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 Asia, 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

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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[1,8-11]. 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, Germany, 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[17].

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
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 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

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**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 | *php* 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 rpoB gene\(^{[18]}\) | Mutation of the rpoB 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 (987) | 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.

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**Figure 1** Antibiotic resistance rates to 4 most common used antibiotics in different continental areas.
Table 3  Quantitative data of the articles

| Countries         | Year | Isolates (N) | Cla (%) | Amo (%) | Met (%) | Tet (%) | Lev (%) | Rif (%) | Fur (%) | Method | Ref. |
|-------------------|------|--------------|---------|---------|---------|---------|---------|---------|---------|--------|------|
| South Korea       | 2013 | 17731        | 21.5    | 0.1     | 95.4    | 20.6    | 0.1     | ADM     | E-Test  | [40]   |
| China             | 2012 | 374          | 0.3     | 8.2     | 25.1    | 0       | 71.3    | 0.1     | PCR     | [31]   |
| Japan             | 2011 | 120          | 5       | 0       | 14.8    | 0       | 36.3    | 0       | E-Test  | [34]   |
| Malaysia          | 2014 | 61           | 36.1    | 0       | 14.8    | 0       | 36.3    | 0       | E-Test  | [47]   |
| Pakistan          | 2012 | 178          | 36      | 0       | 2.0     | 1.2     | 49.7    | 0       | E-Test  | [49]   |
| Turkey            | 2012 | 161          | 1.2     | 2.2     | 30.3    | 0       | 36.6    | 0       | E-Test  | [44]   |
| Taiwan            | 2011 | 38           | 0       | 2.0     | 18.2    | 0       | 33.5    | 0       | PCR     | [38]   |
| Thailand          | 2012 | 61           | 21.3    | 0       | 46.4    | 1.2     | 25.1    | 1.2     | E-Test  | [52]   |
| Vietnam           | 2013 | 121          | 5       | 0       | 24.5    | 0       | 11.5    | 0       | ADM     | [40]   |
| South American    | 2014 | 17731        | 21.5    | 0.1     | 95.4    | 20.6    | 0.1     | ADM     | E-Test  | [30]   |
| Brazil            | 2012 | 120          | 5       | 0       | 14.8    | 0       | 36.3    | 0       | E-Test  | [47]   |
| Colombia          | 2012 | 120          | 29.2    | 0       | 26.7    | 9.4     | 29.2    | 0       | PCR     | [59]   |
| Cuba              | 2011 | 95           | 36.9    | 0       | 35.4    | 3.8     | 11.1    | 1.9     | ADM     | [68]   |
| Uruguay and North America | 2012 | 61           | 21.3    | 0       | 46.4    | 1.2     | 25.1    | 1.2     | E-Test  | [69]   |
| Mexico            | 2011 | 38           | 0       | 2.0     | 18.2    | 0       | 33.5    | 0       | PCR     | [58]   |
| Canada            | 2012 | 61           | 21.3    | 0       | 46.4    | 1.2     | 25.1    | 1.2     | E-Test  | [52]   |
| United States     | 2011 | 38           | 0       | 2.0     | 18.2    | 0       | 33.5    | 0       | PCR     | [59]   |
| Senegal           | 2013 | 120          | 29.2    | 0       | 26.7    | 9.4     | 29.2    | 0       | PCR     | [59]   |
| Nigeria           | 2009 | 186          | 66      | 95      | 100     | 100     | 76.8    | 40.5    | E-Test  | [74]   |
| Gambia            | 2012 | 61           | 21.3    | 0       | 46.4    | 1.2     | 25.1    | 1.2     | E-Test  | [74]   |
| Tunisia           | 2010 | 273          | 13.4    | 0       | 51.3    | 0       | 29.4    | 8.9     | ADM     | [77]   |
| South Africa      | 2011 | 120          | 5       | 0       | 85.0    | 0       | 108     | 9.8     | E-Test  | [78]   |

Ghotsaslou R et al. Helicobacter pylori resistance to antibiotics
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. 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. 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.

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.

| Region            | Year | Cases | Rate (%) |
|-------------------|------|-------|----------|
| Germany           | 2013 | 5296  | 67.1     |
|                   | 2014 | 436   | 7.5      |
| Italy             | 2012 | 111   | 35.2     |
|                   | 2013 | 255   | 19.9     |
| England           | 2009 | 343   | 23.5     |
|                   | 2011 | 71    | 14.7     |
| Spain             | 2010 | 118   | 35.6     |
|                   | 2011 | 305   | 8       |
|                   | 2012 | 588   | 20.1     |
|                   | 2013 | 519   | 17.9     |
|                   | 2014 | 1057  | 18.7     |
| Norway            | 2013 | 508   | 8       |
|                   | 2011 | 517   | 17.9     |
|                   | 2012 | 1071  | 18.7     |
| Finland           | 2013 | 382   | 11.9     |
|                   | 2014 | 210   |          |
| Croatia           | 2013 | 165   | 10.9     |
|                   | 2011 | 51    | 22       |
| Portugal          | 2014 | 180   | 50       |
|                   | 2011 | 1115  | 34.7     |
| Belgium           | 2013 | 189   | 13.3     |
|                   | 2011 | 10070 | 20.3    |
| Netherlands       | 2014 | 417   | 6.14     |
|                   | 2013 | 746   | 20.5     |
| Ireland           | 2013 | 85    | 20.5     |
|                   | 2010 | 219   | 13.2     |
| Southern Europe   | 2014 | 74    | 34.7     |

Amox: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Tet: Tetracycline; Lev: Levofloxacin; Rif: Rifabutin; Fur: Furazolidon; DDM: Disk Diffusion Agar; ADM: Agar Dilution Agar.
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\cite{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 resis-
tance 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\cite{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\cite{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*\cite{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[60]. 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.

**REFERENCES**

1 Rafeczy M, Ghotaslou R, Nikvash S, Hafez AA. Primary resistance in Helicobacter pylori isolated in children from Iran. J Infect Chemother 2007; 13: 291-295 [PMID: 17982716]
2 Ghotaslou R, Milani M, Akhi MT, Hejazi MS, Naahai MR, Hasani A, Sharifi Y. Relationship between drug resistance and cagA Gene in Helicobacter pylori. Jundishapur J Microbiol 2013; 6: 8480
3 Ghotaslou R, Milani M, Akhi MT, Naahai MR, Hasani A, Hejazi MS, Meshkini M. Diversity of Helicobacter Pylori cagA and vacA Genes and Its Relationship with Clinical Outcomes in Azerbaijan, Iran. Adv Pharm Bull 2013; 3: 57-62 [PMID: 24312813 DOI: 10.5681/apb.2013.010]
4 Gasbarrini G, Racco S, Franceschi F, Miele L, Cammarota G, Grieco A, Gasbarrini A. [Helicobacter pylori infection: from gastric to systemic disease]. Recenti Prog Med 2010; 101: 27-33 [PMID: 20391683]
5 Malfertheiner P, Megraud F, O’Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut 2007; 56: 772-781 [PMID: 17170018]
6 Smith SM, O’Morain C, McNamara D. Antimicrobial susceptibility testing for Helicobacter pylori in children: an update. Pediatr Infect Dis J 2008; 27: 848-849 [PMID: 19001973]
7 Maastricht III Consensus Report. Gut 2007; 56: 772-781 [PMID: 17170018]
8 World J Gastroenterol 2014; 20: 5205-5211 [PMID: 24833850 DOI: 10.3748/wjg.v20.i29.9912]
9 Gut 2007; 56: 772-781 [PMID: 17170018]
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pylori from 2007 to 2014: has the tide turned? J Clin Microbiol 2015; 53: 522-527 [PMID: 25428158 DOI: 10.1128/JCM.03001-14]

Kupcinis L, Rassmusen L, Jonaitis L, Kiidels G, Jorgensen M, Urbonaviciene N, Tamosianas V, Kupcinis J, Miculeviciene J, Kadavecijus E, Berg D, Andersen LP. Evolution of Helicobacter pylori susceptibility to antibiotics during a 10-year period in Lithuania. APMIS 2013; 121: 431-436 [PMID: 23078193 DOI: 10.1111/apm.12012]

Cameron EA, Powell KU, Baldwin L, Jones P, Bell GD, Williams SG. Helicobacter pylori: antibiotic resistance and eradication rates in Salford, UK, 1991-2001. J Med Microbiol 2004; 53: 535-538 [PMID: 15158091]

Glupczynski Y, Mégraudo F, Lopez-Brea M, Andersen LP. European multicentre survey of in vitro antimicrobial resistance in Helicobacter pylori. Eur J Clin Microbiol Infect Dis 2001; 20: 820-823 [PMID: 11783701]

Kist M, Gloeker E. ResiNet - A nationwide German sentinel study for surveillance and analysis of antimicrobial resistance in Helicobacter pylori. Eurosurveillance 2004; 9: 44-46

Kovistö TT, Rautelin HI, Vuolteenaho ME, Niemelä SE, Heikkinen M, Sipponen PI, Färkkilä MA. Primary Helicobacter pylori resistance to metronidazole and clarithromycin in the Finnish population. Aliment Pharmacol Ther 2004; 19: 1009-1017 [PMID: 15113363]

Gerrits MM, van der Wouden EJ, Bax DA, van Zewet AA, van Vliet AH, de Jong A, Kusters JG, Thijis JC, Kuipers EJ. Role of the mxaF and frrA genes in oxygen-dependent metronidazole resistance of Helicobacter pylori. J Med Microbiol 2004; 53: 1123-1128 [PMID: 15496391]

De Francesco V, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, Ierardi E, Zullo A. Worldwide Helicobacter pylori resistance to clarithromycin, metronidazole, and amoxicillin in Isfahan, Iran. Drug Resist Updates 2014; 19: 274-279 [PMID: 24188557 DOI: 10.1016/j.drup.2014.03.007]

De Francesco V, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, Ierardi E, Zullo A. Antibiotic susceptibility profile of Helicobacter pylori isolated from the dyspepsia patients in Tehran, Iran. Saudi J Gastroenterol 2011; 17: 261-264 [PMID: 21727733 DOI: 10.4103/1319-3767.82851]

Farshad S, Alborzi A, Japoni A, Ranjarb R, Hosseini Asl K, Badiee P, Amin Shahidi M, Hosseini M. Antimicrobial susceptibility of Helicobacter pylori strains isolated from patients in Shiraz, Southern Iran. World J Gastroenterol 2010; 16: 5746-5751 [PMID: 2128326]

Talebi Bezmim Abadi A, Mobarez AM, Taghvaei T, Wolfram L. Antibiotic resistance of Helicobacter pylori in Mazandaran, North of Iran. Helicobacter 2010; 15: 505-509 [PMID: 21073606 DOI: 10.1111/j.1101-2223.2010.00307.x]

Su P, Li Y, Li H, Zhang J, Lin L, Wang Q, Guo F, Ji Z, Mao J, Tang W, Shi Z, Shao W, Mao J, Zhu X, Zhang X, Tong Y, Tu H, Jiang M, Jin F, Yang N, Zhang J. Antibiotic resistance of Helicobacter pylori isolated in the Southeast Coastal Region of China. Helicobacter 2013; 18: 274-279 [PMID: 23418857 DOI: 10.1111/hel.1204]

Liu G, Xu X, He L, Ding Z, Gu Y, Zhang J, Zhou L. Primary antibiotic resistance of Helicobacter pylori isolated from Beijing children. Helicobacter 2011; 16: 356-362 [PMID: 21923681 DOI: 10.1111/j.1523-5378.2011.00856.x]

Gao W, Cheng H, Hu F, Li J, Wang L, Yang G, Xu L, Zheng X. The evolution of Helicobacter pylori antibiotics resistance over 10 years in Beijing, China. Helicobacter 2010; 15: 460-466 [PMID: 21083752 DOI: 10.1111/j.1523-5378.2010.00788.x]

Huang LP, Zhuang ML, Gu CP. [Antimicrobial resistance of 36 strains of Helicobacter pylori in adolescents]. Zhongguo Dang Dai Er Ke Za Zhi 2009; 11: 210-212 [PMID: 19292962]

Nishizawa T, Maekawa T, Watanabe N, Harada N, Hosoda Y, Yoshimaga M, Yoshio T, Ohta H, Inoue S, Toyokawa T, Yamashita H, Saito H, Kuwai T, Katayama S, Masuda E, Miyabayashi H, Kimura T, Nishizawa Y, Takahashi M, Suzuki H. Clarithromycin Versus Metronidazole as First-line Helicobacter pylori Eradication: A Multicenter, Prospectiv, Randomised Controlled Study in Japan. J Clin Gastroenterol 2015; 49: 468-471 [PMID: 24921211]

Morimoto N, Takeuchi H, Nishida Y, Morisawa M, Yoshikawa T, Morita T, Morimoto M, Sugimoto C, Matsumura Y, Sugita J. Clinical Application of the DiversiLab Microbial Typing System Using Repetitive Sequence-Based PCR for Characterization of Helicobacter pylori in Japan. J Clin Lab Anal 2015; 29: 250-253 [PMID: 24796554 DOI: 10.1002/jcl.22158]

Okamura T, Suganuma T, Arakawa N, Kakumoto T, Isoda Y, Morita Y. Antibiotic resistance of Helicobacter pylori isolated from children of a single institution in Japan. Jpn J Pediatr 2010; 63: 43-49 [PMID: 20422614]

Murakami K, Furuta T, Tomita T, Nakajima T, Imai Y, Oshima T, Tomita T, Mabe K, Sasaki M, Suganuma T, Nomura H, Sato H, Morita Y, Inoue S, Tomokane T, Kudo M, Inaba T, Take S, Okhusa T, Yamamoto S, Mizuno S, Kamoshida T, Amagai K, Iwamoto H, Miwa J, Kodama M, Okimato T, Kato M, Asaka M. Multi-center randomized controlled study to establish the standard third-line regimen for Helicobacter pylori eradication in Japan. J Gastroenterol 2013; 48: 1128-1135 [PMID: 23307042 DOI: 10.1007/s00535-012-0731-8]

Yamada M, Sugimoto M, Uotani T, Nishino M, Kodaira C, Furuta T. Resistance of Helicobacter pylori to quinolones and clarithromycin assessed by genetic testing in Japan. J Gastroenterol Hepatol 2011; 26: 1457-1461 [PMID: 21679250 DOI: 10.1111/j.1440-1746.2011.06815.x]

Kato S, Fujimura S. Primary antimicrobial resistance of Helicobacter pylori in children during the past 9 years. Pediatr Int 2010; 52: 187-190 [PMID: 19563459 DOI: 10.1111/j.1442-200X.2009.02915.x]

Yoon KH, Park SW, Lee SW, Kim BJ, Kim JG. Clarithromycin-
Haldane D, Veldhuyzen van Zanten S. Pyrosequencing assay to rapidly detect clarithromycin resistance mutations in Canadian Helicobacter pylori isolates. Can J Gastroenterol 2009; 23: 609-612 [PMID: 19676602].

72 Twet AH, Bruce MG, Bruden DL, Morris J, Reasonover A, Hurhburt DA, Hennessy TW, McMahon B. Alaska sentinel surveillance study of Helicobacter pylori isolates from Alaska Native persons from 2000 to 2008. J Clin Microbiol 2011; 49: 3638-3643 [PMID: 21813276 DOI: 10.1128/JCM.0106711].

73 Seek A, Burucua C, Dia D, Mbengue M, Onambele M, Raymond J, Breure S. Primary antibiotic resistance and associated mechanisms in Helicobacter pylori isolates from Senegalese patients. Ann Clin Microbiol Antimicrob 2013; 12: 3 [PMID: 23298145 DOI: 10.1186/1476-0711-12-3].

74 Oyedeji KS, Smith SI, Coker AO, Arigbabu AO. Antibiotic susceptibility patterns in Helicobacter pylori strains from patients with upper gastrointestinal pathology in western Nigeria. Br J Biomed Sci 2009; 66: 10-13 [PMID: 19384120].

75 Secka O, Berg DE, Antonio M, Corrah T, Tapgun M, Walton M, Thomas V, Gallo JJ, Sancho J, Adegbola RA, Thomas JE. Antimicrobial susceptibility and resistance patterns among Helicobacter pylori strains from The Gambia, West Africa. Antimicrob Agents Chemother 2013; 57: 1231-1237 [PMID: 23263004 DOI: 10.1128/AAC.00517-12].

76 Ben Mansour K, Burucua C, Zribi M, Masmoudi A, Karoui S, Kallel L, Chouaib S, Matri S, Fekih M, Zarrour S, Labbene M, Boubaker J, Cheikh I, Hriz MB, Ayadi A, Filali A, Mami NB, Najjar T, Maherzi A, Sfar MT, Vaira D. High prevalence of primary and secondary resistance to quinolones in German Helicobacter pylori isolates in Italy. Br J Pharmcol 2011; 23263004 [PMID: 23668128 DOI: 10.1128/JCM.00431-10].

77 Tanih NF, Okeleye BI, Naidoo N, Clarke AM, Mkwetshana N, Owen RJ. Frequency and molecular characteristics of ciprofloxacin- and rifampicin-resistant Helicobacter pylori from populations in high rates of antibiotic resistance. Gastroenterology 2013; 145: 121-128.e1 [PMID: 23562754 DOI: 10.1053/j.gastro.2013.03.050].

78 Cuadrado-Lavin A, Salcines-Caviedes JR, Carrascosa MF, Mellado P, Monteagudo I, Llorca J, Cobo M, Campos MR, Ayestaran B, Fernandez-Pousa A, Gonzalez-Colominaes E. Antimicrobial susceptibility of Helicobacter pylori to six antibiotics currently used in Spain. J Antimicrob Chemother 2012; 67: 170-173 [PMID: 21965436 DOI: 10.1093/jac/dkr410].

79 Agudo S, Pérez-Pérez G, Alarcón T, López-Brea M. High prevalence of clarithromycin-resistant Helicobacter pylori strains and risk factors associated with resistance in Madrid, Spain. J Clin Microbiol 2010; 48: 3703-3707 [PMID: 20668128 DOI: 10.1128/JCM.01244-10].

80 Boyanova L, Ilieva J, Gergova G, Evstatiev I, Nikolov R, Mitov I. Living in Sofia is associated with a risk for antibiotic resistance in Helicobacter pylori: a Bulgarian study. Folia Microbiol (Praha) 2013; 58: 587-591 [PMID: 23580173 DOI: 10.1007/s12020-013-0251-9].

81 Boyanova L, Ilieva J, Gergova G, Dakovik L, Spassova Z, Kamburov V, Katsarov N, Mitov I. Numerous risk factors for Helicobacter pylori antibiotic resistance revealed by extended anamnesis: a Bulgarian study. J Med Microbiol 2012; 61: 85-93 [PMID: 21873378 DOI: 10.1099/jmm.0.035588-0].

82 Boyanova L. Prevalence of multidrug-resistant Helicobacter pylori in Bulgaria. J Med Microbiol 2009; 58: 930-935 [PMID: 19502370 DOI: 10.1099/jmm.0.009903-0].

83 Hajsz J, Kov T, Dunancí J, Hribič Z, Jaderán O, Jakke Kekeza, Lukić Grlíč, Kolaček S. Antibiotic resistance of Helicobacter pylori in pediatric patients -- 10 years’ experience. Eur J Pediatr 2012; 171: 1325-1330 [PMID: 22430353 DOI: 10.1007/s00431-012-2722-8].

84 Karczewa E, Klesziewicz K, Wojtas-Bonior I, Skiba I, Sito E, Czajek K, Zawilska-Wcislo M, Budak A. Levofloxacin resistance of Helicobacter pylori strains isolated from patients in southern Poland, between 2006-2012. Acta Pol Pharm 2014; 71: 477-483 [PMID: 25265828].

85 Gościński G, Biernat M, Grabińska J, Bąkowska A, Poniewierka E, Iwańczak B. The antimicrobial susceptibility of Helicobacter pylori strains isolated from children and adults with primary infection in the Lower Silesia Region, Poland. Pol J Microbiol 2014; 63: 57-61 [PMID: 25033663].

86 Karczewa E, Klesziewicz K, Skiba I, Wojtas-Bonior I, Sito E, Czajek K, Zawilska-Wcislo M, Budak A. Variability in Prevalence of Helicobacter pylori Strains Resistant to Clarithromycin and Levofloxacin in Southern Poland. Gastroenterol Res Pract 2012; 2012: 418010 [PMID: 22693400 DOI: 10.1155/2012/418010].

87 Karczewa E, Wojtas-Bonior I, Sito E, Zawilska-Wcislo M, Budak A. Primary and secondary clarithromycin, metronidazole, amoxicillin and levofloxacin resistance to Helicobacter pylori in southern Poland. Pharmacol Rep 2011; 63: 799-807 [PMID: 21857091].
Ghotaslou R et al. Helicobacter pylori resistance to antibiotics

98 Almeida N, Romolozinho JM, Donato MM, Luxo C, Cardoso O, Cipriano MA, Marinho C, Fernandes A, Calhau C, Sofia C. Helicobacter pylori antimicrobial resistance rates in the central region of Portugal. Clin Microbiol Infect 2014; 20: 1127-1133 [PMID: 24890952 DOI: 10.1111/1469-0691.12701]

99 Okeabast M, Cabral J, Ramalho PM, Lemos PS, Paixão E, Benoliel J, Santos A, Lopes AI. Primary antibiotic resistance of Helicobacter pylori strains isolated from Portuguese children: a prospective multicentre study over a 10 year period. J Antimicrob Chemother 2011; 66: 2308-2311 [PMID: 21764826 DOI: 10.1093/jac/dkr293]

100 Vekens K, Vandebosch S, De Bel A, Urbain D, Mana F. Primary antimicrobial resistance of Helicobacter pylori in Belgium. Acta Clin Belg 2013; 68: 183-187 [PMID: 24156217]

101 Miendje Deyi VY, Bontens P, Vanderpas J, De Koster E, Ntounda R, Van den Borre C, Cadranel S, Burette A. Multicenter survey of routine determinations of resistance of Helicobacter pylori to antimicrobials over the last 20 years (1990 to 2009) in Belgium. J Clin Microbiol 2011; 49: 2200-2209 [PMID: 21450969 DOI: 10.1128/JCM.02642-10]

102 de Boer EM, Schneeberger PM, de Boer WA. [Antibiotic resistance of Helicobacter pylori: prevalence in one region in the southern Netherlands and implications for treatment]. Ned Tijdschr Geneeskd 2014; 158: A7501 [PMID: 25159698]

103 Loffeld RJ, Werdumller BF. Changes in Antibiotic Susceptibility of Helicobacter pylori in the Course of Eight Years in the Zaanstreek Region in The Netherlands. Gastroenterol Res Pract 2013; 2013: 625937 [PMID: 23573077 DOI: 10.1155/2013/625937]

104 O’Connor A, Taneihe I, Nami A, Fitzgerald N, Ryan B, Breslin N, O’Connor H, McNamara D, Murphy P, O’Morain C. Helicobacter pylori resistance rates for levofloxacin, tetracycline and rifabutin among Irish isolates at a reference centre. Ir J Med Sci 2013; 182: 693-695 [PMID: 23625165 DOI: 10.1007/s11845-013-0957-3]

105 O’Connor A, Taneihe I, Nami A, Fitzgerald N, Murphy P, Ryan B, O’Connor H, Qasim A, Breslin N, O’morain C. Helicobacter pylori resistance to metronidazole and clarithromycin in Ireland. Eur J Gastroenterol Hepatol 2010; 22: 1123-1127 [PMID: 20354442 DOI: 10.1097/MEG.0b013e328338e43d]

106 Montes M, Villalon FN, Elizaguirre FJ, Delgado M, Muñoz-Seca IM, Fernández-Reyes M, Pérez-Trallero E. Helicobacter pylori Infection in Children. Antimicrobial Resistance and Treatment Response. Helicobacter 2015; 20: 169-175 [PMID: 25382231 DOI: 10.1111/hel.12187]

107 Megraud F. Current recommendations for Helicobacter pylori therapies in a world of evolving resistance. Gut Microbes 2013; 4: 541-548 [PMID: 23929066 DOI: 10.4161/gmic.25930]

108 Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Giczypczynski Y. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013; 62: 34-42 [PMID: 22580412 DOI: 10.1136/gutjnl-2012-302254]

109 Mégraud F, Lamouliatte H. Review article: the treatment of refractory Helicobacter pylori infection. Aliment Pharmacol Ther 2003; 17: 1333-1343 [PMID: 12786627]

110 Dammann HG, Fölsch UR, Hahn EG, von Kleist DH, Klör HU, Kirchner T, Strobel S, Kist M. Eradication of H. pylori with pantoprazole, clarithromycin, and metronidazole in duodenal ulcer patients: a head-to-head comparison between two regimens of different duration. Helicobacter 2000; 5: 41-51 [PMID: 10672051]

111 Frenck RW, Clemens J. Helicobacter in the developing world. Microbes Infect 2003; 5: 705-713 [PMID: 12814771]

112 Ecclissato C, Marchioretto MA, Mendonça S, Godoy AP, Gauzensi RA, Deguer M, Piovesan H, Ferraz JG, Pedrazzoli J. Increased primary resistance to recommended antibiotics negatively affects Helicobacter pylori eradication. Helicobacter 2002; 7: 53-59 [PMID: 11886474]

113 Realld G, Dore MP, Piana A, Atzei A, Carta M, Cugia L, Manca A, Are BM, Massarelli G, Mura I, Maida A, Graham DY. Pretreatment antibiotic resistance in Helicobacter pylori infection: results of three randomized controlled studies. Helicobacter 1999; 4: 106-112 [PMID: 10382124]

114 Gisbert JP, Castro-Fernandez M, Perez-Aisa A, Cosme A, Molina-Infante J, Rodrigo L, Modolell I, Cabriada JL, Gisbert JL, Lamas E, Marcos E, Calvet X. Fourth-line rescue therapy with rifabutin in patients with three Helicobacter pylori eradication failures. Aliment Pharmacol Ther 2012; 35: 941-947 [PMID: 22372560 DOI: 10.1111/j.1365-2036.2012.05053.x]

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