



# Comparison of Clarithromycin-based Triple Therapy and Furazolidone-based Quadruple Therapy in Eradicating *Helicobacter pylori* Infection

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## Abstract

**Background:** *Helicobacter pylori* infection is the most common infection of human. This organism is responsible for the majority of peptic ulcer diseases, MALToma and gastric cancer, worldwide. Several regimen therapies against *H. pylori* had developed and are prescribed empirically, but therapies have rarely been optimized.

**Objectives:** In this study, we compared two regimens that are widely used in Iran, triple regimen (clarithromycin, amoxicillin, and omeprazole) and furazolidone-based quadruple regimen (furazolidone, amoxicillin, bismuth, and omeprazole) in some dyspeptic patients.

**Methods:** In this cross-sectional study, 373 consecutive dyspeptic patients that *H. pylori* infection was established, randomized into one of the following groups; 188 in group A (treated with clarithromycin 500 mg, amoxicillin 1,000 mg, and omeprazole 20 mg twice daily for 10 days) and 185 in group B (furazolidone 200 mg, amoxicillin 1000 mg, bismuth subcitrate 240 mg and omeprazole 20 mg twice daily for 14 days). One month after discontinuation of the treatment, *H. pylori* eradication was evaluated with UBT.

**Results:** Mean age of the patients was  $35.9 \pm 12.3$  years, and the male to female ratio was 1: 1.6. In the per-protocol analysis, the eradication rate of *H. pylori* was 63.7% in comparison to 93% in group A and B, respectively ( $P < 0.004$ ).

**Conclusions:** Our study showed furazolidone-based quadruple regimen is superior to the standard triple regimen; thus, it is recommended as the first choice.

**Keywords:** *Helicobacter pylori*, Eradication, Quadruple, Triple, Regimen

## 1. Background

Gastric infection with *H. pylori* is responsible for most cases of peptic ulcer disease, gastric adenocarcinoma, and gastric MALToma (1-3). Therefore, eradication of the infection will prevent many of these complications (3). On the other hand, *H. pylori* infection is present in nearly 90% of the adult population and appears to occur early in life, and more than 50% of children are infected before age 15 (3, 4). There are different regimens for the first-line treatment of the infection, and the eradication rates of most successful regimens range from 75% to 92% (4). Epidemiological studies in Iran have revealed the prevalence of *H. pylori* infection in patients over 35 years old is about 86%; however, according to clinical studies conducted in Iran, the rate of eradication of the infection is less than the reported level in western and some developing countries (5, 6).

Many researchers have reported high levels of resistance to metronidazole (37%) and clarithromycin (28%) (2, 3, 7-11). Fakheri et al. (12), in a study, showed that furazolidone-based quadruple therapy is a good alternative for eradication of *H. pylori* infection in regions with high resistance to metronidazole and clarithromycin. Based on an academic standpoint, the best regimen for eradication of *H. pylori* infection should be selected by regional studies (1, 2, 10, 12) but such recommendation, in practice, is difficult.

## 2. Objectives

In this study, we compared two regimens that widely were used in Iran, triple regimen (clarithromycin, amoxicillin, and omeprazole) and furazolidone-based quadruple

regimen (furazolidone, amoxicillin, bismuth, and omeprazole), in some dyspeptic patients who were infected with *H. pylori*.

### 3. Methods

This cross-sectional study was conducted on 18 years older patients who were referred to gastroenterology clinic of Ali-ebn-Abitaleb teaching hospital in Zahedan, suffering from dyspepsia and had confirmed *H. pylori* infection using Urea Breath test (UBT) or Rapid Urease test (RUT). Pregnant women, patients with a history of chronic kidney, liver, and lung diseases, malignancy, G6PD deficiency, gastrointestinal (GI) surgery, GI bleeding, history of taking non-steroidal anti-inflammatory drugs (NSAIDs), taking antibiotic during recent 4 weeks, anti-*H. pylori* treatment during recent years and a history of known drug sensitivity to each of the study drugs were excluded from the study. Our main outcome was *H. pylori* eradication as established by a negative UBT at least four weeks after the end of the treatment.

Eligible patients were randomly divided into one of the following groups; group A (treated with clarithromycin 500 mg, amoxicillin 1,000 mg, and omeprazole, 20 mg twice daily for 10 days) or group B (furazolidone 200 mg, amoxicillin 1,000 mg, bismuth subcitrate 240 mg, and omeprazole 20 mg twice daily for 14 days). Patients were evaluated for eradication of *H. pylori* infection using the respiratory<sup>13</sup>C-urea test four weeks after the treatment. All of the patients were instructed about the correct use of the drugs and probable adverse effects by a face to face interview and a leaflet, containing all recommendation about the medications and their side effects. Moreover, they were advised to call us in the event of any adverse effect(s) without consumption stops. We also, every week, checked the patients' compliance by pill counting and recorded any adverse events and, with patient assurance, encourage them to drug consumption. In a newly started medication for other propose(s), if medication had potential interaction with the study medications, the patient was excluded from the study. If the patient consumed continuously (without any disruption or gap at consumption) at least 90 percent of the given regimen, it was considered acceptable compliance. The project was approved by the local Ethics Committee of Zahedan University of Medical Sciences, and written informed consent was obtained from each individual participating in this study. The collected data were analyzed by SPSS ver. 18, and for statistical analysis, we used chi-square and student *t*-test, and a P-value of less than 0.05 was considered statistically significant.

### 4. Results

Among 512 dyspeptic patients, 373 people were eligible to enter the study who were randomly divided into one of the two groups, 188 in group A and 185 patients in B. Of these patients, five (0.25 %) and seven (0.29 %) patients of group A and B were dropped, respectively, due to consent withdrawal or not returning for UBT, and finally, 183 patients in group A and 178 patients in group B completed the course of the project. The patients were between 18-59 years old with an average age of  $35.9 \pm 12.3$  and male to female ratio of 1:1.63. The demographic characteristics of the patients and their response rate to each regimen are summarized in [Table 1](#).

The mean age of the patients of group A who responded to the treatment was not statistically different from those who did not. However, patients that did not respond to the treatment had statistically significant older mean age in group B ( $P = 0.001$ ). Regarding side effects of the regimen, there was no statistically significant difference between the two groups. The frequencies of adverse effects in the two groups are summarized in [Table 2](#).

### 5. Discussion

Just three to four decades after the identification of *H. pylori* and multiple regimens that were used for eradication of this microbe in human, now it appears that a considerable number of infected patients have no response to some of the eradication regimens; thus, most authors advised performing culture and antibiogram sensitivity. However, in practice, especially in low-income countries, this academic recommendation is often difficult and occasionally impossible. In clinical practice, the eligible rate of eradication of *H. pylori* infection according to the intention-to-treat studies is 85% to 90%. Our study showed that triple-clarithromycin based and probably most prescribed *H. pylori*-eradicating regimens ([2, 3, 13, 14](#)), provide inferior results compared with antimicrobial therapies for other common infectious diseases, and furazolidone-based quadruple regimen is superior to standard triple regimen; thus it is recommended with greater confidence.

Studies have demonstrated an increasing number of patients with failure to respond well to the treatment due to antibiotic resistance in recent years. In two decades ago, triple-drug regimens, including a proton pump inhibitor (PPI) and two antibiotics, as the first-line treatment for *H. pylori* resulted in an 80% eradication rate in the world, and now, probably is effective in some regions ([3, 14-17](#)). However, according to some studies in Iran, about 37.5% of *H.*

**Table 1.** Demographic Characteristics and Rate of Eradication in Both Groups

Group	No (M/F)	Mean Age $\pm$ SD	Eradication, No. (%)		Non-eradication, No. (%)	
			Male	Female	Male	Female
Triple-drug regimen	183 (65/118)	36 $\pm$ 12.7	44 (68)	73 (62)	21(32)	45 (38)
Quadruple-drug regimen	178 (74/104)	35.7 $\pm$ 11.9	71 (96)	95 (91)	3 (4)	9 (9)
P-value	0.787	0.152	0.115	0.341		

Abbreviations: F, female; M, male; N, number; SD, standard deviation.

**Table 2.** Adverse Effects of the Study Groups<sup>a</sup>

Adverse Effect	Triple-Drug	Quadruple-Drug	P-Value
Weakness and fatigue	50 (27.3)	46 (27.3)	NS
Nausea	50 (27.3)	54 (32.1)	NS
Anorexia	32 (17.4)	40 (23.8)	NS
Foul taste	22 (12)	30 (17.8)	NS
Dry mouth	20 (10.9)	22 (13)	NS
Diarrhea	10 (5.4)	14 (8.3)	NS
Abdominal distention	7 (3.8)	9 (5.3)	NS
Abdominal pain	5 (2.7)	3 (1.7)	NS
Headache	3 (1.6)	5 (2.9)	NS
Rash	1 (0.5)	0	NS
Vomiting	0	1 (0.5)	NS

<sup>a</sup>Values are expressed as No. (%).

*pylori* strains are resistant to metronidazole, 28% to clarithromycin, and among 140 isolates tested for susceptibility to furazolidone, seven (5) were resistant.

In addition, some studies 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 the metronidazole-based group). For these reasons, it seems that the most effective first-line treatment is quadruple therapy with furazolidone for 14 days. The rate of eradication in the furazolidone-based branch in the current study is similar to the other researches in our country (9). Therefore, it is better to encourage practitioners for its prescription. However, treatment-associated side effects were more common in the furazolidone-based regimen (4, 5, 12).

Although we did not perform culture and antibiotic sensitivity, the low efficacy of the triple-based regimen in the present study is probably due to resistance to clarithromycin. Clarithromycin is not only expensive but also has GI adverse effects and must be overlooked for *H. pylori* eradication regimen, at least in low-income countries (6, 7). Rimbara et al. (16) in a review in 2011 recommended practitioners to avoid clarithromycin-based triple

therapy. The rate of eradication of *H. pylori* infection by furazolidone-based regimen was reported to be approximately 80% in various studies (1, 6, 9). Furazolidone, a nitrofurantoin derivative with bacteriostatic or bactericidal properties against both Gram-negative and Gram-positive bacteria, is absorbed well from the intestinal wall and has no tissue concentration, and since relatively low resistance strains of *H. pylori* to furazolidone has been reported yet, it could be administered for the treatment of *H. pylori* infection instead of metronidazole.

One of the major drawbacks of furazolidone is GI intolerance due to bloating, which may result in discontinuation of therapy by some patients and therefore, its use is limited (8, 12, 13). However, side effects are reduced by lowering the dose. Some researchers selected a dose of 100 mg of furazolidone twice a day to reduce the rate of adverse effects meanwhile increase patients' compliance. According to these studies, when a low dose of furazolidone (100 mg B.D.) is used, does not yield acceptable success rates. Researchers have reported that the rate of eradication of furazolidone-based quadruple drug regimen was 54% and 72% based on intention-to-treat and per-protocol analysis, respectively (12). accordingly, if furazolidone dose was increased to 200 mg two times per day, eradication rate might dramatically improve. Patient adherence is essential for the successful eradication of *H. pylori*. Given the high pill burden, the increased frequency of administration, and the prolonged duration of treatment, a thorough understanding of the importance of completing the treatment regimen, as prescribed, is paramount, and we can improve our patients' compliance and *H. pylori* eradication rate by encouraging and assuring patients. However, choosing the treatment should be based on regional patterns of drug susceptibility and resistance and other factors such as a history of recent taking antibiotics (2, 11, 14, 15, 17-19).

One of the positive points of the current study is high patient number than previous studies, and it was done almost ten years after previous research, and our findings showed that furazolidone-based quadruple therapy is still superior to clarithromycin-based regimen. But one of the

weak points of our research was the absence of culture and antibiogram for *H. pylori* sensitivity. Furthermore, it was better to perform UBT six months after completion of the treatment for recrudescence of *H. pylori* infection and absolute *H. pylori* eradication.

In conclusion, because the eradication of *H. pylori* plays a critical role in the treatment of peptic ulcer disease, MALToma and probably gastric adenocarcinoma prevention, we recommend furazolidone-based quadruple therapy with furazolidone 200 mg twice a day.

## Footnotes

**Authors' Contribution:** AB, NM, and SH contributed to study concept and design, acquisition of data, analysis and interpretation of data. MM and AB contributed to drafting the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical, and material support. AB supervised the study.

**Conflict of Interests:** The authors declared no conflict of interests.

**Ethical Approval:** The project was approved by the local Ethics Committee of Zahedan University of Medical Sciences.

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**Informed Consent:** Written informed consent was obtained from each individual before this study.

## References

- Khademi F, Poursina F, Hosseini E, Akbari M, Safaei HG. Helicobacter pylori in Iran: A systematic review on the antibiotic resistance. *Iran J Basic Med Sci.* 2015;**18**(1):2-7. [PubMed: 25810869]. [PubMed Central: PMC4366738].
- Farshad S, Alborzi A, Japoni A, Ranjbar R, Hosseini Asl K, Badiee P, et al. Antimicrobial susceptibility of Helicobacter pylori strains isolated from patients in Shiraz, Southern Iran. *World J Gastroenterol.* 2010;**16**(45):5746-51. doi: 10.3748/wjg.v16.i45.5746. [PubMed: 21128326]. [PubMed Central: PMC2997992].
- Saniee P, Hosseini F, Kadkhodaei S, Siavoshi F, Khalili-Samani S. Helicobacter pylori Multidrug Resistance Due to Misuse of Antibiotics in Iran. *Arch Iran Med.* 2018;**21**(7):283-8. [PubMed: 30041525].
- Fakheri H, Saberi Firoozi M, Bari Z. Eradication of Helicobacter Pylori in Iran: A Review. *Middle East J Dig Dis.* 2018;**10**(1):5-17. doi: 10.15171/mejdd.2017.84. [PubMed: 29682242]. [PubMed Central: PMC5903928].
- Fakheri H, Bari Z, Aarabi M, Malekzadeh R. Helicobacter pylori eradication in West Asia: a review. *World J Gastroenterol.* 2014;**20**(30):10355-67. doi: 10.3748/wjg.v20.i30.10355. [PubMed: 25132752]. [PubMed Central: PMC4130843].
- Hosseini E, Poursina F, de Wiele TV, Safaei HG, Adibi P. Helicobacter pylori in Iran: A systematic review on the association of genotypes and gastroduodenal diseases. *J Res Med Sci.* 2012;**17**(3):280-92. [PubMed: 23267382]. [PubMed Central: PMC3527048].
- Malekzadeh R, Sotoudeh M, Derakhshan MH, Mikaeli J, Yazdanbod A, Merat S, et al. Prevalence of gastric precancerous lesions in Ardabil, a high incidence province for gastric adenocarcinoma in the northwest of Iran. *J Clin Pathol.* 2004;**57**(1):37-42. doi: 10.1136/jcp.57.1.37. [PubMed: 14693833]. [PubMed Central: PMC1770167].
- Malekzadeh R, Ansari R, Vahedi H, Siavoshi F, Alizadeh BZ, Eshraghian MR, et al. Furazolidone versus metronidazole in quadruple therapy for eradication of Helicobacter pylori in duodenal ulcer disease. *Aliment Pharmacol Ther.* 2000;**14**(3):299-303. doi: 10.1046/j.1365-2036.2000.00709.x. [PubMed: 10735922].
- Khatibian M, Ajvadi Y, Nasserri-Moghaddam S, Ebrahimi-Darmani N, Vahedi H, Zendehtdel N, et al. Furazolidone-based, metronidazole-based, or a combination regimen for eradication of Helicobacter pylori in peptic ulcer disease. *Arch Iran Med.* 2007;**10**(2):161-7. [PubMed: 17367217].
- Fallahi GH, Maleknejad S. Helicobacter pylori culture and antimicrobial resistance in Iran. *Indian J Pediatr.* 2007;**74**(2):127-30. doi: 10.1007/s12098-007-0003-4. [PubMed: 17337822].
- Hasan SR, Vahid V, Reza PM, Roham SR. Short-duration furazolidone therapy in combination with amoxicillin, bismuth subcitrate, and omeprazole for eradication of Helicobacter pylori. *Saudi J Gastroenterol.* 2010;**16**(1):14-8. doi: 10.4103/s1319-3767.58762. [PubMed: 20065568]. [PubMed Central: PMC3023095].
- Fakheri H, Merat S, Hosseini V, Malekzadeh R. Low-dose furazolidone in triple and quadruple regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther.* 2004;**19**(1):89-93. doi: 10.1046/j.1365-2036.2003.01822.x. [PubMed: 14687170].
- Eisig JN, Silva FM, Rodriguez TN, Hashimoto CL, Barbuti RC. A furazolidone-based quadruple therapy for Helicobacter pylori retreatment in patients with peptic ulcer disease. *Clinics (Sao Paulo).* 2005;**60**(6):485-8. doi: 10.1590/s1807-59322005000600010. [PubMed: 16358139].
- Salmanroghani H, Mirvakili M, Baghbanian M, Salmanroghani R, Sanati G, Yazdian P. Efficacy and Tolerability of Two Quadruple Regimens: Bismuth, Omeprazole, Metronidazole with Amoxicillin or Tetracycline as First-Line Treatment for Eradication of Helicobacter Pylori in Patients with Duodenal Ulcer: A Randomized Clinical Trial. *PLoS One.* 2018;**13**(6). e0197096. doi: 10.1371/journal.pone.0197096. [PubMed: 29889843]. [PubMed Central: PMC5995362].
- Yuan Y, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, et al. Optimum duration of regimens for Helicobacter pylori eradication. *Cochrane Database Syst Rev.* 2013;(12). CD008337. doi: 10.1002/14651858.CD008337.pub2. [PubMed: 24338763].
- Rimbara E, Fischbach LA, Graham DY. Optimal therapy for Helicobacter pylori infections. *Nat Rev Gastroenterol Hepatol.* 2011;**8**(2):79-88. doi:10.1038/nrgastro.2010.210. [PubMed: 21293508].
- Sardarian H, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for Helicobacter pylori eradication in Iran: a prospective randomized trial. *Helicobacter.* 2013;**18**(2):129-34. doi: 10.1111/hel.12017. [PubMed: 23121338].
- Farahmand F, Mohammadi T, Najafi M, Fallahi G, Khodadad A, Motamed F, et al. Comparison of Ciprofloxacin-Based Triple Therapy with Conventional Triple Regimen for Helicobacter pylori Eradication in Children. *Acta Med Iran.* 2016;**54**(6):395-400. [PubMed: 27306347].
- Ghadir MR, Shafaghi A, Iranikhah A, Pakdin A, Joukar F, Mansour-Ghanaei F. Furazolidone, amoxicillin and omeprazole with or without bismuth for eradication of Helicobacter pylori in peptic ulcer disease. *Turk J Gastroenterol.* 2011;**22**(1):1-5. [PubMed: 21480103].