Review: *Helicobacter pylori* in pediatrics

Zrinjka Mišak1,2 | Iva Hojsak1,2,3 | Matjaž Homan4

1Referral Center for Pediatric Gastroenterology and Nutrition, Children’s Hospital Zagreb, Zagreb, Croatia
2University of Zagreb School of Medicine, Zagreb, Croatia
3School of Medicine, University J. J. Strossmayer, Osijek, Croatia
4Department of Gastroenterology, Hepatology, and Nutrition, Faculty of Medicine, University Children’s Hospital, University of Ljubljana, Ljubljana, Slovenia

Correspondence Matjaž Homan, Department of Gastroenterology, Hepatology, and Nutrition, University Children’s Hospital, 1000 Ljubljana, Slovenia. Email: matjaz.homan@guest.arnes.si

1 INTRODUCTION

Although infection with *Helicobacter pylori* occurs most commonly in early childhood, its clinical presentation, as well as the need for diagnostic tests, the eradication strategy, and antibiotic resistance, significantly differs from adults. Increasing evidence on *H pylori* gives rise to the need for a clinical update on its epidemiology, virulence, antibiotic resistance, and clinical presentation. The aim of this review is therefore to provide an update on the evidence published in the last year (April 2018-March 2019) on the specific features of *H pylori* infection in children.

2 EPIDEMIOLOGY

The epidemiology of *H pylori* is rapidly changing, as shown by the high number of epidemiologic studies published in the last year. The world prevalence of *H pylori* varies significantly, from 2.5% in Japan to 34.6% in Ethiopia1-8 (Table 1). Nonetheless, a decreasing trend in the prevalence of *H pylori* infection among children is being observed. Tang et al2 reported a statistically significant decrease in the *H pylori* infection rate in symptomatic children between 2005 (25.6%) and 2017 (12.8%) in China. However, infection rates remain higher in some groups of children, dependent on factors such as low socioeconomic status and bad sanitary conditions as was concluded in studies from Poland, Peru, China, and Ethiopia.1,3-5

3 PATHOPHYSIOLOGY

Gastric mucosal host factors as well as environmental and virulence factors of the bacteria are associated with the clinical outcome of *H pylori* infection. The number of studies investigating these interactions is limited, but several studies published last year included pediatric patients and provided a new insight into their pathophysiology.

Alvarez et al9 studied gastric mucosal factors and gastric cancer risk and evaluated the effect of *H pylori* infection on the regulation of GATA-5 and Trefoil factor 1 (TFF1). In the study, GATA-5 methylation was associated with infection in both pediatric and adult samples, as well as in cancer samples. That suggests that *H pylori* infection might synergize with epigenetic silencing in the gastric mucosa in earlier stages of the disease and may promote cancer progression.
by preventing transcription of tumor suppressor genes. GATA-5 may thus constitute a methylation signature for past exposure to *H. pylori* infection and may prove to be a valuable marker for assessing gastric cancer risk.

Various studies have demonstrated a relationship between *H. pylori* gastritis and altered microRNAs (miRNA) expression in the gastric lesions of adult patients.\(^{10}\) MiRNA-155 is a crucial regulator of innate immunity and is expressed in a variety of immune cells during the inflammatory response. Cortes-Marquez et al\(^ {11}\) analyzed for the first time the expression of miRNAs associated with *H. pylori* infection in pediatric patients. The results showed that increased expression of miRNA-146a and miRNA-155 was associated with the duration and outcome of *H. pylori* infection, suggesting that different expression of miRNAs is indicative of the chronicity of infection and disease severity.

The *oipA* gene, which encodes the OipA outer membrane protein, is one of the possible bacterial virulence factors.\(^ {12}\) A study from Brazil showed that the frequency of *oipA* “on” (functional *oipA*) status did not differ between children and adults.\(^ {13}\) In addition, the *oipA* “on” status was significantly correlated with the presence of *cagA* and vacA s1 m1 genes. Furthermore, the *oipA* “on” status was associated with gastric cancer patients. It is possible that these findings differ among regions with different prevalences of *H. pylori* infection and gastric cancer and therefore should be further investigated.

Serum-derived exosomes from CagA-positive *H. pylori*-infected patients were shown to be involved in the pathogenesis of *H. pylori* infection, particularly in the development of extragastric disorders.\(^ {14}\) Chen et al\(^ {15}\) investigated their impact on the production of inflammatory cytokines during the mucosal inflammatory response after *H. pylori* infection. They observed that serum exosomes, taken up by gastric epithelial cells, activated a soluble form of interleukin (IL)-6 receptor expression that promotes the expression of the pro-inflammatory cytokine IL-1α, which participates in inflammatory responses.

Quintana et al\(^ {16}\) characterized the binding ability and adherence modes of *H. pylori* strains from pediatric patients. The results showed that *H. pylori* isolated from children with peptic ulcer disease binds to mucins with higher avidity at both acidic and neutral pH than those isolated from children with non-ulcer dyspepsia. Furthermore, it was suggested that the higher avidity was caused by a higher prevalence of BabA binding to sulphated and sialic acid containing structures at an acidic pH.

A Slovenian study evaluated the clinical significance of the *homA* and *homB* genes and investigated their correlation with other important *H. pylori* virulence genes: *vacA*, *cagA*, and *babA*\(^ {2.17}\). The presence of either *homA* or *homB* was identified in 96.5% of strains but histological analysis of gastric biopsy specimens showed no correlation between its presence and scores for *H. pylori* density, activity of inflammation, chronic inflammation, atrophy, and intestinal metaplasia. However, additional analysis showed that combinations of certain genes were associated with a higher degree of gastric mucosal damage. Thus, although the *homA* and *homB* genes were not important individual virulence markers, they may act synergistically with other *H. pylori* virulence genes, causing severe gastritis in children.

### 4 | CLINICAL PRESENTATION

#### 4.1 | Digestive manifestations

In recent ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) and NASPGHAN (North American Society for Paediatric Gastroenterology,
Hepatology and Nutrition) guidelines for H pylori infection in children, the recommendation is that the primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of H pylori infection.18 Despite that, discussions continue regarding whether the management of pediatric dyspepsia should include the determination of H pylori status.5,19 Studies from Poland, Turkey, and Peru failed to demonstrate significant differences concerning symptoms in H pylori-positive vs H pylori-negative children with dyspepsia, further supporting the recommendations given in latest guidelines.3,5,7,18,19

With the aim of evaluating the etiology of giant peptic ulcers (diameter > 2.0 cm) in children from Shanghai, China, the authors retrospectively analyzed 19 208 children who underwent endoscopy and found peptic ulcer disease in 7.2% of them.20 Out of 83 patients with giant peptic ulcers, 71.1% were positive for H pylori infection (prevalence of infection 36%), suggesting a strong association between ulcers and H pylori infection.

4.2 | Extra-digestive manifestations

A large prospective multicenter case-control study was conducted in Spain, Italy, France, and Colombia (N = 808), in order to investigate a possible association between H pylori infection and eosinophilic esophagitis (EoE).21 No significant difference in the prevalence of H pylori infection was identified between cases and controls in children (42% vs 46%), questioning an inverse association of H pylori and EoE. It was suggested that data showing parallel declining of H pylori infection and rising incidence of EoE might only reflect a coincidental divergent trend, rather than a causal relationship, but further studies are needed for clarification.

A study investigated the relationship between otitis media with effusion (OME) and the presence of H pylori in the middle ear. Damghani et al22 investigated the presence of H pylori in adenoid tissue of children with adenoid hyperplasia with and without OME. The frequency of H pylori in the middle ear fluid in the infected group (70% of patients) was higher than its frequency in adenoid tissues of both case and control groups (4 and 12%, respectively). It was therefore suggested that H pylori may be an etiologic factor for the development of OME, but it must be borne in mind that the study was performed in a high prevalence country (Iran) and that the number of included patients was limited.

5 | DIAGNOSIS

Two reviews were recently published presenting diagnostic tests available for detecting H pylori infection.23,24 Additionally, there are new studies in which the accuracy of different tests in detecting H pylori infection in a pediatric population was analyzed.

The accuracy of six different diagnostic methods was assessed by Hasosah et al25 in a prospective cross-sectional study in Saudi Arabia: four invasive (rapid urease test [RUT], histology, antral nodularity, biopsy culture) and two non-invasive (serologic test, stool antigen test [SAT]). The gold standard was positive tissue culture or concordant-positive results for histology and the RUT. The RUT had the highest sensitivity (87%) and specificity (65%), while the sensitivity/specificity of antral nodularity and the monoclonal SAT were 62%/74% and 69%/73%, respectively. Serology test had a sensitivity of 51% and a specificity of 78%, confirming that it is not a reliable diagnostic test for H pylori detection in children, which is in accordance with ESPGHAN/NASPGHAN guidelines.18

Two studies evaluated SAT.26,27 Kakiuchi et al26 in Japan compared two SAT targeting for one the catalase of H pylori to a new test kit that uses a protein flagellin. It was shown that the new test can detect H pylori in stool specimens, with high sensitivity, regardless of clarithromycin sensitivity.

Moubri et al27 conducted a prospective study on treatment of naïve Algerian children and evaluated the monoclonal SAT (using enzyme immunoassay) to detect H pylori infection. Positive culture or histology and the RUT were used as the gold standard for diagnosis, as well as for eradication control. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the stool test before (93.6%, 100%, 100%, 87.3%, 96%, respectively) and after treatment (100%, 92.8%, 78.6%, 100%, 94.2%, respectively) were high, showing good performance rates for both initial detection and control of H pylori eradication.

Regardless of new and improved non-invasive tests, based on recommendations, the non-invasive tests are not recommended for diagnosis of H pylori infection in children.18

5.1 | H pylori and microbiota

The impact that H pylori may have on gastrointestinal microbiota composition is attracting a lot of attention.

Benavides-Ward et al28 studied variations in the composition of gut microbiota in asymptomatic children from a rural area in Peru, infected or not with H pylori. They showed that H pylori-positive children had an increased number and variety of bacteria in their colonic microbiota. In addition, the presence of Proteobacteria, Clostridium, Firmicutes, and Prevotella was significantly higher.

The gut microbiota is affected by antibiotics used for eradication treatment. A prospective study in teenagers was carried out using next-generation sequencing of 16S rDNA gene and amplicon analysis of 24 hours fecal samples.29 Pre-treatment gut microbiota contained predominantly Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Eradication therapy using potassium-competitive acid blockers (P-CAB), amoxicillin, and clarithromycin for 7 days significantly decreased the diversity of gut microbiota. However, 2 months after eradication therapy, the bacterial profiles had returned to their pre-eradication levels in most of the patients. Since eradication therapy was not in accordance with ESPGHAN/NASPGHAN guidelines, more studies on the impact of proper therapy on gut microbiota are needed.18
5.2 | Resistance and eradication regimens

In the latest guidelines, the pediatric protocols suggested for *H pylori* eradication should consist of an association of a proton pump inhibitor (PPI) and two antimicrobial agents at high doses, prescribed for 2 weeks.18 The treatment success should be over 90% in per-protocol analysis to prevent the induction of secondary antimicrobial resistance and reduce expensive and risky procedures required by rescue treatment. This number is rarely described in pediatric trials, also because of the high rate of antibiotic resistance of *H pylori*.30,31 Furthermore, high multiple resistance and secondary resistance rates significantly affect *H pylori* eradication.32,33 The prevalence of *H pylori* resistant to antibiotics differs among countries (Table 2) and is usually explained by the different exposure to the corresponding antibiotics in each population.34 First-line treatment should, therefore, be tailored according to the strain’s susceptibility or, if tests are not available, at least according to the regional antibiotic resistance rates of *H pylori* strains.18,24,32,35,36

A study from Iran evaluated the efficacy of sequential therapy for treatment of *H pylori* infection in 40 symptomatic children.39 Patients received amoxicillin and lansoprazole for 5 days and clarithromycin, metronidazole, and lansoprazole (1 mg/kg/day) for the next 5 days. The eradication rate, evaluated by SAT 6 weeks after the completion of therapy, was 82.5%. However, the limitations of the study were the lack of control group and unknown antibiotic susceptibility, in contrast to what is proposed in the guidelines for sequential therapy.18

Potassium-competitive acid blockers are a new class of gastric acid suppressant agents. Like PPIs, P-CABs inhibit gastric H+/K+-ATPase; however, unlike PPIs, P-CABs inhibit the enzyme in a K+ competitive and reversible manner.38 P-CABs have a potent and durable inhibition profile, which increases their antimicrobial potential.39

### TABLE 2 Summary of resistance studies

<table>
<thead>
<tr>
<th>Region</th>
<th>Author (Reference)</th>
<th>No of HP pos patients</th>
<th>HP prevalence</th>
<th>Resistance to amoxicillin</th>
<th>Resistance to metronidazol</th>
<th>Resistance to clarithromycin</th>
<th>Multidrug resistance</th>
<th>Resistance to other antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombia</td>
<td>Rosero et al34</td>
<td>62</td>
<td>47%</td>
<td>-</td>
<td>-</td>
<td>8%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Japan</td>
<td>Mabe et al35</td>
<td>21</td>
<td>NA</td>
<td>0%</td>
<td>12.9%</td>
<td>39.6%</td>
<td>6%</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>Lopo et al33</td>
<td>review</td>
<td>31.6%-66.25%</td>
<td>0%</td>
<td>12.9%</td>
<td>39.6%</td>
<td>6%</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>Silva et al30</td>
<td>74</td>
<td>NA</td>
<td>6.7%</td>
<td>3.3%</td>
<td>23.3% (phenotypic)</td>
<td>0%</td>
<td>Levofloxacin 0%</td>
</tr>
<tr>
<td>Peru</td>
<td>Aguilar-Luis et al5</td>
<td>49</td>
<td>17.2%</td>
<td>-</td>
<td>-</td>
<td>79.6%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### TABLE 3 Studies of different treatment strategies and corresponding eradication rates

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Treatment</th>
<th>Eradication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silva et al30</td>
<td>Tailored antibiotics + PPI (14 d)</td>
<td>97.8%</td>
</tr>
<tr>
<td>Dehghani et al39</td>
<td>sequential</td>
<td>82.5%</td>
</tr>
<tr>
<td>Mabe et al35</td>
<td>PPI + amoxicillin + clarithromycin (7 d)</td>
<td>60.5%</td>
</tr>
<tr>
<td></td>
<td>PPI + amoxicillin + metronidazole (7 d)</td>
<td>98.3%</td>
</tr>
<tr>
<td>Moubri et al36</td>
<td>Omeprazole + amoxicillin + clarithromycin (7 d)</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>Omeprazole + amoxicillin + metronidazole (10 d)</td>
<td>80%</td>
</tr>
<tr>
<td>Zhou et al4</td>
<td>PPI + amoxicillin + clarithromycin (14 d)</td>
<td>60%</td>
</tr>
<tr>
<td>Zhang et al37</td>
<td>Omeprazole + amoxicillin + clarithromycin or metronidazole (14 d)</td>
<td>64.5%</td>
</tr>
<tr>
<td>Tang et al2</td>
<td>Omeprazole + amoxicillin + clarithromycin (7 d)</td>
<td>70%</td>
</tr>
<tr>
<td>Kusano et al38</td>
<td>P-CAB + amoxicillin + clarithromycin (7 d)</td>
<td>81.3%</td>
</tr>
<tr>
<td>Kakiuchi et al8</td>
<td>P-CAB + amoxicillin + clarithromycin (7 d)</td>
<td>85.1%</td>
</tr>
</tbody>
</table>

Abbreviations: PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blockers.
long-lasting anti-secretory effect on H⁺/K⁺-ATPase, due to their high accumulation and slow clearance from gastric tissue. Given their stronger acid-inhibitory effect, P-CABs are expected to be more effective as PPIs in H pylori eradication therapy.

Two Japanese studies evaluated the usefulness and safety of triple therapy with P-CAB for H pylori eradication in children. Unfortunately, both studies were performed within a screening program, with no control group and a short treatment duration.8,38 It has to be highlighted that ESPGHAN/NASPGHAN guidelines recommend against “screen-and-treat” strategy. Furthermore, treatment used in both studies (20 mg P-CAB, 750 mg amoxicillin, 200 mg clarithromycin twice a day for 7 days) did not match the regime recommended in the guidelines.18 Results showed eradication rates of 81.3% and 85.1%, and it was concluded that 7-day P-CAB-based triple therapy was safe and well tolerated in children.8,38

Fang et al10 performed a meta-analysis aimed at investigating the efficacy of probiotic Lactobacillus-supplemented triple therapy on H pylori eradication rates and therapy-related side effects in children. The meta-analysis included five studies, involving 484 pediatric patients. The pooled relative risk (RR) for eradication rates in the Lactobacillus group vs the control group was 1.19 (95% confidence interval [CI] 1.07-1.33). Eradication rates increased more in the high-dose group (1.36 [95% CI 1.15-1.60]) and longer duration supplementation group (1.24 [95% CI 1.06-1.46]). Regarding side effects, Lactobacillus supplementation significantly reduced the incidence of diarrhea (RR = 0.30, 95% CI 0.10-0.85). Although a meta-analysis suggests that Lactobacillus supplementation may be beneficial, the studies included in these meta-analyses used different Lactobacillus strains and concentrations making it difficult to draw meaningful conclusions.

6 | CONCLUSION

Helicobacter pylori studies in children published in the past year have provided new insight into the pathophysiology of the infection, but also raise some new questions that require larger, multicenter pediatric studies. In order to improve eradication rates, susceptibility testing, encouraging adherence to treatment, adequate antibiotic dosing, and proper duration of treatment are recommended.

DISCLOSURES OF INTERESTS

The authors declare no conflict of interests.

REFERENCES
