

Review Article



Clinical Dilemmas for the Diagnosis and Treatment of *Helicobacter pylori* Infection in Children: From Guideline to Practice

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ABSTRACT

Helicobacter pylori infection is often acquired in early childhood. While most infected children remain asymptomatic, *H. pylori* can cause chronic gastritis, gastric ulceration, and, in the long term, gastric cancer. This article aimed to review different diagnostic and treatment options and discuss the challenges associated with applying the current guidelines in the real world. Relevant articles published from 2015 to August 2023 in the English language in PubMed and Medline electronic databases were extracted using subject headings and keywords of interest to the topic. References of interest in the selected articles were also considered. Invasive and noninvasive diagnostic tests have advantages but also disadvantages and limitations according to the clinical setting and age of the child. Guidelines recommend not performing diagnostic testing in children with long-lasting or recurrent abdominal complaints or cases of a family history of severe disease caused by *H. pylori*. However, parents regularly consult with the explicit demand to test for *H. pylori* because of them or a close family member experiencing severe gastric disease caused by *H. pylori*. In some situations, it may be challenging for the healthcare professional to stick to evidence-based guidelines and not consider “patient-centered care,” with the risk of putting a trustful relationship in danger. Physicians may find it challenging not to perform diagnostic tests for *H. pylori* and prescribe eradication treatment in specific clinical settings when maintaining a trusting patient-physician relationship by applying this “patient-centered care” method when evidence-based guidelines recommend differently.

Keywords: *Helicobacter pylori*; Children; Therapeutics; Diagnosis

INTRODUCTION

Helicobacter pylori is the most common cause of chronic gastritis and peptic ulcers. For decades, *H. pylori* has colonized the gastric mucosa of children and adults. More than half the global population is estimated to be infected [1]. The prevalence of this gram-negative bacterium is higher in developing countries and the Mediterranean population [2]. Not all *H. pylori* strains are equally virulent. The effects of infection depend on these virulence factors,

Conflict of Interest

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as well as the genetic background of the host [3]. Transmission takes place via the gastro-oral, feco-oral, or oro-oral routes. Therefore, good hygiene is important to decrease the transmission rate.

Most infected individuals are healthy carriers of *H. pylori* without signs or symptoms. However, this bacterium is also associated with many gastrointestinal (GI) conditions, such as chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma [4,5]. Overall, the development of gastric ulcers due to *H. pylori* infection is rare in children. There is a lack of evidence that chronic or recurrent abdominal pain (RAP) or irritable bowel syndrome is caused by *H. pylori*. *Helicobacter pylori* is also associated with extraintestinal diseases, such as iron-deficiency anemia and chronic primary immune thrombocytopenia [6].

Many parents consult a healthcare professional (HCP) because of anxiety regarding *H. pylori* that is induced by severe *H. pylori*-related symptoms or complications within their family. In Western Europe, primary HCPs frequently perform diagnostic testing on children with chronic upper abdominal pain and dyspepsia under parental pressure. In many countries, this test is performed using the stool antigen test [7]. If positive, blind eradication treatment is often initiated, which increases the risk of antibiotic resistance. Therefore, a primary HCP with a trusting relationship with a family may find applying the guidelines challenging. They may find it difficult to refuse a patient demanding for his children to be tested for *H. pylori* because he just experienced bleeding from a gastric ulcer. Consequently, if *H. pylori* is detected, convincing that parent that there is no indication for eradication is not simple.

This review discusses the difficulties encountered in daily practice regarding the diagnosis and management of *H. pylori* infection in children [3]. The development of pediatric-specific and region-specific guidelines seems a recommendable step forward because of the differences in the prevalence and invasiveness of *H. pylori* and diagnostic and treatment availabilities. For example, bismuth therapy is not available in Western Europe [8].

METHOD

We searched for relevant articles published in the English language in PubMed and MEDLINE between 2015 and August 2023. The final search was run on August 25, 2023, and 480 articles were identified. Two keywords (*Helicobacter pylori* and pediatrics) and related synonyms were used to create the search strategy. All synonyms were combined with the Boolean command “AND” and were linked by the Boolean command “OR” (“*Helicobacter pylori*” [Mesh] OR “*Helicobacter pylori*” [tiab] OR “*Helicobacter* Infections” [Mesh] OR “*Helicobacter* Infections” [tiab] OR “*Helicobacter* Infection” [tiab] OR “*Helicobacter*” [Mesh] OR “*Helicobacter*” [tiab] OR “*Gastrospirillum*” [tiab]) AND (“Pediatrics” [Mesh] OR “Pediatrics” [tiab] OR “Minors” [Mesh] OR “Minors” [tiab] OR “Minor” [tiab] OR “Child” [Mesh] OR “Child” [tiab] OR “Children” [tiab] OR “Infant” [Mesh] OR “Infant” [tiab] OR “Infants” [tiab]) AND (“Diagnosis” [Mesh] OR “Diagnosis” [tiab] OR “Diagnoses” [tiab] OR “Diagnoses and Examinations” [tiab] OR “Examinations and Diagnoses” [tiab] OR “Antemortem Diagnosis” [tiab] OR “Antemortem Diagnoses” [tiab])). Articles were extracted using subject headings and keywords of interest. The second selection was performed by reading the abstracts. References of interest in the included articles were also considered.

DIAGNOSTIC AND SCREENING TEST

The latest European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/North America Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines from 2016 recommend testing limited to children clinically suspected of having gastric or duodenal ulcerations [3]. Symptoms indicative of ulcers include epigastric discomfort, pain, appetite loss, and weight loss [6].

Guidelines do not recommend performing diagnostic tests in children with RAP in the absence of alarm signs such as chronic nocturnal diarrhea, unexplained fever, involuntary weight loss, and pain that wakes the child from sleep [9]. Over 10% of the children present with RAP, but in less than 10%, the cause is organic [10]. Children infected with *H. pylori* are not protected from RAP because of one of the many reported etiologies ranging from stress over constipation and irritable bowel syndrome to inflammatory bowel disease. Many HCPs prescribe (long-term) empirical treatment with proton pump inhibitors (PPI) for children presenting with RAP, especially when the pain is in the epigastric region. However, if a child consults multiple times for abdominal and/or epigastric pain without an obvious cause, it may be difficult for the HCP to resist the demands of the parents to test for *H. pylori*. Parents go on social media, which is often full of misleading information regarding all the harm that *H. pylori* can cause. Social media also mention *H. pylori* as a carcinogen [11]. Non-validated diagnostic testing without the involvement of an HCP is available online (www.diagnoseathome.com). The risk exists that parents may use non-validated tests, making it more difficult for HCPs to refuse further testing or treatment.

In contrast to the 2009 guidelines [12], the 2016 guidelines no longer recommend testing for *H. pylori* in cases with a family history of gastric malignancy or MALT lymphoma because these conditions are rare [3]. A major shortcoming of these guidelines is that patient groups and primary HCPs were not included. However, declining to testing to parents who have children with stomach pain and a family history of gastric malignancy is challenging. These parents are anxious that *H. pylori* may cause cancer in their children. Denying this parental request will not bring reassurance; stress and anxiousness will persist, and parents will continue to search for answers to their questions. The validated diagnostic test results are presented in **Supplementary Table 1** [3]. Parents suspecting *H. pylori* infection in their child because of a positive family history demand noninvasive testing (urea/stool). Primary HCPs and parents often prefer noninvasive diagnostic testing under family pressure. Blind treatment without obtaining a culture of *H. pylori* and an antibiogram can be a consequence, although this should be avoided as much as possible. Endoscopy and biopsies are required to obtain a culture and determine the subsequent antibiotic susceptibility, allowing for adequate antibiotic choice. The availability and cost of upper GI tract endoscopy differ significantly among countries. However, even in countries where endoscopy is relatively inexpensive and readily available, it remains an invasive investigation that requires anesthesia.

Patient-centered care is a useful concept in such situations, focusing on the needs and preferences of patients and their families. It will improve clinical outcomes and patient satisfaction while decreasing healthcare costs, for example, by decreasing “shopping from hospital to hospital” [13]. It may also avoid the use of non-validated diagnostic tests that are available online. Shared decision-making involves parents, and if possible, the child is equal to the HCP in making a decision incorporating medical evidence and family/patient preferences or priorities. Humanistic quality is one of the most frequently ranked domains relevant in patient-physician relationships as it is a crucial aspect of quality care [13,14].

TREATMENT

Eradication therapy is not recommended if *H. pylori* infection is detected incidentally, such as when performing endoscopy for another indication [9,15-17]. However, eradication decreases the risk of developing peptic ulcer and malignancy [18]. In areas with a high rate of infection and gastric malignancy, such as Japan, the benefits of treatment to reduce the risk of developing malignancy may outweigh the disadvantages [19]. Owing to information on social media, parents are aware of the possible deleterious effects of *H. pylori*, especially if parents or close family members have experienced diseases caused by *H. pylori*. However, despite a low risk of re-infection, *H. pylori* is not eradicated in children [19]. It is difficult for HCP to withhold eradication. According to the ESPGHAN/NASPGHAN guidelines, denying the demand for treatment is scientifically justified because the risk of developing malignancy during childhood is low [3,9]. However, eradication schemes can be found on the internet, and anxious parents may be creative enough to obtain antibiotics and PPIs and give uncontrolled eradication treatment a chance. According to the updated ESPGHAN/NASPGHAN guidelines, eradication treatment in children should be based on antibiotic susceptibility testing [3,17,20]. Eradication of *H. pylori* in children remains challenging because of antibiotic resistance, compliance, duration, dosage, and frequency of drug administration [17]. An important part of therapy is the PPIs [3]. According to the guidelines, PPI dosage should consider body weight (**Supplementary Table 2**) [3,16,20-22]. Esomeprazole and rabeprazole are less susceptible to degradation by rapid metabolizers with CYP2C19 genetic polymorphism [3,23].

The most common adverse effects of eradication treatments are diarrhea, nausea, and vomiting [24]. Probiotics reduce these adverse events and may, therefore, increase the eradication rate [23,25-28]. The beneficial effects of probiotics are strain- and dose-dependent [29]. Probiotics administered in combination with *H. pylori* eradication therapy have been reported to improve the eradication rates by approximately 10% [23,25,26]. *Lactiseibacillus rhamnosus* GG, *Limisolactobacillus reuteri* DSM 17938, several strains of Bifidobacteria, and *Saccharomyces boulardii* CNCM-I-745 are reported to decrease *H. pylori* bacterial load, but without eradication [23,26,30].

DILEMMAS IN CHILDREN

Most of the infected children are asymptomatic. The development of symptoms depends on the virulence features and characteristics of the host and environment [31]. However, parents often consult primary HCPs to test their children for *H. pylori* because they or close family members have experienced severe symptoms caused by *H. Pylori* infection.

The cumulative risk of developing a peptic ulcer during a person's lifespan is approximately 10%, whereas the reported risk during childhood is between 0.4% and 12% [6]. Chronic *H. pylori* infection induces an up to eight-fold increased risk of developing adenocarcinomas and MALT lymphomas compared to no infection [4,5]. The World Health Organization considers *H. pylori* a class 1 carcinogen [11]. The extent of inflammation and density of *H. pylori* colonization determine its clinical presentation. If the prevalence of infection increases, there will be a higher prevalence of peptic ulcers and gastric cancer in the long term [15]. Still, in children, *H. pylori* infection is a main cause of duodenal ulcers and chronic gastritis [8]. Symptoms such as postprandial fullness, epigastric abdominal pain, and epigastric

burning are suggestive of ulcers. Patients with duodenal ulcers can complain of worsening abdominal pain on an empty stomach, whereas patients with gastric ulcers report nausea, vomiting, weight loss, and postprandial pain [9]. Symptomatic children with *H. pylori* gastritis also present with nonspecific symptoms, such as nausea, heartburn, and abdominal pain [31]. However, no correlation is found between RAP, nausea, heartburn, and *H. pylori* infection in pediatric patients [17,32,33].

Furthermore, *H. pylori* infection is associated with extra-intestinal conditions such as iron deficiency anemia, Henoch–Schönlein purpura, and acute idiopathic thrombocytopenic purpura [31]. Although testing for *H. pylori* infection as part of the workup in children with iron-deficiency anemia is not recommended, in regions with a high prevalence of chronic, relapsing iron deficiency despite adequate intake in combination with a high prevalence of *H. pylori* infection, a deviation from the recommendation could be considered [3,31,34]. A family history of *H. pylori* infection can be considered in this situation.

All the above information regarding symptomatology is found by parents on the internet.

CONCLUSION

The ESPGHAN/NASPGHAN guidelines provide evidence-based recommendations for the diagnosis and treatment of *H. pylori* infections. However, evidence-based healthcare may sometimes insufficiently consider “patient-centered care,” which is fundamental in primary healthcare. It is difficult for a primary HCP to refuse parental diagnostic testing for *H. pylori*, followed by eradication treatment, especially in regions with a high prevalence of *H. pylori* complications, such as MALT lymphoma and adenocarcinoma, or in families who have experienced these severe complications.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Diagnostic methods advised by the ESPGHAN/NASPGHAN guidelines

Supplementary Table 2

Summary of the recommended treatment

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