REVIEWS

Worldwide *H. pylori* Antibiotic Resistance: a Systematic Review

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Abstract

Background and Aims. Prevalence of H. pylori antibiotic resistance is increasing worldwide, and it is the main factor affecting efficacy of current therapeutic regimens. Our aim was to review recent data on H. pylori resistance towards antibiotics in different countries. **Methods**. A systematic review of studies concerning primary H. pylori antibiotic resistance published through January 2006 to December 2009 was performed. Data were analyzed according to geographic area, age, sex, and gastroduodenal pathology. **Results**. The overall H. pylori antibiotic resistance rates were 17.2% (95% CI: 16.5-17.9%) for clarithromycin, 26.7% (95% CI: 25.2-28.1%) for metronidazole, 11.2% (95% CI: 9.6-12.7%) for amoxycillin, 16.2% (95% CI: 14.4-18%) for levofloxacin, 5.9% (95% CI: 4.7-7.1%) for tetracycline, 1.4% (95% CI: 0.81-9%) for rifabutin and 9.6% (95% CI: 8.5-10.7%) for multiple antibiotics. Prevalence rate of clarithromycin, metronidazole, and levofloxacin resistance significantly increased from Europe to Asia, America and Africa. Tetracycline resistance is low (<3%) in all countries, but Africa (43.9%). Prevalence of clarithromycin resistance was higher in non-ulcer dyspepsia patients, whilst metronidazole resistance was higher in peptic ulcer patients. Both resistances were significantly higher in female than in male patients. Data regarding amoxicillin resistance are highly conflicting. **Conclusion**. The worldwide H. pylori antibiotic resistance towards different antibiotics has increased. Such a phenomenon may affect therapeutic management in different countries.

Key words

Helicobacter pylori – antibiotic – resistance – worldwide.

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Introduction

H. pylori antibiotic resistance is the main factor affecting efficacy of current therapeutic regimens [1]. Prevalence of bacterial resistance varies in different geographic areas, and it has been correlated with the consumption of antibiotics in the general population [2, 3]. For instance, clarithromycin consumption and its resistance similarly increased fourfold in Japan between 1993 and 2000 [4]. On the contrary, a prudent use of macrolides in Northern European countries during the past decades was associated with a lower H. pylori clarithromycin resistance rate as compared to Southern European countries, where clarithromycin is largely used [5-7]. The current European guidelines on H. pylori management suggest that first-line therapy should be tailored according to both clarithromycin and metronidazole resistance. Indeed, a longer, 14-day triple therapy is advised where primary clarithromycin resistance is >15-20%, preferring the association with amoxicillin if primary metronidazole resistance is >40% [8]. On this basis, monitoring antibiotic resistance prevalence is meaningful for H. pylori infection management in clinical practice. We pooled recent data on primary H. pylori resistance towards different antibiotics in different countries.

Methods

Literature search

Separate computer-assisted searches were performed using PubMed. Each search was performed on all English language articles published through January 2006 to December 2009, using the exploded medical subject heading terms Helicobacter pylori resistance, antibiotic, clarithromycin, metronidazole, amoxicillin, levofloxacin, ciprofloxacin, quinolones, tetracycline, rifabutin, and rifampicin. Boolean operators (NOT, AND, OR) also were used in succession to narrow and widen the search. Only those studies concerning primary antibiotic resistance were taken into account, whilst data on secondary resistance following treatment was not considered. Full articles of all relevant studies were retrieved, and manual searches

of reference lists from identified relevant articles were performed to find any additional studies that might have been missed. When more than one publication from the same investigator or group was available, only the most updated version, including the entire sample size, was included in this pooled-data analysis, whilst data published only in abstract form were not considered.

Data extraction

Two investigators (V.D.F and A.Z.) extracted the data from the studies that met the selection criteria. Data were extracted concerning the following: (1) number of patients included, (2) number of cases with bacterial resistance to one or different antibiotics, (3) number of cases with antibiotic resistance according to: age (<18 years: young patients, and >18 years: adult patients), sex distribution, and gastroduodenal pathology, either directly provided or calculated, (4) the method used for resistance assessment, and (5) the geographic area involved. Both investigators of this study approved the data extraction method and a final accord was achieved for the three trials with discordant data interpretation.

Statistical analysis

Statistical analysis was performed by using the chi-squared test and Fisher's exact test, as appropriate. The odds ratio and 95% confidence interval were also calculated. Differences were considered significant at 5% probability level. Analyses were performed by using Statsoft 7.1 program for Windows XP.

Results

Overall resistance

A total of 31 studies meeting the inclusion criteria were identified, reporting data of patients enrolled from 1993 to 2009. In detail, there were 17 European [9-25], 10 Asian [26-35], 2 African [36, 37] and 2 American studies [38, 39]. The overall H. pylori antibiotic resistance rates were 17.2% (16.5-17.9%) for clarithromycin, 26.7% (25.2-28.1%) for metronidazole, 11.2% (9.6-12.7%) for amoxycillin, 16.2% (14.4-18.0%) for levofloxacin, 5.9% (4.7-7.1%) for tetracycline, 1.4 (0.8-1.9%) for rifabutin, and 9.6% (8.5-10.7%) for two or more antibiotics. Detailed resistance rates towards antibiotics in different continental areas and countries are reported in Tables I and II.

Primary clarithromycin resistance

As shown in Table I, primary clarithromycin resistance was detected in 2,014 (17.2%, 95% CI: 16.5-17.9) out of 11,697 cases. An increasing trend was observed in Europe (352/3,156, 11.1%; 95% CI: 10.0-12.2), in Asia (1,544/8,139, 18.9%; 95% CI: 18.1-19.8) and America (118/402, 29.3%; 95% CI: 24.9-33.8), the difference being statistically significant ($p<0.001$) among the three geographical areas. Among the European countries, the highest resistance was reported in Spain (49/101, 49.2%, 95% CI: 38.7-58.2), whilst the lowest in Sweden (5/333, 1.5%, 95% CI: 0.1-2.8) and The Netherlands (11/1223, 0.8%, 95% CI: 0.3-1.4). In Asian countries, a high clarithromycin resistance rate was detected in Japan (25/61, 40.7%, 95% CI: 28.5-53.3), while the lowest value was found in Malaysia (4/187, 2.1%, 95% CI: 0.06-4.2).

Overall, clarithromycin resistance was present in 790 out of 3,851 female and in 964 out of 6,185 male patients (20.5% vs. 15.5%, $p<0.001$; OR: 1.4, 95% CI = 1.2-1.5), as well as in 386 out of 1,490 non-ulcer dyspepsia and in 408 out of 2,240 peptic ulcer patients (25.9% vs. 18.2%, $p<0.001$; OR: 1.6, 95% CI = 1.3-1.8). Similar values were detected in young (36 out of 174) as compared to adult (2,031 out of 11,794) patients (20.6% vs. 17.2%, $p>0.05$). According to the method used, clarithromycin resistance was detected in 208 out of 943 cases evaluated by using PCR-based methods and in 1,729 out of 10,377 cases studied by a culture-dependent method (E-test, agar dilution, disk diffusion). The difference was statistically significant (22.0% vs. 16.6%, $p<0.001$; OR: 1.4, 95% CI = 1.2-1.6).

Primary metronidazole resistance

Primary metronidazole resistance was detected in 948 out of 3,549 patients (26.7%; 95% CI: 25.2-28.1), decreasing in Africa (159/172, 92.4%; 95% CI: 88.4-96.3), America (177/401, 44.1%, 95% CI: 39.2-49.0), Asia (192/517, 37.1%; 95% CI: 32.9-41.3), to Europe (420/2,459, 17.0%; 95% CI: 15.5-18.5). The difference was statistically significant ($p<0.05$) among the four geographic areas. As shown in

Table I. Antibiotic resistance rates in different continental areas.

Area	Amoxycillin	Clarithromycin	Metronidazole	Tetracycline	Levofloxacin	Multidrugs
America	8/352	118/402	177/401	11/393	NA	53/352
	(2.2%)	(29.3%)	(44.1%)	(2.7%)		(15.0%)
Africa	113/172	NA	159/172	58/132	0/40	NA
	(65.6%)		(92.4%)	(43.9%)	(0.0%)	
Asia	60/517	1,544/8,139	192/517	11/456	106/908	21/252
	(11.6%)	(18.9%)	(37.1%)	(2.4%)	(11.6%)	(8.3%)
Europe	3/599	352/3156	420/2,459	14/599	148/614	204/2,272
	(0.5%)	(11.1%)	(17.0%)	(2.1%)	(24.1%)	(8.9%)
Overall	184/1,640	2,014/11,697	948/3,549	94/1,580	254/1,562	278/2,876
	(11.2%)	(17.2%)	(26.7%)	(5.9%)	(16.2%)	(9.6%)

Table II. Antibiotic resistance rates in different countries

	Year	Patients	AMO (%)	CLA (%)	MTZ (%)	TET (%)	LEV (%)	RIF (%)	Multidrug (%)	Ref
Europe										
Bulgaria	2004-08	266	1.1	15.4	24	4.9			4.9	9
Denmark	2001-03	81		11	28					10
Ireland	2005-06	45		8.8	20				2.2	12
Italy	2003-06	146		37.6						13
Italy	2001	156		24.3						14
Italy	2004-06	255		11.0	20		10.6		10.5	15
Italy	2003	300		12.5	23.9				4.3	16
Germany	2003-06	1585						1.4		17
Germany	2006-07	1118							15.1	18
Spain	2002-06	101		49.2	32.8					19
Sweden	2002	333	0	1.5	14.4	0.3			0.6	20
The Netherlands	1997-02	1123		1	14.4					21
Turkey	2002-03	87		27.5						22
Turkey	2003-04	110		48.2						23
Turkey	2005-06	92		40.5						24
Turkey	2006-07	61		16.4						25
United Kingdom	2008	255					7.5	6.6		11
Asia										
China	2000	41		32						30
Japan	1996-08	3521		20.6						26
Japan	2001-04	507					14.9			27
Japan	2002-05	3707		22.7						28
Japan	2002-07	61 (children)	0	40.7	14.8					29
Hong Kong	2004-05	191					2.6		8.9	32
Korea	2003-05	113	8.8	12.4	49.6	8.8	12.3			31
Malaysia	2005-07	120		2.1						35
Taiwan	1998-07	210	1	9.5	27.6	0.5	11.9			33
Taiwan	2004-05	133	36.1	13.5	51.9	0				34
North America										
Alaska	1999-03	352	2.2	31	44	0			15	36
South America										
Chile	2005-06	50		20	44.9	26.8				37
Africa										
Senegal	1999-00	40	0		90		0			38
Cameroon	2006	132	85.6	44.7	93.2	43.9				39

AMO - amoxycillin; CLA - clarithromycin; MTZ - metronidazol; TET - tetracycline; LEV - levofloxacin; RIF - rifabutin

Table III, the lowest metronidazole resistance in Europe was observed in Sweden (48/333, 14.4%; 95% CI: 10.6-18.1) and The Netherlands (162/1,123, 14.4%; 95% CI: 12.3-16.4), the highest being detected in Denmark (23/81, 28.3%, 95% CI: 18.5-38.2). In Asia, metronidazole resistance rate was high in Korea (56/113, 49.6%; 95% CI: 40.3-58.7) and low in Japan (9/61, 14.7%; 95% CI: 5.8-23.6).

Overall, metronidazole resistance was present in 416 out of 1,321 female and in 276 out of 1,302 male patients (31.4% vs. 21.1%, p<0.001; OR: 1.7, 95% CI = 1.4-2.0). Resistance was detected in 61 out of 169 patients with peptic ulcer and in 59 out of 453 patients with non-ulcer dyspepsia (36.0% vs. 13.0%, p<0.01, OR: 3.7, 95%CI: 2.4-5.7).

Primary amoxicillin resistance

Amoxicillin resistance was detected in 184 out of 1,640 tested patients (11.2%; 95% CI: 9.6-12.7). In Europe, available data from two studies enrolling 599 patients found a prevalence rate <1% (3/599, 0.5%, 95%CI: 0.06-1,06). On the contrary, conflicting data were reported in two African studies. Indeed, amoxicillin resistance was absent in a study from Senegal enrolling 40 patients, whilst an astonishingly

Table III. Multidrug resistance rates in different countries

	CLA+MTZ (%)	CLA+LEV (%)	MTZ+LEV (%)	CLA+MTZ+ LEV (%)	CLA+MTZ+ RIF (%)	CLA+LEV+ RIF (%)	CLA+LEV+ RIF+MTZ (%)	REF
Alaska				15				36
Bulgaria	4.9						4.9	9
Germany				13.4	0.9	0.08	0.7	18
Hong Kong	5.2	3.7						32
Ireland	2.2							12
Italy	4.3							16
Italy	3.5	1.6	4.9	0.8				15
Japan	6.6							29
Sweden	0.6							20

CLA - clarithromycin; MTZ - metronidazol; LEV - levofloxacin; RIF - rifabutin

high prevalence was reported in Cameroon (113/132, 85.6%; 95% CI: 76.9-91.5). Similarly, the prevalence of amoxicillin resistance widely varies in Asian countries, ranging from 0% in 61 patients in Japan, 8.8% (10/113; 95% CI: 3.6-14.0) in Korea, and 36.1% (48/133; 95% CI: 27.9-44.2) in Taiwan, although another study performed in Taiwan found a prevalence as low as 0.9% (2/210, 95% CI: 0.3-2.2). A single study enrolling 352 patients found a 2.2% (8/352, 95% CI: 0.7-3.8) amoxicillin resistance prevalence in Alaska. Amoxicillin resistance was similarly detected in male and female patients, being present in 4 (0.8%) out of 497 cases and in 7 (1.5%) out of 454 cases, respectively (p>0.05).

Primary levofloxacin resistance

Levofloxacin resistance was found in 254 out of 1,562 (16.2%, 95% CI: 14.4-18.0). The prevalence rate was higher in Europe (148/614, 24.1%, 95%CI: 20.7-27.4) as compared to Asia (106/908, 11.6%; 95% CI: 9.5-13.7%), and it was absent in 40 African tested patients. In Asia, different values among countries were detected, the resistance rate being 14.9% (76/507; 95% CI: 11.8-18.0) in Japan, 11.9% (25/210, 95% CI: 7.5-16.2) in Taiwan, and 2.6% (5/191, 95%CI: 0.3%-4.8%) in Hong Kong. In a single Italian study testing 246 patients, levofloxacin resistance was higher in older (>45 years) than younger patients (28.4% vs. 14.4%, p<0.05, OR: 1.8, 95%CI: 1.2-3.9).15

Primary tetracycline resistance

Tetracycline resistance was detected in 94 out of 1,580 tested patients (5.9%; 95% CI: 4.7-7.1). The overall prevalence rate did not significantly differ between Europe (14/599, 2.1%; 95% CI: 1.1-3.5), Asia (11/456, 2.4%; 95% CI: 1.0-3.8) and America (11/393, 2.7%, 95% CI: 1.1-4.4), whilst it was significantly higher in Africa (58/132, 43.9%; 95% CI: 35.4-52.4). In detail, the resistance was absent in 352 patients from Alaska, and very low in Sweden (1/333, 0.3%; 95% CI: 0-2) and in Taiwan (1/343; 0.2%; 95% CI: 0-2). In contrast, increased values were found in Korea (10/113, 8.8%; 95% CI: 3.6-14.0), Chile (11/41, 26.8%; 95% CI: 13.2-40.3) and Cameroon (58/132, 43.9%; 95% CI: 35.4-52.4).

Tetracycline resistance was similarly present in male and female, being detected in 7 (1.2%) out of 552 male and in 7 (1.3%) out of 532 female patients (p>0.05).

Primary rifabutin resistance

Isolate rifabutin resistance was tested in only two studies, [11, 17] showing the presence of a resistant strain in 22 out of 1,585 patients in Germany (1.4%; 95% CI: 0.8-1.9), and in 17 out of 255 patients in England (6.6%; 95% CI: 3.6-9.7).

Primary multiple antibiotic resistance

Overall, a multiple antibiotic resistance was found in 278 out of 2,876 tested (9.6%, 95% CI: 8.5-10.7). Multiple resistant strains were detected in 21 out of 252 Asiatic patients (8.3%, 95%CI: 4.9-11.7), in 53 out of 352 American patients (15.0%, 95%CI: 11.3-18.7) and in 204 out of 2,272 European patients (8.9%, 95% CI: 7.8-10.1). Low values of clarithromycin/metronidazole double resistance have been observed in Sweden (0.6%) and in Ireland (2.2%), whilst a peak of multiple resistance is observed in Germany (15.1%). Detailed multiple antibiotic resistance rates in different continental areas and countries are reported in Table III.

Discussion

During the last two decades a widespread use of certain antibiotics (i.e. clarithromycin for respiratory infections or levofloxacin for urinary infections) in the general population has increased the occurrence of primary H. pylori resistance in different countries [1-4]. Primary H. pylori resistance towards antibiotics involved in the current eradication regimens affects the therapeutic outcome. In detail, the presence of either clarithromycin or metronidazole resistance significantly reduces the success rate of first-line anti H. pylori therapy [3]. Based on these observations, current European guidelines suggest to prolong standard triple therapy to 14 days where primary clarithromycin resistance is >15-20%, preferring the association with amoxicillin if primary metronidazole resistance is >40% [8]. Therefore, the knowledge of the actual prevalence towards the most used antibiotics for H. pylori eradication is of pivotal relevance

for clinical practice. The present study systematically reviewed the recent data on primary antibiotic resistance. The first relevant finding was that H. pylori resistance toward clarithromycin - the most powerful antibiotic currently available for infection - is increasing worldwide. Updated data of the present study found levels of primary clarithromycin resistance as high as 48.2-49.2% (with values >20% in 6 studies) in some European countries whilst the highest values previously found in 2000 were 22-23.4% (with values >20% in 2 studies) [3]. We also calculated that clarithromycin resistance is significantly higher when estimated by a PCR-based method as compared to culture, leading to some uncertainty for the clinical application of information. However, we recently observed that when phenotypic clarithromycin resistance is genetically due to a specific point mutation - namely A2143G - the eradication rate is extremely low [40]. Of note, primary clarithromycin resistance rates are significantly higher in female than in male patients, as well as in non-ulcer dyspepsia than in peptic ulcer patients. These observations could be taken into account for tailoring first-line therapy in clinical practice.

We calculated that metronidazole resistance significantly increased from Europe to America, Asia and Africa. In detail, the overall European resistance is 17%, being constantly <40% in all countries, whilst it is distinctly higher in both Asia and America. The comparison with data of studies previously published showed that primary metronidazole resistance remains substantially stable in European countries [3]. Therefore, according to current guidelines, metronidazole should be preferred to amoxicillin in first-line therapy in Europe [8] but not in Asian patients. A study performed in Italy found that primary metronidazole resistance was present in 22.9% and in 50% of Italian and immigrant patients, respectively, suggesting that foreign patients probably should be given a different first-line therapy [15]. As for clarithromycin, our analysis demonstrated a significantly higher prevalence of metronidazole resistance in females. Therefore, for a clinical perspective, a female patient may have a low probability of success with a clarithromycin-metronidazole combination, such a hypothesis deserving a specific prospective study.

The prevalence of levofloxacin resistance seems to be increasing worldwide. This could reduce the efficacy of H. pylori eradication with therapeutic regimens including levofloxacin. Therefore, its use should be reserved as a second-line therapy as suggested in current Italian, US and Asian guidelines [41-43]. With the exclusion of Africa (43.9%), tetracycline resistance rate remains very low (<3%) in all countries, showing no substantial increase as compared with the data of studies published before 2000 [3]. Unfortunately, tetracycline-based regimens require the use of bismuth salts which are no longer available in several European countries due to possible side-effects [44, 45]. Finally, data on primary amoxicillin resistance are highly conflicting. Indeed, it is virtually absent in several countries and as high as 85% in Cameroon. It remains difficult to interpret this observation, and the complexity of amoxicillin resistance mechanisms (pbp gene mutations, membrane permeability alterations, efflux pumps, etc.) may play a role.

Conclusion

Worldwide H. pylori antibiotic resistance towards different antibiotics is increasing. These data highlight the need of a constant surveillance of H. pylori antibiotic resistance, so that tailoring therapy is feasible for clinical practice.

Conflicts of interest

No funding required. No conflict of interest.

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