Helicobacter pylori in children: Diagnosis and management

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Introduction

The prevalence of *Helicobacter pylori* (*H. pylori*) infection in children has decreased over the last decade, particularly in resource-rich countries, but it remains one of the most common human infections worldwide (1-7).

H. pylori is a spiral-shaped, Gram-negative bacillus, first isolated by Warren and Marshall in 1983 on the surface of the stomach (8–10). *H. pylori* colonises the gastric mucosa, generally in childhood, and remains asymptomatic in most patients, in whom it will remain throughout life in the absence of eradication therapy. Infected patients may develop gastritis, gastric or duodenal ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (8, 11). In 1994, the World Health Organisation (WHO) considered *H. pylori* as a causative agent of gastric cancer (12, 13). However, severe gastroduodenal disease in paediatric patients is uncommon and, in comparison with adults, children are much less likely to develop complications of the infection such as duodenal and gastric ulcers. In addition, extra-gastrointestinal manifestations have been reported, including iron deficiency anaemia (14–16), chronic immune thrombocytopenic purpura (17, 18), and impaired growth (19, 20).

Making the diagnosis in children requires the use of invasive methods with endoscopy, while non-invasive assessment methods are used to determine whether *H. pylori* has been eradicated. Since most infections occur during childhood, this topic review will provide an overview of screening, diagnosis, and management of *H. pylori* infection in children and adolescents.

Diagnosis

Who to test for *H. pylori* infection

The Joint ESPGHAN and NASPGHAN 2016 guidelines recommend diagnostic investigation for *H. pylori* in children only when the expected benefits outweigh the costs and risks of testing and subsequent treatment (22).

Therefore, diagnostic testing for *H. pylori* infection is not recommended in children with functional abdominal pain (23–26) and/or short stature (27–29), in children as part of the initial investigation of iron deficiency anaemia (IDA) (30–32), and in the setting of a family history of gastric cancer or mucosa-associated lymphoid tissue (MALT).

These conditions do not predict the presence of *H. pylori* infection in children, and, if *H. pylori* is detected, eradication is unlikely to improve symptoms. A positive non-invasive test may induce anxiety in children with functional pain or their parents, resulting in a referral for upper endoscopy. Indeed, the primary goal of clinical investigation of gastrointestinal symptoms should be to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection (22).

How to test for *H. pylori*

The initial diagnosis of *H. pylori* infection should be made using invasive gastric biopsy-based methods including the following: positive bacterial culture or *H. pylori* gastritis on histopathology using the updated Sydney classification with at least one other positive test such as the rapid urease test, or molecular-based assays where available, including polymerase chain reaction (PCR), or fluorescent in situ hybridization. At least six gastric biopsies should be taken for the initial diagnosis of *H. pylori* infection. Two biopsies should be obtained from the antrum and two from the corpus for histopathological evaluation using the updated Sydney classification (33), at least one biopsy from the antrum and one from the corpus for culture (if available) and at least one biopsy from the antrum for any additional diagnostic tests (rapid urease, or molecular-based assays).

Non-invasive tests should not be used for the initial diagnosis of *H. pylori* infection, but to evaluate the outcome of anti–*H. pylori* therapy. When non-invasive testing is performed, either of the following may be used: a two-step monoclonal stool *H. pylori* antigen test, unrelated to age, and the ^{13}C-urea breath test (^{13}C-UBT), rarely indicated in children younger than six years due to the lower distribution volume and different CO_2 production rate (34–36) and technical difficulties with swallowing, and contamination from oral urease-producing organisms.

The ^{13}C-UBT has excellent sensitivity and specificity for the diagnosis of *H. pylori* infection in older children. A recent meta-analysis showed a sensitivity of 96.6% and a specificity of 97.7% in children older than six years of age. In children younger than two years of age, however, the ^{13}C-UBT may have reduced specificity (37, 38).

For both the ^{13}C-UBT and faecal antigen testing, false-negative results can occur when medications are taken that decrease the bacterial load or suppress gastric acid. Therefore, it is recommended that clinicians wait at least two weeks after stopping proton pump inhibitors (PPIs) and four weeks after stopping antibiotics before performing a ^{13}C-UBT (22).

In contrast to paediatric guidelines, non-invasive testing is often used for the initial diagnosis of *H. pylori* in adults, where ^{13}C-UBT is a principal component of the algorithm for undiagnosed dyspepsia (39) since there are broader indications for *H. pylori* testing in adults, several of which do not also require endoscopy.

Serological testing has no place in the management of *H. pylori* infection in children and is not recommended for either diagnosis or follow-up after treatment. These tests have poor sensitivity and specificity and, therefore, a low positive predictive value in low-prevalence settings. In addition, these tests do not distinguish between active and past infection (22).

Who should be treated for *H. pylori* infection

Based on current evidence and recent guidelines (22), treatment to eliminate *H. pylori* infection is not expected to improve symptoms in children, except in cases of peptic ulcer disease (40), where it will be beneficial (41–43). Therefore, treatment should be prescribed when it is clinically indicated, or if it is deemed appropriate to treat an incidental finding of *H. pylori* in children after discussion with their parents. The family should understand that treatment may not improve symptoms (especially non-specific abdominal pain), that there is a possibility of treatment failure or reinfection, and that close adherence to a complicated treatment regimen for two weeks is required.

Chronic immune thrombocytopenia (ITP) and refractory iron deficiency anaemia are also relative indications for treatment.

How to treat infected patients

Successful eradication of paediatric *H. pylori* infection depends on the knowledge of *H. pylori* susceptibility to antibiotics and adherence to treatment (44). The recommended goal for *H. pylori* treatment is an eradication rate of at least 90% to avoid further investigations and antibiotic use (22).

Antimicrobial resistance patterns vary depending on national/geographical regions and are a major factor in determining the success of eradication therapy (45–50). Treatment failure will result in increased healthcare utilisation and likely put the child through additional unnecessary procedures and therapies, with their associated risks (47). The development of antibiotic resistance may also occur if children are on long-term antibiotics for other comorbidities.

In a systematic review (51) of randomised controlled trials on treatment regimens for *H. pylori* infection in children, standard triple therapy was still found to be the most highly recommended and the most commonly used regimen. Its eradication rates were found to vary according to the *H. pylori* susceptibility profiles in different world regions (2). First-line therapy for *H. pylori* infection is listed in Table 1.

Compared to adults, there are fewer options for rescue therapy in children and the choice should consider initial antibiotic susceptibility status (if known) and the first-line regimens employed (Table 2).

Recurrence of the infection after successful eradication is another problem related to *H. pylori*. Children have higher rates of reinfection than adults if the initial *H. pylori* infection is eradicated. In a prospective case-control study, the recurrence rate of *H. pylori* infection after successful eradication was 18.8% in Chinese children and was closely correlated to socioeconomic factors (2, 52). Risk factors for reinfection are similar to those for pri-

mary infection (53). In older children, household contact with siblings younger than five years is also a risk factor for reinfection (54).

During the last year, research has continued regarding the addition of probiotics to the standard *H. pylori* eradication therapy. Several studies have proposed that probiotics can inhibit *H. pylori* by immunological and non-immunological mechanisms, including regulating pro-inflammatory cytokines in the gastric mucosa, increasing the local IgA concentration, and secreting antibacterial substances such as lactic acid, short-chain fatty acids, hydrogen peroxide and bacteriocin (55). During the last year, promising results have been observed in a few studies that aimed to address this topic (56, 57), but additional sufficiently powered paediatric studies should be performed to develop more reliable conclusions about the benefit of probiotics in *H. pylori* eradication regimens.

Future prospects

Future studies should focus on obtaining antibiotic resistance rates across regions to help direct optimal therapy and a best practice for paediatric *H. pylori* infection. In addition, high-quality studies to evaluate novel approaches and therapies in children and the role of supplemental probiotics are needed. Importantly, studies on the prevention of infection with the optimisation of vaccine strategies should be performed (22).

Antimicrobial susceptibility		Suggested treatment
CLA	MET	
Susceptible	Susceptible	PPI-AMO-CLA 14 days with standard dose
Resistant	Susceptible	PPI-AMO-MET 14 days or bismuth-based
Susceptible	Resistant	PPI-AMO-CLA 14 days or bismuth-based
Resistant	Resistant	PPI-AMO-MET with high-dose AMO or Bismuth-PPI-AMO-MET (if <8 years), or Bismuth-PPI-MET-tetracycline (if ≥8 years)
Unknown	Unknown	

TABLE 1. FIRST-LINE THERAPY FOR H. PYLORI INFECTION

Abbreviations: CLA: clarithromycin; MET: metronidazole; PPI: proton pump inhibitor; AMO: amoxicillin.
Adapted from: Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr 2017; 64:991.

Initial antibiotic susceptibility	Past treatment regimen	Rescue treatment
CLA and MET susceptible	PPI-AMO-CLA	PPI-AMO-MET
	PPI-AMO-MET	PPI-AMO-CLA
CLA resistant	PPI-AMO-MET	Treat like double resistance
CLA susceptible	PPI-AMO-CLA	Treat like double resistance or consider performing a second endoscopy and use a tailored treatment for 14 days
Primary antimicrobial sensitivity unknown or double resistance	Triple therapy	Consider performing a second endoscopy to assess secondary antimicrobial susceptibility or treat like double resistance

TABLE 2. RESCUE THERAPIES IN PAEDIATRIC PATIENTS WHO FAILED INITIAL TREATMENT

Abbreviations: CLA: clarithromycin; MET: metronidazole; PPI: proton pump inhibitor; AMO: amoxicillin.
Adapted from: Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents (Update 2016). J Pediatr Gastroenterol Nutr 2017; 64:991.

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