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REVIEW – *HELICOBACTER PYLORI* INFECTION IN CHILDREN

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Abstract: *Helicobacter pylori* infection is usually acquired during childhood. Therefore, it is important to study *H. pylori* infection in childhood in regard to the risk factors for its acquisition, the clinical and histopathologic manifestations, the inflammatory and physiologic responses to infection, the genotypic characteristics and pathogenesis of *H. pylori* strains, the efficacy of different treatment regimens and the accuracy of invasive and non-invasive diagnostic methods. This review summarizes relevant publications from April 2020 to March 2021. Despite the decline in infection in most areas, the prevalence in some others continues to be high. A possible association of infection with otitis media with effusion (OME) was again reported but without definite proof of a causal relationship, as it concerns growth and immune thrombocytopenic purpura (ITP). A reverse association of infection with asthma and celiac disease was also found. Resistance rates to antibiotics is extremely high all over the world and it is probably the main cause of eradication failure. Thus, in addition to culture, new invasive and non-invasive techniques are proposed for identification of resistance. Standard triple therapy, ideally prescribed according to the *H. pylori* susceptibility, is still the most used regimen.

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

INTRODUCTION

Helicobacter pylori infection is usually acquired during childhood and, for the most part, persists lifelong if left untreated. Despite the decline in prevalence of *H. pylori* infection in children, it remains very high in some areas. Recent advances in epidemiology are described in the next paragraph. Since inflammation starts early, non-invasive markers might help to identify the degree of inflammation and its impact on gastric and extraintestinal diseases and serve as a guide towards finding the ideal treatment for its eradication. As in adults, several studies on *H. pylori* in childhood are published every year. The objective of this review is to provide an update of the relevant pediatric literature focused on *H. pylori* infection and published from April 2020 to March 2021.

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EPIDEMIOLOGY OF INFECTION

H. pylori infection is a significant burden to the population. Since most infections occur during childhood, it is necessary to know the recent prevalence and risk factors of this infection in children. During the last year, no studies on the prevalence of *H. pylori* infection in children living in Europe and the USA were published, but there are reports from other continents.

In Asia, in a cross-sectional study conducted in China on 1,355 children, aged 6-12 years, the prevalence was 16.7%. Overall, better educated parent(s) played a protective role against the childhood acquisition of *H. pylori* infection. Testing bottle feed temperature using the mouth, cutlery sharing between the feeding person and young children, and snacking posed a low but significant risk for *H. pylori* infection[1]. Another Chinese study showed that low socioeconomic family status, specific food habits and parents suffering from gastropathy were independent risk factors for *H. pylori* infection in children[2].

The changes in seroprevalence of *H. pylori* infection over 20 years in Korea, from newborns to the elderly, were studied in three cross-sectional analyses conducted concurrently. Anti-CagA IgG seropositivities in children and young adults aged 10-29 years decreased from 1994 (60.0% and 85.0%) to 2015 (12.5% and 28.9%), respectively[3]. A low prevalence of *H. pylori* infection was also found (5.8%) among 2,399 Japanese adolescents, aged 13-15 years, tested by serology[4].

A high prevalence of *H. pylori* infection among asymptomatic healthy populations continued to be observed in South Asia, particularly in children and adolescents. An analysis of 19 studies showed a pooled prevalence of 56.5%, ranging from 10.3 to 91.7%. In subgroup analysis by country, the highest prevalence rate was reported from Bangladesh (86.3%), whereas the lowest prevalence was from Sri Lanka (10.3%). Prevalence among children and adolescents was 65.3%, greater than in adults, which was 56.9%. The prevalence rate showed a decreasing trend upon a comparison of studies conducted before and after 2000[5].

In Africa, a high prevalence (65.7%) of *H. pylori* infection among young Ethiopian school children was found[6], where the coinfection of children with intestinal parasites and *H. pylori* was 23%[7].

In the Middle East, a study on 436 Iranian children showed positivity of a multi-monoclonal stool antigen test (SAT) for *H. pylori* in 25% of the neonates, 22% of children aged 6 months to 3 years, 19.5% of the 10-year-olds, and 29.2% of the 15-year-old children[8]. A relatively low prevalence (14.6%) was found in Jordanian children, where urban living and a family history of previous *H. pylori* infection were risk factors for the acquisition of infection[9]. However, the histology-based prevalence rate of *H. pylori* was high (54%) among symptomatic children in the same country[10]. Also, in a hospital-based Turkish study, 47.2% of symptomatic children who underwent endoscopy (EGD) were positive for *H. pylori*[11]. On the contrary, in a similar study on symptomatic Lebanese children, the prevalence of *H. pylori* infection was only 16.5%[12].

A high prevalence of *H. pylori* was detected (44%) among 80 pediatric patients with severe obesity and metabolic comorbidities who underwent endoscopy prior to bariatric surgery, many of whom required treatment. These findings support incorporating an EGD into the preoperative evaluation of this patient population[13].

Recurrence of the infection after successful eradication is another burden related to *H. pylori*. In a prospective, nested case-control study the recurrence rate of *H. pylori* infection after successful eradication was 18.8% in Chinese children, closely correlated to socioeconomic factors. The IFNGR1 gene polymorphism may be an independent risk factor for *H. pylori* infection recurrence[14].

PATHOPHYSIOLOGY OF DISEASE IN CHILDREN

H. pylori is acquired largely in early childhood, but its association with symptoms and indirect biomarkers of gastric damage in apparently healthy children remains controversial. Chilean children aged 4-5 years with persistent *H. pylori* infection, as well as controls, were followed up for at least 3 years. Persistent infection was associated with higher levels of pepsinogen II, but no difference in other inflammatory biomarkers (cytokines and tissue inhibitor metalloproteinase1) or expression of cancer-related genes KLK1, BTG3, and SLC5A8 was observed[15].

The number of D-cells producing somatostatin, the main paracrine inhibitor of acid secretion and gastrointestinal (GI) motility, was lower in the gastric body of Korean children with current *H. pylori* infection, but further studies concerning peptide-secreting cells with a control group would provide information on the pathogenic pathways of upper GI disorders[16]. Indonesian symptomatic children with *H. pylori* gastritis had higher IL-8 production. There was also an increased risk of developing *H. pylori* infection in heterozygous -251 AT and +781 CT[17].

HISTOLOGY

Foveolar hyperplasia (FH) was significantly associated with the presence of *H. pylori* ($p \leq 0.001$) in Romanian children, being an important histologic characteristic of gastropathy, and may be considered for reporting when evaluating pediatric gastric biopsies[18]. In another study[19] from the same group, the expression of secretory mucins in infected children was investigated. *H. pylori* infection may not play a role in children with autoimmune atrophic gastritis (AIG) as found in a recent Turkish study, where none of the children with AIG-was infected[20].

Endoscopic nodularity (43%) and active moderate to severe gastritis by histology (59%) were positive predictors for the presence of *H. pylori* ($p \leq 0.05$) in Jordanian children[10]. In a similar study on 651 Lebanese children, nodular gastritis was higher in infected patients compared to non-infected (41.5% *vs.* 7.9%, respectively; $p \leq 0.05$). However, histological gastritis was mostly of mild and moderate degree, and again, much higher than in non-infected patients (mild: 53.8% *vs.* 14%; moderate: 27.4% *vs.* 2.4%, respectively)[12]. A higher prevalence of antral nodularity (77.8%) was reported in a multicenter European study of the EuroPedHP registry, where gastric or duodenal ulcers and erosions were found to be 5.1% and 12.8%, respectively[21].

H. PYLORI AND GUT MICROBIOTA

Considering that the antimicrobial agents used to eradicate *H. pylori* can affect the intestinal microbiota, a few studies during the last year aimed to address this topic. In a Japanese study the safety of *H. pylori* eradication with vonoprazan containing triple therapy was evaluated by examining gut microbiota changes in adolescents 3 months post-therapy. There was no change in the relative abundance at the genus level. The alpha-diversity was lost immediately after eradication therapy; however, it recovered in 8 to 12 weeks afterwards, at the time of the control, and had been restored to pretreatment conditions[22]. The long-term changes in the gut microbiota after a 14-day bismuth quadruple therapy in Chinese children were investigated. At week 2, alpha and beta diversity were reduced, some changes persisted at week 6, but diversity was restored at week 52[23]. In a study on Taiwanese children, the authors concluded that ingestion of yogurt containing probiotics four weeks before and at the time of *H. pylori* eradication can restore the decrease in *Faecalibacterium prausnitzii* in *H. pylori*-infected children[24].

CLINICAL MANIFESTATIONS OF *H. PYLORI*

Gastrointestinal Manifestations

In a Lebanese study, among 651 children who underwent EGD, the prevalence of *H. pylori* infection was 16.5%. Epigastric pain was more frequent in those with *H. pylori* (61.3% *vs.* 14.6% in non-infected patients; $p \leq 0.05$)[12]. The role of *H. pylori* in celiac disease (CD) was investigated in two studies from Turkey. The rate of *H. pylori* infection in pediatric patients was significantly lower in the CD group compared to controls (26.3% *vs.* 50.1%, $p \leq 0.01$)[25]. An even lower prevalence of *H. pylori* infection among children with concurrent CD and type 1 diabetes mellitus was found compared to children with CD and to controls (20.6% *vs.* 32.1% *vs.* 49.1%, respectively, $p \leq 0.01$)[26].

Extraintestinal Manifestations

A number of publications regarding extraintestinal manifestations in *H. pylori* infected children appeared last year. In a Japanese study[4] *H. pylori* antibody-positive status in adolescents was associated with anemia in both sexes. There was no association between *H. pylori* antibody status, BMI percentile, and birth delivery method. In a retrospective Bulgarian cohort study[27] a high prevalence of *H. pylori* infection was found in anemic children (76.6% *vs.* 21.3% of the non-anemic patients, $p \leq 0.0001$) and those with weight loss (82.2% *vs.* 17.8% of the control children, $p \leq 0.0001$). Relative risk of anemia, weight loss and both conditions was 3.6, 4.6 and 5.7, respectively, in the children with *H. pylori* infection.

The question whether *H. pylori* infection may be a potential risk factor for delayed childhood growth has not yet been answered. In a meta-analysis[28] of 15 observational studies comprising 4,199 subjects, a higher frequency of delayed growth was observed in *H. pylori* positive children compared to *H. pylori* negative children (OR: 1.51), particularly for linear growth (OR: 1.63), only in areas with a *H. pylori* prevalence of ≤30% (OR: 1.71, 95%CI: 1.312.23) or >30% but not >50% (OR: 1.43, 95%CI: 1.101.86). The association between infection and growth was only statistically significant in the cross sectional (OR: 1.43, 95%CI: 1.181.73) and case control (OR: 1.81, 95%CI: 1.232.67) studies.

H. pylori does not seem to be associated with childhood overweight/obesity as shown in an Israeli study[29].

Studies regarding the impact of *H. pylori* on immune thrombocytopenic purpura (ITP) were published last year. In an Egyptian study the prevalence of *H. pylori* in children with chronic ITP was 63%. Eradication therapy was effective in increasing the platelet count in *H. pylori* positive chronic ITP patients[30]. On the contrary, in a Turkish study[31] no statistically significant difference was found between *H. pylori* positive and negative patients in terms of neutrophil/lymphocyte ratio (NLR) and mean platelet volume (MPV) ($p \geq 0.05$), nor between pre- and post-treatment values of NLR ratio and MPV. Similarly, in a prospective case–control Romanian study, no significant difference was found between either of the study groups and the control group in terms of platelet number [number/μL, mean±SD (median) (*H. pylori* 311,032 ± 81,816 (288,000) *vs.* controls 301,103 ± 71,209 (294,000)], mean platelet volume, NLR and PLR ($p \geq 0.05$)[32].

In a systematic review and meta-analysis[33], a significant association between *H. pylori* infection and otitis media with effusion (OME) was detected for both adenoid samples (OR: 2.75, $p=0.002$) and middle ear fluid samples (OR: 4.45, $p=0.00001$) from the case group of children, with a stronger correlation in African and Asian populations. In another systematic review[34], the detection rate of *H. pylori* in the middle ear, tonsil and gastric juice in children with OME was higher than that in children without OME. *H. pylori* was detected in the middle ear effusion of children with OME in 9 studies, using PCR, rapid urease test, culture and other methods. Further well-designed studies regarding the Caucasian population are strongly recommended in the future.

Controversy still exists regarding an association of *H. pylori* infection and asthma in children, with the following two recent studies supporting a negative association. *H. pylori* IgG seropositivity was 25% and 40% among asthmatic Israeli children and controls, respectively ($p=0.03$). *H. pylori* CagA IgG seropositivity was associated with a reduced risk of asthma (OR=0.33) but was not observed for those with a CagA negative serology (OR: 0.70)[35]. The above findings were confirmed by a recent meta-analysis[36] of 18 studies enrolling 17,196 children. Overall, there was a significant negative association between *H. pylori* and the risk of childhood asthma. Again, the observed inverse association persisted for CagA (+) strains of *H. pylori* but not for CagA (-) strains.

In a Chinese study[37] on children with *H. pylori* infection-related gastritis, the levels of 25-OH vitamin D3 in the non-eradicated group were lower, and the IL-1βlevels were higher than those in the eradicated and the control groups. The possible role of severe dental caries as a reservoir for *H. pylori* dissemination to other sites of the body was investigated by PCR in 48 children aged 4 to 7 years. *H. pylori* was detected in the dentine sample in 30% of children with severe caries lesions[38].

DIAGNOSIS

A variety of studies addressed diagnostic testing for *H. pylori* infection and rapid detection of drug resistance in children in the last year. A Chinese study[39] evaluated the clinical significance of gastric mucosal gene chip technology in the rapid diagnosis of *H. pylori* infection and detection of drug resistance in children. The sensitivity, specificity, and accuracy of the gene chip technology for diagnosing *H. pylori* infection were 96.1, 85.0, and 93.6%, respectively. In Japan, a new method for detecting clarithromycin (CLA)-resistant *H. pylori* using the remnant solution from *H. pylori* SAT was developed. This non-invasive method may enable simultaneous identification of the presence of the *H. pylori* gene and CLA resistance mutations[40]. Another Japanese study[41] on the accuracy of the serum antibody test for *H. pylori* infection showed that the optimal cutoff for children was 5.4 U/mL, with a specificity of 99.5% and a sensitivity of 93.3%. Different primer sets were used to detect the prevalence of the *H. pylori bab*A2 gene in *H. pylori*-positive pediatric samples using the 832 bp, 139 bp, and 271 bp PCR primer sets. The authors concluded that *bab*A2 detection methods should be carefully selected[42].

Biomarkers

Persistent infection in apparently healthy school-aged Chilean children was associated with higher levels of pepsinogen II suggesting early gastric involvement, while no difference was observed in other biomarkers or gene expression profiles[15]. A study[43] using ^{1}H NMR-based metabolomics demonstrated that the disturbances of metabolism in energy, amino acids, lipids and microbiota could play an important role in the pathogenesis of GI and extra GI diseases caused by *H. pylori* infection. Trimethylamine N-oxide and lactate might serve as potential serum biomarkers for evaluating the efficacy of *H. pylori* eradication therapies. A Polish study[44] concluded that Fourier transform infrared spectroscopy and artificial neural networks may help to confirm *H. pylori*-driven growth disorders in children. Regarding fecal biomarkers, Bangladeshi children infected with *H. pylori* had a significant positive association with fecal alpha-1 antitrypsin concentrations. However, *H. pylori* infection was not associated with the indicators of childhood growth[45].

The ENIGMA study[46] in Chile (including two areas with different gastric cancer incidence and mortality, lower and higher rates), showed that *H. pylori* seroprevalence and antibodies against CagA and VacA were similar in both sites. Pepsinogen levels suggestive of gastric atrophy were significantly more common and occurred at earlier ages in the higher risk area, while dietary factors could partly explain higher rates of atrophy and gastric cancer in this area.

TREATMENT

In a multicenter European study of the EuroPedHP registry, among 1,333 recruited patients with a median age of 12.6 years, 1,168 (87.6%) were therapy naive and 165 (12.4%) had a failed treatment. Primary resistance to CLA and metronidazole (MET) occurred in 25% and 21%, respectively, and increased after failed therapy. Bacterial strains from naive patients were fully susceptible in 60.5%, but only in 27.4% after failed treatment. Primary CLA resistance was higher in Southern and Eastern Europe (adjusted odds ratio [ORadj] ¼ 3.442.22-5.32, $p \leq 0.001$, and 2.62, $p \leq 0.001$, respectively) compared to Northern/Western Europe. Children born outside Europe showed higher primary MET resistance (ORadj ¼ 3.81, $p \leq 0.001$). Primary resistance to CLA and MET is markedly dependent on regions of birth and residence. Treatment success in naive children reached only 79.8% with a 7-to-14-day triple therapy, in spite of being tailored to antibiotic susceptibility[21].

A high prevalence of antibiotic resistance was observed for CLA and MET, at frequencies of 54.5% and 31.8%, respectively, in Polish children, while amoxicillin (AMO)-resistant strains were not observed[47]. In another Polish study[48], resistance to CLA was detected in 31%, while resistance to both MET and CLA was detected in 35% of the strains. The authors noted that, in children, a higher frequency of *H. pylori* multi-resistant strains was observed compared to the previous study in the same area.

An extremely high rate of antibiotic resistant strains was isolated from pediatric patients in Southwest China. Primary resistance rates were 45.3% for CLA, 73.6% for MET, 15.1% for levofloxacin, and 60.4% for rifampicin, while no isolate was found to be resistant to AMO, tetracycline, and furazolidone. Secondary resistance rates were much higher compared to primary[49].

A high resistance rate was also found in Japanese children. The overall primary CLA resistance rate was 71.1%. This rate for the 2013-2018 period was significantly higher than for the 2007-2012 period (84.6% *vs.* 52.6%, $p \leq 0.05$). The eradication rate based on the antimicrobial susceptibility test was 97.7%[50]. In Japan a comparison of the effectiveness and side effects between vonoprazan-based dual therapy with AMO (VA-dual) for *H. pylori* infection in a treatment-naive cohort of junior high school students showed that VA-dual therapy was not inferior to VAC-triple therapy[51].

A novel sequential treatment regimen was used in 75 Turkish children ≥8 years of age with *H. pylori* gastritis. Eradication rate was achieved in 92% of the cases[52].

Regarding the impact of GI adverse reactions on the success rate of *H. pylori* eradication therapy, a multicenter prospective cohort study on high school students showed that stool softening was related to the eradication failure[53].

The two critical concerns during *H. pylori* eradication are the successful eradication and the recurrence rate. In a systematic review and meta-analysis[54], it was shown that whole family-based *H. pylori* treatment can partially increase the eradication rate and reduce the recurrence rate over the single-infected patient treatment approach.

In a systematic review[55] of randomized controlled trials on treatment regimens for *H. pylori* infection in children, standard triple therapy is still the most highly recommended and the most commonly used regimen and its eradication rates vary according to the *H. pylori* susceptibility profiles in different world regions. The addition of probiotics to therapeutic schemes shows discrepant results in eradication rate.

The effectiveness of an *H. pylori* test-and-treat strategy for high school students was evaluated in Japan for the prevention of gastric cancer later in life. A 7-day triple vonoprazan-based therapy was more efficient than a rabeprazole-based triple therapy (83.8% *vs.* 45.9%). The authors concluded that their results support the feasibility of the *H. pylori* test-and-treat strategy as a safe approach for this goal in junior high school students[56]. However, according to the recently updated JSPGHAN guidelines, an *H. pylori* culture from gastric biopsies is recommended. The guidelines also recommend against a "test-and-treat" strategy for *H. pylori* infection in asymptomatic children to protect against the development of gastric cancer because there has been no evidence supporting this strategy[57].

CONCLUSIONS

Recent publications on *H. pylori* infection in children highlight its possible association with extraintestinal manifestations, the persistent high prevalence in some areas despite the overall decline, and the high prevalence of antibiotic resistance. A variety of studies addressed diagnostic testing for *H. pylori* infection and rapid detection of drug resistance in children, as well as biomarkers. Standard triple therapy is still the most widely used regimen and its eradication rates vary according to the *H. pylori* susceptibility profiles in the different world regions.

Conflict of interest

The authors have no disclosures of interest.

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