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Helicobacter pylori in Iran: A systematic review on the antibiotic resistance

Farzad Khademi [1], Farkhondeh Poursina [2], Elham Hosseini [3], Mojtaba Akbari [4], Hajieh Ghasemian Safaei [1]*

[1] Antimicrobial Resistance Research Center, Department of Medical Bacteriology and Virology, Qaem University Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Department of Microbiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4] Department of Biostatistics and Epidemiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Objective(s): *Helicobacter pylori* (*H. pylori*) is a pathogenic bacterium that colonizes the stomachs of approximately 50% of the world's population. Resistance of *H. pylori* to antibiotics is considered as the main reason for the failure to eradicate this bacterium. The aim of this study was to determine the rate of resistant *H. pylori* strains to various antimicrobial agents in different areas of Iran.

Materials and Methods: A systematic review of literatures on *H. pylori* antibiotic resistance in Iran was performed within the time span of 1997 to 2013. Data obtained from various studies were tabulated as following, 1) year of research and number strains tested, 2) number of *H. pylori* positive patients, 3) study place, 4) resistance of *H. pylori* to various antibiotics as percentage, and 5) methods used for evaluation of antibiotic resistance.

Results: Over the period, a total of 21 studies on *H. pylori* antibiotic resistance have been conducted in different parts of Iran. In these studies, *H. pylori* resistance to various antibiotics, including metronidazole, clarithromycin, amoxicillin, tetracycline, ciprofloxacin, levofloxacin and furazolidone were 61.6%, 22.4%, 16.0%, 12.2%, 21.0%, 5.3% and 21.6%, respectively. We found no study on *H. pylori* resistance to rifabutin in Iran.

Conclusion: Compared to the global average, we noted that the prevalence of *H. pylori* resistance to metronidazole, clarithromycin, amoxicillin, and tetracycline has been rapidly growing in Iran. This study showed that in order to determine an appropriate drug regimen against *H. pylori*, information on antibiotic susceptibility of the bacterium within different geographical areas of Iran is required.

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Introduction

Helicobacter pylori (H. pylori) is a Gram-negative, helical shaped and microaerophilic bacterium that colonizes in the gastric mucosa of approximately 50% of the world's population (1, 2). The organism is involved in gastric diseases such as gastritis, peptic ulcer and two forms of stomach cancer, adenocarcinoma and MALT lymphoma (3, 4). *H. pylori* infection appears to occur early in life and in most cases remains for all life time, unless treated (5). The distribution pattern of *H. pylori* infection ranges from 25 to 50% in developed countries to more than 80% in the developing world (5). Although the bacterium is susceptible to most antimicrobial agents *in vitro*, but the successful treatment of *H. pylori* is a challenge (6). In Iran with extremely high rate of *H. pylori* infection (more than 80%), antibiotic resistance to various antimicrobials is considered as the major cause of the *H. pylori* treatment failure. On the other hand, the low eradication rate and a considerable reinfection rate (20%), indicate the significance of controlling *H. pylori* infection as an important health problem in Iran (6). Several reasons are attributed to bacterial resistance to antimicrobials; i) an intrinsic property related to or an occurred mutation in the chromosomal genes, ii) acquisition of foreign genes carried on mobile genetic elements, iii) frequently use of antimicrobials (selection pressure), so that the resistant bacteria survive the harsh environment and could then spread the resistance genes. The later can then be transferred by mobile genetic elements among bacterial population (6).

Eradication and treatment of *H. pylori* infection by a triple or quadruple therapy regimen is recommended, but the emergence of antibiotic resistance is an important problem for the treatment of diseases (7, 8). Prevalence of antibiotic resistance

*Corresponding author: Hajieh Ghasemian Safaei. Department of Microbiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-311-7922469; Fax: +98-311-6688597; email: ghasemian@med.mui.ac.ir

of *H. pylori* strains varies in different geographical regions, and is associated with the consumption of antibiotics in those areas (9). The present review has focused on some aspects related to antimicrobial resistance including antimicrobial characteristics, and different methods for the assessment of antimicrobial resistance rate. Table 1 is a summary of the most vastly studied antimicrobials in Iran representing the resistance rates, and the methods used to assess the resistance rate.

Material and Methods

Literature search

Using PubMed and the Scientific Information Database (SID), a computer search was performed for this review, and the terms antibiotic resistance of *H. pylori* and Iran were looked up and the relevant papers, both English and Persian language articles published, were selected within the time span of 1997 to 2013. In total, 21 studies were reported on antibiotic resistance of *H. pylori* or/and the treatment. Hand searching, we also included the references of the selected articles, and all the papers were fully reviewed.

The data were extracted from the studies on the basis of selection criteria. Data from the various articles were tabulated as following: (1) year of research and number strains tested, (2) number of *H. pylori* positive patients, (3) study place, (4) resistance of *H. pylori* to various antibiotics as percentage, and (5) methods used for evaluation of antibiotic resistance.

Statistical analysis

The pooled estimate was calculated as number (percent) and 95% confidence interval estimated based on the weighted least square performed through the STATA software (version 10).

Results

From a total of 21 studies, data were collected on resistance rates of *H. pylori*in different parts of Iran from 1997 to 2013. In this review, there were 9 studies from Tehran, 2 studies from Isfahan, 3 studies from Sari, 2 studies from Shiraz, 2 studies from Kerman, 1 study from Tabriz, 1 study from Shahrekord and 1 study from Mashhad. It is noted that, in this study we investigated different studies from the same cities (for example, Tehran) for the possibility of duplication and overlap between the study's results, but duplication was not found.

Resistance to metronidazole

Metronidazole is a pro-drug activated by nitro-reductases in the bacterial cell, and absence or the inactivation of these enzymes leads to metronidazole resistance. Primary resistance to metronidazole is due to the frequent use of the drug which is common for treatment of parasitic diseases, and periodontal or gynecological infections. In this study, the resistance of *H. pylori* to metronidazole was detected in 956 (61.6%, 95% CI: 59.18% to 64.02%) out of 1553 cases in Iran. As can be observed in Table 1, among Iranian cities, the highest *H. pylori* resistance to metronidazole was reported in Tabriz (95%), and

Table 1. Antibiotic resistance rate of *Helicobacter pylori* in different areas of Iran

Area	Year	Patients	Strains	Methods	MTZ (%)	CLA (%)	AMO (%)	TET (%)	CIP (%)	LEV (%)	RIF (%)	FRZ (%)	Ref
Tehran	2005-2008	160	110	Disk diffusion	55.6	7.3	7.3	38.1	NA	NA	NA	4.5	11
Tehran	2001-2004	135	NA	Disk diffusion	36.3	3.7	3.7	0.7	NA	NA	NA	0	12
Tehran	1997-2000	NA	70	Disk diffusion	33	1.4	1.4	0	NA	NA	NA	0	11
Tabriz	2003-2005	NA	100	E-test and Disk diffusion	95	16	59	5	7	NA	NA	9	13
Tehran	2007-2008	104	NA	Disk diffusion	51.1	0	0	0	NA	NA	NA	0	14
Tehran	2002-2003	62	24	Disk diffusion	54.16	4.16	8.33	0	NA	NA	NA	0	15
Kerman	2011	191	63	Disk diffusion	NA	31.7	NA	NA	NA	NA	NA	NA	16
Isfahan	2006	230	80	Disk diffusion	30	6.25	2.5	3.75	8.75	NA	NA	NA	19
Tehran	2006-2007	NA	128	E-test and Disk diffusion	64	23	2.5	0	NA	NA	NA	NA	20
Tehran	1997-2000	250	70	Screening agar and Disk diffusion	72-79	75	58	68	65	NA	NA	NA	21
Tehran	2001-2002	NA	120	Disk diffusion	57.5	16.7	1.7	0	NA	NA	NA	NA	22
Shiraz	2007	NA	106	Agar dilution	72.6	9.4	20.8	4.7	4.7	NA	NA	9.4	23
Sari	2007-2010	132	NA	E-test	73.4	30	6.8	9	NA	NA	NA	NA	24
Sari	2009	210	197	Disk diffusion	65.5	45.2	23.9	37.1	34.5	NA	NA	61.4	25
Shiraz	2008-2009	266	121	E-test	44	5	20	3	NA	NA	NA	NA	26
Kerman	2009	191	63	Disk diffusion	55.5	30.1	26.9	3.1	7.9	NA	NA	0	SID
Sari	2009-2010	170	150	Agar dilution and E-test	78.6	34	10	9.3	NA	5.3	NA	NA	27
Tehran	2007-2008	92	42	Agar dilution	40.5	14.3	2.4	4.8	2.4	NA	NA	NA	28
Shahrekord	2007	263	NA	Agar dilution	NA	22.62	NA	NA	NA	NA	NA	NA	29
Isfahan	2013	110	48	E-test	56.35	14.6	4.2	NA	NA	NA	NA	NA	30
Mashhad	2009	185	124	Agar dilution and Disk diffusion	64.6	17.1	9.8	0	NA	NA	NA	NA	SID
Overall					61.6	22.4	16.0	12.2	21.0	5.3	NA	21.6	

MTZ-metronidazole; CLA-clarithromycin; AMO-amoxycillin; TET-tetracycline; LEV-levofloxacin; RIF-rifabutin; FRZ-furazolidone; CIP-ciprofloxacin; SID-Scientific Information Database; NA-not available

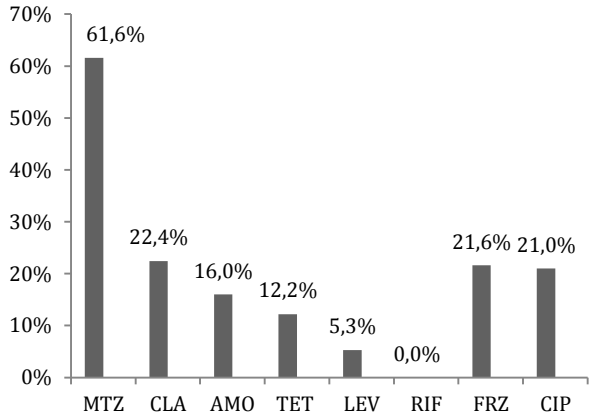

Figure 1. Status of *Helicobacter pylori* antibiotic resistance in Iran MTZ-metronidazole; CLA-clarithromycin; AMO-amoxycillin; TET-tetracycline; LEV-levofloxacin; RIF-rifabutin; FRZ-furazolidone; CIP-ciprofloxaci

the lowest resistance was reported in Isfahan (30%), Shiraz (44%), and Tehran (40.5%). *H. pylori* resistance to metronidazole in Tehran from 1997 to 2010 had increasing trend and has reached from 33% to 78.6%. The trend of increasing resistance is observed in other Iranian cities such as Isfahan (30% to 56.35%). But in Shiraz shows a declining trend (72.6% to 44%).

Resistance to clarithromycin

Previous consumption of macrolides which induces cross resistance to clarithromycin has been attributed to its bacterial resistance. Despite the low frequency of its consumption, a high prevalence of resistance to clarithromycin (75%) has been reported in Tehran. Mechanism of clarithromycin resistance is due to the mutations occurred in a few positions in the chromosomal genes. In this study, the resistance of *H. pylori* to clarithromycin was detected in 362 (22.4%, 95% CI: 20.37% to 24.43%) out of 1616 cases in Iran. The highest (75%) and the lowest (0%) *H. pylori* resistance to clarithromycin was detected in Tehran. *H. pylori* resistance to clarithromycin, in different years, showed a sinusoidal trend in Tehran, but an increasing trend in Isfahan (6.25% to 14.6%).

Resistance to amoxicillin

A mutation in *pbp-1A* gene has been found as a primary cause for bacterial resistance to this antibiotic. *H. pylori* resistance to amoxicillin was detected in 258 of 1616 cases in Iran (16.0%; 95% CI: 14.21% to 17.79%). The highest and the lowest rate of resistance to amoxicillin among Iranian cities were reported in Tabriz (59%) and Tehran (0%), respectively. *H. pylori* resistance to amoxicillin in Tehran from 1997 to 2011, similar to clarithromycin, have had sinusoidal trend in different times. However, this study shows an increasing trend in Sari (6.8% to 23.9%) and Isfahan (2.5% to 4.2%).

Resistance to tetracycline

The average percentage of tetracycline resistance rate in Iran is 12.2%. Like other antibiotics, resistance to tetracycline increases with the use of the drug (selection pressure). The resistance mechanism has been described as a change in three contiguous nucleotides in the *16S rRNA* gene. *H. pylori* resistance to tetracycline was detected in 197 out of 1616 cases in Iran (12.2%; 95% CI: 10.6% to 13.8%). The studies which conducted in Iran indicate that *H. pylori* resistance to tetracycline is low and varies from 0% to 68%.

Resistance to ciprofloxacin

In this study, the resistance of *H. pylori* to ciprofloxacin was detected in 138 (21.0%, 95% CI: 17.89% to 24.11%) out of 658 cases in Iran. Bacterial resistance to ciprofloxacin has been studied less than other antibiotics in Iran. The highest (65%) and the lowest (2.4%) *H. pylori* resistance to ciprofloxacin was reported in Tehran.

Resistance to levofloxacin and rifabutin

From 1997 to 2013, only one study was conducted in Tehran which has assessed bacterial resistance to levofloxacin, and detected *H. pylori* resistance to levofloxacin in 8 out of 150 cases in Iran (5.3%; 95% CI:1.71% to 8.89%). However, study on *H. pylori* resistance to rifabutin has not been tested in Iran

Resistance to furazolidone

The reports showed that the highest percent of resistance to furazolidone was in Sari (61.4%) and the lowest rate was in Tehran (0%) and Kerman (0%). In this study, the resistance of *H. pylori* to furazolidone was detected in 145 (21.6 %, 95% CI: 18.48% to 24.72%) out of 670 cases in Iran.

Discussion

H. pylori infection is diagnosed with a variety of tests and in most cases is treated successfully with antibiotics, but bacterial resistance to antibiotics has an unpleasant impact on the treatment (10). For eradication of the *H. pylori*, triple and quadruple therapy is effective and can improve the disease caused by this organism (11, 12). However, the low eradication rate of *H. pylori* showed antimicrobial therapy failure in developing countries such as Iran (13). So, determining antibiotic susceptibility, particularly in treatment failure is important (14).

Although CLSI has suggested agar dilution method as a reference method for the determination of antibiotic susceptibility (14); however, according to the results in Table 1, E-test and disk diffusion

methods are constantly used to determine the antibiotic susceptibility in Iran.

Highest antibiotic resistance of *H. pylori* to metronidazole has been reported. *H. pylori* resistance to metronidazole in developed countries is about 35%, however in developing countries, resistance rate of *H. pylori* to metronidazole is very high, and in some areas almost all strains are resistant to metronidazole (15, 16). Among the Middle Eastern countries, resistance to metronidazole in Iran was higher than Israel (38.2%) (17). While, it was lower than Egypt (100%), Saudi Arabia (80%) and Kuwait (70%) (18). In Iran, the resistance of *H. pylori* to metronidazole is detected in 956 (61.6%, 95% CI: 59.18% to 64.02%) out of 1553 cases that show the high rate of resistance compare to the developed countries.

In contrast with bacterial resistance to metronidazole, the prevalence of *H. pylori* resistance to clarithromycin is much lower. In developed countries, approximately 10% of the *H. pylori* are clarithromycin-resistant, but in developing countries, resistance rate to clarithromycin is higher ranging from 25% to 50% (16, 19). Low resistance to clarithromycin has been reported in the Middle Eastern countries, Israel (8.2%), Egypt (4%), Saudi Arabia (4%) and Kuwait (0%) (17, 18). In Iran, the resistance of *H. pylori* to clarithromycin is detected in 362 (22.4%, 95% CI: 20.37% to 24.43%) out of 1616 cases. Therefore, resistance rate of *H. pylori* strains to clarithromycin in Iran is lower than in other developing countries, and is higher than in Middle Eastern and developed countries.

By the end of the 20th century, it was thought that *H. pylori* resistance to amoxicillin and tetracyclineis rare or does not exist. However, *H. pylori* resistance to amoxicillin and tetracycline antibiotics shows increased resistance rate in different geographic areas that can be obtained without a drug prescription (20). Prevalence of *H. pylori* resistance in different geographic areas to amoxicillin and tetracycline is 0 to 30% and 0 to 10%, respectively (1). This study shows that the *H. pylori* resistance to amoxicillin (16.0%, 95% CI: 14.21% to 17.79%) and tetracycline (12.2%, 95% CI: 10.6% to 13.8%) is different in Iran. Prevalence of *H. pylori* resistance to amoxicillin and tetracycline in different Middle Eastern countries was lower than Iran (17, 18).

Since the *H. pylori* resistance to typically used antibioticsis increasing, fluoroquinolones (i.e. ciprofloxacin, moxifloxacin, trovafloxacin and levofloxacin), nitrofurans (i.e. furazolidone), or rifamycins (i.e. rifabutin) are sometimes used in the second and third line treatment (21). Preliminary results obtained with the use of these antibiotics in the treatment of *H. Pylori* is encouraging, but very soon resistance to these antibiotics have emerged. Prevalence of *H. pylori* resistance to fluoroquinolones (i.e. ciprofloxacin, moxifloxacin, trovafloxacin and levofloxacin), nitrofurans (i.e. furazolidone), and rifamycins (i.e. rifabutin) in different geographic regions of the world is 0 to 20%, 0 to 5% and 0 to 2%, respectively (1). In the Middle Eastern countries, the low level of resistance to these antibiotics has been reported, or no studies have been conducted (17, 18).

Several studies in Iran demonstrate the inefficiency of the common antibiotics such as metronidazole, clarithromycin, and tetracycline. These studies recommend fluoroquinolones as possible candidates for the treatment of *H. pylori* infection (27, 31). In the present review, similar to the global average, the resistance of *H. pylori* to ciprofloxacin is detected in 138 (21.0%, 95% CI: 17.89% to 24.11%) out of 658 cases. Also, only one study has reported resistance to levofloxacin (5.3%) and moxifloxacine (4.6%) (27). *H. pylori* resistance to levofloxacin is detected in 8 out of 150 cases (5.3%; 95% CI: 1.71% to 8.89%) in Iran. So, low resistance rate to levofloxacin and moxifloxacine indicates that these antibiotics can be helpful to eradicate *H. Pylori* infection. In recent years, due to low price and good efficacy, furazolidone is considered as a good alternative to metronidazole and tetracycline in quadruple therapy for eradication of *H. pylori* in Iran (32, 33), but at the moment, the resistance of *H. pylori* to furazolidone is detected in 145 (21.6 %, 95% CI: 18.48% to 24.72%) out of 670 cases which is higher than the global average. However, study on *H. pylori* resistance to rifabutin has not been tested in Iran. Finally, the overall agreement between the results of various antimicrobial tests (Disk diffusion, E-test and Agar dilution) was observed among the studies reviewed in this review article.

Conclusion

Comparison of our data with results from other countries showed that the prevalence of *H. pylori* resistance to metronidazole, clarithromycin, amoxicillin and tetracycline is rapidly growing in Iran compared to the global average, but *H. pylori* antibiotic resistance to levofloxacin and moxifloxacin was much lower than the global average. Comparing this study with studies in other countries indicated that *H. pylori* resistance may be changed in time even in the same population; however, in order to prevent antibiotic resistance and to determine the most effective anti *H. pylor*i drugs, continuous surveillances is needed.

Conflicts of interest

This plan does not have any financial burden, and there is no conflict of interest.

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