Unacceptable Antibiotic Resistance Rates for Helicobacter pylori *in Turkey: Something Must Change*

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Cite this article as: Gökçekuyu BM, Yılmaz Ö, Soytürk M, Ellidokuz H, Akpınar H, Şimşek İ. Unacceptable antibiotic resistance rates for *Helicobacter pylori* in turkey: Something must change. *Turk J Gastroenterol.* 2021; 32(3): 269-275.

ABSTRACT

Background: *It is known that clarithromycin resistance has increased over the years (success rate 60%). The aim of the study was to investigate the importance of regional antimicrobial resistance rates for full accuracy of both diagnosis and treatment of Helicobacter pylori infection.*

Methods: *This study was carried out in the University Hospital Department of Gastroenterology. A total of 116 patients were evaluated with upper gastrointestinal endoscopy. Gastric antrum and corpus biopsy samples were taken for the rapid urease test (RUT), culture, and antimicrobial susceptibility testing for the presence of H. pylori. Antimicrobial susceptibilities of isolated H. pylori strains for clarithromycin and levofloxacin were determined by the epsilometer test (E-test). Minimal inhibitory concentration values for clarithromycin and levofloxacin were ≥1 and >1 µg/mL, respectively.*

Results: *H. pylori infection was considered clinically positive in 93 (80.2%) patients with either the RUT, culture, or histopathological examination. Seventy (60.3%) of the patients had RUT positivity. Sixty (85.7%) of these 70 patients had RUT positivity within the first 20 min. Among the 90 patients, who had a histopathological examination, HLO was positive in 76 (84.4%) patients. Fifty-two (44.8%) out of 116 patients were culture positive. Resistance rates for both clarithromycin and levofloxacin were high. In these 52 culture-positive patients, resistance rates determined for clarithromycin and levofloxacin were 26.9% and 25.5%, respectively.*

Conclusion: *Clarithromycin or levofloxacin-based treatment regimen may not be an ideal alternative therapy for Turkish patients regardless of culture.*

Keywords: *H. pylori, clarithromycin, levofloxacin, culture susceptibility, diagnosis*

INTRODUCTION

Helicobacter pylori is one of the most common infectious agents in the world and was identified by the International Agency for Research on Cancer Group of the World Health Organization (WHO) in 1994 as a Group 1 (definitive) human carcinogen.[1] According to the TURHEP study, published in 2013 using the ^{13}C-urea breath test, the prevalence of *H. pylori* was detected in Turkey at a rate of 82.5%.[2] The conditions requiring treatment for *H. pylori* eradication are indicated in the Maastricht V/Florence Consensus Report.[3] Today, the first-line treatment protocol recommended for *H. pylori* eradication consists of proton pump inhibitors (PPI) and clarithromycin, amoxicillin, or metronidazole. Antibiotic resistance is currently considered the biggest obstacle to eradication success. If clarithromycin resistance is above 15% in 1 region, it is recommended not to use clarithromycin in an eradication treatment.[3] The widespread use of macrolides in the community is a facilitating factor for the development of resistance.[4]

In Turkey, clarithromycin resistance has increased significantly over the years and because of this, the effectiveness of the classical triple treatment protocol has been reported to decrease and the success rate of eradication is below 60%.[5] According to the Maastricht V/Florence Consensus report, clarithromycin resistance is reported as 30% in Italy and Japan, 40% in Turkey, 50% in China, and 15% in both Sweden and Taiwan.[3]

There are some studies on levofloxacin-based eradication treatments and resistance to this drug. The aim of this study was to determine the primary resistance rates in *H. pylori* strains isolated in the study hospital by using the

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Received: **April 1, 2020** *Accepted:* **September 8, 2020** *Available Online Date: X XX 2021*

DOI: **10.5152/tjg.2021.20210**

E-test method for clarithromycin and levofloxacin. It was aimed to contribute to the literature on the importance of culture sensitivity test for the correctness of diagnosis and treatment.

MATERIALS AND METHODS

A total of 116 patients who were admitted to our hospital, Department of Gastroenterology with the complaint of dyspepsia or pain and were indicated for upper gastrointestinal endoscopy were included in the cross-sectional study. All volunteers signed an informed constant form and the regional ethics committee of the University approved this study (decision no: 2010/02-06: 26.05.2010).

The criteria for inclusion were upper gastrointestinal endoscopy indication due to dyspepsia and patients >17 years of age. The exclusion criteria included gastric cancer, gastric lymphoma, gastrointestinal bleeding, history of gastroduodenal surgery, pregnancy or lactation, previous *H. pylori* eradication therapy, those who had used antibiotics or PPI drugs up to 4 weeks before the study, patients with the concomitant major disease (liver, cardiac, respiratory, kidney disease, neoplastic diseases, coagulopathy disorders).

Endoscopy and Biopsy Sampling

Gastric biopsy specimens (2 antrum and 2 corpus biopsies) were taken from each of the patients included in the study for rapid urease test (RUT) (house-made), culture, and antimicrobial susceptibility testing. In addition, 1 antrum and 1 corpus gastric biopsy samples were taken for histopathological examination when the endoscopist deemed it necessary. In case of culture growth from the corpus and/or antrum from gastric biopsy samples, clarithromycin and levofloxacin susceptibility tests were studied by E-test and the minimal inhibitory concentration (MIC) results were evaluated.

MAIN POINTS

Not taking histopathological specimen during endoscopy, but taking only RUT samples may lead to skipping of IM and atrophy cases and even worse early gastric cancer. Another feature of this study is that no hasty decision be made for the interpretation of the RUT examination, for the negative values. In addition to RUT, the importance of performing culture and histopathological examination should be emphasized. In this study, resistance rates for both clarithromycin and levofloxacin were high. Once performing an invasive procedure such as endoscopy, sampling for culture, will also be an important step in preventing antibiotic resistance and treatment success.

Histopathological Examination of Biopsy Specimens

Patients' antrum and corpus biopsy specimens were immediately put into separate vials containing 10% formalin solution and were sent to the Department of Pathology for routine histopathological examination if deemed necessary by the endoscopist. Paraffin-embedded 90 gastric biopsy specimens were stained by Hematoxylin–Eosin (H&E), Alcian blue, and Giemsa stains. The Updated Sydney system was used for grading bacterial density of *H. pylori* and gastritis activity. The samples were examined morphologically under a light microscope (Nikon E600) for HLO. In lamina propria, inflammation of the pits, atrophy, intestinal metaplasia (IM), and HLO were ranked between 0 and 3 according to the Updated Sydney System [none (grade 0), mild (grade 1), moderate (grade 2), and marked (grade 3)].[8] Histopathological assessment was performed by an experienced pathologist.

Evaluation of Patients with H. pylori Infection

Each corpus and antrum gastric biopsy specimen was taken and histopathological examination, the RUT, and culture tests were performed. Cases, where at least 1 of these tests was positive, were considered clinically positive for *H. pylori* infection. Patients with negative results for all 3 tests were considered clinically negative for *H. pylori* infection.

Microbiological Examination of Biopsy Specimens and H. pylori Culture

Biopsy samples obtained from the antrum and corpus from each patient were immersed in Brucella Broth (Beckton Dickinson, Sparks, USA) *H. pylori* transport medium containing 20% glycerol and delivered to the laboratory of the Department of Medical Microbiology. Each biopsy specimen was cultivated separately on Columbia Blood Agar (Oxoid Ltd. Basingstole, Hampshire, UK) containing 7% defibrinated horse blood (Oxoid Ltd. Basingstole, Hampshire, UK) and *H. pylori* Selective Supplement (DENT, Oxoid Ltd. Basingstole, UK). Plates were incubated at 37°C under microaerophilic conditions (GasPak Campy Container System, Becton Dickinson, and Company, Maryland, USA) for 3-7 days. If no growth was observed, the incubation period was extended to 10-14 days. The culture was regarded as negative for *H. pylori* if no growth was observed at the end of this period. Cultured *H. pylori* colonies were evaluated with positive catalase, oxidase, and urease tests and Gram

staining. The presence of Gram-negative *H. pylori* and its typical morphology were evaluated. Biopsy samples from the antrum and corpus were also used for imprint preparation, Gram staining, and underwent direct urease testing in Christensen Urea Agar. The presence of *H. pylori* between the tissue cells and typical morphology were identified. *H. pylori* strain isolated from the antrum and/or corpus from each patient were placed in brain heart infusion broth (Oxoid Ltd. Basingstole, Hampshire, England) containing 20% glycerol and kept at −80°C.

Determination of MIC Values (µg/mL) for Clarithromycin and Levofloxacin Using the E-test Method

Bacterial suspensions from the subcultured *H. pylori* colonies were adjusted to the turbidity of 3 McFarland standard (9×10^{-8} CFU/mL) and inoculated onto Mueller Hinton Agar (Oxoid Limited Basinstole, Hampshire, England) containing 5% defibrinated sheep blood (Oxoid Limited Basinstole, Hampshire, England). Plates were incubated at 37°C under microaerophilic conditions (GasPak Campy Container System, Becton Dickinson, and Company, Maryland, USA) for 3-7 days. E-test (bio-Mérieux) method was used to determine the MICs of clarithromycin and levofloxacin. The MIC value for clarithromycin was determined by the National Committee for Clinical Laboratory Standards (NCCLS).[7] This value, which was determined for clarithromycin, has been used in many publications in the literature.[7-9] The MIC value for levofloxacin was determined in reference to previous studies.[7,10] The MIC values used in this study for clarithromycin and levofloxacin were ≥1 µg/ml and >1 µg/mL, respectively.[7,11]

Statistical Analysis

The data was processed using an SPSS 11.0 package program. Numeric variables were analyzed using the chi-square test. The level of statistical significance was set at $P < .05$.

RESULTS

A total of 116 patients (32 males, 84 females, mean age: 40.5 ± 14.9 years) were involved in this study. *H. pylori* was positive in 64 (76.2%) women and 29 (90.6%) men ($P = .081$).

The patient was considered positive for *H. pylori* if any of the RUT, HPE, or culture indicated *H. pylori*.

Table 1. Endoscopic Diagnoses and Distribution of Patients

Endoscopic Diagnoses	Patients (*n*)	Percentage of Patients (%)
Esophagitis	80	68.9
Gastritis	60	51.7
Gastric erosion	38	32.7
Hiatus hernia	20	17.2
Duodenal ulcer	13	11.2
Gastric ulcer	11	9.4
Duodenitis	5	4.3
Duodenal erosion	3	2.5
Gastric polyp	3	2.5

While the presence of *H. pylori* was demonstrated in 93 (80.2%) patients, it was not detected in 23 (19.8%) patients.

Evaluation of Endoscopic Findings of the Patients

Endoscopic findings of the patients are shown in Table 1. Multiple endoscopic diagnoses were observed for some patients.

RAPID UREASE TEST RESULTS IN ENDOSCOPIC BIOPSIES

From all patients, 2 biopsy samples were obtained, from the antrum and corpus, for the RUT. Samples showing negative results for the first 20 min were kept under observation for 24 h. The latest positive result was read at 4 h. Of 116 patients undergoing upper gastrointestinal endoscopy, the RUT was positive in 70 (60.3%) and negative in 46 (39.7%). Of these 70 patients, a positive result in the RUT was read within the first 20 min in 60 patients (85.7%) whereas a positive result was read after 20 min in 10 patients (14.3%).

Of the 93 patients, whose *H. pylori* positivity was shown by 1 of the 3 tests, 70 (75.2%) were positive with RUT.

Histopathological Examination of Endoscopic Biopsies

As a matter of endoscopist clinical discretion, the biopsy was not performed in 26 out of 116 patients and therefore these patients did not have samples for histopathological examination. Distributions of histopathological diagnoses were illustrated in Table 2.

Table 2. Distribution of Histopathological Diagnoses

Pathological Diagnoses	No of Patients (*n*)	Percentage of Patients (%)
Chronic gastritis	31	34.4
Active chronic gastritis	31	34.4
Active chronic gastritis and chronic gastritis	27	30
Intestinal metaplasia	20	22.2
Atrophy	7	7.7
Intestinal metaplasia and atrophy	3	3.3
Acute gastritis	1	1.1
Dysplasia	0	0

Comparison of the patients for test positivity by using RUT and histopathology was showed in Table 3.

Evaluation of Culture Results

Among the patients with a negative RUT obtained during upper gastrointestinal endoscopy ($n=46$), culture reproduction was obtained from the samples of 2 patients. One of these 2 patients had histopathological evidence of HLO. The culture was not positive in any specimen where the RUT was negative and only HLO was shown in histopathology. The rate of *H. pylori* presence in 116 patients by culture was found to be 44.8%. Of the 93 patients with positive *H. pylori* in at least 1 of the 3 tests, 52 (55.9%) had culture growth and 41 (44.1%) had no culture growth. Evaluation of RUT and culture results are showed in Table 4.

Table 3. Evaluation of RUT and Histopathology Results From Patients

Pathological Condition	Number of Patients (*n*)	Percentage of Patients (%)
	90	100
HLO (+)	76	84.4
HLO (–)	14	15.6
IM (+)	20	22.2
IM (–)	70	78.8
IM (+) and RUT (–)	8	8.8
IM (+) and RUT (+)	12	13.3
IM (+) and RUT (–) and HLO (+)	7	7.7
IM (+) and RUT (–) and HLO (–)	1	1.1
Atrofy	7	7.7
Atrofy (+) RUT (–)	4	4.4
Atrofy (+) RUT (+)	3	3.3
Atrofy (+) RUT (–) HLO (+)	3	3.3
Atrofy (+) RUT (–) HLO (–)	1	1.1

HLO, presence of *Helicobacter*-like organism histopathologically; IM, intestinal metaplasia; RUT, rapid urease test.

Table 4. Evaluation of RUT and Culture Results

RUT and Kx Test Results	Number of Patients (*n*)	Percentage of Patients (%)
RUT (+) Kx (+)	50	43.1
RUT (–) Kx (+)	2	1.7
Kx (+)	52	44.8
In general, reproduction cannot be shown or Kx (–) ones	64	55.1
RUT (+) or (–) and Kx (–) or (+)	116	100

RUT, rapid urease test; Kx, culture for *Helicobacter pylori*.

Clinical Evaluation of H. pylori Infection

When *H. pylori* was detected in 1 of the patients' RUT, histopathological evaluation, or culture tests, that patient was considered clinically *H. pylori* infection positive. While 93 (80.2%) of 116 patients had *H. pylori*, 23 (19.8%) had no *H. pylori*. While 70 (60.3%) of 116 patients had RUT positivity, HLO was positive in 76 (84.4%) out of 90 patients for histopathological examination. The *H. pylori* culture positivity ($n=116$) was 44.8% in this study. Comparison of RUT, histopathology, and culture results are showed in Table 5.

Evaluation of Antimicrobial Susceptibility Test Results

Clarithromycin resistance was shown in 14 (26.9%) patients. Levofloxacin resistance was shown in 13 (25.5%) patients (Table 6).

Table 5. Comparison of Rapid Urease Test, Histopathology, and Culture Results

Test	Number of patients (*n*)	HP (+) detection (%)	HP (–) detection (%)
RUT	116	60.3	39.7
Kx	116	44.8	55.1
HLO	90	84.4	15.6

RUT, rapid urease test; Kx, culture for *H. pylori*; HLO, histopathologically presence of *Helicobacter*-like organism.

Table 6. Resistance Rates for Antibiotics

Antibiotic resistance	Number of patients	Percentage of patients (%)
Clarithromycin	14	26.9
Levofloxacin	13	25.5

DISCUSSION

Clarithromycin resistance varies in different countries and even in different regions.[12-14] In Turkey, clarithromycin resistance is known to have increased over the years.[12,15] In a recent study examining primary antibiotic resistance, the resistance rate for *H. pylori* was reported to be 24.8%.[12] In this review, which is conducted in Turkey in 2015, different resistance rates for clarithromycin were determined by year and region. These rates are reported in the center, south, west, north, and east of Turkey as 15-50%, 8.8-18.1%, 8.8-48.2%, 30%, 16.4-24%, respectively.[12] In a study conducted in the Eastern Black Sea region of Turkey in 2018, the clarithromycin resistance rate was found to be 28.2%.[16] Another study aimed to determine the resistance rates of antibiotics used in eradication therapy in Istanbul in 2015, clarithromycin resistance rate was 36.7%.[17]

In other recent studies investigating clarithromycin resistance in the Aegean region, resistance rates were reported to be higher than 30% in the years 2007 and 2015.[22,23] In this study, clarithromycin resistance was 26.9%. The 26.9% resistance rate for clarithromycin was found to be lower than the resistance rates found in Turkey in recent years. However, this resistance value is over 15%, which is the limit resistance value determined by the Maastricht V/Florence Consensus for clarithromycin-based treatment regimens.[3] The high rates of resistance shown for clarithromycin may explain why it has been difficult to achieve high enough success with conventional triple therapy.[14,19,20] This should mean that the treatment regimen containing clarithromycin is not the right or sufficient choice for primary care.[20]

Levofloxacin resistance varies worldwide, usually between 10 and 30%.[12,14] There are some studies about levofloxacin resistance in Turkey. Levofloxacin-containing regimens are a treatment modality proposed as an alternative to clarithromycin resistance.[16,21,22] In a review which is conducted in Turkey in 2015, the primary resistance rate was found to be 23.7% for levofloxacin.[12] Another antibiotic resistance study in Istanbul in 2015, levofloxacin resistance rate was 29.5%.[17] In the study conducted in the Eastern Black Sea region of Turkey in 2018, the levofloxacin resistance rate was found to be 34%.[16]

In this study, the fact that levofloxacin resistance was found to be 25.5% constitutes serious reservations about the introduction of levofloxacin in first-line treatment. Therefore, in light of the available data, it is possible to say that a treatment regimen containing levofloxacin cannot achieve high eradication success in empirical practice. Mutations related to fluoroquinolone resistance often arise from quinolone resistance determining regions. Fluoroquinolones inhibit bacterial DNA gyrase and topoisomerase. *H. pylori* does not have topoisomerase, so mutations in the DNA gyrase A gene are thought to be the main cause of resistance.[23,24] Levofloxacin resistance, like clarithromycin, is affected by differences in drug use habits of that region.[16,25]

In this study, *H. pylori* was considered positive when *H. pylori* was shown in 1 of the RUT, histopathological examination, or culture. Of 116 patients, 93 (80.2%) were shown to have *H. pylori* infection whereas 23 (19.8%) were negative for *H. pylori.* In another study conducted with 344 patients in Turkey *H. pylori positivity,* it was found to be 40.4%.[16] In this study patients with a positive culture test or with a positive RUT and HLO positivity in the histopathological examination were considered to be *H. pylori* positive.[16]

For patients with endoscopy indications and without contraindications for biopsy, it is recommended to take samples for RUT from both the antrum and the corpus, according to the Maastricht V/Florence Consensus Report.[3] There are many commercial RUT kits available. It is often recommended to take multiple biopsies and wait for 24 h for the result. New types of RUT kits can often respond in less than 1 h.[26]

Of 116 patients undergoing upper gastrointestinal endoscopy, RUT was positive in 70 (60.3%) and negative in 46 (39.7%). Of these 70 patients, a positive result in RUT was read within the first 20 min in 60 patients (85.7%). One of the valuable results of this study would be to recommend that no rush decision be made regarding the interpretation of the RUT test. The RUT showed that 14.3% of the study patients were positive after the first 20 min. One of the patients was detected test positive 4 h after the endoscopic examination. This finding may be corrected with big-scale trials. It is known in the light of the available literature that waiting less than recommended time may

cause false-negative results.[27] There are kits that require 24 h monitoring, while there are kits that provide very fast results.[26,27] It will be appropriate for the clinician to wait for the appropriate time for the kit used to interpret the RUT result.

Although the bacterial culture test is accepted as the gold standard for the diagnosis of *H. pylori*, it is not always easy to get positive results. False-negative results may be due to some reasons arising from the patient, the fastidious nature of the bacteria.[28] There are studies indicating that the sensitivity is 70%-80%.[28] In this study culture was positive in 52 (55.9%) of 93 *H. pylori* infection-positive patients. The detection rate of *H. pylori* in culture for the whole population was 44.8%. RUT positivity was shown in 50 (96.1%) of 52 patients and was negative in 2 (3.8%) patients. Histopathological examination revealed HLO positive in 1 of these 2 patients. This shows the additional benefit of culture or histopathological evaluation. *H. pylori* strain isolated from gastric biopsy samples of these 52 patients were also subjected to antimicrobial susceptibility test E-test. Clarithromycin resistance was detected in 14 (26.9%) patients and levofloxacin resistance in 13 (25.5%) patients. In an Italian study conducted between 2010 and 2016, it was found that clarithromycin resistance increased from 19% to 35.6% and levofloxacin resistance increased from 19% to 29%.[29] In another study examining 124 *H. pylori* gastritis cases in the United States, the overall resistance rate for clarithromycin was reported to be 32.3% (23.1%-45.8%).[30] According to a study on 178 studies and 66 142 isolates within the WHO regions in 2018; clarithromycin resistance was 10% in America and South East Asia, whereas levofloxacin resistance was 10% in European regions. Apart from these, resistance rates for clarithromycin, levofloxacin, and metronidazole were found to be greater than 15% in all WHO regions.[14] This emphasizes the importance of knowing regional resistance rates in determining treatment regimens.[14] Compared to recent world resistance data, it can be said that the result of our study is compatible with general data.

Although it seems insufficient to detect *H. pylori* by culture alone, the study of culture to prevent antibiotic resistance and to provide effective eradication treatment to patients seems to be important, as stated in the Maastricht V/Florence Consensus report.[3] We believe that results that are more efficient can be obtained by performing the cultural procedure in experienced centers on an individual and community basis. Of the 90 patients who underwent a histopathological evaluation, 76 (84.4%) were HLO positive and 14 (15.6%) were HLO negative. Of these 90 patients, 20 (22.2%) had intestinal metaplasia (IM) and 7 (7.7%) had atrophy. According to these results, not taking histopathological specimens during upper gastrointestinal endoscopy, and only taking RUT samples may lead to the missing of IM and atrophy cases and even worse early gastric cancer. We suggest that histopathological samples be taken to evaluate actual efficacy, to assess cellular and mucosal changes, and to show the presence of HLO at the beginning of treatment and monitor stages in the studies to determine prevalence and resistance. In this study, leaving the histopathological sample collection to clinical necessity was a weakness of this study.

In this study, the primary resistance rates for clarithromycin and levofloxacin, which can be used in primary care in Turkey, are higher than the internationally desired rates, and it is necessary to investigate other regimens in first-line eradication therapy in *H. pylori* infection. Until the ideal eradication treatment regimen is achieved for Turkey, it would be wiser to plan treatment according to the presence of resistance by culture-based methods. Once a costly and invasive procedure, such as endoscopy, has been planned for the patient, it is concluded that it would be beneficial for the patient to obtain RUT, culture, antimicrobial resistance tests, and even histopathological specimens for correct diagnosis and subsequent effective treatment. It is considered to be an important step in preventing future antimicrobial resistance.

Ethics Committee Approval: The regional ethics committee of Dokuz Eylül University approved this study (decision no: 2010/02-06: 26.05.2010).

Informed Consent: All volunteers signed an informed constant form.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – İ.Ş., M.S., Ö.Y., B.M.G.; Design – İ.Ş., M.S., Ö.Y., B.M.G.; Supervision – İ.Ş., M.S., Ö.Y., B.M.G., M.S.; Resources – İ.Ş., M.S., Ö.Y., B.M.G.; Materials – İ.Ş., M.S., Ö.Y., B.M.G.; Data Collection and/or Processing – İ.Ş., M.S., Ö.Y., B.M.G., M.S.; Analysis and/or Interpretation – H.E., H.A., İ.Ş., M.S., Ö.Y., B.M.G.; Literature Search – B.M.G., Ö.Y., M.S.; Writing Manuscript – B.M.G., Ö.Y.; Critical Review – Ö.Y., H.A.

Acknowledgments: We thank Maria Guglielmino Iskenderoglu for her revision of the English style of this manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This research was supported by Dokuz Eylül University Research Foundation grant 2008.KB.SAĞ.

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