evaluation in Iran.

SUMMARY AND RECOMMENDATIONS

Since several good trials of *H. pylori* eradication have been performed in this country, Iranian physicians should be familiar with the best treatment regimen. PPI-based triple therapy which

has good results in most trials in the western world is not ideal in Iran. Instead, as for the first line treatment, one of the following two regimens can be used: bismuth, PPI, amoxicillin, full dose of furazolidone; or bismuth, PPI, amoxicillin, clarithromycin. A quadruple regimen consisting of omeprazole, bismuth, amoxicillin, and metronidazole has low eradication rate and therefore is not recommended in Iran. In situations of treatment failure, two weeks of quadruple therapy containing omeprazole, bismuth, and two antibiotics should be used. In these situations if a clarithromycin-based regimen was used initially, a furazolidone-based regimen can be used afterwards, and vice versa. Alternatively, a quadruple therapy containing a PPI, bismuth, tetracycline, and metronidazole can be used as second line treatment. Culture and antibiotic susceptibility testing is not recommended unless after failure of the second line treatment. As a third line treatment, bismuth compounds, high dose omeprazole, and two antibiotics (such as furazolidone, clarithromycin, rifabutin, or tetracycline) can be used if the *H. pylori* strain is susceptible to them.

Finally, it is notable that different types of PPIs are of comparable efficacy for *H. pylori* eradication.⁶⁰ Thus, though increasing the dose of any given PPI may have a beneficial role in refractory *H. pylori* infections,⁴⁴ but switching to another PPI is of undocumented efficacy.

Areas for future research

Since triple therapies generally are not successful in Iran, some new quadruple regimens for reducing drug side effects should be evaluated. One week of furazolidone-based quadruple therapy (for reducing side effects of furazolidone), and two weeks of tetracycline based quadruple therapy (PPI, bismuth, metronidazole, tetracycline) would be interesting areas for future research. Also, evaluation of the effect of ketokonazole on reinfection rate of *H. pylori* is another interesting area for further investigation.

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