Clinical differences of *Helicobacter pylori* infection in children

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Abstract

*Helicobacter pylori* infection is widely spread all over the world. The prevalence of *H. pylori* infection in the world varies and depends on numerous factors such as age, ethnicity, geographical and socioeconomic status. Humans have been in a symbiotic relationship with this bacterium for thousands of years. However 10–20% of people infected with *H. pylori* are likely to develop gastroduodenal diseases such as peptic ulcer disease, iron deficiency anemia, gastric mucosal atrophy, metaplasia, dysplasia, MALT lymphoma, or gastric adenocarcinoma. Most of these diseases develop as the infection progresses and they are likely to occur later in life among the elderly. In the following years, the use of modern molecular techniques has led to the discovery of new *Helicobacter* strains and their genotypic differentiation. Newly discovered *Helicobacter* microorganisms can colonize human gastrointestinal tract and bile ducts. This article summarizes the distinct features of *H. pylori* infection in children including its prevalence, clinical manifestation, indications for treatment and recommended schemes of eradication.

Key words: children, treatment, epidemiology, *Helicobacter pylori*, clinical presentation
**Epidemiology of *H. pylori* infection**

The prevalence of *H. pylori* infection in the world varies and depends on numerous factors such as age, ethnicity, geographical and socioeconomic status. *H. pylori* infection is the most prevalent in developing countries of Africa, South America and Asia; whereas highly developed countries are the least infected. Goh et al. assessed the prevalence of *H. pylori* infection based on 31 publications from the Asia-Pacific region, Africa, Europe, and North and South America. H. pylori serological tests were the most commonly used methods in determining the infection. The authors reported the high infection rates in the healthy population of South Korea (50.8%), Shanghai (71.7%), South Africa (66.1%), and the lowest rates in the USA (7.5%) and Australia (15.5%), respectively. In developing countries, *H. pylori* infection is markedly more prevalent at a younger age than it is in developed countries. According to Hunt et al., the prevalence of *H. pylori* infection in Ethiopian children, aged 2–4 years, was 48%, while in adults was over 95%; in Nigeria the prevalence of infection in children aged 2–4 years was 48%, while in adults was over 95%; and in adults ranging from 70 to 90%. In Mexico, children aged 5–9 years was 43%, and in adults ranging from 70 to 90%. On the other hand, the *H. pylori* infection rate has shown a decrease in the number of people infected. This is related to the improvement of socioeconomic conditions, and frequent antibiotic treatment administered to cure other diseases.

Kosunen et al., in a Finnish study, showed a fall in the seroprevalence rate from 56% to 31% between 1973 and 1994. In addition, the prevalence of the pathogenic cagA(+) strains significantly decreased (34% to 8%, p < 0.001) more than in the case of cagA(−) strains (from 12% to 6%). The estimated seroconversion rate amounted to 0.4%, and the reversion rate to 0.13% per year. Andreasson et al., in the prospective study carried out in Sweden, proved that for 23 years (1989–2012) the seroprevalence significantly fell from 38% to 16% (OR: 0.25; 95% CI: 0.11–0.59, p = 0.001, per decade). The results from these studies confirm the cohort effect in developed countries. However, Rosenstock et al., in a Danish study, did not report a fall in the seroprevalence of *H. pylori* infection in 1983–1994. In this study, the number of people infected with *H. pylori* was stable and ranged from 24.7% to 24.5%. It should be, however, noted that the reported *H. pylori* infection rate also depends on the detection methods. Serological methods give falsely higher
rates compared to the urea breath test or to the culture of *H. pylori* from stool samples as the methods can be related to *H. pylori* antibodies, presence for several months after eradication.

The incidence of pathogenic *H. pylori* strains cagA(+) in children has been also analyzed in various studies. The occurrence of pathogenic *H. pylori* strains cagA(+) was more frequently reported in children than in adults (77.0% vs 63.8%, p < 0.001). Significant differences in the percentage of cagA(+) strains in particular studies regions of Poland have been also confirmed ranging from 40.6% to 91.6%. The most frequently observed genotypes of *H. pylori* strains cagA(+) was more frequently observed in children than in adults (77.0% vs 63.8%, p < 0.001). Significant differences in the percentage of cagA(+) strains in particular studies regions of Poland have been also confirmed ranging from 40.6% to 91.6%. The most frequently observed genotypes of *H. pylori* strains cagA(+) in particular studies regions of Poland have been also confirmed ranging from 40.6% to 91.6%

The spontaneous resolution of infection or the infection with new strains primarily after eradication have been reported in people infected with *H. pylori*. Vanderpas et al. reported that the reinfection after eradication for negative people amounted to 38.7%. The risk of acquisitions that occurred in the period of 10 years in previously infected people has no statistically significant symptoms and remain free of symptoms throughout their lives.

**Infection transmission and reinfection**

Urita et al. evaluated the potential relationship between *H. pylori* prevalence among children and grandparents in three-generation households in a Japanese rural town. Based on this study, *H. pylori* spread in a 3-generation households occur not only through mother to child transmission but also through the grandmother to child route. Interestingly, having an infected father or grandfather was not a significant predictor for the infection being present in children.

The spontaneous resolution of infection or the infection with new strains primarily after eradication have been reported in people infected with *H. pylori*. Vanderpas et al. reported that the reinfection after eradication for the period of 5 years amounted to 48.6%, and new infections that occurred in the period of 10 years in previously negative people amounted to 38.7%. The risk of acquiring the infection was fourfold higher in non-European than in European children (p < 0.001). Other authors have also reported *H. pylori* seroconversion. Kumagai et al., in longitudinal cohort studies in children and adults between 1986 and 1997, reported *H. pylori* seroconversion rates were 1.1% and 1.0% per year for children and adults, respectively.

**Clinical presentation**

*H. pylori* colonizes the gastric mucosa, leading to chronic inflammation in all infected humans, including children and adolescents. However, the majority of infected people have no statistically significant symptoms and remain free of symptoms throughout their lives.

Approximately 10–20% of people with *H. pylori* infection may develop stomach ulcers and/or duodenal ulcers, gastri c mucosal atrophy, metaplasia, dysplasia, lymphoma, or gastric adenocarcinoma. The specific presentation depends on the virulence features of the bacteria, host characteristics and environmental factors. Many studies have shown that the most virulent genotypes of *H. pylori* are cagA(+), vacA (+). The recently published large multicenter study analyzing genotypic and clinical differences of *H. pylori* infection in the Polish population demonstrated that the presence of cagA(+) s1m2 and cagA(+) s1m1 strains is found more frequently in children than in adults. Genotype cagA(+) s1m1 has been detected statistically more often in children than in adults (34.0% vs 23.1%, p < 0.0279). However, *H. pylori* cagA(–) s2m2 strain occurred more frequently in adults than in children (27.1 % vs 14%, p = 0.003). There was no effect of *H. pylori* infection on clinical symptoms such as nausea, regurgitation, vomiting, heartburn and abdominal pain in pediatric population. In contrast, adults infected with *H. pylori* had more frequent episodes of heartburn and abdominal pain.

Other studies demonstrated that in both children and adults, there is a statistically significant association between the seroprevalence of *H. pylori* and duodenal ulcer disease. Biernat et al. analyzed the relationship between clinical outcomes of infection and the prevalence of *H. pylori* cagA, vacA, ICEA and babA2 genotypes in 130 children and adolescents aged 4–18 years. The authors demonstrated a statistically significant association between the presence of cagA gene and duodenal ulcer (p < 0.05) whereas vacAs1/m1 genotype of *H. pylori* was frequent in children with gastritis and gastroesophageal reflux disease (GERD). In children with dyspepsia and GERD, vacAs2/cagA(–)/iceA1(+)/babA2(–) were frequent. Bontems et al. in a multicenter, prospective study enrolling 124 children from 11 European centers evaluated the risk factors for peptic ulcer and/or erosion of the stomach or duodenum. The investigators demonstrated that *H. pylori* infection is the risk factor only for the occurrence of erosions and duodenal ulcers. In other studies the seroprevalence of *H. pylori* was more frequently observed in children than in adults. The granulation of gastric mucosa associated with the lymphoid follicles hypertrophy and the thickening of the gastric mucosa folds were also seen. However, gastric mucosal atrophy, intestinal metaplasia and dysplasia occurred less frequently in children than in adults.

De Sablet et al. have reported that *H. pylori* strain of European origin as compared to African origin was strongly predictive of the increased risk of precancerous gastric lesions, even in the low risk region. Gonzalez et al. analyzed the gastric precancerous lesions in 312 patients. The median follow-up was 12.8 years. The authors demonstrated advanced premalignant lesions in patients infected with *H. pylori* cagA(+) vacAs1/m1 strains of *H. pylori*.
in comparison to patients infected with cagA(−) vacAs2m2 strains. This led to the conclusion that genotyping 
*Helicobacter pylori* strains may be useful in identifying higher risk patients infected with virulent strains of *H. pylori* that require more intensive surveillance.

**Extra-intestinal manifestations**

Many studies investigated the relationship between infection with *H. pylori* and iron-deficiency anemia, B12 deficiency, acute idiopathic thrombocytopenic purpura (ITP), and allergic diseases. Infection in children are less susceptible to wheezing, allergic rhinitis and skin allergies. Several meta-analyses have confirmed the relationship between unexplained iron deficiency anemia and infection with *H. pylori*, both in children and adults. Harris et al., in a prospective study, have demonstrated the correlation between *H. pylori* infection associated hypochlorhydia and the development of iron deficiency in 123 children. Lu et al., evaluated the role of *H. pylori* in the pathogenesis of acute idiopathic thrombocytopenic purpura (ITP) and have shown that the prevalence of pediatric infections with *H. pylori* and controls ITP group were similar and amounted to 41.30% and 35.71%, respectively. No difference was found between the initial platelet counts and megakaryocytes. Xiong et al., in a meta-analysis study, have demonstrated a possible link between *H. pylori* infection in Henoch-Schonlein purpura (HSP) as compared to the control group (49.27% vs 23.39%) in Chinese children. Eradication of *H. pylori* infection reduced the recurrence of HSP. Wang et al., in a meta-analysis, have evaluated the association between asthma and *H. pylori* infection. This analysis has shown a weak inverse association between asthma and *H. pylori* infection in children and adults. In contrast, Karimi et al. have not confirmed the relationship between *H. pylori* infection and asthma in children.

**Diagnosis of *H. pylori* infection in children**

According to the guidelines from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) diagnostic testing for *H. pylori* infection in children should be performed only when symptoms such as vomiting, persistent abdominal pain, and gastrointestinal bleeding can justify the gastroduodenoscopy with biopsy samples for examination. In such cases it is important to determine the underlying cause of the symptoms and not solely focus on the presence of *H. pylori* infection. If there are no symptoms suggestive of organic disease, a decision whether to conduct diagnostic testing for *H. pylori* infection should be taken individually. Diagnostic testing for *H. pylori* infection may be considered in children with refractory iron-deficiency anemia, and idiopathic thrombocytopenic purpura. Diagnostic testing for *H. pylori* infection is not recommended in children with functional abdominal pain.

A diagnosis of the infection should be based on invasive tests, i.e., culture, rapid urease test, polymerase chain reaction (PCR), or non-invasive tests, which include the urea breath test (UBT), detection of *H. pylori* antigens in stool or detection of antibodies to *H. pylori* in serum. Diagnostic testing should be carried out at least 2 weeks after the completion of proton pump inhibitors (PPI) therapy, and 4 weeks after antibiotic treatment. The effectiveness of *H. pylori* eradication treatment is most commonly assessed with a non-invasive test, i.e., the urea breath test, or with *H. pylori* antigen stool test 4–8 weeks after eradication therapy. Serological tests measuring antibodies in serum or urine are not recommended for the evaluation of the treatment effectiveness, since antibodies can be present after *H. pylori* eradication for several months.

**Recommendations for *H. pylori* treatment in children**

The main indication for treating *H. pylori* infection in children is peptic ulcer disease. *H. pylori* infection should be considered in the case of its prevalence in the esophageal mucosa without peptic ulcer disease. First-degree relatives of patients with gastric cancer may be offered the eradication of *H. pylori*. A “test and treat” strategy is not recommended in case of children.

**Treatment of *H. pylori* infection in children**

Studies on the effectiveness of *H. pylori* eradication are focused on selecting regimens which aim to achieve the highest eradication rates with the lowest incidence of side effects. The effectiveness of treatment regimens depends on the sensitivity of *H. pylori* strains to drugs used, the duration of the treatment and patients’ compliance in taking medication. It is recommended that drugs are tailored to the antibiotic susceptibility of *H. pylori* strains in a given region. The best results of *H. pylori* eradication are achieved after the first treatment; subsequent treatments with the same antibiotic may be less effective due to the increasing secondary antibiotic-resistance of *H. pylori* strains. Clarithromycin has the most significant impact on the effectiveness of *H. pylori* eradication, followed by metronidazole. Low-level amoxicillin resistance (4.9–10.8%) has been reported in China,
Thailand and Korea; whereas high-level resistance to clarithromycin has been reported in European countries (15–24%) and in China (37.8%). The prevalence of metronidazole resistance has been even higher. In Poland, the resistance to clarithromycin depends on the region; in children it was between 9% and 26%, in adults from 3% to 27%; the resistance to metronidazole in children was from 16% to 43%, in adults from 27% to 52%. However, it should be noted that in different countries *H. pylori* antibiotic resistance varies, and depends mainly on the frequency of antibiotics used for treatment of other infections in a given region.

ESPGHAN and NASPGHAN recommend the following regimens in the first-line therapy:

1. PPI (proton pump inhibitor) 1–2 mg/kg/day + amoxicillin (50 mg/kg/day) + metronidazole (20 mg/kg/day) or,
2. PPI + amoxicillin + clarithromycin (20 mg/kg/day) if the resistance to *H. pylori* does not exceed 15% in the region or,
3. Bismuth salts (bismuth subcitrate or subsalicylate) 8 mg/kg/day + amoxicillin + metronidazole.

The aforementioned medications may be administered in divided doses 2 times a day (with the maximum daily dose for amoxicillin amounting to 2000 mg, 1000 mg for metronidazole, 1000 mg/day for clarithromycin) for 10–14 days. Sequential therapy, which includes dual therapy with PPI and amoxicillin for 5 days, followed by 5 days of triple therapy: PPI with clarithromycin and metronidazole/tinidazole has also been used in the last decade. If *H. pylori* resistance to clarithromycin is high in the given region, PPI therapy in combination with bismuth and two antibiotics is recommended.

In the second-line therapy, if *H. pylori* are not eradicated with clarithromycin, a four-drug regimen with a new antibiotic is recommended. Moreover, determining the clarithromycin-susceptible *H. pylori* isolates is advocated.

**Conclusions**

For thousands of years people have lived in symbiosis with *H. pylori*. Only some patients with *H. pylori* infection may develop health issues and life threatening diseases. This depends on the bacterial virulence, host characteristics, and environmental factors. Chronic infections with *H. pylori* can lead to peptic ulcer disease, iron deficiency anemia, MALT lymphoma, or gastric cancer. Children infected with *H. pylori* are less susceptible to wheezing, allergic rhinitis, and other allergic diseases. Indications for eradication *H. pylori* infection in children are limited to peptic ulcer disease. A “test and treat” strategy does not apply in pediatric patients. Due to the increased *H. pylori* resistance to clarithromycin, its efficacy in *H. pylori* eradication is limited, and antimicrobial sensitivity testing is advocated.


