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CURRENT CONSIDERATIONS ON *HELICOBACTER PYLORI* INFECTION IN CHILDREN: A COMPREHENSIVE REVIEW OF THE AVAILABLE EVIDENCE

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Abstract – Infection with *Helicobacter pylori* (*H. pylori*) is usually acquired in childhood. The prevalence of *H. pylori* is largely related to socioeconomic status and living conditions, especially those characterized by overcrowding and poor hygiene, with a high rate of intrafamilial transmission. Despite the global decline of *H. pylori* infection in most areas, prevalence remains high in some other areas. In children, severe disease associated with *H. pylori* infection is rare. Standard triple therapy, ideally prescribed according to susceptibility to *H. pylori*, is still the most commonly used form of therapy. The antibiotic resistance rate is high and probably the main cause of eradication failure. Several other factors are also being investigated for their influence on eradication rates. This review summarizes relevant publications on *H. pylori* infection in children from April 2023 to March 2024.

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

Abbreviations: UBT: Urea Breath test; PCR: Polymerase Chain Reaction; VacA: Vacuolating cytotoxin A; CagA: Cytotoxin-associated antigen A; IBD: Inflammatory bowel disease; EoE: Eosinophilic Esophagitis; IL-7: Interleukin 7; INF-γ: Interferon γ; MMPs: Matrix Metalloproteinases; MMP-2 matrix metalloproteinase- 2; MMP-9: matrix metalloproteinase-9; TIMP-2: Tissue Inhibitors of Metalloproteinases-2; MGIs: Multiple Genotypes; GWAS: Genome-wide Association Studies; SNVS: Single Nucleotide Variants; DNA: Deoxyribonucleic acid; NG: Nodular Gastritis; MetS: Metabolic Syndrome; BMI: Body Mass Index; T1DM: Type 1 Diabetes Mellitus; DMFT: Decayed, Missing, Filled Teeth; ICDAS: International Caries Detection and Assessment System; OME: Otitis media effusion; ITP: Immune Thrombocytopenic Purpura; UC: Ulcerative Colitis; CD: Crohn's disease; IBDU: inflammatory bowel disease unclassified; EGD: Esophagogastroduodenoscopy; NZ: New Zealand; USA: Unites States of America; AMO: Amoxicillin; HpSA: *H. pylori* stool antigen; NGS: next-generation sequencing; CLA: Clarithromycin; MET: Metronidazole; LEV: Levofloxacin; TET: Tetracycline; STT: standard triple therapy; AMP: antimicrobial peptide; VPZ: Vonoprazan; PPIS: Proton Pump Inhibitors; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition.

BACKGROUND

Infection with *Helicobacter pylori* (*H. pylori*) is usually acquired in childhood. Despite the declining incidence of *H. pylori* infection worldwide, there is ongoing research interest, and several studies

on *H. pylori* infections are published each year. The aim of this review is to summarize and update the most relevant literature on *H. pylori* infection in children. A broad literature search was performed using PubMed for articles published from April 2023 to March 2024. The search was restricted to human studies and English papers using the following terms: *Helicobacter pylori, H. pylori*, and children.

EPIDEMIOLOGY AND TRANSMISSION

The worldwide prevalence of *H. pylori* infection has declined in adults over the last 3 decades but is estimated to be around 35% in children and adolescents. Prevalence appears to be lower in the European and Western Pacific regions and higher in the African, Eastern Mediterranean, and Southeast Asian regions[1].

In the European region, the prevalence of *H. pylori* infection was investigated in 421 Slovenian children and adolescents using monoclonal stool antigens. The infection rate was (10.9%) and was dependent on regional rather than socioeconomic factors[2].

In a 20-year longitudinal study from Taiwan, blood samples were analyzed for anti-*H. pylori* IgG by enzyme-linked immunosorbent assay. A remarkable decrease in the seroprevalence of *H. pylori* was found from 9.2% in 1998, 7.8% in 2005, 6.2% in 2010, and 4.7% in 2018. Low household income was the main risk factor for pediatric *H. pylori* seropositivity[3].

In a national study from China, *H. pylori* infection was tested using a ^{13}C-UBT Kit (UREA – ^{13}C breath test Heliforce kits, Beijing Richen-Force Science & Technology, Beijing, China). The sensitivity and specificity of the assay were 95.52% and 94.74%, respectively. The family-based *H. pylori* infection rate was much higher than the individual-based rate. This study examined 10,735 families (31,098 individuals) from mainland China and the associated factors and transmission patterns. The average familial infection rate was 71.21%. The average individual *H. pylori* infection rate was 40.66%, and 20.55% in children. 71.13% of families had 1-7 infected members, and in 19.70% all members were infected. Intrafamilial transmission correlates with the frequency of infection, suggesting an important source of disease spread[4].

In another study from southern China[5], *H. pylori* was tested using a uniform kit ^{13}C-UBT. The prevalence of *H. pylori* infection on an individual basis was 46.72% and in children 24.89%. Risk factors for *H. pylori* transmission include living in a household with five or more people and having a parent who is infected, which increases the risk of the child becoming infected. A high household income and drinking boiled tap water were protective factors for *H. pylori* infection[5].

H. pylori seropositivity was present in mothers with dirt under uncut nails, in mothers who did not wash their hands before handling food and after using the toilet, and in children with dirt under uncut nails. This study from India[6] highlights the role of mother-to-child transmission as one of the routes of transmission of *H. pylori*, with poor hand hygiene appearing to play an important role.

In a study from Vietnam[7], infection status was assessed using stool antigen tests, which showed similar results. A very high prevalence of *H. pylori* infection (87.7%) was found in children and adolescents. *H. pylori* infection was associated with poor hygiene practices, crowded living conditions, larger family size, and younger age, highlighting the importance of the fecal-oral route and crowded living conditions for the spread of *H. pylori*[7].

The prevalence of *H. pylori* was estimated in a region of Mexico using real-time PCR in dental plaque samples from 36 families. The main finding of this study was the presence of vacA s1/m1/cagA genotypes prevalent in the mother, suggesting possible transmission between mother and child in the first years of life[8].

In the Mild East region, in a study from Israel, *H. pylori* infection was incidentally detected during gastroscopy to investigate other gastrointestinal diseases, such as Inflammatory Bowel Disease (IBD), celiac disease, and Eosinophilic Esofagitis (EoE). *H. pylori* gastritis was diagnosed in 21.5% of patients, based on a histopathology report and/or a positive culture for *H. pylori*[9].

In Africa, the overall prevalence of *H. pylori* infection was 8.4% in a cross-sectional study from Sudan[10], using *H. pylori* antibody blood rapid test or the qualitative detection of IgM and IgG antibodies. Parental age, education, occupation, and body mass index were not associated with *H. pylori* infection. Female adolescents had a higher risk of becoming infected with *H. pylori*[10]. Finally, in a study from Morocco, 45% of patients who underwent gastroscopy were found to have

an *H. pylori* infection. Detection of *H. pylori* infection was confirmed by Giemsa stain. Infection rates increased with increasing age of the children, while no significant association was found between *H. pylori* infection and symptoms[11].

It is clear that the transmission of *H. pylori* from mother to child is the most important intrafamilial transmission route. A study from China aimed to detect intracellular *H. pylori* in vaginal and fecal yeasts and showed that *H. pylori* can be harbored in the yeasts that colonize the vagina and that the fecal yeasts of newborns are genetically related to the vaginal yeasts of their mothers. Thus, vaginal yeast is a potential reservoir for *H. pylori* and plays an important role in transmission from mother to newborn[12].

PATHOPHYSIOLOGY OF GASTRIC DISEASE AND IMMUNITY

H. pylori is an important causative factor in chronic gastritis, peptic ulcers, lymphomas associated with the gastric mucosal and lymphoid tissue, and gastric cancer. A recent Korean study[13] attempted to investigate the role of CD8+T cells as host immune factors in pediatric patients with *H. pylori* gastritis. They found that the frequency of CD8+ and T-bet + T cells was higher in the *H. pylori*-positive group than in the control group. At the same time, the frequency of IL-7 RαlowCX3CR1 + CD8 + and T-bet + INF-γ + CD8+T cells between surface staining and intracellular staining was not significantly different between the control group and the *H. pylori*-positive group. CD8+T and Th1 cells secreting IFN-γ may play an important role in gastric mucosal immunity in children with *H. pylori* infection[13].

H. pylori gastritis is strongly associated with the upregulation of the expression of various matrix metalloproteinases (MMPs) in the gastric mucosa. Helmin-Basa et al[14] attempted to investigate the role of MMP-2 and MMP-9 and their inhibitors in a total of 84 children. Children with *H. pylori*-induced gastritis showed the following: (1) increased MMP-2 and TIMP-2 plasma levels, (2) increased intracellular expression of MMP-2 in circulating lymphocytes and neutrophils, (3) low frequencies of circulating TIMP-1+ and TIMP-2+ leukocytes, and (4) high expression of mRNA for MMP-9 together with low expression of mRNA for MMP-2 in the gastric mucosa. They showed that MMPs make an important contribution to gastric remodeling in children with *H. pylori*-induced gastritis. Unsuccessful *H. pylori* eradication is associated with an increase of MMP-9 in plasma, circulating lymphocytes, and gastric mucosa[14].

The frequency and characteristics of mixed *H. pylori* infections (multiple genotypes; MGIs) were investigated in 155 Bulgarian symptomatic patients (21 children). MGIs were common (36.1%), including infections with two strains (34.8%) and with three strains (1.3%). Eighteen multiple allele combinations were detected, of which the most common subtypes (17.4%) were vacA s1as2 and vacA s1cs2. The prevalence of MGIs (51.7%) was twofold higher from 2020 to 2022 than from 2015 to 2019 (26.3%). The MGIs rates corresponded to the high seroprevalence of the infection (72.4% in 2011) in Bulgaria. Detection of mixed *H. pylori* infections (with multiple genotypes) may play a role in strain adaptation to the gastric mucosa and susceptibility testing, leading to low eradication rates that may result in the recurrence of the infection[15].

Genome-wide association studies (GWAS) of susceptibility to *H. pylori* infection have been conducted to identify genetic factors associated with *H. pylori* serostatus. In a cross-sectional study of 1,161 children from an urban center in Brazil, 22 single nucleotide variants (SNVs) were found to be suggestively (p<10-5) associated with *H. pylori* seropositivity. The most suggestive SNV was rs77955022 (p=4.83e-07), which is located in an intronic region of EXOC3 at 5p15.33. The second most suggestive associated SNV was rs10914996 (p=8.97e-07), located in an intergenic region at 1p34.3[16].

Gastric cancer is a rare disease in pediatric patients, but it is still possible. Several biomarkers have been identified as important contributors to the long-lasting process of carcinogenesis, such as pepsinogens, gastrin 17, parameters of lipid, glucose, and iron metabolism, immunity actors, aberrant bacterial DNA methylation, independent of the presence of premalignant lesions, which have also been detected in a subset of *H. pylori*-infected children, especially those carrying extremely virulent strains[17].

HISTOLOGY

Nodular gastritis (NG) is a frequently observed finding of *H. pylori* infection in pediatric patients. A study from China[18] investigated the microbiota and histological features of the gastric mucosa

in children with *H. pylori* colonized NG. The NG group had significantly higher inflammation and activity scores on histologic assessment than the non-NG group[18].

In a Moroccan study[11], nodular gastritis was found in 64.61% of infected patients, and histologic examination revealed chronic gastritis, mainly in the infected group (98%). With regards to the severity of gastritis, chronic gastritis was mild in 83% of cases, moderate in 11%, and severe in 4%. Gastric atrophy was higher in the infected group (53%). This association requires surveillance of the mucosa in children with atrophic gastritis to identify factors that may contribute to gastric cancer[11].

CLINICAL MANIFESTATIONS

Manifestations from the Digestive Tract

H. pylori remains a major cause of gastroduodenal disease. A prospective multicenter study from Vietnam[19] investigated the presence of peptic ulcers in children infected with *H. pylori*. *H. pylori* infection was positive in 80%, and the most common mucosal abnormalities were gastric nodularity (60.7%), followed by ulcers (19.4%). There was a significant association between nodularity, PUD, and *H. pylori* infection. Ulcers were more common in boys, increased with age, and 25% were associated with anemia. CagA+ strains were detected more frequently in children with ulcers[19].

The clinical spectrum of *H. pylori* infection can range from an asymptomatic form to non-specific dyspepsia and ulcerations with acute bleeding. Sometimes unusual severe complications may occur, as described in some case reports, such as diverticular protrusion between the stomach and pancreas due to gastric ulcer[20], obstructive jaundice due to duodenal ulcer[21] and B-cell lymphoma localized in the gastric antrum[22], all due to *H. pylori* infection.

Extra-Digestive Manifestations

An association between *H. pylori* infection and metabolic syndrome (MetS) and its components has been described in adults. *H. pylori* infection in children with an increased BMI without diabetes mellitus was associated with an increased prevalence of the genus Prevotella, which was also found in patients with obesity, nonalcoholic steatohepatitis, and hyperlipidemia, suggesting that children infected with *H. pylori* may be at risk for MetS[23].

A systematic meta-analysis [12 articles (2,797 participants)] investigated the association between *H. pylori* infection and type 1 diabetes mellitus (T1DM). *H. pylori* infection was significantly associated with a longer duration of T1DM and higher hemoglobin A1c levels but not with age at T1DM diagnosis. Pediatric patients with long-standing T1DM and poor glycemic control should possibly be considered for *H. pylori* screening[24].

H. pylori can either be transiently present in the oral cavity or pose a threat to oral tissues in some situations. A cross-sectional study from India[25] investigated the presence of *H. pylori* in deep carious lesions in children and its association with dental status and caries severity using the Decayed, Missing, Filled Teeth (DMFT) and International Caries Detection and Assessment System (ICDAS) II indices. *H. pylori* was detected in 70% of children with severe caries. The mean DMFT score was significantly higher in the group with *H. pylori* and in the group with ICDAS II code 6 than in the group with ICDAS II code 5 caries. Cavitated carious lesions may serve as a reservoir for *H. pylori*, perhaps replacing the plaque ecosystem in favor of *Streptococcus mutans*, the main bacterial source in dental caries[25].

In a study from Egypt[26], 186 patients with otitis media effusion (OME), nasal polyposis or recurrent adenotonsillitis were examined. The frequency of *H. pylori* in the effusion fluid was 28.6% in patients with OME and adenoid hyperplasia and 17.4% in those with OME. No association was found between *H. pylori* and the occurrence of OME, nasal polyposis or recurrent adenotonsillitis[26].

A comprehensive review attempted to determine the impact of *H. pylori* infection and its eradication on platelet count and recovery in pediatric ITP. The low prevalence of *H. pylori* in children with ITP suggests that the infection plays a minor role in the pathogenesis of this disease in children and how treatment of this infection affects platelet counts in the long term[27].

A systematic review and meta-analysis attempted to evaluate the association between *H. pylori* infection and inflammatory bowel disease (IBD) in children. Six studies for a total of 2,236 patients

were investigated. *H. pylori* infection rates were higher in children with ulcerative colitis (UC) and Crohn's disease (CD) than in children with IBD-unclassified (IBDU). Overall, no association was found between *H. pylori* infection and the incidence of IBD in children[28].

Observational studies have reported that *H. pylori* infection during pregnancy is associated with neonatal outcomes. A two-sample Mendelian randomization (MR) study was conducted. Genetically predicted anti-*H. pylori* IgG levels were significantly associated with an increased risk of pre-eclampsia, eclampsia, and premature membrane rupture. The results confirm the epidemiologic evidence for the adverse effects of *H. pylori* in pregnancy[29].

A study from China[30] investigated the 25(OH)D level in children of different ages and with different degrees of *H. pylori* infection and other immunological characteristics. Ninety-four children after Esophagogastroduodenoscopy (EGD) were divided into an *H. pylori*-positive group without peptic ulcers (Group A), an *H. pylori*-positive group with peptic ulcers (Group B) and an *H. pylori*-negative control group (Group C). The 25(OH)D level of the *H. pylori*-positive groups was significantly lower than that of the *H. pylori*-negative group. The 25(OH)D level of Group B was lower than that of Group A and significantly lower than that of Group C. The 25(OH)D level was negatively correlated with *HP* colonization and the degree of inflammation. The percentages of lymphocyte subsets and immunoglobulin levels among Groups A, B, and C did not differ significantly[30].

DIAGNOSIS

According to a recommendation of the Hong Kong Consensus Panel on Screening, Diagnosis, and Treatment of *H. pylori* infections, non-invasive routine testing is not usually recommended in asymptomatic children. When a child presents with gastrointestinal symptoms, the clinical examination should focus on identifying the cause of the child's symptoms, not just confirming the presence of *H. pylori*. However, children with peptic ulcers should be tested for *H. pylori* and treated (if positive)[31].

A study from the South Island of New Zealand[32] (NZ) retrospectively analyzed pediatric *H. pylori* infections and investigated whether diagnostic and treatment strategies were in line with national and international guidelines. Overall, 58% of children were diagnosed by stool antigen testing, 32% by serum testing, and only 10% adhered to international guidelines by being confirmed by gastroscopy and biopsy. Only 25% of children received eradication therapy, and 66% were retested to determine the success of eradication, with 82% testing negative and 18% remaining positive. Of the 75% for whom eradication status was unknown, 28% had a repeat test, with 73% testing negative and 27% testing positive, suggesting that a significant proportion had received eradication therapy without adhering to international guidelines[32].

A study from the USA[33] comparing infection between indigenous and non-indigenous patients found that 39.1% of all immigrant patients had endoscopically proven *HP* infection compared to only 12.7% of indigenous US patients. The severity of *H. pylori* infection was worse in immigrant patients. Empiric high-dose amoxicillin (AMO) triple therapy was equally effective in reducing symptoms in gastritis and PUD patients. Empirical therapy is still very effective in relieving symptoms. These results suggest that the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition guidelines may not be adequate for non-native pediatric patients. Changes in approach may be due to recent changes in the practice of adult gastroenterology[33].

A study evaluated the PyloPlus UBT assay, a new breath test for the detection of *H. pylori* in the pediatric patient population. The PyloPlus UBT assay's performance is equivalent to that of the existing FDA-approved BreathTek UBT system. The added advantages of the PyloPlus UBT system are the lack of a calculation factor required for results and the two-way valve system that facilitates sample collection[34].

Gastric juice is a unique body fluid that contains all the components secreted by the stomach. Therefore, the analysis of molecular markers and protein components in gastric juice further improves the detection rates of gastroduodenal diseases, such as *H. pylori* infection. Gastric juice and serum samples were obtained from 53 children aged <15 years who underwent gastric endoscopy. This study identified three autoantigens – gastric lipase, pepsin A, and pepsin C – which are enzymes that are normally secreted under acidic conditions[35].

A study from Vietnam[36] evaluated the diagnostic value of a monoclonal immunoassay stool antigen (HpSA) test for *H. pylori* infection and eradication results. The HpSA test has high sensitivity (87%) and optimal specificity (100%) in Vietnamese children and is reliable for the identification of *H. pylori* infection in epidemiologic studies and the evaluation of eradication outcomes[36].

RESISTANCE TO ANTIBIOTICS

Pediatric gastroenterology guidelines strongly recommend determining the antimicrobial susceptibility of *H. pylori* before prescribing treatment. One of the most extensive pediatric studies in the US on the efficacy of an NGS-based technique[37] to characterize microbial resistance rates in *H. pylori* from gastric biopsies showed that the overall eradication rate was 73.6%, with only quadruple therapies reaching the recommended target for effective therapies of 90%. The highest resistance rate was found for clarithromycin (CLA) (23.5%) and metronidazole (MET) (21.9%). The fluoroquinolone (LEV) resistance rate was 8.4%, compared with the pooled prevalence of 37% in the US. Resistance to rifabutin (9, 3.6%), amoxicillin (AMO) (6, 2.4%), and tetracycline (TET) (1, <1%) was also low[38].

The rates of primary antibiotic resistance in *H. pylori* among East Asian children and adolescents have been assessed in a systematic review and meta-analysis from China, which included 15 observational studies/4831 *H. pylori* patients. The rates of primary resistance were 51% for metronidazole, 37% for clarithromycin, 19% for levofloxacin, and less than 3% each for amoxicillin, tetracycline, and furazolidone. Resistance rates for metronidazole, clarithromycin, and levofloxacin were significantly higher in mainland China than in other East Asian regions. Rates of dual and multiple antibiotic resistance were 28%, highlighting the potential for different resistance patterns[39].

A multicenter, retrospective study was conducted from 2016 to 2023 in 96 hospitals in Northern, Southwestern, and Southeastern China. A high prevalence of resistance to clarithromycin (36.7%) and metronidazole (77.3%) in Chinese children has increased over time. A relatively high rate of resistance to levofloxacin (16.6%) was also found in children, while almost all strains were susceptible to amoxicillin, furazolidone, and tetracycline. Significant regional differences were found in the distribution of resistance to clarithromycin and metronidazole. Multidrug resistance to two or more antibiotics was found in 36.3% of *H. pylori* strains[40].

In another study from Vietnam[41], the antibiotic resistance patterns of *H. pylori* were investigated in 123 children. A high primary resistance rate was found for CLA (68.5%), followed by LEV (55.1%), MET (31.5%), AMO (25.8%), and TET (1.1%). Secondary resistance rates were 82.1% (7/28), 71.4%, 53.6%, and 3.6% for CLA, LEV, MET, and TET, respectively. Multiple drug resistance was common (67.7%), with common patterns including CLA + LEV (20.3%) and CLA + MET + LEV (15.2%).

Eight children (6.5%) had heteroresistance. The A2143G mutation was detected in 97.5% of the children. 86.1% of children had positive cagA strains, and 27.9% had multiple vacA genotypes. No factor was significantly associated with antibiotic resistance[41].

In Europe, a study from Romania[42] investigated the rate of clarithromycin resistance in 84 pediatric patients diagnosed with *H. pylori* infection by gastric biopsy. Clarithromycin resistance was found in 41.6%, and one in 2.4 children infected with *H. pylori* had a strain resistant to clarithromycin[42].

Antibiotic-resistant strains of *H. pylori* were examined in 50 antibiotic-resistant children in Northeastern Poland. *H. pylori* resistance was most common to clarithromycin (38%), followed by metronidazole (30%), and least common to amoxicillin (26%). Resistance to 1 antibiotic was found in (28%). Dual resistance was noted in (6%) and triple resistance in (18%). The whole group (48%) was sensitive to all 3 antibiotics[43].

TREATMENT

In contrast to the guidelines for adults, the pediatric guidelines do not recommend the “test and treat” strategy for children. However, it is questionable whether this strategy can be implemented globally or tailored to the specific location and whether the benefits outweigh the associated risks[44].

Eradication treatment of *H. pylori* in children aims to achieve at least 90% eradication on the first attempt. A high eradication rate prevents the development of antibiotic resistance and the spread of resistant strains of *H. pylori* in the population and reduces the number of follow-up treatments and eradication controls[45].

The two critical points in the eradication of *H. pylori* are successful eradication and the recurrence rate. The options for therapeutic eradication of *H. pylori* infection in children were summarized in a review that attempted to analyze common treatment regimens and alternative therapeutic approaches, such as probiotics, prebiotics, symbiotics, and phytotherapy.

Gastroscopy with antimicrobial susceptibility testing by culture on gastric biopsies should be performed before starting eradication therapy in children to evaluate all possible causes of symptomatology and increase the eradication rate. In children, the limited availability of antibiotics compared to adults necessitates basing treatments on antimicrobial susceptibility testing to reduce the likelihood of treatment failure. The main antibiotics used in children are amoxicillin, clarithromycin, and metronidazole in various combinations. For empirical treatment, triple therapy for 14 days is usually recommended based on either local antimicrobial susceptibility or personal antibiotic history. Triple therapy with a high dose of amoxicillin is a good choice, either in cases of dual resistance or as a second-line treatment. Quadruple therapy with or without bismuth salts can also be used. However, all treatment regimens have some side effects that reduce compliance in children[46].

A systematic review and meta-analysis attempted to clarify the extent to which the use of *Saccharomyces boulardii (S. boulardii)* as part of standard triple therapy (STT) is effective in eradicating *H. pylori* infection in children. Fifteen randomized control trials (2,156 patients) were included. *S. boulardii*, in combination with STT, was more effective than STT alone. Similar results were also observed in the incidence of symptoms, such as vomiting, constipation, abdominal pain, bloating, epigastric discomfort, loss of appetite, and stomatitis[47].

According to a study from China[48], vitamin D3 (VitD3) can reduce *H. pylori*-induced inflammation in the gastric mucosa and prevent or eliminate *H. pylori via* various pathways and mechanisms, including immune regulation and stimulation of antimicrobial peptide (AMP) secretion and Ca2+ influx to restore lysosomal acidification; thus, Vit D may play a role in eliminating drug-resistant *H. pylori* strains[48].

Another study has shown that low serum ferritin levels may be a risk factor for difficulty in eradication and for recurrence after eradication in children with *H. pylori* infection and that low hemoglobin and serum iron levels may be influencing factors for difficulty in eradication in children with *H. pylori* infection[49].

Acid suppression plays a very important role in eradication treatment. In a study from Japan[50], the success rate of *H. pylori* eradication in adults and children with vonoprazan (VPZ)-based treatment was compared with that of proton pump inhibitors (PPIs). The success rate of VPZ-based treatment as first-line therapy was lower in children than in adults[50].

To improve treatment adherence, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has developed flyers that can be distributed to patients with *H. pylori* infection at diagnosis, which can be found translated into various languages on the ESPGHAN website (https://www.espghan.org/knowledge-center/education/H-Pylori-Patient-Parent-Guide).

CONCLUSIONS

Recent publications on *H. pylori* infection show that the prevalence of infection in children is decreasing despite the high prevalence in some areas. The gastric and extra-gastric manifestations of *H. pylori* infection are not clearly defined in childhood. Regional strategies for *H. pylori* screening and treatment should be based on local microbial susceptibility and cancer risk. Standard triple therapy is still the most commonly used treatment. However, we must note that increasing antibiotic resistance is observed. Eradication rates depend on several factors, including the susceptibility profile of *H. pylori* and the patient's adherence to therapy.

Authors' contributions

Maria Rogalidou wrote and reviewed the manuscript & Alexandra Papadopoulou reviewed and revised the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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