Helicobacter pylori in Pediatric Patients

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PRACTICE GAPS

Helicobacter pylori guidelines have recently been updated. Due to rising resistance it is important that clinicians be aware of the current guidelines for appropriate diagnosis and management of *H pylori* in children and are able to identify children who require further evaluation by pediatric gastroenterology.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe *Helicobacter pylori* epidemiology and clinical manifestations.
2. Understand the diagnostic approach to and treatment of *H pylori*.
3. Recognize red flags associated with *H pylori*.

ABSTRACT

Helicobacter pylori causes one of the most common chronic bacterial infections. Clinical manifestations include asymptomatic chronic gastritis, gastric and duodenal ulcers, adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma in adults. In children, most *H pylori* infections are asymptomatic despite being associated with microscopic gastric inflammation, and children rarely develop complications associated with infection. Due to rising resistance and lack of symptomatic improvement in the absence of peptic ulcer disease, testing and eradication therapy are recommended only for the subset of patients in whom there is a high suspicion of peptic ulcer disease. Studies do not support the role of *H pylori* infection in functional disorders such as recurrent abdominal pain. A variety of diagnostic modalities exist; therefore, it is important to understand the appropriate approach to diagnosing *H pylori* infection. The joint European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines were updated in 2016. Antibiotic and proton pump inhibitor weight-based dosing guidelines have changed to prevent ineffective treatment from increasing antimicrobial resistance. Treatment can also be guided by antibiotic sensitivities obtained from *H pylori* culture. Patients should be tested again after treatment to confirm eradication.

INTRODUCTION

Helicobacter pylori is suited for living in the acidic environment of the human stomach. *H pylori* has several properties that allow it to colonize and survive the

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ABBREVIATIONS

AMO	amoxicillin
CLA	clarithromycin
FDA	Food and Drug Administration
Ig	immunoglobulin
IL	interleukin
ITP	idiopathic thrombocytopenic purpura
MALT	mucosa-associated lymphoid tissue
MET	metronidazole
PPI	proton pump inhibitor
PUD	peptic ulcer disease

harsh gastric environment. Chronic gastric colonization by *H pylori* causes disruption in gastric epithelial cell function, which initiates intense local inflammation, systemic immune response, and alteration in acid secretion. (1)

Clinical manifestations of *H pylori* vary from asymptomatic chronic gastritis to peptic ulcer disease (PUD), adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma in adults. Most children with *H pylori* remain asymptomatic, and children are less likely to develop complications of infection, such as PUD or cancer. The features contributing to the variety of clinical manifestations are due to a combination of host genetics, bacterial characteristics, and environment. (1)(2)

EPIDEMIOLOGY

H pylori causes one of the most common bacterial infections worldwide. (1)(2)(3) *H pylori* infection is found in 50% of the world's population, which includes approximately 70% of the population of developing nations and 30% to 40% of the population living in industrialized countries. (1)(2)(4) In northern Europe, the *H pylori* prevalence is similar to that in North America. A Canadian study found an adult prevalence of 38%, which is similar to the prevalence of 32% found in the native Dutch population in the Netherlands. (5) Overall, higher prevalence is reported in southern Europe (84% in Portugal), eastern Europe (82% in Turkey), and Mexico (52%). In Asia, prevalence ranges from 54% to 76%. (5) Similarly, in some African countries (Ethiopia and Morocco), the prevalence is 65% and 75%, respectively. (5) In Iran, a recent meta-analysis found that the prevalence of *H pylori* infection in both children and adults was 54%. (6) In the United States, infection in any age group is most common in Hispanic immigrants and second-generation relatives (58%), followed by African Americans (51%), and, last, whites (27%). (1) Overall, the prevalence of *H pylori* infection is decreasing in the United States; however, international adoptees and immigrant children are at an increased risk similar to that of the residents of their native countries. (4) Children often carry a genotype strain identical to their parents even after moving to another environment. (7)

Most infections are acquired in childhood. Low socioeconomic status is a primary risk factor. (1)(3)(4) Risk factors of infection include household crowding, living in a rural area, family size, bed-sharing, and lack of running water. (1)(5)(8) In developing countries, most children acquire the infection by age 5 years. Some children spontaneously clear the infection but become infected again. Therefore, *H pylori* prevalence can exceed 80% by age 20 to 30 years. (1) In developed countries, young children also acquire infection, which may be spontaneously cleared, but reinfection is much less common than in developing countries.

Humans seem to be the major reservoir of *H pylori*. In developing countries, water contamination is also a source because *H pylori* can remain viable in water for several days. (1) This likely contributes to the higher prevalence of infection in those countries. (1) Data on zoonotic sources has been inconsistent. Transmission of the bacteria is predominantly via the gastro-oral and fecal-oral routes. Oral-oral transmission has also been described. (1)(2)(4) Transmission is more frequent between close relatives or individuals living together. (5)(8)

PATHOGENESIS

The bacterial properties of *H pylori,* including virulence factors, allow it to colonize (bind the epithelium) and adapt to the acidic gastric climate. (1)(9) Subsequently, the host response further contributes to the pathogenesis of infection. (1) *H pylori* produces urease, allowing the organism to manipulate the gastric milieu to survive the acidic environment. (9) Their spiral shape and multiple unipolar flagella permit migration of the bacteria below the mucus layer for successful colonization of the gastric epithelium. *H pylori* adhesion to cellular receptors protects the bacteria from displacement. (7) The epithelial cells express Lewis (Le) antigens, which are receptors for the bacteria to bind. (1) BabA is a specific bacterial gene product that acts as a ligand for the Lewis b (Leb) receptor. (1)(7) *H pylori* can also bind to epithelia via 2 binding sites, including the molecular complex of invariant chain (CD74) and class II major histocompatibility complex. (1) The cytotoxin-associated gene pathogenicity island (cag PAI) is a segment of bacterial DNA that plays an important role in the interactions between bacteria and the gastric epithelium. (7) Genes in the cag PAI encode for proteins that form a type IV secretion system, which delivers bacterial CagA, an oncoprotein, into host cells. (1)(2)(7) *H pylori* strains that are cag A positive have higher levels of interleukin (IL)-8 expression, leading to inflammation in the gastric mucosa, and are associated with a higher risk of PUD and gastric cancers. (1)(7) All strains of *H pylori* have a vacuolating cytotoxin A (vacA) gene, and more than half express VacA, a cytotoxin secreted from the bacteria. (1) VacA induces gastric epithelial cellular alterations, creating a channel that aids in *H pylori* colonization. (7)(9)

H pylori–induced chemokines cause both acute inflammation with neutrophils and chronic inflammation with macrophages and lymphocytes. (1) There is evidence to

suggest that the host response to *H pylori* plays a role in the development of gastrointestinal disease. (1) Genetic polymorphisms of cytokines such as IL-1β induced by *H pylori* are associated with gastric cancer. (1)(2) Similarly, polymorphisms in tumor necrosis factor α genes and IL-16 also have associations with increased risk of gastric cancer. (7)

CLINICAL MANIFESTATIONS

Most individuals who are chronically infected since childhood are asymptomatic, despite having microscopic gastric inflammation. Only 10% to 15% of patients will develop signs or symptoms of clinical disease. (1) Clinical manifestations most commonly include chronic gastritis and PUD with gastric or duodenal ulcers. Adenocarcinoma and MALT lymphoma are more commonly seen in adults; however, rare cases of MALT lymphoma and gastric adenocarcinoma associated with *H pylori* have been reported in pediatric patients. (10) To determine which patients need testing for *H pylori* and referral to a pediatric gastroenterologist, clinicians must distinguish individuals with functional dyspepsia symptoms from those more likely to have PUD. Without evidence of PUD, treatment for *H pylori* is unlikely to improve symptoms of generalized abdominal pain. (10) There is not a strong relationship between recurrent abdominal pain and *H pylori* infection. (10) Therefore, indiscriminate testing for *H pylori* is not recommended for the routine evaluation of functional abdominal pain and may increase anxiety in the patient and the family. (10) The signs and symptoms of PUD include epigastric pain or tenderness on examination, nausea, emesis, hematemesis, and melena- or guaiac-positive stools. Individuals with these findings, or any other alarm signs or symptoms (Table 1), should be seen by a pediatric gastroenterologist for endoscopic evaluation.

Table 1. Red Flags (Alarm Signs)

Persistent epigastric, right upper or right lower quadrant pain
Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal blood loss
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fevers
Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease

Adapted from the ESPGHAN/NASPGHAN guidelines. (4)

Previously, extraintestinal manifestations of *H pylori* have included iron deficiency anemia, growth restriction, and idiopathic thrombocytopenic purpura (ITP); however, these associations have come under question. Recent studies have not been able to demonstrate a causal relationship between *H pylori* and iron deficiency anemia. (10) Screening for *H pylori* as part of an initial evaluation for iron deficiency anemia is, therefore, not recommended. (10) Patients with refractory iron deficiency anemia, despite recommended management, may need to be referred to pediatric gastroenterology once other causes of anemia have been ruled out. In patients with short stature, routine screening for *H pylori* is not recommended due to lack of evidence that *H pylori* infection causes poor growth. (10) In patients with chronic ITP, *H pylori* infection treatment has been shown to be helpful. In a recent study of children with chronic ITP, eradication of *H pylori* infection increased the platelet count in more than half of the children. (10) In such patients, noninvasive testing for *H pylori* can be helpful if platelet counts are too low for endoscopic evaluation.

DIAGNOSIS

Routine screening of pediatric patients for *H pylori* infection, without suspicion of PUD, is not recommended. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition strongly recommend against a test-and-treat approach. (10) The purpose of testing should be to investigate the cause of PUD symptoms, not to simply determine whether *H pylori* is present. (10) Testing can be considered in patients with chronic ITP. *H pylori* testing is not required for patients with a family history of gastric malignancies.

H pylori infection should be confirmed by endoscopy. (10) Elective upper endoscopy is generally considered safe in children. (11) Complications are rare and generally reversible but may include reaction to anesthesia, hypoxia, bleeding, or perforation. (11) At the time of endoscopy, biopsy samples are obtained from both the antrum and the body of the stomach. Biopsies can be obtained for rapid urease testing, histopathologic analysis, polymerase chain reaction assay or fluorescence in situ hybridization, and culture. (3)(4) For rapid urease testing, biopsy samples are placed in a medium containing urea and a pH reagent. (1)(4) Bacterial ureases hydrolyze the urea, producing ammonia, which increases the pH and results in a color change of the test medium. (1) The rapid urease test has high sensitivity and specificity, 90% to 95% and 85% to 100%, respectively. (1)(3) Use of a proton pump inhibitor (PPI), bismuth, and antibiotics all decrease

Table 2. First-line Treatment Regimens (14 Days)

MEDICATION	WEIGHT RANGE (KG)	MORNING DOSE (MG)	EVENING DOSE (MG)
Susceptible to Clarithromycin—Standard-Dose Amoxicillin			
PPI[a]	15–24	20	20
	25–34	30	30
	>35	40	40
Amoxicillin	15–24	500	500
	25–34	750	750
	>35	1,000	1,000
Clarithromycin	15–24	250	250
	25–34	500	250
	>35	500	500
Resistant to Clarithromycin, Susceptible to Metronidazole—Standard-Dose Amoxicillin or Bismuth[b]			
PPI[a]	15–24	20	20
	25–34	30	30
	>35	40	40
Amoxicillin	15–24	500	500
	25–34	750	750
	>35	1,000	1,000
Metronidazole	15–24	250	250
	25–34	500	250
	>35	500	500
Unknown Susceptibility or Resistant to Metronidazole and Clarithromycin—High-Dose Amoxicillin or Bismuth[b]			
PPI[a]	15–24	20	20
	25–34	30	30
	>35	40	40
Amoxicillin	15–24	750	750
	25–34	1,000	1,000
	>35	1,500	1,500
Metronidazole	15–24	250	250
	25–34	500	250
	>35	500	500

PPI=proton pump inhibitor.
[a]Dosing based on esomeprazole and omeprazole. Dose should be adapted for other PPIs.
[b]Alternative bismuth quadruple therapy: if younger than 8 years, bismuth plus standard triple antibiotic therapy (PPI, amoxicillin, metronidazole); if 8 years old or older, bismuth plus PPI, metronidazole, and tetracycline. Bismuth subsalicylate dosing: if younger than 10 years, 262 mg 4 times daily; if 10 years or older, 524 mg 4 times daily.
Adapted from the ESPGHAN/NASPGHAN guidelines. (4)

accuracy of the test. Organisms can be detected by polymerase chain reaction assay or fluorescence in situ hybridization of gastric biopsy tissue. (4) Evaluation of gastric histopathology also provides information about the degree of inflammation, including detection of possible *H pylori*–associated precancerous lesions. Histopathologic analysis has high sensitivity and specificity of greater than 90%; however, both may be affected by sampling and PPI use. (1)(3) *H pylori* culture with antibiotic sensitivity can be very helpful in guiding treatment, especially in refractory cases. Culture has a specificity of 100% but low sensitivity because *H pylori* is difficult to culture due to its slow growth and requirement for special media. (1) Transport of biopsy samples for culture in special media improves the success of the culture. (10)

The most useful noninvasive screening test for *H pylori* is the fecal antigen test. The fecal antigen test is a commercially available monoclonal immunoassay. It has high sensitivity and specificity, 94% and 97%, respectively, no matter the age of the patient. (1)(10) Testing is easy to perform, especially in young children. *H pylori* stool antigen testing can be used to establish the diagnosis in certain situations. It is the most cost-effective test for confirming clearance of *H pylori* infection. Accuracy of testing is reduced by PPI, bismuth, and antibiotic use due to a decrease in bacterial load, so repeated testing should not be performed until 2 to 4 weeks after treatment is completed. (1)(10)

Another noninvasive screening test is the urea breath test, which is based on the hydrolysis of urea by *H pylori* to produce carbon dioxide and ammonia. Urea-labeled carbon

isotope (^{13}C or ^{14}C) is given by mouth, and the *H pylori* liberate labeled carbon dioxide, which can be detected in expired breath samples. (1)(4) The test requires 15 to 20 minutes to perform and the patient's cooperation; therefore, it is approved by the US Food and Drug Administration (FDA) for children older than 3 years. (4) Sensitivity and specificity are 88% to 95% and 95% to 100%, respectively. Sensitivity is decreased during an active peptic ulcer bleed, and false-negative results can occur with PPI, bismuth, or antibiotic use. The urea breath test can also be used to confirm eradication of *H pylori* infection. (1)(2)(3)(4)(10)

Serum antibody–based testing (immunoglobulin [Ig] G, IgA) for *H pylori* strains is not recommended due to poor sensitivity and specificity of the assay in children. (3)(10) In addition, antibody testing is not valid after treatment of *H pylori* infection due to the long-lasting *H pylori*–specific IgG antibodies that persist for years after clearance of infection. (1)(2)(3)(4)(10)

To summarize, noninvasive testing can be used for screening, but diagnosis of *H pylori* should be made by histopathologic analysis and another biopsy-based test, including culture. (10) Testing should ideally be performed before tstarting PPI therapy or at least 2 weeks after stopping. The use of bismuth and antibiotics within 4 weeks of testing can decrease sensitivity of both endoscopic and noninvasive testing.

MANAGEMENT

After confirmation of symptomatic *H pylori* infection, therapy should be guided by antibiotic resistance profiles (Table 2). Culture with sensitivities can guide treatment. Treatment should provide adequate doses of medication for 14 days. Higher weight-based doses of PPI therapy are required for younger children compared with adolescents and adults, and higher PPI doses have been shown to improve success of therapy. (10)(12) When antibiotic susceptibility is unknown, triple therapy with high-dose PPI, amoxicillin (AMO), and metronidazole (MET) for 14 days is recommended as first-line therapy. (10) Bismuth quadruple therapy can be used as an alternative therapy for *H pylori* infection in cases of unknown antibiotic susceptibility or known resistance, particularly resistance to both MET and clarithromycin (CLA). (4)(10) CLA-based therapies are not recommended as first-line empirical therapy due to increasing resistance around the world. (10) Adherence to therapy is critical for eradication of the infection. (6) Use of a single antibiotic or a shorter duration than recommended reduces the effectiveness of eradication therapy. (1) Discussing the adverse effects of medications and setting realistic expectations for clinical symptomatic improvement can improve adherence. (3)(10)

For patients who fail initial therapy, the choice of the alternative therapy should take into consideration the initial treatment strategy and the regional susceptibility. (10)(13) Generally, patients should not be treated with a previous regimen, especially CLA-based regimens. Endoscopy with culture to assess antibiotic susceptibilities can guide subsequent therapy.

In the case of penicillin allergy, if the strain is susceptible to CLA and to MET, standard-dose triple therapy with MET in place of AMO can be used. If there is resistance to CLA, then bismuth-based therapy with tetracycline instead of AMO should be used in children older than 8 years.

For patients who were incidentally found to have *H pylori* gastritis on endoscopy, without gastric or duodenal ulcers or erosions, the need for treatment is less clear. The risks and benefits of treatment and the adverse effects of therapy should be discussed with the patient and family to come to a treatment decision. (10) The most common adverse effects from antibiotic treatment include abdominal pain, nausea, diarrhea, and antibiotic resistance.

FOLLOW-UP

Confirmation of eradication should be performed in all patients due to increased antibiotic resistance. (10) Repeated testing should be performed at least 4 weeks after completion of antibiotic treatment and 2 weeks after PPI discontinuation using the stool antigen or urea breath test. Endoscopy with biopsy for culture and sensitivity should be performed in patients with persistent *H pylori* infection after 2 courses of antibiotic treatment. Serologic testing should not be performed because antibodies can persist despite eradication. Successful *H pylori* eradication is associated with long-term cure of PUD. (10)

SUMMARY

- Based on consensus of expert opinion, the goal of testing for *Helicobacter pylori* should be to determine the underlying cause of symptoms, not to simply determine the presence of *H pylori* in asymptomatic patients who may have possible exposure. (10)
- Based on strong research, testing is recommended for patients with signs or symptoms of peptic ulcer disease. (10)
- Based on some research and consensus, testing can be considered in patients with chronic idiopathic thrombocytopenic purpura. (10)
- Based on strong research, diagnosis should be confirmed by endoscopy. (10)

- Based on strong research, testing is not recommended for patients with suspected functional abdominal pain who do not have alarm signs. (10)
- Based on some research and expert opinion, testing is not recommended for patients as part of the initial evaluation for chronic iron deficiency anemia or short stature. (10)
- Based primarily on consensus owing to the rare occurrence in clinical practice, testing is not required for patients with a family history of gastric malignancies. (10)
- Based on strong evidence, serum antibody-based testing (immunoglobulin A or G) for *H pylori* is not recommended for diagnosis or confirmation of eradication. (10)
- Based on some research and consensus, if antibiotic susceptibility is unknown, triple therapy with high-dose proton pump inhibitor (PPI), amoxicillin, and metronidazole for 14 days is recommended as first-line therapy. Quadruple bismuth therapy is another option. (10)
- Based on strong research evidence, *H pylori* eradication is confirmed by the absence of *H pylori* stool antigen, a negative urea breath test, or negative endoscopy-based testing after at least 4-week completion of antibiotic treatment and 2 weeks after PPI discontinuation. (10)

SUGGESTED QUALITY IMPROVEMENT PROJECTS:

- Providers should be educated about updates on *Helicobacter pylori* diagnosis, treatment, and eradication of infection.
- Guidelines should be easily accessible.
- Track whether patients adhered to the full course of treatment, or whether eradication testing after completion of therapy was performed (such as stool antigen testing).

References for this article can be found at http://pedsinreview.aappublications.org/content/41/No. 11/585.

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1. Epidemiologic studies show that *Helicobacter pylori* causes one of the most common infections worldwide. Which one of the following signs and symptoms is most likely to be manifested in young adults chronically infected with *H pylori* since childhood?

   A. Iron deficiency anemia.
   B. No symptoms.
   C. Peripheral eosinophilia.
   D. Periumbilical pain.
   E. Short stature.

2. You are lecturing to a group of first-year pediatric gastroenterology fellows about the indications for the treatment of patients with *H pylori*. You emphasize that a patient with which one of the following constellations of signs and symptoms is most likely to benefit from eradicative treatment if found to be *H pylori* positive?

   A. Chronic periumbilical abdominal pain and tenderness.
   B. Difficulty swallowing and sensation of food impaction.
   C. Early satiety and postprandial epigastric bloating.
   D. Epigastric tenderness and heme-positive stools.
   E. Loose stools with flatulence and dyschezia.

3. The pediatric gastroenterology division is in the process of building order sets and pathways for the newly implemented electronic health record based on national evidence-based practice guidelines. These order sets and pathways will be linked to, and triggered by, patient diagnoses. Which one of the following clinical scenarios should trigger the screening for *H pylori* infection order set for consideration by the clinician?

   A. Preschool-age girl with a family history of gastric cancer.
   B. School-age boy with short stature.
   C. School-age girl with chronic idiopathic thrombocytopenic purpura.
   D. Teenage girl with functional dyspepsia.
   E. Teenage girl with newly identified iron deficiency anemia.

4. A 16-year-old previously healthy boy has had epigastric pain for 3 months. Upper endoscopy revealed evidence of erosive gastritis. Rapid urease test results are positive, and gastric biopsy histology shows inflammation along with spiral-shaped bacteria. He has no known drug allergies. Which one of the following is the most appropriate 14-day treatment regimen for this patient?

   A. Amoxicillin, clarithromycin, and metronidazole.
   B. Amoxicillin, high-dose proton pump inhibitor (PPI), and bismuth subsalicylate.
   C. Amoxicillin, high-dose PPI, and clarithromycin.
   D. Amoxicillin, high-dose PPI, and metronidazole.
   E. Bismuth subsalicylate, high-dose PPI, and clarithromycin.

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5. A month ago, a 12-year-old girl finished a 2-week course of triple therapy for endoscopically confirmed peptic ulcer disease with *H pylori* identified on gastric biopsies. This was her first course of antibiotics. Which one of the following is the most appropriate follow-up test to obtain to confirm the eradication of *H pylori?*

   A. Lactose breath hydrogen test.
   B. Peripheral eosinophil count.
   C. Repeated endoscopy.
   D. Serologic antibody test.
   E. Stool antigen test.

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