Helicobacter pylori in childhood : aspects of prevalence, diagnosis and treatment

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CHAPTER 5

Frequency and risk factors of gastric and duodenal ulcers or erosions in children: a prospective 1-month European multicenter study

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ABSTRACT

There are no solid figures of the frequency of ulcer disease during childhood in Europe. We assessed its frequency and analyzed known risk factors.

Patients and methods

Ulcers, erosions, indications, and risk factors were recorded in all children undergoing an upper gastrointestinal endoscopy in a prospective study carried out during one month simultaneously in 19 centers of 14 European countries.

Results

Ulcers and/or erosions were observed in 56 out of 694 children. Children with ulcers/erosions were significantly older than those without lesions (10.3±5.5 vs. 8.1± 5.7 years, P = 0.002). *Helicobacter pylori* infection was present in 15 of 56 children (27%); NSAIDs were used in eight, steroids in five, immune-suppressive drugs in five, antibiotics in six, antacids in one, H_2-blockers in six and proton pump inhibitors in eight children (more than one risk factor was detected in 32 of 56 children). No risk factors were observed in 24 of 56 children (43%). The main indications for endoscopy were epigastric or abdominal pain (24%) and suspicion of gastroesophageal reflux disease (15%). Similarly, epigastric tenderness, hematemesis, melena, and weight stagnation were significantly associated with ulcers/erosions, whereas sex, *H. pylori* infection, socioeconomic status and lifestyle factors were equally distributed.

Conclusion

Although limited by the short-time duration and the heterogeneity of the patients included throughout the 19 centers, our study shows a frequency of 8.1% of ulcers and/or erosions in children, occurring mainly in the second decade of life. *H. pylori* infection and gastrotoxic medications were less frequently implicated than expected.

Keywords: child, erosion, ulcer, *Helicobacter pylori*

INTRODUCTION

Not only peptic ulcers, but also erosions, reported in 10–20% of symptomatic children infected with *Helicobacter pylori* undergoing upper endoscopy [1–6] remain less frequent than in adults. However, these data originate from monocentric studies enrolling a small series of children. In one large prospective European multicenter study, aimed at assessing antibiotic resistance of *H. pylori* strains, including more than 1400 symptomatic infected children, gastric, or duodenal ulcers were found during endoscopy in 3.5% of children below 6 years of age, in 4.6% children aged 6–11 years, but in 10.4% of those older than 12 years [7].

Ulcers or erosions also occur in *H. pylori* negative children, especially those receiving NSAIDs [8]. Other known causes of peptic lesions are stress, Crohn's disease, and various exogenous agents [1–4].

There is a lack of solid data about the frequency of ulcer disease in children and the frequency of *H. pylori* and other etiologic risk factors in children with peptic ulcer disease. The European Paediatric Task Force for *H. pylori* decided to conduct a descriptive prospective study in 14 European countries to evaluate in a population of children referred for upper gastrointestinal (GI) endoscopy, not only the frequency of gastric or duodenal ulcers, but also erosions in relation to *H. pylori* infection and various other risk factors.

PATIENTS AND METHODS

Patients

The study was carried out for one month (January - February 2007) in 19 centers in 14 European countries. In each center, all the children aged below 18 years undergoing an upper gastrointestinal endoscopy were enrolled. Parental informed consent and child ascent was obtained as requested by local ethical policy in the different European countries for the collection of clinical information in an anonymous form including the following items: presence of gastric or duodenal ulcers and/or erosions, age, sex, known chronic disease, and indication for endoscopy. In addition, in children with ulcers and/or erosions, macroscopic and microscopic findings were collected including the *H. pylori* status and further information on potential risk factors such as medications during the last 4 weeks, ethnic background, and education level of the parents. Lifestyle habits including smoking and alcohol consumption were also collected. The Ethics Committee of Queen Fabiola Children's University Hospital, Brussels, Belgium approved the protocol for anonymous data collection and analysis.

H. pylori status was determined in patients exhibiting gastric and or duodenal

ulcers but also erosions according to various diagnostic methods as already defined by our conference consensus [9]: histology according to the updated Sydney classification [10], culture, rapid urease test, ^{13}C urea breath test, and stool antigen. *H. pylori* infection was confirmed when culture or at least two diagnostic tests were positive. The *H. pylori* status was considered as not valid, that is, false negative result, when children received antibiotics, proton pump inhibitors (PPI's), H2 -blockers or antacids within 4 weeks before endoscopy.

To limit interindividual interpretation of endoscopic findings between observers in the different centers, a clear description and definition of ulcers and erosions was adopted by consensus according to the minimal standard terminology for digestive endoscopy: ulcer was defined as a deep defect in the mucosa with an inflamed edge; erosion was defined as a small (<3mm) superficial defect in the mucosa, of white or yellow color [11]. Endoscopic bleeding signs were noted according to the Forrest *et al* [12] classification into six classes: IA arterial spurting bleeding, IB arterial oozing bleeding, IIA visible vessel, IIB sentinel clot, IIC hematin covered flat spot, and no stigmata of hemorrhage.

Ulcers and/or erosions were also subclassified as secondary, when children showed *H. pylori* infection, received either NSAIDs or steroids during the four weeks preceding endoscopy, or presented with a known chronic disease, that is, inflammatory bowel syndrome (IBD), polyarthritis, and other rheumatic diseases. Primary lesions were those without an identified etiology.

Statistical Analysis

Calculation of mean, median, standard deviation, and range of all quantitative parameters, descriptive analysis of repartition for qualitative parameters, performance of the $\chi 2$ test or Fisher's exact test when appropriate and the monovariate analysis were done using the Stat-View System (Abacus, California, USA), whereas the multivariate analysis was done using the STATA 7.0 System (Stata Inc., California, USA). All tests performed were two-tailed, with P value less than 0.05 considered significant.

Frequency of gastric and/or duodenal ulcer/erosion was analyzed in the study cohort, and their clinical signs and additional descriptive data. Frequencies of risk factors in the group of children with gastric and/or duodenal ulcer/ erosion compared with those without lesions were precise with 95% confidence interval. The risk factors considered are sex, age as a variable divided into two age groups (<10 and >10 years), indications of endoscopy, and known chronic disease. Risk factors were first analyzed using monovariate analysis, then logistic regression analyses using a backward stepwise procedure to adjust for every variable. Only variables exhibiting a *P* value less than 0.2 by the monovariate analysis were analyzed by

Table 1 Distribution of patients with gastroduodenal ulcers and/or erosions according to age with their risk factors in the investigator centers*

	Patients without ulcers and/or erosions n (%)	Patients with ulcers and/or erosions n (%)	Total	Age (years) Mean (SD)	Number of patients Age > 10 years n (%)	OR	95% CI	*P value*
Belgium	46 (78.0)	13 (22.0)	59	7.69 (5.8)	22 (37.2)	3.9	2,0-7.7	0.00004
Italy	25 (80.7)	6 (19.4)	31	7.85 (5.2)	14 (45.1)	3.1	1.3-7.7	0.01
Turkey	30 (83.3)	6 (16.7)	36	6.17 (3.5)	5 (13.8)	2.6	1.0-6.3	0.05
France-Bordeaux	25 (86.2)	4 (13.8)	29	7.13 (4.9)	10 (34.4)	2.1	0.7-5.8	NS
Poland-Wroclaw	77 (89.5)	9 (10.5)	86	11.1 (4.3)	52 (60.4)	1.5	0.7-3.0	NS
Sweden	28 (90.3)	3 (9.7)	31	10.4 (5.4)	18 (58,0)	1.4	0.4-4.4	NS
Poland-Warsaw	90 (91.8)	8 (8.2)	98	10.11 (5.4)	54 (55.1)	1.1	0.5-2.3	NS
Spain-centre 1	54 (93.1)	4 (6.9)	58	9.51 (5.8)	33 (56.8)	0.9	0.3-2.5	NS
Spain-centre 2	31 (96.9)	1 (3.1)	32	9.03 (6.3)	15 (46.8)	0.5	0.1-2.8	NS
France-Lille-centre 1	65 (98.5)	1 (1.5)	66	3.5 (4.4)	11 (16.6)	0.2	0.1-1.2	0.04
Hungary	19 (99.5)	1 (0.5)	20	7.26 (5.1)	8 (40,0)	0.9	0.2-4.6	NS
France-Lille-centre 2	51	0	51	3.4 (4.3)	6 (11.7)	0	0	0
Germany	26	0	26	9.15 (5.3)	11 (42.3)	0	0	0
Czech Republic	26	0	26	12.08 (5.2)	19 (73,0)	0	0	0
Greece	24	0	24	9.09 (4.6)	12 (50,0)	0	0	0
Netherlands	14	0	14	7.99 (6.2)	5 (35.7)	0	0	0
United Kingdom	7	0	7	10.92 (5.7)	5 (71.4)	0	0	0
Total	638	56 (8.1)	694					

CI : confidence interval ; NS : not significant ; OR : Odds ratio ; SD : standard deviation

* The age was significantly different between the different investigator centers, $p < 0.0001$ according to the multivariate analysis of variance analysis.

the multivariate logistic model. Results were expressed as odds ratios (ORs) with 95% confidence intervals. Statistical significance was set up at the P value less than 0.005, and all *P* values were two-tailed.

RESULTS

Frequency and description of ulcers and/or erosions

A total of 694 children were enrolled, 349 female and 345 male, median age 8.2 years (range 1 month–18 years), unevenly distributed between the different centers.

Ulcers and/or erosions were observed in 56 of 694 children (8.1%), with a wide variation (0–22%) in the 19 European centers (Table 1). In each and all centers, children with ulcers and/or erosions were significantly older than those without lesions (10.26±5.5 vs. 8.11± 5.7 years, P=0.002).

Endoscopic lesions were reported as gastric ulcers in seventeen and duodenal ulcers in seven, gastric erosions in 31, and duodenal erosions in 15 children. Most of the gastric lesions were located in the antrum (44/48) and the majority of the duodenal lesions were located in the bulb (15/22). Duodenal erosions in nine, duodenal erosions and ulcer in two, duodenal erosions and gastric ulcers in one, duodenal ulcers in five, gastric erosions in 21, gastric and duodenal erosions in two, gastric and duodenal erosions and gastric ulcers in one, gastric erosions and ulcers in seven, and finally gastric ulcers in eight. Endoscopic bleeding signs were present in nine of 56 children (16%). No age difference was observed between children with gastric compared with those with duodenal lesions. Among the 56 children with peptic ulcers and/or erosions, 24 lesions (11 ulcers and 13 erosions) were classified as primary and 32 (13 ulcers and 19 erosions) as secondary (Table 2).

H. pylori infection was present in 15 of 56 children (27%). These *H. pylori* infected children showed gastric erosions in five, duodenal erosions in three, combined gastric and duodenal erosions in one, combined gastric erosions and ulcers in four, gastric ulcers in one, and duodenal ulcers were found in one. No significant relationship could be found between *H. pylori* infection and the type of peptic lesions. *H. pylori* status was considered as not valid in six of 24 (25%) and 12 of 32 (37.5%) patients of the primary and secondary lesions (Table 2).

Gastro–duodenal ulcers versus erosions

The risk factors in children with ulcers were compared with those with erosions and did not show any statistically significant difference: age more than 10 years 14 of 24 (58.3%) versus 19 of 32 (59.4%), female sex ratio 13 of 24 (54.1%) versus 15 of 32 (46.8%), *H. pylori* infection six of 24 (25%) versus six of 32 (18.7%), previous intake of medication 13 of 24 (54.1%) versus 16 of 32 (50%) recurrent abdominal pain and

Table 2 Primary and secondary ulcers and/or erosions characteristics

	Primary Lesions (n=24)		Secondary Lesions (n=32)	
	Ulcers +/- erosions n=11	Erosions only n=13	Ulcers +/- erosions n=13	Erosions only n=19
***H. pylori* status**				
Positive	0	0	6	9
Negative	11	10	7	10
Not tested	0	3	0	0
***H. pylori* status**				
Valid	9	9	9	11
Not valid*	2	4	4	8
Known chronic diseases				
IBD	0	0	3	4
Polyarthritis or other rheumatic diseases	0	0	0	2
Chronic neurologic disease	1	2	0	1
Chronic lung disease	0	0	1	0
Chronic liver disease	0	1	0	2
Food allergy	0	0	0	1
Other allergic disease (except food allergy)	0	0	0	1
Oncology (during chemotherapy)	1	0	0	0
Celiac disease	1	1	0	0
Others	2	0	2	0
Absence of known chronic disease	6	9	7	8
Drug consumptions				
None	5	7	6	9
Yes	6	6	7	10
NSAIDs	0	0	5	3
PPIs	0	3	0	5
H2 blockers	2	1	2	1
Antacids	0	0	1	0
Antibiotics	0	0	3	3
Steroids	0	0	1	4
Immuno-suppressive drugs	0	0	1	4

* *H. pylori* status not valid, i.e. due to the use of either antibiotics, or PPIs or H2 blockers during the 4 weeks preceding endoscopy

IBD: inflammatory bowel disease; PPIs: protonpump inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs

Table 3 Known chronic diseases in all enrolled patients

Known chronic diseases	Patients without ulcers and/or erosions n (%)	Patients with ulcers and/or erosions n (%)	Total n	OR	95% CI	*P* value
Chronic neurologic disease	34 (5.3)	4 (7.1)	38	1.5	0.5 - 4.2	NS
Chronic cardiac disease	4 (0.6)	0	4	1.3	0.1 - 23.3	NS
Chronic lung disease	22 (3.4)	1 (1.7)	23	0.7	0.1 - 3.9	NS
Chronic liver disease	31 (4.8)	2 (3.5)	33	0.9	0.2 - 3.3	NS
Chronic renal disease	4 (0.6)	0	4	1.3	0.1 - 23.3	NS
Food allergy (FA)	12 (1.8)	1 (1.7)	13	1.3	0.2 - 7.6	NS
Other allergic disease (except FA)	18 (2.8)	1 (1.7)	19	0.9	0.2 - 5.0	NS
IBD	40 (6.3)	7 (12.5)	47	2.2	1.0 - 5.2	0.05
Celiac disease	37 (5.7)	2 (3.5)	39	0.7	0.2 - 7.8	NS
Polyarthitis or other rheumatic diseases	5 (0.7)	2 (3.5)	7	5.3	1.2 - 24.1	0.04
Clotting disorders	4 (0.6)	0	4	1.3	0.1 - 23.3	NS
Prematurity	8 (1.2)	0	8	0.7	0.1 - 11.6	NS
Post-Transplant	4 (0.6)	1 (1.7)	5	3.8	0.6 - 24.8	NS
Oncology (during chemotherapy)	4 (0.6)	1 (1.7)	5	3.8	0.6 - 24.8	NS
Others	68 (10.6)	4 (7.1)	72	0.7	0.3 - 1.9	NS
Absence of known chronic disease	343 (53.7)	30 (53.57)	373	1.0	0.6 - 1.7	NS
Total	638	56	694			

CI : confidence interval ; IBD : inflammatory bowel disease ;
NS: not significant ; OR : Odds ratio

epigastric pain as main symptoms 17 of 24 (70.8%) versus 16 of 32 (50%), known chronic diseases 10 of 24 (41.6%) versus 18 of 32 (56.3%). In three children with gastro–duodenal erosions *H. pylori* status was not assessed.

Complementary data

The median age of the 56 children presenting with ulcers or erosions was 11.38 years (range 0.16–17.8) with a sex ratio of 1. Known chronic diseases were reported in 321 of 694 children (Table 3), which were significantly higher in patients with ulcers and/or erosions as compared with those without lesions. Seven of 32 children presented with IBD and two of 32 with polyarthritis, or other rheumatic diseases (Tables 2 and 3). Main indications for endoscopy were epigastric or abdominal pain and suspicion

of gastroesophageal reflux disease (Table 4). Epigastric pain, hematemesis, melena, and weight stagnation were significantly found as the main indication of endoscopy in patients with ulcers and/or erosions as compared with those who lacked lesions (Table 4).

H. pylori infection was detected in only 15 children (27%) using different diagnostic methods: culture in 11, histology in 11, rapid urease test in 4, ^{13}C urea breath test in three, and stool antigen test in two. In three children, histology failed to detect *H. pylori*, whereas culture was positive. *H. pylori* infection may, however, be underestimated as *H. pylori* status was considered as not valid in six of 24 (25%) and 12 of 32 (37.5%) patients with primary and secondary lesions and in three children *H. pylori* status was not assessed (Table 2). In three children (5.3%), *H. pylori* was eradicated earlier.

Other complementary data concerned previous *H. pylori* eradication in three children (5.3%). Thirty children were born in Western Europe (53.5%), 24 in Eastern Europe (43%), and two in Africa (3.5%); 20 mothers were born in Western Europe (35.7%), 22 in Eastern Europe (39.2%), 10 in Africa (17.8%), two in the Middle East, one in Asia, and one in North America.

The educational level of mothers and fathers, according to the number of schooling years, was unevenly distributed: less than 9 years for thirteen mothers and nine fathers, respectively, 9–11 years for 6 mothers and 13 fathers, more than 12 years for 23 mothers and 16 fathers, and university degree for six mothers and ten fathers; the educational level was not known in eight couples of parents.

A median of four members of the family were living in the house (range 2 -9), and 36 children (64%) slept in a personal bedroom.

A history of peptic ulcer in a first-degree family member was reported in six children (10.7%). A history of use of medication within four weeks before endoscopy was reported in 29 children (51.7%); some children were taking more than one drug: NSAIDs in eight (14.3%) where five of 13 and three of 19 in the secondary ulcers and/or erosions and erosions only groups, respectively, antacids in one (1.7%), H2-blockers in six (10.7%) where three of 24 (two ulcers and/or erosions, one erosions only) and three of 32 (two ulcers and/or erosions, one erosions only) in the primary and secondary lesions groups, respectively, PPIs in eight (14.3%) where three of 24 (three erosions only) in the primary and five of 32 (five erosions only) in the secondary lesions groups, antibiotics in six (10.7%) where three of 13 (three ulcers and/or erosions) and three of 19 (three erosions only) in the secondary lesions groups, steroids in five (8.9%) where one of 13 (one ulcer and/or erosion) and four of 19 (four erosions only) in the secondary lesions groups, and immuno-suppressive drugs in five (8.9%) where one of 13 (one ulcer and/or erosion) and four of 19 (four erosions only) in the secondary lesions groups (Table 2). In addition, a history of

Table 4 Indications of endoscopy in all enrolled patients

Indications of endoscopy	Patients without ulcers and/or erosions n (%)	Patients with ulcers and/or erosions n (%)	*Total* n	OR	95% CI	*P* value
Suspected gastroesophageal reflux disease	87 (13.6)	3 (5.3)	90	0.4	0.14-1.25	NS
Established gastroesophageal reflux disease	66 (10.3)	1 (1.7)	67	0.2	0.1-1.2	0.05
Abdominal distress/pain	92 (14.4)	11 (19.6)	103	1.5	0.7-2.9	NS
Epigastric pain	51 (7.9)	9 (16.1)	60	2.3	1.1-4.8	0.03
Pain awaking child at night	23 (3.6)	4 (7.1)	27	2.2	0.8-6.4	NS
Heartburn	5 (0.7)	0	5	1.0	0.1-18.7	NS
Nausea	2 (0.3)	0	2	2.6	0.1-47.5	NS
Vomiting	16 (2.5)	0	16	0.3	0.1-5.6	NS
Halitosis (foul smelling breath)	1 (0.01)	0	1	3.8	0.2-92.7	NS
Hematemesis	8 (1.2)	5 (8.9)	13	7.9	2.6-24.1	0.00005
Melena	9 (1.3)	3 (5.3)	12	4.3	1.2-15.3	0.03
Weight stagnation	32 (5.0)	7 (12.5)	39	2.8	1.2-6.6	0.02
Chronic diarrhea	20 (3.1)	1 (1.7)	21	0.8	0.2-4.4	NS
Anemia	7 (1.1)	0	7	0.8	0.1-13.3	NS
Iron deficiency	2 (0.3)	0	2	2.3	0.1-47.5	NS
Anorexia	5 (0.7)	0	5	1.0	0.1-18.7	NS
Malaise	11 (1.7)	1 (1.7)	12	1.5	0.3-8.3	NS
G-Tube	22 (3.4)	1 (1.7)	23	0.7	0.1-4.0	NS
Foreign body	4 (0.6)	0	4	1.3	0.1-23.3	NS
Suspected caustic ingestion	9 (1.4)	1 (1.7)	10	0.9	0.2-5.3	NS
Work-up for celiac disease	60 (9.4)	0	60	0.1	0-1.3	0.02
Work-up for IBD	34 (5.3)	6 (10.7)	40	2.3	0.9-5.5	NS
Work-up for portal hypertension	34 (5.3)	2 (3.5)	36	0.8	0.2-3.0	NS
Other	38 (5.9)	1 (1.7)	39	0.4	0.1-2.2	NS
Total	638	56	694			

CI: confidence interval; IBD: inflammatory bowel disease; NS: not significant; OR: Odds ratio

Table 5 Multivariate analysis of children with gastroduodenal ulcers and/or erosions

	Adjusted OR[a]	95% CI	*P* value*
Results of the multivariate analysis were adjusted according to the investigator centers Age (vs <10 yrs)			
> 10 yrs	1.6	0,7-3,6	0,28
Indication of endoscopy (vs. all other indications)[b]			
Suspected or established gastroesophageal reflux	0.4	0.1-1.2	0.08
Epigastric pain	2.9	1.0-8.2	0.05
Pain awaking child at night	4.4	1.2-16.7	0.03
Hematemesis	12.7	3.0-53.2	0.001
Melena	6.6	1.4-31.9	0.02
Weight stagnation	3.6	1.3-10.2	0.015
Known chronic diseases (vs. all other relevant)			
IBD	2.1	0.8-5.7	0.13
Polyarthritis or other rheumatic diseases	6.7	0.5-84.3	0.14

CI: confidence index; IBD: inflammatory bowel disease; OD: Odds ratio

[a] Odds ratio adjusted on all the variables of the model

* *P* value obtained by a multivariate logistic model

[b] only variables exhibited a *P* value <0.20 by the monovariate analysis were analyzed by multivariate logistic model

alcohol consumption was reported in seven (12.5%) and tobacco smoking in three children (5.4%).

Risk factors

Ulcers and/or erosions were more frequently reported in three centers located in Belgium, Italy and Turkey (Table 1). In all enrolled children, the analysis of gastro–duodenal ulcers and/or erosions showed the same risk factor results when analyzed separately and as conjointly that epigastric pain, hematemesis, melena, and weight stagnation were reported as the most significant clinical symptoms considered as risk factors for erosions or ulcers (Table 4). Known chronic diseases such as IBD, polyarthritis, or other rheumatic diseases were also considered significant risk factors (Table 3).

Children aged above 10 years represented another significant risk factor. Adjust-

ment of the multivariate analysis according to the centers showed that the same risk factors were as significant and that pain-awaking at night also reached a level of significance (Table 5).
Finally, no significant relationship could be shown between *H. pylori* infection and the type of peptic lesions. As *H. pylori* status was not systematically determined in children without ulcers and/or erosions, thus an OR could not be determined for children with or without ulcers/erosions.

DISCUSSION

In this prospective European study, the frequency of ulcers or erosions in children referred for upper endoscopy reached the unexpected high figure of 8.1%. This frequency is possibly underestimated because of the use of gastro-protective drugs including H2 -blockers and PPIs preceding the endoscopic procedure.
An important variation of this frequency was observed among the different centers participating in the study (0–22%). This can be because of several factors in the different countries: referral habits, use of gastro-protective drugs before endoscopy, interference of adult gastroenterologists taking care of adolescents, and possible unknown geographical influences.
Lesions of ulcers or erosions were observed mainly around the second decade of life, and children older than 10 years were significantly more at risk for ulcers and erosions alike. Epigastric tenderness, pain-awaking at night, hematemesis, melena, and weight stagnation were significant risk factors for lesions of ulcers or erosions alike.
The fact that *H. pylori* infection was observed in only 15 of 56 (27%) children in different European centers is in agreement with the decreasing prevalence of *H. pylori* infection in adults observed in Europe [13]. The relationship between chronic peptic ulcer disease and *H. pylori* is widely documented in adults, especially in relation with duodenal ulcers. A higher rate of *H. pylori* infection was also described[3] in children with duodenal ulcers compared with those with gastric ulcers (62 vs. 20%, $P<0.001$). However, in other pediatric papers, *H. pylori* infection was detected in only three of 11 (27%) children with duodenal ulcer [5]. Similarly, in an older publication, it was reported in six of 11 children with duodenal ulcers (55%) versus two of four with gastric ulcers (50%) [14]. In this study, we did not find in any of the different European countries a significant relationship between *H. pylori* infection, present in 15 of 56 children (27%) and the location of the gastric or duodenal ulcers/erosions. Furthermore, the fact that *H. pylori* status was considered as unreliable because of the use of either PPIs, H2 - blockers or antibiotics in the period preceding endoscopy in six of 24 and 12 of 32 children with primary and secondary lesions, may also influence the low frequency of *H. pylori* infection observed in our series (Table 2). A recent review

of studies published during the last 10 years including a total of 16 080 patients, showed that *H. pylori* was found in 81% of duodenal ulcers, but a lower frequency of 77% was reported when only the last 5 years were considered[15]. Associations with *H. pylori*-negative duodenal ulcer were mainly because of false negative results of diagnostic methods and the use of NSAIDs [15]. This important puzzling observation needs a confirmation by a study on a wider scale taking into consideration a longer period of time extending necessarily over several seasons. Even more important is the correlation to the prevalence of *H. pylori* infection in each specific geographic area as stressed by a recent Israeli paper [6] describing a high incidence of ulcers in their Israeli Arab or Russian immigrant children and also as observed, in this study, in three European centers of Belgium, Italy, and Turkey (Table 1).
A much lower frequency of ulcers and erosions (2%) is reported in earlier papers [3, 5] without reference to age, although with a higher frequency of *H. pylori* associated ulcers and the same trend is reported in the PEDS-CORI database [16]. In contrast, ulcers were detected in 80 of 1180 *H. pylori*-positive children (6.8%) in a prospective European multicenter study [7].
Our results confirm data published earlier stressing the fact that the age of the children is an important risk factor: OR of 3.1 in children older than 11 years [7] and OR of 2.1 in this study in children older than 10 years. However, we did not observe the age difference between children with gastric ulcer reported [3] to be younger than those with duodenal ulcer (6.5 vs. 10.5 years).
Several investigators have suggested that night-time pain associated with nocturnal awakening, fasting pain relieved by food intake, pain associated with meals or postprandial bitter taste, heartburn and epigastric pain are clinical signs that help to distinguish ulcer-positive from ulcer-negative children, although positive for *H. pylori* infection [2]. However, in contrast, these clinical symptoms are not found to be specific by Roma *et al* [3], as no significant difference was found with regard to clinical symptoms between children with and without ulcer. In this study, the main indications for endoscopy were epigastric or abdominal pain (24%) and suspicion of gastroesophageal reflux disease (15%). Hematemesis, melena, epigastric tenderness, and weight stagnation can be considered as significant risk factors for erosions or ulcers alike.
Together with *H. pylori* infection, the use of NSAIDs is considered as an important risk factor not only for gastrointestinal mucosal injuries in adults, but also in children [17]. In adults, both *H. pylori* infection and the use of NSAIDs independently and significantly increase the risk of peptic ulcer and upper gastrointestinal bleeding (UGIB) [18]. In children, few studies address the relationship between NSAIDs intake, *H. pylori* infection, and other risk factors inducing mucosal injuries and UGIB.
In a retrospective review of the medical records of 112 Taiwanese children who

presented with UGIB, *H. pylori* infection was present and closely related to primary duodenal ulcers in 55% of patients without any other underlying disease, contrasting with the lower figure of only 17% in children with several underlying diseases[19]. UGIB is frequently related to drug ingestion with almost 50% of cases showing gastric erosions secondary to drug intake [20].

In a recent study based on data of the French Pharmacovigilance system [21] analyzing all serious upper gastrointestinal complications such as gastritis, duodenitis and esophageal lesions, gastric or duodenal ulcers were reported in 61 children aged 11 months - 15 years during treatment with niflumic acid, ibuprofen, and tiaprofenic acid, associated with NSAIDs in children. This important study concludes that NSAIDs used in children for fever or moderate pain are associated with a risk of serious UGIB complications that increase with duration, dose, and association with a salicylate.

In our study, medication intake during the last 4 weeks was reported in 29 out of 56 children with erosions or ulcers (51.7%), but NSAIDs consumption in only eight children (14.3%) and steroids in another five (8.9%). The frequency of tobacco (three cases, 5.4%) and alcohol (seven cases, 12.5%) consumption is low in the population of children with ulcers and/or erosions and does not allow drawing firm conclusions about their influence on the pathogenesis of ulcers.

In this study, we found that the frequency of primary gastric and duodenal ulcers and/or erosions was slightly lower than those of secondary lesions (24/56 and 32/56), lower than the figures of 19 of 36 primary peptic ulcers and 17 of 36 secondary lesions published by Drumm *et al.* [22] 20 years ago.

Finally, because the results of this study show, in children, a higher frequency than expected of ulcers or erosions, the evaluation of the multiple risk factors for the detection or prevention of ulcers and/or erosions needs a prospective case–control study over several seasons taking into account the specific prevalence of *H. pylori* infection in each different geographical area. These lesions should be systematically screened in symptomatic children with epigastric pain, hematemesis, melena, or weight stagnation to adapt adequately the subsequent treatment.

CONCLUSION

In this prospective European multicenter study a frequency of 8.1% of ulcers and/or erosions was observed in children mainly around their second decade of life with a high variability among different centers. Epigastric tenderness, pain awakening the child at night, hematemesis, melena and weight stagnation can be considered as significant risk factors for ulcers or erosions indifferently. The unexpectedly low frequency of *H. pylori* infection and NSAID-use in these patients questions its etiologic role causing ulcers and/or erosions.

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