Treatment choices in young patients with *Helicobacter pylori* infection: Standard triple or bismuth-based quadruple therapies

Helicobacter pylori infeksiyonlu genç hastalarda tedavi seçenekleri; Standard üçlü veya bismuth bazlı dörtlü tedavi

Nurten SAVAŞ

Başkent University Faculty of Medicine, Department of Gastroenterology, İstanbul

Background and Aims: *Helicobacter pylori is the most abundant pathogen in all age groups worldwide, and eradication rates of this pathogen are decreasing over time. We aimed to determine the efficacy rates of standard triple and bismuth-based quadruple therapies in young patients with dyspepsia, and in the event of eradication failure, to assess the success rates of rescue treatments with bismuth-based quadruple or levofloxacin-based triple protocols.* ***Materials and Methods:*** *A total of 116 Helicobacter pylori -positive young patients (≤35 years old) with dyspepsia were given either lansoprazole 30 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 14 days or colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid for 14 days. In case of eradication failure, levofloxacin, amoxicillin, and lansoprazole or colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid therapies were given as rescue treatments.* ***Results:*** *Helicobacter pylori eradication rates were 85.7% in the colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid group and 63.3% in the lansoprazole 30 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid group. Smoking, alcohol, and nonsteroidal antiinflammatory drug use had no effect on response; the only factor affecting the res-ponse rate was colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid treatment. The nonresponder patients in the lansoprazole 30 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid group and colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid groups were given colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid and levofloxacin, amoxicillin, and lansoprazole rescue treatments, respectively, and a 70% success rate was achieved in both groups.* ***Conclusions:*** *Even in young patients, who are supposed to be susceptible to clarithromycin-based treatment, the Helicobacter pylori eradication rates were lower with lansoprazole 30 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid treatment; thus, colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid protocol should be preferred as first-line treatment. There was no difference between the second-line treatment response rates of levofloxacin, amoxicillin, and lansoprazole and colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid protocols.*

Key words: *Helicobacter pylori, dyspepsia, triple treatment, quadruple treatment, bismuth, clarithromycin, levofloxacin*

Corresponding Author: Nurten SAVAŞ
Başkent University Faculty of Medicine, Department of Gastroenterology
Oymacı sok. No: 7 Altunizade, İstanbul • Phone: +90 216 554 15 00
E-mail: nakyurek2000@yahoo.com

Giriş ve Amaç: *Helicobacter pylori dünyada tüm yaş gruplarında en sık görülen gastrik patojen olup bu patojenin eradikasyon oranları gün geçtikçe azalmaktadır. Bu çalışmanın amacı dispepsisi olan Helicobacter pylori pozitif genç hastalarda standard üçlü ve bizmut bazlı dörtlü tadavilerin başarı oranlarını belirlemek ve tedaviye cevapsızlık durumunda levofloksasin bazlı üçlü ve yine bizmut bazlı dörtlü ikinci basamak tedavilerinin başarı oranlarını saptamaktır.* ***Gereç ve Yöntem:*** *Otuz beş yaş altı 116 Helicobacter pylori pozitif dispepsili hasta çalışmaya alındı. Hastalar iki gruba ayrıldı bir gruba lansoprazol 30 mg bid, amoksisilin 1 gr bid, klaritromisin 500 mg bid 14 günlük tedavi diğer gruba kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid 14 günlük tedavi olarak verildi. Tedaviye yanıtsız olgulara, levofloksasin, amoksisilin, lansoprazol veya kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid tedavileri ikinci basamak tedavi olarak verildi.* ***Bulgular:*** *Helicobacter pylori eradikasyon oranları kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid grubunda %85.7 ve lansoprazol 30 mg bid, amoksisilin 1 gr bid, klaritromisin 500 mg bid grubunda %63.3 bulundu. İstatistiksel olarak sigara, alkol ve nonsteroid-antiinflamatuvar kullanımının tedavi cevabı üzerinde hiçbir etkisi bulunmaz iken tedaviyi etkileyen tek faktörün kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid tedavi seçeneği olduğu belirlendi. Tedaviye yanıtsızlarda ikinci basamak tedavi olarak lansoprazol 30 mg bid, amoksisilin 1 gr bid, klaritromisin 500 mg bid grubunda olanlara kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid ve kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid grubunda olanlara levofloksasin, amoksisilin, lansoprazol tedavisi verildi, her iki grupta da ikinci basamak tedavi ile %70 oranında başarı elde edildi.* ***Sonuç:*** *Klaritromisine duyarlı olmasını beklediğimiz genç hastalarda dahi Helicobacter pylori eradikasyon oranları lansoprazol 30 mg bid, amoksisilin 1 gr bid, klaritromisin 500 mg bid grubunda düşük olup bu hastalarda da kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid tedavisi ilk basamak tedavi olarak düşünülmelidir. İlk basamak tedaviye yanıtsız gençlerde ikinci basamak tedavi seçeneklerinden kolloidal bizmut subsitrat 300 mg qid, lansoprazol 30 mg bid, metronidazol 500 mg tid, tetrasiklin 500 mg tid ve levofloksasin, amoksisilin, lansoprazol arasında fark olmadığı saptanmıştır.*

Anahtar kelimeler: *Helicobacter pylori, dispepsi, üçlü tedavi, dörtlü tedavi, bizmut, klaritromisin, levofloksasin*

Manuscript Received: 11.03.2014 • **Accepted:** 28.03.2014

INTRODUCTION

Helicobacter pylori (H. pylori) is the most abundant human pathogen infecting an estimated 50% of the global population. *H. pylori* is associated with a number of clinical conditions, including gastric cancer and mucosa-associated lymphoid tissue (MALT). In Turkey, *H. pylori* prevalence is 82.5% in patients over 18 years old (1). According to the Maastricht IV, in countries where *H. pylori* prevalence is high (≥20%), the test and treat strategy is appropriate for uninvestigated dyspepsia in situations where the risk of the patient having gastric cancer is low. This includes patients below a locally determined cut-off point for age, without alarm symptoms of weight loss, dysphagia, overt gastrointestinal bleeding, abdominal mass, iron deficient anemia, or signs associated with increased gastric cancer risk (2), and with no family history of gastric cancer or gastric lymphoma. The test and treat strategy is both easy and cost-effective. Among the tests for *H. pylori,* the urea breath test is an acceptable noninvasive test, with a sensitivity of 88-95% and specificity of 95-100% (3). Standard triple therapy with proton pump inhibitor (PPI), amoxicillin and clarithromycin remains the most commonly prescribed *H. pylori* eradication regimen as a first-line treatment, but with the increased clarithromycin resistance, quadruple therapy consisting of bismuth, PPI, metronidazole, and tetracycline treatment is also suggested as a first-line treatment (2). The widespread use of antibiotics throughout the world has resulted in the emergence of antibiotic resistance, which decreases *H. pylori* eradication rates. *H. pylori* eradication rates in Turkey are 50-57% and 89-90% in clarithromycin-based triple and bismuth-based quadruple therapies, respectively, in all age groups (4-8). The aim of this study was to determine the efficacy rates of standard triple and bismuth-based quadruple therapies in young patients with dyspepsia who are presumed to be less frequent antibiotic users, and in case of *H. pylori* eradication failure, to ascertain the success rate of rescue treatments with bismuth-based quadruple or levofloxacin-based triple protocols.

MATERIALS AND METHODS

This study was conducted as a randomized, open label, prospective single-center study in an academic hospital in accordance with Good Clinical Practice and the Declaration of Helsinki. An informed consent was obtained from all patients. All patients were admitted with the complaint of dyspepsia in the absence of alarm symptoms and without a family history of gastric cancer, MALT lymphoma, or gastric surgery. The patients with alarm symptoms such as weight loss, vomiting, dysphagia, gastrointestinal bleeding, and anemia were not included in the study. *H. pylori* positivity is proven with the ^{13}C urea breath test performed in our clinic. Cigarette smoking >5/day, alcohol consumption >25 g/week, and nonsteroidal antiinflammatory drug (NSAID) use >2/week were all recorded. The patients were randomized into two groups. Sixty patients were given lansoprazole 30 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid (LAC) for 14 days, while 56 patients were given colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, and tetracycline 500 mg tid (BLMT) for 14 days. *H. pylori* eradication was confirmed by ^{13}C urea breath test, which was performed four weeks after the completion of the treatment. In case of failure of *H. pylori* eradication, the nonresponder patients in the LAC group were given rescue therapies of either the BLMT protocol for 14 days or the levofloxacin 500 mg bid, amoxicillin 1 g bid, and lansoprazole 30 mg bid (LAL) protocol for 7 days. The nonresponder patients in the first-line BLMT group were given LAL protocol as rescue treatment. Patients were asked to return for a follow-up visit at the end of the treatment to assess their compliance and adverse effects. The 13C urea breath test was repeated four weeks after the rescue treatment.

^{13}C Urea Breath Test

After an overnight fast, a baseline breath sample was collected before the patient ingested ^{13}C-urea/citric acid composition (UBT; UBiT kit; Otsuka Pharmaceutical, Tokyo, Japan). Second breath samples of patients were collected shortly after ingestion, with the cut-off value for positivity being delta value >3.5 units, as validated before. Patients were asked to avoid antacid treatments for two weeks and antibiotics for one month before performing urea breath test.

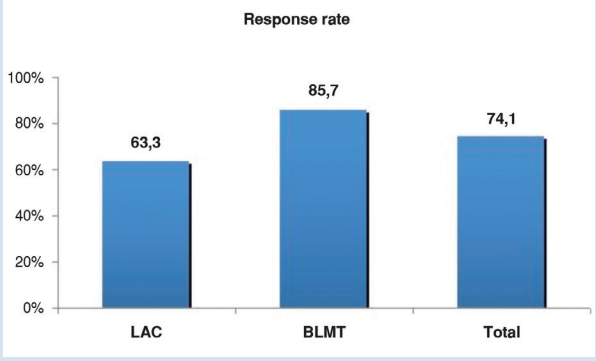

Figure: Response rates to the first line *H. pylori* eradication treatments

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 15.0 for Windows was used for statistical analysis. The descriptive statistics for categoric variables are given as numeric and percentile, while quantitative variables are given as mean, minimum, maximum, and standard deviation (SD). Mann-Whitney U test was used for the comparison between two groups. For the factors affecting the response rate to the treatment, multivariate regression analysis was used. The difference between the categoric variables was tested with x^2 test. A p value <0.05 was accepted as statistically significant.

RESULTS

One hundred and sixteen patients were included in the study. Patients were aged 19-35 years (mean age, 29.5±4.2 years). Of 116 patients, 79 (68.1%) were female, and 37 (31.9%) were male. Cigarette smoking >5/day was positive in 19 (16.4%) patients, alcohol consumption >25 g/week was positive in 6 (5.2%) patients, and NSAID use >2/week was positive in 14 (12.2%) patients. Sixty patients were given LAC protocol for 14 days and 56 patients were given BLMT for 14 days. All patients completed the treatment. Of 60 patients given LAC protocol, 38 (63.3%) were *H. pylori* negative and of 56 patients given BLMT protocol, 48 (85.7%) were *H. pylori* negative with urea breath test performed four weeks after the treatment. The success rate of BLMT treatment was higher than of LAC treatment, and the difference was statistically significant (p=0.006) (Table 1). Totally,

Table 1. The baseline demographic characteristics of patients and response rates to the treatments

		N	LAC (n:60)	BLMT (n:56)	p
Mean age±SD		29.5±4.2	30.1±4.4 (19-35)	28.8±3.8 (19-35)	0.028
Gender (%)	Female Male	79 (68.1) 37 (31.9)	43 (71.7) 17 (28.3)	36 (64.3) 20 (35.7)	0.394
Smoking (%)		19 (16.4)	4 (6.7)	15 (26.8)	0.003
Alcohol (%)		6 (5.2)	1 (1.7)	5 (8.9)	0.105
NSAID (%)		14 (12.2)	1 (1.7)	13 (23.2)	<0.001
Response (%)		86 (74.1)	38 (63.3)	48 (85.7)	0.006

LAC: Lansoprazole 30 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid. **BLMT:** Colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, tetracycline 500 mg tid. **NSAID:** Non-steroidal antiinflammatory drug.

Table 2. The comparison of patients with and without response to the first-line *H. pylori* eradication treatments

		No response	Response	p
Mean age±SD		29.9±4.1 (19-35)	29.3±4.2 (19-35)	0.892
Gender (%)	Female Male	19 (63.3) 11 (36.7)	60 (69.8) 26 (30.2)	0.515
Smoking (%)		5(16.7)	14 (16.3)	1.000
Alcohol (%)		3 (10.0)	3 (3.5)	0.178
NSAID (%)		2 (6.7)	12 (14.1)	0.351

NSAID: Non-steroidal antiinflammatory drug.

Table 3. Multivariate regression analysis of the factors affecting the response rate to the first-line *H. pylori* eradication treatments

	P	OR	95% CI	
Age	0.812	0.987	0.884	1.101
Gender	0.412	0.674	0.263	1.730
Smoking	0.726	0.787	0.206	3.007
Alcohol	0.052	0.131	0.017	1.015
NSAID	0.458	2.254	0.264	19.262
BLMT	0.008	4.351	1.469	12.891

NSAID: Non-steroidal antiinflammatory drug. **BLMT:** Colloidal bismuth subcitrate 300 mg qid, lansoprazole 30 mg bid, metronidazole 500 mg tid, tetracycline 500 mg tid.

a 74.1% success rate was achieved with these first-line treatments (Figure 1). When patients with and without response to *H. pylori* eradication treatment were compared, there was no statistically significant difference between the patients with regard to age, gender, smoking, alcohol, and NSAID use (Table 2). Although the patients were younger and the ratio of cigarette smoking and NSAID usage was higher in the BLMT group than the LAC group, on multivariate analysis, age, gender, cigarette smoking, alcohol consumption, and NSAID usage had no effects on *H. pylori* eradication; the only factor affecting eradication was found to be the choice of BLMT treatment (p=0.008; odds ratio [OR] 4.351) (Table 3). Intention-to–treat (ITT) and per protocol (PP) ratios were 63.3% for LAC protocol and 85.7% for BLMT protocol. Of 22 patients in the LAC group in whom *H. pylori* eradication failed, 11 (50%) were given BLMT protocol as rescue treatment for 14 days and 6 (27.2%) were given LAL protocol for 7 days. *H. pylori* become negative in 8 (72%) of these 11 patients in the rescue BLMT group, and in 4 (66%) of 6 patients in the rescue LAL group at the end of treatment. Of 12 patients who were *H. pylori* positive at the end of the first-line BLMT treatment, 7 patients accepted rescue treatment with LAL, and at the end of the rescue treatment, 5 (71%) of them became *H. pylori* negative. There was no statistically significant difference in response rates between the rescue groups (p>0.05).

DISCUSSION

H. pylori is one of the most important clinical causes of gastroduodenal diseases. The test and treat strategy is an accepted approach in high prevalence regions like Turkey (2), and the urea breath test is one of the main non-invasive tests for detection of *H. pylori* infection (9). Although currently, standard first-line treatment to eradicate *H. pylori* is triple therapy with LAC protocol, given the increased clarithromycin resistance, quadruple therapy with BLMT protocol is also suggested as a first-line treatment in all age groups. In this study, we evaluated these two protocols in young patients, who presumably use fewer antibiotics and are less resistant to clarithromycin, and we also studied the second-line treatments of BLMT and LAL therapies in the event of eradication failure with the first-line treatments.

The triple regimen including PPI, clarithromycin and amoxicillin to treat *H. pylori* infection (10) was proposed in the first Maastricht Conference and its use became universal worldwide, but with the increase in *H. pylori* resistance to clarithromycin, *H. pylori* eradication rates decreased. In areas in which *H. pylori* resistance to clarithromycin is high, bismuth- containing quadruple treatments are recommended as first-line treatments (2).

The generally accepted minimum success rate of a treatment regimen for *H. pylori* eradication should be >80% (11). In a study conducted by Kadayifci et al. (12), it was shown that *H. pylori* eradication rates with triple treatment have decreased over time in Turkey especially after the 2000's, from 79.4% to 68.8%, suggesting the bismuth-based treatments as first-line treatment. Recently, *H. pylori* eradication rates in Turkey were found to be 50-57% with clarithromycin-based triple treatment (4-6) and 89-90% with bismuth-based quadruple treatment (7,8).

Bismuth salts markedly reduce the bacterial load of *H. pylori* and have a synergistic effect with some antibiotics (13), and most importantly, no resistance to bismuth salts develops, which is a very important factor for the preference of this agent for *H. pylori* eradication, especially in areas where there are high rates of antibiotic resistance (14).

Proton pump inhibitors (PPIs) do not eradicate *H. pylori,* but lead to an important decrease in the bacterial load. If the patient receives the antibiotic to which *H. pylori* has point mutations, the susceptible organisms will be destroyed and resistant organisms will be selected for survival and emerge as a full population of resistant organisms (15). A multi-center European study revealed the resistance rates of 17.5% for clarithromycin, 14.1% for levofloxacin, and 34.9% for metronidazole, with a significant association found between outpatient antibiotic use and the proportion of antibiotic resistance (16). Clarithromycin resistance is reported as 48.2% in Turkey (17), resulting in the use of bismuth-based quadruple treatment as first-line treatment for *H. pylori* eradication. For metronidazole, there is a lack of reproducibility in testing it in vitro. There is also a lack of clinical correlation between the minimum inhibitory concentration observed and the clinical outcome, in that, despite a high minimum inhibitory concentration, *H. pylori* eradication still occurs, which is explained by synergy with other antibiotics and the high concentration obtained in the mucus when treatment is prolonged (15). Metronidazole resistance is reported as between 41.9% and 45.5% in Turkey (18,19), and it is suggested that the best results with bismuth-based quadruple therapies are obtained in areas with moderate to high rates of metronidazole resistance (i.e. ≥40%) (20-22).

Our patient group was younger, and therefore suspected to use antibiotics less frequently than older patients, and thus, the resistance to clarithromycin or metronidazole was supposed to be lower. For this reason, both clarithromycin- and bismuth-based treatments were used, but the

H. pylori eradication rate with the LAC protocol was still lower, as in the other studies performed in all age groups (4-6,12,23,24), while the bismuth-based quadruple treatment result was 85.7% (>80%), making it an acceptable success rate. In the event of failure after clarithromycin-containing treatment, either bismuth-based quadruple therapies or levofloxacin-based triple therapies are recommended (2). Since the eradication rates for *H. pylori* are not satisfactory, sequential therapies of 10 days involving a PPI plus amoxicillin for 5 days followed by PPI, clarithromycin, and tinidazole for an additional 5 days are suggested, and in a meta-analysis, the eradication rate of this sequential treatment was found to be 93%, which is greater than eradication rates for standard triple therapy (76%), and the authors concluded that 10 days of sequential therapy could become a standard treatment for *H. pylori* infection in naive patients (25). In a study from Turkey conducted by Uygun et al. (26), patients were given PPI and colloidal bismuth subcitrate for 14 days, amoxicillin for the first 7 days, and tetracycline and metronidazole for the last 7 days, and PP eradication rates were found to be 92%, while ITT eradication rates were found to be 81%. In another study from Turkey, patients were randomized into two groups - one group of patients was given PPI and amoxicillin for the first week, followed by PPI, clarithromycin, and metronidazole for the second week, while the second group of patients was given PPI and amoxicillin for the first week and PPI, clarithromycin and tetracycline for the second week. At the end of the treatment, PP eradication rates were found as 70.1% for the first group and 78.2% for the second group (27). According to the authors, the lower eradication rates were related to high clarithromycin and metronidazole resistance. Levofloxacin is a broad-spectrum fluoroquinolone, which shows a significant activity on *H. pylori* in both in vitro and in vivo studies. Levofloxacin has been used successfully instead of clarithromycin in *H. pylori* rescue therapies as well as in the first-line therapies (28,29). According to PP analysis, *H. pylori* eradication rates with the levofloxacin protocols ranged between 60-90% (30-32). In Turkey, there are limited studies with second-line levofloxacin-based treatments. In one of those studies, patients were given the first LAC treatment for 14 days, and those who were *H. pylori* positive after treatment were given PPI, amoxicillin, and levofloxacin for 7 days as second-line therapy. Success rates of 57% and 37.8% were achieved after LAC treatment and levofloxacin-based second-line treatment, respectively. In another study, patients were given either levofloxacin-containing sequential (PPI and amoxicillin for the first 5 days, followed by PPI, metronidazole and levofloxacin for 7 days) or levofloxacin-containing quadruple treatments (PPI, levofloxacin, bismuth subcitrate, and tetracycline for 10 days) as second-line therapies, and ITT rates of 82.2% in levofloxacin-based sequential second-line therapy and of 90.6% in levofloxacin-based second-line quadruple therapy were achieved (5,33). In our study, the success rates of second-line treatments with BLMT or LAL were similar and lower than 80%, which suggests that the success rates of second-line treatments are independent of the choice of the first-line treatments and thus other protocols should be considered as rescue treatments for young patients with dyspepsia. In our study, on multivariate regression analysis, it was shown that smoking, alcohol consumption and NSAID use had no effect on *H. pylori* eradication rates, which was in contrast with the study by Namiot et al. (34), in which smoking was found to decrease the *H. pylori* eradication rates while alcohol consumption was not. In our study, the only factor affecting the treatment response was found to be BLMT treatment, which suggests that BLMT treatment should be preferred as the first-line treatment in Turkey.

Although the sample in this study was small, we showed that in areas with high H. pylori prevalence rates, the test and treat strategy is an acceptable, easy method to diagnose and treat young patients with dyspepsia and without alarm symptoms. Even in young patients who are presumed to be susceptible to clarithromycin-based triple treatment, the H. pylori eradication rates with clarithromycin-based triple treatments were lower, as seen in other age groups. Thus, even in young patients, bismuth-based quadruple treatment should be preferred as the first-line treatment in countries like Turkey where clarithromycin resistance is high.

REFERENCES

1. Ozaydin ANG, Cali S, Türkyilmaz AS. Turkey *Helicobacter pylori* prevalence survey 2003. [In Turkish]. İstanbul: Marmara Saglik ve Egitim Arastirma Vakfi, 2007; 42.
2. Malfertheiner P, Megraud F, O'Morain CA, et al. European Helicobacter Study Group. Management of *Helicobacter pylori* infection - the Maastricht IV/Florence Consensus Report. Gut 2012; 61: 646-64.
3. Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on practice parameters of American College of Gastroenterology. Am J Gastroenterol 1998; 93: 2330-8.
4. Nadir I, Yonem O, Ozin Y, et al. Comparison of two different treatment protocols in Helicobacter pylori eradication. South Med J 2011; 104: 102-5.

5. Ermis F, Akyüz F, Uyanikoglu A, et al. Second-line levofloxacin-based triple therapy's efficiency for *Helicobacter pylori* eradication in patients with peptic ulcer. South Med J 2011; 104: 579-83.
6. Polat Z, Kadayifci A, Kantarcioglu M, et al. Comparison of levofloxacin-containing sequential and standard triple therapies for the eradiation of *Helicobacter pylori*. Eur J Intern Med 2012; 23: 165-8.
7. Uygun A, Kadayifci A, Polat Z, et al. Comparison of bismuth–containing quadruple and concomitant therapies as a first–line treatment option for *Helicobacter pylori*. Turk J Gastroenterol 2012; 23: 8-13.
8. Ergül B, Dogan Z, Sarikaya M, et al. The efficacy of two-week quadruple first-line therapy with bismuth, lansoprazole, amoxicillin, clarithromycin on *Helicobacter pylori* eradication: a prospective study. Helicobacter 2013; 18: 454-8.
9. Gisbert JP, Pajares JM. 13 C-urea breath test in the diagnosis of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2004; 20: 1001-17.
10. Malfertheiner P, Mégraud F, O'Morain C, et al. Current European concepts in the management of *Helicobacter pylori* infection the Maastricht Consensus Report. The European *Helicobacter Pylori* Study Group (EHPSG). Eur J Gastroenterol Hepatol 1997; 9: 1-2.
11. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection. J Gastroenterol Hepatol 1998; 13: 1-12.
12. Kadayifci A, Buyukhatipoglu H, Savas CM, et al. Eradication of *Helicobacter pylori* with triple therapy: an epidemiologic analysis of trends in Turkey over 10 years. Clin Ther 2006; 28: 1960-6.
13. Philips RH, Whitehead MW, Lacey S, et al. Solubility, absorption, and anti-*Helicobacter pylori* activity of bismuth subnitrate and colloidal bismuth subcitrate: in vitro data do not predict in vivo efficacy. Helicobacter 2000; 5: 176-82.
14. Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for *Helicobacter pylori:* lessons from China. Eur J Gastroenterol Hepatol 2013; 25: 1134-40.
15. Couturier MR, Marshall BJ, Goodman KJ, et al. *Helicobacter pylori* diagnostics and treatment: Could a lack of universal consensus be the best consensus? Clin Chem 2013; 60: 4 (Epub ahead of print).
16. Megraud F, Coenen S, Versporten A, et al.; Study Group participants. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013; 62: 34-42.
17. Onder G, Aydın A, Akarca U, et al. High *Helicobacter pylori* resistance rate to clarithromycin in Turkey. J Clin Gastroenterol 2007; 41: 747-50.
18. Cagdas U, Otag F, Tezcan S, et al. Detection of *Helicobacter pylori* and antimicrobial resistance in gastric biopsy specimens. Microbiol Bul. 2012; 46: 398-409.
19. Bakir Ozbey S, Ozakin C, Keskin M. Antibiotic resistance rates of *Helicobacter pylori* isolates and the comparison of E-test and fluorescent in situ hybridization methods for the detection of clarithromycin resistant strains. Mikrobiol Bul 2009; 43: 227-34.
20. Fischbach LA, van Zanten S, Dickason J. Meta-analysis: the efficacy, adverse events, and adherence related to first line anti-*Helicobacter pylori* quadruple therapies. Alimentary Pharmacol Ther 2004; 20: 1071-82.
21. Salazar CO, Cardenas VM, Reddy RK, et al. Greater than 95% success with 14-day bismuth quadruple anti-*Helicobacter pylori* therapy: a pilot study in US Hispanics. Helicobacter 2012; 17: 382-90.
22. Rimbara E, Fiscbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. Nat Rev Gastroenterol Hepatol 2011; 8: 79-88.
23. Songür Y, Senol A, Balkarli A, et al. Triple or quadruple tetracycline based therapies versus standard triple treatment for *Helicobacter pylori* treatment. Am J Med Sci 2009; 338: 50-3.
24. Uygun A, Kadayifci A, Yesilova Z, et al. Comparison of sequential and standard triple drug regimen for *Helicobacter pylori* eradication: a 14 day, open label, randomized, prospective, parallel-arm study in adult patients with non ulcer dyspepsia. Clin Ther 2008; 30: 528-34.
25. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. Ann Intern Med 2008; 148: 923-31.
26. Uygun A, Ozel AM, Sivri B, et al. Efficacy of a modified sequential therapy including bismuth subcitrate as first line therapy to eradicate *Helicobacter pylori* in Turkish population. Helicobacter 2012; 17: 486-90.
27. Kadayifci A, Uygun A, Kilciler G, et al. Low efficacy of clarithromycin including sequential regimens for *Helicobacter pylori* infection. Helicobacter 2012; 17: 121-6.
28. Molina-Infante J, Perez Gallardo B, Fernandez-Bermejo M, et al. Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2010; 31: 1077-84.
29. Zullo A, De Francesco V, Manes G, et al. Second-line and rescue therapies for *Helicobacter pylori* eradication in clinical practice. J Gastrointest Liver Dis 2010; 19: 131-4.
30. Wong WM, Gu Q, Chu KM, et al. Lansoprazole, levofloxacin and amoxicillin triple therapy vs. quadruple therapy as secondary line treatment of resistant *Helicobacter pylori* infection. Aliment Pharmacol Ther 2006; 23: 421-7.
31. Giannini EG, Bilardi C, Dulbecco P, et al. A study of 4- and 7-day triple therapy with rabeprazole, high dose levofloxacin and tinidazole rescue treatment for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2006; 23: 281-7.
32. Gispert JP, Castro-Fernandez M, Bermejo F, et al.; H. pylori Study Group of the Asociacion Espanola de Gastroenterologia. Third line rescue therapy with levofloxacin after two *H. pylori* treatment failures. Am J Gastroenterol 2006; 101: 243-7.
33. Calhan T, Kahraman R, Sahin A, et al. Efficacy of two levofloxacin-containing second-line therapies for *Helicobacter pylori:* a pilot study. Helicobacter 2013; 18: 378-83.
34. Namiot DB, Leszczynska K, Namiot Z, et al. Smoking and drinking habits are important predictors of Helicobacter pylori eradication. Adv Med Sci 2008; 53: 310-5.