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A review on Helicobacter Pylori and its antibiotic resistance

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Abstract
Helicobacter Pylori (H. Pylori) has infected about 50% of the world population. The annual incidence of Helicobacter pylori infection is significant: 4-15% and 0.5% in the developing and developed countries, respectively. This study is thus aimed to review H. pylori and its relationship with antibiotic resistance.
Research Methods:
In this research, Google Scholar, Embase, (SID), ISI Scopus, and Pubmed research databases were fully explored to obtain different articles in this field. Here, 48 articles conducted in Iran and foreign countries from 1995 to 2018 were reviewed; among which, 35 papers were investigated while the rest were excluded. This research is aimed to survey the antibiotic resistance of H. pylori.
Results:
Studies have revealed quit high levels of resistance to metronidazole and clarithromycin (two well-known therapeutic antibiotics). Moreover, different studies reported different antibiotic susceptibility of H. pylori which can be assigned to various factors such as improper choice of antibiotics, excessive use of antibiotics, lack of sufficient care on the duration of treatment, inability of all laboratories to culture this bacterium and its subsequent antibiogram testing and most importantly non-compliance with standard conditions, especially in different stages of antibiogram testing. Given the various statistics on antibiotic resistance, it is necessary to perform antibiotic tests to provide better treatment for the patients.

Keywords: infection, antibiotic resistance, Helicobacter Pylori

1. INTRODUCTION

Helicobacter pylori (H. Pylori) is an S-shaped helical bacterium or curved bacillus aerobic (microaerophilic) gram-negative and spore-less bacterium with the length of 3.5 µm and width of 0.5 µm. Due to having single or multiple, single-pole, or dipole or peripheral flagella, they are highly mobile. Hydrogen stimulates their growth and some species need that to grow. It does not hydrolyze sucrose and is oxidase and catalase-positive. However, H.canis is an exception as it is catalase-negative [8]. Upon 1-2 h exposure to air at ambient temperature, H. pylori becomes cocci-shaped under such condition, the microorganism cannot be subculture. This means that the bacterium does not grow if it is transferred to a new culture medium. H. pylori fails to grow at 25 ° C. H. pylori can be classified into two groups: one is those forming colonies in the gastric mucosa of humans and animals and the other group includes those that colonize in the intestine. Gastric species produce high amounts of urease. H. pylori plays a pivotal role in the pathogenicity of peptic ulcer and gastric cancer. H. pylori has slow growth in the laboratory and, like Campylobacter, it is microaerophilic and requires 0.2 and high moisture for growth. It can be cultured in specific blood gel culture media at 37 ^{0} C and 5% oxygen pressure of 5% within 3-7 days. Under a high-magnification microscope, up to 7 flagella can be observed in each bacterium, which are used to move the bacterium in jelly environments (surface of gastric mucosa). Coxy-shaped (circular) bacteria are sometimes observed in culture media, which are probably an adapted and resistant form of the bacterium which is formed during its life outside the body, such as water and feces. In general, this bacterium is catalase-positive, oxidase-positive, and urease-positive, and the presence of urease in the bacterium plays an essential role in its survival [9-10].

H. Pylori history

The presence of bacterial factors in the stomach was detected 100 years ago. But its association with gastritis (inflammation of the gastric mucus) was recognized in 1970. An Italian scientist, Bizozor, is among the first people finding a mysterious bacterium in the stomach. In 193, he (as a pathologist and anatomist) observed this bacterium in the gastric mucus of human and dog and named it Spirilli. an Irish scholar, Fitz Gerald, in 1924, realized that urease should be present in the mammalian stomach is high quantities. This enzyme will result in the release of high volumes of ammonia in the gastric acid with concentrations 50-100 times higher than the blood. It will then go to the liver at high concentrations through the venous port. The ammonia concentration of the blood is directly related to its content in gastric acid [11]. After studies, he concluded that the ammonia in the gastric acid should have a bacterial origin. In 1958, a physician in Athens accidentally used antibiotics due to having a frequent gastric ulcer-induced hemorrhage. He then observed that all the problems due to gastric ulcer completely vanished. He pursued this treatment in several patients with gastric and peptic ulcers and observed improvements. The outcomes of this treatment method were so promising that he decided to treat all the peptic and gastric ulcer patients with antibiotics. In 1921, Adkins (gastrin discoverer in 1905) described the physiology of H. Felis in cats. In 1938, Dongs reported a relationship between spirochete and gastric inflammation in macaques monkeys. In 1940, Fridberg and Baron emphasized the non-ethologic role of these microorganisms in human digestive system diseases. in 1904, Gorham was the first one hypothesizing that an acidophil bacterium is involved in gastric ulcer. In 1979, Varen identified campylobacter pylori as the main cause of gastritis in humans [4-5]. Today, this bacterium is recognized as

the etiologic cause of chronic gastritis, most of the peptic ulcers, adenocarcinoma, and gastric lymphoma. The diseases due to peptic acid are treated as an infectious disease. Although no ideal treatment capable of 100% eradication of the infection has not been found and the compounds needed for the treatment are under progress, significant advancements have been made in the pathogenicity of this disease and its treatment [12-15].

Helicobacter species

Upon the discovery of H. pylori, researchers started to investigate the presence of this organism in other animals which resulted in the detection of the other species of this bacterium which have not been identified so far. Various species of helicobacter isolated from the animals and rarely from humans are listed in Table 1.

Table 1: Helicobacter species

Helicobacter species			
Site	Urease activity	Host	Species
Stomach	+	Human, monkey, cat	H. pylori
Stomach	+	Macaque	H.nemestrinace
Stomach	+	Cheetah	H.acinonyx
Stomach	+	Human and other mammalians	H.heilmannii
Stomach	+	Dog and cat	H.fleis
Stomach	+	Ferret	H.mustelae
Stomach and intestine	+	Human and other mammalians	H.rappini
Stomach and intestine	+	Rat and mouse	H.muridarum
Liver	+	Mouse	H.hepaticus
Intestine	-	Dog	H.canis
Intestine	-	Human	H.fennelliac
Intestine	-	Human	H.cinaedi

Pathogenicity

Helicobacter genome (DNA) is a circular single-molecule and depending on the bacterial strain ranges from 1.4 to 1.73 MB (mean of 1.7). It codes about 1500 protein. aDNA plasmid is seen in about 45% of the bacterium strains. The genome diversity of H.pylori is extraordinarily higher than the other bacteria. The reason for such diversity is not clear, but it has been suggested that the strain may rearrange its genome upon infecting a new host. The silent mutation could be the mechanism enabling H. pylori to survive under harsh conditions for a long time [19].

Laboratory detection

Clinically, H. pylori infection identification requires a precise, cost-effective, and accessible test. H. pylori detections can be classified into invasive (direct) and non-invasive (indirect) methods. The former includes methods requiring sampling (biopsy) from the gastric or peptic ulcer or the intestine; while the latter involves urease respiration tests, serologic tests, or bacterium antigen detection in feces [20-22].

Virulence factors and mechanism

After the settlement in the stomach, H. pylori is protected through various factors and products, starts to proliferate and affect the host. Some of these factors are presented in Table 2 [23].

Table 2: Factors and Activity

Factor	Activity
Spiral shape	Providing the possibility to move in the mucus
Flagella	Strong movement in the mucus
Adhesive molecules mediating the attachment to phosphatidylethanolamine, Ganglioside, GM, and B Lewis antigen	Attachment to surficial receptors, selective colonization of the stomach, and mucus-secreting epithelial cells
Urease enzyme	Survival in the stomach, neutralizing the destroying acids of the gastric mucus
Catalase	Resistance against macrophages oxidative killing
Oxidase	Protection against H_2O_2
Phospholipase	Digestion of the epithelial cells and increasing the water content of the mucus
Protease	Digestion of the epithelial cells and increasing the solubility of the mucus
Neutrophil monocyte chemotactic factors	Adsorption of monocytes and neutrophils
Cytotoxin	Intracytoplasmic vacuolation and cell damage
CagA protein	Along with cytotoxicity
Gastric acid-inhibiting protein	Unknown
Heat shock protein	Unknown

2. TREATMENT

Proper treatment of peptic ulcers requires some information on the H. pylori infection status. The patients will be treated for H. pylori only when their relevant tests are positive. Eradication of H. pylori by

antimicrobial compounds is not an easy task as these compounds should have various properties including fast solubility, proper distribution in the stomach (and peptic ulcers in some cases), suitable size and charge to penetrate the mucus, absorption of the mucus-secreted materials, proper activity against the bacterium such as cocides. Moreover, the local and systemic side effects should be minimal. Intrinsic and acquired resistance of H. pylori against antimicrobial compounds is an important factor that can affect the treatment efficacy. The bacterium may also remain beneath or inside the mucus, gastric glands, and inter-cellular space as well as the peptic mucus providing the condition for recurrence after the treatment [24]. Clinical trials to eradicate H. pylori infections through various regimens have shown that the combinational regimens are more effective compared to single-drug medications, moreover, resistance can be inhibited in combination treatments, hence avoiding the recurrence after the end of the treatment. following drugs have been so far used to treat H. pylori infections:

1- Amoxicillin: H. pylori is susceptible to this drug and has not shown any resistance to that. The presence of this drug in the gastric secretions has shown desirable results. its intravenous injection is also effective.
2- Tetracycline: it is effective on helicobacter and is also active in acidic media. No resistance has been observed.
3- Metronidazole: one of the major drugs in H. pylori treatment (especially in three-drug regimens), it is secreted through saliva and stomach. Some resistances have been observed.
4- Bismuth: Bismuth subsalicylate destroys the microbe wall and prevents its adhesion to the gastric wall. This drug also inhibits phospholipase, protease, and urease enzymes.
5- Clarithromycin: It is among the macrolide antibiotics and prevents the bacterium proliferation. This drug is similar to azithromycin but is more stable in acidic media, some resistances have been observed.
6- Omeprazole: by inhibiting enzyme, it severely inhibits acid secretion in parietal cells. Thus by increasing the gastric pH it will intensify the effects of the antibiotic. This drug is also directly effective on helicobacter [25-26].

Resistance to antibiotics:

The development of drugs capable of preventing or treating microbial infections is one of the major advances in improving the quality of life in recent years. Antimicrobial drugs are among the high-consumption drugs. They can survive the patient if used correctly, but their improper application can enhance the costs and complications promote drug interference and drug resistance, and thus decline the value of these valuable drugs. The rational application of antimicrobial drugs requires a proper understanding of the pharmacokinetics, complications, interferences, and some approaches to decline drug resistance and increase the microbe susceptibility. Drug resistance is a phenomenon that has attracted the attention of scientists and academic communities [1]. Several years ago, a scientist has predicted that regarding the fast development of drug resistance, all the antibiotics will lose their effectiveness in several decades. This means that the human will return to the pre-penicillin era! It seems that the predictions are coming to the truth as new reports on antibiotic resistance are publishing now and then. Although antibiotics have saved the lives of numerous humans and animals, many of these incredible drugs reached the end of the line as the pathogenic bacteria now learn how to resist them [2]. Antibiotic resistance refers to the bacteria's ability to resist antibiotics through various mechanisms. Some other bacteria can neutralize antibiotics before their effect is exerted. Some other out-pump antibiotics thus the drug can’t affect the bacterial performance. Treatment of the food-producing animals with antibiotics use for a human can endanger public health and decline the effect of the antibiotic by transferring resistance zoonotic pathogenic factors or resistant genes from animals to the human. This may increase the demand for substitution drugs at a higher price and lower risk. A study on poultry slaughterhouse has reported 94.8% antibiotic residual in chicken organs [1, 3].

Resistance mechanisms

Some bacteria are intrinsically resistant to a specific group of antibacterial drugs (for instance, obligatory anaerobic bacteria to aminoglycosides and gram-negative bacteria relative to vancomycin). Therefore, these drugs, alone, can’t be used in the treatment of resistant bacteria. Moreover, drugs susceptible to antibacterial drugs can also acquire resistance [4]. Acquired resistance is one of the main limitations of effective antibacterial chemotherapy. Resistance is developed by gene mutation or acquiring a new gene. The new resistance-inducing genes are often propagated cell by cell by genetic elements such as a plasmid, transposon, and bacteriophage. The population of resistant bacteria selectively grows in places where antimicrobial drugs are consumed at high amounts. The major methods of developing resistance against antimicrobial drugs are as follows: 1- drug inactivation, 2- changing or over-production of the drug target by gene mutation protein, 3- acquiring a new gene producing unsusceptible target, 4- declined permeability of the cell coverage toward the drug, and 5- active removal of the drug from periplasm or inside the cell [1].

Origin of the drug resistance

The origin of the drug resistance can be genetic or non-genetic

Non-genetic origins of drug resistance

Active transcription of the bacteria is needed for the performance of most of the antimicrobial drugs. Therefore, the metabolically inactive microorganisms may be phenotypically resistant to the drugs. The new cells from them are, however, completely susceptible. For instance, mycobacteria often remain in the tissues several days after the infection and are stopped by the host defense system and will be no more proliferated. These remaining organisms are resistant to the treatment

and can't be eradicated by the drugs. Now, if these organisms start to proliferate (for instance upon inhibiting the cell immunity) they will be susceptible to these drugs [4]. After several generations, microorganisms may lose the drug-specific target structure and get resistant. For instance, the penicillin-susceptible organism may transform to L shape (which has no wall), due to lacking the wall, they are resistant to cell wall-inhibitory agents (penicillin, Cephalosporins) and may remain in this state for several generations. When these organisms retain their parent major shape and produce cell walls, they will become penicillin-susceptible again [1, 4].

Genetic origin of the drug resistance

The majority of drug-resistant microbes are formed due to genetic alternations and selection by antimicrobial drugs [1].

Chromosomal resistance

This resistance occurs as the result of a spontaneous mutation in a locus (gene site) which is responsible for the susceptibility to an antimicrobial drug. The presence of the antimicrobial drug weakens the susceptible organisms in a selective mechanism and enhances the growth of the resistant mutated bacteria. The spontaneous mutation occurs at the probability of 10-7 to 10-12. Thus it is an uncommon reason for clinical resistance to the drug in a patient. However, resistance to Rifampin due to chromosomal mutation occurs at high probabilities (about 10-5 to 10-7). Therefore, the treatment of bacterial infections single-use of Rifampin will often fail. Bacteria with chromosomal mutation mostly develop resistance due to changes in the structure of drug-receptor. Thus, p12 protein will work on 30s component of the bacterial ribosome such as the receptor for attachment of azithromycin. A mutation in the gene responsible for controlling this constructional protein will end in azithromycin resistance. The mutation may result in a lack of penicillin-binding proteins (PBPs). Such bacteria are resistant to *β-lactam [1-5]*.

Extrachromosomal resistance

Most bacteria have genetic elements beyond the chromosome which are called a plasmid.

Some plasmids carry resistance genes to one or several antimicrobial drugs. These plasmid genes often produce enzymes which control the destruction of the antimicrobial drugs. Therefore, plasmids determine resistance to penicillin and Cephalosporins through carrying β-lactamase producing genes. Plasmids encode the following enzymes: Chloramphenicol-degrading enzymes (acetyltransferase), acetylating, adenylating, and phosphorylating enzymes of various aminoglycosides and enzymes determining active transfer of tetracycline, …

Genetic substances and plasmids can be transferred through the following mechanisms: transduction, transformation, and conjugation [6].

Cross-resistance

Microorganisms that are resistant to a specific drug may be resistant to other drugs with similar mechanisms of action. It is often observed in the drugs which are chemically similar to each other (such as various aminoglycosides) or the drugs with similar binding or action (such as macrolides and lincomycin). In some classes of the drugs, the active chemical core may be similar in several members of that class (such as tetracycline) which may result in extensive cross-resistance [1, 7].

3. RESULTS AND DISCUSSION

This bacterium has infected about 50% of the world population. Based on statistics, the annual incidence of H. pylori is 4-15% and 5% in the developing and developed countries, respectively. H. pylori infection can be detected by several methods such as culturing, urease test, and histological tests. In most of the studies, H. pylori was cultured in a Colombia agar medium enriched with 10% horse blood and specified by Vancomycin, trimethoprim, cefazolin, amphotericin B under the microaerophilic condition at 37 ℃ for 3 to 5 days. after H. pylori growth and confirmation by morphological investigations, catalase oxidase and urease tests, antibiogram tests (by disc diffusion, Etest on Muller Hinton agar containing 10% horse blood or agar dilution, based on well-known CLSI standards) will be conducted [27]. The reason for the decrease of H. pylori infection in developed countries is the social and economic enhancement of lifestyle and augmented personal hygiene. The stability of this infection is under several factors such as blood type of ABO, Lewis blood antigen, and the difference in susceptibility to specific strains of this bacterium [28, 32].

In summary of the studies conducted in Iran, resistance to Metronidazole was very high (57.4%) which is in line with the results obtained from other Asian countries (46.6%). Such consistency can be assigned to the regional distribution of the infection. The mean resistance in Iran is lower than the African countries (97.55%). In comparison with Metronidazole-resistance in Europe and America continents (34.9, and 3.3%, respectively), Iran possesses high resistance which highlights the need for revising the use of antibiotics as the first-line treatment of H. pylori. In this study, the resistance to Clarithromycin was 17% in Iran, which is lower than the other Asian countries (24%). Compared to the European countries (25.1) Iran possesses relatively lower resistance against Clarithromycin. These statistics are however controversial due to a few studies conducted on this field. Basically, resistance to Clarithromycin may differ depending on its use in therapeutic regimes of the patients in different regions. Compared to the other Asian countries, resistance to tetracycline, and amoxicillin is lower; but the resistance to Metronidazole, clarithromycin, rifamycin is significantly higher. This requires substituting new drugs.

4. CONSLUSION

Regarding the high infection with H. pylori in various communities and its severe complications, the detection of the bacterium is of high importance. H. pylori is a common infection throughout the world with strong variants and the antibiotic resistance is rapidly

developing in this bacterium. Different results have been observed in terms of antibiotic susceptibility oo H. pylori which can be due to various reasons such as improper choice of antibiotics, over-application of antibiotics, lack of care in the duration of treatment, the inability of the laboratories to culture this bacterium and hence its antibiogram test, and more importantly, non-compliance with the standard conditions especially in different stages of antibiogram tests. Studies have shown relatively high levels of resistance to Metronidazole, and clarithromycin which are well-known antibiotics. Regarding various statistics on antibiotic resistance, antibiotics tests are highly necessary to improve the treatment of the patients.

5. REFFERENCES

1) Milani M, Ghotaslou R, Akhi MT, Nahaei MR, Hasani A, Somi MH, et al. The status of antimicrobial resistance of Helicobacter pylori in Eastern Azerbaijan, Iran: comparative study according to demographics. J Infect Chemother 2012; 18:848-52.
2) Antonakis N, Xylouri I, Alexandrakis M, Cavoura C, Lionis C. Seeking prescribing pattern in rural Crete: a pharmacy epidemiological study from a primary care area. Int. Electron. J Rural Remote Health 2006; 6 (488): 1-10.
3) Jahangiri Gh. [MSc thesis]. Estimation of drug demand function in Iran. Tehran: Tehran University; 2001:78-79.
4) Gold BD, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E, et al. Helicobacter pylori infection in children: recommendations for diagnosis and treatment. J Pediatr Gastroenterol Nutr 2000; 31:490-7.
5) Fallone CA, Bitton A. Is IBD caused by a Helicobacter pylori infection? Inflamm Bowel Dis 2008; 14:S37-8.
6) Marandi A. Health in the Islamic Republic of Iran. Medical Education 1997; 30: 370-5. (in Persian).
7) World Health Organization. Policy perspectives on medicines; promoting rational use for medicine: core components. Geneva: 2002:1-6.
8) Moriai T, Hirahara N. Clinical course of acute gastric mucosal lesions caused by acute infection with Helicobacter pylori. N Engl J Med 1999; 341:456-7.
9) Picoli SU, Mazzoleni LE, Fernandez H, De Bona LR, Neuhauss E, Longo L, et al. Resistance to amoxicillin, clarithromycin and ciprofloxacin of Helicobacter pylori isolated from Southern Brazil patients. Rev Inst Med Trop Sao Paulo 2014; 56:197-200.
10) Shokrzadeh L, Jafari F, Dabiri H, Baghaei K, Zojaji H, Alizadeh AH, et al. Antibiotic susceptibility profile of Helicobacter pylori isolated from the dyspepsia patients in Tehran, Iran. Saudi J Gastroenterol 2011; 17:261-4.
11) Montecucco, C., and Rappuoli, R. Living dangerously: how *Heli-cobacter pylori* survives in the human stomach. *Nat. Rev. Mol. Cell Biol*. 2001; 2:457-466.
12) Achtman, M., and Suerbaum, S. *Helicobacter pylori: molecular and cel lular biology*. Horizon Scientific Press. Wymondham, United Kingdom. 2001.
13) Marshall, B.J., Barrett, L.J., Prakash, C., McCallum, R.W., and Guerrant, R.L.Urea protects *Helicobacter* (*Campylobacter*) *pylori* from the bac-tericidal effect of acid. *Gastroenterology.* 1990; 99:697-702.
14) Bauerfeind, P., Garner, R., Dunn, B.E., and Mobley, L.T. Synthesis and activity of *Helicobacter pylori* urease and catalase at low pH. *Gut.* 1997; 40:25-30.
15) Scott, D.R., et al. The role of internal urease in acid resistance of *Helicobacter pylori*. *Gastroenterology*. 1998;114:58-67.
16) Stingl, K., et al. Prolonged survival and cytoplasmic pH home-ostasis of *Helicobacter pylori* at pH 1. *Infect. Immun.* 2000; 69:1178-1181.
17) Kusters, J. G., VanVlient, A. H. M. and Kuipers, E. Pathogenesis of Helicobacter pylori infection. Clinical Microbiology reviews. 2006; 19 (3); 449-490.
18) Khashei R, Shojaei H, Adibi P, Shavakhi A, Aslani MM, Daei Naser A. Genetic diversity and drug resistance of Helicobacter pylori strains in Isfahan, Iran. Iran J Basic Med Sci 2008; 11:174-82.
19) Mirzaei N, Poursina F, Faghri J, Talebi M, Khataminezhad MR, Hasanzadeh A, et al. Prevalence of resistance of Helicobacter pylori strains to selected antibiotics in Isfahan, Iran. Jundishapur J Microbiol 2013; 6:5.
20) Kohanteb J, Bazargani A, Saberi-Firoozi M, Mobasser A. Antimicrobial susceptibility testing of Helicobacter pylori to selected agents by agar dilution method in Shiraz-Iran. Indian J Med Microbiol 2007; 25:374-7.
21) Farshad S, Alborzi A, Japoni A, Ranjbar R, Hosseini Asl K, Badiee P, et al. Antimicrobial susceptibility of Helicobacter pylori strains isolated from patients in Shiraz, Southern Iran. World J Gastroenterol 2010; 16:5746-51.
22) Abadi AT, Taghvaei T, Mobarez AM, Carpenter BM, Merrell DS. Frequency of antibiotic resistance in Helicobacter pylori strains isolated from the northern population of Iran. J Microbiol 2011; 49:987-93.
23) Qiao, W., Hu, J., Xiao, B., Wu, K., Peng, D., Atherton, J. and Xue, H. CagA and VacA genotypes of Helicobacter pylori associated with gastric diseases inXian area. World journal of gastroenterology. 2003;9(8): 1762-1766.
24) Selbach, M., Moese, S., Hurwitz, R., Hauck, C.R., Meyer, T.F. and Backert, S. The Helicobacter pylori CagA protein induces cortactin dephosphorylation and actin rearrangement by c-Src inactivation. Embo J. 2018; 22: 515–28.
25) Siavoshi, F., Malekzadeh. R, Daneshmand, M. and Ashktorab, H. Helicobacter pylori endemic and gastric disease. Digestive Diseases and Sciences. 2005; 50:11, 2075–2080.

26) Smith, S., Kirsch, C., Oyedeji, K., Arigbabu, A., Coker, A., Bayerdoffer, E. and Miehlke, S. Prevalence of Helicobacter pylori VacA, CagA and iceA genotypes in Nigerian patients with duodenal ulcer disease. 2002; Medical microbiology.35: 851-854.
27) Milani M, Ghotaslou R, Akhi MT, Nahaei MR, Hasani A, Somi MH, et al. The status of antimicrobial resistance of Helicobacter pylori in Eastern Azerbaijan, Iran: comparative study according to demographics. J Infect Chemother 2012; 18:848-52.
28) Pajavand H, Alvandi A, Mohajeri P, Bakhtyari S, Bashiri H, Kalali B, et al. High frequency of vacA s1m2 genotypes among helicobacter pylori isolates from patients with gastroduodenal disorders in Kermanshah, Iran. Jundishapur J Microbiol 2015; 8:e25425.
29) Zendedel A, Moradimoghadam F, Almasi V, Zivarifar H. Antibiotic resistance of Helicobacter pylori in Mashhad, Iran. J Pak Med Assoc 2013; 63:336-9
30) Khademi F, Faghri J, Poursina F, Esfahani BN, Moghim S, Fazeli H, et al. Resistance pattern of Helicobacter pylori strains to clarithromycin, metronidazole, and amoxicillin in Isfahan, Iran. J Res Med Sci 2013; 18:1056-60.
31) Mégraud F. Antibiotic resistance in Helicobacter pylori infection. Br Med Bull 1998; 54:207-16.
32) Falsafi T, Mobasheri F, Nariman F, Najafi M. Susceptibilities to different antibiotics of Helicobacter pylori strains isolated from patients at the pediatric medical center of Tehran, Iran. J Clin Microbiol 2004; 42:387-9.
33) Seo JH, Jun JS, Yeom JS, Park JS, Youn HS, Ko GH, et al. Changing pattern of antibiotic resistance of Helicobacter pylori in children during 20 years in Jinju, South Korea. Pediatr Int 2013; 55:332-6.
34) Wu IT, Chuah SK, Lee CH, Liang CM, Lu LS, Kuo YH, et al. Five-year sequential changes in secondary antibiotic resistance of Helicobacter pylori in Taiwan. World J Gastroenterol 2015; 21(37):10669-74.