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New Diagnostic Strategies for Detection of
Helicobacter pylori Infection in Pediatric Patients

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Abstract

Helicobacter pylori (H pylori) is a common chronic bacterial infection that is an important cause of peptic ulcer disease and gastroduodenal disease in children. H pylori is also associated with extragastric manifestations, including growth reduction, iron-deficiency anemia, and idiopathic thrombocytopenic purpura. Current guidelines recommend endoscopy with biopsy for the definitive demonstration of H pylori infection. In contrast to serology, the fecal antigen test and the urea breath test provide reliable, sensitive, and specific results for detecting active H pylori infection in children before and after treatment. The first-line treatment option for pediatric patients is triple therapy with a proton pump inhibitor and 2 antibiotics, which include amoxicillin and clarithromycin or metronidazole. Decreasing eradication rates and the emergence of antibiotic-resistant strains of H pylori have led to the use of other treatments, such as sequential therapy or triple therapy with newer antibiotics, particularly in geographic areas with high rates of antibiotic resistance. Patients should be tested after treatment to confirm eradication, as the absence of symptoms does not necessarily mean that H pylori is no longer present. This clinical roundtable monograph provides an overview of H pylori infection, as well as expert insight into the diagnosis and management of H pylori infection in children.
Table of Contents

*Helicobacter pylori* Infection in Pediatric Patients: Introduction

Benjamin D. Gold, MD 3

Diagnosis of *Helicobacter pylori* Infection in Pediatric Patients

Mark A. Gilger, MD 9

Treatment Options for Pediatric Patients With *Helicobacter pylori* Infection

Steven J. Czinn, MD 13

New Diagnostic Strategies for Detection of *Helicobacter pylori* Infection in Pediatric Patients: Discussion

Benjamin D. Gold, MD, Mark A. Gilger, MD, and Steven J. Czinn, MD 17

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Helicobacter pylori Infection in Pediatric Patients: Introduction

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Helicobacter pylori (H pylori) was first identified in gastric biopsy specimens by Dr Barry Marshall and his mentor, Dr Robin Warren, in the early 1980s. Several years after, it became apparent that in pediatric patients, the infection was associated with gastritis as well as peptic ulcer disease (to a lesser extent). Dr Steven J. Czinn was one of the first pediatric investigators to describe the association between H pylori and gastritis as well as peptic ulcer disease in children. At that time, the bacteria were known as Campylobacter pylori based on morphology, growth conditions, and sensitivity to metronidazole, among other factors. However, there were several key differences between Campylobacter pylori and the Campylobacter species. Through a series of molecular and biochemical assays, Campylobacter pylori was characterized in 1989 into its own genus, H pylori.

To this day, H pylori infection remains an important cause of gastroduodenal disease, including peptic ulcer disease, in children. When the role of H pylori infection as a pathogen in pediatric patients was identified, several consensus-based guidelines were subsequently developed. In 1999, the Canadian Helicobacter Study Group released guidelines for the management of pediatric H pylori infection. In 2000, recommendations for the diagnosis and management of H pylori infection in children were published by the European Paediatric Task Force, the North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN), and the European Society of Pediatric Gastroenterology (ESPGHAN). Since those original clinical practice guidelines were published, several reports have evaluated treatment and diagnosis. Revised guidelines from Canada were published in 2005 and joint NASPGHAN-ESPGHAN guidelines were published in 2011. These consensus guidelines focused not only on the prevalence, epidemiology, and symptoms of H pylori infection, but also on the patient’s family, home environment, geographic location, and quality of life.

Epidemiology

H pylori is estimated to have infected two-thirds of individuals living in developing countries, and 30% to 40% of individuals living in industrialized countries. Pediatricians have continued to contend that H pylori is essentially a childhood-acquired infection in the majority of populations where it is found. In the developing world, household overcrowding and poor water hygiene (particularly fecally contaminated water) has led to a higher overall infection prevalence of H pylori as compared with developed countries. Most individuals are infected during early childhood; in developing countries, 50% of children are infected by the age of 5 years. In contrast, in the United States, only 5% of the population is infected by 5 years of age. However, some data suggest that with immigrant populations moving to the United States, there continues to be a relatively high level of prevalence in pediatric patients. In addition, H pylori is 2-fold to 6-fold more prevalent in black or Hispanic individuals than in white individuals, an increase that may be attributed to a generation cohort phenomenon.

Transmission

Similar to other enteric pathogens, H pylori is primarily transmitted by a fecal-oral route, although gastro-oral and oral-oral transmission is also possible. Although reports regarding zoonotic sources have been inconsistent, there are some provocative data about cats (and, to a lesser extent, dogs) that acquire the infection and pass it back to humans. Some data suggest that there may also be an environmental reservoir of H pylori in water, specifically in fecally contaminated water. This observation may partially explain why this pathogen is so prevalent in countries with poor infrastructure and water hygiene.

Symptoms Associated With H pylori Infection

The presence of symptoms is a controversial area in the
diagnosis and management of *H pylori* infection. In the development of the *H pylori* management guidelines, the focus has been to target the disease manifestations as the potential cause of the symptoms and not necessarily the infection itself.6-8,31 Many *H pylori* infections are silent and without clinically apparent symptoms. When symptoms do occur, they are primarily the result of gastric or peptic ulcer disease, rather than the actual infection. It is important to distinguish between the symptoms of infection and symptoms from gastric or duodenal inflammation and ulcer disease. Although clinical experience may suggest that upper gastrointestinal symptoms will disappear after *H pylori* eradication, it is still important to identify the causes of these symptoms. The ESPGHAN and NASPGHAN guidelines recommend that “the primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *H pylori* infection.”11

Abdominal pain and nausea, among other dyspeptic symptoms, are nonspecific and may be attributable to various diseases, including gastroesophageal reflux disease and functional gastrointestinal disorders.11 To date, treatment trials have failed to clearly and reproducibly demonstrate that any particular symptoms are specifically linked to *H pylori* or resolve after the infection is eradicated.25,26 In fact, a large meta-analysis determined that there was no association between *H pylori* infection status and abdominal pain in children.27 Similarly, large studies of 1221 German children and 695 Swedish children found that *H pylori* infection was not associated with abdominal pain.28,29 Moreover, there are some data to suggest that even in the face of *H pylori* infection eradication, the underlying gastritis can persist for weeks to months before resolving.30-32

Although several interventional studies have demonstrated some improvement of symptoms after treatment of *H pylori* infection, these studies were uncontrolled, and eradication of *H pylori* was not always confirmed following treatment.33-36 Therefore, if a child has symptoms that suggest upper gastrointestinal tract disease, it is important to focus the evaluation on potential causes of those symptoms, such as *H pylori*-associated gastroduodenal disease.

**Influence of Family History**

Family history of gastric cancer is an important component of the diagnosis and management of *H pylori* infection in children. For years, reports have noted an association between peptic ulcer disease and families with a strong history of upper gastrointestinal tract disease—in particular, between gastric or duodenal ulcers and gastric cancer—irrespective of whether testing for *H pylori* infection was performed. The World Health Organization classified *H pylori* as a class I pathogen based on data showing that patients with the infection were found to have a 2-fold to 6-fold greater risk of developing noncardia gastric cancer.11-37 As a result, the ESPGHAN and NASPGHAN revised guidelines consider children to be at high risk of *H pylori* infection if they have a positive family history of gastric cancer.11 Children with a mother or father with gastric cancer are considered to be at a very high risk owing to shared genetic characteristics, environmental factors, and virulence features of the infecting strain of *H pylori*.11 In fact, several studies in adults have shown that eradication of *H pylori* reduces the prevalence of precancerous gastric lesions and may reduce gastric cancer incidence.38-40 As such, diagnostic testing is recommended for children with a primary relative who has gastric cancer.11

**Impact on Quality of Life**

Findings differ regarding *H pylori* infection and quality of life. Some studies have suggested that *H pylori* impacts quality of life in patients with dyspepsia and peptic ulcer disease,41-43 whereas others have indicated that treatment of *H pylori* infection does not impact quality of life in patients with dyspepsia or acid reflux disease.44,45 The proviso here is that it is the disease associated with *H pylori* infection that reduces quality of life. Therefore, as outlined in the updated guidelines (both the Canadian and the NASPGHAN-ESPGHAN documents), the goal of clinicians should be to identify the underlying cause of symptoms, and not just the presence of *H pylori* infection.10,11 Because *H pylori* is a chronic infection of the gastric mucosa that causes persistent inflammation that the host cannot spontaneously clear and resolve, the organism requires eradication when detected or it can impact quality of life.

**Gastroduodenal Disease**

There is a clear association between *H pylori* and gastritis, gastric ulcers, and duodenal ulcers.46-47 Studies have shown that this pathogen causes mucosa-associated lymphoid tissue (MALT) lymphoma in both children and adults.48-51 In fact, when the organism is eradicated, extragastric metastases or sites of MALT lymphoma resolve.11,51-53

Gastric adenocarcinoma is also associated with *H pylori*. The presence of precancerous lesions, intestinal metaplasia, and atrophic gastritis in pediatric patients with *H pylori* was first described by Guarner and colleagues in 2003.38 Frank adenocarcinoma has not been described in pediatric patients, with the exception of a few isolated case reports; however, gastric cancer is clearly
associated with *H. pylori* infection.\(^5^5\),\(^5^6\) It is important to remember when counseling parents about whether to treat *H. pylori* infection in children that gastric cancer is a potential long-term sequelae, especially if the infection is left untreated.

**Extragastric Disease Associations**

Since the original guidelines were published in 1999, research has focused on the association between *H. pylori* and extragastric conditions (ie, those that manifest in areas outside of the stomach and duodenum). Examples of extragastric disease include growth reduction, iron-deficiency anemia, and idiopathic thrombocytopenic purpura (ITP).

The impact of *H. pylori* infection on growth was clearly demonstrated in a study of indigenous populations in Colombia, South America, where gastric cancer rates are high.\(^5^7\) In children aged 4 to 8 years, those infected with *H. pylori* grew an average of 0.022 cm/month slower than *H. pylori*–negative children after adjustment for age, sex, and height (95% CI, 0.008-0.035; Figure 1).\(^5^8\) In a multivariate mixed model of 295 school-aged children that adjusted for age, sex, father’s education, and number of siblings, children who were negative for *H. pylori* infection or who cleared the infection grew significantly faster than children positive for *H. pylori* infection (Figure 2).\(^5^9\)

Studies have also demonstrated an association between *H. pylori* infection and iron-deficiency anemia in children. For example, in a study of 688 children aged 7 to 11 years in native villages in southwestern Alaska, 91% of those with iron deficiency also tested positive for *H. pylori* infection.\(^6^0\) In addition, *H. pylori*–infected children were more likely to have iron deficiency and iron-deficiency anemia than uninfected children. Once the infection was cleared, the iron deficiency and the iron-deficiency anemia resolved. In a study of 219 native Alaskan children...

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**Figure 1.** In a study of indigenous populations in Colombia, children ages 4 to 8 years infected with *Helicobacter pylori* grew more slowly than children without the infection. Adapted from Goodman KJ et al. *Epidemiology*. 2011;22(1):118-126.\(^5^4\)
aged 7 to 11 years who had *H pylori* infection and iron deficiency, treatment and eradication of *H pylori* resulted in a significant reduction in iron deficiency and anemia (Figure 3). Compared with *H pylori*-positive children in the control group, *H pylori*-negative children in the treatment group had a lower prevalence of iron deficiency (adjusted relative risk, 0.62 [95% CI, 0.38-1.01]) and iron deficiency and anemia (adjusted relative risk, 0.22 [95% CI, 0.03-1.50]).

*H pylori* may play a role in the pathogenesis of ITP. A number of studies evaluating *H pylori* eradication and ITP have been conducted in children, albeit with conflicting results. For example, in a randomized controlled trial that included 16 children with ITP and *H pylori* infection, there was no positive effect of *H pylori* eradication on platelet recovery. In contrast, a prospective, controlled multicenter study of children with ITP, including 50 patients who also tested positive for *H pylori*, found that platelet recovery occurred in 39% of patients who had successful *H pylori* eradication (33 of 37) vs 10% of *H pylori*-negative patients who experienced spontaneous remission (17 of 166; *P*<.005). Although the data from these studies did not demonstrate definitive causality between *H pylori* infection and ITP disease, they suggest that gastric colonization by this organism may result in more systemic immune-mediated effects than previously believed.

**Impact on Health as an Adult**

Early exposure to infections may predispose individuals to chronic disease, as well as significantly increase the risk of gastric cancer. The impact on health as an adult highlights the need for eradication. Although data now suggest that *H pylori* might have once been part of the human microflora, the fact remains that if this infection is left untreated, it can have a significant impact on adult health.

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Figure 3. In a study of native Alaskan children ages 7 to 11 years with Helicobacter pylori infection and iron deficiency, treatment and eradication of H pylori reduced iron deficiency and anemia.


References


27. Macarthur C. Helicobacter pylori infection and childhood recurrent abdomi-


40. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to pre-


53. Ohno Y, Kosaka T, Murakoshi K, et al. Remission of primary low-grade gastric lym-


There are no specific symptoms of *H pylori* infection in children. Upper gastrointestinal symptoms, such as recurrent abdominal pain, are not an immediate indication for treatment of *H pylori* infection. The current ESPGHAN and NASPGHAN guidelines do not recommend diagnostic testing for *H pylori* infection in children experiencing pain, nausea, or other dyspeptic symptoms, owing to the nonspecific nature of these events. Several studies have failed to find an association or causal relationship between abdominal pain and *H pylori* infection. In contrast, symptoms of peptic ulcer disease, such as epigastric pain and upper gastrointestinal bleeding, are suggestive of *H pylori* infection. Children with these symptoms should undergo diagnostic evaluation for the infection.

Since symptoms are nonspecific, other factors will help determine whether a symptomatic child should be tested for *H pylori* infection. Children living in poor socioeconomic conditions may benefit from testing. Since rates of *H pylori* are higher in developing countries, children who have lived in these areas are at higher risk. The presence of an immediate family member with gastric adenocarcinoma or gastric MALT lymphoma is a definite indication for pediatric diagnostic testing.

ESPGHAN and NASPGHAN guidelines also recommend *H pylori* diagnostic testing for children with iron-deficiency anemia or anemia that is unresponsive to oral iron therapy, when other causes have been ruled out. Although several studies have found an association between iron deficiency and *H pylori* infection, there are conflicting study data regarding whether treatment of *H pylori* infection corrects iron-deficiency anemia.

### Invasive Testing

Diagnostic testing can be divided into invasive and noninvasive methods. Invasive testing consists of an upper gastrointestinal endoscopy and biopsy followed by culture, rapid urease testing, histopathology, polymerase chain reaction, or fluorescence in situ hybridization (FISH) to assess whether *H pylori* is present in the gastric tissue (Table 1). At this time, upper endoscopy with biopsy is the gold standard for diagnosing *H pylori* infection in children. The ESPGHAN and NASPGHAN guidelines

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>Widely available; evaluates underlying mucosal damage</td>
<td>Expensive; 3 biopsies required; recent use of antibiotics or proton pump inhibitors can lead to false-negative results</td>
</tr>
<tr>
<td>Culture</td>
<td>64</td>
<td>100</td>
<td>Determines antibiotic susceptibility</td>
<td>Expensive; requires special transfer and culture technique; requires up to 1 week for results; recent use of antibiotics or proton pump inhibitors can lead to false-negative results</td>
</tr>
<tr>
<td>Rapid urease tests</td>
<td>95</td>
<td>85</td>
<td>Rapid results; easy to perform; less expensive than histology and culture</td>
<td>Use of formalin, antibiotics, bismuth, or proton pump inhibitors can lead to false-negative results; poor technique or handling will affect results</td>
</tr>
</tbody>
</table>
recommend at least 2 tests to confirm *H pylori* infection: positive histopathology plus a positive rapid urease test or a positive culture.\(^1\) To determine negative *H pylori* status, 2 or 3 negative results from invasive tests are necessary.\(^1\) It is important to remember that the use of antibiotics and proton pump inhibitors can confound test results. As such, these medications should be discontinued for 2 to 4 weeks prior to *H pylori* testing.\(^{1,9,10}\)

Invasive testing is led by histology, which is more than 90% sensitive and specific, widely available, and easily performed but expensive.\(^{11}\) The benefit of histopathology is that it may identify the underlying disease pathology (eg, gastritis and intestinal metaplasia). Culture of biopsy specimens is somewhat less sensitive than histopathology, but 100% specific; however, this approach is expensive, somewhat complicated, and not widely available.\(^{12,13}\) Rapid urease testing tends to be more specific than histology; these tests are approximately 95% sensitive and 85% specific.\(^{11,13,14}\) Although these assays obtain very rapid results, they require an invasive approach, which is more difficult in the pediatric population.

### Noninvasive Testing

Noninvasive testing includes antibody testing of the serum, urine, or saliva; the fecal antigen test of stool; and the urea breath test (Table 2). Although the ESPGHAN and NASPGHAN guidelines state that endoscopy should be a component of the initial diagnosis of *H pylori*,\(^3\) other authors suggest that a noninvasive test, such as the fecal antigen test or the urea breath test, may be sufficient.\(^5,15\) Antibody testing is not recommended for diagnosis of *H pylori* infection.\(^1\)

### Antibody Testing

ESPGHAN and NASPGHAN guidelines state that detection of *H pylori*-specific antibodies in the serum, whole blood, urine, and saliva is not reliable enough for a clinical diagnosis in children.\(^1\) This recommendation is supported by a high grade of evidence from studies showing that the sensitivity and specificity of assays that detect *H pylori* antibodies vary in children.\(^1\) In particular, variability has been observed in serologic testing of children in different age groups.\(^{16}\) In a study of 130 consecutive children who underwent upper gastrointestinal endoscopy, 68 were positive for *H pylori* infection. With the use of a second-generation enzyme-linked immunosorbent assay (ELISA), *H pylori*-specific immunoglobulin G (IgG) antibodies were detected in only 79% of the infected children and 8% of the uninfected children. The sensitivity of the assay was low in children aged 2 to 6 years (44%). Sensitivity improved in older children, to 76.7% in those aged 7 to 11 years and 93.1% in those aged 12 to 16 years. In addition, results

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology (ELISA)</td>
<td>85</td>
<td>79</td>
<td>Widely available; inexpensive</td>
<td>Not recommended for use in clinical practice</td>
</tr>
<tr>
<td>Rapid serology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stool</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool antigen testing</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>Inexpensive</td>
<td>Need to handle fecal sample</td>
</tr>
<tr>
<td>Monoclonal Polyclonal</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Saliva</strong></td>
<td></td>
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</tr>
<tr>
<td>Saliva</td>
<td>71-93</td>
<td>82-92</td>
<td>Easy to collect; inexpensive</td>
<td>Low sensitivity; not recommended for diagnosis</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine (Anti–<em>H pylori</em> IgG antibodies in urine)</td>
<td>85</td>
<td>79</td>
<td>Rapid results; easy to perform</td>
<td>Low sensitivity; not recommended for documenting eradication</td>
</tr>
</tbody>
</table>

ELISA, enzyme-linked immunosorbent assay; FDA, US Food and Drug Administration; IgG, immunoglobulin G.
Sensitivity and a 99% specificity for detection test. A monoclonal enzyme immunoassay had a 98% high (>90%). Although serology testing kits are widely logic modalities, from 40% to 99%, but specificity is needed to prove eradication is unknown. In a study of 101 Japanese children (age range, 2-15 years; median, 7 years), this test had a 91.9% sensitivity (96.9% specificity) and an accuracy of 92.1%. In a comparison with gastric biopsy histology, the sensitivity of the oral-fluid–based ELISA was 71% (specificity, 90.4%).

Sensitivity of the anti–H pylori IgG antibody testing in urine varies from 90% to 100%. This test provides rapid results and is easy to perform, but the length of time needed to prove eradication is unknown. In a study of 101 Japanese children (age range, 2-15 years; median, 7 years), this test had a 91.9% sensitivity (96.9% specificity) and an accuracy of 95.0%. In the same study, an immunochromatography-based assay for antibodies in the urine had a much lower sensitivity of 78.4% (100% specificity) and an accuracy of 92.1%.

The Fecal Antigen Test
Fecal antigen testing remains a very good, reliable, and reasonably priced screening test for H pylori infection, both before and after eradication. Although this test is inexpensive, it requires a stool collection, which may be difficult or off-putting for some patients. ESPGHAN and NASPghan guidelines indicate that a validated ELISA for H pylori detection in stool can reliably determine whether H pylori has been eradicated in children.

This test may be easier to collect in children younger than 3 years than the urea breath test. In addition, the age of the patient does not appear to influence the accuracy of the results. In a study of 302 symptomatic children (age range, 6 months-18.7 years), 92 children tested positive for H pylori infection by culture, histology, the rapid urease test, and the 13C urea breath test. A monoclonal enzyme immunoassay had a 98% sensitivity and a 99% specificity for H pylori detection in the stool samples of these children.

The monoclonal enzyme immunoassay appears to have greater sensitivity and specificity than the polyclonal enzyme immunoassays. A meta-analysis was recently conducted to determine the accuracy of the fecal antigen test for the diagnosis of H pylori infection in children. The analysis included 45 studies and 5931 patients. The overall pooled sensitivity was 92%, and the pooled specificity was 94%. A subgroup analysis revealed that sensitivity (96.2% [95% CI, 94.9%-97.2%]) and specificity (94.7% [95% CI, 93.6%-95.6%]) were higher with the monoclonal enzyme immunoassay compared with the polyclonal enzyme immunoassays (sensitivity, 88.0% [95% CI, 85.0%-90.5%]; specificity, 93.0% [95% CI, 91.3%-94.5%]) and the rapid 1-step tests (sensitivity, 88.1% [95% CI, 85.2%-90.6%]; specificity, 94.2% [95% CI, 92.5%-95.5%]).

The Urea Breath Test
The 13C urea breath test is a reliable noninvasive test for eradication of H pylori infection in children. Guidelines from the American College of Gastroenterology state that it can be used for diagnosis. The 13C urea breath test is associated with high sensitivity and specificity. This test is not radioactive, in contrast to the 14C urea breath test. The 13C urea test is relatively inexpensive. As with the fecal antigen test, the ESPGHAN and NASPghan guidelines indicate that the 13C urea breath test can reliably determine whether H pylori has been eradicated in children with high accuracy, specificity, and sensitivity.

Among children and adolescents, the 13C urea breath test has a sensitivity of more than 95% and a specificity of 93% to 97%. In a multicenter European study that compared the specificity and sensitivity of the 13C urea breath test, the fecal antigen test, antibody detection in serum, and antibody detection in urine, the 13C urea breath test had the highest sensitivity (96%) among the 4 noninvasive approaches. In a prospective study conducted in the United States, the 13C urea breath test had a sensitivity of 98% and a specificity of 96%. It should be noted that diagnostic accuracy may be lower in children younger than 6 years, owing to increased false-positive results. As the pediatric community becomes more familiar with the 13C urea breath test, it could become as common as fecal antigen testing.

Selecting the Best Option for Each Patient
In a child, the best option is a noninvasive test. The fecal antigen test and the urea breath test are simple and noninvasive approaches for detecting H pylori infection, and they have potential for use as screening tests in the pediatric population. However, the gold standard for diagnosis remains a
positive histopathology plus a positive rapid urease test or a positive culture. At this time, ESPGHAN and NASPGHAN guidelines recommend against the test-and-treat approach for pediatric patients based on a lack of supporting evidence. The guidelines emphasize that the goal of testing in pediatric patients is to determine the underlying cause of the symptoms, not merely the presence of *H. pylori*. Dr Gilger is a consultant for Otsuka.

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References

The current dogma is to treat *H pylori* infection because of its associated disease burden, which includes dyspepsia, gastroduodenal ulcerative diseases, MALT lymphoma, and gastric malignancies. The first step in the management of a pediatric patient with *H pylori* infection is to confirm that a reliable test was used to diagnose the infection. The ESPGHAN and NASPGHAN guidelines recommend that diagnosis be based on a positive histopathology plus a positive rapid urease test or a positive culture. Other authors suggest that a noninvasive test, such as the fecal antigen test or the urea breath test, can be used. Routine serology is not sensitive or specific enough in children to be used for diagnosis.

After confirmation of an accurate diagnosis, the next step is to discuss with the family whether the child should receive treatment. In most cases, the recommendation should be to eradicate *H pylori*, which always causes aggressive histologic inflammation in the stomach whether the child has symptoms or not. Eradicating *H pylori* in children dramatically decreases the risk that they will develop peptic ulcer disease or gastric cancer later in life. Treatment is currently recommended for pediatric patients who have *H pylori*-positive peptic ulcer disease, *H pylori* infection detected by biopsy-based methods in the absence of peptic ulcer disease, or *H pylori* infection and a first-degree relative with gastric cancer. Treatment is not indicated for pediatric patients with recurrent functional abdominal pain because this nonspecific symptom can be caused by several diseases or disorders.

A provocative question is whether there is ever a situation in which therapy for *H pylori* infection should be withheld. Generally speaking, a diagnosed infection should be treated. However, treatment of *H pylori* remains controversial even 20 years after its discovery. Some studies have suggested that infection with *H pylori* might be beneficial for children, at least for a period of time. This benefit is related to asthma and allergies. For example, in a study of 6959 children ages 5 to 18 years (average age, 12.4±3.5 years) who underwent urea breath testing, 45.6% were positive for *H pylori* infection and 8.3% had asthma. There was a significant inverse relationship between *H pylori* infection and asthma in these children; among *H pylori*-positive children, the rate of asthma was 7.3% compared with 9.1% in *H pylori*-negative children (odds ratio [OR], 0.82 [95% CI, 0.69-0.98]; *P*=.032). In addition, a recent longitudinal birth-cohort study of 863 Ethiopian children assessed at ages 1 year, 3 years, and 5 years found that *H pylori* infection at age 3 years was significantly associated with a decreased risk of eczema (adjusted OR, 0.31 [95% CI, 0.10-0.94]; *P*=.02). In addition, the study found an inverse association between *H pylori* infection and skin sensitization at age 5 (adjusted OR, 0.26 [95% CI, 0.07-0.92]; *P*=.02). However, several studies found no relationship between *H pylori*-infection status and allergies or asthma, and therefore the evidence is currently inconclusive. It may be prudent to withhold or delay treatment in a child with a very strong family history of asthma and allergy or in a child suffering from symptoms of these conditions. With the exception of those rare situations, once a pediatric patient receives a diagnosis of *H pylori* infection based on a reliable test, the approach is to provide treatment in an effort to eradicate the infection.

**Treatment Approaches**

The NASPGHAN and ESPGHAN 2011 guidelines for *H pylori* infection in children recommend triple therapy as a first-line eradication regimen (Table 3). The general treatment regimen for *H pylori* infection for children, as well as adults, consists of 3 medications: a proton pump inhibitor, amoxicillin, and an additional antibiotic, usually either clarithromycin or metronidazole (Table 4). The guidelines also recommended bismuth salts plus amoxicillin and metronidazole as an alternative first-line therapy. Triple therapy should be administered for 7 to 14 days. Clinicians should emphasize the necessity for patients to complete the entire prescribed regimen.
After treatment, it is important to follow-up with testing to confirm eradication because antibiotic resistance is a pervasive concern, and eradication rates are far from optimal. Four to 8 weeks after completing therapy, pediatric patients should be tested to confirm *H pylori* eradication using the urea breath test or the fecal antigen test. It is important to remember that the absence of symptoms is not a reliable measure of *H pylori* eradication.

Numerous studies have examined other approaches to the treatment of *H pylori* infection. One such approach is sequential therapy, in which the proton pump inhibitor and amoxicillin are started before the third antibiotic. Several clinical trials have shown that sequential therapy has better eradication rates than conventional triple therapy. In a double-blind, randomized, controlled trial, 107 children with confirmed *H pylori* infection were treated with a sequential regimen (amoxicillin and omeprazole for 5 days followed by clarithromycin, tinidazole, and omeprazole for 5 days) or a 7-day standard triple-eradication regimen (amoxicillin, clarithromycin, and omeprazole). Six to 8 weeks after treatment, the eradication rates in children who received sequential therapy were significantly higher than in children treated with the standard triple therapy (86.5% vs 68.6%; relative risk, 1.26 [95% CI, 1.02-1.60]). Comparable eradication rates were observed in randomized controlled trials conducted in Kenya and China. In both of these studies, sequential regimens had higher eradication rates than standard triple-therapy regimens (81%-85% vs 49%-61.9%, respectively). Although the mechanisms behind the improved eradication rates are not completely understood, some investigators believe that because the organism does not become resistant to amoxicillin, administration of the amoxicillin/proton pump inhibitor combination in the first 5 days will dramatically decrease the bacterial load and help protect against clarithromycin resistance. After that initial 5-day period, there is less likelihood that resistance will develop when the other antibiotic is added. At this time, many clinicians believe that sequential therapy is better than standard triple therapy; some data support the use of sequential therapy as first-line treatment.

Several studies have examined the addition of probiotics to standard triple therapy. A recent meta-analysis evaluated randomized controlled trials in pediatric patients that compared the use of *H pylori* eradication therapy with probiotic supplementation vs the same eradication therapy with placebo or no extra intervention. The analysis included 7 studies with 508 patients. The ORs of eradication rates in the probiotic group vs the control group were 1.96 (95% CI, 1.28-3.02) in the intent-to-treat analysis and 2.25 (95% CI, 1.41-3.57) in the per protocol analysis. Although most of these 7 studies demonstrated some efficacy in terms of symptom improvement, eradication rates were not significantly improved with probiotics. For example, in a study of 68 *H pylori*-positive children treated with either standard triple therapy (omeprazole, amoxicillin, and clarithromycin) alone or triple therapy plus a probiotic, the eradication rates were higher in the group that received probiotics (88% vs 76%), although the difference was not significant (P=.10). The patients receiving probiotics experienced significantly fewer episodes of epigastric pain, nausea, vomiting, and diarrhea. However, a recent double-blind, randomized, placebo-controlled study of 66 children with confirmed *H pylori* infection (median age, 9.09 years) found that the eradication rate was significantly higher in the children who received probiotics along with triple therapy (omeprazole, amoxicillin, and furazolidon) than in the children who received placebo plus triple therapy (90% vs 70%; P=.04). The addition of probiotics also reduced the rate of nausea/vomiting (P=.02) and diarrhea (P=.04). It is important to keep in mind that different probiotics, as well as different triple therapies, were used across the various studies. Additional studies are needed to definitively determine the effect of probiotics on *H pylori* eradication in children.

### Eradication and Resistance

When treating *H pylori* infection, the goal is to achieve an eradication rate of at least 90% with first-line therapy. Successful eradication is important to prevent the development of antibiotic resistance, as well as to reduce the number of treatments and procedures. Among children receiving the standard triple-therapy regimen, eradication rates are declining. In part, this decrease can be attributed to increasing antibiotic resistance (Table 5). Unfortunately, *H pylori* becomes resistant to most antimicrobials, with the exception of amoxicillin, easily and quickly.
H pylori can also develop resistance to clarithromycin—one of the mainstay drugs for treatment—and metronidazole. High resistance rates of 16% to 27% for clarithromycin and 25% for metronidazole have been observed. The end result is that the standard triple therapies, with either clarithromycin or metronidazole, are no longer providing outstanding eradication results. As such, it is important for the clinician to be aware of local resistance rates when choosing the initial therapy.

Treatment outcomes are severely impacted by primary antibiotic resistance. Clarithromycin resistance significantly reduces the efficacy of the standard triple therapy. Children may be highly susceptible to secondary antibiotic resistance; in a 12-year observation study from Belgium, 46% of children acquired secondary antibiotic resistance after primary eradication failure. This finding highlights the importance of eradicating the H pylori infection during first-line treatment.

It is important for clinicians to be aware of the rates of antibiotic resistance in their geographic area when selecting first-line therapy for H pylori infection. In areas of high clarithromycin resistance (≥20%), such as Spain, Turkey, Italy (the central region), Alaska, China, Japan, and Cameroon, it is recommended that standard triple therapy not be used. Low levels of clarithromycin resistance are still found in other parts of the world, including the Netherlands, Sweden, Ireland, Germany, Malaysia, and Taiwan (the southern region); in these areas, treatment with the standard triple therapy still results in high eradication rates. For those geographic areas known to have high resistance rates to clarithromycin, antibiotic sensitivity testing should be performed before therapy is initiated.

### Management After Treatment Failure

When treatment fails, the ESPGHAN and NASPGHAN guidelines recommend: 1) performing endoscopy with culture and susceptibility testing; 2) testing for clarithromycin susceptibility in paraffin-embedded biopsy samples (if this test was not performed before the initial therapy); and 3) modifying treatment to include alternate agents than were used in the initial therapy (such as different antibiotics), adding bismuth, and/or increasing the dose and duration of treatment (Table 6). Salvage regimens include a proton pump inhibitor plus metronidazole, amoxicillin, and bismuth; or a triple therapy with a proton pump inhibitor plus levofloxacin (moxifloxacin) and amoxicillin. It is important that patients are not re-treated with the same antibiotic that was administered during first-line treatment. (One exception would be if sensitivity assays indicate that the patient still might respond to such treatment.)

One of the more recent novel approaches for the treatment of H pylori infection is concomitant therapy. This 4-drug regimen includes a proton pump inhibitor, amoxicillin, clarithromycin, and metronidazole (or tinidazole). In essence, 2 triple therapies are being administered at the same time. If treatment is extended from 5 days to 14 days, eradication rates reach 86% for first-line therapy. As a salvage therapy, concomitant therapy has been shown to be effective in eradicating H pylori infection in patients with dual antibiotic resistance, resulting in eradication rates of 75% (vs 92.4% for patients without dual antibiotic resistance). Similar results were achieved in a study from Spain, which found that concomitant therapy resulted in the eradication of 100% of clarithromycin-resistant infections and 75% of dual-resistant H pylori infections. Given the success of concomitant therapy, many practices are moving toward incorporating this regimen into the treatment of H pylori infection. The standard 14-day triple therapies are becoming obsolete in many practices, particularly in areas with considerable antibiotic resistance.

Several newer antibiotics, such as rifabutin, are under investigation for the treatment of H pylori infection. Rifabutin-based triple therapy is showing good results in areas with high levels of resistance. A 10-day course of rifabutin (300 mg) with pantoprazole and amoxicillin in patients with eradication failure after standard triple therapy resulted in an eradication rate of 86%. In a prospective multicenter study of patients who had failed 3 prior H pylori treatments, a regimen of rifabutin (150 mg), amoxicillin (1 g), and a proton pump inhibitor resulted in an H pylori eradication rate of 52% (95% CI, 41%-63%). It should be noted that neither of these studies was conducted in pediatric patients.

Another agent under investigation in H pylori is nitazoxanide, which is used to treat diarrhea. A recent report

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**Table 5.** Reasons for Treatment Failure

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<th>Reason for Treatment Failure</th>
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<tr>
<td>Host genetic factors</td>
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<tr>
<td><em>Helicobacter pylori</em> virulent factors</td>
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<tr>
<td>Antibiotic resistance to <em>H pylori</em> strains</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Inadequate compliance to therapy</td>
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<td>Insufficient duration of therapy</td>
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<td>Household crowding</td>
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**Table 6.** Strategies for Rescue Treatment After Failure of *Helicobacter pylori* Eradication

- Check status of resistance to antibiotics
- Ensure patient compliance
- Screen family members
- Avoid previously used antibiotics
- Use full doses or longer treatment duration
- Use quadruple therapy as backup
- Use sequential therapy
demonstrated that a 4-drug regimen consisting of levofloxacin, omeprazole, nitazoxanide, and doxycycline resulted in better efficacy and eradication rates than standard triple therapy (Figure 4).38

Conclusion

There is still much to learn about the treatment of \textit{H pylori} infection. Eradication rates are falling owing to rising antibiotic resistance. Unfortunately, there are many situations in which a child with \textit{H pylori} is treated multiple times and, despite compliance, the infection is not eradicated.

Acknowledgment

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References


New Diagnostic Strategies for Detection of Helicobacter pylori Infection in Pediatric Patients: Discussion

G&H Should serology be used as a screening test?

Benjamin D. Gold, MD

Many published studies have demonstrated that commercially available assays are not a good testing option, particularly because they lack validation in the populations for which they are used. Despite clear recommendations in the ESPGHAN and NASPGHAN guidelines that serology is not a reliable indicator of H pylori infection, we continue to have patients sent to us from other pediatric gastroenterologists who use serology as a screening test.

G&H What are some recent findings on treatment?

Mark A. Gilger, MD

As a general statement regarding treatment, the fact that there are so many regimens for eradication and yet suboptimal success highlights how little we understand about H pylori.

Benjamin D. Gold, MD

Yes, I agree. Following the initial discovery of H pylori, there was a stretch of 10 to 15 years in which every randomized controlled trial published, particularly in adults, showed eradication rates of 95% to 100%. Currently, eradication rates have dropped dramatically and much faster than the overall prevalence of the organism, which has stabilized. Many years ago, when eradication rates were so high, physicians did not often test for eradication after treatment. However, it is now absolutely critical to test for a cure and to make sure that the organism has been eradicated even if the symptoms have resolved. Given that there are so many regimens available, it is absolutely critical that there is more research to find the best options for the clinician to use, particularly in areas where there are higher rates of resistance.
much sense. If you are treating to eradicate \textit{H pylori}, you must make sure you actually did so.

**Steven J. Czinn, MD** I completely agree.

**G&H** Are there any misconceptions in the community setting about \textit{H pylori}?

**Benjamin D. Gold, MD** There is a need for ongoing up-to-date education in the community. I still see patients who have been tested with serology, or who were treated with the wrong course of an eradication regimen. Although awareness of the organism has risen, the relative awareness of the appropriate approaches in management methodologies has not. This lack of knowledge has contributed to the increasing rates of eradication failure and resistance.

**Mark A. Gilger, MD** It is important for the general practitioner to understand that abdominal pain in children is multifactorial, and that eradicating \textit{H pylori} is the right course of action. By eradicating \textit{H pylori} infection, the risk of ulcer disease and gastric cancer later in life decreases. Also, eradication will normalize the lining of the stomach and significantly reduce inflammation. However, in 50% of cases with successful eradication, patients continue to have stomach pain, which reinforces the point that abdominal pain in children has many etiologies. As such, the physician should never guarantee that the stomach pain will resolve once the infection is gone. Nevertheless, it is important for physicians to recognize that they should still treat the infection.

**G&H** Do family members of children with \textit{H pylori} need to be tested?

**Benjamin D. Gold, MD** When recurrent infection occurs, one of the first things that comes to mind with enteric infections is transmission among family members. The important thing to recognize with \textit{H pylori} infection is that not all patients will develop immediate symptoms, and if symptoms do occur, they may not be specific for the infection. This creates a dilemma when deciding whom to test for infection. However, if you have a patient with diagnosed \textit{H pylori} infection who is treated and the infection either persists or, more importantly, recurs, then I would consider testing other family members. To echo what both Dr Czinn and Dr Gilger said, a noninvasive test for infection, namely, the $^{13}$C urea breath test or the fecal antigen test, should be used. If \textit{H pylori} is detected in the family member, I would treat and then test for cure after therapy is completed.

**Mark A. Gilger, MD** It is important to screen children adopted from the developing world to make sure that they are \textit{H pylori}–negative, since the infection rate is so high in developing countries. We have had situations where we believe that the adopted child, who was not screened or treated, was responsible for infecting the other family members with \textit{H pylori}. As a result, we have had to treat all of the family members.

**Benjamin D. Gold, MD** Yes, we have had the same situation.

**Steven J. Czinn, MD** Those are very good points. Children are often the reservoirs of \textit{H pylori} infection, and they are unaware that they are infected. As such, they are going to transmit the infection. Children adopted from the developing world should definitely be screened.

**Acknowledgment**

Drs Gold, Gilger, and Czinn were paid by Otsuka America Pharmaceutical, Inc. for participation in this roundtable and development of this monograph. Dr Gold is a consultant and scientific advisor for Otsuka Pharmaceuticals, Inc. and Takeda Pharmaceuticals. He is a consultant and speaker for Nestle USA and Mead Johnson Nutritionals. Dr Gilger is a consultant for Otsuka.
**Helicobacter pylori in Pediatric Patients**

- *H. pylori* is estimated to have infected two-thirds of individuals in developing countries, and 30% to 40% of individuals living in industrialized countries.
- Most individuals are infected during early childhood; in developing countries, 50% of children are infected by the age of 3 years.
- In contrast, in the United States, only 5% of the population is infected by the age of 3 years.


**Diagnostic Testing of *H. pylori***

- **Invasive**
  - Upper gastrointestinal endoscopy and biopsy, followed by culture; rapid urease testing; histopathology; polymerase chain reaction (PCR)
- **Noninvasive**
  - Antibody testing of the serum, urine, or saliva; the fecal antigen test; a stick the urea breath test

**First-Line Treatment of *H. pylori***

- The general treatment regimen for *H. pylori* infection for children, as well as adults, consists of 3 medications: a proton pump inhibitor, amoxicillin, and an additional antibiotic, usually either clarithromycin or metronidazole.**3**
- Triple therapy should be administered for 7 to 14 days.**2**
- An alternative regimen is bismuth salts plus amoxicillin and metronidazole.**2**

**Noninvasive Testing of *H. pylori***

- Fecal antigen testing
  - A reliable screening test for use both before and after eradication
  - The age of the patient does not appear to influence the accuracy of the results
- The *13C* urea breath test
  - A reliable test for detection of *H. pylori* infection
  - Can determine whether *H. pylori* has been eradicated in children with high accuracy, specificity, and sensitivity
  - Relatively inexpensive
  - Diagnostic accuracy may be lower in children younger than 6 years, owing to increased false-positive results.**1**


**Management After Treatment Failure***

- Perform endoscopy with culture and susceptibility testing
- Test for clarithromycin susceptibility in punch-embedded biopsy samples
- Modify treatment to include alternative agents that were used in the initial therapy, add bismuth, and/or increase the dose and duration of treatment
- Use salvage regimens that include a proton pump inhibitor plus metronidazole, amoxicillin, and bismuth; or a triple therapy with a proton pump inhibitor plus levofloxacin or metronidazole and amoxicillin
- Do not re-treat with the same antibiotic administered during first-line treatment.
Brief Summary about BreathTek UBT

Intended Use
The BreathTek® UBT for H. pylori Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with H. pylori in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of H. pylori infection in adult patients and pediatric patients 3 to 17 years old. The test may be used for monitoring treatment if used at least 4 weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of $^{13}$CO$_2$ to $^{12}$CO$_2$ in breath samples, in clinical laboratories or point-of-care settings. The Pediatric Urea Hydrolysis Rate Calculation Application (pUHR-CA), provided as a web-based calculation program, is required to obtain pediatric test results.

The BreathTek UBT Kit is for administration by a health care professional, as ordered by a licensed health care practitioner.

Warnings and Precautions

• For in vitro diagnostic use only. The Pranactin®-Citric solution is taken orally as part of the diagnostic procedure and contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit, and should be used with caution in diabetic patients. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)

• A negative result does not rule out the possibility of H. pylori infection. False negative results do occur with this procedure. If clinical signs are suggestive of H. pylori infection, retest with a new sample or an alternate method.

• False negative test results may be caused by:
  — Ingestion of proton pump inhibitors (PPIs) within 2 weeks prior to performing the BreathTek UBT. If a negative result is obtained from a patient ingesting a PPI within 2 weeks prior to the BreathTek UBT, it may be a false-negative result and the test should be repeated 2 weeks after discontinuing the PPI treatment. A positive result for a patient on a PPI could be considered positive and be acted upon.
  — Ingestion of antimicrobials, or bismuth preparations within 2 weeks prior to performing the BreathTek UBT
  — Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
  — Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of the treatment for the eradication of H. pylori.

• False positive test results may be caused by urease associated with other gastric spiral organisms observed in humans such as Helicobacter heilmannii or achlorhydria.

• If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.

• Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients. Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.

• No information is available on use of the Pranactin-Citric solution during pregnancy.

• For pediatric test results, the Urea Hydrolysis Rate (UHR) results must be calculated. The Delta over Baseline (DOB) results are only used to calculate the UHR metrics to determine H. pylori infection in pediatric patients. DOB results cannot be used to determine the infection status of pediatric patients. Use the web-based pUHR-CA (https://BreathTekKids.com) to calculate the UHR.

• Safety and effectiveness has not been established in children below the age of 3 years.

Adverse Events

During post-approval use of the BreathTek UBT in adults, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

In two clinical studies conducted in 176 (analyzed) pediatric patients ages 3 to 17 years to determine the initial diagnosis and post treatment monitoring of H. pylori, the following adverse events experienced by ≥1% of these patients were: vomiting (5.1%), oropharyngeal pain (4.5% to include throat irritation, sore throat, throat burning), nausea (2.3%), restlessness (2.3%), stomach ache/belly pain (1.1%), and diarrhea (1.1%). Most of the adverse events were experienced by patients within minutes to hours of ingestion of the Pranactin-Citric solution.

In another clinical study comparing the UBiT®-IR300 and POCone® in pediatric patients ages 3 to 17 years, the following adverse events were observed among the 99 subjects enrolled: 2 incidences of headache, and 1 incidence each of cough, dry mouth and acute upper respiratory infection.