What Is New Related to *Helicobacter pylori* Infection in Children and Teenagers?

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*Helicobacter pylori* infection is a common bacterial infection for humans, and the organism is the most prevalent gastric microbial pathogen. However, the major route of transmission remains poorly understood. The outcome of chronic *H pylori* infection varies from asymptomatic gastritis to peptic ulceration and gastric malignancies. Recently, *H pylori* has been associated with the development of extradigestive disorders, including refractory iron-deficiency (sideropenic) anemia and chronic autoimmune thrombocytopenic purpura. Virulence factors of *H pylori* and host genetic factors are both considered important determinants of disease outcome. Multiple tests, including novel noninvasive approaches, are available for establishing the presence of *H pylori* infection, but there is still little consensus about which study should be performed and in what clinical setting. Eradicating *H pylori* uses combination therapy, including a proton pump inhibitor and 2 antibiotics taken twice daily for 7 to 14 days. Antibiotic resistance is a growing and serious problem that interferes with the success of eradication therapy. Testing and eradication therapy for *H pylori* are currently recommended only for the subset of infected persons in whom the disease sequelae are proven or highly suspected.


It is currently estimated that approximately half of the world’s human population is infected with the gastric bacterial pathogen *Helicobacter pylori*.1 However, the prevalence of *H pylori* is not homogeneous worldwide: it varies depending on the patient’s chronological age, country of origin, ethnic background, and socio-economic conditions during childhood.1,2 There are vigorous innate and adaptive immune responses to *H pylori* infection. Nevertheless, unless specific eradication therapy is provided, the gastric infection persists for a lifetime.3 Even though childhood is the critical time for acquiring *H pylori*, the major route of bacterial transmission remains poorly understood. It is believed that *H pylori* infection spreads via person-to-person transmission, including fecal-oral, gastric-oral, and oral-oral routes.1,2 Humans appear to be the main reservoir for the organism. Recent epidemiological studies and research using molecular typing of *H pylori* strains demonstrate that the intrafamilial transmission of infection, especially mother-to-child or child-to-child, is important.3,4 On the other hand, waterborne transmission of *H pylori*, via contaminated well water and river water, also appears likely.6

Among identified Helicobacter species, *Helicobacter heilmannii* is now recognized...
as a second gastric bacterium that is pathogenic in humans. The prevalence of *H. heilmannii* in humans is 0.5%, much lower than that of *H. pylori*. The organism causes mild gastritis in infected persons but may also, like *H. pylori*, cause mucosa-associated lymphoid tissue (MALT) gastric lymphoma. There are sporadic cases reported in children of *H. heilmannii*–induced gastritis and associated peptic ulcer disease. *Helicobacter heilmannii* is transmitted from infected household pets, such as dogs and cats.

**DISEASE OUTCOME, INCLUDING EXTRADIGESTIVE DISORDERS**

**Gastroduodenal Diseases**

*Helicobacter pylori* is now firmly established as the most common gastric microbial pathogen causing gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric MALT lymphoma in adults. Based on 3 large-scale seroepidemiological case-control studies, the International Agency for Research on Cancer (World Health Organization; Geneva, Switzerland) in 1994 classified *H. pylori* as a group 1 (definite) carcinogen. A recent prospective human study strongly supports an association between *H. pylori* infection and the development of gastric cancer in adults. In more than 60% of patients with low-grade gastric MALT lymphoma, *H. pylori* eradication results in a favorable long-term outcome.

On the other hand, *H. pylori* is associated with chronic gastritis and duodenal ulcers during the childhood years. Successful eradication of *H. pylori* markedly reduces the rate of recurrence of duodenal ulcers in affected children. Gastric ulcers are much less common for children than they are for adults. Nevertheless, a retrospective multicenter study in Japan demonstrated a relationship between *H. pylori* infection and the development of gastric ulcers in children. However, most children with *H. pylori* infection are asymptomatic without disease sequelae. In relation to *H. pylori*–associated gastric malignancies in pediatrics, there are a few cases of the MALT lymphoma, but there are no reports of adenocarcinoma.

Apparent symptomatic benefits of *H. pylori* eradication in children with gastritis alone (ie, no evidence of mucosal ulceration) have been reported by some authors, but others report negative results. In a meta-analysis of studies undertaken in children, Macarthur et al found no relationship between recurrent abdominal pain and *H. pylori* infection.

**Hematologic Diseases**

Since the first report suggesting a link between *H. pylori* infection and refractory iron-deficiency anemia, many studies support a role for *H. pylori* in the development of refractory (also called sideropenic) iron-deficiency anemia. The prevalence of *H. pylori* is higher in patients with anemia than in control subjects. The relative risk of iron-deficiency anemia in *H. pylori*–infected adolescents is 2.9 (95% confidence interval, 1.5-5.6) compared with age- and community-matched uninfected controls. A prospective open study demonstrated that 92% of adults receiving from anemia, showing increased serum ferritin levels, after *H. pylori* infection is eradicated. A recent cohort study in children also indicates a role for *H. pylori* infection in the development of iron-deficiency anemia. Interestingly, sideropenic anemia is not associated with hematemesis or tarry stools, suggesting that long-standing *H. pylori* infection itself can cause anemia in the absence of active bleeding from the gastrointestinal tract. A relationship between *H. pylori* and iron-deficiency anemia remains controversial because it is not clear why anemia occurs only among a subset of infected persons.

An increasing number of reports about adults suggest a relationship between chronic autoimmune idiopathic thrombocytopenic purpura (ITP) and *H. pylori* infection. In a recent review, more than half of chronic ITP patients showed either complete or partial platelet response after the successful eradication of *H. pylori*. However, the prevalence of *H. pylori* infection in patients with chronic ITP varies wildly, from 22% to 100% in previous reports, with an average of 58%. Eradicating *H. pylori* resulted in an increase in platelet count in 5 of 9 children with chronic ITP. Possible mechanisms include direct bacterial effects, systemic effects provoked by inflammatory mediators, or cross reaction between bacterial and host antigens. Takahashi et al reported that molecular mimicry between antiplatelet antibodies and an *H. pylori* protein (cytotoxin-associated gene product; CagA) could be responsible for the pathogenesis of *H. pylori*–associated chronic ITP.

**Skin Diseases and Others**

Large-scale epidemiological studies also indicate a potential role for *H. pylori* infection in the pathogenesis of atopic disorders. In addition, an association of *H. pylori* infection with chronic urticaria has been reported in case studies but not yet confirmed in case-control studies. Possible pathogenesis could include *H. pylori*–induced IgE production or molecular mimicry.

In adults, microorganisms such as *Chlamydia pneumoniae* and cytomegalovirus have been considered risk factors for cardiovascular diseases. *Helicobacter pylori* also has been proposed as a risk factor for cardiovascular disorders, but this association remains controversial.

*Helicobacter pylori* infections may be associated with growth retardation in children, although there are results both for and against this association. Potential biological possibility for this association could relate to the effect of *H. pylori* and resulting inflammation on gastrin-derived hormones (eg, leptin, ghrelin) involved in controlling appetite. In the pathogenesis of sudden infant death syndrome, most investigators now agree on the absence of a relationship with *H. pylori* infection.

**PATHOGENESIS OF GASTRODUODENAL DISEASES**

**Disease Spectrum**

The outcome of chronic *H. pylori* infection varies from asymptomatic gastritis to peptic ulceration and gastric malignancies. It has been estimated that roughly 13% to
20% of individuals infected with *H. pylori* will develop either peptic ulcer disease or gastric malignancies in their lifetimes. Recognition of the wide spectrum of *H. pylori* disease outcome is essential in establishing appropriate clinical strategies for managing the infection. At present, however, it is impossible to predict future disease outcome for an infected individual. The high prevalence of *H. pylori* infection but low incidence of gastric cancer in African countries suggests that there is much more to understand about the pathogenesis of *H. pylori* infection.

**Gastric Inflammation**

Long-term infection with *H. pylori* induces chronic inflammation in gastric mucosa in virtually all infected persons. Mucosal atrophy results in a subset of those who are infected. Chronic imbalance between epithelial cell proliferation and programmed cell death can result in mucosal atrophy in the stomach, which is the first event in a series that ultimately lead to gastric carcinogenesis. In the lamina propria of the gastric mucosa, *H. pylori* induces a T-cell infiltrate that is predominantly of the T\(_\eta\) phenotype (that is, interferon-\(\gamma\) predominant). The severity and distribution of *H. pylori*-induced inflammation differs among infected persons. In some, chronic inflammation results in antral-predominant gastritis with hyperacidity and predisposition to peptic ulcer disease. In others, the infection results in corpus-predominant atrophic gastritis with hypoacidity and a predisposition to the development of adenocarcinoma. Both virulence factors of the organism and host genetic factors are considered important determinants of ultimate clinical outcome. Early infection with *H. pylori* appears to be an additional risk factor for gastric cancer. The long-term responses to infection likely explain why there are no *H. pylori*-related gastric cancers reported in children.

**Virulence of H Pylori**

A vacuolating cytotoxin (VacA), CagA, factors related to a pathogenicity island (the *cag* pathogenicity island), and attachment factors such as BabA and SabA have been the subject of recent interest. The *cag* pathogenicity island includes the *cag* gene, which encodes the CagA protein and several genes encoding a type 4 secretion system. Recent studies demonstrate that *H. pylori* injects the CagA protein into the cytosol of the host cell via a molecular syringe formed by the type 4 secretion system. The translocated CagA protein then is phosphorylated on tyrosine residues and results in alterations in the morphology of epithelial cells. An epidemiological study has shown that *H. pylori* strains carrying the *cag* pathogenicity island are linked to more severe disease outcomes. In Japan, where the prevalence of gastric cancer is high, more than 90% of *H. pylori* strains carry the *cag* gene, and the presence of CagA antibody does not correlate with disease outcome. It appears that the number of repeated sequences of tyrosine phosphorylated residues on CagA is more important for pathogenesis than the presence of the *cag* marker alone.

**Genetic Factors of the Host**

Twin studies implicate a genetic link with duodenal ulcers that is independent of *H. pylori* infection. Additional evidence for the role of genetic factors is the increased risk of cancer among first-degree relatives of persons with gastric adenocarcinoma. Moreover, in children with *H. pylori* infection, pentagastrin-stimulated gastric acid secretion is significantly higher for individuals with duodenal ulcers compared with subjects with gastritis alone. Recent studies report that genetic polymorphisms of cytokines, including the interleukin IL-1\(\beta\), the IL-1R receptor, the tumor necrosis factor TNF-\(\alpha\), and the interleukin IL-10, are associated with gastric cancer.

**DIAGNOSTIC TOOLS**

About testing for *H. pylori* infection, practice guidelines for children have been published by the Canadian *Helicobacter* Study Group (Toronto, Ontario), the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (Flourtown, Pa), the European Paediatric Task Force on *Helicobacter pylori* (Budapest, Hungary), and the Japan Pediatric *Helicobacter* Study Group (Tokyo). All of the reports recommend *H. pylori* testing only when symptoms are sufficient to justify the potential risks of eradication therapy and when peptic ulcer disease is either proven or strongly suspected. Because there is no compelling evidence about a positive relationship between recurrent abdominal pain and gastric infection, *H. pylori* testing is not recommended in this common clinical setting. In addition, there is little evidence to support the contention that there is a substantial public health benefit to screening for *H. pylori* infection in populations of asymptomatic children.

When testing to establish the diagnosis of *H. pylori* infection is judged necessary and appropriate, several methods—both invasive and noninvasive—are available for use in clinical practice. However, there is still little consensus about which test should be performed. Invasive diagnostic methods require endoscopic biopsies and include rapid urease testing, histological examination, and culture. Used in combination, these tests are still considered the gold standard. Therefore, biopsies-based tests are recommended as the most reliable diagnostic method in children. However, the relatively invasive and costly approach of endoscopic biopsies has raised questions about the merits of indirect testing to determine *H. pylori* status. Serum *H. pylori*-specific IgG antibodies can be tested with available commercial immunoassay kits, but these are not reliable for use in children, particularly in a setting of low prevalence. Especially in young children (<10 years), levels of *H. pylori*-specific antibodies can be low and result in false-negative test results. Recently, a novel serum *H. pylori*-specific IgG immunoassay using microchannels has been developed, showing an overall diagnostic accuracy of 95%. Serum titers of *H. pylori*-specific antibodies, both IgG and IgA subclasses, also continue to show positive results for several months or longer after *H. pylori* is eliminated from the host with specific eradication therapy. Thus, positive results from IgG antibody
tests do not necessarily represent active infection with *H pylori*.

Among noninvasive tests, 13C-urea breath testing (13C-UBT) detects urease activity, which is a feature of all *H pylori* strains. Multiple studies have shown that 13C-UBT has both high sensitivity and high specificity for diagnosing active *H pylori* infection in children.33-55 Some authors also report that the 13C-UBT is reliable for use in children under 6 years of age.6 However, it is often difficult to perform 13C-UBT in young children.57 Furthermore, oral urease-producing bacteria may cause false-positive results.55 Graham et al57 reported that proton pump inhibitors (PPIs) decrease the diagnostic sensitivity of 13C-UBT, suggesting that PPIs reduce the urease activity of *H pylori*. Although the precise cutoff value for use in children remains to be determined, 1 multicenter study used operating characteristic curve analysis to demonstrate that 13C-UBT with a cutoff value of 3.5% stable isotope enrichment over baseline produces a sensitivity of 97% and specificity of 98%, compared with biopsy test results used as the gold standard.55 Levels of 13C in end-expiratory breath samples was measured by isotope ratio mass spectrometry, but less expensive infrared isotope ratio spectrometry is also widely used as an alternative.55

More recently, another noninvasive test, the stool antigen enzyme-linked immunosorbent assay, has been developed. *Helicobacter pylori* antigens are in excreted stools and can be detected by commercial test kits using either polyclonal or monoclonal antibodies. Multicenter studies with children have shown that the stool antigen test with polyclonal antibodies has a sensitivity and specificity of more than 93%.58,59 However, in 1 pediatric study in Italy, the positive predictive value was only 54%.60 Stool antigen testing with monoclonal antibodies may prove to have better accuracy.61 A novel stool antigen test with monoclonal antibodies using a chromatographic method has shown good test results in both adults62 and children.63 The advantage of this test is that it can be performed in a doctor’s office and the result is known within 10 minutes. Verification of these findings in prospective trials in a variety of clinical settings is needed before the stool antigen test can be considered for routine use by physicians working in a primary care setting.

With regards to *H pylori* eradication, the Maastricht 2-2000 consensus report recommended either 13C-UBT or biopsy and stool antigen testing as an alternative if 13C-UBT is not available.64 The Canadian *Helicobacter* Study Group recommended 13C-UBT as a reliable test for estimating *H pylori* eradication in children.66 However, objective evidence of the reliability of indirect tests for estimating *H pylori* eradication is lacking, particularly for children. Testing at least 4 weeks after the completion of a full course of the therapy is recommended,48,50 both to avoid false-positive test results and to capture those patients with inadequate therapy who develop recrudescence of the gastric infection.

### TREATMENT CONSIDERATIONS

#### Indications for *H pylori* Eradication

All current recommendations for managing cases with children66,68-70 indicate that evidence of *H pylori* infection in a child with peptic ulcer disease is a definite indication for instituting eradication therapy. In addition, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition also recommends eradication therapy for the very small subset of *H pylori*-infected children with either MALT lymphoma or atrophic gastritis accompanied by intestinal metaplasia.49 Eradication therapy likely is also recommended for *H pylori*-infected children with a family history of gastric adenocarcinoma.1 The Maastricht 2-2000 consensus report strongly recommended *H pylori* eradication in infected adults with atrophic gastritis and in those with a first-degree relative with gastric cancer.48 On the other hand, it remains to be proven whether eradicating *H pylori* has any benefit for the majority of children without ulcers who have gastritis alone.48,49 In *H pylori*-infected children with unexplained dyspepsia, symptoms could possibly relate to other conditions, including gastroesophageal reflux disease or irritable bowel syndrome. Based on currently available evidence, it is doubtful that *H pylori* eradication provides better symptomatic relief compared with acid suppression treatment alone in patients with nonulcer dyspepsia and coexisting *H pylori*-induced gastritis.45,66

In settings of unexplained iron-deficiency anemia and chronic autoimmune ITP, recommending *H pylori* eradication therapy still has not been fully justified. Although *H pylori* eradication results in complete or partial response in roughly half the cases, some authors advise eradication therapy for all chronic ITP patients with the infection.49 Such an approach may well be warranted to avoid the disadvantages of long-term immunosuppressive treatments in at least a subset of affected patients.45 However, larger studies are needed to confirm the validity of such an approach.66 Updated guidelines do not recommend eradication therapy for chronic ITP, even though *H pylori* testing might be warranted in some patients.67 Eradication of *H pylori* could be considered an option for therapy for children with chronic ITP, especially for those who are refractory to conventional therapies and those who have frequent episodes of disease recurrence.

Eradicating *H pylori* also improves long-standing refractory iron-deficiency anemia.68 At present, children with a first episode of iron-deficiency anemia and no complications should be initially treated with iron supplementation alone irrespective of *H pylori* status. Eradicating *H pylori* could be considered in cases refractory to iron supplementation and in the setting of frequent relapses, assuming that screening serology for celiac disease has been taken and the test results are negative.

#### Eradication Regimens

In adults, a 7- to 14-day course of triple therapy—using regimens consisting of a PPI (or ranitidine bismuth citrate, if available) combined with clarithromycin and amoxicillin or metronidazole—is currently recommended as the first line of treatment options.48 In children, 7- to 14-day courses of the same PPI-based triple therapy are recommended.48,66 Dosages based on body weight for use in children are provided in the clinical practice guideline of the North American Society for Pediatric...
Failure of Eradication Therapy

The major factors that cause eradication therapy to fail are inadequate compliance and antibiotic resistance (both primary and secondary) of *H pylori* strains. Antibiotic resistance of *H pylori* is a growing serious problem in children. For instance, clarithromycin resistance is detected in up to 45% of *H pylori* isolates from children. A point mutation of the 23S ribosomal RNA gene, most commonly A-to-G substitution at nucleotide 2142 or 2143 (A2142G or A2143G), is found in *H pylori* strains resistant to clarithromycin. Resistance is a critical issue because eradication rates with a 7-day course of triple therapy (PPI, amoxicillin, and clarithromycin) are significantly higher among subjects infected with clarithromycin-resistant strains (89%) compared with those with drug-resistant strains (36%).

Acquired metronidazole resistance of *H pylori* is also a concern. However, the broad range of minimum inhibitory concentrations of metronidazole against *H pylori* isolates indicates that it can be difficult to determine a precise cutoff value. In practice, if compliance is ensured, more than three quarters of metronidazole-resistant *H pylori* strains can be successfully eradicated with a triple regimen.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition clinical practice guideline presents 2 second-line options for use in children. These include either (1) bismuth subsalicylate, metronidazole, a PPI, and tetracycline or amoxicillin or (2) ranitidine bismuth citrate, clarithromycin, and metronidazole. However, issues of drug availability and lack of consensus about the safety of using bismuth-containing compounds in children limit the practical use of these treatment recommendations. Another approach is to prescribe an alternative triple-therapy regimen but avoid using an antibiotic used in a prior course of therapy. For instance, if clarithromycin was prescribed previously, then metronidazole is substituted in the second course of eradication therapy. One randomized study showed that eradication rates are statistically higher in patients when susceptibility testing directs therapy compared with those without testing. However, practical issues of access to culture and antibiotic susceptibility testing and cost considerations currently limit this approach in daily clinical practice.

FUTURE DIRECTIONS

With respect to therapeutic strategies for *H pylori*-associated diseases, the development of highly effective and safe monotherapy is urgently required. Although many studies report the prophylactic and therapeutic efficacy of an *H pylori* vaccine in animal models, making the transition to humans has proven difficult. As in lower intestine, probiotics also transiently colonize the stomach. Some studies show that administrations of probiotics are effective in reducing and preventing *H pylori* infection both in animal models and in humans.

Further studies are also necessary to identify early markers of an increased risk for gastric cancer. Although the prevalence of gastric cancer varies among countries, gastric cancer is the third most frequent cancer worldwide and the second leading cause of death from cancer. To clarify the pathogenesis of gastric cancer, it is important to perform comparative studies about both the spectrum of gastric pathology and the differences between *H pylori* strains isolated in developed countries in North America and Europe and those from the Far East, including Japan. The occurrence of gastric ulcers associated with *H pylori* in children serves as a useful model for identifying early markers of gastric cancer risk.

It appears that *H pylori* has infected humans for thousands of years. Some studies suggest that *H pylori* colonization of the stomach serves as a protective factor against gastroesophageal reflux disease, Barrett esophagus, and adenocarcinoma of the esophagus. Thus, the development of prevention and therapeutic strategies against *H pylori* infection may have to target the subset of infected humans most likely to develop disease sequelae. Creating genetic profiles of both the microbe and the host likely will serve to achieve this goal.

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REFERENCES


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**Announcement**

Pediatric Dermatology Articles in May *Archives of Dermatology*. Original studies and observations concerned with the diagnosis and treatment of diseases commonly or exclusively seen in children are the focus of the May issue of the *Archives of Dermatology*. Common therapeutic concerns of children and adolescents are immunotherapy of warts, isotretinoin to treat acne, and the use of general anesthesia for pediatric dermatologic procedures. More unusual treatment is presented for brown recluse spider bites and infantile digital fibromatosis. Pediatric diagnostic reports include aplasia cutis congenita and the risk of sagittal sinus thrombosis, restrictive dermopathy associated with transposition of the great arteries, and aquagenic wrinkling of the palms in patients with cystic fibrosis.