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REVIEW: *HELICOBACTER PYLORI* INFECTION IN CHILDREN

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Abstract – A decreased incidence in *Helicobacter pylori* infection has been globally reported but many countries still struggle with a high prevalence of paediatric *H. pylori* infection and its consequences.
New insights around childhood *H. pylori* infection led to updated perspectives on growth, blood and immune disorders. Databases from high incidence countries show us how empowerment in eradication can be invested. Underdeveloped countries seem to pay attention to their local practice and recognise risk factors in their specific population.
Extra-gastric diseases such as growth and anaemia have newly published data supporting a causal relation between *H. pylori* infection and short stature and as well as immune function.
Quadruple therapy including bismuth has been described as the most successful eradication therapy compared to conventional triple therapy. Gut microbiota changes after therapy seem to be limited to a short-term period after eradication.
Important reflection focused on the adherence to guidelines in clinical practice, due to COVID-19 needed adaptation facing the pandemic threat or by divergent standards of care for years in regional settings after the implementation of clinical guidelines.
This review covers the relevant published literature from April 2021 to March 2022, where the crosstalk between old and new issues took place.

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

INTRODUCTION

Helicobacter pylori is an inspiration for continuously upgrading research all over the world. Even under a pandemic threat that changed world practice, 2021 was very fruitful year in the number of publications, with more than 80 related to paediatric *H. pylori*.

Paediatric infection seems to elicit a differential immune response in children as well as a wide extra-gastric disease spectrum. Research could add extraordinary information in this field, including an update on therapeutics and outcome in adulthood. Studies with updated epidemiology and new data from treatment strategies were published, however, the most burning issue seems to be *H. pylori* immune modulation and microbiota changes in patients before and after *H. pylori* eradication.

This article aims to review the most relevant published literature in the field from April 2021 to March 2022 bringing updated information in this field.

MATERIALS AND METHODS

A broad literature search was performed using PubMed from April 2021 to March 2022. The search was restricted to human studies and English language papers using the following terms: *Helicobacter pylori*, *H. pylori*, children. From 81 papers, 48 were selected where relevant and updated information was available.

EPIDEMIOLOGY AND TRANSMISSION

The epidemiology of *H. pylori* infection has been continuously updated and shows a global decline in worldwide incidence[1]. A systematic review of worldwide studies reviewed 198 papers involving over 152.650 children and found a global prevalence of 32.3% of *H. pylori* infection (95% CI 27.3-37.8), which varied according to diagnostic test used [28.6% (23.0-35.0) for serology *vs.* 35.9% (29.2-43.2) for urea breath tests (UBT) or stool antigen tests (STA)]. The higher prevalence of *H. pylori* was found in the older children (13-18 years compared to 7-12 years) and low-income families, low social status, room sharing and *H. pylori* infected mother[2].

Park et al. described a huge decline in *H. pylori* infection in the last 30 years in South Korea, related to improved screening and adult eradication. In this period the overall seroprevalence among asymptomatic patients under 19-years-old decreased from 62.2 to 18.2%[3]. Although high income countries have a declining infection rate, low income or rural regions have not followed the national trend and have higher infection rates, as seen in some regions of Northwest China[4].

Reports from countries with limited resources still present a high rate of childhood infection, such as the Siberian region where *H. pylori* prevalence varies from 44 to 64% (younger children versus teenagers, n= 270)[5], in Lebanon where mixed adult and children's data led to a 31% prevalence[6], and the enigmatic African continent where data show a continuous rise in *H. pylori* infection and antibiotic resistance without a parallel increase in gastric cancer[7].

A large nation-wide prevalence study (SAT under 5-year-old and serum IgG) was performed on Nepalese children: *H. pylori* positivity was 18.2% for the under 5-year-old children (n=1,523, 8.9% and 11% at 12 months and 2-year-old, respectively), and seroprevalence was 14/16% for the 10 to 19 year old group (n= 1023 /1811, male/female respectively)[8].

Lowering the cancer risk through massive *H. pylori* screening in the young as the ideal method is still a matter of debate. A review of the results of population-based *H. pylori* screening in young people was analysed. This meta-analysis reviewed 39 studies mostly in Asian countries (29 studies from Japan and only 4 studies from the Western Europe) but heterogeneity of both age and accuracy of screening methods (serum, stools, breath and urine tests) limited the impact of the results on health policies[9].

In Japan, the accuracy of a highly sensitive ELISA-antibody test was performed on high school students (n=410) in comparison to monoclonal SAT results. A cut-off levels of 5.4 U/mL showed a specificity of 99.5% (95% CI 98.2-99.9) and a sensitivity of 93.3% (95% CI 68.1-99.8) which was considered enough to be an effective screening method in adolescents[10].

Although maternal infection has been a major risk for child transmission, in a US birth cohort, breast feeding was inversely related to the *H. pylori* transmission risk, leading to the assumption that immune protection can be derived from breast milk[11]. A laboratory study by Baltierra et al[12] concluded that human IgA from colostrum has a reactivity against *H. pylori* antigens, which may play a crucial role in preventing the bacterial colonisation during the first months of life.

PATHOPHYSIOLOGY OF GASTRIC DISEASE AND IMMUNITY

H. pylori infection in paediatrics is associated with nodular gastritis in most cases but rarely with peptic ulcer disease. Few publications addressed the effects of *H. pylori* infection on the gastric mucosa. A meta-analysis of 75 studies concerning 5,990 *H. pylori*-infected and 17,782 uninfected children evaluated histologic changes in the gastric mucosa according to

the Updated Sydney System[13]. *H. pylori* positive children presented a higher proportion of cases with nodular gastritis and duodenal ulcer than *H. pylori* negative children. The *H. pylori* infection was also associated with a higher relative risk for gastric antral and corpus chronic inflammation, presence of neutrophils and lymphoid follicles, but rarely gastric mucosa atrophy. Intestinal metaplasia was only significantly higher in the antral area of patients with chronic active inflammation. This study showed uniformised histological changes after *H. pylori* infection in paediatrics[13]. A paediatric study from Taiwan included 92 *H. pylori* positive gastric biopsies from 1998 to 2019. In this cohort, the Sydney classification and tissue metaplasia specific lineages were analysed, including not only intestinal metaplasia but spasmolytic peptide-expressing metaplasia (SPEM), an early cancer precursor. A higher rate of gastric atrophy (30.4%), intestinal metaplasia (4.3%) and other metaplasia precursor lineages (8.7%) were found. Although this cohort had an abnormally high rate of duodenal ulcers (42.2%) and could define selected patient phenotypes, the *H. pylori* associated risk lesions in paediatric patients should set off alarms considering the carcinogenesis cascade in high-risk cancer countries[14].

A Japanese study[15] with mixed paediatric and adult patients showed different histopathological patterns of gastritis across age categories. In paediatric patients, 84% had a pattern of nodular gastritis, present in 68% of the young adult group and only 8% of the older group. In the latter, inflammatory changes seem to be more pronounced in the gastric body than in the antrum with strong mucosal inflammation. Persistent nodular gastritis and mononuclear infiltrate may evolve to cancer or atrophy after years of a concurrent balance between Th1 and Th2 immune response[15].

An immune response connection to *H. pylori* infection during aging is not clear. Previous studies showed balanced innate immune response with a Th2 type cytokine pattern in children. Toll-like receptors (TLR) recognise surface and molecular patterns of the bacteria, responsible for *H. pylori* recognition and chronic persistence in mucosa. Melit et al[16] studied TLR2 and NLRP3 gene polymorphisms in the mucosa of 269 children (51 *H. pylori* positive gastritis). Patients carrying CT and TT variants of TLR2 rs3804099, as well as CC carriers of NLRP3 rs10754558, had a higher degree of systemic inflammation with neutrophil activation. Polymorphism at position -511 of the IL1β gene was associated with an increased risk of *H. pylori* infection as well as of severity of corpus gastric disease in Egyptian children[17]. TLR interaction can be modulated through micro-RNA (miRNA) expression. These can be potential useful non-invasive biomarkers, but evidence is limited to extrapolations from basic to clinical settings, especially in children[18].

An elegant study[19] involving 40 *H. pylori* infected children and adults analyzed Th17A, Treg response and gastric inflammation. Treg was expressed by levels of FOXP3 cells on antral mucosa and Th1 by Th17A expression. Both pathways were overexpressed in the mucosa of *H. pylori* positive patients. Children presented an important regulatory response that inhibits inflammation (with higher FOXP3 cells), and significantly lower Th17A levels during *H. pylori* infection than in adults[19]. The Treg system is more predominant in children than in adults which may allow bacteria to hide from host immunity and persistence of infection. Different immune responses can be the key to the differential mucosal profile of paediatric and adult *H. pylori* infections.

EXTRA-GASTRIC DISEASES RELATED TO PEDIATRIC *H. PYLORI* INFECTION

H. pylori infection remains a complex infection. Previous studies linked *H. pylori* infection in children with the extent of digestive and extra-digestive diseases such as autoimmune gastritis, coeliac disease, parasitic infection and auto-immune thrombocytopaenia[20].

The incidental finding of *H. pylori* is a less well studied subject. Incidental finding in gastric biopsies is not rare, as has been shown in routine endoscopies of bariatric paediatric patients awaiting surgery. A prevalence of 44% *H. pylori* positive patients with abnormal endoscopic findings was reported, even though they were asymptomatic[21]. Another cohort of asymptomatic children showed *H. pylori* isolation in saliva, dental plaque and stool samples (overall prevalence of 59.8%)[22]. This leads to a cautious interpretation of non-invasive versus invasive incidental *H. pylori* found in asymptomatic patients.

The current guidelines from the ESPGHAN/NASPGHAN recommend not testing for *H. pylori* in the investigation of short stature[23]. Although controversial studies have been previously published, Xu et al. analysed 29 studies and data from 9,384 subjects regarding the association between *H. pylori* infection and growth failure. The meta-analysis indicated a significant association of *H. pylori* infection with ponderal growth disorders (OR: 2.47; 95% CI 1.13, 5.37; $p = 0.02$) and linear growth disorders (OR =1.76; 95% CI 1.15, 2.69, $p = 0.01$) with an adverse impact in height-for-age Z scores. This adds substantial information to the work-up of growth in children[24].

Numerous studies were published on iron deficient anaemia and *H. pylori* infection, leading to cautious recommendations derived from the current guidelines. A cohort of adolescents (n= 2,399) whose *H. pylori* antibodies were positive showed a positive association with low hemoglobin and hematocrit levels[25]. A retrospective study from Israel assessed the haemoglobin and ferritin levels in a group of *H. pylori* gastritis patients. Iron deficient patients improved hematologic parameters without iron supplementation 9 months after *H. pylori* eradication. These retrospective data suggest a treatment association with haematological improvement but not causal evidence[26].

Immune activation after *H. pylori* infection may not be confined to the stomach. A report found *H. pylori* infection in a group of patients undergoing endoscopy for coeliac disease (CD) who failed histologic confirmation. Among them, 80% returned to TTG IgA baselines 6 months after *H. pylori* eradication on a free diet, suggesting a systemic immune activation secondary to *H. pylori* infection rather than an effect of *H. pylori* in CD pathogenesis[27].

The latest meta-analysis published in 2022 addressed 25 papers and a total of 141,355 participants. *H. pylori* infection and CD showed a weak but inverse correlation. *H. pylori* infection appeared to be less frequent in CD (OR = 0.57, 95% CI 0.44-0.75). *H. pylori* intraepithelial lymphocytosis and early stages of CD have a similar histological appearance and, as an unspecific mucosal response so similar, they can confound the interpretation. Early *H. pylori* infection can modulate T cell response and stimulate T reg response, diminishing immune activation that could trigger coeliac immune response[28]. More studies regarding systemic effects on *H. pylori* immune activation are needed to evaluate these preliminary findings.

TREATMENT

The first goal of therapy in paediatrics should be to control peptic ulcer disease and/or nodular gastritis, and the second goal is the prevention of gastric cancer. Increasing antibiotic resistance has been occurring in recent years and treatment failure challenges the management of *H. pylori*.

Ongoing ESPGHAN/NASPGHAN guidelines suggest therapy if a real benefit is expected from the *H. pylori* eradication[23]. A proper diagnosis should include tissue collection for culture and antibiotic susceptibility testing, so therapy should be guided by local antibiotic resistance data, where available[23]. First-line treatment in unknown or in high rate clarithromycin resistance countries should be triple therapy combining an adequate dose of amoxicillin plus metronidazole and a proton pump inhibitor (PPI) or quadruple therapy containing bismuth[23].

UBTs are the first-line option to evaluate treatment efficacy. In a recent ESPGHAN /UEG paper, ^{13}C UBT was also indicated in *H. pylori* diagnosis when biopsies were contraindicated. Adequate fasting at least of 4 hours before, PPI avoidance for two weeks and antibiotic clearance for 4 weeks were recommended to avoid false negative results[29,30].

Several reports[31-33] from different countries relate increasing antibiotic resistance and, in some series, more than half of the patients are known to have *H. pylori* resistant strains to at least one antibiotic and the number of strains with multiple resistance is increasing. When compared to adults, resistance to clarithromycin is higher in children (86.7%) and the opposite is seen for metronidazole[31,34]. Molecular diagnosis of mutations encoding for antimicrobial resistance using gastric samples from patients can improve the selection of antibiotic treatment when culture is lacking. Wang et al. reported the genetic profile of resistance in a cohort of children and adults and found that, among *H. pylori* resistant strains in children 23S rRNA gene mutations were detected in all patients resistant to clarithromycin. For metronidazole, resistant mutation G616A of the *rdx*A gene was the most common (26.7%). Mutations

of the *gyr*A gene responsible for levofloxacin-resistant *H. pylori* strains (N87K, D91G, D91Y and D91N) as well as mutations of the *pbp*1 gene in amoxicillin-resistant *H. pylori* and two mutated tetracycline-resistant strains were detected[32].

A retrospective study[34] from Taiwan regarding 87 therapy naïve children described the success of 14-day sequential therapy (97.4% eradication rate), superior to 7- and 14-day triple therapy (80%, $p = 0.032$, 83%, $p = 0.07$, respectively). In this cohort, the presence of clarithromycin resistance was associated with eradication failure, which declined over six years from 27.5% to 16%. An immigrant community was analyzed retrospectively with a comparable native inhabitant community in Singapore, showing substantially higher rates of clarithromycin and metronidazole resistance in migrant patients. This highlights the importance of local antibiotic use policy in paediatrics, which can modulate different regional resistance to antimicrobial therapy[35].

A prospective study enrolling 36 children evaluated the safety of a 10-day quadruple therapy containing colloidal bismuth subcitrate, esomeprazole, amoxicillin, and metronidazole for *H. pylori* eradication. Eradication was achieved in 97.2% of the patients (95% CI: 85-99) with excellent compliance and tolerance[36]. A Vietnamese study also described a higher eradication rate after bismuth use in a high antibiotic resistance population (3.69-fold increase)[37]. This data adds support to bismuth efficacy and the need for further studies in pediatrics.

The use of probiotics has been widespread in recent years mainly aiming at the diminution of side-effects during antibiotic treatment[38]. *Limosilactobacillus reuteri* has the capacity to inhibit *H. pylori* growth and can potentiate the antimicrobial properties of antibiotics. This bacterium can be used not only to improve antimicrobial efficacy, but also to decrease digestive symptoms[39].

Eradication failure after *H. pylori* recurrence is a problem especially in high incidence countries where family clusters can be a source of re-infection[40]. A whole family-based treatment group versus single-infected patient treatment group was analysed in several studies up to July 2020 in China. Pooled analysis of six studies (n=881) showed that the overall recurrence rate of the whole family-based treatment group was lower than that of single-infected patient treatment group (OR=0.3; 95% CI 0.19-0.48), more than 24 months post-treatment. This strategy can be useful in high incidence settings, for population guideline policies[41].

H. PYLORI AND THE MICROBIOME

Previous studies in children demonstrated changes in the gastric and gut microbiota in *H. pylori* infected children. *H. pylori* infection is associated with a higher diversity of gut microbiota[42], and an increase in *Prevotella* species in infected individuals when compared to controls[43]. Some studies addressed changes in the microbiota after antibiotic use (triple therapy) for eradication. A small Japanese cohort assessed the effect of triple therapy on faecal microbiota of *H. pylori* positive adolescents (n=16). The first assessment was performed before eradication with triple therapy, then repeated immediately after eradication and 3 months later. The effect of therapy led to immediate dysbiosis that recovered by the three-month assessment, returning to pre-eradication microbiota[44].

Another study evaluated faecal microbiota changes in a large cohort of children (n=63) after eradication therapy (mixed triple therapy, sequential and quadruple therapy) for *H. pylori* gastritis. The microbiota was assessed early after eradication and followed for 52 weeks. The results showed transient dysbiosis with diminished alpha diversity and a return to basal levels at week 6. These results were reproducible at week 52 which means that the microbiota remains stable after *H. pylori* eradication[45].

GUIDELINES AND CLINICAL PRACTICE

Long-term *H. pylori* infection through infancy until adulthood in high incidence gastric cancer countries has been a matter of concern. Eradication early in adulthood has an unknown value for gastric cancer prevention but in childhood benefits may not surpass potential hazards[9]. The massive testing and treatment in adolescence in these countries can superimpose measures that do not fit the current guidelines. Prevention can be the key to improve the global situation.

Interestingly in Asia, where *H. pylori* infection and gastric cancer are still a concern, family-based screening, education and the spread of preventive measures to avoid transmission have been reinforced. A Chinese consensus concerning family transmission presents a useful and family-based strategy to improve *H. pylori* eradication based on family screening and adjusted to age policy of diagnosis and eradication[41,46].

In Western countries, the ESPGHAN/NASPGHAN guidelines approach led to better outcomes as has been documented by several studies where eradication rate is higher when compared to non-guideline approaches (80% versus 55% success)[31].

Some regions have adapted joint guidelines to their local settings, as is the case of Latin America where real world, cultural studies and regional microbial resistance are not known and an easy practical approach has been instituted[47].

During the COVID-19 pandemic crisis, *H. pylori* management changed somewhat because of the lower number of endoscopic procedures performed due to restrictions. Many centres across Europe restricted endoscopic procedures to emergent or severe cases. *H. pylori* diagnoses, as defined by ESPGHAN/NASPGHAN criteria, were scarce.

COVID-19 manifestations in children had unspecific gastrointestinal complaints, namely abdominal pain, vomiting and diarrhoea, which limits the causality of *H. pylori* for these complaints. Reasonable use and access to endoscopic confirmation of gastric infection could have been naturally delayed or suspended. Some functional disorders were increased in children during the pandemic lockdown with increased functional dyspeptic symptoms in emergency visits. Some authors proposed a test-and-treat strategy during this period, to limit the delayed diagnosis and treatment of *H. pylori* infection[48].

New ESPGHAN/NASPGHAN guidelines are in progress, but it is essential to adjust the main guideline principles to improve the outcomes.

CONCLUSIONS

Recent publications of *H. pylori* infection in children highlight a decreasing prevalence of infection and an increasing challenge concerning treatment due to antibiotic resistance.

Gastric and extra-gastric manifestations of *H. pylori* infection in childhood are poorly standardised and their consequences are not clearly defined because of the heterogeneity of published studies. Regional policies of *H. pylori* screening and treatment should be based on local microbial susceptibility and cancer risk. Evidence of positive or negative effects of *H. pylori* in paediatrics should be addressed in huge standardized, intercontinental studies. Further knowledge will consolidate ongoing evidence and revisit old questions.

Conflict of Interest

The authors declare no conflict of interest.

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