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SYSTEMATIC REVIEWS

Prevalence of antibiotic resistance in *Helicobacter pylori*: A recent literature review

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Abstract

AIM: To review previous studies (the last 6 years) about the *Helicobacter pylori* (*H. pylori*) antibiotic resistance in order to evaluate the trend in antibiotic resistance.

METHODS: In this study, the PubMed, MEDLINE, Science Direct, Google Scholar and Scielo manuscripts were reviewed from 2009 to 2014.

RESULTS: On the whole rates of *H. pylori* antibiotic resistance were 47.22% (30.5%-75.02%) for metronidazole, 19.74% (5.46%-30.8%) for clarithromycin, 18.94% (14.19%-25.28%) for levofloxacin, and 14.67% (2%-40.87%) for amoxicillin, 11.70% (0%-50%) for tetracycline, 11.5% (0%-23%) for furazolidon and 6.75% (1%-12.45%) for rifabutin. The frequency of tetracycline, metronidazole and amoxicillin resistance was higher in Africa, while clarithromycin and levofloxacin resistance was higher in North America and Asian, respectively.

CONCLUSION: The most sensitive drug is rifabutin and the lowest sensitive drug is metronidazole in the world. The worldwide *H. pylori* antibiotic resistance to clarithromycin and levofloxacin has increased during the last 6 years. The present systematic review show alarming results and a novel plan is needed for eradication therapy of *H. pylori* infections.

Key words: Antibiotic resistance; *Helicobacter pylori*; Worldwide

Core tip: Because of the rising frequency of antimicrobial resistance, management of *Helicobacter pylori* (*H. pylori*) infections is a challenge for physicians. We found global frequency rate of resistance is high in Africa. The

most sensitive drug is rifabutin and the lowest sensitive drug is metronidazole in the world. The worldwide *H. pylori* antibiotic resistance to clarithromycin and levofloxacin has increased during the last 6 years. Resistances to antimicrobial agent's reports describe dramatic decrease of antibiotics efficacy.

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INTRODUCTION

Helicobacter pylori (H. pylori) is a motile, curved and Gram negative bacillus[1]. *H. pylori* certainly is the most prevalent human infection, the frequency of infection due to *H. pylori* is nearly 50% in the world and in developing country is as high as 80%-90%[2]. This bacterium colonizes the stomach of human and its infection is correlated with gastritis, peptic ulcer disease and extra-digestive diseases[3,4]. *H. pylori* is also considered as a human carcinogen[5]. Since, *H. pylori* eradication therapy represents a key clinical essential. Unfortunately, therapy against *H. pylori* has turned out to be more difficult over the years, principally due to the great decrease of standard eradication therapies efficacy.

Although *H. pylori* is sensitive to many antibiotics *in vitro*, just a few antibiotics can be used *in vivo* to treat infected patients. Management of *H. pylori* infections are recommended in all suggestive individuals[6]. According to the latest Maastricht Guidelines, in regions of low clarithromycin resistance, clarithromycin-containing treatments are recommended for first-line empirical treatment[7]. In regions of high resistance to clarithromycin, the quadruple treatment including bismuth has been proposed as first-line treatment. In case of unavailability of this therapy, non-bismuth (three antibiotics plus Proton pump inhibitors) quadruple therapy and the so-called "sequential therapy" (that includes five days of PPIs plus amoxicillin followed by five more days of PPIs plus metronidazole and clarithromycin) have been recommended as an alternative[7]. Table 1 is shown mode of actions and resistance mechanisms of antibiotics used for treatment of *H. pylori* infection.

Failure of treatment in *H. pylori* infections has become an actual subject for physicians. The cause of treatment failure is many that can be grouped into microorganism-related factors, host-related factors and treatment-related factors. *H. pylori* resistance to antibiotic is widely recognized as the chief reason for treatment failure[1,8]. Furthermore, antibiotic resistance should be considered as a lively idea, since its prevalence can change not only among diverse countries, but also between two different periods in the same area[1,9-11]. The rate of antibiotic resistance in *H. pylori* has been evaluated worldwide. However, most researches originated from single center, included only a small number of bacteria, were often restricted to selected patients, and used different techniques to evaluate antibiotic susceptibility. Though, the investigation platform is luxurious; and only performed in few countries as: United Kingdom, German, Finland[12-18]. Antibiotic use for infections other than *H. pylori* is accounting for the extensive raise antibiotic resistance rate in *H. pylori*[19]. Because of the value of *H. pylori* therapy, antimicrobial susceptibility testing has been widely done. Since, *H. pylori* antibiotic resistance is fast growing worldwide, an eradication policy based on pre-treatment susceptibility testing is going to get more attractive than in the past[1,7].

The objective of this paper was to review previous studies about the rates of antimicrobial resistance in *H. pylori* isolates obtained from worldwide during last 6 years in order to evaluate the trend of antibiotic resistance.

MATERIALS AND METHODS

In the present study, different computer-assisted searches were achieved using PubMed, MEDLINE, Science Direct, Google Scholar and Scielo. Separately searches were carried out on all English language literatures published through 2009 to 2014, by the key words: *Helicobacter pylori*, *H. pylori,* resistance, metronidazole, levofloxacin, amoxicillin, clarithromycin, tetracycline, and rifabutin. Full articles related searches were saved, and articles written in foreign languages were translated when essential. When more than one publication from the same author was obtainable, only new version, counting the whole population was enrolled. Two investigators (Ebrahimzadeh Leylabadlo H and Mohammadzadeh Asl Y) independently and in a blinded manner assessed the articles using pre-designed data extraction.

The following information was collected: (1) sum of bacteria incorporated; (2) rate of antibiotic resistant; and (3) the geographic area involved. The data were summarized in extraction table and analyzed manually. Finally, Excel 2007 software was used to draw charts.

RESULTS

During 6 years a total of 52008 *H. pylori* isolates meeting the inclusion criteria were identified. Eighty-seven studies from 2009 to 2014 on *H. pylori* antimicrobial resistance in the different countries were included; there were 43 Asian[20-62], 10 American[63-72], 5 African[73-77], and 29 European studies[78-106]. On the whole rates of *H. pylori* antibiotic resistance were 47.22% (30.5%-75.02%) for metronidazole, 19.74% (5.46%-30.8%) for clarithromycin, 18.94% (14.19%-25.28%) for levofloxacin, and 14.67% (2%-40.87%) for amoxicillin, 11.70% (0%-50%) for tetracycline, 11.5% (0%-23%) for

Table 1 Mode of action, resistance mechanisms of antimicrobial agents used for treatment of *Helicobacter pylori* infection

Antibiotic	Mode of action	Resistance mechanisms
Metronidazole	Electron reduction processes, leads to the formation of nitro-anion radicals and subsequent DNA damage	(1) Poor drug uptake and/or increased drug efflux; (2) enhanced activity of DNA repair enzymes; (3) increased oxygen scavenging abilities; and (4) decreased antibiotic activation arising from changes in metronidazole-reducing enzymes[16]
Clarithromycin	The inhibition of protein synthesis by binding and slowing down the activity of the bacterial ribosomal unit[17]	rRNA-point mutations
Amoxicillin	The inhibition cell wall synthesis	*pbp* gene mutations, membrane permeability alterations and efflux pumps[17]
Tetracycline	Reversible inhibition protein synthesis	Three contiguous nucleotides mutation in the 16S rRNA gene[17]
Fluoroquinolones	Inhibiting DNA gyrase, type Ⅱ topoisomerase, and topoisomerase Ⅳ[17]	Point mutations in the quinolones resistance determining regions
Rifabutin	Inhibits the b-subunit of *H. pylori* DNA-dependent RNA polymerase encoded by the *rpo*B gene[18]	Mutation of the *rpo*B gene[18]

H. pylori: *Helicobacter pylori*.

Table 2 Antibiotic resistance rates in different continental areas

Region (*n*)	Cla %	Amo %	Met %	Tet %	Lev %	Rif %	Fur %
Asia (23748)	27.46	23.61	46.57	7.38	25.28	12.45	23
South America (587)	12.88	6.56	52.85	0	21.23	NR	0
North America (818)	30.8	2	30.5	0	19	NR	NR
Europe (26024)	22.11	0.35	31.19	1.15	14.19	1	NR
Africa (831)	5.46	40.87	75.02	50	15	NR	NR
Total (52008)	19.74	14.67	47.22	11.70	18.94	6.75	11.5

Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Tet: Tetracycline; Lev: Levofloxacin; Rif: Rifabutin; Fur: Furazolidon; *n*: Number; NR: Not reported.

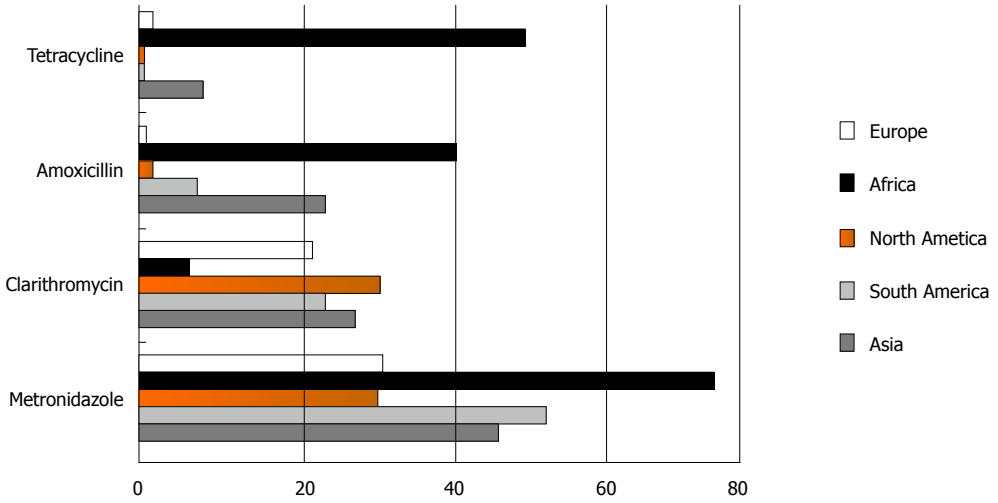

Figure 1 Antibiotic resistance rates to 4 most common used antibiotics in different continental areas.

furazolidon and 6.75% (1%-12.45%) for rifabutin. The frequency of resistance to antibiotics in various continents and countries are demonstrated in Tables 2 and 3, Figures 1 and 2.

DISCUSSION

Monitoring of resistance to antimicrobial agents is important for *H. pylori* infections therapy in medical practice[17]. Resistance to antimicrobial agents creates at risk *H. pylori* eradication in the world[10,98]. The most recent recommendations on *H. pylori* therapy suggested that initially management had better be personalized based on clarithromycin and metronidazole resistance. In fact, fourteen days triple-therapy is recommended in area where resistance to clarithromycin is more than 15% to 20%, if resistance to metronidazole is more than 40%, the association with amoxicillin is

Table 3 Quantitative data of the articles

Countries	Year	Isolates (*N*)	Cla (%)	Amo (%)	Met (%)	Tet (%)	Lev (%)	Rif (%)	Fur (%)	Method	Ref.
	2014	95	33.7							E-Test	[20]
	2013	82	17.1	9.8	64.4	0				DDM	[21]
	2013	78	15.3	6.4	55.1					DDM	[22]
Iran	2012	150	34	10	78.6	9.3	5.3			E-T,ADM	[23]
	2012	112	14.3	28.6	76.8	18.7		28.6		DDM	[24]
	2011	197	45.2	23.9	65.5	37.1			61.4	DDM	[25]
	2011	42	14.3	2.4	40.5	4.8				ADM	[26]
	2010	121	5	20	44	3				E-Test	[27]
	2010	132	30	6.8	73.4	9				E-Test	[28]
	2014	73	80.8	0	58.9		12.3			E-Test	[29]
	2013	17731	21.5	0.1	95.4		20.6		0.1	ADM	[30]
China	2011	73	84.9	0	61.6	0	13.7	6.8		PCR	[31]
	2010	374	37.2	0.3	63.9	1.2	50.3			E-Test	[32]
	2009	36	8.3	33.3	94.4		0		16.7	DDM	[33]
	2014	124	36.2	0	2.1					E-Test	[34]
Japan	2014	135	25.9		20.7					E-Test	[35]
	2014	1073	31.1		40.2					ADM	[36]
	2013	204	86.4	8.2	71.3		57			ADM	[37]
	2011	153	55.6							PCR	[38]
	2010	61	36.1	0	14.8					ADM	[39]
	2014	212	8.5	9	36.3	0				ADM	[40]
South Korea	2013	165	11.5	2.45	50.7	0	24.55			ADM	[41]
	2013	150		6						ADM	[42]
	2012	185	10.8	2.2	30.3	0.05				ADM	[43]
	2014	161	1.2		36.6					E-Test	[44]
Malaysia	2014	102	6.8	0	32.3	0	6.8	0		E-Test	[45]
	2011	90	0	0	75.5		0	14.4		E-Test	[46]
	2011	187	2.1	0	37.4	0	1			E-Test	[47]
	2009	187	2.1							E-Test	[48]
	2014	46	47.8	54.3	73.9	4.3				E-Test	[49]
Pakistan	2012	178	36	37	89	12				ADM	[50]
	2010	92	33	2	48					E-Test	[51]
	2014	98	23.5	3.9	11.7					DDM	[52]
	2012	149	18.2	0	45.5		18.2			E-Test	[53]
Turkey	2012	61	21.3	0	42.6	9.1	3.3			DDM	[54]
	2009	31	41.9	3.2	41.9	3.2				E-Test	[55]
	2009	38	13.5							ADM	[56]
Taiwan	2014	61	35.3	0	17.6	0	23.5			E-Test	[57]
	2009	180	10.6	0	26.7		9.4			E-Test	[58]
Thailand	2009	120	29.2							PCR	[59]
UAE	2010	26	19.2							E-Test	[60]
India	2014	80	58.8	72.5	83.8	53.8	13.8		13.8	DDM	[61]
Vietnam	2013	103	33	0	69.9	5.8	18.4			E-Test	[62]
South American											
	2014	54	11.1	1.9						E-Test	[63]
Brazil	2013	77	19.5	10.4	40	0			0	ADM	[64]
	2011	39	8	0	51	0	23		0	ADM	[65]
Colombia	2012	203	19.8	20.5						ADM	[66]
Cuba	2010	40	10		85					E-Test PCR	[67]
Peru	2011	95					36.9			ADM DDM	[68]
Uruguay	2009	79	8.9	0	35.4	0	3.8			E-Test	[69]
North America											
Mexico	2011	90	5.5		19					E-Test	[70]
Canada	2009	42	57							E-Test	[71]
United States	2011	686	30	2	42	0	19			E-Test ADM	[72]
Senegal	2013	108	1	0	85	0	15			E-test DDM	[73]
Nigeria	2009	186		66	95	100				E-test	[74]
Gambia	2012	64	0		68.8					ADM	[75]
Tunisia	2010	273	15.4	0	51.3					E-test	[76]
South Africa	2010	200		97.5						ADM DDM	[77]
	2014	1651	6.7		29.4					E-test	[78]

Germany	2013	5296	67.1	0	67.1		24.9		E-test	[79]
	2013	436	7.5	0	32.7		11.7		E-test	[80]
Italy	2012	111	35.2		59.3		22.1		E-test	[81]
	2011	253	9.9						PCR	[82]
England	2009	255						1	E-test DDM	[83]
	2013	343	23.5		33				E-test	[84]
Spain	2011	71	14.7	1.4	45.1	0	14.5		E-test	[85]
	2010	118	35.6						E-test	[86]
	2009	101	54.6		35.7				E-test	[87]
Norway	2012	102	5.9	0	22.5	0			E-test	[88]
Finland	2010	505	8	0	41		7		E-test	[89]
	2013	588	20.1		34.5	2.6			ADM	[90]
Bulgaria	2011	519	17.9		29.5	4			ADM	[91]
	2009	1057	18.7	0.5	21.35	3.15			ADM	[92]
Croatia	2012	382	11.9	0.6	10.1				E-test	[93]
	2014	210					8.1		E-test	[94]
Poland	2013	165	10.9		32.7		1.2		E-test	[95]
	2012	51	22				16		E-test	[96]
	2011	115	34	0	44		5		E-test	[97]
Portugal	2014	180	50	0.6	34.4	0.6	33.9		E-test	[98]
	2011	1115	34.7	0	13.9	0			E-test	[99]
Belgium	2013	189	13.3	0.8	26.1					[100]
	2011	10670	20.3	0	27				ADM	[101]
Netherlands	2014	417	6.14		10.1				E-test	[102]
	2013	746	20.5	0.68	19.9				E-test	[103]
Ireland	2013	85				0	11.7	0	E-test	[104]
	2010	219	13.2		31.5				E-test	[105]
Southern Europe	2014	74	34.7		16.7				E-test	[106]

Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Tet: Tetracycline; Lev: Levofloxacin; Rif: Rifabutin; Fur: Furazolidon; DDM: Disk Diffusion Agar; ADM: Agar Dilution Agar.

preferred[17]. At the present, due to *H. pylori* antibiotics resistance, eradication therapy appears was not carried out as simple as and we are now founded many failures which make the use of standard therapy unacceptable in many parts of the world[107]. This article systematically studied the latest data on *H. pylori* resistance to antibiotic.

Clarithromycin resistance

Because clarithromycin is the most potent antibiotic involved in the management of *H. pylori* infections, resistance to clarithromycin is important[8,17,105]. As presented in Table 2, the rate of clarithromycin resistance was 19.74%, and occurrence of clarithromycin resistance is increasing worldwide (Figure 2). The rate of clarithromycin resistance has been broadly studied, and information are on hand from nearly all areas in the world: it ranges from 5.46% to 30.8% (Figure 1).

In European regions, the lowest clarithromycin resistance was reported from Norway (5.9%), whilst the highest in Spain (32.01%) and Portugal (42.35%). European studies performed at the past 6 years intervals reported that *H. pylori* resistance decrease from 36.65% in 2009 to 24.38% in 2014. In Asian regions, a surprising clarithromycin resistance frequency was reported from India (58.8%) and China (46.54%), whereas the lowest rate was discovered in Malaysia (2.4%). An increase in clarithromycin resistance has been faced in the Asia, from 15.28% in 2009 to 32.46% in 2014, probably in the Asian countries macrolid drugs used more. In recent years due to widespread use of clarithromycin for respiratory infections in the public especially in children, clarithromycin resistance has augmented in diverse regions, and there is an association between outpatient use of long-acting macrolide and clarithromycin resistance[10,17,108].

In conclusion, the highest clarithromycin resistant area was North America, and this study showed a slight increasing tendency of clarithromycin resistance of *H. pylori* in the world. Since clarithromycin is the most potent antimicrobial agent involved in the standard treatment protocol as well as the resistance rates were still at the low level, where clarithromycin-containing triple therapies could be used empirically.

Metronidazole resistance

Metronidazole is used against *H. pylori* infections and is one of the few antibacterial agents as drug of choice that is effective in eradicated the microorganism. Some researcher reported that the rate of treatment failure is more than 20% with triple therapy in which metronidazole is the drug of choice, also *H. pylori* resistance to metronidazole is the chief solitary reason responsible for management failure[109,110].

Metronidazole resistance is the most common antibiotic resistance in *H. pylori* and overall metronidazole resistance found in 47.22% in descending order in Africa 75.02%, South America 52.85%, Asia 46.57%, Europe 31.19%, to 30.5% in North America. In developed countries about 30% of the *H. pylori* strains

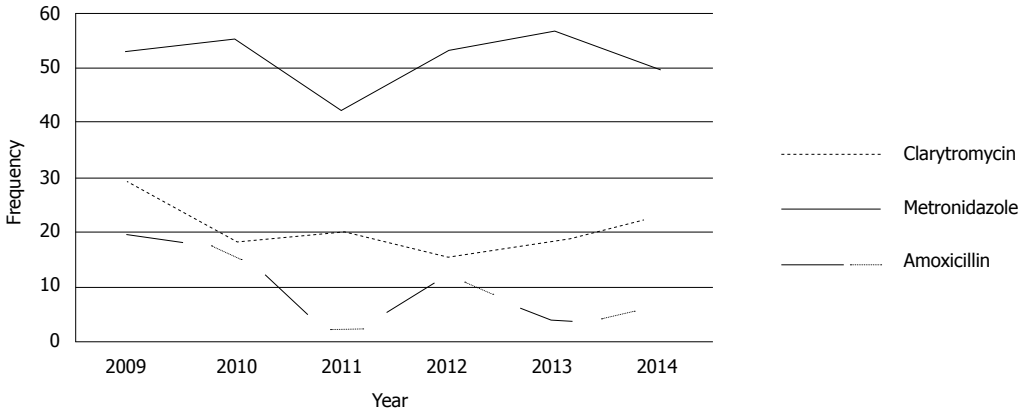

Figure 2 Trend of *Helicobacter pylori* resistance to metronidazole, clarithromycin, and amoxicillin during 6-years.

are metronidazole resistant, whereas in developing countries, the occurrence of resistance is very high. This association between metronidazole resistance and socioeconomic state level is maybe due to use of metronidazole and related drugs for gynecological, dental and parasitic related infectious diseases[13,111]. The comparison of results indicated that resistance to metronidazole have remained significantly unchanging in Asian, European and North American countries but is increasing in African countries (51.3% in 2010 to 85% in 2013). Furthermore metronidazole resistance in 2014 has stayed approximately at the similar level as in early 2009 in Europe. So, in accordance with latest guidelines, metronidazole is favored to amoxicillin in first-line therapy in Asian, Europe and North American but not in African patients.

Amoxicillin resistance

Amoxicillin is suggested for anti-*H. pylori* triple therapy in region where metronidazole resistance is high. Universal resistance to amoxicillin is uncommon; it was detected in 14.67%. The frequency of amoxicillin resistance extensively differs in Asian regions, ranging from zero in Malaysia, Taiwan and Vietnam to 72.5% in India. The rate of amoxicillin resistance in Africa was 40.87%.

The prevalence of amoxicillin resistance in Europe countries and North American is low from zero in certain area as Finland, Germany, Norway and Poland, 1.4% in Spain to 2% in United States. It seems the government policy possibly to limit the use of antibiotic for infectious diseases in European and North American countries. The incidence of amoxicillin resistance in *H. pylori* seems to increase specially in Asia and South America, where these antibiotics can be obtained without prescription. *H. pylori* resistance rates of 97.5%, 72.5%, 66% and 20.5% for amoxicillin have recently been reported in South Africa, India, Nigeria and Colombia, respectively.

Tetracycline resistance

Among the 4 most common used antimicrobial agents, tetracycline resistance was the lowest (Table 3). In general *H. pylori* resistance to tetracycline was detected 11.7% in the world. The total rate of tetracycline resistance did not vary in South America and North America (the resistance was absent), whilst it was relatively high in Africa (50%). In Asia, the resistance was absent in Thailand, and very low in China (0.6%) and South Korea (0.01%). In contrast, increased values were found in India (53.8%), and Iran (11.7%). The prevalence of tetracycline resistance stays very low (less than 7.4%) in almost most parts of the world except for Africa. The comparison of data showed that tetracycline resistance is decreasing in the world, 26.85% in 2009 to 6.11% in 2014.

Tetracycline is a bacteriostatic and broad spectrum antimicrobial agent that is active against *H. pylori* and tetracycline is the most generally used antibiotic for treatment of *H. pylori* and other infectious diseases[109]. Tetracycline is extensively used in many countries, but resistance to this antibiotic has not become a great problem yet. Management failure owing to the tetracycline resistant has been reported[112,113], though there is not enough data obtainable until now to determine the impact of this resistance on management success.

Rifabutin resistance

However, the study on *H. pylori* rifabutin resistance is inadequate and in South America, North America and Africa has not been done during previous 6 years. The rate of rifabutin resistance was higher in Asia (12.45%) as compared to Europe (1%). The frequency of rifabutin resistance differs in Asian countries, ranging from 28.6% in Iran to about 7% in China and Malaysia. Rifabutin is structurally related to rifampin group, and it has potential efficacy against *H. pylori*[114]. Rifabutin is usually used to treat mycobacterium diseases, so the secondary resistance of *H. pylori* to rifabutin is not currently expected in the healthy people.

Levofloxacin resistance

Generally, resistance to levofloxacin is low (< 19%) worldwide. The prevalence rate was higher in Asia

(25.28%) and South America (21.23%) as compared to Africa and Europe (less than 15%). The frequency of levofloxacin resistance widely differs in Asian regions, about 57% in Japan, 24.55% in South Korea, 5.3% in Iran and 2.6% in Malaysia. In addition the levofloxacin resistance rate differs between European countries, ranging from 7% to 33.9%. The rate of levofloxacin resistance seems to be increasing universal from 4.25% in 2009 to 17.55% in 2014. Furthermore, during the past 3 years levofloxacin resistance rates have even been more increasing.

Due to the dramatic increase in clarithromycin resistance, levofloxacin, a wide spectrum quinolone, has been used as an option of clarithromycin in some regimens. But the frequent use of quinolones for urinary tract infections has increased the incidence of *H. pylori* resistance in the world[17]. Failure of therapy due to levofloxacin resistance and the emerging development of quinolones resistance, use of levofloxacin as first-line therapy is generally discouraged, and its utilize should be reserved as a second-line or save regimens after failure of a clarithromycin and/or a metronidazole based regimen[7,80].

Furazolidon resistance

The study on furazolidon resistance was not widely performed in the world, and in Europe, North America and Africa has not been achieved during past 6 years. The rate of furazolidon resistance was higher in Asia (13.8%) as compared to South America (0%). The rate of furazolidon resistance broadly differs in Asia, from 61.4% in Iran to 16.8% in China and 13.8% in India. Furazolidon is a cheap and synthetic nitrofuran with a wide spectrum activities usually used in the treatment of bacterial and protozoa infections. Since high *H. pylori* resistance to metronidazole in some region as China and South America, furazolidon sometimes has been used as an option for *H. pylori* infections[65]. However some researchers were reported that the rate of cure with furazolidon-based regimens is low and a large amount of furazolidon increases the therapy rate but it significantly raises complications[81].

The prevalence of *H. pylori* metronidazole resistance is at a high level, and resistance to clarithromycin and levofloxacin is increasing worldwide. The most effective drug is rifabutin and the lowest sensitive drug is metronidazole. Resistance to levofloxacin does not show any region difference. There are no studies regarding rifabutin and furazolidon resistance of *H. pylori* in America and Africa. According to the present findings, the mean resistance rate in *H. pylori* isolated from European and North American patients is lower than other countries. The rate of tetracycline, metronidazole and amoxicillin resistance is higher in African patients, while clarithromycin and levofloxacin resistance is higher in North America and Asian patients. In conclusion, antibiotic resistance is increasing, so empirical therapy must be based on information of antimicrobial drug resistance, and this paper highlight a steady worldwide surveillance of *H. pylori* antibiotic resistance.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) is a most important human pathogen associated with significant disease and fatality.

Research frontiers

Due to the rising frequency of antimicrobial resistance, management of *H. pylori* remains a challenge for physicians in most parts of the world.

Innovations and breakthroughs

Search was carried out about *H. pylori* antimicrobial resistance literatures published through 2009 to 2014.

Applications

The frequency of antibiotic resistance is increasing, and this article highlight a steady worldwide surveillance of *H. pylori* antibiotic resistance.

Peer-review

This is a systematic review article on *H. pylori* resistance to antibiotics. The manuscript is well written and the topic of interest.

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