„CAROL DAVILA" UNIVERSITY OF MEDICINE
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PEDIATRIC INFECTION WITH *HELICOBACTER PYLORI* – PARTICULAR ASPECTS

PhD THESIS

Coordinator:
PROFESSOR MD PhD DOINA ANCA PLESCA

Student:
MD PREDA CAS. BORDEI ELENA LUIZA

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CONTENT

Introduction

Since the discovery of the bacterium in 1983 have been published numerous studies, the most recent attest the progress in the study of the pathogenesis of *Helicobacter pylori (H. pylori)* infection, the host-pathogen interaction, as well as the role of the virulence factors in the progression of the disease. The literature studies dedicated to pediatric *H. pylori* infection are extremely limited at present, most being focused on adults.

H. pylori is a highly specialized bacterium, who is incriminated in the pathogenesis of a wide spectrum of digestive and extradigestive diseases. Although the recent epidemiological studies confirm the current decline in the prevalence of *H. pylori* infection in developed *versus* developing countries. The *H. pylori* infection still remains a global public health problem.

H. pylori infection in children and adolescents differs from adults in many aspects: prevalence, clinical manifestations, rate of complications, low frequency of gastric malignancies, difficulties in diagnosis and treatment, high level of antibiotic resistance. Also, in children, the etiology and diagnostic approach of the abdominal pain and dyspeptic manifestations (pathognomonic symptomatology for *H pylori* infection) present particular aspects, including due to the difficulties created by the inability of infants to specify the location and character of the abdominal pain.

The ESPGHAN guideline published in 2017 does not recommended the *"test and treat"* strategy for pediatric *H. pylori* infection in children, with adominal pain in the abcence of alarm signs.

H. pylori infection is usually asymptomatic, approximately 10-20% of infected people become symptomatic and develop duodenal and/or gastric ulcer, chronic atrophic gastritis, intestinal metaplasia, dysplasia, gastric adenocarcinoma, MALT lymphoma.

Unlike adults, the peptic ulcer disease is endoscopically documented in only 5-10% of children infected with *H. pylori.* The gastric cancer associated with *H. pylori* infection is extremely rarely reported in children, the most common form is the MALT lymphoma.

In Romania, there are insufficient epidemiological data on the prevalence of *H. pylori* infection. The studies published in the last decade in pediatric population report an increased prevalence of infection, similar to the prevalence reported in developing countries.

The particular aspects of pediatric *H pylori* infection justify the need to develop and use specific diagnostic and therapeutic guidelines for children, whose primary objective is the prevention of gastric cancer and extradigestive complications caused by persistent *H. pylori* infection. All pediatric guidelines elaborated by the various pediatric gastroenterology societies attempt to answer to the four key questions – Who? How? When? With what? – we treat *H. pylori.*

General part

The general part includes a synthesis of data and studies published in the specialized literature in the last decade, regarding: microbiological features, epidemiological data, prevalence and geographic distribution, source and mode of transmission, pathogenesis, clinical manifestation, diagnosis and treatment of pediatric *H. pylori* infection.

H. pylori infection remains a serious public health problem and is considered, according to specialized literature, one of the most common chronic infections worldwide, both in adults and children.

Numerous epidemiological studies have demonstrated the role of *H. pylori* infection as a major risk factor in the development of gastric cancer and its precursor lesions, gastric cancer being the second most widespread and the fourth cause of death worldwide. (Banic, 2017) In 1994, *H. pylori* was classified by the World Health Organization (WHO) and the International Agency for Research on Cancer as a class 1 carcinogen. (Ishaq, 2015)

PERSONAL CONTRIBUTION

Aim and objectives

The personal contribution part includes a prospective study that was performed in ″Victor Gomoiu″ Children's Clinical Hospital from Bucharest, during the period January 1, 2017-December 31, 2022. The study included children aged range between 1-18 years, who were admitted in our hospital for digestive or extra-digestive symptoms, suggestive of *H. pylori* infection. All the patients required upper digestive endoscopic evaluation.

The main objectives of the study was to evaluate:

1. The prevalence of *H. pylori* infection in the pediatric population in a tertiary center from Romania
2. To evaluate the role of risk factors in the transmission of pediatric *H. pylori* infection
3. The analysis of epidemiological and anamnestic and clinical aspects
4. The evaluation of the nutritional status and the inadequate nutritional patterns, according to the CDC, 2000 international criteria
5. The evaluation of the documented endoscopic lesions according to the updated Sydney system and the correlation with the clinical-epidemiological and nutritional profile of the children in order to assess the immediate and late prognosis
6. To evaluate the histological specific aspects of *H. pylori* infection
7. To assess the inflammatory activity by non-invasive methods respectively by the neutrophil-lymphocyte ratio (NLR) and to evaluated the correlation between *H. pylori* gastritis and NLR or reactive C protein
8. To evaluate the correlation between *H. pylori* infection and iron deficiency anemia
9. To evaluate the relationship between *H. pylori* infection and food allergies
10. To evaluate the relationship between *H. pylori* infection and gastroesophageal reflux
11. To evaluate the relationship between *H. pylori* infection and vitamin D status in children
12. To evaluate the monitoring of the eradication rate

Also, the personal contribution part refers to the data published in 3 studies, which were carried out as part of doctoral research.

The first study has evaluated the accuracy of non-invasive diagnostic tests (C^{13} urea breath test and faecal antigen determination) in the diagnosis of infection. The study was performed in ″Victor Gomoiu″ Children's Clinical Hospital from Bucharest, during the period July - September 2020. The ^{13}C urea breath test was used as gold standard method for the diagnosis of *H. pylori* infection, according to the latest recommendations of the ESPGHAN and NASPGHAN international guidelines. In our study the ^{13}C UBT had a sensitivity rate of

80,76%, which can be compared to results from other studies. The fecal antigen test and the urea breath test are reliable and non-invasive approaches for detecting *H pylori* infection, and they have a potential use as screening tests in the pediatric population. The study was published in Pediatru.ro 2023; 28-3.

The second prospective study included 132 children, admitted ″Victor Gomoiu″ Children's Clinical Hospital between January and December 2019 and has evaluated the endoscopic and histopathological changes of the gastric mucosa in *H. pylori* children infected. The study confirms the role of upper digestive endoscopy as a "gold standard" method for the diagnosis of *H. pylori* infection in the pediatric population with digestive symptoms suggestive of organic or extradigestive etiology. Nodular gastritis was statistically significantly associated with *H. pylori* infection and gastritis severity. The study was published in Journal of Pediatric and Neonatal Individualized Medicine 2022;11(2):e110244.

The aim of the third study was to assess the nutritional status of symptomatic children evaluated in an upper digestive endoscopy service and assess the nutritional impact of pediatric *H. pylori* infection. The analysis of the nutritional impact of *H. pylori* infection in the studied group revealed a series of particular aspects in relation to data from the specialized literature, respectively: a higher prevalence of obesity in *H. pylori* infected children. The study results revealed a higher prevalence of undernutrition in *H. pylori* uninfected patients, a fact that supports the controversial role of *H. pylori* infection on the nutritional status of infected children. This study was published in Romanian Journal of Pediatrics, vol. LXVIII, suppl, 2019.

General research methodology

Material and method

In order to achieve the proposed objectives, we conducted a prospective study, that was performed in ″Victor Gomoiu″ Children's Clinical Hospital from Bucharest, during the period January 1, 2017 to December 31, 2022. The study included 563 symptomatic children age range 1-18 years, who were admitted for digestive or extra-digestive symptoms suggestive *for H. pylori* infection. All the cases required upper digestive endoscopic evaluation.

The main inclusion criteria in the study were represented by the presence of digestive or extradigestive signs suggestive for an organic disease requiring an endoscopic evaluation, respectively: chronic abdominal pain with particular features (epigastric localization, nocturnal character and "hunger pain"), dyspeptic syndrome suggestive for an organic etiology, recurrent alimentary vomiting, growth failure/peripubertal stunting, hypochromic hyposideremic anemia refractory to the martial iron therapy, occult or manifest upper digestive hemorrhage.

Before participating to the study an informed written consent was obtained from the parents of all the patients. The study was conducted according to the good clinical practice and was approved by the local ethical committee. A standardized questionnaire was completed for each patient, the demographic, socioeconomic and anamnestic-clinical data were recorded.

The main assessment criteria of the demographic and socioeconomic status, recorded by the elaborated questionnaire, were represented by: age and sex of the patients, the environment education level of parental (no schooling, primary/secondary/higher education), average family income (minimum/medium/high), family and sibling size, children admitted in housing charities, hygienic and sanitary conditions.

The most important history and clinical data evaluated by the standardized questionnaire were represented by: family history of digestive diseases, maternal infection with *H pylori,* significant digestive and extradigestive history, the evolution of clinical manifestations, personal eating habits, the nutritional status assessed according to the recorded anthropometric data, the evaluation of the body mass index for age and sex - BMI, according to the growth charts recommended by the CDC, 2000.

The main exclusion criteria from the study were represented by the cases that received prior anti-*H pylori* treatment, respectively: gastric antisecretory treatment and/or antibiotic, administered 4-6 weeks before the endoscopic examination.

All patients included in the study were evaluated by conventional upper digestive endoscopy with Olympus fiberendoscope under general anesthesia. The endoscopic examination of the esophagus, stomach and duodenum was completed with the topographical and macroscopic evaluation of the lesions according to the updated Sydney System. The gastric biopsy specimens from antrum and body were taken from all studied children.

The diagnosis of *H pylori* infection was established by at least two positive invasive tests, respectively urea test and histopathological examination, according to the ESPGHAN guideline recommendations.

In all the studied cases, an endoscopic diagnosis was made, respectively:

- identification of the topographical pattern of gastritis and atrophy lesions, respectively: antral gastritis - type B; multifocal atrophic pangastritis – type AB; corporeal/fundal gastritis - type A
- identification of endoscopic changes were defined by: normal endoscopic appearance, hyperaemia, nodularity, erosions, hemorrhagic spots and gastric/duodenal ulcer.

The rapid urease test was performed in all studied children, with a 20% indole urea solution, which identify the presence or absence of urease produced by *H pylori* in antral biopsy samples. The histopathological examination was performed from the antral and corporeal biopsy specimens, who were fixed in 4% formaldehyde solution and embedded in paraffin performed by an anatomopathologist, according to standardized procedures. Histological sections were stained with: hematoxylin-eosin (evaluation of the type of inflammatory cells), Giemsa (for the assessment of *H pylori* density) and alcian-blue (identification of gastric atrophy and intestinal metaplasia).

The balance of histological changes was made according to the updated Sydney System: the intensity of polymorphonuclear infiltrate (activity); degree of infiltration with mononuclear cells (chronic inflammation); gastric atrophy; intestinal metaplasia and *H pylori* density. The studied parameters were evaluated from 0-3 (absent, mild, moderate, severe).

Statistical analysis

Statistical analysis was performed used the IBM SPSS Statistics for Windows, Versiunea 29.0. (30-day trial version) Armonk, NY: IBM Corp. A p-value less than 0,05 was considered as statistically significant.

Results

The *H. pylori* infection was documented in 220 of 563 symptomatic children, corresponding to a global prevalence of 39.1%.

The sex repartition of *H. pylori* infected children showed a higher prevalence in girls group compared with boys, respectively: 61.8% versus 38.2%, without statistically significant association (p=0.4075).

The overall structure of the studied group revealed the relatively low proportion of *H. pylori* infection in the 1-6 years age group (52/220 cases, respectively 23.6%) with a higher frequency of cases in schoolchild (7-12 years) compared to teenagers (40.5% *versus* 35.9%), without statistically significant association (p=0.0524).

Out of the total number of *H. pylori* infected children 64.55% (142/220 cases) origened from urban areas compared to those origened from the rural environment (78/220 cases; 35.45%)), without a statistically significant association between environment of origin and *H.pylori* infection (p= 0.85).

The analysis of the standardized questionnaires regarding the global socioeconomic status of *H. pylori* infected children revealed the predominance of the high socioeconomic level (95/220 cases, 43.2%) followed by the medium one (74/220 cases, 33.6%) and respectively the low socioeconomic level (51/220 cases, 23.2%), corresponding to a no statistically significant association (p=0.050).

The most of the cases in the studied lot (99.8%) come from families with 3-4 people and only 0.3% come from large families, with more than 5 people, without statistically significant association (p=0.42). Only in 3 cases (0.5%) was detected the presence of maternal *H. pylori* infection, respectively only one child was diagnosed with *H. pylori* infection.

53.6% of the children included in the study (302/563 cases) had a balanced, healthy diet, respectively 46.4% of the children (261/563 cases) consume semi-prepared foods, fast food and soft drinks.

The evaluation of the anamnestic data revealed the predominance of positive family history for digestive diseases in symptomatic uninfected children, compared to the infected ones (10/343, 2.91% versus 4/220, 1.82%), without a statistically significant association (p= 0.41).

In the studied group, the evaluation of the anamnestic data regarding the personal history of digestive pathology revealed predominace of chronic gastritis or gastroesophageal reflux in symptomatic infected children (45/220 cases, 20.5%). In the *H. pylori* positive group the most frequent extragastric pathology was food allergies (14/220 cases, 6.4%), followed by

inflammatory bowel disease (9/220 cases, 4.1%) with statistically significant association (p= 0.02) and celiac disease (3/220 cases, 1.4%). The statistical analysis shows that there is a statistically significant association in the distribution of *H. pylori* positive cases according to digestive pathological antecedents (p=0.004).

The most common extra-digestive pathology associated with *H. pylori* infection was diabetes mellitus type 1 (38/220 cases, 17.3%), with high statistical association (p=0.00008), followed by chronic cough/wheezing recurrent/asthma (13/220 cases, 5.9%). It is noted that the 2 cases of thrombocytopenic purpura did not associated *H. pylori* infection, with a statistically significant association (p=0.002).

The analysis of the nutritional status of the infected respetively uninfected children revealed the following aspects:

- a higher prevalence of uninfected children with a normal nutritional status *versus* infected ones (61.6% versus 38.4%)

- undernutrition prevalence was increased in uninfected children *versus* the infected ones (59.83% versus 40.16%)

- overweight prevalence was increased in uninfected children compared with the infected ones (60% versus 40%)

- the surprising frequency of obesity in symptomatic *H. pylori* infected children compared to the uninfected ones (62.5% versus 37.5%).

The statistical analysis revelaed no statistically significant association in the distribution of *H. pylori* positive cases according to undernutrition (p= 0.72) or obesity (p =0.16).

The stunting was documented in only 4 cases of the 563 studied children (0.7%), with the predominance of uninfected cases. The statistical analysis shows that there is no statistically significant association in the distribution of *H. pylori* positive cases according to growth retardation (p= 0.423).

The overall prevalence of chronic/recurrent abdominal pain in the study group was 100% of all the children included in the study. In the majority of children in the study group (93.8%) the duration of clinical signs and symptoms was between 3 and 12 months, while in 5.2% of the children the duration of clinical signs and symptoms was between 12 and 24 months , and for 0.4% over 24 months. The comparison of the main features of abdominal pain in the studied group revealed the following aspects:

- the epigastric abdominal pain was highlighted predominantly in *H. pylori* infected children (76/220 cases; 34.5%) compared with uninfected ones (107/343 cases; 31.2%) with a statistically significant association (p=0.001)

- the periumbilical abdominal pain was also highlighted predominantly in *H. pylori* infected children, (88/220 cases; 40%) compared with uninfected ones (99/343 cases; 28.9%) with a statistically significant association (p=0.001)

- the periumbilical pain was highlighted predominantly in *H. pylori* infected children, compared to the epigastric pain (40% versus 34.5%)

- the nocturnal character of abdominal pain was especially noted in *H. pylori* infected children (162/220 cases, 73.6%) *versus* those uninfected (208/343 cases), with a statistically significant association (p=0.002).

- abdominal "hunger" pain relieved by food intake are a suggestive element for diagnosis, being observed in 158 of the 220 *H. pylori* infected children (71.8%) compared to uninfected ones (193/343 cases; 56.3%) , with a statistically significant association (p<0.001).

Other clinical manifestations observed in *H pylori* infected patients compared to uninfected ones were represented by the dyspeptic syndrome dominated by nausea with or without morning or postprandial vomiting and the postprandial fullness or early satiety, as follows:

- the nausea represented the second clinical manifestation in the studied group, with a global prevalence of 47.06% (265/563 cases), with a higher prevalence in children infected with *H pylori versus* the uninfected ones (132/220 cases , 60% versus 133/343 cases; 38.8%) with statistically significant association (p<0.001).

- the prevalence of morning or postprandial vomiting in the studied group was higher in children infected with *H pylori* compared to the uninfected ones (93/220 cases, 42.3% respectively 7/220 cases, 3.2% *versus* 86/343 cases; 25.1% respectively 5/343 cases, 1.5%) with statistically significant association (p<0.001).

- dyspeptic manifestations such as early satiety/postprandial fullness in the studied group were highlighted in a very small number of studied patients, with a similar frequency in both uninfected and *H. pylori* infected children (2/343 cases, 0.6 %; versus 1/220 cases, 0.5%), without a statistically significant association (p= 0.838)

- occult or manifest digestive bleeding was observed especially in children with erosive or hemorrhagic gastroduodenitis with a reduced overall prevalence in the studied group of 3%, without statistically significant association (p= 0.738) in *H pylori* infected children (5/220 cases); 2.3% versus 6/343 cases; 1.7%).

The statistical analysis shows that there is a statistically significant association in the distribution of cases without *H. pylori* infection according to reflux symptoms, respectively: retrosternal esophageal pain 9% (p=0.04), belching 5.5% (p=0.005) and regurgitation 30.3% (p= 0.001).

The topographic patterns analysis of endoscopically documented gastritis and atrophy lesions revealed a higher global prevalence of antral gastritis type B (428/563 cases, 76.02%), followed by multifocal atrophic pangastritis type AB documented in 130/563 of cases (23.1%). Corporeal/fungal gastritis type A was documented in 5/563 cases, respectively 0.88%. Regarding gastritis associated with pediatric *H. pylori* infection, a higher prevalence of antral gastritis type B was documented in the studied group, respectively 198/220 cases (90%). In patients with multifocal atrophic pangastritis type AB, *H. pylori* infection was documented in 21/220 cases, respectively 9.6%.

The statistical analysis shows that there is a highly statistically significant association in the distribution of *H. pylori* positive cases according to antral gastritis type B (p<0.0001). In the studied group, the regression model indicates that children diagnosed with *H. pylori* infection have a higher probability (Odds Ratio=4.42, 95% CI 2.69-7.25) of associating antral gastritis type B compared to uninfected ones.

It was also observed that there is a highly statistically significant association in the distribution of *H. pylori* positive cases and according to multifocal atrophic pangastritis type AB (p<0.0001). In the studied group, the regression model indicates that *H. pylori* infection is a protective factor for multifocal atrophic pangastritis type AB (odds ratio =0.23, 95% CI 0.13-0.37).

A significant proportion of *H. pylori* positive cases present edema, erythema or pallor of the gastric mucosa (99.5% versus 100%). Superficial exudate was documented in 80.5% of cases, with a similar proportion of increased friability and vascularity observed (78.6% *versus* 85.9%). Also, the antral nodular paving stone appearance was highlighted in a significantly increased proportion 176/220 cases (80%). The presence of a statistically significant

association between *H. pylori* infection and the presence of superficial exudate, increased friability, as well as antral nodular appearance (p=0.010, p=0.001 respectively p<0.001) was found.

Antral nodular gastritis was identified endoscopically in the majority of *H pylori* infected children (176/220 cases; 80%). The statistical analysis revealed the presence of a highly statistically significant association (p<0.001). Antral nodular appearance observed at endoscopic examination was associated with the presence of infection, regardless of the degree of bacterial colonization ($p < 0.001$). The regression model indicates that children diagnosed with *H. pylori* infection have a higher probability (Odds Ratio=11.24) of associating nodular gastritis compared to uninfected children.

Atrophic gastritis was predominantly documented in uninfected patients (1.7% of cases), corresponding to a statistically significant association (p=0.049). 99.1% of *H. pylori* positive cases have associated erythemato-exudative gastritis. In the studied group, only 1 case of gastric ulcer was documented in a child without *H. pylori* infection.

Contrary to the published studies, in our study the Cohen's k coefficient determined in the statistical analysis demonstrated a very good correlation between the two methods used for the diagnosis of *H. pylori* infection.

The main histological type of gastritis noted in patients infected with *H. pylori* was chronic inactive gastritis (142/220 cases; 64.5%). Chronic active gastritis was identified in a lower proportion of infected patients than in uninfected ones (78/220 cases; 35.5% *versus* 154/343 cases, 44.9%). Gastric atrophy and intestinal metaplasia were not evident in any of the *H. pylori* positive or negative cases. There is a statistically significant association of *H. pylori* infection with the histological type of gastritis (p=0.02).

Antral nodular gastritis was identified endoscopically in the majority of *H pylori* infected children (176/220 cases; 80%) being statistically significantly associated with the increased level of chronic inflammatory infiltrate with mononuclear cells (98/142 cases, 69%) along with significant activity of the inflammatory process (60/78 cases, 76.9%), p<0001. The presence of chronic inflammation increased the odds of nodular gastritis at endoscopic examination by 4.34 times (OR = 4.34, 95% CI 2.38-7.92), with significant activity increasing the odds of nodular gastritis by 3.1 times (OR = 3.1, 95% CI 2.42-15.9).

H. pylori positive children presented in 45.45% of cases severe chronic inflammation of the gastric mucosa, respectively in a similar proportion moderate and mild chronic inflammation (11.37% *versus* 7.73%). In the studied group, 38/220 (17.3%) *H pylori* positive cases presented increased values of NLR, without statistically significant association (p= 0.33). 28 of the cases with positive NLR values (73.7%) were associated with nodular gastritis, without statistically significant association (p= 0.29). *H. pylori* positive cases were associated in a small proportion with elevated CRP values (4/220 cases, 1.8%) compared to the negative ones (17/343 cases, 4.96%), without significant statistically association (p= 0.46).

The analysis of the endoscopic lesions according to the updated Sydney system and the correlation with the clinical-epidemiological and nutritional profile of the children highlighted the following:

- the analysis of the nutritional profile of *H pylori* infected children with gastritis type B revealed a significant proportion of normal nutritional status, respectively 79.8% (158/198 cases) compared to that of undernutrition, which was identified in 20.2 % of cases (40/198 cases)

- 2% (4/198 cases) of *H. pylori* infected children with gastritis type B had obesity, respectively 6/198 cases (3.03%) were overweight.

- the statistical analysis shows a statistically significant association in the distribution of *H. pylori* positive cases with gastritis type B according to undernutrition (p= 0.02), without showing a statistically significant association in regarding the distribution of cases according to obesity (p=0.45).

- the statistical analysis also revealed a no statistically significant association in the distribution of *H. pylori* positive patients with nodular gastritis, according to undernutrition (40/176 cases, 22.73%, p=0, 74)

- following the statistical analysis, a statistically significant association was observed in the distribution of *H. pylori* positive children with chronic inactive gastritis, (40/142 cases, 28.17%, p=0.0014), respectively of children with chronic active gastritis (9/142 cases, 11.54 %, p=0.004) according to undernutrition

- children with chronic active gastritis with *H. pylori* infection have a higher probability (Odds Ratio=3) of associating undernutrition.

Our study revealed an overall prevalence of iron deficiency anemia of 34.81%, with the predominance of *H. pylori* infected children compared to uninfected ones (120/196 cases, 61.2% *versus* 76/196 cases , 38.8%), with a statistically significant association in the distribution of *H. pylori* positive cases in relation to iron deficiency anemia (p=0.0000).

Regarding the association between the *H. pylori* infection and vitamin D deficiency, our study revealed an overall prevalence of vitamin D deficiency of 46.71%, with predominant involvement in *H. pylori*-infected children compared to uninfected ones (162 /263 cases, 61.6% versus 101/263 cases, 38.4%), a highly statistically significant association (p<0.00001).

The overall prevalence of food allergies reported in the study group was 20.4% (115/563 cases), with a higher prevalence of food allergies being observed in infected *versus* uninfected children (48/220 cases, 21.81% *versus* 67/343 cases, 19.53%), without statistically significant association (p=0.512). Also, our study reported an equal prevalence of cow's milk protein allergy in both infected versus uninfected children, with a statistically significant association (p=0.02465). Other food allergies observed more frequently in uninfected children compared to infected ones are represented by: wheat allergy, egg or multiple food allergies (20/343 cases versus 2/220 cases).

Regarding the appearance of duodenal lesions in the studied group, 54.9% of the cases presented a nodular appearance of the mucosa, 16.7% a mosaic appearance, 0.5% an atrophic appearance, respectively 0.2% aphthoid ulcerations. 1.4% of children with celiac disease had *H. pylori* infection.

The relationship between *H. pylori* infection and gastroesophageal reflux was analyzed in the studied group. The share of *H. pylori* infection is similar in both children with gastroesophageal reflux (37.9%) and those without gastroesophageal reflux (41.1%), but with the predominance of gastroesophageal reflux in uninfected patients (62.1%). with a statistically insignificant association (p=0.461).

The eradication therapies recommended for *H. pylori* positive patients in the studied group, according to the ESPGHAN guide, were represented by:

- Proton pump inhibitors (PPI) + Amoxicillin + Clarithromycin (AKN) x 7-14 days recommended in 53.6% of cases (118/220 cases)

- PPI + Amoxicillin + Metronidazole (AMN) x 7-14 days recommended in 20.9% of cases (46/220 cases)

- Sequential therapy: PPI + Amoxicillin for 5 days followed by PPI + Clarithromycin + Metronidazole, recommended in 25.5% of cases (56/220 cases).

AKN therapy was used in higher proportions in children aged 1-6 years (26.4%), while AMN therapy was used more frequently in children aged 7-12 and 13-18 years. Sequential therapy was also used more frequently in older children aged 7–12 years and 13–18 years.

At the time of the study, microbial resistance could not be determined in the patients of the studied group.

The statistical analysis shows that there is a statistically significant association between the type of therapy used and the age of the patients ($p<0.0001$). The instituted therapy did not differ significantly according to the gender of the patients ($p=0.640$). The monitoring of the effectiveness of the eradication therapy was carried out according to ESPGHAN recommendations, by performing the faecal antigen for *H. pylori,* 4-8 weeks after the end of the therapy. In the studied group, the overall eradication rate of *H.pylori* infection was 81.8% (180/220 cases). The analysis of the eradication rate of *H. pylori* infection revealed better efficiency of AMN therapy (84.8%) followed by AKN therapy (80.5%) and sequential therapy (80.8%) with similar eradication rates.

Conclusions

Our study reveals the materialization of the proposed objectives through the following results and conclusions:

- The global prevalence of *H. pylori* infection (39.1%) reported in the patients included in the study is high, similar to that reported in developing countries.

- The frequency of *H. pylori* infection was relatively low in the 1-6 years age group (23.6%), with a higher frequency of cases in schoolchild *versus* adolescents (40.5% *versus* 35.9%).

- In our study, there is no linear increase in the frequency of *H. pylori* infection directly proportional to the age of the children, according to the data reported in the literature.

- The evaluation of the *H pylori* infection status revealed the predominance of patients origened from the rural environment

- Contrary to the data from the specialized literature, our study did not reveal a rate of colonization inversely proportional to the socioeconomic status of the patients, the highest value being found in children from families with a high socioeconomic level followed by medium and low socioeconomic levels.

- In the studied sample, in accordance with the data from the specialized literature, the prevalence of allergic diseases and asthma was higher in uninfected patients compared to the infected ones, results that support the protective role of *H. pylori* infection.

- Contrary to literature data, our study revealed a higher prevalence of *H. pylori* infection in patients with inflammatory bowel disease as well as in children with type 1 diabetes.

- The analysis of the nutritional profile of the studied children revealed a higher prevalence of undernutrition and overweight in uninfected children compared to the infected ones, and respectively a higher prevalence of obesity in the case of infected children.

- Chronic abdominal pain with epigastric localization is more common in children infected with *H. pylori* compared to uninfected ones.

- Morning or postprandial vomiting and occult/manifest digestive bleeding were associated with *H. pylori* positive cases.

- Dyspeptic manifestations such as early satiety/postprandial fullness were highlighted in a very small number of the studied patients, with a similar frequency in both uninfected and *H. pylori* infected children.

- In the studied sample, an increased prevalence of gastroesophageal reflux symptoms was found in non-infected patients compared to the infected ones, with the predominance of endoscopically documented gastroesophageal reflux in non-infected patients.

- Contrary to the published studies, in our study the Cohen's k coefficient determined by the statistical analysis demonstrated a very good correlation between the two methods used for the diagnosis of *H. pylori* infection.

- Similar to the recent reported data in the specialized literature, a higher prevalence of antral gastritis type B was documented in the studied group, followed by multifocal atrophic pangastritis type AB and corporeal/fundal gastritis type A.

- Children with chronic active gastritis with *H. pylori* have a higher probability (Odds Ratio=3) of associating malnutrition.

- Antral nodular gastritis was endoscopically documented in most children infected with H pylori (80%), being statistically significantly associated with the increased level of chronic inflammatory infiltrate with mononuclear cells and with the significant activity of the inflammatory process.

- The positive children presented severe chronic inflammation of the gastric mucosa in 45.45% of cases.

- Atrophic gastritis has been documented predominantly in uninfected patients.

- The main histological type of gastritis noted in our study, in patients infected with *H pylori* was represented by chronic inactive gastritis followed by chronic active gastritis.

- In the studied group, no cases of gastric atrophy and intestinal metaplasia were documented in patients with *H. pylori* infection.

- NLR values were not statistically significantly increased in *H. pylori* positive patients.

- *H. pylori* positive cases associated in a small proportion increased CRP values compared to negative ones.

The study revealed an increased prevalence of iron deficiency anemia in children infected with *H. pylori.*

- Children with vitamin D deficiency showed an increased prevalence of *H. pylori* infection, with a statistically significant association between chronic inflammation and vitamin D deficiency.

- Similar to data from the specialized literature, the study reported a higher prevalence of food allergies in infected versus uninfected children.

- In the studied group, the general eradication rate of *H. pylori* infection was 81.8%

- Our study revealed better efficiency of AMN therapy (84.8%) followed by sequential therapy (80.8%) and AKN therapy (80.5%), with similar eradication rates.

The increased local prevalence of *H. pylori* infection (39.1%), in contrast to the current decline reported in developed countries, justifies the approach and the implementation of modern diagnostic tools according to international guidelines, to improve the immediate and late prognosis of the disease, by reducing the risk digestive and extra-digestive

complications, recognized as conditions with a high impact on the health of the population in our country.

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