Review Article

A review article on *Helicobacter pylori* antibiotic resistant profile in Iran

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, 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 *iv 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 nitrose free radical. Nitrose 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 table1, the incidence of metronidazole-resistance *H. pylori* isolates in all investigations that have been done in different provinces of Iran are greater than 30% (table1). 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 (center 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(56.3%), 53/121(44%), 77/106(72.6%) 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) 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% ,42.6% and 100%, respectively) like Iran is high [35-39]. This may be refereed to use of this inexpensive drug for treating of other infections such as parasitic, dental or periodontal, urological and genital infections in this countries[40, 41]. In some studies resistance to metronidazole is associated with patient's gender. Mirzaei *et al.* showed that the rate of metronidazole resistance among *H. pylori* isolates in women was higher than men[17]. The same data has been achieved by Farshad *et al.* in Shiraz province [18], 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.* found this mutation in six isolates of 120 resistant *H. pylori* isolates (5%) by PCR method[30]. In another study with the same method, Abdollahi *et al.* detected this mutation in 8 of 35(22.9%) *H. pylori* resistant isolates[42]. 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.* showed these mutations in metronidazole-resistance isolates and described new W (209) R substitution by PCR amplification of *rdxA* and further sequencing[44]. Another metronidazole-resistance mechanism in *H. pylori* isolates may related to efflux pumps[45]. Mehrabadi *et al.* investigated the role of RND family of efflux pumps in resistance to 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[46]. The relationship between metronidazole resistance and *cagA* virulence-factor genotype of *H. pylori* has 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.* study resistance to tinidazole was observed in 70 isolates of 186 (37.6%) (MIC>8µg/ml) and 29 isolates (15.6%) were moderately resistance (MIC 4-8 µg/ml)[48]. In second study has been conducted by Falsafi *et al.* 78% of the 70 isolates were resistance to tinidazol[33].

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

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

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			Reference
									CIP	LVX	MOX	
Isfahan	2013	E-test, MDDM[a]	78	55.1%	15.3%	Nd[e]	6.4%	Nd	Nd	Nd	Nd	Khademi *et al.*[16]
Isfahan	2012	E-test	48	56.3%	14.6%	Nd	4.2%	Nd	Nd	Nd	Nd	Mirzaei *et al.*[17]
Isfahan	2008	MDDM	80	30%	6.25%	3.75%	2.50%	Nd	8.75 %	Nd	Nd	Naser et al.[15]
Mashhad	2013	DDM[b]	185	64.6%	17.1%	0	9.8%	Nd	Nd	Nd	Nd	Zendedel *et al* .[21]
Tehran	2004	SAM[c], MDDM	70	79%	21%	32%	42%	Nd	35%	Nd	Nd	Falsafi *et al* .[33]
Tehran	2005	MDDM	120	57.5%	16.7%	0	1.6%	Nd	Nd	Nd	Nd	Mohammadi *et al.*[30]
Tehran	2010	DDM	110	55.6%	7.3%	38.1%	7.3%	4.5%	Nd	Nd	Nd	Siavoshi *et al* .[29]
Tehran	2011	ADM[d]	42	40.5%	14.3%	4.8%	2.4%	Nd	2.4%	Nd	Nd	Shokrzadeh *et al* .[26]
Tehran	2010	DDM	104	51.5%	0	0	0	0	Nd	Nd	Nd	Sirous *et al* [27]
Tehran	2010	MDDM, E-test	128	64%	23%	0	2.5%	Nd	Nd	Nd	Nd	Tomatari *et al* [31]
Tehran	2007	DDM	24	54.16%	4.16%	0	8.33%	0	Nd	Nd	Nd	Fallahi *et al* [28]
Tehran	2014	ADM	111	61.3%	32.4%	Nd	Nd	Nd	30.6 %	30.6 %	Nd	Shokrzadeh *et al* .[49]
Tehran	2011	ADM	Not mentioned	60%	17%	5%	10%	Nd	27%	Nd	Nd	Sayadi *et al* .[34]
Tabriz	2007	DDM, E-test	100	95%	16%	5%	59%	9%	7%	Nd	Nd	Rafeey *et al* [12]

Tabriz	2012	DDM	112	76.8%	14.3%	18.7%	28.6%	Nd	33%	Nd	Nd	Milani *et al* .[13]
Tabriz	2013	MDDM	123	78.86%	17.07%	ND	27.68%	Nd	Nd	Nd	Nd	Ghotaslou *et al* .[14]
Sari	2011	DDM	197	65.5%	45.2%	37.1%	23.9%	61.4%	34.5 %	Nd	Nd	Abadi *et al* .[24]
Sari	2010	E-test	132	72.4%	30%	9%	6.8%	Nd	Nd	Nd	Nd	Talebi Bezmin Abadi *et al* .[23]
Sari	2011	ADM,E-test	30	78.6%	34%	9.6%	Nd	Nd	Nd	5.3 %	4.6%	Abadi *et al* .[25]
Ilam	2013	DDM	50	88%	32%	12%	12%	Nd	Nd	Nd	Nd	Sadeghifard *et al* .[22]
Shiraz	2010	E-test	121	44%	5%	3%	20%	Ndd	Nd	Nd	Nd	Farshad *et al* .[18]
Shiraz	2007	ADM	106	72.6%	9.4%	4.7%	20.8%	9.4%	4.7%	Nd	Nd	Kohanteb *et al* [19]
Yazd	2014	DDM	144	77.8%	18.8%	21.5%	7.6%	Nd	19.4 %	14.6 %	Nd	Navidifar *et al* .[20]

MDDM[a]: Modified disk diffusion method

DDM[b]: Disc diffusion method

SAM[c]: Screening agar method

ADM[d]: Agar dilution method

Nd[e]: None defined

4. RESISTANCE TO CLARITHROMYCIN

Clarithromycin (6-O-methyl erythromycin) (CLA) is a macrolide antibiotic that is active against a wide variety of bacterial infection. 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), 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 Shiraz(5% and 9.4%)[18, 19], Tehran (4.16% and 7.3%)[28, 29] and 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.* 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[30]. The same method has been employed by Kargar *et al.* The frequency of these mutations in their study was 68.40% for A2143G, 10.52% for A2142C, and 15.78% for A2142G[22, 54]. In Sadeghifard'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.* and Keshavarz-Azizi-Raftar *et al.* confirmed this result with the similar method[55, 56]. Also, in another study, Kargar *et al.* confirmed this result by TaqMan real-time PCR method in gastric biopsies[57]. But Abdollahi *et al.* used PCR-RFLP method and observed the A2143G mutation in 15% and A2142G mutation in 55% of clarithromycin-resistance *H. pylori* isolates[58]. Also, they showed 30% of resistant isolates have A2142C by 3'mismatch PCR[58]. In a study conducted by Naserpour Farivar *et al.* by Scorpion real-time PCR, the most prevalent genotypes was A2142G followed by A2143G[59]. Khademi *et al.* observed all clarithromycin-resistant isolates have T2243C mutation by PCR and sequencing methods[60].

Azithromycin 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.* and Shokrzadeh *et al.* studies, resistance rate to erythromycin and clarithromycin is identical (32.4% and 4.16% respectively) [28, 49]. But in Falsafi *et al.* and Milani et al. studies, resistance rate to erythromycin is higher than clarithromycin (32%>20% and 26%>14.3% respectively)[13, 33]. Two other studies in Iran investigated azithromycin resistance in *H. pylori* isolates, as (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 in few studies in some countries such as China(58.8%)[69] and Cameroon(43.9%)[70], it was greater than 30%. 5 studies in Iran indicated 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.* (32%), Siavoshi *et al.(* 38.1%) and Abadi *et al*. (37.1%), respectively [24, 29, 33]. 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 is may be due to availability and overusing of this antibiotic or transferring of resistance genes from other bacteria. Dadashzadeh *et al.* used Real-Time PCR method for detection of 16S rRNA mutations in tetracycline-resistance *H. pylori* isolates. Melting temperature and type of mutation in 5/11 and 2/11 strains were 83.90°-84℃ for A926G and 87.35℃ for A928C, respectively. Two isolates liked all wild type (AGA) sequences showed melting temperature at 88.75℃. Also they found a novel mut ation in 2 strains with 84℃ as their melting temperatures and exhibition of an A939C mutation[71]. Anoushiravani *et al.* reported that proton motive force (PMF)-dependent efflux plays an important role in the resistance of clinical isolates of *H. pylori* to tetracycline[72].

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.* indicated 59% of *H. pylori* strains (59/100) were amoxicillin resistance[12]. In other studies from Tabriz (Gotaslu *et al.* and Milani *et al.*) the resistance rates were 27.68% and 28.6%, respectively[13, 14]. 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 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 oorD genes which encode δ-subunits of the

pyruvate flavodoxin oxidoreductase and 2-oxoglutarate reductase, respectively[80]. Prevalence of resistance to furazolidone in most of provinces of 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.* in Yazd[20]. Similarly, in other studies, furazolidone resistance rates were low as follow; 4.5%, 7.87%, 9%, and 9.4% [12, 19, 29, 32]. But in a study that has been reported from Sari(a city of 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(STX), garenoxacin(GNX), 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 had 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 resistances rates have been 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 as 7% and 33 %, showed 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.* study [25].

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 codons 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 in 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.* reported that 28.6% of *H. pylori* isolates were rifampin resistance in Tabriz[13]. Resistance to rifampin is also observed in other bacteria including *Enterococcus spp.* and *staphylococcus spp*. isolates in Iran[97].

Figure1; The different regions of Iran with high rate of antibiotic resistance among *H. pylori* isolates

- *Metronidazole resistance*
- *Clarithromycin resistance*
- *Amoxicillin resistance*
- *Tetracycline resistance*
- *Furazolidone resistance*
- *Fluoroquinolones resistance*

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.* and Falsafi *et al.* studies the rate of resistance to four keys antibiotics(metronidazole, clarithromycin, tetracycline, amoxicillin) were 3.3% and 7% respectively[25, 33]. 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 remarkable in some provinces. Similarly, resistance to fluroquinolons 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.

REFERENCES

1. KUSTERS, J.G., A.H. VAN VLIET, AND E.J. KUIPERS, *PATHOGENESIS OF HELICOBACTER PYLORI INFECTION.* CLINICAL MICROBIOLOGY REVIEWS, 2006. **19**(3): P. 449-490.
2. PEREZ-PEREZ, G.I., D. ROTHENBACHER, AND H. BRENNER, *EPIDEMIOLOGY OF HELICOBACTER PYLORI INFECTION.* HELICOBACTER, 2004. **9**(S1): P. 1-6.
3. ISIK, A., ET AL., *A NEW PROGNOSTIC STRATEGY FOR GASTRIC CARCINOMA: ALBUMIN LEVEL AND METASTATIC LYMPH NODE RATIO.* MINERVA CHIRURGICA, 2014. **69**(3): P. 147-153.
4. MALFERTHEINER, P., ET AL., *CURRENT CONCEPTS IN THE MANAGEMENT OF HELICOBACTER PYLORI INFECTION—THE MAASTRICHT 2-2000 CONSENSUS REPORT.* ALIMENTARY PHARMACOLOGY & THERAPEUTICS, 2002. **16**(2): P. 167-180.
5. GUMURDULU, Y., ET AL., *LOW ERADICATION RATE OF HELICOBACTER PYLORI WITH TRIPLE 7-14 DAYS AND QUADRIPLE THERAPY IN TURKEY.* WORLD JOURNAL OF GASTROENTEROLOGY, 2004. **10**(5): P. 668-671.
6. GRAHAM, D.Y. AND L. FISCHBACH, *HELICOBACTER PYLORI TREATMENT IN THE ERA OF INCREASING ANTIBIOTIC RESISTANCE.* GUT, 2010: P. GUT. 2009.192757.
7. O'CONNOR, J.P.A., I. TANEIKE, AND C. O'MORAIN, *IMPROVING COMPLIANCE WITH HELICOBACTER PYLORI ERADICATION THERAPY: WHEN AND HOW?* THERAPEUTIC ADVANCES IN GASTROENTEROLOGY, 2009. **2**(5): P. 273-279.
8. DORJI, D., ET AL., *EPIDEMIOLOGY OF HELICOBACTER PYLORI IN BHUTAN: THE ROLE OF ENVIRONMENT AND GEOGRAPHIC LOCATION.* HELICOBACTER, 2014. **19**(1): P. 69-73.
9. JOHNSON, M., *METRONIDAZOLE: AN OVERVIEW.* UPTODATE INC, 2009. **23**.
10. GOODWIN, A., ET AL., *METRONIDAZOLE RESISTANCE IN HELICOBACTER PYLORI IS DUE TO NULL MUTATIONS IN A GENE (RDXA) THAT ENCODES AN OXYGEN-INSENSITIVE NADPH NITROREDUCTASE.* MOLECULAR MICROBIOLOGY, 1998. **28**(2): P. 383-393.
11. DE FRANCESCO, V., ET AL., *WORLDWIDE H. PYLORI ANTIBIOTIC RESISTANCE: A SYSTEMATIC.* J GASTROINTESTIN LIVER DIS, 2010. **19**(4): P. 409-414.
12. RAFEEY, M., ET AL., *PRIMARY RESISTANCE IN HELICOBACTER PYLORI ISOLATED IN CHILDREN FROM IRAN.* JOURNAL OF INFECTION AND CHEMOTHERAPY, 2007. **13**(5): P. 291-295.
13. MILANI, M., ET AL., *THE STATUS OF ANTIMICROBIAL RESISTANCE OF HELICOBACTER PYLORI IN EASTERN AZERBAIJAN, IRAN: COMPARATIVE STUDY ACCORDING TO DEMOGRAPHICS.* JOURNAL OF INFECTION AND CHEMOTHERAPY, 2012. **18**(6): P. 848-852.
14. GHOTASLOU, R., ET AL., *RELATIONSHIP BETWEEN DRUG RESISTANCE AND CAGA GENE IN HELICOBACTER PYLORI.* JUNDISHAPUR JOURNAL OF MICROBIOLOGY, 2013. **6**(10).
15. NASER, D., *GENETIC DIVERSITY AND DRUG RESISTANCE OF HELICOBACTER PYLORI STRAINS IN ISFAHAN, IRAN.* IRAN J BASIC MED SCI, 2008. **11**: P. 174-82.
16. KHADEMI, F., ET AL., *RESISTANCE PATTERN OF HELICOBACTER PYLORI STRAINS TO CLARITHROMYCIN, METRONIDAZOLE, AND AMOXICILLIN IN ISFAHAN, IRAN.* JOURNAL OF RESEARCH IN MEDICAL SCIENCES: THE OFFICIAL JOURNAL OF ISFAHAN UNIVERSITY OF MEDICAL SCIENCES, 2013. **18**(12): P. 1056.
17. MIRZAEI, N., ET AL., *PREVALENCE OF RESISTANCE TO HELICOBACTER PYLORI STRAINS TO SELECTED ANTIBIOTICS IN ISFAHAN, IRAN.* JUNDISHAPUR J MICROBIOL, 2013. **6**: P. E6342.
18. FARSHAD, S., ET AL., *ANTIMICROBIAL SUSCEPTIBILITY OF HELICOBACTER PYLORI STRAINS ISOLATED FROM PATIENTS IN SHIRAZ, SOUTHERN IRAN.* WORLD JOURNAL OF GASTROENTEROLOGY: WJG, 2010. **16**(45): P. 5746.

19. KOHANTEB, J., ET AL., *ANTIMICROBIAL SUSCEPTIBILITY TESTING OF HELICOBACTER PYLORI TO SELECTED AGENTS BY AGAR DILUTION METHOD IN SHIRAZ-IRAN.* INDIAN JOURNAL OF MEDICAL MICROBIOLOGY, 2007. **25**(4): P. 374.
20. NAVIDIFAR, T., ET AL., *ANTIBACTERIAL RESISTANCE PATTERNS OF HELICOBACTER PYLORICLINICAL ISOLATES FROM GASTRIC BIOPSY OF PATIENTS IN YAZD.* INT J ENTERIC PATHOG, 2014. **2**(2): P. E17791.
21. ZENDEDEL, A., ET AL., *ANTIBIOTIC RESISTANCE OF HELICOBACTER PYLORI IN MASHHAD, IRAN.* J PAK MED ASSOC, 2013. **63**(3): P. 336-339.
22. SADEGHIFARD, N., ET AL., *SURVEY IN IRAN OF CLARITHROMYCIN RESISTANCE IN HELICOBACTER PYLORI ISOLATES BY PCR-RFLP.* SOUTHEAST ASIAN JOURNAL OF TROPICAL MEDICINE & PUBLIC HEALTH, 2013. **44**(1): P. 89-95.
23. TALEBI BEZMIN ABADI, A., ET AL., *ANTIBIOTIC RESISTANCE OF HELICOBACTER PYLORI IN MAZANDARAN, NORTH OF IRAN.* HELICOBACTER, 2010. **15**(6): P. 505-509.
24. ABADI, A.T.B., ET AL., *FREQUENCY OF ANTIBIOTIC RESISTANCE IN HELICOBACTER PYLORI STRAINS ISOLATED FROM THE NORTHERN POPULATION OF IRAN.* THE JOURNAL OF MICROBIOLOGY, 2011. **49**(6): P. 987-993.
25. ABADI, A.T.B., ET AL., *PRIMARY RESISTANCE OF HELICOBACTER PYLORI TO LEVOFLOXACIN AND MOXIFLOXACINE IN IRAN.* INTERNAL AND EMERGENCY MEDICINE, 2012. **7**(5): P. 447-452.
26. SHOKRZADEH, L., ET AL., *ANTIBIOTIC SUSCEPTIBILITY PROFILE OF HELICOBACTER PYLORI ISOLATED FROM THE DYSPEPSIA PATIENTS IN TEHRAN, IRAN.* SAUDI JOURNAL OF GASTROENTEROLOGY: OFFICIAL JOURNAL OF THE SAUDI GASTROENTEROLOGY ASSOCIATION, 2011. **17**(4): P. 261.
27. SIROUS, M., ET AL., *PREVALENCE OF ANTIMICROBIAL RESISTANCE IN HELICOBACTER PYLORI ISOLATES FROM IRAN.* AFRICAN JOURNAL OF BIOTECHNOLOGY, 2013. **9**(36).
28. FALLAHI, G.-H. AND S. MALEKNEJAD, *HELICOBACTER PYLORI CULTURE AND ANTIMICROBIAL RESISTANCE IN IRAN.* THE INDIAN JOURNAL OF PEDIATRICS, 2007. **74**(2): P. 127-130.
29. SIAVOSHI, F., ET AL., *INCREASE IN RESISTANCE RATES OF H. PYLORI ISOLATES TO METRONIDAZOLE AND TETRACYCLINE-COMPARISON OF THREE 3-YEAR STUDIES.* ARCH IRAN MED, 2010. **13**(3): P. 177-87.
30. MOHAMMADI, M., ET AL., *HELICOBACTER PYLORI ANTIBIOTIC RESISTANCE IN IRAN.* WORLD JOURNAL OF GASTROENTEROLOGY, 2005. **11**(38): P. 6009.
31. TOMATARI, F.H., ET AL., *HELICOBACTER PYLORI RESISTANCE TO METRONIDAZOLE AND CLARITHROMYCIN IN DYSPEPTIC PATIENTS IN IRAN.* IRANIAN RED CRESCENT MEDICAL JOURNAL, 2010. **12**(4): P. 409-412.
32. EYVAZI, *ANTIBIOTIC RESISTANCE OF H.PYLORI ISOLATES FROM DYSPEPTIC PATIENTS*, IN *BIOLOGY*2012, UNIVERSITY OF TEHRAN: UNIVERSITY COLLEGE OF SCIENCE.
33. FALSAFI, T., ET AL., *SUSCEPTIBILITIES TO DIFFERENT ANTIBIOTICS OF HELICOBACTER PYLORI STRAINS ISOLATED FROM PATIENTS AT THE PEDIATRIC MEDICAL CENTER OF TEHRAN, IRAN.* J CLIN MICROBIOL, 2004. **42**(1): P. 387-389.
34. SAYADI, S., ET AL., *STUDY OF ANTIBIOTIC RESISTANT H. PYLORI ISOLATED FROM IRANIAN PATIENTS DURING 2009-2010.* HEALTHMED, 2011. **5**.
35. MOHAMMED RIZWAN, N.F. AND A. ALVI, *EPIDEMIOLOGY AND PATTERN OF ANTIBIOTIC RESISTANCE IN HELICOBACTER PYLORI: SCENARIO FROM SAUDI ARABIA.* SAUDI JOURNAL OF GASTROENTEROLOGY: OFFICIAL JOURNAL OF THE SAUDI GASTROENTEROLOGY ASSOCIATION, 2014. **20**(4): P. 212.
36. RASHEED, F., ET AL., *ANALYSIS OF CLINICAL ISOLATES OF HELICOBACTER PYLORI IN PAKISTAN REVEALS HIGH DEGREES OF PATHOGENICITY AND HIGH FREQUENCIES OF ANTIBIOTIC RESISTANCE.* HELICOBACTER, 2014. **19**(5): P. 387-399.
37. JOHN ALBERT, M., ET AL., *HIGH PREVALENCE AND LEVEL OF RESISTANCE TO METRONIDAZOLE, BUT LACK OF RESISTANCE TO OTHER ANTIMICROBIALS IN HELICOBACTER PYLORI, ISOLATED FROM A MULTIRACIAL POPULATION IN*

KUWAIT. ALIMENTARY PHARMACOLOGY & THERAPEUTICS, 2006. **24**(9): P. 1359-1366.

38. OZBEY, G., B.I. HALIL, AND A.M. NURI, *PAPER: RESISTANCE RATES TO VARIOUS ANTIMICROBIAL AGENTS OF HELICOBACTER PYLORI ISOLATES IN EASTERN TURKEY.*
39. SHERIF, M., ET AL., *UNIVERSAL HIGH-LEVEL PRIMARY METRONIDAZOLE RESISTANCE IN HELICOBACTER PYLORI ISOLATED FROM CHILDREN IN EGYPT.* JOURNAL OF CLINICAL MICROBIOLOGY, 2004. **42**(10): P. 4832-4834.
40. WILLIAMS, O., *PHARMACY REVIEW: METRONIDAZOLE AND ADVERSE DRUG REACTIONS.* 2014.
41. MENDONÇA, S., ET AL., *PREVALENCE OF HELICOBACTER PYLORI RESISTANCE TO METRONIDAZOLE, CLARITHROMYCIN, AMOXICILLIN, TETRACYCLINE, AND FURAZOLIDONE IN BRAZIL.* HELICOBACTER, 2000. **5**(2): P. 79-83.
42. ABDOLLAHI, H., ET AL., *A STUDY OF RDXA GENE DELETION IN METRONIDAZOLE RESISTANT AND SENSITIVE HELICOBACTER PYLORI ISOLATES IN KERMAN, IRAN.* JUNDISHAPUR JOURNAL OF MICROBIOLOGY, 2012. **4**(2): P. 0-0.
43. KWON, D.H., ET AL., *FRAMESHIFT MUTATIONS IN RDXA AND METRONIDAZOLE RESISTANCE IN NORTH AMERICAN HELICOBACTER PYLORI ISOLATES.* JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, 2000. **46**(5): P. 793-796.
44. MIRZAEI, N., ET AL., *THE MUTATION OF THE RDXA GENE IN METRONIDAZOLE-RESISTANT HELICOBACTER PYLORI CLINICAL ISOLATES.* ADVANCED BIOMEDICAL RESEARCH, 2014. **3**.
45. BINA, J., ET AL., *HELICOBACTER PYLORI UPTAKE AND EFFLUX: BASIS FOR INTRINSIC SUSCEPTIBILITY TO ANTIBIOTICS IN VITRO.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2000. **44**(2): P. 248-254.
46. MEHRABADI, J.F., ET AL., *ASSESSING THE ROLE OF THE RND EFFLUX PUMP IN METRONIDAZOLE RESISTANCE OF HELICOBACTER PYLORI BY RT-PCR ASSAY.* THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES, 2010. **5**(02): P. 88-93.
47. ODERDA, G., ET AL., *EIGHTEEN MONTH FOLLOW UP OF HELICOBACTER PYLORI POSITIVE CHILDREN TREATED WITH AMOXYCILLIN AND TINIDAZOLE.* GUT, 1992. **33**(10): P. 1328-1330.
48. SIAVASHI, F., ET AL., *SUSCEPTIBILITY OF VARIOUS STRAINS OF HELICOBACTER PYLORI TO SELECTED AGENTS.* ARCHIVES OF IRANIAN MEDICINE, 2000. **3**(2): P. 0.
49. SHOKRZADEH, L., ET AL., *PREVALENCE OF MULTIPLE DRUG-RESISTANT HELICOBACTER PYLORI STRAINS AMONG PATIENTS WITH DIFFERENT GASTRIC DISORDERS IN IRAN.* MICROBIAL DRUG RESISTANCE, 2014.
50. PISCITELLI, S., L. DANZIGER, AND K. RODVOLD, *CLARITHROMYCIN AND AZITHROMYCIN: NEW MACROLIDE ANTIBIOTICS.* CLINICAL PHARMACY, 1992. **11**(2): P. 137-152.
51. KIM, K.S., ET AL., *MUTATIONS IN THE 23S RRNA GENE OF HELICOBACTER PYLORI ASSOCIATED WITH CLARITHROMYCIN RESISTANCE.* JOURNAL OF KOREAN MEDICAL SCIENCE, 2002. **17**(5): P. 599.
52. VALA, H., *FREQUENCY AND MOLECULAR MECHANISM OF H.PYLORI ISOLATES FROM IRANIAN PATIENTS BY E-TEST AND REAL TIME PCR*, 2013.
53. VERSALOVIC, J., ET AL., *MUTATIONS IN 23S RRNA ARE ASSOCIATED WITH CLARITHROMYCIN RESISTANCE IN HELICOBACTER PYLORI.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1996. **40**(2): P. 477-480.
54. KARGAR, M., ET AL., *CLARITHROMYCIN RESISTANCE AND 23S RRNA MUTATIONS IN HELICOBACTER PYLORI ISOLATES IN IRAN.* AFR J MICROBIOL RES, 2011. **5**(8): P. 853-856.
55. ABADI, A.T., ET AL., *HIGH FREQUENCY OF A2143G MUTATION IN CLARITHROMYCIN-RESISTANT HELICOBACTER PYLORI ISOLATES RECOVERED FROM DYSPEPTIC PATIENTS IN IRAN.* SAUDI JOURNAL OF GASTROENTEROLOGY: OFFICIAL JOURNAL OF THE SAUDI GASTROENTEROLOGY ASSOCIATION, 2011. **17**(6): P. 396.

56. KESHAVARZ AZIZI RAFTAR, S., ET AL., *THE HELICOBACTER PYLORI RESISTANCE RATE TO CLARITHROMYCIN IN IRAN.* MICROBIAL DRUG RESISTANCE, 2014.
57. KARGAR, M., ET AL., *REAL-TIME PCR FOR HELICOBACTER PYLORI QUANTIFICATION AND DETECTION OF CLARITHROMYCIN RESISTANCE IN GASTRIC TISSUE FROM PATIENTS WITH GASTROINTESTINAL DISORDERS.* RESEARCH IN MICROBIOLOGY, 2012. **163**(2): P. 109-113.
58. ABDOLLAHI, H., ET AL., *DETECTION OF A2142C, A2142G, AND A2143G MUTATIONS IN 23S RRNA GENE CONFERRING RESISTANCE TO CLARITHROMYCIN AMONG HELICOBACTER PYLORI ISOLATES IN KERMAN, IRAN.* IRANIAN JOURNAL OF MEDICAL SCIENCES, 2011. **36**(2): P. 104.
59. NASERPOUR FARIVAR, T., R. NAJAFIPOUR, AND P. JOHARI, *PREVALENCE OF CLARITHROMYCIN-RESISTANT HELICOBACTER PYLORI IN PATIENTS WITH CHRONIC TONSILLITIS BY ALLELE-SPECIFIC SCORPION REAL-TIME POLYMERASE CHAIN REACTION ASSAY.* THE LARYNGOSCOPE, 2013. **123**(6): P. 1478-1482.
60. KHADEMI, F., ET AL., *THE STUDY OF MUTATION IN 23S RRNA RESISTANCE GENE OF HELICOBACTER PYLORI TO CLARITHROMYCIN IN PATIENTS WITH GASTROINTESTINAL DISORDERS IN ISFAHAN—IRAN.* ADVANCED BIOMEDICAL RESEARCH, 2014. **3**.
61. LOO, V., P. SHERMAN, AND A. MATLOW, *HELICOBACTER PYLORI INFECTION IN A PEDIATRIC POPULATION: IN VITRO SUSCEPTIBILITIES TO OMEPRAZOLE AND EIGHT ANTIMICROBIAL AGENTS.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1992. **36**(5): P. 1133-1135.
62. HAAS, C., D. NIX, AND J. SCHENTAG, *IN VITRO SELECTION OF RESISTANT HELICOBACTER PYLORI.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1990. **34**(9): P. 1637-1641.
63. IVASHKIN, V.T., ET AL., *AZITHROMYCIN IN A TRIPLE THERAPY FOR H. PYLORI ERADICATION IN ACTIVE DUODENAL ULCER.* WORLD JOURNAL OF GASTROENTEROLOGY, 2002. **8**(5): P. 879-882.
64. LOGAN, R., ET AL., *ERADICATION OF HELICOBACTER PYLORI WITH CLARITHROMYCIN AND OMEPRAZOLE.* GUT, 1994. **35**(3): P. 323-326.
65. CHOPRA, I. AND M. ROBERTS, *TETRACYCLINE ANTIBIOTICS: MODE OF ACTION, APPLICATIONS, MOLECULAR BIOLOGY, AND EPIDEMIOLOGY OF BACTERIAL RESISTANCE.* MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS, 2001. **65**(2): P. 232-260.
66. GRAHAM, D., ET AL., *TWICE A DAY QUADRUPLE THERAPY (BISMUTH SUBSALICYLATE, TETRACYCLINE, METRONIDAZOLE PLUS LANSOPRAZOLE) FOR TREATMENT OF HELICOBACTER PYLORI INFECTION.* ALIMENT PHARMACOL THER, 1997. **11**(5): P. 935-938.
67. CHEY, W.D. AND B.C. WONG, *AMERICAN COLLEGE OF GASTROENTEROLOGY GUIDELINE ON THE MANAGEMENT OF HELICOBACTER PYLORI INFECTION.* THE AMERICAN JOURNAL OF GASTROENTEROLOGY, 2007. **102**(8): P. 1808-1825.
68. GERRITS, M.M., ET AL., *HELICOBACTER PYLORI AND ANTIMICROBIAL RESISTANCE: MOLECULAR MECHANISMS AND CLINICAL IMPLICATIONS.* THE LANCET INFECTIOUS DISEASES, 2006. **6**(11): P. 699-709.
69. WU, H., ET AL., *RESISTANCE OF HELICOBACTER PYLORI TO METRONIDAZOLE, TETRACYCLINE AND AMOXYCILLIN.* JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, 2000. **46**(1): P. 121-123.
70. VALLEJOS, C., ET AL., *[PREVALENCE OF METRONIDAZOLE, CLARITHROMYCIN AND TETRACYCLINE RESISTANCE IN HELICOBACTER PYLORI ISOLATED FROM CHILEAN PATIENTS].* REVISTA MEDICA DE CHILE, 2007. **135**(3): P. 287-293.
71. DADASHZADEH, K., ET AL., *REAL-TIME PCR DETECTION OF 16S RRNA NOVEL MUTATIONS ASSOCIATED WITH HELICOBACTER PYLORI TETRACYCLINE RESISTANCE IN IRAN.* ASIAN PACIFIC JOURNAL OF CANCER PREVENTION: APJCP, 2014. **15**(20): P. 8883.
72. ANOUSHIRAVANI, M., T. FALSAFI, AND V. NIKNAM, *PROTON MOTIVE FORCE-DEPENDENT EFFLUX OF TETRACYCLINE IN CLINICAL ISOLATES OF*

HELICOBACTER PYLORI. JOURNAL OF MEDICAL MICROBIOLOGY, 2009. **58**(10): P. 1309-1313.

73. KAUR, S.P., R. RAO, AND S. NANDA, *AMOXICILLIN: A BROAD SPECTRUM ANTIBIOTIC.* INTERNATIONAL J PHARM PHARM SCI [SERIAL ON THE INTERNET], 2011. **3**(3).
74. GERRITS, M., ET AL., *ALTERATIONS IN PENICILLIN-BINDING PROTEIN 1A CONFER RESISTANCE TO B-LACTAM ANTIBIOTICS IN HELICOBACTER PYLORI.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2002. **46**(7): P. 2229-2233.
75. SALEHI, T.Z. AND S.F. BONAB, *ANTIBIOTICS SUSCEPTIBILITY PATTERN OF ESCHERICHIA COLI STRAINS ISOLATED FROM CHICKENS WITH COLISEPTICEMIA IN TABRIZ PROVINCE, IRAN.* INTERNATIONAL JOURNAL OF POULTRY SCIENCE, 2006. **5**(7): P. 677-684.
76. BAYATMAKOO, Z. AND R. BAYATMAKOO, *A STUDY MULTI-DRUG RESISTANT OF SALMONELLA TYPHI STRAINS TABRIZ.* JOURNAL OF ARDABIL UNIVERSITY OF MEDICAL SCIENCES, 2004. **4**(1): P. 12-17.
77. VARSHOCHI, M., ET AL., *IN–VITRO SUSCEPTIBILITY OF MYCOBACTERIUM TUBERCULOSIS TO AMOXICILLIN–CLAVULANATE.* ARCHIVES OF CLINICAL INFECTIOUS DISEASES, 2006. **1**(3).
78. LANGARIZADEH, N., ET AL., *PREVALENCE OF MULTI-DRUG RESISTANT (MDR) KLEBSIELLA PNEUMONIAE AMONG CHILDREN AND ADULTS WITH URINARY TRACT INFECTION REFERRED TO TABRIZ TEACHING HOSPITALS.* THE QUARTERLY JOURNAL OF BIOLOGICAL SCIENCES, 2011. **1**: P. 12.
79. VASS, M., K. HRUSKA, AND M. FRANEK, *NITROFURAN ANTIBIOTICS: A REVIEW ON THE APPLICATION, PROHIBITION AND RESIDUAL ANALYSIS.* VETERINARNI MEDICINA, 2008. **53**(9): P. 469-500.
80. MAEV, I., ET AL., *MOLECULAR MECHANISMS OF HELICOBACTER PYLORI ANTIBIOTIC RESISTANCE.* EDITORIAL ADVISORY BOARD: P. 27.
81. ZULLO, A., ET AL., *FURAZOLIDONE-BASED THERAPIES FOR HELICOBACTER PYLORI INFECTION: A POOLED-DATA ANALYSIS.* SAUDI JOURNAL OF GASTROENTEROLOGY: OFFICIAL JOURNAL OF THE SAUDI GASTROENTEROLOGY ASSOCIATION, 2012. **18**(1): P. 11.
82. KING, D.E., R. MALONE, AND S.H. LILLEY, *NEW CLASSIFICATION AND UPDATE ON THE QUINOLONE ANTIBIOTICS.* AMERICAN FAMILY PHYSICIAN, 2000. **61**(9): P. 2741-2748.
83. DE SOUZA, M.V., *NEW FLUOROQUINOLONES: A CLASS OF POTENT ANTIBIOTICS.* MINI REVIEWS IN MEDICINAL CHEMISTRY, 2005. **5**(11): P. 1009-1017.
84. SPRANDEL, K.A. AND K.A. ROCIVOLD, *SAFETY AND TOLERABILITY OF FLUOROQUINOLONES.* CLINICAL CORNERSTONE, 2003. **5**: P. S29-S36.
85. KIM, J.M., ET AL., *DISTRIBUTION OF FLUOROQUINOLONE MICS IN HELICOBACTER PYLORI STRAINS FROM KOREAN PATIENTS.* JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, 2005. **56**(5): P. 965-967.
86. WATANABE, Y., ET AL., *LEVOFLOXACIN BASED TRIPLE THERAPY AS A SECOND-LINE TREATMENT AFTER FAILURE OF HELICOBACTER PYLORI ERADICATION WITH STANDARD TRIPLE THERAPY.* DIGESTIVE AND LIVER DISEASE, 2003. **35**(10): P. 711-715.
87. GISBERT, J. AND F. MORENA, *SYSTEMATIC REVIEW AND META-ANALYSIS: LEVOFLOXACIN-BASED RESCUE REGIMENS AFTER HELICOBACTER PYLORI TREATMENT FAILURE.* ALIMENT PHARMACOL THER, 2006. **23**(1): P. 35-44.
88. MATSUZAKI, J., ET AL., *EFFICACY OF SITAFLOXACIN-BASED RESCUE THERAPY FOR HELICOBACTER PYLORI AFTER FAILURES OF FIRST-AND SECOND-LINE THERAPIES.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2012. **56**(3): P. 1643-1645.
89. MOORE, R.A., ET AL., *NUCLEOTIDE SEQUENCE OF THE GYRA GENE AND CHARACTERIZATION OF CIPROFLOXACIN-RESISTANT MUTANTS OF HELICOBACTER PYLORI.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1995. **39**(1): P. 107-111.

90. BARLUENGA, J., ET AL., *NEW RIFABUTIN ANALOGS: SYNTHESIS AND BIOLOGICAL ACTIVITY AGAINST MYCOBACTERIUM TUBERCULOSIS.* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, 2006. **16**(22): P. 5717-5722.
91. PILOTTO, A., ET AL., *IN VITRO ACTIVITY OF RIFABUTIN AGAINST STRAINS OF HELICOBACTER PYLORI RESISTANT TO METRONIDAZOLE AND CLARITHROMYCIN.* THE AMERICAN JOURNAL OF GASTROENTEROLOGY, 2000. **95**(3): P. 833-834.
92. HEEP, M., ET AL., *RIFAMPIN AND RIFABUTIN RESISTANCE MECHANISM INHELICOBACTER PYLORI.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1999. **43**(6): P. 1497-1499.
93. PERRI, F., ET AL., *RIFABUTIN-BASED'RESCUE THERAPY'FOR HELICOBACTER PYLORI INFECTED PATIENTS AFTER FAILURE OF STANDARD REGIMENS.* ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, 2000. **14**(3): P. 311-316.
94. GLOCKER, E., C. BOGDAN, AND M. KIST, *CHARACTERIZATION OF RIFAMPICIN-RESISTANT CLINICAL HELICOBACTER PYLORI ISOLATES FROM GERMANY.* JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, 2007. **59**(5): P. 874-879.
95. NISHIZAWA, T., ET AL., *HELICOBACTER PYLORI RESISTANCE TO RIFABUTIN IN THE LAST 7 YEARS.* ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2011. **55**(11): P. 5374-5375.
96. PETRI, W., *CHEMOTHERAPY OF TUBERCULOSIS, MYCOBACTERIUM AVIUM COMPLEX DISEASE, AND LEPROSY.* GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. NEW YORK: MC GRAW-HILL, 2006: P. 1203-24.
97. ABDINIA, B., M.A. REZAEE, AND S.A. OSKOUIE, *ETIOLOGY AND ANTIMICROBIAL RESISTANCE PATTERNS OF ACUTE BACTERIAL MENINGITIS IN CHILDREN: A 10-YEAR REFERRAL HOSPITAL-BASED STUDY IN NORTHWEST IRAN.* IRANIAN RED CRESCENT MEDICAL JOURNAL, 2014. **16**(7).