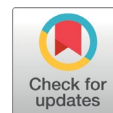




ORIGINAL ARTICLE



Children and adolescents' health on focus: Gastrointestinal injuries associated with *Helicobacter pylori*

Saúde de crianças e adolescentes em questão: Lesões gastrointestinais associadas a *Helicobacter pylori*

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Received in 20 Jul 2020, accepted in 4 Nov 2020, published in 15 Dec 2020

KEYWORDS

Adolescent
Child
Gastrointestinal
endoscopy
Helicobacter pylori
Public health
Wounds and injuries

ABSTRACT

Objective: To describe the prevalence of *Helicobacter pylori* (HP) in children and adolescents, and to assess its association with lesions in the esophagus, stomach, and duodenum according to the patient's life cycle.

Methods: A cross-sectional analytical study with children and adolescents referred to a gastroenterology service and underwent esophagogastroduodenoscopy at a hospital in Vitória, Espírito Santo, Brazil, from 2001 to 2013. Variables analyzed were the following: sex, age, macro and microscopic alterations and severity of infestation. The Chi-square and Fisher's exact tests and adjusted residue analysis were used ($\alpha = 5\%$).

Results: the prevalence of infection was 24.4%. Esophagitis (29.4%) and gastritis (34.1%) were associated with HP. The life cycle was associated with esophagitis and duodenitis. Infection was associated with life cycle: infants (0.8%), preschool children (10.5%), school-aged children (16.5%), and adolescents (72.2%). The residues showed a strong association between HP and gastritis, and no association between the school-aged and esophagitis. Adolescents were the major contributors to the association between life cycle and infection, and life cycle and lesion.

Conclusions: Infection with HP was associated with esophagitis and gastritis and was higher among adolescents, who had a marked tendency to develop gastritis and a milder tendency to develop esophagitis. The tendency of developing infection and gastritis was not present in the other life cycles. Public policies focusing on promotion and protecting health, especially in vulnerable population groups, are needed.

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<https://doi.org/10.21876/rcshci.v10i4.1026>

How to cite this article: Guariento MRB, Silva JP, Guariento GB, Pinasco GC, Sales AB, Alves CBR, et al. Children and adolescents' health on focus: Gastrointestinal injuries associated with *Helicobacter pylori*. Rev Cienc Saude. 2020;10(4):117-124.
<https://doi.org/10.21876/rcshci.v10i4.1026>

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PALAVRAS-CHAVE

Adolescente
Criança
Endoscopia
gastrointestinal
Ferimentos e lesões
Helicobacter pylori
Saúde pública

RESUMO

Objetivo: Descrever a prevalência de *Helicobacter pylori* (HP) em crianças e adolescentes, e avaliar a sua associação com lesões no esôfago, estômago, e duodeno de acordo com o ciclo de vida (CV).

Métodos: Estudo analítico transversal com crianças e adolescentes encaminhados para um serviço de gastroenterologia e submetidos a esofagogastroduodenoscopia num hospital em Vitória, Espírito Santo, Brasil de 2001 a 2013. Variáveis analisadas: sexo, idade, alterações macro e microscópicas e gravidade da infestação. Foram utilizados os testes do qui-quadrado e exato de Fisher, e a análise de resíduos ajustados ($\alpha = 5\%$).

Resultados: A prevalência da infecção foi de 24,4%. Esofagite (29,4%) e gastrite (34,1%) foram associadas à HP. O CV foi associado à esofagite e à duodenite. A infecção estava associada ao CV: bebês (0,8%), crianças em idade pré-escolar (10,5%), crianças em idade escolar (16,5%), e adolescentes (72,2%). A análise de resíduos mostrou forte associação entre a HP e a gastrite, e nenhuma associação entre a idade escolar e a esofagite. Os adolescentes foram os que mais contribuíram para a associação entre CV e infecção, e entre CV e lesão.

Conclusões: A infecção por HP esteve associada à esofagite e à gastrite e foi mais elevada entre os adolescentes, que tinham uma marcada tendência para o desenvolvimento da gastrite e uma tendência mais branda para o desenvolvimento da esofagite. A tendência de desenvolvimento de infecção e gastrite não estava presente nos outros CV. São necessárias políticas públicas centradas na promoção e proteção da saúde, especialmente em grupos populacionais vulneráveis.

INTRODUCTION

Helicobacter pylori is a Gram-negative bacterium that affects nearly half of the world's population, and two-thirds of them are under 18 years of age. Among children and adults, this prevalence has dropped during the past few years¹. In Brazil, it was not found a representative population-based study to establish the prevalence of *H. pylori* among children and adolescents. A similar Brazilian study highlighted a prevalence of 19.3% (in 2004) and 14.3% (in 2014), with a 5.0% decrease over ten years in the pediatric population². This fact draws attention to the need for public policies to monitor this population in life cycles in vulnerability conditions, such as those addressed in this study.

This disease is one of the most common globally and is more prevalent among children from the peripheral countries. Socioeconomic factors, such as poor hygiene and precarious access to potable water, are associated with *H. pylori*³. To improve people's hygiene habits, the adoption of specific policies is crucial. Policies focusing on oral hygiene and on the use of individual cutlery may help reduce the dissemination of bacteria within the family and children in schools. This may justify the lower prevalence found in more developed countries⁴⁻⁶. Social factors, motivated by poverty and low income, might be the source for inequalities and social injustice and explain the transmission of diseases and the health condition among more vulnerable populational groups⁷.

Although controversial, it seems that the infection with *H. pylori* is acquired early in childhood, which justifies the possibility of abdominal pain and the development of cancer in adulthood⁸. The diagnosis of this infection is made with upper gastrointestinal endoscopy with a biopsy. A gastric lesion is the main finding in such an examination, especially among adolescents, although also observed in infants.

Therefore, this study evaluated the prevalence of *H. pylori* in children and adolescents, as well as its

association with the occurrence of lesions in the esophagus, stomach, and duodenum in each life cycle of the sample studied.

METHODS

A cross-sectional analytical study was conducted with data obtained from medical records from patients referred to a gastroenterology service and who underwent esophagogastroduodenoscopy (EGD) from 2001 to 2013. The service is located in Vitória, ES, Brazil, and it is a regional pediatric reference. The age groups considered in this study were those established by the Brazilian Pediatric Society (*Sociedade Brasileira de Pediatria*)⁹.

- Infants (from 29 days to 2 incomplete years of age);
- Pre-schoolers (from 2 years to 6 incomplete years of age);
- School-aged (from 7 years to 9 incomplete years of age) and;
- Adolescents defined by the World Health Organization (WHO)¹⁰ as those from 10 years to 19 incomplete years of age.

This study was conducted at the Nossa Senhora da Glória Children's Hospital (HINSG), founded in 1932. The hospital is located in a 4,700 m² area, with 149 medium and high complexity beds, including an emergency service working 24 hours a day. The institution also provides outpatient care of diverse pediatric specialties. The hospital has maintained programs of medical residence in Pediatrics for 42 years (16 positions), Pneumology (3 positions), Infectiology (2 positions), and Intensive Pediatric Care (2 positions). Due to the relevant services provided, the HINSG is a referral institution for other states nearby, such as Minas Gerais, Bahia and Rio de Janeiro.

The clinical data that justified the referral for EGD were obtained from medical requests from public and

private services. The following variables were collected from medical requests, patient's medical records, and reports from the pathology service: sex, age, clinical manifestations, macroscopic descriptions of the mucosa, histologic diagnoses and the presence and severity of infestation with *H. pylori*. A convenience sample was set and included all patients that underwent EGD.

The EGDs were performed at the HINSG by one of four specialists from the medical service. They had more than 20 years of experience in the procedure and used the same technique and equipment, the Olympus GIF-V Video Gastroscope (Olympus C. Tokyo, Japan). Patients were sedated with 3 to 5 mg/kg Propofol (diisopropyl phenol) *in bolus*, following an infusion of 80 - 150 mg/kg/min, adjusted according to the patient's response. All patients received 2 L/min oxygen via a nasal catheter and were monitored with a cardioscope and oximetry during the whole procedure, and no complications were observed.

During the procedure, patients systematically underwent three biopsies of each organ: esophagus, stomach (antrum, angular notch, and body) and duodenum. The suspected and harsh lesions of the mucosa were also biopsied. The fragments were put in a container with 10% formalin solution and underwent the standard histological process: alcohol dehydration, diaphanization in xylol, inclusion in paraffin, slicing into 5-micron thick and stained with hematoxylin-eosin and Giemsa to identify the presence of *H. pylori*.

A fragment of the antrum was transferred into a test tube and mixed with a urea solution (Probac do Brasil®). The mixture was maintained at a room temperature of approximately 36 °C to run the urease test six hours after the biopsy.

The same pathologist conducted the analysis at the pathological anatomy laboratory of the HINSG. The hospital has two pathologists with over 20 years of experience in pediatrics, which reviewed all microscope slides.

Chi-square and Fisher's exact tests and the analysis of adjusted residues were used to evaluate the association between *H. pylori* and microscopic lesions, between micro and macroscopic findings, and between the severity of infestation with the bacterium and the patient's life cycle. The variables sex and macroscopic lesions are described by their absolute and relative frequencies. Age is described by its arithmetic mean and standard deviation (SD) and shown in a contingency table according to SBP⁹ and WHO criteria¹⁰, along with the variables of the presence of *H. pylori* and the microscopic lesions identified in biopsies. The variables: identified microscopic lesions, the presence of *H. pylori*, and severity of infestation are also shown in a contingency table. IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.) was used.

Adjusted residuals (AR) analysis was used as an additional tool in interpreting data organized in the contingency tables with two or more degrees of freedom. It was possible to assess how the various values in the table contribute to the Chi-square value and how they contributed to the association between the variables tested, despite the absolute and relative values acquired by the variables shown in the contingency table. Considering a 5% significance, an AR

that exceeded 1.96 SD was considered relevant for the analysis and impacted the difference between the analyzed groups. As a result, positive and significant ARs expressed a positive trend, which means that the number of observed cases surpassed what was expected. Alternatively, negative and significant ARs expressed a negative trend, meaning that the number of observed cases was less than expected¹¹.

This study was approved by the Research Ethics Committee of the School of Sciences of Santa Casa de Misericórdia de Vitória, under the license number of 3.356.631/2019.

RESULTS

A total of 545 EGDs were realized in the sample. From those, 280 (51.4%) were discovered until 2011 and 265 (48.61%) in 2012 - 2013. Nearly 54% (n = 295) of patients were women with a mean age of 9.3 ± 4.8 years. According to the patient's life cycle, the total sample was composed of 32 (5.9%) infants, 84 (15.4%) preschool children, 147 (27.0%) school-aged children, and 282 (51.7%) adolescents.

The patients were referred to EGD according to the following clinical conditions: epigastric pain (46/8.4%), abdominal pain (31/5.7%), nausea/vomiting (17/3.1%), duodenal atrophy (12/2.2%), and other causes (25/4.6%). These conditions were not associated with the presence of *H. pylori* (p = 0.309). In 414 cases (76.0%), the clinical referrals did not accompany the medical record available for this research.

During EGD, macroscopic alterations were observed in 62 (11.6%) patients. They were gastritis (47/74.6%), esophagitis (4/6.3%), duodenal ulcer (4/6.3%), nodular duodenal hyperplasia (2/3.2%), duodenitis (2/3.2%), esophageal thickening (1/1.6%), micronodules in the distal esophagus (1/1.6%), and Barrett's esophagus (1/1.6%). These findings were also unassociated with the presence of *H. pylori* (p = 0.612).

Table 1 shows the distribution of macroscopic lesions from the biopsied tissues from patients who underwent EGD, and the severity of the infection. Esophagitis was diagnosed in 160 (29.4%) biopsies, gastritis in 186 (34.1%), and duodenitis in 37 (6.8%). The association of *H. pylori* infection and the presence of esophagitis and gastritis was statistically significant. In the microscopic analysis, the bacterium was present in 133 (24.4%) of the 545 cases, and the severity of the infestation was stratified in crosses by the responsible professional, varying from one (less severe) to three crosses (more severe) as well as the chronic stage (Table 1).

H. pylori was present in infants (1/0.8%), in preschool and school-aged children (14/10.5% and 22/16.5%, respectively), and adolescents (96/72.2%). Table 2 evidences the significant association between the patient's life cycle and infection with *H. pylori* (p < 0.001), and that adolescents presented the highest percentage (34.0%) of infection. The patient's life cycle was also associated with esophagitis and gastritis.

In both Tables 1 and 2, the adjusted residues are not significant when the Chi-square test is also not significant. ARs were not significant for pre-schoolers

regarding the presence of *H. pylori* and between the patient’s life cycle and duodenitis. Table 2 shows that older patients have higher absolute AR values, with

adolescents being the major contributors to the Chi-square value for the association between the bacterium and the microscopic lesions in esophagitis and gastritis.

Table 1 - Association between the presence of microscopic lesions in material biopsied, and the severity of infestation with *H. pylori* in children and adolescents who underwent EGD.

Microscopic lesion diagnosed	<i>Helicobacter pylori</i>			Severity of infection with <i>Helicobacter pylori</i>				
	Absent	Present	Total	+	++	+++	Chronic stage	Total
Esophagitis		p = 0.004*					p = 0.317†	
Present (AF/AR)	134/+2.86‡	26/-2.86‡	160	5/+0.54	5/-1.67	16/+1.35	0/-0.70	26
Absent (AF/AR)	278/-2.86‡	107/+2.86‡	385	16/-0.54	39/+1.67	50/-1.35	2/+0.70	107
Total	412	133	545	21	44	66	2	133
Gastritis		p < 0.001*					p = 0.606†	
Present (AF/AR)	56/-17.8‡	130/+17.8‡	186	20/-0.84	44/+1.23	64/-0.60	2/0.22	130
Absent (AF/AR)	356/17.8‡	3/-17.8‡	359	1/+0.84	0/-1.23	2/+0.60	0/-0.22	3
Total	412	133	545	21	44	66	2	133
Duodenitis		p = 0.110*					p = 0.499†	
Present (AF/AR)	32/+1.60	5/-1.60	37	2/+1.51	1/-0.63	2/-0.44	0/-0.28	5
Absent (AF/AR)	380/-1.60	128/+1.60	508	19/-1.51	43/+0.63	64/+0.44	2/+0.28	128
Total	412	133	545	21	44	66	2	133

*Chi-square test, †Fisher’s exact test, ‡Significant adjusted residues, AF: Absolute frequency, AR: Adjusted residues.

DISCUSSION

The most relevant findings in this study refer to the prevalence of 24.4% of infection with *H. pylori*, which was more common in adolescents (72.2% of patients), and its significant association with the presence of gastritis. This high prevalence might be justified because the sample in this study was composed of children and adolescents with a higher possibility of being infected, as the sample was composed of patients referred to a gastroenterology service. This fact limits the comparison with studies using other populational samples, such as those quoted in Frugis et al.². AR for adolescents was positive for the presence of *H. pylori* (+5.42), suggesting a tendency for infestation with this bacterium in this specific life cycle once the observed frequencies are higher than the expected for this association. It is

important to consider that other life cycles presented significant and negative ARs or even insignificant residues for the presence of the bacterium, where fewer cases of infection than expected were observed for these patients. This result suggests no apparent tendency of infestation with *H. pylori* for all life cycles considered in this study, except for the adolescents.

There is evidence that children living under precarious hygiene and poverty conditions (which were not evaluated in this study) are infected with *H. pylori* very early in their lives, with a high prevalence of infection being found³⁻⁶, although many of them are asymptomatic¹². The lack of clinical symptoms could have contributed to lowering the number of infants and school-aged children to be screened and referred to EGD in this study, as the clinical evaluation is the main reason for the EGD examination.

Table 2 - Associations between the patient's life cycle and the presence of microscopic lesions, as well as the presence of *H. pylori* in children and adolescents who underwent EGD.

Life cycle	<i>Helicobacter pylori</i> (p < 0.001)*			Diagnosed lesion								
	Absent	Present	TOTAL	Esophagitis (p < 0.001)*			Gastritis (p < 0.001)*			Duodenitis (p = 0.561)*		
				Absent	Present	TOTAL	Absent	Present	TOTAL	Absent	Present	TOTAL
Infant (AF/AR)	31/+2.89†	1/-2.89†	32	15/-3.04†	17/+3.04†	32	28/+2.66†	4/-2.66†	32	29/-0.60	3/+0.60	32
Preschoolers (AF/AR)	70/+1.80	14/-1.80	84	49/-2.89†	35/+2.89†	84	66/+2.67†	18/-2.67†	84	77/-0.61	7/+0.61	84
School-aged (AF/AR)	125/+3.12†	22/-3.12†	147	97/-1.45	50/+1.45	147	112/+3.09†	35/-3.09†	147	135/-0.78	12/+0.78	147
Adolescents (AF/AR)	186/-5.42†	96/+5.42†	282	224/+4.67†	58/-4.67†	282	153/-5.92†	129/+5.92†	282	267/+1.41	15/-1.41	282
TOTAL	412	133	545	385	160	545	359	186	545	508	37	545

†Chi-square test, †Fisher's exact test, AF: Absolute frequency, AR: Adjusted residues.

Although the prevalence of *H. pylori* is decreasing worldwide, during the past hundred years, even in peripheral countries¹³, the high value found in this study might be explained by the evidence that this infection is associated with poverty, agglomeration, non-potable water consumption, and inadequate sanitation¹⁴. These conditions are justified due to some reasons, like Brazil's inequalities, although they were not assessed in this study. These factors need to be related to the occurrence of this social phenomenon, since it impacts the quality of life, health, education, work and the environment, which undoubtedly deserves further studies to deepen the discussion.

Poverty is a phenomenon that has been rising in absolute terms, and it affects childhood even in developed countries such as the United Kingdom, causing impairments to health and poorer long-term outcomes in social and psychological fields¹⁵. Thus, in Brazil, it is essential to strengthen policies to reduce poverty, with a better evaluation of the health indicators to improve the evaluation of the actions taken in such policies and improve the quality of the services provided to the population.

The demographic changes caused by rapid urban growth contributed to the emergence of urban agglomerates, where poverty and environmental risks due to potable water contamination are widespread. In these localities, the cycle comprising water, poverty and health must be treated in that same policy destined to fight poverty. Without this, the adverse health effects due to this cycle remain acting on the population, which may justify the *H. pylori*'s high frequency in the group studied¹⁶.

Human beings and this bacterium have been in a symbiotic relationship for decades¹⁷, although 10% to 20% of infected people are susceptible to gastroduodenal diseases, such as peptic ulcer disease, iron deficiency anemia, gastric mucosa atrophy, metaplasia, dysplasia, lymphoma, or gastric adenocarcinoma. Most of them develop as the *H. pylori* infection progresses. This is very important considering that inflammation and chronic infection with this bacterium are relevant risk factors for gastric carcinogenesis, especially for young adults¹⁸.

The abdominal and epigastric pain, nausea/vomiting, and dyspepsia related in this study were inferior compared with Obayo et al.¹⁹ who found a higher frequency of dyspepsia in children and adolescents who were positive for infection. The literature reports that clinical manifestations of gastrointestinal diseases with functional impairments, frequently associated with *H. pylori* in children, include dyspepsia, functional abdominal pain, irritable bowel syndrome, and abdominal migraine. In these cases, the diagnosis of infection with the bacterium must be ruled out since the frequency of *H. pylori* can be greater than 30%^{20,21}. In this study, we could not obtain a clinical indication in 76% of cases, which might justify the observed differences.

Through the analysis of the ARs, there were more cases than expected for those with esophagitis and those

without *H. pylori*, as well as for those with *H. pylori* but without esophagitis (both with AR = +2.86). Regarding this specific lesion, the residues also suggested a higher tendency of the presence of esophagitis in infants and preschoolers (+3.04 and +2.89, respectively). However, the presence of the bacterium does not represent a tendency in such life cycles, as the residues were positive for the absence of *H. pylori* in infants (+2.89), and they were not significant for preschoolers. The residues for school-aged children and adolescents (+4.67) also suggested that the presence of esophagitis is not a tendency, as they were not significant and were positive for the absence of this lesion, respectively.

The cases of esophagitis in infants and school-aged children observed in this study can be explained by the presence of gastroesophageal reflux, which is a natural phenomenon occurring mainly in infants due to the functional immaturity of their gastroesophageal junction, regardless of the status of infection with *H. pylori*^{22,23}. Gastroesophageal reflux disease (GERD) might result in the dilatation of intercellular space, an important histologic biomarker for erosive esophagitis in children²⁴. Lupu et al.²⁵ demonstrated a parallel relation between the scores of pHmetry and the endoscopic lesion. Thus, EGD is reserved for cases of GERD that are unresponsive to clinical treatment.

Regarding gastritis, ARs were positive for its absence in infants (+2.66), preschoolers (+2.67), and school-aged children (+3.09). Apparently, gastritis does not represent a tendency in such life cycles. The values of residues for the absence of *H. pylori* were also positive, and this is in accordance with what was observed, where infection with this bacterium progresses with gastritis.

This study used a sample with selection bias, as the patients who were selected had a higher chance of contamination with *H. pylori*. Another limitation of the study is the partial lack of clinical data for patients referred to EGD. Notwithstanding, these limitations do not make our work unfeasible, considering that a study using a similar sample found a lower frequency of *H. pylori*²⁶. This suggests a high prevalence of this bacterium in the population in which the children live. In this sense, note that the guarantee of social and economic public policies could contribute to reducing the risk of diseases and other injuries for the promotion, protection and recovery of health.

CONCLUSION

In conclusion, the prevalence of *H. pylori* was 24.4%. Adolescents were the ones with the highest prevalence of this bacterium, and they also presented a tendency to develop gastritis. Esophagitis was not a tendency among them. EGD was most commonly indicated when patients presented with abdominal pain, epigastric pain, nausea/vomiting, and dyspepsia. In microscopy, esophagitis, gastritis and duodenitis were the most frequent findings, with the last one not being associated with infection with *H. pylori*.

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Conflicts of interest: No conflicts of interest declared concerning the publication of this article.

Indications about the contributions of each author:

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Statistical analysis: MRBG, JPS, GBG, GCP, ABS, LHSP, VRS

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*All authors have read and approved of the final version of the article submitted to Rev Cienc Saude.

Funding information: Not applicable.