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

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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.

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...
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 published, were selected within the time span of Iran's cities, and is associated with the consumption of the most vastly studied antimicrobials in Iran antibiotic resistance rate. 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 Shahrakord 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 nitroreductases 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

<table>
<thead>
<tr>
<th>Area</th>
<th>Year</th>
<th>Patients</th>
<th>Strains</th>
<th>Methods</th>
<th>MTZ (%)</th>
<th>CLA (%)</th>
<th>AMO (%)</th>
<th>TET (%)</th>
<th>CIP (%)</th>
<th>LEV (%)</th>
<th>RIF (%)</th>
<th>FRZ (%)</th>
<th>Ref</th>
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<tbody>
<tr>
<td>Tehran</td>
<td>2005-2008</td>
<td>160</td>
<td>110</td>
<td>Disk diffusion</td>
<td>55.6</td>
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<td>16</td>
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<td>26.9</td>
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MTZ—metronidazole; CLA—clarithromycin; AMO—amoxycillin; TET—tetracycline; LEV—levofloxacin; RIF—rifabutin; FRZ—furazolidone; CIP—ciprofloxacin; SID—Scientific Information Database; NA—not available
his 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 tetracycline is 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 antibiotics is increasing, 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 moxifloxacin (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 moxifloxacin 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. pylori* drugs, continuous surveillances is needed.

**Conflicts of interest**

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

**References**


