A Review Article on *Helicobacter pylori* Antibiotic Resistance Profile in Iran

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**Authors’ contributions**

This work was carried out in collaboration between both authors. Author MHV did the study design and prepared the structure of the article. Author SE did the literature searches and writes the paper draft. Both authors read and approved the final manuscript.

**Article Information**

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**ABSTRACT**

Now a day, antibiotic resistance is a global health threat which is considered as the major cause of treatment failures in bacterial infection. *H. pylori* (*Helicobacter pylori*) is a spiral-shaped gram negative bacterium that colonizes in gastric mucosa and is responsible for serious gastrointestinal diseases including peptic ulcers and gastric cancer. Appearance and increasing of antibiotic resistance in the recent years, mainly to metronidazole (in developing countries) and clarithromycin (in developed countries) have decreased the efficacy of *H. pylori* treatment regimens. The prevalence of *H. pylori* antibiotic resistance is not the same in all over the world and shows geographical variations. So, antibiotic treatment regimens should be administrating according to local antibiotic susceptibility pattern. Iran is a developing country in Middle East with the high prevalence of *H. pylori* infection about 80%. Many Iranian researchers from different provinces have...
investigated the susceptibility of H. pylori isolates to common antibiotics. So, the aim of this review paper was survey on the existence reports of Iranian authors to access an accurate antibiotic profile of H. pylori for efficient eradication therapy in the future.

Keywords: Helicobacter pylori; antibiotic resistance; metronidazole; clarithromycin; Iran

1. INTRODUCTION

Helicobacter pylori (H. pylori) is an important pathogen of gastric mucosa that infects half of the world’s population [1]. The prevalence of H. pylori infection is different among developing and developed countries [2]. H. pylori is a major cause of some dyspeptic disorders including chronic active gastritis, peptic ulcer diseases and gastric malignancies [1,3]. As other bacterial infections, H. pylori infection can be treated with antibiotics. Although H. pylori is susceptible to many antibiotics in vitro, its eradication is difficult in vivo. Standard triple therapy including a proton pump inhibitor (PPI) and two antibiotics e.g. metronidazole, clarithromycin and or amoxicillin, is used to cure H. pylori infection [4]. But eradication rates are lower than 80% in several areas [5,6] due to patient’s poor compliance or antibiotic resistance [7]. Prevalence of H. pylori antibiotic resistance shows geographical variation between and within countries [8]. For choosing the best treatment regimen, a local susceptibility pattern is necessary. Our aim in this review article was to survey on the resistance rate to common antibiotics against H. pylori infection based on several reports of different provinces of our country, Iran.

2. LITERATURE SEARCH

A comprehensive literature search was performed about prevalence of antibiotic resistance of H. pylori strains isolated from Iranian patients by using PubMed (http://www.ncbi.nlm.nih.gov) and Google Scholar (scholar.google.com). Also, molecular mechanism of resistance in H. pylori isolates that have been investigated by Iranian authors was collected and analyzed. Some data that were in abstract form or only in Persian language were excluded from this literature review.

3. RESISTANCE TO METRONIDAZOLE

Metronidazole (MTZ) is a 5-nitroimidazole antibiotic that is used for treatment of a variety of infections such as parasitic infections, anaerobic and microaerophilic bacterial infections (including H. pylori). Metronidazole is administered in its inactive form (2-methyl-5-nitro-1H-imidazole-1-ethanol) [9]. It could be cytotoxic by transferring an electron from some metabolites such as ferredoxin (fdx A) to its nitro group in cytoplasm of anaerobic and micro-aerophilic pathogens. So, reduction of nitro group in inactive form of metronidazole, converts it to active form which has nitro free radical. Nitro free radical destroys all cell compounds such as DNA, RNA and proteins [9]. Metronidazole resistance in H. pylori is associated with null mutations in rdxA, the gene encoding an oxygen-insensitive NADPH nitroreductase [10]. Prevalence of metronidazole-resistance H. pylori in developing countries (such as Iran) is more than developed countries [11]. As shown in the Table 1, the incidence of metronidazole-resistance H. pylori isolates in all investigations that have been done in different provinces of Iran are greater than 30% (Table 1). The greatest once, has been reported from Tabriz (northwest), 95% (95/100) [12]. Other studies from this province showed metronidazole resistance in 86 strains of 112 (76.8%) [13] and 97 strains of 123 (78.86%) [14]. The lowest metronidazole resistance rate has been reported from Isfahan (central province of Iran), 30% (24/80) [15]. In two other studies from this province and its adjacent regions, Shiraz (two studies) and Yazd, metronidazole resistance rate has been reported about 43/78 (55.1%), 27/43 (65.3%), 53/121 (44%), 77/106 (72.8%) and 112/144 (77.8%) respectively [16-20]. The rate of metronidazole-resistance H. pylori isolates that has been reported from Mashhad (east of Iran) and Ilam (west of Iran) was 74.6% and 88%, respectively [21,22]. Also the three studies in Sari (north of Iran) reported that 73.4%, 65.5% and 78.6% of H. pylori isolates were resistance to metronidazole [23-25]. The incidence of metronidazole-resistance H. pylori isolates in Tehran (capital of Iran) has been investigated by some studies (40.5%, 51.5%, 54.16%, 55.6%, 57.5%, 64%, 64.35%, 77% and 60%) [26-34]. The rate of metronidazole-resistance H. pylori isolates in near countries such as Saudi Arabia, Pakistan, Kuwait, Turkey and Egypt (70%, 73.9%, 70%, 42.8% and 100%, respectively) like Iran is high [35-39].
| Province | Years | Method of testing | No of strains tested | MTZ resistance rate | CLA resistance rate | TET resistance rate | AMX resistance rate | FRZ resistance rate | Fluoroquinolones resistance rate | References |
|----------|-------|-------------------|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------------------|------------|
| Isfahan  | 2014  | E-test, MDDM⁶      | 78                  | 55.1%              | 15.3%              | Nd⁵                | 6.4%               | Nd                 | Nd                 | Nd                 | Khademi et al. [16]            |
| Isfahan  | 2012  | E-test            | 48                  | 56.3%              | 14.6%              | Nd                 | 4.2%               | Nd                 | Nd                 | Nd                 | Mirzaei et al. [17]            |
| Isfahan  | 2008  | MDDM             | 80                  | 30%                | 6.25%              | 3.75%              | 2.50%              | Nd                 | 8.75%              | Nd                 | Nasr et al. [15]               |
| Mashad   | 2013  | DDM⁵             | 185                 | 64.6%              | 17.1%              | 0                  | 9.8%               | Nd                 | Nd                 | Nd                 | Zendedel et al. [21]           |
| Tehran   | 2004  | SAM⁹, MDDM       | 70                  | 79%                | 21%                | 32%                | 42%                | Nd                 | 35%                | Nd                 | Falsafi et al. [33]            |
| Tehran   | 2005  | MDDM             | 120                 | 57.5%              | 16.7%              | 0                  | 1.6%               | Nd                 | Nd                 | Nd                 | Mohammadi et al. [30]          |
| Tehran   | 2010  | DDM              | 110                 | 55.6%              | 7.3%               | 38.1%              | 7.3%               | Nd                 | 4.5%               | Nd                 | Slavoshi et al. [29]           |
| Tehran   | 2011  | ADM⁶             | 42                  | 40.5%              | 14.3%              | 4.8%               | 2.4%               | Nd                 | 2.4%               | Nd                 | Shokrzadeh et al. [26]         |
| Tehran   | 2010  | DDM              | 104                 | 51.5%              | 0                  | 0                  | 0                  | Nd                 | Nd                 | Nd                 | Siouss et al. [27]             |
| Tehran   | 2007  | MDDM, E-test     | 128                 | 64%                | 23%                | 0                  | 2.5%               | Nd                 | Nd                 | Nd                 | Tomatari et al. [31]           |
| Tehran   | 2007  | DDM              | 24                  | 54.16%             | 4.18%              | 0                  | 8.33%              | Nd                 | Nd                 | Nd                 | Fallahi et al. [28]            |
| Tehran   | 2014  | ADM              | 111                 | 61.3%              | 32.4%              | Nd                 | Nd                 | Nd                 | 30.6%              | Nd                 | Shokrzadeh et al. [49]         |
| Tehran   | 2011  | ADM              | Not mentioned       | 60%                | 17%                | 5%                 | 10%                | Nd                 | 27%                | Nd                 | Sayadi et al. [34]             |
| Tabriz   | 2007  | DDM, E-test      | 100                 | 95%                | 16%                | 5%                 | 59%                | 9%                 | 7%                 | Nd                 | Rafeey et al. [12]             |
| Tabriz   | 2012  | DDM              | 112                 | 76.8%              | 14.3%              | 18.7%              | 28.6%              | Nd                 | 33%                | Nd                 | Milanil et al. [13]            |
| Tabriz   | 2013  | MDDM             | 123                 | 78.86%             | 17.07%             | ND                 | 27.68%             | Nd                 | Nd                 | Nd                 | Ghomasi et al. [14]            |
| Sari     | 2011  | DDM              | 197                 | 65.5%              | 45.2%              | 37.1%              | 23.9%              | 61.4%              | 34.5%              | Nd                 | Abadi et al. [24]              |
| Sari     | 2010  | E-test           | 132                 | 72.4%              | 30%                | 9%                 | 6.8%               | Nd                 | Nd                 | Nd                 | Talebi Bezmin Abadi et al. [23]|
| Sari     | 2011  | ADM, E-test      | 30                  | 76.8%              | 34%                | 9.6%               | Nd                 | Nd                 | 5.3%               | 4.6%              | Abadi et al. [25]              |
| Ilam     | 2013  | DDM              | 50                  | 88%                | 32%                | 12%                | 12%                | Nd                 | Nd                 | Nd                 | SadeghiFar et al. [22]         |
| Shiraz   | 2010  | E-test           | 121                 | 44%                | 5%                 | 3%                 | 20%                | Ndd                | Nd                 | Nd                 | Farshad et al. [18]            |
| Shiraz   | 2007  | ADM              | 106                 | 72.6%              | 9.4%               | 4.7%               | 20.8%              | 9.4%               | 4.7%               | Nd                 | Kohanteb et al. [19]           |
| Yazd     | 2014  | DDM              | 144                 | 77.8%              | 18.8%              | 21.5%              | 7.6%               | Nd                 | 19.4%              | 14.6%             | Navidifar et al. [20]          |

**Table 1. Antibiotic resistance pattern of *H. pylori* isolates in some Iranian studies**

**Legend:**
- **MTZ:** Metronidazole
- **CLA:** Clarithromycin
- **TET:** Tetracycline
- **AMX:** Amoxicillin
- **FRZ:** Fluoroquinolone
- **CIP:** Ciprofloxacin
- **LVX:** Levofloxacin
- **MOX:** Moxifloxacin

**Method abbreviations:**
- **MDDM:** Modified disk diffusion method
- **DDM:** Disc diffusion method
- **SAM:** Screening agar method
- **ADM:** Agar dilution method
- **Nd:** None defined

Reference: 18719
This may be referred to use of this inexpensive drug for treating of other infections such as parasitic, dental or periodontal, urological and genital infections in these countries [40,41]. In some studies resistance to metronidazole is associated with patient's gender. Mirzaei et al. [17] showed that the rate of metronidazole resistance among H. pylori isolates in women was higher than men. The same data has been achieved by Farshad et al. [18] in Shiraz province, it could be due to frequent use of this antibiotic for gynecological infections in Iranian women. But in other studies in Iran the difference was not statistically significant [15,28]. As mentioned above there are null mutations in rdxA, in metronidazole-resistance H. pylori isolates. Mohammadi et al. [30] found this mutation in six isolates of 120 resistant H. pylori isolates (5%) by PCR method. In another study with the same method, Abdollahi et al. [42] detected this mutation in 8 of 3522.9% H. pylori resistant isolates. Also, instead of null mutation in rdxA gene, some amino-acid substitution mutations in this gene may be contributed in resistance to metronidazole [43]. Mirzaei et al. [44] showed these mutations in metronidazole-resistance isolates and described new W (209) R substitution by PCR amplification of rdxA and further sequencing. Another metronidazole-resistance mechanism in H. pylori isolates may related to efflux pumps [45]. Mehrabadi et al. [46] investigated the role of RND family of efflux pumps in metronidazole in H. pylori isolates. They showed that the expression level of RND family of efflux pumps genes had been increased in presence of excess amounts of metronidazole. The relationship between metronidazole resistance and cagA virulence-factor genotype of H. pylori had been analyzed by Ghotaslou et al. in Tabriz [14]. In their study, of 97 resistant H. pylori isolates, 67 isolates (54.47%) were cagA-positive. It was not statistically significant. The same result has been achieved in a recent study in Tehran [32].

Tinidazole is another nitroimidazole antibiotic which is used in some H. pylori eradication regimens [47]. Resistance rate of this antibiotic has been reported by two studies in Iran. In Siavoshi et al. [48] study resistance to tinidazole was observed in 70 isolates of 186 (37.6%) (MIC>8 μg/ml) and 29 isolates (15.6%) were moderately resistance (MIC 4-8 μg/ml). In second study has been conducted by Falsafi et al. [33] 78% of the 70 isolates were resistance to tinidazole.

Because of high rate nitroimidazole resistance in H. pylori isolates from Iran, these antibiotics are not recommended for the first line of H. pylori infection therapy.

4. RESISTANCE TO CLARITHROMYCIN

Clarithromycin (6-O-methyl erythromycin) (CLA) is a kind of macrolide antibiotics that is active against a wide variety of bacterial infections. The action mechanism of macrolides antibiotics is binding to peptidyl transferase loop of domain V the 23S rRNA molecule in ribosomes and blocking bacterial protein synthesis [50]. Clarithromycin resistance in H. pylori is associated with A-to-G transition at position 2142 (A2142G) or 2143 (A2143G) and less frequently, A2142C [51]. Prevalence of H. pylori resistance to clarithromycin in Iran is variable. The high rate of clarithromycin resistance has been reported in Sari (north of Iran) from three studies 45.2% (89/197), 34% and 30% [23-25], Ilam (west of Iran) 32% (16/50) [22] and a study in Tehran 32.4% (36/111) [49]. Also, three studies from Tehran (21%, 21.7% and 23%) [31,33,52] and one study in Yazd (18.8%) [20], reported that clarithromycin resistance rate was remarkable. There is only one study that reported all H. pylori isolates were sensitive to clarithromycin [27]. Low resistance rates have been reported from 2 studies of Shiraz (5% and 9.4%) [18,19], 2 studies of Tehran (4.16% and 7.3%) [28,29] and 1 study from Isfahan (6.25%) [15]. Other reports were the same approximately such as; 14.6% and 15.3% in Isfahan [16,17], 14.4%, 16% and 17.07% in Tabriz [12-14], 13.38%, 14.3%, 16.7% and 17% in Tehran [26,30,32,34] and 17.0% in Mashhad [21]. Clarithromycin is an expensive drug and not commonly used in Iran so these rates of resistance could be related to cross-reactivity with other macrolides [53]. In all studies there was no relationship between clarithromycin resistance and gender, clinical outcomes and genotype of virulence factors. Molecular mechanism of clarithromycin resistance among H. pylori isolates has been investigated by some authors. We observed that all of H. pylori isolates had A2143G by real-time PCR method [52]. Mohammadi et al. [30] investigated 23S rRNA gene mutations in clarithromycin-resistant H. pylori isolates by PCR-RFLP method. They showed 73.68% of isolates have the A2143G mutation, 21.05% have the A2142C mutation, and 5.26% have the A2142G mutation. The same method has been employed by Kargar et al. [54]. The frequency of these mutations in their study was 68.40% for A2143G, 10.52% for
A2142C, and 15.78% for A2142G [22]. In Sadeghifar's study with the same method, all resistant isolates had point mutation A2143G in 23S rRNA gene [22]. So, the frequency of A2143G mutation is higher than mutation in the other locations of 23S rRNA. Abadi et al. [55] and Keshavarz-Azizi-Raftar et al. [56] confirmed this result with the similar method. Also, Kargar et al. [57] confirmed this result by TaqMan real-time PCR method for gastric biopsies. In contrast Abdollahi et al. [58] used PCR-RFLP method and observed the A2143G mutation in 15% and A2142G mutation in 55% of clarithromycin-resistant *H. pylori* isolates. Also, they showed 30% of resistant isolates have A2142C by 3'mismatch PCR [58]. In a study conducted by Naserpour Farivar et al. [59] by Scorpion real-time PCR, the most prevalent genotypes was A2142G followed by A2143G. Khademi et al. [60] observed all clarithromycin-resistant isolates have T2243C mutation by PCR and sequencing methods.

Azithromycin (Azides) and erythromycin are others macrolide antibiotic that show good activity against *H. pylori* isolates *in vitro* [61,62]. Azithromycin is used in some triple therapy regimens successfully [63], but poor acid stability of erythromycin limits its use in the treatment of *H. pylori* infection [64]. In Fallahi et al. [28] and Shokrzadeh et al. [49] studies, resistance rate to erythromycin and clarithromycin is identical (32.4% and 4.16% respectively). But in Falsafi et al. [33] and Milani et al. [13] studies, resistance rate to erythromycin is higher than clarithromycin (32%-20% and 26%-14.3% respectively). Two other studies in Iran reported azithromycin resistance in *H. pylori* isolates was (3.75%) and (8%), respectively [15,22].

5. RESISTANCE TO TETRACYCLINE

Tetracycline (TET) is an antibiotic that blocks protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site [65]. It is used in quadruple therapy for *H. pylori* infection eradication [66,67]. Tetracycline resistance in *H. pylori* strains is associated with mutations in 16S rRNA-encoding genes [68]. Resistance to tetracycline is low, or even absent, in many areas. For example this is about 2.1% in European countries and 2.7% in US [11]. But based on the few studies from other countries such as China (58.8%) [69] and Cameroon (43.9%) [70], it was greater than 30%. Five studies in Iran indicated that all *H. pylori* isolates were sensitive to tetracycline [21,27,28,30,31]. Also sensitivity rates which were reported in 7 studies in Iran was very high [15,18,19,23,25,26,34]. So it seems that prevalence of tetracycline resistance in *H. pylori* strains in our country is low. However, the rate of tetracycline resistant was higher in three studies, Falsafi et al. [33] (32%), Siavoshi et al. [29] (38.1%) and Abadi et al. [24] (37.1%), respectively. Also in Siavoshi et al. study, rate of tetracycline resistance, has increased over the time (0 – 0.7% to 38.1% from 2005 to 2008, respectively). They explained it may be due to availability and overusing of this antibiotic or transferring of resistance genes from other bacteria. Dadashzadeh et al. [71] used Real-Time PCR method for detection of 16S rRNA mutations in tetracycline-resistance *H. pylori* isolates. Metting temperature and type of mutation in 5/11 and 2/11 strains were 83.90°-84°C for A926G and 87.35°C for A928C, respectively. Two isolates like wild type (AGA) sequence showed metting temperature at 88.75°C. Also they found a novel mutation in 2 strains with 84°C as their metting temperatures and exhibition of an A939C mutation. Anoushiravani et al. [72] reported that proton motive force (PMF)-dependent efflux plays an important role in the resistance of clinical isolates of *H. pylori* to tetracycline.

6. RESISTANCE TO AMOXICILLIN

Amoxicillin (AMX) is a broad spectrum antibiotic that belongs to the class of β-lactams. This group of antibiotics bind to penicillin-binding proteins (PBP) in bacterial cell wall and inhibit cell division [73]. Mechanism of amoxicillin resistance in *H. pylori* isolates is alterations in penicillin-binding proteins (PBP) [74]. Resistance to amoxicillin in most regions is low, Europe 0.5%, Asia 11.16% and USA 2.2% [11]. Also in majority of Iranian studies resistance rates were low (0, 1.6%, 2.4%, 2.5%, 2.5%, 4.2%, 6.4%, 6.8%, 7.3%, 8.33%, 7.87%, 9.8%, 10% and 12%) [15-17,21-23,26-32,34]. But, resistance to amoxicillin has been reported with higher rate in Tabriz (northwest of Iran). Rafeey et al. [12] indicated 59% of *H. pylori* strains (59/100) were amoxicillin resistance. In other studies from Tabriz (Gotaslui et al. [14] and Milani et al. [13]) the resistance rates were 27.68% and 28.6%, respectively. Resistance to amoxicillin has been observed in *E. coli* spp. [75], *salmonella* spp. [76], *Mycobacterium tuberculosis* [77], *Klebsiella pneumonia* isolates in Tabriz [78], too. The incidence of amoxicillin-resistance among *H. pylori* isolates in Shiraz (20% and 28%) [18,19] and in Sari (23.9%) [24] is
remarkable, too. Only one study in Tehran reported high rate of amoxicillin resistance among _H. pylori_ isolates (42%) [33]. Over all, low rate of amoxicillin resistance in majority of provinces, indicated that it is a good choice in triple therapy of _H. pylori_ infection but the using of this antibiotic in Tabriz, Shiraz and Sari should be cautiously.

Ampicillin is another antibiotic from penicillin family; its activity is equivalent to amoxicillin. There were two studies in Iran that have investigated and reported ampicillin resistance among _H. pylori_ isolates as 15.3% and 31%, respectively [33,49].

### 7. RESISTANCE TO FURAZOLIDONE

Furazolidone (FRZ) and nitrofurantoin belong to nitrofuran antibiotics. They are nitroheterocyclic and nitroaromatic compounds that have structure similarity with metronidazole [79]. Mechanism of resistance to this antibiotic is poorly studied. It is may be associated with mutations in the _porD_ and _oocD_ genes which encode 5-subunits of the pyruvate flavodoxin oxidoreductase and 2-oxoglutarate reductase, respectively [80]. Prevalence of resistance to furazolidone in most of provinces in Iran is relatively low. Sirous et al. [27] and Fallahi et al. [28] reported that all _H. pylori_ isolates from Tehran are sensitive to this antibiotic. The same data has been achieved by Navidifar _et al._ from Yazd [20]. Similarly, in other studies, furazolidone resistance rates were as low as follow: 4.5%, 7.87%, 9%, and 9.4% [12,19,29,32]. But in a study from Sari (a city in the north of Iran), 61.4% of _H. pylori_ isolates were resistance to furazolidone [24]. Resistance to nitrofurantoin has been observed in 11.6% of isolates in Tabriz [13]. Existence of low resistance rate and low cost of furazolidon made this antibiotic as a good choice for _H. pylori_ eradication regimen. Although using of high-dose of furazolidone has shown best results for _H. pylori_ eradication therapy, but it should be used only in low-dose, because it has severe side effects in high dose [81].

### 8. RESISTANCE TO FLUOROQUINOLONES

Fluoroquinolones, including ciprofloxacin (CIP), levofloxacin (LVX), sitafloxacin (STFX), garenoxacin (GRNX), moxifloxacin (MXF), and ofloxacin (OFX) are as broad spectrum antibiotics. Their mode of action is inhibition of both DNA gyrase and topoisomerase IV, a related type II topoisomerase [82,83]. These are well-tolerated antibiotics with no major side effects and show good activity against _H. pylori_ [84,85]. Fluoroquinolones such as levofloxacin or sitafloxacin are used as a component of triple therapy when first line therapy are failed to eradicate _H. pylori_ infection [86-88]. Mechanism of resistance to fluoroquinolones in _H. pylori_ is mediated by point mutations in the Quinolones Resistance-Determining Region (QRDR) of DNA gyrase A (gyrA) gene [89]. Widely variable rates of fluoroquinolones resistance have been reported in _H. pylori_ isolates in Iran. In most of them only resistance to ciprofloxacin has been reported. The maximum and minimum resistant rates which were reported from Tehran were 35% and 2.4%, respectively [26,33]. Others were as follow: 34.5% (Sari) [24], 4.7% (Shiraz) [19], 8.75% (Isfahan) [15], 19.4% (Yazd) [20], 27%, 30.6%, 33.7% (Tehran) [32,34,49]. Two reported rates from Tabriz were 7% and 33 %, with high discrepancy [12,13]. Resistance to levofloxacin has been investigated in four other studies, 5.3% in Sari [25], 14.6% in Yazd [20] and 30.6% and 37% in Tehran [32,49]. Moxifloxacin resistance has been observed in 4.6% (7/150) of _H. pylori_ isolates in Abadi _et al._ [25] study.

### 9. RESISTANCE TO RIFABUTIN

Rifabutin (RFB) is a bactericidal antibiotic that is derived from rifamycin-S and is using in the treatment of tuberculosis (TB) [90]. Rifabutin shows good activity against _H. pylori_ isolates _in vitro_ [91]. The mechanism of action of this antibiotic, is inhibition of the β-subunit of _H. pylori_ RNA polymerase encoded by the _rpoB_ gene [92]. It can be used in triple therapy (rifabutin-containing rescue therapy), if the previous _H. pylori_ eradication regimens with key antibiotics such as metronidazole, clarithromycin, tetracycline, amoxicillin and fluoroquinolones has been failed [93]. Mechanism of resistance to rifabutin in _H. pylori_ isolates is related to mutations in codon of 524-545 or codon 585 of the _rpoB_ gene [92]. According to few global studies that investigated prevalence of resistance to rifabutin, the resistance rate is very low e.g. 1.4% in Germany [94] and 0.24% in Japan [95]. Rifabutin is not currently used as an anti _H. pylori_ antibiotic in _H. pylori_ eradication regimen in Iran. In a study of Tehran, 8 of 127 _H. pylori_ isolates, were resistance to rifabutin (MIC 0.06 g/mL) [32].

Rifampin has a structural similarity to rifabutin. It binds to the β-subunit of bacterial RNA polymerase [92].
Rifampin is used in the treatment of tuberculosis; TB [96]. Millani et al. [13] reported that 28.6% of *H. pylori* isolates were rifampin resistance in Tabriz. Resistance to rifampin is also observed in other bacteria including *Enterococcus spp.* and *staphylococcus spp.* isolates in Iran [97].

10. MULTIPLE DRUG RESISTANCE

Simultaneously resistance to two or three antibiotics is a risk factor for treatment failure. Prevalence of multiple resistance (MDR) of *H. pylori* isolates to antibiotics, have been investigated in some Iranian studies. For instance, in Abadi et al. [25] and Falsafi et al. [33] studies the rate of resistance to four keys antibiotics (metronidazole, clarithromycin, tetracycline, amoxicillin) were 3.3% and 7% respectively. Of 80 *H. pylori* isolates in Isfahan, only one (1.25%) was resistant to six antibiotics (Metronidazole, clarithromycin, tetracycline, amoxicillin, ciprofloxacin and azithromycin) [15].

11. CONCLUSION

*H. pylori*, is a human gastric pathogen responsible for most gastrointestinal diseases. Antibiotic resistance is a key determinant of the outcome of eradication therapy for this infection. In the past decades efficacy of standard triple therapies has decreased. It is because of emerging of new antibiotic resistance *H. pylori* strains especially in developing countries for over using antibiotics in a board range of infections. According to mentioned studies above, there are some variations in the resistant rate to different antibiotics between Iran’s provinces, even in the same province or in the same time. These differences may be due to some variations including using of different susceptibility methods, turbidity of bacterial suspension, fresh or freeze biopsies and duration of incubation. However, according to mentioned studies before, the prevalence of metronidazole resistance is higher than other antibiotics varied from 30%-95%. Also resistance to clarithromycin, tetracycline and amoxicillin is remarkably high in some provinces. Similarly, resistance to fluoroquinolons that have been used as an alternative therapy in *H. pylori* infection treatment is remarkable; they are not recommended for the first-line therapy against *H. pylori* infections in Iran.

CONSENT

It is not applicable.
ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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