Helicobacter pylori Infection in Pediatric Patients Living in Europe: Results of the EuroPed*HP* Registry 2013 to 2016

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ABSTRACT

Objectives: The aim of the study was to assess clinical presentation, endoscopic findings, antibiotic susceptibility and treatment success of *Helicobacter pylori (H. pylori)* infected pediatric patients.

Methods: Between 2013 and 2016, 23 pediatric hospitals from 17 countries prospectively submitted data on consecutive *H. pylori*-infected (culture positive) patients to the EuroPed*HP*-Registry.

Results: Of 1333 patients recruited (55.1% girls, median age 12.6 years), 1168 (87.6%) were therapy naïve (group A) and 165 (12.4%) had failed treatment (group B). Patients resided in North/Western (29.6%), Southern (34.1%) and Eastern Europe (23.0%), or Israel/Turkey (13.4%). Main indications for endoscopy were abdominal pain or dyspepsia (81.2%, 1078/1328). Antral nodularity was reported in 77.8% (1031/1326) of patients, gastric or duodenal ulcers and erosions in 5.1% and 12.8%, respectively. Primary resistance to clarithromycin (CLA) and metronidazole (MET) occurred in 25% and 21%, respectively, and increased after failed therapy. Bacterial strains were fully susceptible in 60.5% of group A, but in only 27.4% of group B. Primary CLA resistance was higher in Southern and Eastern Europe (adjusted odds ratio [OR_{adj}] = 3.44, 95% confidence interval [CI] 2.22–5.32, $P < 0.001$ and 2.62, 95% CI: 1.63–4.22, $P < 0.001$, respectively) compared with Northern/Western Europe. Children born outside Europe showed higher primary MET resistance ($OR_{adj} = 3.81$, 95% CI: 2.25–6.45, $P < 0.001$). Treatment success in group A reached only 79.8% (568/712) with 7 to 14 days triple therapy tailored to antibiotic susceptibility.

Conclusions: Peptic ulcers are rare in dyspeptic *H. pylori*-infected children. Primary resistance to CLA and MET is markedly dependent on geographical regions of birth and residence. The ongoing survey will show whether implementation of the updated ESPGHAN/NASPGHAN guidelines will improve the eradication success.

Key Words: abdominal pain, clarithromycin, endoscopy, *Helicobacter pylori*, metronidazole, pediatric gastroenterology, peptic ulcer disease

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What Is Known

- Antibiotic susceptibility and treatment adherence are crucial for successful *Helicobacter pylori* eradication.
- In 2006, we reported antibiotic resistance in 1233 infected children (1033 treatment-naïve) living in 14 European countries. Primary resistance rates to clarithromycin and metronidazole were 20% and 23%, respectively.

What Is New

- This second survey in 1333 culture-positive children revealed increasing primary resistance for clarithromycin (25%), but not for metronidazole (21%). Antibiotic resistance significantly depended on geographical regions and migration status, questioning country-based recommendations.
- Prescribed drug doses were too low, particularly for protein pump inhibitors (PPI). Improved eradication rates can be expected if current European Society of Pediatric Gastroenterology, Hepatology and Nutrition/ North American Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines are followed.

Helicobacter pylori (H. pylori) infection is acquired in early childhood in high and low prevalence countries and persists in most cases, unless treated (1–4). The incidence and prevalence of *H. pylori* infection decreased worldwide (5–9). Infection rates

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remain high in populations residing in or immigrating from Africa, South and Middle America, and many Asian, Middle East, Eastern and Southern European countries (9–12).

Chronic *H. pylori* infection causes gastric inflammation, but in children compared with adults, gastritis is mostly antrum-dominant with lower degree of chronicity and activity and predominant regulatory cell infiltrate (13,14). Epidemiological and animal studies revealed an inverse relationship between early *H. pylori* infection and immune-mediated disease (15–17). Most infected children are asymptomatic (18). Recurrent abdominal pain is not associated with the infection considering age, sex and socioeconomic characteristics (19). Despite rare development of peptic lesions in children, many children with abdominal pain or dyspepsia are investigated for *H. pylori* infection and treated if tested positive.

Efficacy of *H. pylori* eradication therapy in children decreased. Success rates depend on the choice of antibiotics, dose and duration of therapy, antibiotic susceptibility (20,21), and adherence to therapy (22).

Between 1999 and 2002, we performed the first international survey investigating antibiotic resistance rates in 1233 infected children living in Europe (23). Fifteen years later, we initiated the EuroPed*HP* registry to study clinical presentation, endoscopic findings, antibiotic susceptibility, and treatment success. The interim results had major impact on the updated management guidelines of the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) (24).

METHODS

Design of the Prospective Registry

Between 2013 and 2016, members of the *H. pylori* working group of ESPGHAN from 23 centers in 17 countries submitted anonymized demographical and clinical data on *H. pylori* culture-positive patients. Participating centers were from Northern (Sweden), Western (Belgium, France, Germany, The United Kingdom, The Netherlands), Eastern (Slovenia, Poland, Croatia, Lithuania, Hungary), Southern Europe (Portugal, Spain, Greece, Italy), and the Middle East (Israel, Turkey). The ethical committee of the leading center at the Ludwig Maximillian's University of Munich approved the protocol of the anonymous data collection. In the other centers, the respective local ethical committees granted approval whenever required. Physicians were encouraged to follow the *H. pylori* management guidelines published in 2012 (25). After interim analysis in May 2015, higher dosing and longer duration (14 days) of treatment were recommended.

Bacterial Culture and Antibiotic Susceptibility Testing

Antibiotic susceptibility testing was locally performed for metronidazole, clarithromycin, and amoxicillin using E-test or disk diffusion. Minimal inhibitory concentrations (MIC) for resistance were defined as follows: metronidazole at least 16 μg/ml, clarithromycin at least 1.0 μg/ml, and amoxicillin at least 0.5 μg/ml. A strain was considered double resistant if results for metronidazole and clarithromycin were above breakpoints.

Statistical Analysis

The distribution of resistance to metronidazole, clarithromycin, or both was compared in different strata of variables in relation to geographical regions (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). A univariate logistic analysis was performed including all subjects with no missing of considered variables except for ''mother's country of birth.'' Odds were calculated for antibiotic resistance and presence

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The details on the members of the *Helicobacter pylori* working group of ESPGHAN are provided in the Appendix.

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of mucosal lesions. All statistically significant variables associated with resistance or the presence of peptic ulcer or erosions ($P \leq 0.25$) in the univariate analysis were considered in the multivariate logistic regression. Using the same samples as in the univariate analysis, the final multivariate logistic models were adjusted for sex and age (below and above 12 years) after applying backward elimination. Estimated risks (odds ratio, OR) and 95% confidence intervals (95% CI) were reported. Data were analyzed using SAS (Statistical Analysis Software 9.4, SAS Institute Inc., Cary, NC).

RESULTS

Study Population and Patient Characteristics

Between 2013 and 2016, data on 1460 patients with biopsy-proven, culture-positive *H. pylori* infection were submitted to the EuroPed*HP* Registry; 127 patients were excluded because of failing inclusion criteria or missing data (Supplemental Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Of the remaining 1333 children (55.1% girls, median age 12.6 years), 87.6% were treatment-naïve (group A), whereas 165 (12.4%) had failed treatment at least once (group B). Twenty-two percentage of the children, but 34.7% (n = 329) of the mothers were born outside of Europe, Turkey, or Israel (Table 1). There was an equal distribution of *H. pylori*-infected patients reported to the registry each year.

Indications for Endoscopy and Endoscopic Findings of Ulcers and Erosions

Abdominal pain and dyspepsia were the indication for endoscopy in 81.2% of patients (Table 1). Antral nodularity was observed during endoscopy in 77.8% of patients, gastric or duodenal ulcers and erosions in 5.1% and 12.8% of children, respectively. Erosions were significantly more prevalent than ulcers, with no significant differences between group A and group B (Table 1).

Among treatment-naïve children (group A), boys had a higher risk of having ulcers or erosions than girls (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Children older than 12 years were more likely to have ulcers than younger children (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Children living in Northern/Western Europe were 4 times more frequently reported to have peptic ulcers compared to children living in Southern Europe or Israel and Turkey (OR = 0.26, 95% CI: 0.13–0.55, $P = 0.0004$ and OR = 0.24, 95% CI: 0.08–0.70, $P = 0.009$, respectively) (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B866*).

Antibiotic Susceptibility

Antimicrobial susceptibility was tested with the E-test in 771 (57.8%), with disk diffusion in 546 (41.0%), and RT-PCR in 16 (1.2%) patients.

Antibiotic Resistance in Treatment-naïve Patients (Group A)

Metronidazole

Resistance to metronidazole was detected in 20.9% (95% CI: 18.4–23.5) of the strains obtained from treatment-naïve children (primary resistance) (Table 1). In the univariate analysis, the following risk factors were identified for a primary metronidazole resistance: age older than 12 years, country of residence, and birth of the child (Table 2). Children born outside of Europe had a 3.8 times higher risk (95% CI: 2.25–6.45, $P < .0001$) of being resistant to MET than children born in Northern/Western Europe (Table 3).

Clarithromycin

Primary resistance to clarithromycin was detected in 24.8% (95% CI: 22.1–27.5) of the strains (Table 1). The univariate analysis identified 2 important risk factors for primary clarithromycin resistance: region of residence and region of birth of the child (Table 2). Children living in Southern or Eastern Europe had a 3.4 and 2.6 times increased risk for primary clarithromycin resistance, respectively, compared with children living in Northern/Western Europe (Table 4).

Double Resistance

Primary resistance against both, clarithromycin and metronidazole, was found in 5.8% of the strains (57/976) (Table 1).

Amoxicillin

Resistance to amoxicillin (AMO) was a rare event (1.2%) in the cohort, with a slight increase in group B compared with group A patients ($P = 0.024$) (Table 1).

Antibiotic Resistance After Failed Treatment (Group B)

Out of 165 patients with treatment failure, the majority were born and lived in Southern Europe, whereas their mothers were also more likely to be born in Southern Europe (Table 1). The proportion of patients infected with strains susceptible to both CLA and MET was significantly lower in group B (27.4%) compared with group A (60.5%) ($P < 0.0001$) (Table 1). The chance to harbor a resistant strain increased after failed treatment, for amoxicillin from 0.9% to 3.3% ($P = 0.024$), for metronidazole from 20.9% to 52.4% ($P < 0.0001$), for clarithromycin from 24.8% to 47.6% ($P < 0.0001$), and for double resistance from 5.8% to 27.4% ($P < 0.0001$) (Table 1).

Factors Associated With Antibiotic Resistance in Treatment-naïve Patients

The comparison of antibiotic susceptibility in the 4 geographical regions demonstrated marked differences in the primary antibiotic resistance for both CLA and MET. CLA had the highest primary resistance rate in Southern Europe (36.7%) and the lowest in Northern/Western Europe (13.6%) (Supplemental Figure 3, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). MET had the highest primary resistance rate in children residing in Israel or Turkey (44.1%), whereas in the other regions, resistance ranged from 14.2% to 20.5%. After failed therapy (group B), antibiotic resistance increased for both antibiotics in all regions, but because of the small numbers in some of the subgroups, interpretations should be done with caution.

Treatment

Treatment regimens were prescribed tailored to antibiotic susceptibility. The majority of the patients received standard triple therapy ranging from 7 to 14 days' duration, whereas 14% (116/828) were treated with sequential therapy for 10 days. A small proportion received other therapy regimens. During the 4-year period, the median daily dose of protein pump inhibitors (PPI)

TABLE 1. Patient characteristics and clinical presentation (N = 1333)

Factors	All patients (N = 1333) No. (%)	Group A before treatment (n = 1168) No. (%)	Group B after treatment failed (n = 165) No. (%)	*P*-value†
Demographical characteristics				
Female	735 (55.1)	646 (55.3)	89 (53.9)	0.741
Age group (years), N = 1333				0.492
Age <12	605 (45.4)	526 (45.0)	79 (47.9)	
Age ≥12	728 (54.6)	642 (55.0)	86 (52.1)	
Country of residence*, N = 1333				0.0015
Northern/Western Europe	394 (29.6)	343 (29.4)	51 (30.9)	
Southern Europe	455 (34.1)	384 (32.9)	71 (43.0)	
Eastern Europe	306 (23.0)	287 (24.6)	19 (11.5)	
Israel & Turkey	178 (13.4)	154 (13.2)	24 (14.5)	
Country of birth*, N = 1118				0.0001
Northern/Western Europe	240 (21.5)	206 (21.2)	34 (23.3)	
Southern Europe	399 (35.7)	331 (34.1)	68 (46.6)	
Eastern Europe	226 (20.2)	216 (22.2)	10 (6.8)	
Asia, Africa, America & Middle East	253 (22.6)	219 (22.5)	34 (23.3)	
Mother's country of birth*, N = 947				<.0001
Northern/Western Europe	50 (5.3)	38 (4.6)	12 (10.4)	
Southern Europe	347 (36.6)	290 (34.9)	57 (49.6)	
Eastern Europe	221 (23.3)	213 (25.6)	8 (7.0)	
Asia, Africa, America & Middle East	329 (34.7)	291 (35.0)	38 (33.0)	
Diagnostic year, N = 1333				0.199
2016	335 (25.1)	299 (25.6)	36 (21.8)	
2015	342 (25.7)	302 (25.9)	40 (24.2)	
2014	325 (24.4)	288 (24.7)	37 (22.4)	
2013	331 (24.8)	279 (23.9)	52 (31.5)	
Endoscopic findings				
Indication for endoscopy, N = 1328				0.225
Abdominal pain	793 (59.7)	679 (58.4)	114 (69.1)	
Dyspepsia incl. nausea, vomiting	285 (21.5)	252 (21.7)	33 (20.0)	
Anemia	54 (4.1)	51 (4.4)	3 (1.8)	
Celiac disease	31 (2.3)	28 (2.4)	3 (1.8)	
GI-bleeding	28 (2.1)	27 (2.3)	1 (0.6)	
GERD, reflux	21 (1.6)	19 (1.6)	2 (1.2)	
IBD	9 (0.7)	8 (0.7)	1 (0.6)	
Eosinophilic esophagitis	6 (0.5)	5 (0.4)	1 (0.6)	
Others: weight loss, diarrhea etc.	101 (7.6)	94 (8.1)	7 (4.2)	
Antral nodularity, N = 1326	1031 (77.8)	898 (77.3)	133 (80.6)	0.346
Ulcers, N = 1325	67 (5.1)	60 (5.2)	7 (4.2)	0.610
Erosions, N = 1325	170 (12.8)	152 (13.1)	18 (10.9)	0.430
Results of antibiotic susceptibility testing				
Metronidazole resistance, N = 1126	282 (25.0)	205 (20.9)	77 (52.4)	<.0001
Clarithromycin resistance, N = 1131	314 (27.8)	244 (24.8)	70 (47.6)	<.0001
Amoxicillin resistance, N = 1000	12 (1.2)	8 (0.9)	4 (3.3)	0.024
Metronidazole and Clarithromycin resistance - Susceptibility subgroups, N = 1122				<.0001
MET-S/CLA-S	630 (56.1)	590 (60.5)	40 (27.4)	
MET-S/CLA-R	212 (18.9)	183 (18.8)	29 (19.9)	
MET-R/CLA-S	183 (16.3)	146 (15.0)	37 (25.3)	
MET-R/CLA-R	97 (8.6)	57 (5.8)	40 (27.4)	

N represents total number of available data for each factor in the cohort.
*Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.
†*P*-values refer to comparison between group A (before treatment) and group B (after treatment failed) obtained by the Pearson's Chi-square test.

had increased from 1.05 mg/kg body weight (2013) to 1.24 mg/kg (2016) and of amoxicillin from 46.6 mg/kg (2013) to 57.8 mg/kg (2016) (Supplemental Figure 4, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). There was a minor increase in the median dose of clarithromycin and metronidazole over the 4 years. The duration of treatment increased from 7 to 10 to 14 days in the majority of patients throughout the study, particularly after the interim analysis in May 2015 (Supplemental Figure 5, Supplemental Digital Content, *http://links.lww.com/MPG/B866*).

Eradication Success

Treatment outcome was available in 76.2% (1016/1333) of all patients. Among treatment-naïve patients infected with fully

TABLE 2. Univariate analysis of factors associated with metronidazole and clarithromycin resistance among pediatric patients not previously treated for *Helicobacter pylori* infection

	MET susceptibility, N = 797				CLA susceptibility, N = 801			
Factors	MET resistant (n = 180)	OR	(95% CI)	*P*-value[†]	CLA resistant (n = 210)	OR	(95% CI)	*P*-value[†]
Gender								
Female	103	1			116	1		
Male	77	0.92	(0.66 to 1.29)	0.642	94	1.03	(0.75 to 1.42)	0.847
Age group (years)								
Age <12	64	1			79	1		
Age ≥12	116	1.45	(1.03 to 2.04)	0.035	131	1.33	(0.96 to 1.84)	0.084
Country of residence[*]								
Northern/Western Europe	52	1			35	1		
Southern Europe	39	0.61	(0.39 to 0.97)	0.035	100	3.48	(2.25 to 5.38)	<.0001
Eastern Europe	45	1.15	(0.73 to 1.82)	0.538	58	2.66	(1.66 to 4.27)	<.0001
Israel & Turkey	44	2.79	(1.70 to 4.60)	<.0001	17	1.18	(0.63 to 2.23)	0.603
Country of birth[*]								
Northern/Western Europe	27	1			25	1		
Southern Europe	37	0.87	(0.51 to 1.50)	0.623	96	3.43	(2.10 to 5.61)	<.0001
Eastern Europe	47	1.71	(1.01 to 2.89)	0.046	63	2.86	(1.70 to 4.80)	<.0001
Asia, Africa, America & Middle East	69	4.01	(2.40 to 6.72)	<.0001	26	1.17	(0.65 to 2.13)	0.604
Mother's country of birth[*]								
Northern/Western Europe	6	1			9	1		
Southern Europe	30	0.69	(0.27 to 1.81)	0.455	94	2.04	(0.92 to 4.54)	0.080
Eastern Europe	50	1.68	(0.66 to 4.30)	0.280	58	1.33	(0.59 to 3.00)	0.495
Asia, Africa, America & Middle East	64	1.93	(0.76 to 4.88)	0.166	30	0.47	(0.20 to 1.11)	0.084
Diagnostic year								
2016	54	1			57	1		
2015	34	0.54	(0.33 to 0.87)	0.012	50	0.79	(0.51 to 1.24)	0.304
2014	49	0.79	(0.51 to 1.23)	0.296	51	0.76	(0.49 to 1.18)	0.221
2013	43	0.88	(0.55 to 1.40)	0.592	52	1.01	(0.64 to 1.57)	0.983
Ulcers								
No	169	1			199	1		
Yes	11	1.48	(0.72 to 3.06)	0.290	11	1.20	(0.58 to 2.48)	0.619

Odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the univariate analysis are given. Analyses were performed with complete datasets with no missing values in covariates, excepted the variable ''mother's country of birth.''

[*]Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.

[†]*P*-values obtained from the Wald Chi-Square Test for the significance of OR.

susceptible strains, triple therapy for 14 days showed a higher eradication success than for a shorter duration of 7 to 10 days (85% vs 75.6% respectively, $P = 0.03$) (Supplemental Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). No significant difference was detected by comparing triple therapy with different duration in other susceptibility groups. The eradication success did not achieve the treatment goal of 90% eradication rate in any subgroup (Supplemental

TABLE 3. Final logistic regression model for metronidazole resistance among pediatric patients not previously treated for *Helicobacter pylori* infection and no missing data for all of the factors considered in the univariate analysis (n = 797)

Factors	Unadjusted OR	Adjusted OR	(95% CI)	*P*-value[†]
Gender (Male vs. Female)	0.92	0.93	(0.65 to 1.32)	0.682
Age (Age ≥ 12 vs. Age <12)	1.45	1.18	(0.82 to 1.70)	0.374
Country of birth[*] (vs. Northern/Western Europe)				
Southern Europe	0.87	0.85	(0.50 to 1.46)	0.551
Eastern Europe	1.71	1.66	(0.98 to 2.81)	0.061
Asia, Africa, America & Middle East	4.01	3.81	(2.25 to 6.45)	<.0001

Unadjusted odds ratios (OR) were obtained from the univariate analysis.

Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the multivariate logistic regression model with sex and age group (below or above 12 years old) are given. Analyses were performed with complete datasets with no missing values in covariates.

[*]Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.

[†]*P*-values obtained from the Wald chi-square test for the significance of adjusted OR.

TABLE 4. Final logistic regression model for clarithromycin resistance among pediatric patients not previously treated for *Helicobacter pylori* infection and no missing data for all of the factors considered in the univariate analysis (n = 801)

Factors	Unadjusted OR	Adjusted OR	(95% CI)	*P*-value[†]
Gender (Male vs. Female)	1.03	1.15	(0.83 to 1.60)	0.407
Age (Age ≥12 vs. Age <12)	1.33	1.34	(0.96 to 1.88)	0.091
Country of residence[*] (vs. Northern/Western Europe)				
Southern Europe	3.48	3.44	(2.22 to 5.32)	<.0001
Eastern Europe	2.66	2.62	(1.63 to 4.22)	<.0001
Israel & Turkey	1.18	1.11	(0.59 to 2.10)	0.749

Unadjusted odds ratios (OR) were obtained from the univariate analysis.

Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the multivariate logistic regression model with gender and age group (below or above 12 years old) are given. Analyses were performed with complete datasets with no missing values in covariates.

[*]Country distribution was given in Supplemental Table 1, *http://links.lww.com/MPG/B866*.

[†]*P*-values obtained from the Wald chi-square test for the significance of adjusted OR.

Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/B866*).

DISCUSSION

Our analysis of the EuroPed*HP* survey data collected over 4-years disclose problems in the management of *H. pylori*-infected children and allow suggestions for improvement. The number of children included in this survey (n = 1333) is comparable with the previous 15 years ago (n = 1233) (23). The primary antibiotic resistance rates are high with large differences between geographical regions. Resistance rates are also related to migrant status. The rate of peptic ulcers in our cohort was low (5.1%). Prescribed treatments markedly differed, and the anticipated eradication rate of 90% was not reached, even in treatment-naïve children. The causes are multifactorial and other factors, such as adherence to therapy, dosing of the drugs, number of biopsies taken to capture strains with different antibiotic susceptibility in the stomach should be addressed.

With respect to antibiotic susceptibility, our cohort is representative of infected children residing in Europe including Israel and Turkey (Istanbul area). To account for the uneven distribution of patients from different countries, the study population was clustered in 4 geographical regions, which are similar in the accessibility and prescription behavior of antibiotics (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B866*). Patients from Southern Europe contributed a slightly higher percentage whereas there were fewer patients from Israel and Turkey. Selection and reporting bias are unlikely, as all centers prospectively reported every child with culture-positive *H. pylori* infection. Reliable data on previous eradication therapy were obtained from parents and referring physicians. The low ulcer rate argues against a selection bias with preferential testing children with abnormal endoscopic findings. Most European pediatric gastroenterologist take routine gastric and duodenal biopsies during upper endoscopy. Indication for endoscopy were unspecific symptoms, such as abdominal pain and dyspepsia in 4 out of 5 patients, whereas objective alarm signs, such as bleeding or anemia were rare (6.2%).

Compared with our previous survey (23), this registry included more detailed and structured reporting of endoscopic findings. The high rate of antral nodularity (78%) confirms previous pediatric series (26). Antral nodularity is almost pathognomonic to *H. pylori*-infected children, but not related to the presence of symptoms (27). The ulcer rate of 4% in children below 12 years of age was equal to the previous survey, whereas the current rate in teenagers was lower than 15 years back (6% vs 10%, respectively) (23). Teenage boys were more likely to have ulcers than girls pointing to either a lower threshold for endoscopy in girls or a higher exposure to environmental risk factors like tobacco, alcohol, or ulcerogenic drugs in adolescent boys. Our finding that children living in Northern/Western Europe had a 4 times increased chance of ulcer diagnosis may be because of the small number of ulcers found. Also, indication for endoscopy differs between countries depending on expectations of parents, reimbursement systems, use of noninvasive tests and referral for endoscopy based on a positive test result. In Northern/Western countries, children born to immigrant mothers were overrepresented, and immigrant status was related to peptic ulcer disease. This association could be related to different extrinsic or intrinsic factors, like referral for endoscopy or differences in genetic host or bacterial virulence factors.

With respect to primary antibiotic susceptibility, we noticed that metronidazole resistance decreased over the last 15 years in Eastern Europe (from 23.8% to 20.4%) (23) and Southern Europe (from 22.3% to 14.2%) (23). Clarithromycin resistance in Southern Europe, however, further increased, from 32.6% to 36.7% (23). In Eastern Europe, the clarithromycin resistance rate increased by 9% (from 17.5% to 26.3%) (23). Israel and Turkey showed a distinct pattern with a high metronidazole resistance rate (44.1%) but moderate rates for clarithromycin (16.5%).

As in the previous survey, being born outside of Europe was associated with an almost 4 times higher risk of harboring a metronidazole-resistant strain (OR = 3.81 in this vs OR = 2.42 in the previous survey). As the mother is the main source of infection (28), this finding is likely explained by the high use of metronidazole in Africa, the Middle East, and Asia. For clarithromycin resistance, there was a trend for a lower risk in younger children. The strongest association with clarithromycin resistance was the country of residence, confirming the positive relationship between a macrolides prescribed for benign infections and increasing resistant rates in Southern and Eastern Europe in adults (29). Restricting prescriptions for macrolides in Belgium resulted in the decreased clarithromycin resistance rates of *H. pylori* strains from children 10 years later (30). This indicates that intervention programs to reduce antibiotic use in common colds (31) or the antibiotic stewardship initiative may decrease antibiotic resistance within a population including *H. pylori*-infected children.

Treating *H. pylori* in pediatric patients is a challenge as bismuth-based combination drugs and second line antibiotics including levofloxacin and rifabutin are not licensed. Therefore,

a high primary success rate is even more important in children compared with adults. To avoid repeated antibiotic exposures and spreading of resistant strains after failed treatment, pediatric guidelines recommended against the test and treat strategy (24,25,32). The clear recommendation for treating infected children is given when gastric or duodenal peptic lesions are present. There is no evidence that symptomatic children with gastritis only have an immediate benefit of being treated (15). Applying the test and treat strategy to a pediatric population with an assumed *H. pylori* prevalence rate of 10%, would require noninvasive testing in 200 children and exposure to triple therapy in 20 of them in order to benefit 1 child with ulcer. Recent consensus reports recommend for adults to search for infected persons and treat them prior development of intestinal metaplasia and dysplasia to prevent gastric cancer (33,34). This does not apply to Pediatrics (35). In children, endoscopy should be restricted to those with symptoms suggesting organic disease. If *H. pylori* infection is detected during endoscopy and therapy is anticipated, the choice of antibiotics should be tailored to susceptibility testing (24,25). This strategy is superior and more cost effective compared with empiric therapy (36) with less burden to patients and their families by avoiding further endoscopies and antibiotic usage in this vulnerable population.

The strength of our study is the prospective recruitment of a large number of unselected patients with culture-proven infection from different European countries, the structured reporting of birthplace of child and mother, indications for endoscopy, macroscopic findings, antibiotic susceptibility, and outcome data. No such data are available from North America where susceptibility testing prior therapy is rare. The collection period of 4 years and application of the same analysis as in the previous survey allowed comparison of findings almost 15 years apart.

This survey has several limitations: *An uneven distribution of patients from different countries* due to the multicentric method, allowing only an evaluation by geographic regions. *Susceptibility testing was not performed in a central laboratory* due to financial restrictions (29). *Two methods (E-test and disc diffusion)* were used for susceptibility testing, and centers (country of residence) confounded the difference between the two methods. *Local antibiotic resistance breakpoints may not have been unified* over years. However, they were adjusted to the guidelines of the European Committee of Antibiotic Susceptibility Testing (EUCAST) (37) with AMO 0.5 μg/ml or 0.12 μg/ml, CLA 1.0 μg/ml or 0.5 μg/ml and MET 8.0 μg/ml or 16 μg/ml, respectively (38). Nonetheless, by comparing different breakpoints, we might overestimate a few cases of AMO resistance, but not for MET or CLA resistance (38). *Only one biopsy* was recommended for culture. This might underestimate antibiotic resistance, since mixed infections with multiple strains are likely to be missed (39). *A large range of different drug regimens and doses* were used for treatment not allowing solid data on treatment outcomes. *Patients after failed treatment* consisted only a small portion, 12.4% of the registry. Selection bias in this sub cohort cannot be excluded.

CONCLUSIONS

In conclusion, our results demonstrate the importance on continuous surveillance of antibiotic susceptibility of *H. pylori* strains from children considering country of living and migrant background. We also recommend the surveillance of eradication rates in relation to the drug regimen prescribed. Based on our data we suggest obtaining at least two gastric biopsies (antrum and corpus) for culture. We also suggest increasing drug doses, in particular PPI dose, and prolonging therapy to 14 days according to guidelines (24). We recommend improving adherence by providing written information to caregivers (40). The ongoing registry will show whether these measures increase eradication rates of tailored triple therapy to at least 90%.

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REFERENCES

1. Rowland M, Daly L, Vaughan M, et al. Age-specific incidence of Helicobacter pylori. *Gastroenterology* 2006;130:65–72.
2. Rowland M, Clyne M, Daly L, et al. Long-term follow-up of the incidence of Helicobacter pylori. *Clin Microbiol Infect* 2018;24:980–4.
3. Malaty HM, El-Kasabany A, Graham DY, et al. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. *Lancet* 2002;359:931–5.
4. Zeng M, Mao XH, Li JX, et al. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386:1457–64.
5. Burucoa C, Axon A. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2017;22:e12403.
6. Mitchell H, Katelaris P. Epidemiology, clinical impacts and current clinical management of Helicobacter pylori infection. *Med J Aust* 2016;204:376–80.
7. Szaflarska-Poplawska A, Soroczynska-Wrzyszcz A. Prevalence of Helicobacter pylori infection among junior high school students in Grudziadz, Poland. *Helicobacter* 2019;24:e12552.
8. Tang MYL, Chung PHY, Chan HY, et al. Recent trends in the prevalence of Helicobacter Pylori in symptomatic children: a 12-year retrospective study in a tertiary centre. *J Pediatr Surg* 2019;54:255–7.
9. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology* 2017;153:420–9.
10. Bontems P, Kalach N, Vanderpas J, et al. Helicobacter pylori Infection in European children with gastro-duodenal ulcers and erosions. *Pediatr Infect Dis J* 2013;32:1324–9.
11. Zabala Torrres B, Lucero Y, Lagomarcino AJ, et al. Review: prevalence and dynamics of Helicobacter pylori infection during childhood. *Helicobacter* 2017;22:e12399.
12. Zamani M, Ebrahimtabar F, Zamani V, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2018;47:868–76.
13. Harris PR, Wright SW, Serrano C, et al. Helicobacter pylori gastritis in children is associated with a regulatory T-cell response. *Gastroenterology* 2008;134:491–9.
14. Freire de Melo F, Rocha AMC, Rocha GA, et al. A regulatory instead of an IL-17 T response predominates in Helicobacter pylori-associated gastritis in children. *Microbes Infect* 2012;14:341–7.
15. Sierra MS, Hastings EV, Goodman KJ. What do we know about benefits of H. pylori treatment in childhood? *Gut Microbes* 2013;4:549–67.
16. den Hollander WJ, Sonnenschein-van der Voort AM, Holster IL, et al. Helicobacter pylori in children with asthmatic conditions at school age, and their mothers. *Aliment Pharmacol Ther* 2016;43:933–43.
17. Arnold IC, Dehzad N, Reuter S, et al. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. *J Clin Invest* 2011;121:3088–93.
18. Sustmann A, Okuda M, Koletzko S. Helicobacter pylori in children. *Helicobacter* 2016;21 Suppl 1:49–54.
19. Spee LA, Madderom MB, Pijpers M, et al. Association between helicobacter pylori and gastrointestinal symptoms in children. *Pediatrics* 2010;125:e651–69.
20. Megraud F. Antibiotic resistance is the key element in treatment of Helicobacter pylori infection. *Gastroenterology* 2018;155:1300–2.
21. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for Helicobacter pylori. *Aliment Pharmacol Ther* 2007;26:343–57.

22. Kotilea K, Mekhael J, Salame A, et al. Eradication rate of Helicobacter Pylori infection is directly influenced by adherence to therapy in children. *Helicobacter* 2017;22:e12383.
23. Koletzko S, Richy F, Bontems P, et al. Prospective multicentre study on antibiotic resistance of Helicobacter pylori strains obtained from children living in Europe. *Gut* 2006;55:1711–6.
24. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). *J Pediatr Gastroenterol Nutr* 2017;64:991–1003.
25. Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. *J Pediatr Gastroenterol Nutr* 2011;53:230–43.
26. Lazowska-Przeorek I, Kotowska M, Banasiuk M, et al. Value of antral nodularity for the diagnosis of Helicobacter pylori infection in children. *Med Sci Monit* 2015;21:1827–30.
27. Ganga-Zandzou PS, Michaud L, Vincent P, et al. Natural outcome of Helicobacter pylori infection in asymptomatic children: a two-year follow-up study. *Pediatrics* 1999;104 (2 Pt 1):216–21.
28. Weyermann M, Rothenbacher D, Brenner H. Acquisition of Helicobacter pylori infection in early childhood: independent contributions of infected mothers, fathers, and siblings. *Am J Gastroenterol* 2009;104: 182–9.
29. Megraud F, Coenen S, Versporten A, et al., Study Group participants. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;62:34–42.
30. Miendje Deyi VY, Bontems P, Vanderpas J, et al. 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;49:2200–9.
31. Sabuncu E, David J, Bernede-Bauduin C, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS Med* 2009;6:e1000084.
32. Koletzko S, Jones N. No screen and treat in children for Helicobacter pylori infection. *J Pediatr Gastroenterol Nutr* 2018;67:e87–8.
33. Malfertheiner P, Megraud F, O'Morain CA, et al., European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017;66:6–30.
34. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015;64:1353–67.
35. Leja M, Dumpis U. What would the screen-and-treat strategy for Helicobacter pylori mean in terms of antibiotic consumption? *Dig Dis Sci* 2019;65:1632–42.
36. Wenzhen Y, Yumin L, Quanlin G, et al. Is antimicrobial susceptibility testing necessary before first-line treatment for Helicobacter pylori infection? Meta-analysis of randomized controlled trials. *Intern Med* 2010;49:1103–9.
37. EUCAST Clinical breakpoints - breakpoints and guidance. *http://www.eucast.org/clinical_breakpoints/*. Accessed November 29, 2019.
38. Alarcon T, Urruzuno P, Martinez MJ, et al. Antimicrobial susceptibility of 6 antimicrobial agents in Helicobacter pylori clinical isolates by using EUCAST breakpoints compared with previously used breakpoints. *Enferm Infecc Microbiol Clin* 2017;35:278–82.
39. Feydt-Schmidt A, Russmann H, Lehn N, et al. Fluorescence in situ hybridization vs. epsilometer test for detection of clarithromycin-susceptible and clarithromycin-resistant Helicobacter pylori strains in gastric biopsies from children. *Aliment Pharmacol Ther* 2002;16:2073–9.
40. ESPGHAN - Patient and parent guides. *http://www.espghan.org/education/h-pylori-patientparent-guide/*. Accessed on November 29, 2019.