Microb Health Dis 2023; 5: e905

REVIEW: *HELICOBACTER PYLORI* INFECTION IN PAEDIATRICS

J. Nguyen[1], K. Kotilea[1], V.Y. Miendje Deyi[2], P. Bontems[1]

[1]Department of Pediatric Gastroenterology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium
[2]Department of Microbiology, Laboratoire Hospitalier Universitaire de Bruxelles (LHUB-ULB), Université Libre de Bruxelles, Brussels, Belgium

Corresponding Author: Patrick Bontems, MD, Ph.D, email: patrick.bontems@hubruxelles.be

Abstract – The prevalence of *Helicobacter pylori* infection in children and adults is still decreasing in many countries but remains very high in countries like Vietnam, where more than 80% of school-aged children are contaminated.
Additional reports on the potential role of the infection in some extra-intestinal diseases have been published. Interesting associations are underlined, but causality is difficult to prove.
Antimicrobial resistance rates continue to increase in many countries, especially the frequency of multidrug resistance. Different publications report an increasing rate of resistance of *Helicobacter pylori* to amoxicillin, but some additional proof is needed, particularly whole genome sequencing of these strains to characterize them better. This would threaten the possibility of eradication in children in the future, and adequate stewardship of antibiotic use is urgently needed. When tailored to antimicrobial susceptibility, triple therapies for 14 days perform very well – an eradication rate of 90% has been reached in a multicenter registry with data collected within Europe. However, the same treatments seem less efficient in other regions. Finally, eradication could be improved if the regimen is tailored to genotypic methods (PCR-based) instead of phenotypic (culture-based) susceptibility profiles.

Keywords: *H. pylori*, Children, Epidemiology, Diagnosis, Treatment.

EPIDEMIOLOGY

The epidemiology of *Helicobacter pylori* infection shows a global decline in incidence. The infection rate is usually much lower in Western countries (Western Europe or North America), where it is admitted that most infected children belong to migrant families. However, in Romania, a retrospective study conducted by Lupu et al[1], involving a cohort of 1,757 patients, demonstrates that the incidence of *H. pylori* infection remains high in children, with a prevalence of 30.8%. Furthermore, 75.3% of the infected children were from rural areas. Another retrospective observational study conducted over an 11-year period (2009, 2014, 2019) in Portugal, which included 461 patients under 18 years old who underwent upper endoscopy, reveals an infection rate of 37.3%[2]. Additionally, a decreasing trend in infection rates was observed over the years.

In South America, a cross-sectional study was made in the state of São Paulo, Brazil, in which 161 children aged 5-13 years old (mean age 7.8 years) attending a public school were assessed with a ^{13}C urea breath test[3]. The overall prevalence of *H. pylori* infection was 20.5%-18.7% among girls and 22.2% among boys.

A study on 1,854 pupils across 24 Ho Chi Minh City districts was conducted in Vietnam. Infection was detected by a monoclonal stool antigen test[4]. Che et al[5] showed a very high prevalence of 87.7% of *H. pylori* infection among these school-aged children. The infection rate increased with population or employee density across the city. A second study by the same group demonstrated that the infrequency of handwashing with soap after the toilet, not using toilet paper after toilet (washing with water instead), crowded living areas, larger family size, and younger age independently contributed to an increased prevalence of *H. pylori* infection.

A cohort effect probably explains a slightly higher infection rate in the youngest children. Studies tend to agree that *H. pylori* infection more often affects older children. For example, the study made by Lupu et al[1] showed that infected teenagers were older (14.1 years) compared to non-infected ones (12.8 years). Similarly, in Tyva Republic (a small mountainous area at the geographical center of Asia in southern Siberia with a high incidence of gastric cancer), Polivanova et al[6] showed in 270 Tuvan children that *H. pylori* prevalence increased with age, from 44% among 7 to 10-year-olds to 64% among those aged 14 to 17 (OR = 3.0; 95% CI = 1.6-5.8). Tran et al[7] also examined infection risk factors among 954 schoolchildren in Ethiopia using machine learning algorithms. Their study provides evidence that machine learning approaches are positioned to uncover *H. pylori* infection risk factors and predict *H. pylori* infection status. The machine-learning algorithms identified other important risk factors for *H. pylori* infection, such as electricity usage at home, toilet type, and waste disposal location. Using a 75% cutoff for robustness, machine learning identified five of the eight significant features found by traditional multivariate logistic regression. However, machine learning approaches identified more *H. pylori* risk factors when a lower robustness threshold was used than multivariate logistic regression.

Finally, in Morocco, a study involving 83 patients (38 males and 45 females) aged between 2 and 15 years found that the infected group accounted for 31% of the participants[8]. In Iran, a cross-sectional study performed by Nasri et al[9] showed that only 7.8% of the children who underwent endoscopy were infected by *H. pylori*, the infected ones being older.

CLINICAL MANIFESTATIONS

Digestive Manifestations

Clinical manifestations as recurrent abdominal pain (RAP) are not specific during *H. pylori* infection in children. However, children have chronic gastritis when infected; some will develop ulcerations, metaplasia, precancerous lesions, or (very few) gastric cancers during childhood.

Yorulmaz et al[10] remind us that nodular gastritis is characteristic of infection in children. They observed infection in 83.7% of 282 children with nodular gastritis. Virulence factors of the infecting strains play a role in the physiopathology of these lesions, and the cagA (not oipA) genotype has been associated with gastric ulcers in an Iranian series[11]. Regarding ulcer recurrence, Li et al[12] published a retrospective analysis of 536 children with ulcers who received an eradication therapy. Ulcer recurrence was observed in 25 (4.7%) within one year. Bleeding, number, and size of ulcers, dietary habits, compliance with medication, vomiting, IL-6, and TNF-α were independent risk factors for ulcer recurrence.

Spasmolytic peptide-expressing metaplasia (SPEM) has been found to be an alternative precursor to gastric cancer[13]. Its frequency and other histological findings have been assessed in a Taiwanese series[14]. Atrophic gastritis was found in 30.4% of 92 children, intestinal metaplasia in 4.3%, and SPEM in 8.7%. Li et al[15] reported that intestinal metaplasia increased with age in pediatrics. Similarly, Yu et al[16] reviewed the histopathological changes in 854 infected children from the central China region. Mucosal precancerous lesions were found in 4.3% of them (atrophic gastritis in 17/854, intestinal metaplasia in 11/854, dysplasia in 9/854). Such histological changes at an early age are particularly alarming.

Additionally, the Cerner Health Facts Database was searched by Attard et al[17] for gastric cancer at a pediatric age between 2010-17. In the US, solid gastric tumors' prevalence was 1/33000 at a mean age of 11.8 years. Cardia localization of stomach cancer is the most com-

mon in children and may relate to an association with obesity and esophageal reflux. A family history of colon polyps, intestinal and breast malignancy, and a history of *H. pylori* gastritis was found to be more prevalent in children with stomach cancer.

Extra-Digestive Manifestations

The association between *H. pylori* and some extra-intestinal diseases has been underlined, but causality is difficult to prove. In Northeast Romania, a retrospective cohort of 1,757 children undergoing endoscopy identified 130 children presenting headaches; 41.5% had *H. pylori* infection, and the association between headache and *H. pylori* infection was found statistically significant[18]. From the same cohort, liver cytolysis was found in 112 children; 17.9% of them presented an *H. pylori* infection. The difference was also statistically significant[19]. The authors point out the need to analyze possible confounders and possible effects of *H. pylori* eradication. In a cross-sectional study from Israel, including 43 children with chronic otitis media with effusion and acute otitis media, middle ear fluid was analyzed by culture and PCR and found no *H. pylori* infection[20]. All samples from 43 children were negative for *H. pylori*. Regarding the effect of *H. pylori* infection on micromineral and trace element status, a meta-analysis of six cross-sectional studies demonstrated a lack of evidence for serum, zinc, copper, and calcium but no data available for magnesium, phosphorus, and iodine status[21].

H. pylori prevalence in Western countries has been declining simultaneously with increases in childhood asthma and allergic diseases. The question of an inverse association between *H. pylori* infection and asthma was addressed in a cross-sectional study in Chongqing, China[22]. Two thousand two hundred forty-one healthy children underwent a ^{13}C-urea breath test during medical checkups. The rates of asthma diagnosis in *H. pylori*-negative and -positive children were 7.23% and 3.77%, respectively (odds ratio = 1.99; 95% confidence interval: 1.01-3.97; $p < .05$).

In a cohort study including asymptomatic children with congenital hypothyroidism on levothyroxine replacement, the mean T_3 serum level (3.59 ± 0.84) (but no TSH or T4) was significantly lower ($p = 0.001$) in *H. pylori*-infected children than in those without infection (3.95 ± 0.89)[23]. Infection may lead to impairment in the thyroid hormonal balance but not in the hypothalamic-pituitary-thyroid axis function. *H. pylori* and impaired growth in children is an association studied over the years with controversial conclusions. In a publication from Poland, children with idiopathic short stature were divided into two groups according to *H. pylori* status. Fasting ghrelin, leptin, and IGF-1 concentrations and GH levels in two stimulation tests were assessed. According to this study, short children infected by *H. pylori* seem to have lower ghrelin and IGF-1 concentrations than children without infection; this may be the reason for a worse growth rate in this subgroup[24].

The relationship between anemia and *H. pylori* infection in children is again in the spotlight with four studies and a review[25]. Lupu et al[26] describe a significant association between *H. pylori* infection, iron deficiency, and iron deficiency anemia. However, a publication from Beijing, China, studied a population of 902 children, from which 21.5% were *H. pylori*-infected, and multiple confounders were studied. Logistic regression showed that *H. pylori* infection was not a combined risk factor for iron deficiency. Older age, higher educational background of the mother, living in the city, and higher family income were the combined protective factors to prevent the occurrence of iron deficiency in children[27]. Kato et al[28] published a case series of 7 children with recurrent or refractory iron deficiency anemia who received successful *H. pylori* eradication therapy. Compared with the baseline [values of hemoglobin ($p < 0.001$), serum iron ($p < 0.005$), and ferritin ($p < 0.001$)] significantly increased, on average, 2-3 months after eradication therapy. Finally, in a study from Israel, 60 *H. pylori*-infected children presenting iron deficiency (with and without anemia) received *H. pylori* eradication treatment[29]. Iron was normalized in 60% of patients with iron deficiency without iron supplementation. There were significant improvements in hemoglobin and ferritin concentrations following *H. pylori* eradication. Older age may predict this outcome. Another study performed in Egypt demonstrated that the hemoglobin level, serum ferritin, and zinc significantly increased after eradication[30]. Therefore, screening for *H. pylori* might be considered in the workup of refractory iron deficiency anemia or iron deficiency.

Diagnosis

Methods for diagnosis do not differ from those recommended for adults. However, serology has been shown previously to be less sensitive in children. Interestingly, a Korean study attempted to identify effective antigen-containing epitopes of high diagnostic value in *H. pylori* FlaA[31]. Full-sized FlaA was divided into several fragments and cloned, and its antigenicity was investigated using Western blotting. The FlaA fragment of 1345-1395 bp had strong immunogenicity. ELISA was performed with serum samples from children by using the 1345-1395 bp recombinant antigen fragment. IgG reactivity showed 90.0% sensitivity and 90.5% specificity, and IgM reactivity showed 100% sensitivity and specificity. The authors conclude that the FlaA 1345-1395 bp epitope could be used as a diagnostic marker for *H. pylori* infection.

The urease test is a simple, bedside, and cheap technique that is still indicated in limited resource settings but is no longer used in many reference centers. A Moroccan study involving 83 patients showed that its sensitivity was 88.5%, with a negative predictive value of 94%, a specificity of 84.2%, and a positive predictive value of 72%[8]. Similar results, having been published previously, demonstrated that a rapid urease test cannot be used alone and that another positive test is needed to confirm infection.

The usefulness of molecular methods for *H. pylori* detection in pediatrics is progressively recognized. Since the COVID-19 pandemic, most labs can perform PCR tests that provide susceptibility testing for macrolides and quinolones. In Poland, Bogiel et al[32] compared the results of the PCR test with the histopathological investigations. Among the biopsy samples collected, 44 (42.3%) were positive in PCR, while 43 (41.3%) and 39 (37.5%) presented histologically confirmed signs of inflammation and *H. pylori* colonization, respectively. Moreover, the mean grades of the parameters of the histopathological examination were higher in the group of PCR-positive samples.

Interestingly, Gareayaghi et al[33] have been able to detect clarithromycin resistance mutations *via* RT-PCR using fecal DNA samples. The stool antigen test was positive in 101 children. The A2142G mutation was identified in 6.9%, and the A2143G mutation in 10.9%. If this technique is reproducible and concordant with results obtained from gastric samples, it will be useful for epidemiological studies. Rafeey et al[34] concluded that fecal calprotectin has a poor diagnostic ability for *H. pylori* infection.

Resistance to Antibiotics

Resistance rates tend to increase year by year in children, mainly with the acquisition of resistant strains or poor compliance with the treatment. Therefore, it is recommended to tailor the eradication regimen to a susceptibility test performed before the first treatment is prescribed. It is also recommended to monitor the resistance rates of *H. pylori* to drugs used in treatments and to keep adequate antibiotic stewardship in each country.

Two meta-analyses have been published during the last year. Borka-Balas et al[35] focused on the differences between continents and countries of the same continent. In Asia, the greatest antimicrobial resistance was found to metronidazole (>50%), probably due to its wide use for parasitic infections. Aside from the increased resistance to metronidazole, the reports from different Asian countries also indicated high resistance rates to clarithromycin. The scarce evidence for America revealed that *H. pylori* strains display increased resistance to clarithromycin (up to 79.6%), but not all studies agreed. In Africa, the resistance rate to metronidazole was high (up to 91%). Results in terms of amoxicillin resistance remain contradictory and not fully convincing. Among European children, the most frequent antimicrobial resistance was also noticed for metronidazole and clarithromycin (up to 59% and 45%) but with a predominance for clarithromycin compared to other continents. The authors concluded by emphasizing the differences in antibiotic use among continents and countries are responsible for the discrepancies in antimicrobial resistance.

The second meta-analysis focused on the rate of multidrug resistance from 19 studies published between 2011 and 2022[36]. The overall primary multidrug resistance during this period was 6%, but the rates were higher in the Asian population compared to Western countries. Multidrug resistance is even higher in the most recent data published, as shown later in this chapter.

Resistance rates are particularly alarming in Vietnam, but confirmation of the data is needed, especially for amoxicillin, as mentioned above[37]. Between 2019 and 2022, samples from 237 children showed resistance rates of 80.6% to clarithromycin, 71.7% to amoxicillin, 49.4% to metronidazole, 45.1% to levofloxacin, and 11.4% to tetracycline while resistance to more than one antibiotic was identified in 90% of the isolates. According to data obtained from 112 children in the Chongqing region (Southern China)[38], a neighboring country of Vietnam, the resistance rates are lower. The resistance rates to clarithromycin, metronidazole, and levofloxacin were 47.3%, 88.4%, and 18.8%, respectively. No resistance to amoxicillin, tetracycline, and furazolidone was observed. Dual and triple resistance percentages were 37.5% (42/112) and 10.7% (12/112), respectively. In another study performed in Southern China, resistance rates to clarithromycin, metronidazole, and levofloxacin were 32.8%, 81.7%, and 22.8%, respectively. Double resistance was found in 28.7%, and triple in 9.0%[39].

In Jordania, Burayzat et al[40] found clarithromycin resistance in 25.9%, metronidazole resistance in 50%, and resistance to levofloxacin in 6.9% by E-test among 116 isolates. These results are concordant with antimicrobial testing made by PCR, since mutations concerning clarithromycin resistance were documented in 26.1% of samples, while mutations in gyrA gen-related to levofloxacin resistance were reported in 5.3% of samples. Whereas in Bulgaria[41], resistance rates were 7.5% for amoxicillin, 25.5% for metronidazole, 34.0% for clarithromycin, and 14.1% for ciprofloxacin (106 children).

Helicobacter pylori and Gastric Microbiota

H. pylori infection is an identified risk factor for pediatric chronic gastritis, but its impact on gastric microbiota remains to be further elucidated. Chen et al[42] recruited 20 infected children and 25 negative controls. Gastric juice was collected from them and subsequently analyzed for 16S genes. They found that infected children exhibited altered beta diversity, taxonomic structure, and function, with reduced microbial network connectivity, which could be involved in the disease etiology. Zheng et al[43] also demonstrated an influence of the presence of *H. pylori* on the gastric microbiota that results in a lower abundance of multiple taxonomic levels in 23 children with duodenal ulcers.

Treatment

The triple therapy combining a proton pump inhibitor (PPI) with amoxicillin, and metronidazole or clarithromycin remains the most frequently used eradication scheme in children. According to the last ESPGHAN/NASPGHAN consensus published in 2017, 14 days is recommended, and this treatment must be tailored to antimicrobial susceptibility[44]. A registry was created to assess eradication rates within European centers, and its data were published in 2022[45]. Children were treated following the published recommendations, and the success rate was 90% (452/503) of naïve children but only 59% (41/69) after previous eradication failure. When the treatments are not tailored to susceptibility testing, such as in the study made by Rosu et al[46] in Romania, the eradication rates are much lower. Indeed, among the 149 children that were treated with empirical triple therapy or a sequential quadruple regimen, eradication was obtained in 23% with the triple therapy containing metronidazole, 38% with the sequential regimen, and 40% with the triple therapy containing clarithromycin. Besides antimicrobial resistance, compliance is also a major factor associated with treatment success, as shown before[47].

However, in Vietnam, Le et al[48] showed that the efficacy of a tailored triple therapy did not perform as well as in the European registry. Indeed, among the 237 children included that received a tailored triple therapy or a bismuth quadruple scheme in cases infected with *H. pylori* strains were only susceptible to tetracycline or amoxicillin, eradication rates were 52% (12/23 – triple therapy containing clarithromycin), and 78% (25/32 – triple therapy containing metronidazole). Bismuth quadruple regimen performed better (88%-38/43) and other triple therapies (90% – 95/106 – no details regarding combination or dosage provided). Since the resistance rate was very high (72% for clarithromycin, for example), one may be willing to investigate the role of mixed infection or heteroresistance in this population and compliance to explain such a low efficiency.

Hung et al[49] also advocate for tailored treatment by emphasizing the cost/efficiency ratio. They retrospectively enrolled Taiwanese children diagnosed with *H. pylori* infection from 1998 to 2018. Patients with positive cultures and minimum inhibitory concentration test results were allocated to a culture-based strategy and those with negative cultures or without culture to an empiric therapy strategy. Ninety-six patients were enrolled, of whom 55 received a culture-based strategy, and 41 received an empiric therapy strategy. The eradication rate with the culture-based strategy was 89.1% and 75.6% with the empiric therapy strategy. They calculated that for every 10% increase in those receiving a culture-based strategy, the total cost would have been reduced by US $466 in a hypothetical cohort of 1,000 patients.

Antimicrobial susceptibility testing is commonly carried out using culture-based methods, but molecular-based techniques also allow testing for macrolides and quinolones. While culture sensitivity remains low in some centers, PCR has become widely available since the COVID-19 pandemic, and results are obtained more quickly. Feng et al[50] performed a study comparing the efficacy of treatment tailored to phenotypic testing (culture-based) or genotypic testing (molecular-based). Between September 2017 and October 2020, 226 eligible patients were enrolled. There were 71 with clarithromycin-susceptible strains in the phenotype-guided therapy group and 87 without 23S rRNA point mutations (A2142G, A2142C, and A2143G) in the genotype-guided therapy group. Eradication rates were 70.4% (50/71) for phenotype-guided therapy and 92.0% (80/87) for genotype-guided therapy ($p < 0.01$). This can be due to mixed infections, probably more frequent in regions with higher resistance rates. More studies are, however, needed before concluding on the superiority of the molecular-based techniques to tailor the treatment.

Finally, a meta-analysis was published by a Chinese group that included 163 randomized clinical trials involving 336 arms and 18,257 children[51]. They concluded that the eradication rates of sequential therapies with probiotics, quadruple concomitant, and triple therapies combining proton pump inhibitors with clindamycin and nitroimidazoles were at least 90%. The eradication rates of sequential, triple therapies with probiotics and triple therapies containing amoxicillin and furanes were above 80%. Empirical triple therapies with clarithromycin or nitroimidazoles were 74,2% and 76,2% respectively.

Alternatives to Classical Antimicrobials and Proton Pump Inhibitor Combination

Nitazoxanide was used in one randomized trial performed by an Egyptian group[52]. They enrolled 100 children randomly assigned to a nitazoxanide-based triple therapy (nitazoxanide, proton pump inhibitor, and clarithromycin) for 14 days or a standard triple therapy (metronidazole, omeprazole, and clarithromycin) for 14 days. This treatment seems promising since 92% of the children in the nitazoxanide group and 84% in the metronidazole group recovered from infection.

Conflict of Interest

NJ, KK, and MDVY have no conflict of interest to declare. BP served on advisory boards of Biocodex and received an honorarium for lecturers from Nestlé, Danone, Avanos, Sanofi, and Biocodex.

Acknowledgments

The authors would like to thank Francis Megraud for a critical but kind review of the manuscript.

Informed Consent

Not applicable.

Author's Contributions

All authors critically reviewed and finally agreed with the content of the manuscript. NJ collected and summarized the literature concerning epidemiology and diagnosis, KK the literature concerning clinical manifestation, MDVY the literature concerning microbiological data, and BP the literature concerning the treatment.

Funding

None.

REFERENCES

1. Lupu A, Miron IC, Cernomaz AT, Gavrilovici C, Lupu VV, Starcea IM, Cianga AL, Stana B, Tarca E, Fotea S. Epidemiological Characteristics of Helicobacter pylori Infection in Children in Northeast Romania. Diagnostics (Basel) 2023; 13: 408.
2. Antunes R, Oleastro M, Nogueira JP, Lopes AI. Time trend prevalence of helicobacter pylori infection and endoscopic findings in symptomatic children in Portugal: A retrospective study based on three time points in 2009, 2014, and 2019. Helicobacter 2023: e12963.
3. Carlos ABM, Costa VE, Kobayasi R, Rodrigues MAM. Prevalence of Helicobacter pylori infection among asymptomatic children in southeastern Brazil: a cross-sectional study. Sao Paulo Med J 2022; 140: 719-722.
4. Che TH, Nguyen TC, Ngo DTT, Nguyen HT, Vo KT, Ngo XM, Truong DQ, Bontems P, Robert A, Nguyen PNV. High Prevalence of Helicobacter pylori Infection Among School-Aged Children in Ho Chi Minh City, VietNam. Int J Public Health 2022; 67: 1605354.
5. Che TH, Nguyen TC, Vu VNT, Nguyen HT, Hoang DTP, Ngo XM, Truong DQ, Bontems P, Robert A, Nguyen PNV. Factors Associated With Helicobacter Pylori Infection Among School-Aged Children From a High Prevalence Area in Vietnam. Int J Public Health 2023; 68: 1605908.
6. Polivanova TV, Malaty H, Vshivkov VA. Epidemiology Helicobacter pylori infection in children in the Tyva Republic (Russia). Helicobacter 2022; 27: e12882.
7. Tran V, Saad T, Tesfaye M, Walelign S, Wordofa M, Abera D, Desta K, Tsegaye A, Ay A, Taye B. Helicobacter pylori (H. pylori) risk factor analysis and prevalence prediction: a machine learning-based approach. BMC Infect Dis 2022; 22: 655.
8. Hibaoui L, Massik A, Lebbar Z, Yahyaoui G, Mahmoud M, Bougnouch L, Hamass N, Chbani L, Bennani B, Berrahou MA, Idriss ML, Hida M. The high sensitivity and specificity of rapid urease test in diagnosis of Helicobacter pylori infection in Moroccan children. Iran J Microbiol 2022; 14: 669-676.
9. Nasri P, Saneian H, Famouri F, Khademian M, Salehi F. Helicobacter pylori infection in pediatrics with gastrointestinal complaints. Int J Physiol Pathophysiol Pharmacol 2022; 14: 118-123.
10. Yorulmaz A, Emiroglu HH, Gumus MD, Emiroglu M. The relationship between helicobacter pylori infection and nodular antral gastritis in pediatric patients. J Natl Med Assoc 2022; 114: 440-450.
11. Esteghamati A, Sayyahfar S, Khanaliha K, Tavakoli A, Naghdalipour M, Zarean M, Haghighi Hasanabad M. Prevalence and Clinical Relevance of cagA and oipA Genotypes of Helicobacter pylori in Children and Adults with Gastrointestinal Diseases in Tehran, Iran. Med J Islam Repub Iran 2023; 37: 22.
12. Li R, Wang W, Ma Y, Chen H. Analysis of risk factors for ulcer recurrence and upper gastrointestinal bleeding in children with peptic ulcer treated with Helicobacter pylori eradication therapy. Transl Pediatr 2023; 12: 618-630.
13. Goldenring JR, Nam KT, Wang TC, Mills JC, Wright NA. Spasmolytic polypeptide-expressing metaplasia and intestinal metaplasia: time for reevaluation of metaplasias and the origins of gastric cancer. Gastroenterology 2010; 138: 2207-2210, 2210 e2201.
14. Hsieh H, Yang HB, Sheu BS, Yang YJ. Atrophic gastritis in Helicobacter pylori-infected children. Helicobacter 2022; 27: e12885.
15. Li G, Kelly DR, Mroczek-Musulman E, Wang K, Council L, Zhao L. Gastric Antral Mucosal Changes in Children With Intestinal Metaplasia. Pediatr Dev Pathol 2022; 25: 511-517.
16. Yu M, Ma J, Song XX, Shao QQ, Yu XC, Khan MN, Qi YB, Hu RB, Wei PR, Xiao W, Jia BL, Cheng YB, Kong LF, Chen CL, Ding SZ. Gastric mucosal precancerous lesions in Helicobacter pylori-infected pediatric patients in central China: A single-center, retrospective investigation. World J Gastroenterol 2022; 28: 3682-3694.
17. Attard TM, Omar U, Glynn EF, Stoecklein N, St Peter SD, Thomson MA. Gastric cancer in the pediatric population, a multicenter cross-sectional analysis of presentation and coexisting comorbidities. J Cancer Res Clin Oncol 2023; 149: 1261-1272.
18. Lupu A, Gavrilovici C, Lupu VV, Cianga AL, Cernomaz AT, Starcea IM, Mihai CM, Tarca E, Mocanu A, Fotea S. Helicobacter pylori Infection in Children: A Possible Reason for Headache? Diagnostics (Basel) 2023; 13.
19. Lupu A, Miron IC, Cianga AL, Cernomaz AT, Lupu VV, Gavrilovici C, Starcea IM, Tarca E, Ghica DC, Fotea S. The Prevalence of Liver Cytolysis in Children with Helicobacter pylori Infection. Children (Basel) 2022; 9.
20. Taha A, Pitaro J, Lazarovitch T, Muallem-Kalmovich L, Garti Y, Gavriel H. The association between Helicobacter pylori and chronic otitis media with effusion. Eur Arch Otorhinolaryngol 2023; 280: 891-896.
21. Simoes AM, Araujo D, Teixeira PM, Antunes H. Effect of Helicobacter pylori Infection on Macromineral and Trace Element Status-Systematic Review and Meta-Analysis. J Pediatr Gastroenterol Nutr 2022; 75: 661-665.
22. Wang D, Chen Y, Ding Y, Tu J. Inverse association between Helicobacter pylori infection and childhood asthma in a physical examination population: a cross-sectional study in Chongqing, China. BMC Pediatr 2022; 22: 615.
23. Silva IN, Marcal LV, Queiroz DMM. Helicobacter pylori Infection Is Associated With Thyroid Dysfunction in Children With Congenital Hypothyroidism. Front Pediatr 2022; 10: 875232.
24. Kolasa-Kicinska M, Stawerska R, Stawerski P, Kaluzynski A, Czkwianianc E, Lewinski A. Effects of Helicobacter pylori Infection on Ghrelin and Insulin-like Growth Factor 1 Secretion in Children with Idiopathic Short Stature. J Clin Med 2022; 11: 5868.
25. Kato S, Gold BD, Kato A. Helicobacter pylori-associated Iron Deficiency Anemia in Childhood and Adolescence-Pathogenesis and Clinical Management Strategy. J Clin Med 2022; 11: 7351.

26. Lupu A, Miron IC, Cianga AL, Cernomaz AT, Lupu VV, Munteanu D, Ghica DC, Fotea S. The Relationship between Anemia and Helicobacter Pylori Infection in Children. Children (Basel) 2022; 9: 1324.
27. Zhang Y, Bi J, Wang M, Deng H, Yang W. Correlation between helicobacter pylori infection and iron deficiency in children. Pak J Med Sci 2022; 38: 1188-1192.
28. Kato S, Gold BD, Kato A. The Resolution of Severe Iron-Deficiency Anemia After Successful Eradication of Helicobacter pylori in Teenagers. JPGN Rep 2022; 3: e238.
29. Tanous O, Levin C, Suchdev PS, Luo H, Rinawi F. Resolution of iron deficiency following successful eradication of Helicobacter pylori in children. Acta Paediatr 2022; 111: 1075-1082.
30. Elsaadany E, Amin S, Abdel-Hafez M, El Amrousy D, Kasem S, Abd Elaziz D, Shawky D. Study of Serum Ferritin, Zinc, and Copper Levels in Children With Helicobacter pylori Gastritis and the Effect of the Treatment. J Pediatr Gastroenterol Nutr 2022; 75: e88-e93.
31. Park HE, Park S, Nizamutdinov D, Seo JH, Park JS, Jun JS, Shin JI, Boonyanugomol W, Park JS, Shin MK, Baik SC, Youn HS, Cho MJ, Kang HL, Lee WK, Jung M. Antigenic Determinant of Helicobacter pylori FlaA for Developing Serological Diagnostic Methods in Children. Pathogens 2022; 11: 1544.
32. Bogiel T, Mikucka A, Szaflarska-Poplawska A, Grzanka D. Usefulness of Molecular Methods for Helicobacter pylori Detection in Pediatric Patients and Their Correlation with Histopathological Sydney Classification. Int J Mol Sci 2022; 24: 179.
33. Gareayaghi N, Kocazeybek B. Detection of A2143G, A2142C, and A2142G Point Mutations with Real-Time PCR in Stool Specimens from Children Infected with Helicobacter pylori. Diagnostics (Basel) 2022; 12: 2119.
34. Rafeey M, Nikmanesh P, Javadzadeh F. Diagnostic Value of Fecal Calprotectin in Children with Gastritis, Duodenitis and Helicobacter Pylori. Int J Prev Med 2022; 13: 107.
35. Borka Balas R, Melit LE, Marginean CO. Current Worldwide Trends in Pediatric Helicobacter pylori Antimicrobial Resistance. Children (Basel) 2023; 10: 403.
36. Karbalaei M, Keikha M, Talebi Bezmin Abadi A. Prevalence of Primary Multidrug-resistant Helicobacter pylori in Children: A Systematic Review and Meta-analysis. Arch Med Res 2022; 53: 634-640.
37. Le LTT, Nguyen TA, Nguyen NA, Nguyen YTH, Nguyen HTB, Nguyen LT, Vi MT, Nguyen T. Antibiotic Resistance of Helicobacter pylori in Children with Gastritis and Peptic Ulcers in Mekong Delta, Vietnam. Healthcare (Basel) 2022; 10: 1121.
38. Geng T, Yu ZS, Zhou XX, Liu B, Zhang HH, Li ZY. Correction to: Antibiotic resistance of Helicobacter pylori isolated from children in Chongqing, China. Eur J Pediatr 2023; 182: 473-474.
39. Shu X, Ye D, Hu C, Peng K, Zhao H, Li H, Jiang M. Alarming antibiotics resistance of Helicobacter pylori from children in Southeast China over 6 years. Sci Rep 2022; 12: 17754.
40. Burayzat S, Al-Tamimi M, Barqawi M, Massadi MS, Abu-Raideh J, Albalawi H, Khasawneh AI, Himsawi N, Barber M. Antimicrobial Resistance Molecular Mechanisms of Helicobacter pylori in Jordanian Children: A Cross-Sectional Observational Study. Antibiotics (Basel) 2023; 12: 618.
41. Boyanova L, Hadzhiyski P, Markovska R, Gergova R. Investigation of multidrug-resistant Helicobacter pylori in pediatric patients: A Bulgarian study and literature data. Acta Microbiol Immunol Hung 2022. doi: 10.1556/030.2022.01682. Online ahead of print.
42. Chen Y, Xia SY, Ru FX, Feng JJ, Tao J, Wei ZY, Li X, Qian C, Lin Q, Chen JH. Gastric juice microbiota in pediatric chronic gastritis that clinically tested positive and negative for Helicobacter pylori. Front Microbiol 2023; 14: 1112709.
43. Zheng W, Zhu Z, Ying J, Long G, Chen B, Peng K, Li F, Zhao H, Jiang M. The Effects of Helicobacter pylori Infection on Gastric Microbiota in Children With Duodenal Ulcer. Front Microbiol 2022; 13: 853184.
44. Jones NL, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, Czinn S, Gold BD, Guarner J, Elitsur Y, Homan M, Kalach N, Kori M, Madrazo A, Megraud F, Papadopoulou A, Rowland M, Espghan N. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr 2017; 64: 991-1003.
45. Le Thi TG, Werkstetter K, Kotilea K, Bontems P, Cabral J, Cilleruelo Pascual ML, Kori M, Barrio J, Homan M, Kalach N, Lima R, Tavares M, Urruzuno P, Misak Z, Urbonas V, Koletzko S, Helicobacter pylori Special Interest Group of E. Management of Helicobacter pylori infection in paediatric patients in Europe: results from the EuroPedHp Registry. Infection 2022; 51: 921-934.
46. Rosu OM, Gimiga N, Stefanescu G, Ioniuc I, Tataranu E, Balan GG, Ion LM, Plesca DA, Schiopu CG, Diaconescu S. The Effectiveness of Different Eradication Schemes for Pediatric Helicobacter pylori Infection-A Single-Center Comparative Study from Romania. Children (Basel) 2022; 9: 1391.
47. Kotilea K, Mekhael J, Salame A, Mahler T, Miendje-Deyi VY, Cadranel S, Bontems P. Eradication rate of Helicobacter Pylori infection is directly influenced by adherence to therapy in children. Helicobacter 2017; 22. doi: 10.1111/hel.12383. Epub 2017 Mar 17.
48. Le LTT, Nguyen TA, Nguyen NA, Nguyen YTH, Nguyen HTB, Nguyen LT, Vi MT, Nguyen T. Helicobacter pylori Eradication Efficacy of Therapy Based on the Antimicrobial Susceptibility in Children with Gastritis and Peptic Ulcer in Mekong Delta, Vietnam. Children (Basel) 2022; 9: 1019.
49. Hung CW, Chen SC, Ku LE, Sheu BS, Yang YJ. A Culture-Based Strategy Is More Cost Effective Than an Empiric Therapy Strategy in Managing Pediatric Helicobacter pylori Infection. Front Pediatr 2022; 10: 860960.
50. Feng Y, Hu W, Wang Y, Lu J, Zhang Y, Tang Z, Miao S, Zhou Y, Huang Y. Efficacy of Phenotype-vs. Genotype-Guided Therapy Based on Clarithromycin Resistance for Helicobacter pylori Infection in Children. Front Pediatr 2022; 10: 854519.
51. Liang M, Zhu C, Zhao P, Zhu X, Shi J, Yuan B. Comparison of multiple treatment regimens in children with Helicobacter pylori infection: A network meta-analysis. Front Cell Infect Microbiol 2023; 13: 1068809.
52. Shawky D, Salamah AM, Abd-Elsalam SM, Habba E, Elnaggar MH, Elsawy AA, Baiomy N, Bahaa MM, Gamal RM. Nitazoxanide-based therapeutic regimen as a novel treatment for Helicobacter pylori infection in children and adolescents: a randomized trial. Eur Rev Med Pharmacol Sci 2022; 26: 3132-3137.