

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Helicobacter pylori Detection and Eradication in Pediatric and Adult Patients



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G&H What is the epidemiology of *Helicobacter pylori* infection in the United States?

BG As data from the National Health and Nutrition Evaluation Survey demonstrated, *Helicobacter pylori* infection in the United States occurs at a higher rate among minority groups—as high as 64% in those who are of Mexican American descent and 52% of non-black Hispanics compared with 21% of non-Hispanic whites. Among immigrant populations, these higher rates are not limited to first-generation immigrants but later generations as well.

G&H What is the environmental risk of *H pylori* exposure?

AE *H pylori* is now listed as a US Environmental Protection Agency Contaminant Candidate List 3 pathogen. It is also under consideration for regulation under the National Primary Drinking Water Service, a reflection of an increased recognition that this bacteria can be found in water. In an interesting study from Delaware, in which water samples were tested from fresh water, estuary or typical bay mixed water, and beach sites, the presence of *H pylori* correlated with salinity. Although it might appear obvious to suspect that the bacteria would most easily colonize a fresh water supply, the data showed that, surprisingly, the most saline ocean water samples had the

highest concentrations of *H pylori*. However, it should be noted that *H pylori* was found across all environments.

A second study, conducted in Pennsylvania, tested for the presence of *H pylori* in well water. Interestingly, in addition to *Escherichia coli* (a common contaminant in well systems, especially in more rural areas), *H pylori* was also frequently detected in these well water systems. The suspected mechanism of contamination was attributed to nearby ground septic systems. The families who used these wells were frequently found to be infected with both bacteria, demonstrative of the fecal-oral route of both *H pylori* and *E coli* transmission.

G&H What is the impact of *H pylori* infection in pediatric patients?

BG *H pylori* is a pediatric infection worldwide. Although it is typically acquired in childhood, symptoms and any related diseases often do not present until adulthood. In the United States, *H pylori* should be considered a relatively common infection that can affect approximately 1 in 4 children. The initial bacterial colonization is often achieved in childhood, as there are typically no other conditions that can detract *H pylori* from acquiring its biologic niche in the stomach. In addition, there are gastrophysiologic characteristics unique to children that can enhance colonization and persistence.

G&H How does the natural history of *H pylori* compare between adults and children?

BG The majority of pediatric patients with *H pylori* infection are asymptomatic. When symptoms do occur, many of the same consequences of *H pylori* experienced in the adult population occur in children as well. These include chronic gastritis and peptic ulcer disease. Although duodenal and gastric ulcers occur, they do so less frequently than in adults.

One of the new areas of research in the field of *H pylori* infection of the pediatric population involves extragastric disease (ie, conditions occurring outside of the stomach that have been associated with *H pylori* infection). These extragastric associations that have been described include idiopathic thrombocytopenic purpura (ITP), short stature and poor weight velocity, food allergy, and even sudden infant death syndrome. It is important to recognize that these conditions have been linked to *H pylori* infection primarily based on studies demonstrating an epidemiologic association. However, more recent studies have begun to link *H pylori* eradication with the resolution of iron-deficiency anemia, improvement in growth parameters, and, in adults, resolution of ITP.

AE The sequelae of *H pylori* infection in adults is wide-ranging, with gastritis occurring in nearly every case. However, many adult patients are completely asymptomatic. The frequency and occurrence of dyspepsia remain controversial. What is undisputed are the other more advanced sequelae. For example, there is a significant association with the development of peptic ulcer disease, with duodenal and gastric ulcers occurring in up to 15% of individuals over their lifetime. More insidious diseases such as adenocarcinomas and low-grade B-cell lymphomas occur in a small proportion of infected individuals, with an overall lifetime risk of less than 1%.

However, this association is so important that the World Health Organization has classified *H pylori* as a group 1 carcinogen. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma occurs at a lower rate compared with adenocarcinoma. Interestingly, it remains the only cancer that can be cured with antibiotic therapy and eradication of *H pylori* if caught at an early stage. Patients with *H pylori* gastritis may progress to gastric atrophy, intestinal metaplasia, dysplasia, and ultimately carcinoma.

G&H What are the most common methods of *H pylori* transmission among family members?

AE Three methods of *H pylori* transmission have been proposed: gastro-oral, fecal-oral, and oral-oral. Among

these methods, gastro-oral transmission tends to be the easiest. *H pylori* has been found in emesis, which is the most likely way for family members to spread the infection via gastroenteritis episodes. When a child develops acute infectious enteritis, the risk of infection among other family members is significantly greater.

In a study conducted in California, in which 2700 household members were monitored through 4 public health clinics, an overall incidence of *H pylori* infection of nearly 7% was observed (with an incidence of up to 21% in very young children). Here, the greatest predictive risk factor was the presence of gastroenteritis occurring in 1 of these children during the time frame associated with vomiting and/or diarrhea. In contrast to vomiting, which is particularly amenable for *H pylori* transmission, very little *H pylori* is found in solid stool. However, these levels may be increased in cases of rapid intestinal transit, such as when diarrhea is present.

Transmission can occur between mother and child, but it is most prevalent among siblings. The presence of *H pylori* in an older sibling has a strong effect on the risk of acquired infection in younger siblings, especially when their age difference is small (<3 years). As the number of siblings in the family grows, the adjusted odds ratio increases, indicating an increased risk of having *H pylori* in the familial cohort.

G&H What information should be gathered when assessing a pediatric patient with suspected *H pylori* infection?

BG First, it is necessary to obtain a family history of not only *H pylori* infection but also of upper gastrointestinal tract disease (such as ulcers and gastric cancer). It is also important to consider the demographics of the individual pediatric patient. Low socioeconomic status, certain ethnicities and races, and immigrant status have all been shown to be risk factors for higher rates of *H pylori* infection. Understanding the demographics of the family is a key factor when deciding whether to initiate testing for *H pylori* based on the presenting symptoms, particularly in pediatric patients.

AE We also know that, in addition to demographic factors such as age and socioeconomic status, the risk of acquiring *H pylori* infection is often based on which other family members are infected. As mentioned above, one of the best predictors for infection is the number of siblings in the family. For example, a large Latin American study showed that both crowded living conditions and the number of children in the household (typically greater than 3) significantly increased the risk of acquiring the infection (with odds ratios of 1.7 to 1.8).

G&H What do the American College of Gastroenterology guidelines state regarding *H pylori* testing in children and adults?

BG The most recently published guidelines recommend that *H pylori* testing be performed in a child if there is a first-degree relative with gastric cancer. Additionally, *H pylori* testing should be performed if a child has refractory or persistent iron deficiency and/or iron-deficiency anemia.

AE Guidelines for *H pylori* testing in adults are slightly different than in children, although testing is still clearly grouped into tests of active infection vs tests of exposure. There is an increasing recognition that, in low-prevalence groups, the accuracy of serology is diminished, leading to a general trend in favor of focusing on tests of active infection. If endoscopy is indicated in the adult patient, it would allow confirmation of infection by urease test, histology, or culture. If the patient does not require endoscopy for another reason, noninvasive tests such as the urea breath test and the stool antigen test should be utilized. American College of Gastroenterology (ACG) guidelines state that in populations with a low probability of *H pylori*, nonendoscopic tests such as breath testing and stool antigen tests offer a superior positive predictive value compared with serology testing, which would only indicate past exposure.

G&H When should treatment of *H pylori* infection be initiated in pediatric patients?

BG A global test-and-treat strategy is not recommended. In the presence of *H pylori*-positive peptic ulcer disease, eradication is clearly recommended, and the evidence is irrefutable in this setting. When *H pylori* infection is detected in the absence of peptic ulcer disease, treatment should still be considered. In these cases especially, it is important to obtain a family history for that pediatric patient. If there is a first-degree relative with gastric cancer, treatment should be offered if the pediatric patient is found to be positive for *H pylori*.

G&H What are the main causes of treatment failure for *H pylori* infection?

AE There are 2 main causes for treatment failure. The first is antibiotic resistance of *H pylori* to the particular antibiotic regimen being used, and the second is related to poor patient compliance with the treatment regimen. To overcome the problem of resistance, antibiotic regimens should be chosen carefully to incorporate the drugs known to be most effective. The importance of maintaining full antibiotic sensitivity has led some experts to suggest the use of at least a 3-drug regimen. Knowing the antibiotic sensitivity patterns for the

H pylori strains present in the local area may be helpful for influencing the choice of antibiotics. In addition, an antibiotic history from the patient can be helpful. For example, if the patient has been exposed to clarithromycin or metronidazole in the past (especially as an adult), it is less likely that their bacterial strain will be sensitive to that regimen.

G&H How significant of a problem is compliance in this patient population?

AE Overall, patient compliance is not good. Studies have shown that large numbers of patients are not compliant with their *H pylori* treatment regimens and that most patients probably do not complete their entire regimen. Approximately 10% of patients given antibiotic therapy for *H pylori* infection will fail to take more than 60% of their medication, and approximately 30% of patients will take less than 90% of their medication. This will inevitably impact patient outcome and have a negative effect on future sequelae of the infection and the disease.

G&H What benefits are associated with successful eradication of *H pylori* infection?

AE It is important to ensure that *H pylori* infection is eradicated with the first treatment because data clearly show that subsequent eradication regimens become less effective as *H pylori* becomes sensitized and increasingly resistant.

When *H pylori* is successfully eradicated, studies have shown an associated decrease in ulcer rates. In contrast, when the infection is not successfully eradicated, recurrence of duodenal ulcers (59% within 6 months) and gastric ulcers (69% within 6 months) is typical. Additionally, successful eradication of *H pylori* may result in up to 7 years of improved dyspeptic symptoms in some patients that otherwise would require significant healthcare expenditures. Data also support a reduced risk of adenocarcinoma in eradicated patients.

G&H What types of *H pylori* testing are recommended?

BG ACG guidelines predominantly focus on 2 main categories of diagnostic tests: invasive and noninvasive tests. Invasive tests include endoscopy and biopsy, coupled with a urease test, histology, or culture of the biopsies (if the facilities are available). Noninvasive tests include the breath test and the stool antigen test. The guidelines state that the initial diagnosis of *H pylori* infection should be based upon histopathology in addition to a positive rapid urease test or culture (if the appropriate facilities are available). Although not stated in previous guidelines, testing for eradication of infection is critical following treatment.

As the reference standard of noninvasive tests, the urea breath test is recommended to test for eradication.

G&H What are the current guidelines regarding posttreatment testing for *H pylori* infection?

AE The ACG guidelines recommend posttreatment testing of *H pylori* infection. Specifically, the guidelines recommend the use of a test of active infection such as urea breath testing or stool antigen testing when endoscopy is not required as part of routine follow-up. Urea breath testing is a reliable nonendoscopic test to document eradication, but posttreatment testing must be administered at least 4 weeks after completion of the antibiotic treatment regimen. Furthermore, serologic testing in the posttreatment setting should be avoided, as anti-*H pylori* antibodies may remain detectable for a number of years even after successful eradication. The ACG recommends routine posttreatment testing for those patients who have *H pylori*-associated ulcers, those with persistent dyspeptic symptoms despite apparently successful eradication therapy, all patients with *H pylori*-associated MALT lymphoma, and after resection of early gastric cancer.

BG Adults and children should be tested to make sure that they are completely clear of the infection posttreatment. The urea breath test is an established option for testing in adults and represents a new noninvasive option for testing in children age 3 to 17 years. This test was validated against the gold standard of endoscopy with histology and culture and has demonstrated high sensitivity (95.8%) and specificity (99.2%).

G&H How should the urea breath test be used?

AE This test is intended for the qualitative detection of urease associated with *H pylori* infection in the human stomach. It is indicated for the initial diagnosis and posttreatment monitoring of *H pylori* infection in adult and pediatric patients. (The safety and effectiveness of the test have not been established in children below the age of 3 years.) The urea breath test can be used for monitoring treatment outcome if used at least 4 weeks after completing treatment. For these purposes, the system utilizes an infrared spectrophotometer for the measurement of the ratio of $^{13}\text{CO}_2$ to $^{12}\text{CO}_2$ in breath samples, both in clinical laboratories as well as clinical care settings. The Pediatric Urea Hydrolysis Rate is provided as a web-based calculation for all pediatric test results.

G&H How should a negative urea breath test result be interpreted?

AE A negative result does not rule out the possibility of *H pylori* infection, due to rare cases of false-negative

results. If clinical signs still suggest *H pylori* infection, the patient should be retested using a new sample or an alternative method.

G&H What can cause false-negative or -positive results with this test?

BG False-negative results typically occur due to ingestion of an interfering agent within 2 weeks prior to the test. Potential interfering agents include proton pump inhibitors, certain antibiotics, and bismuth preparations. Premature postdose breath collections may also provide a false-negative result, such as when the test is conducted less than 4 weeks after completing antibiotic eradication therapy. False-positive test results can arise from a urease-producing organism that may also be present in the stomach.

G&H What adverse events have been associated with this test?

AE In postapproval use of this test in adults, a number of adverse events have been identified as occurring in very small percentages of patients. These adverse events include anaphylactic reactions, hypersensitivity, rash, dyspeptic-type symptoms, skin tingling, vomiting, and diarrhea. Because these adverse events were voluntarily reported, it is not always clear if there was actually a causal relationship to the test itself.

In 2 clinical trials of pediatric patients between the ages of 3 and 17, adverse events reported as being experienced by more than 1% of patients included vomiting, oral-pharyngeal pain, nausea, restlessness, stomachache, belly pain, and diarrhea. Most of these were experienced within minutes to hours of ingestion of the solution.

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Dr Gold is a consultant and scientific advisor for Otsuka. Dr Elfant is a consultant and on the speakers bureau for Otsuka.

Suggested Reading

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