

REVIEW

Helicobacter pylori Infection in Pediatrics

Eleftheria Roma* and Erasmo Miele†

*First Department of Pediatrics, University of Athens, Athens, Greece, †Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Naples, Italy

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Reprint requests to: Eleftheria Roma, First Department Of Pediatrics, University of Athens, Agia Sophia Children's Hospital, Papadiamantopoulou and Lebadias Str., 11527, Athens, Greece.

This review includes the main pediatric studies published from April 2014 to March 2015. The host response of Treg cells with increases in FOXP3 and TGF- β 1 combined with a reduction in IFN- γ by Teff cells may contribute to *Helicobacter pylori* susceptibility in children. Genotypic variability in *H. pylori* strains influences the clinical manifestation of the infection. *Helicobacter pylori* infection is associated with variables indicative of a crowded environment and poor living conditions, while breast-feeding has a protective effect. Intrafamilial infection, especially from mother to children and from sibling to sibling, is the dominant transmission route. Studies showed conflicting results regarding the association between *H. pylori* infection and iron deficiency anemia. One study suggests that *H. pylori* eradication plays a role in the management of chronic immune thrombocytopenic purpura in *H. pylori*-infected children and adolescents. The prevalence of *H. pylori* was higher in chronic urticaria patients than in controls and, following *H. pylori* eradication, urticarial symptoms disappeared. An inverse relationship between *H. pylori* infection and allergic disease was reported. Antibiotic resistance and insufficient compliance to treatment limit the efficacy of eradication therapy. Sequential therapy had no advantage over standard triple therapy. In countries where *H. pylori* infection is prevalent, studies focusing on virulence factors and antibiotic susceptibility may provide anticipation of the prognosis and may be helpful to reduce morbidity and mortality.

Pathophysiology

Helicobacter pylori is generally acquired in childhood. A study was conducted to investigate whether the CD4/CD25 regulatory T cells (Treg) and CD4+CD25[−] effector T (Teff)-cell responses determine *H. pylori* susceptibility in children after exposure. The fraction of FOXP3⁺ to CD4+CD25 high cells in PBMCs, FOXP3-positive staining and translation level in gastric tissues were higher in *H. pylori*-infected children than in controls ($p < .05$). The host response of Treg cells with increases in FOXP3 and TGF- β 1 combined with a reduction in IFN- γ by Teff cells may contribute to *H. pylori* susceptibility in children [1].

Several studies evaluated the influence of *H. pylori* virulence on the development of various diseases. Among pathogen-related factors, genotypic differences in *H. pylori* strains were analyzed by Mendoza et al. on a total of 160 *H. pylori* strains; the *cagA* and *cagE* genes

were found in a proportion of 91 and 83%, respectively. Genotypic variability in *H. pylori* strains influenced the clinical manifestations of the infection [2]. Regarding *H. pylori* virulence factors, Oliveira et al. described the prevalence of infection with *cagA*-positive strains in a group of children and adolescents in southern Brazil. The prevalence of *cagA*-positive *H. pylori* was 29.6%. There were no statistically significant differences in clinical or demographic characteristics or in the endoscopic and histologic features of the patients infected with *cagA*-positive strains as compared with those infected with *cagA*-negative strains [3].

Studies have suggested a causal role for CagA EPIYA-C in gastric carcinogenesis, and this factor has been shown to be geographically diverse. Campelo Braga et al. investigated the number of CagA EPIYA motifs and the *vacA* i genotype in *H. pylori* strains from asymptomatic Brazilian children. The authors confirmed that this population was colonized early by the most virulent

H. pylori strains, as demonstrated by the high frequency of the *vacA* i1 allele and the high number of EPIYA-C motifs [4].

Muhsen et al. examined the association between *H. pylori* infection, serum PG levels (as a measure of inflammation), and vibriocidal antibody seroconversion, following oral immunization with the live oral cholera vaccine CVD 103-HgR in children of various ages. The likelihood of vibriocidal antibody seroconversion following vaccination was significantly decreased in *H. pylori*-seropositive children aged 6 months–4 years with a PG II >8 µg/L, as well as in those with a low PG II level, compared to *H. pylori*-seronegative children. *Helicobacter pylori*-seropositive children aged 5–9 years with a serum PG I of 30 mg/L (indicating more severe gastritis) had higher odds of vibriocidal seroconversion than those with lower PG I levels. These data suggest that, as *H. pylori* gastritis progresses with increasing pediatric age, changes in gastric secretion may explain the differences in age-related immune responses to this live oral cholera vaccine [5].

The role of *H. pylori* infection and/or gastritis in several histopathologic changes, that is, p53, p21, and cell proliferation-associated Ki-67 antigen expression, was studied on gastric mucosa samples of children with a mean age of 7.5 ± 4.5 years. Ki-67 and p21 expressions were significantly more frequent in the *H. pylori*-positive group compared to the *H. pylori*-negative group with a normal mucosa. Expression of the precancerous markers studied in significant amounts indicates the importance of *H. pylori* infection in childhood in the constitution of gastric cancer in adulthood [6].

Cam investigated the incidence of *H. pylori* infection in children and the early mucosal changes that may lead to malignant degeneration. A total of 750 children were evaluated, with a mean age of 10.1 years. Fifty-two percent of the patients were found to be infected with *H. pylori*. Among those infected, 289 (74%) were diagnosed with chronic superficial gastritis and 24 (6.2%) had gastric atrophy. Most strikingly, intestinal metaplasia was observed in 11 children, all in the *H. pylori*-positive group. The frequency of gastric cancer in family members ($n = 4$) was higher in patients with *H. pylori* infection. No gastric cancer case was reported from the parents of noninfected children [7].

Finally, Park et al. studied the immunologic expression of gastric mucins in a large number of children, adolescents, and young adults according to age, *H. pylori*, and intestinal metaplasia status. An increased expression of Mucin2 (MUC2), Mucin5AC (MUC5AC), and Mucin6 (MUC6) was noted in subjects with intestinal metaplasia compared with subjects infected with *H. pylori* between 20 and 29 years of age. Gastric

expressions of MUC5AC were decreased in children older than 5 years with *H. pylori* compared to those without *H. pylori* ($p < .001$). MUC2 and MUC6 expression did not change significantly according to *H. pylori* status. These findings might be helpful to understand gastric epithelial changes according to age and chronic *H. pylori* infection [8].

Epidemiology and Transmission

The prevalence of *H. pylori* infection in children has decreased over the last decade, but depending on many factors, it still varies all over the world.

Mohammed et al. studied a total of 303 children from the central and western regions of Saudi Arabia. The prevalence of *H. pylori* infection was 49.8%. Conditions positively associated with the presence of *H. pylori* were as follows: age above 10 years, a low-income level, more than eight persons in the household, bed sharing, and two infected parents [9].

Bin Mohanna et al. studied the prevalence of *H. pylori* infection and parasites in symptomatic children in Yemen. The global prevalence of *H. pylori* was 65%, with 83% in the 6- to 8-year age group, and 52% in the 12- to 15-year age group. The prevalence of giardiasis and amebiasis was 10 and 25%, respectively [10].

Jang et al. investigated changes in the prevalence rates of *H. pylori* infection in Korean children with recurrent abdominal pain (RAP) using the urea breath test (UBT). In their cohort, they found a 7.4% prevalence of *H. pylori* infection, with no significant decrease over the last 11 years; however, the prevalence rate for children <12 years old was significantly lower than that for those ≥ 12 years old. The authors suggest that these data may predict a decrease in the prevalence rate of *H. pylori* [11].

Studies have shown that patients with inflammatory bowel disease (IBD) are less likely to be infected with *H. pylori* compared with non-IBD patients. The study by Roka et al. [12] confirms this inverse association between *H. pylori* and IBD.

Regarding transmission, intrafamilial infection is considered to be one of the main routes of transmission for *H. pylori*. Osaki et al. assessed the genomic profiles of *H. pylori* isolates from family members by multilocus sequence typing (MLST) and identified the original strain infecting the index child. Mother-to-child transmission of *H. pylori* was demonstrated in four of five families, while transmissions from father to child and from sibling to sibling were demonstrated in two families and one family, respectively [13].

Using MLST, Yokota et al. [14] confirmed that intrafamilial infection, especially from mother to chil-

dren and from sibling to sibling, is the dominant transmission route.

The oral cavity has also been implicated as a source of *H. pylori* infection. A novel PCR system was used to examine *H. pylori* distribution in oral specimens. The detection rate of *H. pylori* in 40 inflamed pulp tissue samples was 15%, whereas no positive reaction was found in any of the 40 saliva specimens. These results indicate that an infected root canal may be a reservoir for *H. pylori* [15].

In a meta-analysis, a protective effect of breast-feeding was observed in less economically developed settings [16].

Clinical Presentation

Gastrointestinal Manifestations

Helicobacter pylori infection is well known as the main cause of peptic ulcer disease (PUD). Hernández et al. evaluated which host factors could determine this clinical outcome. Among children with duodenal ulcer (DU) 90.6% were infected with *H. pylori*. DU-infected children had higher levels of mucosal interferon- γ than noninfected and non-DU-infected patients. There was no distinctive clinical presentation of children with PUD. T-helper cytokine balance may influence clinical outcomes in children [17].

An association was found between laryngopharyngeal reflux and *H. pylori* detected in adenoidectomized tissue from adenoid hyperplasia by real-time PCR in children [18].

Extraintestinal Manifestations

Iron deficiency anemia

An association between *H. pylori* infection and iron deficiency anemia (IDA) has been suggested. Darvishi et al. conducted a case-control study to evaluate the association between *H. pylori* infection and IDA among preschool children (age range: 40–75 months) in Iran. In total, 81.3% of children with IDA and 14.3% of nonanemic controls were seropositive for *H. pylori* ($p < .0001$) [19].

On the contrary, in a case-control study on children aged 2–16 years old, 8.2% of the infected patients and 10.5% of the noninfected patients had IDA, with no statistically significant difference ($p = .270$) [20].

It has been suggested that IDA/ID associated with *H. pylori* infection might be mediated by inflammation-driven hepcidin production. In a study on children aged 7–16 years with complaints of RAP and dyspepsia, two

groups were created according to their *H. pylori* status and compared with healthy controls. Initial levels of ferritin ($p = .002$), prohepcidin ($p = .003$), and IL-6 ($p = .004$) were found to be significantly lower in the *H. pylori*-positive group than in the *H. pylori*-negative and the control groups. While significant increases in hematocrit and mean corpuscular volume were observed, no significant difference was found in serum ferritin, prohepcidin, or IL-6 level after eradication in the *H. pylori*-positive group [21].

Immune thrombocytopenic purpura

The association between *H. pylori* infection and chronic immune thrombocytopenic purpura (cITP) is not well established in children, although the cure of thrombocytopenia has been described in approximately half of *H. pylori*-eradicated adult patients [22]. Brito et al. investigated the effect of *H. pylori* eradication on platelet recovery in cITP of children and adolescents in a randomized controlled trial. A complete response after 6–9 months of follow-up was observed in 60.0% of *H. pylori*-eradicated patients versus 18.2% in non-eradicated patients ($p = .08$; OR = 6.75). Among uninfected patients, only 13.8% presented a complete response. Therefore, the study suggests that *H. pylori* eradication plays a role in the management of *H. pylori*-infected cITP children and adolescents [23].

Growth retardation

There are conflicting results regarding the role of *H. pylori* in children's growth. Kopacova et al. led a multicenter study corresponding well to the geographic distribution of the Czech population. They evaluated vital signs and body indices in *H. pylori*-positive and *H. pylori*-negative persons. The overall prevalence of *H. pylori* infection was 5.2%. Chronic *H. pylori* infection appeared to be associated with short stature in children. *H. pylori* infection did not influence blood pressure, body weight, or body mass index either in adults or in children and adolescents [24].

In endemic settings, *H. pylori* infection can occur shortly after birth and may be associated with a reduction in childhood growth. Jaganath et al. investigated which factors promote an early age for an initial *H. pylori* infection and evaluated the role of *H. pylori* infection in infancy (6–11 months) versus early childhood (12–23 months) on the height of children in Peru. Before 12 months of age, 77% were infected, with an association between earlier age of infection and lower socioeconomic status, while the likelihood decreased with longer exclusive breast-feeding. *H. pylori* infection

in infancy was not independently associated with growth deficits [25].

Chronic urticaria

The etiology of chronic urticaria (CU) is usually considered idiopathic. In a prospective, randomized study, Akelma et al. included all pediatric and adult patients who presented themselves at the allergy outpatient clinic for CU. Following *H. pylori* eradication, urticaria symptoms recovered in 15 of 18 adults (83.3%) and 10 of 10 (100%) children ($p = .172$). The authors suggest that CU patients with unknown etiology should be routinely screened for *H. pylori*, even if they do not present GI symptoms, and that those with *H. pylori*-positive results receive eradication treatment [26]. In a meta-analysis of 16 studies involving 965 CU and 325 controls, the prevalence of *H. pylori* was higher in CU patients than in controls [27].

Protective Role of *Helicobacter pylori*

Is *Helicobacter pylori* Infection Inversely Associated with Atopy?

An inverse relationship between *H. pylori* infection and allergic diseases has been reported in a range of independent epidemiological studies, but evidence from longitudinal studies is scarce. Amberbir et al. investigated the effects of *H. pylori* infection on the incidence and prevalence of allergic diseases and sensitization in a low-income birth cohort in Ethiopia, where 1006 babies were followed up at age 1, 3, and 5 years. At age 5, *H. pylori* infection was inversely associated with skin sensitization (adjusted OR 0.26, 95% CI: 0.07–0.92, $p = .02$). These findings provide further evidence to suggest that early-life exposure to *H. pylori* may play a protective role in allergy development [28]. Pedulla et al. performed a study on 290 Italian children, aged 26–142 months, who were consecutively referred for atopic dermatitis (AD). A statistically significant higher prevalence of *H. pylori* seropositivity in children without food allergy (FA) versus FA AD-affected children and an inverse association between FA and *H. pylori* immunization were found. The authors hypothesize that specific *H. pylori* IgG production could protect against the development of both FA and atopy in AD-affected children [29].

A meta-analysis of the existing data published in English literature (1950–2014) on the relationship between *H. pylori*, atopy, and allergic diseases was performed. Pooled results of case-control studies showed a significant inverse association of *H. pylori* infection with atopy/

allergic diseases or exclusively with atopy, but not with allergic disease [30]. The prevalence of allergic asthma and other atopic diseases has reached epidemic proportions in large parts of the developed world. Engler et al. [31] showed that oral or i.p. tolerization with *H. pylori* extract prevents airway hyper-responsiveness, bronchoalveolar eosinophilia, pulmonary inflammation, and Th2 cytokine production which are hallmarks of allergen-induced asthma in mice [31]. In a retrospective chart review of all of the children in a cohort in West Virginia who underwent their first upper endoscopy, a reversed association between *H. pylori* and EoE was found [32].

There are arising theories of the *H. pylori* protective effect in diarrheal diseases. The prevalence of *H. pylori* infection in healthy control children was significantly higher than in patients with acute bacterial diarrhea in one study [33].

Obesity

Recent publications concerning both adults and children support the potential role of *H. pylori* in decreasing the likelihood of obesity. In a retrospective study, Vo et al. compared the prevalence of *H. pylori* infection between obese and healthy weight children. Ten percent of the obese children were *H. pylori* positive compared to 21% of the healthy weight children (RR = 2.1, 95% CI = 1.1–4.0). Conversely, 39% of noninfected children, but only 21% of the infected children, were obese (RR = 1.8, 95% CI = 1.1–3.3). A multivariate analysis revealed that individuals infected with *H. pylori* have a 50% reduction in the odds of being obese (adjusted OR = 0.5, 95% CI = 0.2–1.0) [34].

Diagnosis

In a study by Masumi et al., a stool antigen test (SAT) using a monoclonal antibody against native catalase was compared to a real-time PCR. The SAT showed an 89.5% sensitivity and 100% specificity. Only 10 of 151 patients were PCR positive with a negative SAT, but the results of a UBT conducted on these patients were in agreement with the results of the SAT [35].

Kalach et al. assessed the usefulness of gastric biopsy-based quantitative real-time PCR (qPCR). According to the authors, qPCR is a sensitive, reliable, and specific test for the detection of *H. pylori* infection as well as the identification of clarithromycin-resistant strains. This method is quicker and more sensitive than culture and allows the rapid adaptation of the antimicrobial treatment [36].

In another study, the sensitivity and specificity of Narrow Band Imaging (NBI) was investigated in

H. pylori gastritis compared to those of rapid urease test and UBT. The sensitivity of the mucosal changes observed with NBI indicating the presence of *H. pylori* was 92%, while the specificity was only 62% [37].

Treatment of *Helicobacter pylori* Infection

Resistance to Antibiotics

Antibiotic resistance and insufficient compliance to treatment jeopardize the efficacy of eradication therapy. In a study on children in southern Europe, clarithromycin (CH) and metronidazole (MZ) resistance were found in 34.7 and 16.7% of the strains, respectively. When susceptible antimicrobials were used, eradication occurred in 78.7 versus 37.5% when the treatment included a resistant drug [38]. A high resistance was also found among the strains isolated from children in Poland (33.3% were resistant to CH, 44.8% to MZ, whereas 1.9% of strains were resistant simultaneously to CH, MZ, and levofloxacin (LEV) [39]. An unusually high resistance for amoxicillin (12.2%) was found in Israeli children [40]. In a Japanese study between 2000 and 2013, among 1073 *H. pylori*-positive patients of different ages, the rate of clarithromycin resistance was extremely high (57.9%) in those under the age of 31 years [41].

A marked decrease in the eradication rates of *H. pylori* infection with standard triple therapy is currently observed worldwide. In a prospective, randomized study, the efficacy of sequential versus standard triple therapy in the context of CH resistance was compared. The success rates of the respective therapies were similar (54.7% in sequential, 55% in standard therapy) ($p = .98$). Sequential therapy offered only a small advantage over standard triple therapy in the eradication of CH-resistant strains [42]. A “test and treat strategy” may not be feasible in high-prevalence, low-income settings, especially among children, because the recurrence rates following a population-based screen and treat program were high (20% below the age of 10 years) as shown in Bolivia [43]. There are limited data regarding the pattern of *H. pylori* antibiotic resistance and virulence factors in children. This possible relationship was evaluated in children with *H. pylori* gastritis. The *cagE*-positive and *vacA* s1a/m2 genotypes, which are correlated with increased antibiotic resistance, were indeed predominant [44]. The effect of the CYP2C19 genetic polymorphism on the cure rate of children who received proton-pump inhibitor-based triple therapy was studied. The poor metabolizers had a higher cure rate compared to those of the homozygote extensive metabolizers (HomEMs). The higher cure rate

of *H. pylori* infection may warrant a need for an increased dosage for the HomEMs [45].

Probiotics

During the last year, research has continued regarding the addition of probiotics to the standard *H. pylori* eradication therapy. Promising results have been observed in initial studies with numerous probiotic strains. Nevertheless, many questions remain unanswered. In a study, children with *H. pylori* infection were randomized to receive standard triple therapy without or with probiotics. The *H. pylori* eradication rate was 68.9 and 66.6% ($p = .78$), respectively. There was no evidence of the impact of probiotics in terms of *H. pylori* eradication or rate of adverse events [46]. The efficacy of *Saccharomyces boulardii* CNCM I-745 in addition to standard *H. pylori* eradication treatment in children was also studied. Although diarrhea was significantly less in the treatment group and compliance to eradication treatment was 100%, a slight but not significant increase in *H. pylori* eradication was achieved compared to controls [47].

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