HELICOBACTER PYLORI

Prospective multicentre study on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in Europe

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Aim: To prospectively assess the antibacterial resistance rate in *Helicobacter pylori* strains obtained from symptomatic children in Europe.
Methods: During a 4-year period, 17 paediatric centres from 14 European countries reported prospectively on patients infected with *H pylori*, for whom antibiotic susceptibility was tested.
Results: A total of 1233 patients were reported from Northern (3%), Western (70%), Eastern (9%) and Southern Europe (18%); 41% originated from outside Europe as indicated by mother's birth-country; 13% were <6 years of age, 43% 6–11 years of age and 44% >11 years of age. Testing was carried out before the first treatment (group A, n = 1037), and after treatment failure (group B, n = 196). Overall resistance to clarithromycin was detected in 24% (mean, A: 20%, B: 42%). The primary clarithromycin resistance rate was higher in boys (odds ratio (OR) 1.58; 1.12 to 2.24, p = 0.01), in children <6 years compared with >12 years (OR 1.82, 1.10 to 3.03, p = 0.020) and in patients living in Southern Europe compared with those living in Northern Europe (OR 2.25; 1.52 to 3.30, p<0.001). Overall resistance rate to metronidazole was 25% (A: 23%, B: 35%) and higher in children born outside Europe (A: adjusted. OR 2.42, 95% CI: 1.61 to 3.66, p<0.001). Resistance to both antibiotics occurred in 6.9% (A: 5.3%, B: 15.3%). Resistance to amoxicillin was exceptional (0.6%). Children with peptic ulcer disease (80/1180, 6.8%) were older than patients without ulcer (p = 0.001).
Conclusion: The primary resistance rate of *H pylori* strains obtained from unselected children in Europe is high. The use of antibiotics for other indications seems to be the major risk factor for development of primary resistance.

Triple treatment including a proton pump inhibitor plus two antibiotics (chosen between clarithromycin, metronidazole and amoxicillin) has been recommended to treat children with *Helicobacter pylori* infection.[1 2] The main factors for treatment failure are bacterial resistance to the antibiotics used in the regimen and low compliance with drugs.[3 4] Treatment failure is highly predictive if (1) the *H pylori* strain is resistant to macrolides and (2) clarithromycin is part of the regimen.[5–7] Resistance to metronidazole also affects the efficacy of the treatment if metronidazole is used as part of triple treatment, but to a much lesser extent, in both children[8] and adults.[9 10]

In the Western and Northern European countries, most of the children infected with *H pylori* are from immigrant families originating from African or Asian countries where the primary resistance to metronidazole is high. Resistance to clarithromycin appears to increase in children over time in some European countries, possibly because of the use of macrolides to treat respiratory tract infections.[11 12] In the US, a high resistance rate for clarithromycin in the children infected with *H pylori* was reported and would explain the high failure rate of clarithromycin based triple treatment.[13 14] However, most publications are from single centres or include only a small number of children.

In 1996, a European Paediatric Task Force was founded including paediatric gastroenterologists as well as microbiologists and epidemiologists from different European countries. A consensus report,[15] and several multicentric studies on diagnostic or therapeutic issues in paediatric *H pylori* infection have been published[16 17] or are currently underway. In 1998, a databank was created, in which our group members participated. The aim of the present study was to assess the primary and secondary antibiotic resistance of *H pylori* strains obtained from children living in Europe over a 4-year period. Other aims were to identify risk factors for *H pylori* resistance against amoxicillin, clarithromycin, metronidazole and double resistance against clarithromycin plus metronidazole before the first treatment.

PATIENTS AND METHODS

Study centres and inclusion criteria

Members of the European Paediatric Task Force for *H pylori* infection were asked to submit data on consecutive patients ⩽18 years of age with a positive culture and who had undergone antibiotic susceptibility testing. Seventeen centres from 14 different European countries participated: three Scandinavian countries (Finland, Sweden and Denmark) combined as Northern Europe, three Eastern European countries from the former East block (Poland, Hungary and Croatia), four countries from Southern Europe (Greece, Italy, Spain and Portugal) and four from Western Europe (Belgium, France, Germany and Austria). The ethics committee of the

Abbreviation: MIC, minimal inhibitory concentration

University of Munich approved the protocol for the anonymous data collection and analysis.

Questionnaire

The study centres provided the following items on a standardised questionnaire: age, sex, country at the time of endoscopy (country of study centre), country of birth of the child and the mother, the presence of gastric or duodenal peptic ulcer disease upon endoscopy and whether the child had ever received treatment for *H pylori* infection in the past.

Bacterial culturing and antibiotic susceptibility testing

Cultures for *H pylori* and antibiotic susceptibility testing for metronidazole, clarithromycin and amoxicillin were carried out at the local sites. Minimal inhibitory concentration (MIC) breakpoints for resistance were defined as follows: metronidazole >8 μg/ml; clarithromycin ⩾1.0 μg/ml; amoxicillin ⩾0.5 μg/ml. Most centres used the epsilometer test (E test), but in three centres the agar diffusion technique was followed. A patient was considered to harbour a double resistant strain if testing for metronidazole and clarithromycin gave results above the given breakpoints.

Statistical analysis

Statistical analysis was carried out using STATA 7.0 statistical software (Strata Corporation, Texas, USA, 1997). The distribution of resistance to metronidazole or clarithromycin, and of the presence of ulcer was compared in different strata of variables. A univariate analysis was carried out on all of the patients with no missing values for all of the factors considered. The odds were calculated for the resistance to metronidazole, clarithromycin, metronidazole plus clarithromycin (double resistance) and for the presence of peptic ulcer. All variables significantly associated with the studied event ($p \leqslant 0.25$) were included in a multiple logistic regression model. All models were adjusted for sex and age, as a variable divided into three age groups. All variables associated with resistance or the presence of peptic ulcer were gathered into a final model. The multivariate analysis was carried out by a logistic regression, using a backward elimination procedure of variables not significantly associated with resistance or the presence of an ulcer ($p \leqslant 0.05$). Estimated odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. Interaction and confusion were tested among all of the variables included in the final model.

For each calculation, two populations were considered and two multiple logistic regression analyses conducted. The first one included only the patients having no missing values for the factors included in the multivariate analysis, whereas the second one considered exactly the same population as in the univariate analysis. The aim of the first analysis was to use as many patients as possible, whereas the second analysis simplified the presentation of the results with the same samples as in the univariate analysis. As no major differences were noted between the two models, only the last one is reported in the results section.

RESULTS

Between January 1999 and December 2002, a total of 1233 patients were included in the database; 46.7% were males, 13% were <6 years of age, while equal proportions comprised the other two age groups (6–12 years: 43% and >12 years: 44%). The majority (n = 1037) were tested for upper abdominal symptoms before any specific treatment for *H pylori* infection (group A) was given, while 196 children were tested after, at least one failed treatment. There was a slight, but not significant decrease in registered patients over the 4-year period. The country of birth was outside Europe for 14.6% of the children, but for 41.3% of the mothers, indicating the high percentage of immigrants, particularly from Africa and the Middle East.

Table 1 gives the absolute numbers of the patients and their characteristics, including the results of susceptibility testing for the total study group, and the two subgroups, group A without and group B with previous anti-*H pylori* treatment.

Antibiotic resistance before the first treatment (group A)

Amoxicillin

Resistance to amoxicillin was a rare event (6/1037, 0.6%), with 2 patients reported from Greece, and one each from Croatia, Italy, Finland and Poland.

Clarithromycin

Resistance to clarithromycin was detected in 20% of the strains (199/991) obtained before the first treatment. In the univariate analysis, important risk factors were: age <6 years, male sex, living in Southern Europe and country of birth of the child and his/her mother in Western or Southern Europe (table 2). The final logistic regression model showed a 2.25 times higher risk for primary clarithromycin resistance, if the child grew up in Southern Europe ($p<0.001$). Young age and male sex remained independent major risk factors (table 3).

Metronidazole

Primary resistance to metronidazole was found in 23% of the strains (233/1024). In the univariate analysis, only two factors were found to be of considerable risk for primary resistant to metronidazole: country of birth of the child and the mother (table 4). Multilogistic regression models showed that patients born in Asia, Africa or Middle East had a 2.4 times higher risk (95% CI 1.61 to 3.66) of being infected with a metronidazole resistant strain than patients of equal age and sex born in Western, Northern or Southern Europe ($p<0.001$; table 5). No interaction was found between the different variables in the final model.

Double resistance

A primary resistance against both clarithromycin and metronidazole was found in 53 of 992 (5.3%) strains. No significant risk factors could be identified, except that in 2001 fewer children were diagnosed with a double resistant strain.

Antibiotic resistance after at least one failed treatment (group B)

When patients with treatment failure were compared with untreated children (before the first treatment), no difference was identified in the factors assessed except for antibiotic resistance. The chance to harbour a resistant strain significantly increased after failed treatment, for clarithromycin from 20% to 42% ($p<0.001$), for metronidazole from 23% to 35% ($p = 0.001$), and for resistance to both from 5.3% to 15.3% ($p<0.001$), although the amoxicillin resistance rate remained the same (0.6%; table 1). No other identified risk factor was linked to secondary antibiotic resistance.

Peptic ulcer disease

Peptic ulcer disease was diagnosed in 6.8% of the children (80/1180), with no difference between untreated children (before first treatment) or after treatment failure (table 1). No relation was found between antibiotic susceptibility and peptic ulcer disease. The only significant risk factor linked to peptic ulcer disease was age. Patients with peptic ulcer disease were significantly older (12.5 years, 95% CI 11.8 to 13.2) compared with patients with gastritis only (10.9 years 95% CI 10.6 to 11.1; $p = 0.001$). The rate of peptic ulcer

Table 1 Sex, age, country of residence, country of birth of the child and the mother, year and results of antibiotic susceptibility testing (n = 1233)

Factors	Description	All patients (n = 1233)	Group A before treatment (n = 1037)	Group B after treatment failed (n = 196)
Sex, n = 1197	Male	559	465	94
	Female	638	542	96
Age (years), n = 1232	<6	162	137	25
	6–11	531	448	83
	⩾12	539	452	87
Country of residence, n = 1024	Northern Europe	43	34	9
	Southern Europe	222	192	30
	Eastern Europe	107	88	19
	Western Europe	861	723	138
Country of birth, n = 1108	Northern Europe	29	22	7
	Southern Europe	224	196	28
	Eastern Europe	172	139	33
	Western Europe	521	426	95
	Asia, Africa, America and Middle East	162	147	15
Mother's country of birth, n = 1070	Northern Europe	15	13	2
	Southern Europe	214	187	27
	Eastern Europe	187	150	37
	Western Europe	212	183	29
	Asia, Africa, America and Middle East	442	365	77
Diagnostic year, n = 1233	1999	371	316	55
	2000	298	255	43
	2001	299	245	54
	2002	265	221	44
Peptic ulcer, n = 1180	No	1100	930	170
	Yes	80	68	12
Metronidazole resistance, n = 1216	Susceptible	916	791	125
	Resistant	300	233	67
Clarithromycin resistance, n = 1181	Susceptible	903	792	111
	Resistant	278	199	79
Amoxicillin resistance, n = 1094	Susceptible	1087	923	164
	Resistant	7	6	1
Metronidazole and clarithromycin resistance, n = 1181	Metro and clari susceptible	1099	939	160
	Metro and clari resistant	82	53	29
Metro, Clari and Amox resistance, n = 1146	Metro/clari and amox susceptible	647	579	68
	Only metro resistant	216	179	37
	Only clari resistant	196	146	50
	Only amox resistant	3	3	0
	Metro and clari resistant	80	51	29
	Metro and amox resistant	2	1	1
	Clari and amox resistant	0	0	0
	Metro and clari and amox resistant	2	2	0

disease was low in children <6 years of age (3.5%, 4/118), and between 6 and 11 years of age (4.6%, 17/390); it increased to 10.4% in patients older than 11 years. The final logistic regression model showed an adjusted OR of 3.10 (1.07 to 8.95) for children >11 years compared with the youngest age group (p = 0.036) of the same sex.

DISCUSSION

Antibiotic resistance in *H pylori* is a serious public health problem, because about 10–15% of infected people develop severe complications in adult life like peptic ulcer disease and gastric malignancies, and only cure of the infection prevents these sequelae. Large numbers of cases are needed to obtain reliable results for the prevalence rate of antibiotic resistance. Such studies have been carried out on *H pylori* strains isolated from adults in Europe (n = 1274)[18] and the US (n = 347).[19] However, such investigations have never been conducted on a sufficient number of children despite the fact that the context of prescribing antibiotics is different.

The main aim of our study was to obtain reliable data by including a large number of previously untreated and unselected *H pylori* infected children. To avoid any selection and reporting bias, every child with a successful susceptibility testing was included. The contributing centres conducted culture tests for *H pylori* as part of the routine work up during upper endoscopy with a success rate for culture of >80%, as previously shown.[17] Although the participating centres were mostly University hospitals, a selection bias for children with a higher likelihood for a primary antibiotic resistance rate is unlikely. Most patients in this study were referred for the procedure from the caring doctor because of upper abdominal pain, some with a positive non-invasive diagnostic test indicating *H pylori* infection.

The multicentric character of our study caused several limitations. There was an uneven distribution of patients from the different countries, with fewer patients from Scandinavia. The results of the different countries were analysed separately, and thereafter in groups according to their geographical region. Countries from the former East block were combined, because in these countries the availability of expensive antibiotics, like second-generation macrolides, may be different and could influence the antibiotic resistance pattern.

Owing to logistic and financial constraints, cultures and antibiotic susceptibility testing were not carried out in a central bacteriology laboratory, as was the case in the European and North American studies on adults.[18 19] Two different methods were used for susceptibility testing: E test

Table 2 Univariate analysis of factors associated with metronidazole resistance among paediatric patients not previously treated for *Helicobacter pylori* infection (n = 831)

Factors	Description	Metronidazole susceptible n = 635	Resistant n = 196	OR	95% CI	p Value
Sex	Male	283	91	1		
	Female	352	105	0.93	(0.67 to 1.28)	0.647
Age (years)	<6	90	24	1		
	6–11	280	87	1.17	(0.70 to 1.94)	0.557
	>11	265	85	1.20	(0.72 to 2.01)	0.480
Country of birth	Western Europe	457	117	1		
	Eastern Europe	98	29	1.16	(0.73 to 1.83)	0.538
	Asia, Africa, America and Middle East	80	50	2.44	(1.62 to 3.67)	$<10^{-3}$
Mother's country of birth	Western Europe	281	72	1		
	Eastern Europe	111	33	1.16	(0.73 to 1.85)	0.533
	Asia, Africa, America and Middle East	243	91	1.46	(1.03 to 2.08)	0.035
Country of residence	Northern Europe	23	7	1		
	Southern Europe	143	41	0.94	(0.38 to 2.35)	0.898
	Eastern Europe	64	20	1.03	(0.38 to 2.75)	0.958
	Western Europe	405	128	1.04	(0.44 to 2.48)	0.932
Date of investigation	1999	176	55	1		
	2000	157	53	1.08	(0.70 to 1.67)	0.728
	2001	167	44	0.84	(0.54 to 1.32)	0.457
	2002	135	44	1.04	(0.66 to 1.64)	0.856
Peptic ulcer	No	596	185	1		
	Yes	39	11	0.91	(0.46 to 1.81)	0.785

CI, confidence interval; OR, odds ratio.
p Value obtained by a univariate logistic model.

and agar diffusion. For clarithromycin, a perfect correlation was shown when these two methods were compared on the same isolates.[20] However, differences were observed with respect to metronidazole because there is a continuum of MICs rather that a double population. In this study, MIC values were reported from 852 isolates. As expected, the distribution curve showed a much better separation between positive and negative results for clarithromycin compared with metronidazole. Only 31 (3.6%) patients harboured isolates with MIC values for clarithromycin within 4 dilutions of the cut off value (MIC range 0.25–2.0), whereas this was the case in 73 (8.6%) patients for metronidazole (MIC range 4.0–32). Therefore, differences between the laboratories probably had only a minor effect on the resistance rates, particularly for clarithromycin.

In contrast with the European multicentre study on adults,[18] reliable information was obtained with respect to previous anti-*H pylori* treatment. Parents tended to have reasonable recall of whether or not their child had been treated for the infection. However, they often did not remember the names of the antibiotics the child had taken in the past. Therefore, the term primary resistance applies to the absence of any previous specific anti-*H pylori* treatment, and not to any previous intake of amoxicillin, clarithromycin and metronidazole. In the US data base, previous treatment was recorded, but pre-treatment resistance rates were not calculated.[19] However, this information is essential for the surveillance of primary resistance and to give guidelines for first line treatment.

The primary resistance rate of isolates from children was 20% for clarithromycin and 23% for metronidazole. No representative data for comparison with adults living in Europe are available in the literature. The results of the European multicentre survey represents 17 European countries, but did not distinguish between isolates from patients before or after failed treatment.[18]

By contrast, the European MACH2 study recruited most patients from Northern and Western Europe.[20] Therefore, we could only compare results of primary resistance from 515 adults in Germany during the years 1999 and 2000[21] with the results obtained in our study from children living in Germany (before treatment n = 201). The resistance rate for clarithromycin was markedly lower in adults than in children (2.7% *v* 15.9%). By contrast, for metronidazole the resistance rates were very similar in adults and children (25% *v* 27.5%).

The presence of a resistant strain may indicate the transmission of a resistant strain or in vivo selection of resistance. The similar rate of metronidazole resistance in children and adults is in favour of the transmission of a resistant strain to the children. Children acquire the *H pylori*

Table 3 Final logistic regression model for metronidazole resistance among patients not previously treated for *Helicobacter pylori* infection and no missing data for all of the factors considered in the univariate analysis (n = 831)

	Unadjusted OR	Adjusted OR	95% CI	p Value
Sex (women *v* men)	0.93	0.92	(0.66 to 1.28)	0.620
Age (*v* <6 years)				
6–11	1.17	1.09	(0.65 to 1.83)	0.739
>11	1.20	1.09	(0.64 to 1.85)	0.751
Country of birth (*v* Western Europe)				
Eastern Europe	1.16	1.15	(0.72 to 1.84)	0.557
Asia, Africa, America and Middle East	2.44	2.42	(1.61 to 3.66)	$<10^{-3}$

Table 4 Univariate analysis of factors associated with clarithromycin resistance among paediatric patients not previously treated for *Helicobacter pylori* infection (n = 800)

		Clarithromycin				
		Susceptible n = 633	Resistant n = 167	OR	95% CI	p Value
Sex	Female	364	76	1		
	Male	269	91	1.62	(1.15 to 2.82)	0.006
Age (years)	>11	275	56	1		
	6–11	278	78	1.38	(0.94 to 2.02)	0.100
	<6	80	33	2.03	(1.23 to 3.33)	0.005
Country of birth	Western Europe	437	134	1		
	Eastern Europe	88	14	0.52	(0.29 to 0.94)	0.031
	Asia, Africa, America and Middle East	108	19	0.57	(0.34 to 0.97)	0.038
Mother's country of birth	Western Europe	258	94	1		
	Eastern Europe	98	19	0.53	(0.31 to 0.92)	0.023
	Asia, Africa, America and Middle East	277	54	0.54	(0.37 to 0.78)	0.001
Country of residence	Northern Europe	30	1 (3.3%)	1		
	Southern Europe	122	59 (32.5%)	14.51	(1.93 to 108.98)	0.009
	Eastern Europe	47	10 (17.5%)	6.38	(0.78 to 52.44)	0.085
	Western Europe	434	97 (18.2%)	6.71	(0.90 to 49.77)	0.063
Country of residence	Northern, Eastern and Western Europe	511	108 (17.4)	1		
	Southern Europe	122	59 (32.5%)	2.29	(1.57 to 3.33)	$<10^{-3}$
Date of investigation	⩽1999	178	45	1		
	2000	146	48	1.30	(0.82 to 2.06)	0.265
	2001	161	44	1.08	(0.68 to 1.72)	0.744
	⩾2002	148	30	0.80	(0.48 to 1.34)	0.397
Peptic ulcer	No	589	161	1		
	Yes	44	6	0.50	(0.21 to 1.19)	0.117

p Value obtained by a univariate logistic model.

infection mainly from their infected parents, mostly their mother, in both industrialised and developing countries.[22] In this study, the only risk factor for primary metronidazole resistance was the immigration from a non-European country. Metronidazole is widely used in Africa and Asia to treat parasitic diseases and gynaecological infections. Therefore, in these countries female adults have a higher risk of being exposed to this antibiotic agent.

By contrast, the higher primary clarithromycin resistance rate in isolates from children compared with adults points to an in vivo acquisition of the resistance during childhood. Macrolide resistance is based on defined point mutations in the peptidytransferase loop in both copies of the 23S rRNA gene. Monotherapy with clarithromycin induces these mutations in up to 21% of patients infected with a susceptible *H pylori* strain.[23] Clarithromycin has been used increasingly over the last 10 years to treat upper respiratory tract infection in children. Owing to the high price, the newer macrolides have been less frequently prescribed in countries of the former Eastern block, as well as in Africa and Asia. In fact, children born in these countries harboured considerably less clarithromycin resistant *H pylori* strains than children from countries with a high consumption of macrolides, such as Italy, Spain and Portugal. Other independent risk factors—young age and male sex—which were identified in the multilogistic regression analysis, also pointed to an in vivo acquisition of clarithromycin resistance in our patients. Younger compared with older children, and boys compared with girls, suffer more often from infectious diseases, particularly respiratory tract infections and therefore, are more likely to be exposed to the new macrolides. Our findings confirm a previous report in *H pylori* infected Spanish children, which showed a decreasing prevalence of clarithromycin resistance with age: 45.4%, 30.2% and 9.5% in the age groups 4–8 years, 9–13 years, and 14–18 years, respectively.[24] In Portugal, a higher clarithromycin resistance rate was also reported in children (44.8%) compared with adults (14.8%).[25]

Peptic ulcer disease was a rare finding, with <5% in children <12 years of age. This rate increased to >10% in teenagers. Older age was the only risk factor for this complication. This could be due to the longer duration of the infection itself, but more likely, other risk factors may contribute in teenagers—for example, smoking, consumption of alcohol and ulcerogenic drugs. The low prevalence of peptic ulcer disease in symptomatic children referred for upper endoscopy has implications on the ''test and treat'' strategy. In a paediatric population with a prevalence of 10% for *H pylori* infection, 100 symptomatic teenagers need to be investigated by a reliable non-invasive diagnostic test, and 10

Table 5 Final logistic regression model for clarithromycin resistance among patients not previously treated for *Helicobacter pylori* infection (n = 800)

	Unadjusted. OR	Adjusted OR	95% CI	p Value
Sex (men *v* women)	1.62	1.58	[1.12 to 2.24]	0.010
Age (*v* >11) years.				
6–11	1.38	1.21	(0.81 to 1.78)	0.350
6	2.03	1.82	(1.10 to 3.03)	0.020
Country of residence (Southern Europe *v* Northern and Eastern and Western)	2.29	2.25	(1.53 to 3.30)	$<10^{-3}$

treated with triple treatment, in order for one with peptic ulcer disease to benefit. In children <12 years of age, >200 children need to be screened for one child with *H pylori* related peptic ulcer disease to benefit. In a population with a lower prevalence of *H pylori* infection like in most Northern and Western European countries, the cost/benefit ratio would be even lower.

Our results from more than a thousand *H pylori* infected children before their first treatment have major implications for the first line treatment. Despite the fact that metronidazole has a lower effect on the clinical efficacy of metronidazole-based triple treatment, when the metronidazole resistance rate reaches 40%, as is the case in children born in Africa, Asia or the Middle East, this antibiotic should not be used. Clarithromycin-based triple treatment cannot be recommended without previous susceptibility testing in children living in Southern Europe, where a third of the children are infected with a macrolide resistant strain. Even in Western and Eastern European countries, susceptibility testing should be conducted whenever possible, to obtain a high primary cure rate. This is particularly important in children <12 years of age, for whom no rescue treatment is currently available.

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