Diagnosis and management of Helicobacter pylori infection in children

Laura Toch [a], Pauline De Bruyne [b], Ruth De Bruyne [b], Stephanie Van Biervliet [b], Saskia Vande Velde [b], Myriam Van Winckel [b]

[a] Ghent University, Faculty of Medicine and Health Sciences, Ghent, Belgium
[b] Ghent University, department of Internal Medicine and Pediatrics and Ghent University Hospital, Department of Pediatrics. Pediatric Gastroenterology, Hepatology and Nutrition, Ghent, Belgium

Laura.Toch@hotmail.be

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Abstract

The prevalence of infections with Helicobacter pylori is declining in industrialized countries, yet a significant percentage of children still test positive. Although infection usually occurs in childhood, H. Pylori infection in children differs significantly from infection in adults with respect to clinical presentation, treatment strategy and antibiotic resistance. Because of all these differences, guidelines also differ substantially between children and adults.

Based on the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/ NASPGHAN) guidelines, this article aims to guide the pediatrician when and how to test for H. pylori infection and discusses treatment options.

Given the lack of symptomatic improvement after treating H. pylori in the absence of gastric erosions and ulcers and the rising rate of antibiotic resistance worldwide, the joint European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines were updated in 2017. The society states that the primary goal of testing for H. pylori in children is to find the underlying cause of abdominal symptoms and that eradication therapy is only recommended in patients with confirmed peptic ulcer disease. Furthermore, anti-H. pylori therapy should be tailored accordingly after antimicrobial susceptibility testing and the outcome of the treatment should be assessed at least 4 weeks after completion, using non-invasive tests such as the 13C-breath test or the fecal antigen test.

Introduction

Helicobacter pylori is a gram-negative spiral bacterium with several characteristics that allow it to colonize and survive the acidic conditions of the human stomach (1). Although the gastric mucosa is well protected against most bacterial infections, *H. pylori* is able to enter into the mucus, attach to epithelial cells and evade the immune response, which makes it suited for persistent living in this harsh gastric environment (2, 3). Infection is acquired by oral ingestion of the organism, mainly transmitted within families in early childhood by saliva, vomitus or feces (4).

The clinical outcomes of infection are highly variable, resulting from a combination of bacterial characteristics, host genetics and environment (5, 6). Many patients do not experience any symptoms, but damage to the gastric mucosa caused by *H. pylori* can lead to chronic gastritis which can eventually evolve into peptic ulcer disease (PUD) (2, 3, 6).

The World Health Organization has classified *H. pylori* as a group 1 carcinogen as large epidemiologic data suggest a strong association between the bacterium on the one hand and gastric adenocarcinoma on the other hand (3, 7, 8, 9, 10). Another neoplastic disease due to chronic infection with *H. pylori* is gastric mucosa-associated lymphoid tissue (MALT) lymphoma, though this condition is much less common than PUD or gastric carcinoma (2). Finally there are some extra-intestinal conditions that have also been associated with *H. pylori* infection such as refractory iron deficiency anemia (rIDA) and chronic immune thrombocytopenia (cITP) (5, 8, 11).

Children and adolescents develop these complications much less frequently compared to adults (1, 12). A different immune response to the infection may be a possible explanation. Compared with *H. pylori*-infected adults, studies in infected children show an increased number of local immunosuppressive T regulatory (Treg) cells and anti-inflammatory IL-10, along with a reduced gastric pathology , suggesting that these Treg cells cause a decrease of inflammation and ulceration induced by *H. pylori* (13, 14).

Epidemiology

Over recent decades, the rate of acquisition of *H. pylori* has significantly decreased in developed countries (3, 10, 15). While the overall global prevalence of *H. pylori* infection in children is still estimated at 32.3% (16, 17), epidemiology varies greatly among countries and even among population groups within the same country (3, 15).

A study of 509 Belgian, asymptomatic schoolchildren between the age of 12 and 25 years old in 2010-2011 confirms the latter. By means of a 13C-breath test, the authors showed a very diverse distribution of *H. pylori* infection in our country. The general prevalence is 11%, but in children born in Belgium with Belgian born parents prevalence was only 3,2%. This is in contrast with infection rates rising up to 30% if one or two parents originated from high prevalence countries (prevalence is highest in Africa (70,1%), South America (69,4%) and Western Asia (66,6%)) and even increasing to 60% in children who migrated after birth from a high prevalence country (18).

Further *H. pylori* prevalence studies are needed in the subgroup of symptomatic Belgian children with dyspepsia who have parents originating from a high prevalence country.

In addition to country of parental origin, other associated risk factors are lower socioeconomic status, household crowding, lower parental

education, mental disability, living in a rural area with poor hygiene and sanitation, lack of running water etc. (4, 15, 16).

Diagnosis

Routine testing for *H. pylori* infection is not considered appropriate since the vast majority of pediatric patients are asymptomatic and do not have any related clinical disease, except for some microscopic gastric inflammation (7, 9, 12, 16).

In general, treatment to eliminate *H. pylori* infection outside the context of confirmed PUD, is not expected to improve abdominal symptoms in children. This results in the current European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/ NASPGHAN) guidelines recommending to only undertake (invasive) diagnostic testing for *H. pylori* if peptic lesions are clinically suspected (e.g. epigastric pain during/short after the meal, nocturnal abdominal pain, refractory iron deficiency anemia) or identified by endoscopy (12). An overview of the indications for screening for *H. pylori* (and treatment in confirmed cases) is shown in Table 1.

Table 1: Indications for testing for *H. pylori* infection, according to ESPGHAN/NASPGHAN Guidelines.

Diagnosis of gastric or duodenal erosions/ulcer
Suspicion of PUD in case of dyspeptic complaints (epigastric pain related to meals) and/or nocturnal pain Following extra-intestinal conditions:
• **Diagnosis of gastric or duodenal erosions/ulcer** - Refractory iron deficiency anemia - Chronic immune thrombocytopenic purpura
• **Testing not indicated in the following indications:** - Asymptomatic patients - Chronic (functional) abdominal pain - Gastro-esophageal reflux - First-degree relative with gastric cancer

The threshold for suspicion and testing is lower for immigrant children with one or more parents originating from high prevalence countries.

There are different possibilities to test for the presence of *H. pylori* in children:

13C-breath test

For children older than 6 years, the 13C-breath test can be used to demonstrate the presence of *H. pylori* in the gastric mucosa, relying on the bacteria's high urease activity (an enzyme needed to colonize the acidic environment of the stomach) (12). The test involves drinking 13C-labeled urea which is hydrolyzed to ammonia and bicarbonate. After absorption and diffusion into the blood, the labeled bicarbonate is excreted as CO2 via the lungs and can be measured in the expired breath sample and compared with a baseline value. The 13C-breath test has an excellent sensitivity and specificity for detecting the presence of *H. pylori* in older children, both exceeding 95% (1, 4, 8). Moreover, it is simple to execute and has an excellent safety profile (6).

Fecal antigen test

The lower specificity of the breath test in children younger than 6 years, makes the test not preferable for this age group. A fecal antigen test can be considered as a reliable and simple alternative. The test measures stool excreted *H. pylori* antigen with an enzyme-linked immunosorbent assay (ELISA). A mixture of monoclonal antibodies against *H. pylori* is added to the feces sample, whereafter all the non-binding antibodies are washed away. In the presence of antigen-antibody complexes a chemical reaction will identify the presence of *H. pylori* (8, 9, 12). The fecal antigen test also has a sensitivity and specificity of more than 92% (8,12) and its low cost, ease of use and sample collection at home have made this method increasingly widespread (6).

Endoscopy

Although the non-invasive 13C-breath test and fecal antigen test are commonly used to detect *H. pylori* infection, the gold standard for the diagnosis of *H. pylori* remains the gastroscopy.

In line with the above fact that *H. pylori* infection is not expected to give rise to symptoms in the absence of PUD an upper endoscopy rather than noninvasive testing for *H. pylori* should be performed to determine the underlying cause of the symptoms (12, 16).

Initial diagnosis of the infection is based on culture or histopathology along with one other positive biopsy-based test. During the gastroscopy at least six biopsies should be taken: four biopsies should be obtained from the antrum (two for the histopathological evaluation, one for culture (if available) and at least one for any additional diagnostic tests (e.g. rapid-urease or molecular-based assays)) and three biopsies from the corpus (two for the histopathological evaluation and one for culture (if available)) (12). Complications of this gastroscopy with biopsies are rare and generally reversible, but reaction to anesthesia, hypoxia, perforation or bleeding cannot be ruled out and should be discussed with patients and parents before obtaining informed consent for endoscopy (2).

Importantly, although they are not effective antimicrobial agents, proton pump inhibitors (PPIs) have suppressive effects on *H. pylori* and may give rise to false-negative results. Therefore PPIs should ideally be discontinued two weeks before testing for infection, while antibiotics should be stopped four weeks before testing (9, 12).

Other

Guidelines recommend against serologic testing for *H. pylori* (in serum, whole blood, saliva and urine) in the clinical setting as these tests do not distinguish between past or ongoing infection with *H. pylori*, neither to determine whether the eradication was successful (4, 8, 9, 12, 16).

Management

Because of increasing antimicrobial resistance worldwide, treatment following confirmation of symptomatic *H. pylori* infection should be tailored according to antibiotic resistance profiles (table 2) (11, 12, 16). Moreover, doctors should discuss therapy-related adverse effects (mostly minor, but still relatively frequent), set realistic expectations for clinical symptomatic improvement and emphasize the importance of strict adherence to the anti *H. pylori* therapy which is critical for a successful eradication of the infection (2, 12).

Various drug regimens can be used to eradicate *H. pylori*. Most are based on two antibiotics plus a proton pump inhibitor or a bismuth preparation, always for a duration of 14 days. In patients with a penicillin allergy, metronidazole should be used instead of amoxicillin, if the strain is susceptible to clarithromycin and to metronidazole. In case of clarithromycin resistance however, bismuth-based therapy with tetracycline in place of amoxicillin can be an alternative in children above the age of 8 years (12, 16).

A shorter duration than recommended or the use of a single antibiotic reduces the effectiveness of eradication therapy (2).

Adding supplemental probiotic therapy to the treatment with the aim of reducing adverse effects, which in turn could lead to increased adherence is still under debate and additional pediatric studies are needed to develop more reliable conclusions (12).

Table 2: Standard treatment and dosing regimens – 14 days.

Drug	Bodyweight range	Morning dose, mg	Evening dose, mg
Susceptible to clarithromycin			
PPI[1]	15-24 kg	20	20
	25-34 kg	30	30
	≥35 kg	40	40
Amoxicillin	15-24 kg	500	500
	25-34 kg	750	750
	≥35 kg	1000	1000
Clarithromycin	15-24 kg	250	250
	25-34 kg	500	250
	≥35 kg	500	500
Resistant to clarithromycin, susceptible to metronidazole			
PPI[1]	15-24 kg	20	20
	25-34 kg	30	30
	≥35 kg	40	40
Amoxicillin	15-24 kg	500	500
	25-34 kg	750	750
	≥35 kg	1000	1000
Metronidazole	15-24 kg	250	250
	25-34 kg	500	250
	≥35 kg	500	500
Unknown susceptibility or resistant to clarithromycin and metronidazole[2]			
PPI[1]	15-24 kg	20	20
	25-34 kg	30	30
	≥35 kg	40	40
Amoxicillin	15-24 kg	750	750
	25-34 kg	1000	1000
	≥35 kg	1500	1500
Metronidazole	15-24 kg	250	250
	25-34 kg	500	250
	≥35 kg	500	500

1. Doses are based on omeprazole and esomeprazole. Doses of different PPIs are not equivalent.

2. Alternative bismuth-based therapy:

For children younger than 8 years: bismuth plus standard triple therapy (PPI, amoxicillin, metronidazole);
in children older than 8 years: bismuth plus PPI, metronidazole and tetracycline.
Dosing of Bismuth subsalicylate: if younger than 10 years, 262 mg 4 times a day; if 10 years or older, 542 mg 4 times a day.

Based on 'Helicobacter pylori in Pediatric Patients' (Korotkaya et al. 2020)

The treatment necessity, in case of incidental histopathologic finding of *H. pylori*-associated gastritis during an endoscopy performed for unrelated indications such as the diagnosis of celiac disease or inflammatory bowel disease, without the presence of PUD, is less clear. The patient and family should be explained that *H. pylori* gastritis without PUD rarely causes symptoms nor progresses to more serious disease complications during childhood. The benefits and risks of treatment and the adverse effects (generally abdominal pain, nausea, diarrhea and antibiotic resistance) should also be discussed in order to come to a treatment decision together (2, 12).

Follow-up

Since the relief of symptoms is not an indicator for successful treatment, confirmation of eradication should be performed in all children treated for *H. pylori* with a reliable (noninvasive) test (5, 12), being either the 13C-breath test or the fecal antigen test (see diagnosis).

Gastric acid suppressing medication or antibiotic treatment will increase the false-negative results of both the breath test and the fecal antigen test (8). Therefore, testing for eradication should be performed at least four weeks after completion of the eradication therapy with PPI and antibiotics (12).

Finally, there is no evidence to infer that testing (and treating) family members of *H. pylori*-infected children reduces the risk of reinfection (4, 12).

Conflict of interest

There is no conflict of interest to disclose.

Flowchart

See figure.

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