



## Resistance Rates to Various Antimicrobial Agents of *Helicobacter pylori* Isolates in Eastern Turkey

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### ABSTRACT

The aim of this study was to determine the resistance rates of *Helicobacter pylori* (*H. pylori*) to various antimicrobial agents. The agar disk diffusion method (Kirby Bauer) was used to determine the sensitivity of *H. pylori* isolates to various antimicrobials. Of the 61 *H. pylori* isolates tested, no isolates was resistant to amoxicillin and tetracycline. The resistance rates were 42.6% for metronidazole, 21.3% for clarithromycin, and 3.3% for levofloxacin. Compared to clarithromycin and metronidazole, levofloxacin showed the lowest resistance. This is the first report on the resistance rates of *H. pylori* to antibiotics in Elazig Province, East of Turkey. This study suggests that the large scale studies is needed to help us to understand better the effect of resistance on the *H. pylori* eradication.

### 1. Introduction

*Helicobacter pylori* (*H. pylori*) is associated with a variety of disorders including chronic gastritis, peptic ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (Amieva and El-Omar, 2008; Correa and Houghton, 2007). Therefore, eradication of *H. pylori* colonization is important to prevent peptic ulceration and gastric carcinogenesis (Hung et al., 2009). The most commonly antibiotics used for the treatment of *H. pylori* infections are amoxicillin, tetracycline, metronidazole, and clarithromycin (Unge, 1998). However, side effects, patient's poor compliance, and resistance to antibiotics are causes of treatment failure (Broutet et al., 2000;

Megraud, 1997). In recent years, resistance to amoxicillin, clarithromycin and metronidazole have been on the increase in a number of countries (Megraud, 2004).

Fluoroquinolones have demonstrated inhibition of *H. pylori* growth *in vitro* (Bauernfeind, 1997), and levofloxacin-based triple therapy is effective as first-line anti-*H. pylori* therapy (Nista et al., 2006; Rispo et al., 2007). The mechanism of fluoroquinolone resistance in *H. pylori* has been found to be linked to mutations in the quinolone resistance-determining regions (QRDRs) of *gyrA* (Gerrits et al., 2006).

The prevalence of *H. pylori* infection has become increasingly widespread in Turkey. Therefore, the eradication of this bacterium has

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become a major public health concern worldwide. However, the resistance rate of *H. pylori* to antibiotics in Elazig Province, East of Turkey has not yet been reported. The aim of this study was to investigate the resistance rates of *H. pylori* to antibiotics in our region.

## 2. Material and Methods

### 2.1. Patients and *H. pylori* isolates

Sixty one *H. pylori* isolates used in this study were isolated from the antrum of Turkish patients (29 males and 32 females, age range 20 to 80 years, average 47) with gastrointestinal complaints admitted to Gastroenterology Department of Firat University Hospital, during 2009 and 2010. Patients collected endoscopically in two groups as gastritis in 51 cases and peptic ulcer in 10 cases, consecutively enrolled and selected at random.

This study was approved by the Medical Ethics Committee of Firat University and informed consent was provided from all patients prior to specimen collection.

### 2.2. Isolation and identification of *H. pylori*

Biopsy sample taken for culture was immediately streaked onto Columbia agar base (Oxoid, Basingstoke, UK) containing 7% laked horse blood (SR0048C, Oxoid, Basingstoke, UK) and *H. pylori* supplement SR0147E (trimethoprim 5 mg/l, vancomycin 10 mg/l, amphotericin B 5 mg/l and cefsulodin 5 mg/l) (Oxoid). Plates were incubated at 37°C for 4 to 7 days in microaerophilic conditions obtained by a gas generating kit (Campygen, Oxoid, Lot: 13L08-C25-14) (Chomvarin et al., 2006). Identification of *H. pylori* was evaluated by observation of the colony morphology, gram-staining and biochemical methods (oxidase, and catalase activities) (Goodwin and Wesley, 1993).

Reference *H. pylori* strains (clinical strains) (provided by Dr. Vildan CANER, Pamukkale University, Faculty of Medicine, Department of Medical Biology, Denizli-Turkey) were used as a positive control in this study.

### 2.3. Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed by using disk diffusion method. *H. pylori* colonies were suspended in 1.0 ml sterile saline

solution and adjusted to the density equal to 3.0 McFarland standard ( $1 \times 10^9$  cfu/ml) (Xia et al, 1994). The suspension was spread on Mueller-Hinton blood agar plates (Oxoid). The antibiotic disks containing metronidazole (5 µg), clarithromycin (15 µg), tetracycline (30 µg), amoxicillin (10 µg), levofloxacin (5 µg) were aseptically placed onto the agar. Inhibition zone diameters were measured in millimeters after 3 days of incubation at 37°C under microaerophilic conditions and determined as resistant (R) or susceptible (S) (Boyanova et al, 2000). A zone size <16 mm was evaluated as resistant for metronidazole (Boyanova et al, 2000; Mishra et al, 2006), ≤25 mm for amoxicillin resistance (Lang and Garcia, 2004) and ≤30 mm for clarithromycin and tetracycline resistance (Boyanova et al, 2000; Kulsunti Wong et al., 2008). Reference *H. pylori* strains (clinical strains) were used as positive control (kindly provided by Dr. Vildan CANER).

## 3. Results

### 3.1. Isolation and identification results of *H. pylori*

A total of 61 *H. pylori* isolates was isolated from 51 patients with gastritis and 10 patients with peptic ulcer.

### 3.2. Antimicrobial susceptibility testing results

The results of the susceptibility testing for *H. pylori* isolates are shown in Table 1. Sixty one isolates tested against the different antibiotics. The highest resistance rate was for metronidazole 26 (42.6%), followed by 13 (21.3%) to clarithromycin, and 2 (3.3%) to levofloxacin. No resistance to amycillin and tetracycline in our study was detected.

**Table 1.** Resistance rates to antimicrobial agents of *H. pylori* isolates

Antibiotics	Number of Resistant isolates %	
Metronidazole	26	42.6
Clarithromycin	13	21.3
Amoxicillin	0	0
Tetracycline	0	0
Levofloxacin	2	3.3

## 4. Discussion

*H. pylori* is increasingly resistant to antibiotics, especially metronidazole and clarithromycin (Megraud, 2004; De Francesco et al., 2006).

Determining the antibiotic resistance among *H. pylori* isolates would improve the eradication of the disease.

Numerous studies have performed to investigate the prevalence of *H. pylori* resistance to antibiotics (Megraud and Lehours, 2007). Resistance to metronidazole has been observed worldwide (Eltahawy, 2002) and showed commonly in several countries, ranging from 10 to 90% with the lowest resistance rates in Europe and Australia, the highest rates in Africa whereas in other developing countries, the rate of resistance to metronidazole ranges from 80 to 90% (Quintana-Guzman et al., 1998). Therefore, metronidazole should be preferred to amoxicillin in first-line therapy in Europe (Malfertheiner et al., 2007) but not in Asian patients (De Francesco et al., 2010). The resistant rate (42.6%) to metronidazole in this study is consistent with a previous report (41.9%) in Turkey (Bakir Ozbey et al., 2009) but lower than previous reports (49.2% and 53%, respectively) performed by Kantarceken et al. (2000) and Agel et al. (2000). This may be explained by the wide use of metronidazole in treatment of gynecologic infection and intestinal parasitic infections, which occur in developing countries (Megraud, 1995).

Resistance rates to clarithromycin has been reported as 10-15% in USA, 10% in France, 16% in Italy, and 16.8-56% in Turkey (Duck et al., 2004; Meyer et al., 2002; Fraser et al., 1999; Street et al., 2001; Broutet et al., 2001; Simsek et al., 2005). Resistance rates to clarithromycin (21.3%) was found in this study. The major cause for clarithromycin resistance is a previous use of macrolides, and therefore, an increased prevalence is showed in most countries (Megraud and Lehours, 2007).

Tetracycline is an antibiotic which is commonly used in first- and second-line regimens for the treatment of *H. pylori* (Megraud and Marshall, 2000; Gisbert and Pajares, 2001) and widely available and cheap, had advantage that resistance against it was rare in *H. pylori* (Ribeiro et al., 2004). However, in the past few years, the incidence of tetracycline resistance has increased, especially in countries where tetracycline can be obtained without prescription (Realdi et al., 1999; Wu et al., 2000). This increase is a serious concern because it negatively affects the efficacy of tetracycline-containing regimens (Gisbert and Pajares, 2001;

Silva et al., 2000). The prevalence of *H. pylori* resistance to tetracycline is low (<3%) in all countries, except in Africa (43.9%) (De Francesco et al., 2010). Tetracycline resistance in Turkey is approximately 0-4% (Kantarceken et al., 2000; Agel et al., 2000; Bakir Ozbey et al., 2009).

Amoxicillin resistance has been associated with a mutation in the *pbp-1A* gene and altered uptake of beta-lactams after long exposure of *H. pylori* to amoxicillin (DeLoney and Schiller, 2000). Japanese authors have reported an increase in *H. pylori* resistance rates to amoxicillin from 2000 to 2003 (Watanabe et al., 2005). The results of the present study are similar to a previous study (Yetgin, 2006) in Turkey where no resistance to amoxicillin and tetracycline was detected.

The prevalence of levofloxacin resistance varies ranging from 14.3% in Japan to 16.8% in Belgium, 17% in Brazil, 18% in Hong Kong, 21.5% in Korea, 22.1% in Germany, %19.1 in Italy and 25.5% in Turkey (Bogaerts et al., 2006; Coelho et al., 2005; Glocker et al., 2007; Kim et al., 2006; Watanabe et al., 2003; Wong et al., 2006; Zullo et al., 2007). The resistance towards levofloxacin is rapidly increasing worldwide and a cross-resistance between clarithromycin and levofloxacin resistance have been also reported (Zullo et al., 2007). This could be a cause for concern in using levofloxacin in those areas where primary clarithromycin resistance is high.

This is the first report on the resistance rates of *H. pylori* to antibiotics in Elazig Province, East of Turkey. In our study, metronidazole resistance was found to be high. We found that levofloxacin showed the lowest resistance compared to clarithromycin and metronidazole. Levofloxacin may be used in eradicating *H. pylori*. However, cost of levofloxacin should be taken into account when dealing with widespread infection. Further research and an alternative therapy method is also needed to improve the *H. pylori* eradication rate.

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