Assessment of the relationship between *Helicobacter pylori* infection, endoscopic appearance and histological changes of the gastric mucosa in children with gastritis (a single center experience)

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Abstract

Background: *Helicobacter pylori* infection is an important cause of gastritis in childhood, its role in the pathogenesis of peptic ulcer disease in adults and children being generally known. In some cases, there are therapeutic management issues, because they do not heal or they often relapse, although treatment regimens are applied as recommended. Our aim was to analyze the relationship between endoscopic appearance and histological changes of the gastric mucosa in children with gastritis associated with *H. pylori* infection, in which persistent infection after treatment was found.

Materials and Methods: It was a prospective study on 1332 children assessed in our Service (Ist Pediatric Clinic, Tîrgu Mureș, Romania), between January 2008 and January 2013, for gastritis with various etiologies. There were 609 cases of gastritis-associated with *H. pylori* infection.

Results: The average age of patients was 13.21 years; the higher incidence was noted in 13–18-year-old group, female gender and rural areas provenience; a number of 544 patients diagnosed with gastritis with *H. pylori* were reassessed subsequently; after treatment, gastritis has healed and the infection was eradicated in 88.23% cases after a month, while in 64 patients infection persisted. After a second regimen, endoscopic–histological modifications persisted in 31 (5.69%) cases; 1.28% cases remained positive for longer.

Conclusions: *H. pylori* infection was associated with high age group, as well as with endoscopic modifications; also, the presence of *H. pylori* was correlated with histopathologic diagnostic. We try to emphasize the importance of assessing bacterial resistance to antibiotics, studying of bacterial genome and genetic susceptibility of human subjects.

Keywords: child, gastritis, *Helicobacter pylori*, histopathology.

§ Background

Gastritis are inflammatory processes of the gastric mucosa, confirmed by histological arguments [1] and clinically manifested by postprandial epigastric prolonged plenitude, decrease of appetite, disinclination for food, nausea, gastroesophageal reflux, dyspepsia, distended abdomen, eructations, postprandial epigastric pyrosis, hunger or nocturnal pains, relieving of pains after anti-acid drugs, and different non-specific (extra-digestive) symptoms [1, 2].

Gram-negative bacillus, *Helicobacter pylori* (*H. pylori*) is responsible for one of the most common human infections, an important cause of gastritis in childhood and the most common etiology of gastritis [3, 4].

Epidemiology of *H. pylori* infection has changed in recent years: there are low rates of incidence in North and West European countries (<10% in children and adolescents), but infection remains common in some areas (Eastern Europe, Mexico, immigrants from South America, Africa, many Asian countries and in aborigines of North America) [5, 6].

It is well documented nowadays that *H. pylori* represents a trigger for gastritis and peptic ulcer disease, while the long-term infection associates a high risk for malignancies in adulthood (lymphoma or gastric adenocarcinoma) [7–9].

The microorganism has a number of virulence factors, which help it to affix itself to the gastric mucosa and to generate the disease into the host organism: multiple unipolar flagella, microaerophilic survival ability, enzyme equipment (urease, vacuolated cytotoxin, catalase, lipopolysaccharidasis, cytotoxin-associated antigen – CagA) [2, 10–16].

Besides history and clinical changes mentioned above, the diagnosis of gastritis with *H. pylori* require laboratory investigations; it involves histological identification of bacteria in biopsy taken fragments together with other non-invasive methods.

Superior digestive endoscopy is the elected procedure for the diagnosis. There is a new endoscopic classification...
used for gastritis, including erosive and non-erosive forms in addition with topography (antral, gastric body gastritis or pan-gastric localization); the endoscopic aspect in \textit{H. pylori} gastritis is characterized by a micronodular antral mucosa (>50\% of cases) or pitting stone appearance (98–100\% of cases); gastritis classification uses the Sydney (endoscopic, histologic, etiologic) criteria [17].

The classic treatment for \textit{H. pylori} infections means a double antibiotic therapy: Amoxicillin 20–30 mg/kg/day + Clarithromycin 15 mg/kg/day or Amoxicillin + Metronidazole 15–20 mg/kg/day or Clarithromycin + Metronidazole for two weeks, associated with proton pump inhibitors (PPI) for four weeks [1, 17–21].

For some patients, we could perform immunoenzymatic technique HpSA (\textit{H. pylori} antigens detection in human feces) [20].

In some cases of peptic diseases, despite a correct treatment, \textit{H. pylori} infection do not cure or relapse, the presence of bacteria in the stomach being reconfirmed at post-therapy assessment.

**Aim**

The purpose of our work was to find correlations between \textit{H. pylori} infection, endoscopic appearance at esogastroduodenoscopy (EGD) and histology in cases of gastritis with \textit{H. pylori} in children. We also proposed to analyze the cases, which, despite a properly conducted treatment for eradication of microorganism, failed to heal, as well as endoscopic and histological appearance in this particular cases.

**Materials and Methods**

It was a prospective study including an initial number of 1332 children aged between 2 and 18 years, admitted in the Department of Pediatric Gastroenterology, University of Medicine and Pharmacy of Tîrgu Mureș, Romania, with different types of gastritis between January 2008 and January 2013. The study was conducted based on case report forms, the clinical examination, the endoscopic appearance and histology of biopsy taken gastric mucosa fragments.

The effectiveness of therapy was evaluated by clinical and endoscopic methods after one month of treatment (when there is clinical and histological healing in treated cases); in cases with persistent infection after the first treatment regimen, we continued with a second scheme, followed by a revaluation at two months, respectively.

We had 611 (45.87\%) cases of gastritis with \textit{H. pylori}, diagnosed by clinical findings together with serology, EGD, rapid urease test and results of histological examinations of biopsy fragments; the tissue fragments were processed through standard histological methods: formalin fixation, sampling, paraffin inclusion, sectioning, Hematoxylin–Eosin and Giemsa staining.

The final diagnosis was confirmed endoscopically, bacteriologically and histopathologically. For some patients, we could perform immunoenzymatic technique HpSA.

From the other 721 cases diagnosed with other types of gastritis, a number of 625 patients were considered as control group for comparisons between children with and without \textit{H. pylori} infection.

The recommended treatment in cases of gastritis included hygienic-dietary regime (excluding not tolerated food) and medication (antacids, antisecretory, gastroprotective and Sucralfate) and also an anti-infectious treatment.

The post-therapy evaluation was possible for a number of 544 cases, the rest of patients either followed the prescribed treatment incorrectly, interrupted medication on their own decision, without a medical indication, or were not present for medical at follow-up one and/or two months – so evidence of 67 cases was lost).

The inclusion criteria for study were:

- recurrent abdominal pains, epigastric pains, sometimes rhythmic with eating, periorbital pains, nausea, vomiting and heartburn, loss of appetite with weight loss;
- acute or chronic gastritis diagnosed on clinical, endoscopic and histological criteria, in children with \textit{H. pylori} infection suspected by endoscopic appearance and documented by diagnostic tests;
- cases diagnosed with gastritis associated with \textit{H. pylori} infection, which followed the recommended treatment;
- patients with \textit{H. pylori} gastritis which followed the treatment and presented for one and two month follow-up.

The exclusion criteria in our study were:

- gastrointestinal symptoms that were not gastritis-specific: documented parasitosis or urinary tract infections, functional abdominal pain, abdominal epilepsy;
- acute or chronic gastritis with other etiology, diagnosed on clinical, endoscopic and histological criteria (with the absence of \textit{H. pylori} infection);
- patients who refused digestive endoscopy;
- cases with endoscopic appearance highly suggestive for \textit{H. pylori}, but in which infection was not confirmed by diagnostic tests (or testing was not performed for technical reasons);
- patients which followed incorrectly the prescribed treatment or interrupted medication on their own;
- cases of gastritis with \textit{H. pylori} which started the specific recommended treatment after the diagnosis but who did not present for follow-up.

All patients underwent endoscopy at presentation and at subsequent checks. EGD was performed with Olympus fiberscope, after 8–12 fasting hours, under local anesthesia with 2\% Xylocaine and proper premedication [22]. An informed consent in compliance with the principles of the Helsinki Declaration was obtained from parents or legal tutors of each child. The study was approved by the local Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureș.

**Results**

Distribution by age groups: the average age of patients in the study group was 13.21 years, with a higher incidence in 13–18 years group (Table 1).

When comparing the age distribution between group of children with \textit{H. pylori} gastritis and patients with other types of gastritis, we found that in patients with \textit{H. pylori}-associated gastritis (confirmed by \textit{H. pylori} detection in biopsy fragments), the high age was predominant, with a statistical significant difference (p=0.0002), as appears in Figure 1.
Table 1 – Demographic characteristics of the study group

<table>
<thead>
<tr>
<th>Age groups [years] – n (%)</th>
<th>2–6</th>
<th>7–12</th>
<th>13–18</th>
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<tr>
<td></td>
<td>40 (7.35%)</td>
<td>177 (32.53%)</td>
<td>327 (60.11%)</td>
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<tr>
<td>Median age (range)</td>
<td>13.21 (2–18)</td>
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<table>
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<tr>
<th>Gender – n (%)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>427 (78.49%)</td>
<td>117 (21.5%)</td>
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<tr>
<th>Area of origin – n (%)</th>
<th>Rural</th>
<th>Urban</th>
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<td></td>
<td>361 (66.36%)</td>
<td>183 (33.63%)</td>
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Total – n=544

Figure 1 – Distribution by age groups in cohort of children with and without H. pylori-associated gastritis.

Basic characteristics of the cohort are presented in Table 1; briefly, the females were predominant (78.49%), as well as patients from rural area (66.36%).

The main reasons for which parents brought the child to the doctor were the following (with different subjective complaints at the first presentation): abdominal pain in 408 cases (75%, of which epigastric pains in 341 cases, 83.57% abdominal painful symptoms, perumbilical pain in 11 cases – 2.69%, and diffuse pain in 56 cases, 13.72% abdominal painful symptoms); nausea, vomiting in 100 (18.38%) cases, loss of appetite in 19 (3.49%) cases, weight loss in three (0.55%) cases, other events (bitter taste, heartburn, constipation, rash) in 14 (2.57%) cases.

The initial (at the first presentation) diagnostic EGD (interpreted according to the Sydney criteria) showed antral changes in 100% of the 544 cases, as follows: granular, follicular mucosa in 177 cases, paving stone appearance or mosaic aspect in 278 cases; congestion in 78 cases, denudation, erosion, bleeding in eight cases, gastric ulceration in three cases, changes in the esophagus in 122 cases, changes in the gastric corpus or of the entire stomach (pangastritis) in 192 cases, while changes of duodenum were found in 78 cases.

From these, we found lesions at two levels in 201 cases, injuries at three levels in 51 cases, and in 15 cases – injuries in the esophagus as well as at gastric, antral and duodenal level.

Figures 2 and 3 illustrate the endoscopic aspect of granular mucosa, and paving stone appearance, respectively, the latter being typical of H. pylori gastritis.

Chi-square test showed a very significant association between presence of H. pylori infection and endoscopic “paving stone” or “mosaic” appearance, considered as characteristic for gastritis with H. pylori, as mentioned above [19], with \( p=0.0001 \) regarding changes at antral level, and \( p=0.006 \) regarding changes at gastric level.

Histological changes were represented by (Figure 4): H. pylori acute gastritis in 32 cases, H. pylori chronic gastritis in 430 cases (from which chronic gastritis with marked activity and H. pylori in 338 cases, foveolar regenerative hyperplasia in 16 cases, atrophic gastritis – three cases and intestinal metaplasia – in four cases) and any detectable histological changes, normal mucosa appearance, or not enough material in 82 samples. We mention that in these cases the diagnosis of H. pylori gastritis was based on clinical aspect, positive rapid urease test, positive serology, fecal antigen detection, knowing that the gastrointestinal mucosa may be affected in plots and biopsy material can be taken from healthy tissue, without possibility of thus excluding the H. pylori infection.

Figures 5–7 show the histological images of gastric mucosa: normal appearance, varying degrees of inflammation and H. pylori colonization.
Figure 5 – (5.A.) Normal antral gastric mucosa (HE staining, ob. 10×); (5.B.) Antral mucosa with lymphoid aggregates (HE staining, ob. 2×); (5.C.) Antral mucosa with heavy inflammation diffusely extended in lamina propria (HE staining, ob. 2×); (5.D.) Antral mucosa with numerous inflammatory cells represented by neutrophils, lymphocytes and plasma cells (HE staining, ob. 4×).

Figure 6 – (6.A.) Neutrophils infiltrates between epithelial cells (HE staining, ob. 10×); (6.B.) Body type gastric mucosa with less inflammation superficially distributed (HE staining, ob. 2×); (6.C.) Inflammatory cells appears only between foveole (HE staining, ob. 4×); (6.D.) Neutrophils are also present along lymphocytes and plasma cells (HE staining, ob. 10×).
Statistically, it was no relation found between gender and histopathological diagnostic, but a very significant association between age groups and histopathological diagnostic \((p=0.0002)\), as well as between \textit{H. pylori} infection and chronic gastritis with \textit{H. pylori} and marked activity at histopathological examination \((p=0.0001)\).

Looking for a relation between histopathological diagnostic and endoscopic appearance, we found a statistical significant relation related to gastric corpus changes \((p=0.05)\), as well as related to antral changes \((p=0.0001)\).

**Evolution**

In the group of patients diagnosed with \textit{H. pylori} gastritis, 544 cases could be reassessed; after proper anti-infective treatment associated with proton pump inhibitors (PPI), clinical–histological healing of the disease after a month was found in 480 (88.23%) cases; a number of 64 (11.76%) patients remained positive.

At one month (after the first scheme of treatment), 64 cases were detected with \textit{H. pylori} infection. Control EGD has shown (Figure 8): antral changes in 100% of the 64 cases (congestion – seven cases, granular, follicular mucosa in 11 cases, mosaic or paving stone appearance – 45 cases, gastric ulceration – one case), changes only in the esophagus in 12 cases, changes in the corpus or full stomach in 17 cases, and changes of duodenum 15 cases each. Of these, in 31 cases lesions were detected in two or more levels.

The first control, histopathological examination revealed: changes of chronic gastritis with \textit{H. pylori} in 59 cases (from this, 31 cases were chronic gastritis with intense activity), and without any microscopically detectable changes, but with endoscopic changes suggestive for \textit{H. pylori} infection or positive diagnostic tests in eight cases (rapid urease test, HpSA).

In the cases of recurrence, a second regimen of treatment was prescribed, consisting of Amoxicillin 20–30 mg/kg/day and Clarithromycin 15 mg/kg/day or Clarithromycin and Metronidazole (in doses mentioned above) for another 14 days, associated with PPI for four weeks.

At two months, meaning after the end of a second course of treatment, a number of 31 cases remained positive, presenting the subsequent changes at EGD: antral changes in all cases (simple congestion – three cases, granular, follicular mucosa – 17 cases, mosaic or paving stone aspect – 11 cases), in the esophagus only in four cases, changes in the corpus or full stomach in 15 cases, and changes of duodenum in nine cases.

Of these, in 20 cases lesions in two levels (13 cases) or three levels (seven cases) were detected.

Comparing healing rate at one and two month, we found a statistical significant difference, \(p<0.0001\) (difference between percents 36.67%, 95%, CI=25.1:52.3), with 88.23% cases healed in one month, and 51.56% healing rate after the second treatment cure.
In our study group, a number of seven patients remained positive for *H. pylori* infection for longer time (Figure 9); there were four girls (one of 12, two of 17, and one of 18-year-old) and three boys (13, 15 and 17-year-old, respectively), the first three girls and two boys coming from rural areas.

Endoscopic antral changes were found in all seven cases – four cases with aspect of mosaic, and three cases of follicular, granular mucosa, while the histopathological examination described in all cases chronic gastritis with *H. pylori* and activity.

![Image](image.png)

**Figure 9 – Evolution of *H. pylori* gastritis during the study (endoscopic appearance).**

**Discussion**

The idea of present paper appeared when we observe that endoscopic appearance and histopathology reveal changes of chronic gastritis with persistent *H. pylori* infection, even after two different treatment regimens against *H. pylori* – in some patients with gastritis associated with *H. pylori* infection, in which digestive symptoms recurred at intervals of time after treatment for the eradication of bacteria.

According to current knowledge in digestive pathology, the correct treatment of gastritis and ulcers in children brings a regression of pre-malignant histological modifications [18], knowing that the long-term *H. pylori* infection associates a high-risk for gastric cancer or malignant lymphoma in adults [1, 23].

We performed some clinical and paraclinical analyses on cases of gastritis in children with *H. pylori* infection. The reported incidence of *H. pylori* infection in children from our country is around 40% (according to a PhD thesis research in an academic center in the East of our country) [19].

We mention that in all cases which were positive for *H. pylori* infection for longer time, at least one family member was found positive for *H. pylori*, which is consistent with the literature [24].

As our colleagues also obtained [19], in our study there has been noticed a growing proportion of *H. pylori* infection at older ages, as it is generally observed in epidemiological studies on *H. pylori* infection – prevalence increases with age (“the cohort effect”) [3].

We searched for relations between endoscopic appearance and histopathological appearance, founding statistically significant associations; statistically significant relations were also observed between endoscopic appearance and *H. pylori* infection, and between histopathological aspect and *H. pylori* infection.

It is well recognized that *H. pylori* hold virulence factors that favors its survival in gastric environment, being stipulated that they increase its pathogenicity; other theories assumes that there is a genetic predisposition for the infection with *H. pylori* in some people, meaning that the genetic polymorphism of host influences the pharmacokinetics and the treatment with PPI efficiency [10, 13, 15, 16]. On this basis, we assume that we had cases of unfavorable evolution due to uninterrupted action of favoring factors, the presence of infection in other family members, because of the microorganism peculiarities and even because of host susceptibility.

Based on knowledge in this scientific area and clinical observations, we try to emphasize the importance of introducing and using in current practice of some additional determinations which may help us in identifying bacterial resistance to treatment (culture, drug susceptibility testing – DST) and also to detect elements that confer host susceptibility to infection and treatment resistance, in order to choose the most advantageous therapeutic approach.

**Conclusions**

In our group of child gastritis associated with *H. pylori* infection, the histopathologic diagnostic was associated with presence of *H. pylori* infection and endoscopic changes in gastric corpus, as well at those at antral level. Infection was prevalent in high age group, and correlated with gastric corpus and antral endoscopic appearance (follicular, granular and paving stone aspect).

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**References**


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