Can the treatment duration be shortened in bismuth-containing therapies for *Helicobacter pylori eradication?*

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ABSTRACT

Background/Aims: *The duration of* Helicobacter pylori *(H. pylori) eradication therapy as a range (e.g., 10–14 days) is an ignored problem. There is no any particular treatment duration described in current guidelines, and the conditions for when to use 10-day therapy vs. 14-day therapy have not been elucidated. The aim of this study is to determine an effective and reliable H. pylori treatment duration in clinical practice. There were four different treatment modalities administered to groups, and success rates were compared.*

Materials and Methods: *Patients were eligible to participate in the study if they had a biopsy-proven* H. pylori *infection. Each patient was randomly assigned to one of the four treatment groups according to a predetermined sequence: 14-day or 10-day bismuth-containing quadruple therapy (BQT) groups and 14-day or 10-day moxifloxacin-bismuth-combined treatment (MBCT) groups.*

Results: *A total of 216 patients (54 per group) were enrolled. Two-hundred six patients (95.3%) completed therapy. There was no significant difference in the eradication rates between those patients who received 10- and 14-days BQT regimens (p=0.67). The 14-BQT protocol had the highest eradication rate, the MBCT regimes had the highest compliance, and the 10-MBCT protocol had the poorest results for H. pylori eradication. The posttreatment questionnaire on adverse effects identified nausea/vomiting as the most common side effect (35.7%).*

Conclusion: *Overall, the results of our study suggest that shortening the BQT protocol duration to 10 days does not weaken the* H. pylori *eradication rate. Moreover, quinolone-containing therapies with the lowest eradication rate among the groups should not be offered as a salvage treatment in case of the BQT failure.*

Keywords: *Eradication rate,* Helicobacter pylori*, treatment duration*

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a known etiopathogenetic factor in a wide range of diseases, from gastritis to gastric malignancies, and the infection with this bacterium remains globally a major public health issue (1). Authors from Turkey reported that the overall prevalence of *H. pylori* was 82.5% in asymptomatic adults, but this ratio was significantly higher, especially in men who were >45 years old and of a low socioeconomic status (2). *H. pylori* was detected in 65% for distal gastric tumors in cases settled around east of Turkey in another retrospective and multicentric study (3). In terms of these findings, *H. pylori* eradication seems to be obligatory to prevent the gastroduodenal diseases, particularly gastric cancer (4).

The most recent report by European Helicobacter Study Group formulated the treatment of *H. pylori* infection at the Maastrich V Consensus Conference (5). The proton pump inhibitor (PPI)-clarithromycin-amoxicillin or met-

ronidazol treatment was no longer recommended as the first-line treatment in populations with more than 15% clarithromycin and metronidazole dual resistance. Bismuth-containing quadruple treatments was the best alternative first-line treatments in populations having a higher antibiotic resistance (5). Antimicrobial stewardship was described slightly different in other guidelines depending on the resistance, effectiveness, and adverse effects of antibiotics (6-8). Although quinolone-containing therapies are denoted as the second-line treatment, levofloxacin triple treatment or levofloxacin- and bismuth-combined quadruple treatment were successful as the first-line treatment in some recent publications (9-11).

The duration of *H. pylori* eradication therapy as a range (e.g., 10 to 14 days) is still a hesitant state. The certain treatment duration has not been described in present guidelines, and the conditions for when to use 10-day-

therapy or 14-day- therapy have not been elucidated. The current strategy described in guidelines is to leave this choice to the physician.

Shortening the treatment duration might improve the patient compliance and the cost of medication unless the success of antibiotics is not diminished. Clinicians should ultimately find an efficient treatment duration that is optimal for their population or region. The aim of this study is to determine an effective and reliable *H. pylori* treatment duration in clinical practice. Four different treatment modalities were administered, and success rates of *H. pylori* eradication therapies were compared.

MATERIALS AND METHODS
This prospective study was carried out, and all participants got detailed written information about the research in advance and signed a written consent form. The study protocol was approved by the local Ethics Committee of the hospital (KAEK 11/12).

Patients were eligible to participate if they had a biopsy-proven *H. pylori* infection. Five biopsies were taken from the antrum, incisura angularis, and corpus according to the Sydney protocol (12). Biopsy specimens were immediately fixed in 10% buffered formalin and subsequently stained with hematoxylin and eosin and with Giemsa, Warthin-Starry silver to assess the presence of *H. pylori*. The exclusion criteria were as follows: active bleeding ulcer, gastric cancer, 4 weeks before or with current use of antibiotics, nonsteroidal anti-inflammatory drugs, aspirin, H2-receptor blockers, systemic glucocorticoids, immunosuppressive drugs, pregnancy, lactation, a previous treatment for *H. pylori* or early discontinuation of such drugs, history of gastric surgery, serious systemic comorbidities such as chronic renal failure, hepatic failure, severe cardiopulmonary disease, and malignant diseases.

Eligible patients were referred to the director of research from each department. Each patient was randomly assigned to one of four treatment groups according to a predetermined sequence. A total of 216 patients (54 per group) were enrolled (Figure 1).

Treatment groups
14-day bismuth-containing quadruple therapy group (14-BQT group; n=54): These patients received a PPI (esomeprazole 40 mg bid), bismuth subsalicylate (524 mg bid), metronidazole (500 mg tid), and tetracycline (500 mg qid) for 14 days.
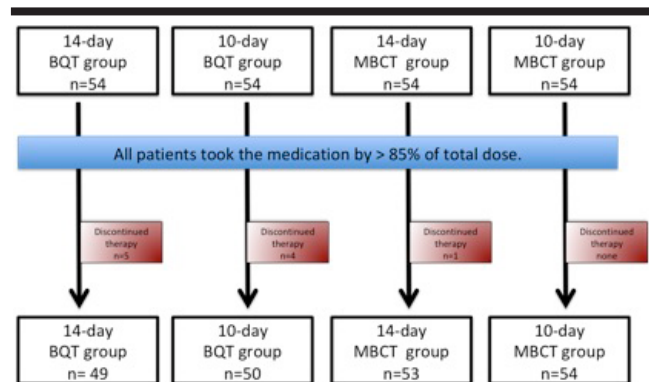

Figure 1. Schematic diagram of the study population
14-day bismuth-containing quadruple treatment group (14-BQT group)
10-day bismuth-containing quadruple treatment group (10-BQT group)
14-day moxifloxacin-bismuth combined treatment group (14-MBCT group)
10-day moxifloxacin-bismuth combined treatment group (10-MBCT group)

10-day bismuth-containing quadruple therapy group (10-BQT group; n=54): These patients received the above-noted BQT regimen for 10 days.

14-day moxifloxacine-bismuth combined therapy group (14-MBCT group; n=54): These patients received a PPI (esomeprazole 40 bid), amoxicillin (1000 mg bid), and moxifloxacin (500 mg qd) and bismuth subsalicylate (524 mg bid) for 14 days.

10-day *moxifloxacine-bismuth combined therapy group* (10-MBCT group; n=54): These patients received the above-noted MBCT regimen for 10 days.

Assessment of data
The data collected for each patient were as follows: gender and age; smoking and alcohol habits; medical history (systemic diseases, drugs, operations); endoscopic diagnosis and histopathologic findings; indications for *H. pylori* eradication; and compliance with treatment prescribed.

Patients underwent a posttreatment evaluation for *H. pylori* eradication at least 6 weeks after the completion of the treatment regimen. This involved a C-13 urea breath test (UBT) and a structured questionnaire that inquired about adverse treatment effects. In UBT, breath samples were analyzed by means of the isotope ratio mass spectrometry. The test results were evaluated as *H. pylori*-negative when the 13-C difference between the 0th minute and 30th minute sample was lower than 3.5 (delta value).

A successful eradication rate was defined as which 90% of patients in the group achieved the *H. pylori*-negative sta-

Table 1. Demographic and clinical characteristics of patients

Characteristics	14-Day BQT Group	10-Day BQT Group	14-Day MBCT Group	10-Day MBCT Group	p
Female (n, %)	35 (64.8)	37 (68.5)	31 (57.4)	32 (59.3)	0.61
Male (n, %)	19 (35.2)	17 (31.5)	23 (42.6)	22 (40.7)	
Median age±standard deviation	44±12.5	40±11.0	43±11.5	41±11.5	0.30
Smoking habit (n, %)	10 (18.5)	8 (14.8)	12 (22.2)	11 (20.3)	0.78
Diagnosis					0.91
Peptic ulcer	13	14	14	12	
Family history of gastric cancer	4	4	6	4	
Atrophic gastritis±intestinal metaplasia	6	4	8	7	
Non-ulcer dyspepsia	31	32	26	31	

14-day bismuth-containing quadruple treatment group (14-BQT group)
10-day bismuth-containing quadruple treatment group (10-BQT group)
14-day moxifloxacin-bismuth combined treatment group (14-MBCT group)
10-day moxifloxacin-bismuth combined treatment group (10-MBCT group)

tus at 6th week after the eradication therapy. This is in accordance with the Maastricht V Consensus Report, which has set the acceptance level for the therapeutic regimens as an 80% and 90% or higher by the per-protocol (PP) and intention-to-treat (ITT) analysis, respectively (7).

Statistical analysis

A power analysis with $\alpha=0.05$ and $\beta=0.80$ identified the required sample size as 48 patients per group; however, 54 patients were enrolled per group to compensate for expected dropouts. Data were analyzed using by the Statistical Package for the Social Sciences software version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Mean values and standard deviations were calculated for demographic characteristics. The rates of *H. pylori* eradication were evaluated using PP and ITT analyses. The chi-squared test and one-way analysis of variance were used to compare the results. A *p*-value <0.05 was considered significant.

RESULTS

Demographic assessment

Table 1 summarizes the patients' demographic findings presented by group. The mean age of the 216 patients was 42.1±11.7 years. One hundred thirty-five (62%) patients were females. There were no significant differences among the four treatment groups with respect to the mean age or sex distribution (p=0.30 and p=0.61, respectively), or frequencies of smoking and alcohol habits use were similar among all treatment groups (p=0.78

and p=0.82, respectively) (Table 1). The indications for *H. pylori* treatment were non-ulcer dyspepsia (56% of the 216 patients), duodenal ulcer (13%), gastric ulcer (12%), atrophic gastritis, and/or intestinal metaplasia (11.1%), and a family history of gastric cancer (7.9%). There were no significant differences among the treatment groups with respect to frequencies of these indications (p=0.91).

Adverse effects and compliance

Two-hundred six patients (95.3%) completed therapy. Ten patients (4.7%) dropped out of the study because of adverse effects, complexity of treatment, and/or excessive numbers of tablets required to be taken daily.

The post treatment questionnaire on adverse effects identified nausea/vomiting as the most common side effect (35.7%), followed by headache, metallic taste in the mouth, diarrhea, and abdominal pain. The BQT groups reported the highest frequency of side effects (44.4%), and they were found to be statistically significant (p<0.001). Discontinuation due to side effects was also most commonly observed in the BQT therapy groups (8.3%); however, it was not statistically different between the 14-BQT (9.2%) and 10-BQT groups (7.4%, p=0.58). Table 2 summarizes the group results for *H. pylori* eradication, compliance, and drug adverse effects.

Helicobacter pylori eradication rate

In the 14-BQT group, 49 patients (90.7%) completed the treatment protocol, and the PP- and ITT-based

Table 2. Treatment compliance, *H. Pylori* eradication rates, and drug adverse effects

Results	14-Day BQT Group	10-Day BQT Group	14-Day MBCT Group	10-Day MBCT Group	p
Completion of treatment, %	90.7	92.5	98.1	100[∗]	0.05
Rate of eradication, %					
ITT	87*	85*	81.4[¶]	72.2[^]	<0.001
PP	96	92	83	72.2	
Adverse effects, Overall, n (%)	24 (44.4)[§]	18 (33.5)	9 (16.6)	5 (9.2)[§]	<0.001
Nausea±vomiting	7	5	5	3	
Headache	6	3	0	1	
Metallic taste	4	4	0	0	
Abdominal discomfort	1	2	2	1	
Others	6	4	2	1	

14-day bismuth-containing quadruple treatment group (14-BQT group)
10-day bismuth-containing quadruple treatment group (10-BQT group)
14-day moxifloxacin-bismuth combined treatment group (14-MBCT group)
10-day moxifloxacin-bismuth combined treatment group (10-MBCT group)
ITT: intent-to-treat analysis; PP: per-protocol analysis
[∗]statistical difference in treatment completion between 14-day BQT group and 10-day MBCT group, p=0.052
*no statistical difference in efficacy between the 14-day BQT group and 10-day BQT group, p=0.67
[¶]statistical difference in efficacy between the 14-day BQT group and 14-day MBCT group, p<0.001
[^]statistical difference in efficacy between the 14-day BQT group and 10-day MBCT group, p<0.001
[§]statistical difference in adverse effects between the 14-day BQT group and 10-day MBCT group, p<0.001

eradication rates were 96% (47/49) and 87% (47/54), respectively. In the 10-BQT group, 50 patients (92.5%) completed the protocol, and the corresponding eradication rates were 92% (46/50) and 85% (46/54). In the 14-MBCT group, 53 patients (98.1%) completed the protocol, and PP- and ITT-based eradication rates were 83% (44/53) and 81.4% (44/54), respectively. The entire 10-MBCT group completed the treatment, and the corresponding eradication rates were 72.2% (39/54) and 72.2% (39/54). Statistical comparison of the respective rates of *H. pylori* eradication success among the treatment groups revealed significant differences in favor of BQT groups (p<0.001 for PP analysis and p<0.001 for ITT analysis). There was no significant difference in the eradication rates between those who received 10- and 14-days BQT regimens (p=0.067).

DISCUSSION
Our main findings were that the 14-BQT protocol had the highest eradication rate, the MBCT regimens had the highest compliance, and the 10-MBCT protocol had the poorest results for *H. pylori* eradication. Overall, the results of our study suggest that both 14-day and 10-day treatment durations for the BQT regimen are highly successful at eradicating *H. pylori* in Turkish patients. Even though these BQT regimens did not reach the healing rate recommended by the Maastricht V Consensus Report, they showed encouraging rates (>80%). However, 10-day quinolone-containing therapy failed in its efficacy with the lowest eradication rate among the groups. While these are not outstanding features, our results indicate that shortening the BQT protocols duration to 10 days does not weaken the *H. pylori* eradication treatments except quinolone protocols.

Problems involved declining *H. pylori* eradication rates, and growing *H. pylori* recurrence are generally related to antibiotic resistance, inefficient combination therapies, inadequate treatment duration, and low socioeconomic and sanitary conditions (10). A study by Smith et al. (11) revealed primary resistance rates of 17.5%, 14.1%, and 34.9% for clarithromycin, levofloxacin, and metronidazole, respectively. In Turkey, the resistance rates to clarithromycin, levofloxacin, and metronidazole in *H. pylori* were reported in a systematic review as 24.9%, 23.8%, and 33.7%, respectively (13). Considering the

geographic variation in the prevalence of bacterial resistance, treatment regimens might need to be modified in accordance with the guidelines for susceptibility testing (14).

Extending the treatment duration and incorporating bismuth salts to all regimens were attempts to overcome the antibiotic resistance. It is known that the bismuth compounds still have no resistance and additive effects on the other antibiotic combinations, despite of some adverse events leading to poor compliance (15). But, the treatment duration with BQT remains controversial when the metronidazole or quinolone are prescribed. Because the resistance rates change in a range of 20%-40% in the United States and Europe, the prevalence of *H. pylori* has been increasing from 50% to 80% in developing countries in the past 10 years (16). The eradication rates of BQT hereby have been reported in a wide range from 57% to 95% (16).

Treatment duration is a critical determinant of the eradication outcome, particularly standard triple therapy. Several meta-analyses disclosed a benefit of prolonging the length of triple therapy. As a result, the 14-day triple therapy was more effective than the 10-day and 7-day triple therapy (17). Therefore, it may be expected that the increased duration of bismuth-containing quadruple therapy would be more effective, mainly in high metronidazole-resistant areas. However, studies from different regions showed that BQT given for 10 days was not inferior to the 14-day treatment in terms of efficacy. In a study from Italy, a total of 417 patients were assigned to receive BQT twice a day for 10 or 14 days. Despite reducing the treatment duration to 10 days, results from an ITT analysis were similar for the 10- and 14-day therapy (18). Another study form Taiwan including 63 patients showed that 10-day quadruple treatment had a high *H. pylori* eradication rate with 93.3% in the PP analysis and 92.1% in the ITT analysis as the second-line treatment (19). Our findings also supported that the 10-day group achieved 85%, and the 14-day group obtained 87% eradication rate in ITT analyses, a difference that did not reach the statistical significance. At this point, we thought the patient compliance is a big deal for the success of such complex therapies. To support the patients' compliance and adherence to therapy, prescribed medications were explained in detail, and medication calendar and mobile phone alarm were offered for all patients. Shortening the period of therapy made the patient's perception of complex therapy easier. Furthermore, a short therapy duration can help

to reduce the risk of developing antibiotic resistance. It seems necessary to establish the cost-effectiveness of the treatment strategies and to compare them in terms of purchasing prices of pharmaceuticals. Although the lack of basic quantitative methods to estimate financial costs of the 10-day vs. 14-day treatments is a limitation to our study, we can argue in favor of the 10-day BQT only from the perspective of drug costs.

In recent years, fluoroquinolones containing triple therapies have been at the forefront among the eradication treatments for *H. pylori*, and that was our basis for testing moxifloxacin regimens as alternative treatments (20,21). A study from Turkey indicated that the efficacy of triple therapy containing moxifloxacin in 102 patients was acceptable as the first-line treatment for *H. pylori* eradication (22). The addition of bismuth salts can be considered a valuable adjuvant to triple therapy in those areas where *H. pylori* shows a high resistance to fluoroquinolones (21). With the reference to the prevalence of primary fluoroquinolone resistance is higher than 15% in Asia (China, Iran, Japan, Pakistan) and Russia, bismuth subsalicylate was added to the combination in our study (23). Kahramanoğlu et al. (24) also found that a 14-day levofloxacin-containing BQT was somewhat more efficient than levofloxacin-containing triple therapy. Although the MBCT regimes had the highest compliance, both the 10-day and 14-day MBCT protocols were a lower eradication rate than BQT regimens in our study. Because quinolones are commonly used in developing countries to treat respiratory or urinary tract infections, many patients show high resistance to quinolones when they are used as the first-line treatment for *H. pylori* eradication (25,26). Therefore, we can speculate that fluoroquinolones should no longer be used as salvage treatment in Turkey, even in combination with bismuth or in extended treatment duration of 14 days. The drawback of antimicrobial susceptibility test is other major limitation of our study.

In conclusion, we proposed that the BQT protocol duration for 10 days does not weaken the *H. pylori* eradication treatment. It is obvious that shortening treatment duration for BQT will improve patient compliance and ultimately decrease the cost of medications without reducing the efficacy. The other important result of our study was the ineffectiveness of the MBCT regimens as a salvage treatment. It is clear that regional studies evaluating the efficacy, safety, and cost of medications will help to determine the most ideal duration of first-line therapies and establish new alternative salvage treatments in case of the BQT failure regarding local factors.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Turkey Yuksek Ihtisas Training and Research Hospital (KAEK 11/12).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. World Gastroenterology Organisation Global Guideline Helicobacter pylori in Developing Countries. Journal of Digestive Diseases 2011; 12: 319-26. **[CrossRef]**
2. Ozaydin N, Turkyilmaz SA, Cali S. Prevalence and risk factors of Helicobacter pylori in Turkey: a nationally-representative, cross-sectional, screening with the ^{13}C. BMC Public Health 2013; 13: 1215. **[CrossRef]**
3. Bor S, Vardar R, Ormeci N, et al. Prevalence patterns of gastric cancers in Turkey: model of a developing country with high occurrence of Helicobacter pylori. J Gastroenterol Hepatol 2007; 22: 2242-5. **[CrossRef]**
4. Available from: globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp
5. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 2017; 66: 6-30. **[CrossRef]**
6. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol 2017; 112: 212-39. **[CrossRef]**
7. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. J Gastroenterol Hepatol 2009; 24: 1587-600. **[CrossRef]**
8. Fu W, Song Z, Zhou L, et al. Randomized Clinical Trial: Esomeprazole, Bismuth, Levofloxacin, and Amoxicillin or Cefuroxime as First-Line Eradication Regimens for Helicobacter pylori Infection. Dig Dis Sci 2017; 62: 1580-9. **[CrossRef]**
9. Su J, Zhou X, Chen H, Hao B, Zhang W, Zhang G. Efficacy of 1st-line bismuth-containing quadruple therapies with levofloxacin or clarithromycin for the eradication of Helicobacter pylori infection: A 1-week, open-label, randomized trial. Medicine (Baltimore) 2017; 96: e5859. **[CrossRef]**
10. Liou JM, WU MS, Lin JT. Treatment of helicobacter pylori infection: Where are we now? J Gastroent Hepatol 2016; 31: 1918-26. **[CrossRef]**
11. Smith SM, O'Morian C, McNamara D. Antimicrobial susceptibility testing for Helicobacter pylori in times of increasing antibiotic resistance. World J Gastroenterol 2014; 20: 9912-21. **[CrossRef]**
12. El-Zimaity HM, Graham DY. Evaluation of gastric mucosal biopsy site and number for identification of Helicobacter pylori or intestinal metaplasia: role of the Sydney System. Hum Pathol 1999; 30: 72-7. **[CrossRef]**
13. Kocazeybek B, Tokman HB. Prevelance of primaryantimicrobial resistance of H. pylori in Turkey: A systematic review. Helicobacter 2016; 21: 251-60. **[CrossRef]**
14. Hu Y, Wan JH, Li XY, et al. Systematic review with meta-analysis: the global recurrence rate of Helicobacter pylori. Aliment Pharmacol Ther 2017; 46: 773-9. **[CrossRef]**
15. Alkim H, Koksal AR, Boga S, Sen I, Alkim C. Role of bismuth in the eradication of Helicobacter pylori. Am J Ther 2017; 24: e751-7. **[CrossRef]**
16. Debraekeleer A, Remaut H. Future perspective for potential Helicobacter pylori eradication therapies. Future Microbiol 2018; 13: 671-87. **[CrossRef]**
17. Federico A, Gravina AG, Miranda A, Loguercio C, Romano M. Eradication of Helicobacter pylori infection: which regimen first? World J Gastroenterol 2014; 20: 665-72. **[CrossRef]**
18. Dore MP, Farina V, Cuccu M, Mameli L, Massarelli G, Graham DY. Twice-a-day bismuth-containing quadruple therapy for Helicobacter pylori eradication: a randomized trial of 10 and 14 days. Helicobacter 2011; 16: 295-300. **[CrossRef]**
19. Jheng GH, Wu IC, Shih HY, et al. Comparison of Second-Line Quadruple Therapies with or without Bismuth for Helicobacter pylori Infection. Biomed Res Int 2015; 2015: 163960. **[CrossRef]**
20. Berning M, Krasz S, Miehlke S. Should quinolones come first in Helicobacter pylori therapy? Therap Adv Gastroenterol 2011; 4: 103-14. **[CrossRef]**
21. Ciccaglione AF, Cellini L, Grossi L, Marzio L. Quadruple therapy with moxifloxacin and bismuth for first-line treatment of Helicobacter pylori. World J Gastroenterol 2012; 18: 4386-90. **[CrossRef]**
22. Rakici H, Ayaz T, Akdogan RA, Bedir R. Comparison of levofloxacin- and moxifloxacin-based triple therapies with standard treatment in eradication of Helicobacter pylori as first-line therapy. Digestion 2014; 90: 261-4. **[CrossRef]**
23. Liao J, Zheng Q, Liang X, et al. Effect of Fluoroquinolone Resistance on 14-day Levofloxacin Triple and Triple Plus Bismuth Quadruple Therapy. Helicobacter 2013; 18: 373-7. **[CrossRef]**
24. Kahramanoğlu Aksoy E, Pirinçci Sapmaz F, Göktaş Z, Uzman M, Nazlıgül Y. Comparison of Helicobacter pylori Eradication Rates of 2-Week Levofloxacin-Containing Triple Therapy, Levofloxacin-Containing Bismuth Quadruple Therapy, and Standard Bismuth Quadruple Therapy as a First-Line Regimen. Med Princ Pract 2017; 26: 523-9. **[CrossRef]**
25. Dalhoff A. Resistance surveillance studies: a multifaceted problem-the fluoroquinolone example. Infection 2012; 40: 239-62. **[CrossRef]**
26. Sezgin O, Altintaş E, Uçbilek E, Tombak A, Tellioğlu B. Low efficacy rate of moxifloxacin-containing Helicobacter pylori eradication treatment: in an observational study in a Turkish population. Helicobacter 2007; 12: 518-22. **[CrossRef]**