Abstract

Objective: To show important aspects of gastroduodenal peptic ulcer and of Helicobacter pylori infection in children and adolescents.

Sources: Technical textbooks and MEDLINE and LILACS databases including publications between 1966 and 2006.

Summary of the findings: The etiology of peptic ulcer in children and adolescents may be primary, associated with H. pylori infection, or secondary, in which etiopathogenic mechanisms rely upon the underlying disease. The infection is acquired predominantly in childhood, with prevalence rates between 56.8 and 83.1% in children who live in the poorest Brazilian regions, amounting to nearly 10% in children aged less than 10 years in industrialized countries. The infection can be diagnosed by invasive methods, which investigate the presence of the bacterium, or of DNA, RNA or bacterial products in biopsy fragments of the gastric mucosa obtained at endoscopic examination; it can also be diagnosed through noninvasive methods, which include the detection of anti-H. pylori antibodies in serum, urine or saliva samples, detection of bacterial antigens in stool samples, and the carbon 13-labeled urea breath test. However, upper gastrointestinal endoscopy is the method of choice for the diagnosis of peptic ulcer, as it allows collecting fragments from the gastric mucosa during the procedure for the diagnosis of infection and for histopathological analysis.

Conclusions: H. pylori infection is the major cause of peptic ulcer among children. Eradication of the bacterium with antimicrobial therapy results in the cure of the disease, and is therefore indicated for all children with H. pylori infection with an active, recurrent, healed, or complicated peptic ulcer.


Introduction

Hippocrates, in 460 B.C., reported a case whose diagnosis was later confirmed as peptic ulcer (PU). In the 18th century, clinicians, who were famous for their accuracy regarding the identification of symptoms, hardly ever missed the diagnosis of perforated PU, which was almost invariably fatal at that time. Legal Medicine compendia, such as that written by Albertus in 1725, mentioned that perforated ulcer was a rare cause of death, and that it should be distinguished from poisonings.

In the second half of the 19th century, ulcers were predominantly gastric. Only after some decades did duodenal ulcer become predominant. In 1962, experts suggested that an environmental factor found in the late 19th century and early 20th century in the western world caused a cohort effect on individuals born at such time. Environmental factors associated with early urbanization, social stress and with the economic crisis after World War I were incorrectly regarded as predisposing factors to the disease.

Contrast radiology was the first complementary method used for the diagnosis of PU. Later on, with the development and improvement of gastrointestinal endoscopy, it was found that radiological methods had high rates of false-positive (21%) and false-negative (32%) results. Schindler was the first author to describe the characteristics of PU on endoscopy, which is currently the method of choice for the diagnosis of the disease.

Up until about 2 decades ago, the pathogenesis of PU was ascribed to an unbalance between acid secretion and mucosal defense mechanisms, whose etiology was unknown. Nevertheless, in 1982, in Australia, Warren &
Marshall isolated a bacterium, later called *Helicobacter pylori*, from gastric mucosal fragments obtained from patients with gastritis and duodenal ulcer. Subsequent studies worldwide confirmed the initial hypothesis that this bacterium was associated with the pathogenesis of peptic ulcer disease in adults and children. In 1994, the World Health Organization (WHO) admitted the role of infection caused by this bacterium in the pathogenesis of gastric carcinoma, based on epidemiological evidence and on biological feasibility; more recently, the disease has been experimentally reproduced in animals.

The description of this bacterium and its association with peptic ulcer disease was so important to Medicine that Australian researchers were awarded the Nobel Prize in Physiology or Medicine in 2005.

**Epidemiology**

The prevalence of PU is difficult to estimate, due to the subjective nature of its symptoms and also because it is frequently mistaken for other dyspeptic disorders. Besides current evidence of a decrease in the incidence of PU, the proportion between males and females has also changed in the last decades. Available data are based on statistics about perforated ulcer cases which, although regarded with skepticism for not representing the whole spectrum of peptic ulcer disease, have been the most uniform material for such assessments.

The actual incidence of PU among children is still unknown. It is common knowledge, though, that it is rare in children aged less than 10 years. Large pediatric centers in North America diagnose on average four to six new cases every year. At the Division of Pediatric Gastroenterology of Hospital das Clínicas of the Federal University of Minas Gerais, Brazil, the annual average amounts to 7.6 new cases, which is quite similar to the average observed at Universidade Federal de São Paulo/Escola Paulista de Medicina, Brazil (7.2 patients/year). Some studies have shown a male predominance for this disease.

As previously mentioned, *H. pylori* is a crucial factor in the pathogenesis of PU. Most children with duodenal PU test positive for the bacterium. As occurs among adults, *H. pylori*-negative duodenal ulcer is uncommon among children. It might, however, occur in other disorders (e.g., Crohn's disease), or be secondary to the use of medications, such as nonsteroidal anti-inflammatory drugs.

After the role of *H. pylori* in the pathogenesis of PU was acknowledged, several studies have shown the association between peptic ulcer disease and infection by more virulent strains of *H. pylori*. Quick and rampant urbanization, combined with poor living conditions in booming cities at the beginning of the Industrial Revolution, in the early 20th century, probably caused a decrease in hygiene standards in most of the population, which may have contributed towards a greater exposure to more virulent strains of *H. pylori*. Subsequently, improved knowledge about the importance of hygiene measures to prevent the dissemination of diseases prompted government actions whose aims were to improve health conditions and the water supply to urban households. Such measures probably managed to reduce the rates of *H. pylori* infection. Thus, the increase and decrease in the prevalence of PU are historical hallmarks of the increase and decrease in *H. pylori* infection rates. Low socioeconomic background and its natural consequences, such as poor hygiene, overcrowding, and absent or insufficient sanitation, predispose to the acquisition of the bacterium, being currently regarded as the major markers for the presence of *H. pylori* infection.

Man is the main reservoir for *H. pylori*. It is transmitted from person to person via the fecal-oral and oral-oral routes. Infection is predominantly acquired in childhood. Studies in our setting and in industrialized countries have demonstrated the importance of mothers and siblings in its transmission. Infection rates significantly increase with age, which is due to the cohort effect, i.e., the higher prevalence among older individuals shows greater risk for the acquisition of the infection than these individuals had as a child.

In Brazil, there has been a paucity of studies assessing the prevalence of this infection among healthy children. Appropriate diagnostic methods for epidemiological surveys in children should include the carbon 13-labeled urea breath test and detection of bacterial antigens in stool samples, due to the low accuracy of serological tests in children aged less than 10 years. Given these premises, there have been studies only in the poorest Brazilian regions. On the outskirts of Fortaleza, state of Ceará, and in the rural area of Melquiades, state of Minas Gerais, the prevalence rates for this infection have been greater than 56.8%, amounting to 75.4% among children aged 12 to 14 years. The prevalence is even higher among riparian and indigenous populations of the state of Rondônia, in northern Brazil, reaching 83.1%. Incidence data have shown that infection is acquired quite early in underprivileged Brazilian regions, ranging from 5.7% per year among children aged up to 5 years in Melquiades to 25.0% per year among children aged up to 2 years among the riparian populations of Rondônia.

On the other hand, in industrialized countries, the infection affects only 10% of children aged less than 10 years, and a sharp decrease in its prevalence has been observed.

**Etiopathogenesis**

PU can be primary, associated with *H. pylori* infection, with a chronic clinical course, affecting mainly the
duodenum, without associated systemic disease and being more prevalent among children older than 10 years; or secondary, with an acute clinical course, commonly affecting the stomach in children aged less than 6 years, especially newborns and infants, in whom etiopathogenic mechanisms rely on the underlying disease.\textsuperscript{17,30} Although injury to the mucous membrane is highly predominant in primary PU, and changes in the mucosal defense mechanisms are prevalent in secondary PU,\textsuperscript{30} usually, the disease originates from an unbalance between defense mechanisms and aggressive factors that act upon the gastroduodenal mucosa. In the stomach, the major protective barrier consists of the confluence between epithelial cells and continuous secretion of mucus bicarbonate (HCO$_3^-$). This layer, which is approximately 200-300 µm thick, provides efficient protection.\textsuperscript{31} It has been demonstrated that the mucus lining the superficial epithelial cells contains bipolar phospholipids which, due to their high polarity, prevent the backdiffusion of mineral acids, such as hydrochloric acid (HCl), from the gastric lumen into the mucosa. However, nonionized organic compounds, such as bile acid (HCl), from the gastric lumen into the mucosa. In the stomach, the major protective barrier consists of the confluence between epithelial cells and continuous secretion of mucus bicarbonate (HCO$_3^-$). This layer, which is approximately 200-300 µm thick, provides efficient protection.\textsuperscript{31} It has been demonstrated that the mucus lining the superficial epithelial cells contains bipolar phospholipids which, due to their high polarity, prevent the backdiffusion of mineral acids, such as hydrochloric acid (HCl), from the gastric lumen into the mucosa. However, nonionized organic compounds, such as bile salts or acetylsalicylic acid, which have a relatively low pKa, can quickly reach the superficial mucosal cells by nonionic diffusion and accumulate within these cells, where they dissociate and cause cellular injury.\textsuperscript{32} The concept of barrier was developed by Code & Scholer\textsuperscript{33} and Davenport,\textsuperscript{34} who proposed the rupture of the barrier representing the initial step in the injury to the mucosa with subsequent release (cascade) of histamine-like substances, mucosal bleeding, and development of acute gastritis. These findings can be observed in human beings after the intake of aspirin or concentrated ethanol, as well as in animals experimentally exposed to different mucosal irritants.\textsuperscript{35,36}

On the other hand, differently from what occurs in the gastric mucosa, where protection is provided by a mucus barrier, hydrogen ions (H$^+$) easily penetrate the mucosal cells of the duodenum, leading to a transient pH reduction. This change activates the basolateral sodium-bicarbonate cotransporters, with consequent excessive migration of HCO$_3^-$ from the extracellular space into the intracellular one, activating the HCO$_3^-$/chloride (Cl$^-$) exchange in the apical portion of the cell membrane. These events result in the increase of HCO$_3^-$ secretion which, combined with the mucus layer, neutralizes the H$^+$ ions that reach the duodenal lumen, warranting the neutrality and integrity of the mucosa.\textsuperscript{37,38}

Even though the pathogenesis of peptic ulcer disease has not been fully elucidated, \textit{H. pylori} infection in adults causes remarkable changes in gastric physiology, especially regarding the acid secretion mechanisms that are closely related to pathogenesis. In infection, mainly by cytotoxin-associated gene A (cagA)-positive strains, there is increased expression of proinflammatory cytokines, including interleukin-8 (IL-8), IL-18 and tumor necrosis factor alpha (TNF-α),\textsuperscript{39,40} which have a large effect on the mucus and on the HCO$_3^-$ concentration on the cell surface, as well as on acid secretion. This is because they act on D cells by inhibiting somatostatin production with consequent hypergastrinemia and increase in acid secretion.\textsuperscript{41,42} Among other consequences of the infection, it should be noted that the bacterium induces the release of several compounds (e.g.: cyclooxygenase 2 (COX-2)), which may compromise mucosal protection through the formation of other proinflammatory substances, such as reactive oxygen species (ROS).\textsuperscript{31}

When infection is restricted to the antral mucosa and is followed by a remarkable increase in plasma gastrin, acid secretion is excessively high. Since infection also reduces the duodenal secretion of HCO$_3^-$ and of mucus, the duodenal mucosa becomes permeable and is “attacked” by H$^+$ ions and other irritants, being replaced with metabolic gastric mucosa. The bacterium in the gastric mucosa migrates and colonizes the metaplastic gastric areas in the duodenum, where it stimulates local inflammatory response, predisposing to the formation of the ulcer niche.

Reduction in the number of D cells and the inhibition of somatostatin production followed by hypergastrinemia are observed in \textit{H. pylori}-positive children.\textsuperscript{43} Since children with duodenal ulcer are more frequently colonized by more virulent strains of \textit{H. pylori}, at least in part, the mechanisms of ulcer formation in children are similar to those found in adults.

\textbf{\textit{H. pylori} virulence factors}

Several virulence factors have been associated with the development of severe diseases linked to \textit{H. pylori} infection.

The \textit{cagA} gene is a pathogenicity island (cag-PAI) marker.\textsuperscript{40} The island genes encode proteins with several functions, including \textit{cagA} protein translocation, of 120 kDa, into the cytoplasm of gastric epithelial cells, where, after being phosphorylated by \textit{c-src} and \textit{Lyn} kinases, the gene binds to and activates SHP-2 cell phosphatase, causing rearrangement of the cytoskeleton and formation of pedestals that allow greater bacterial adherence.\textsuperscript{44} Several island genes are involved in stimulating IL-8 production by gastric epithelial cells. IL-8 is a powerful chemotactic factor and an activator of polymorphonuclear leukocytes and macrophages, contributing to a stronger inflammatory response in patients colonized by cag-PAI-positive strains. Therefore, patients infected by cagA-positive strains have larger bacterial density in the gastric mucosa, more severe epithelial injury, more intense polymorphonuclear leukocyte infiltration, and higher levels of proinflammatory cytokines, which endorses the commonly reported association between infection by cagA-
positive strains and peptic ulcer disease in children\textsuperscript{45,46} and adults,\textsuperscript{5,7,47} or gastric carcinoma in adults.\textsuperscript{48-50} In Brazil, 95.0 and 62.3\% of strains isolated from children with and without duodenal ulcer, respectively, are cagA-positive.\textsuperscript{45}

The vacuolating cytotoxin A (vacA) gene, found in all \textit{H. pylori} strains, encodes the VacA protein, an exotoxin that directly induces the formation of intracytoplasmic vacuoles and apoptosis of epithelial cells.\textsuperscript{51} The toxin also increases epithelial permeability, which can make the passage of toxic substances into the epithelium easier and also help the diffusion of nutrients to the mucus layer, favoring the survival of \textit{H. pylori}. The vacA has an immunomodulatory function; therefore, it sometimes stimulates the inflammatory response of the gastric mucosa by different mechanisms (e.g.: by increasing the expression of COX-2 in T cells, in neutrophils and in macrophages), and sometimes inhibits the IL-2-mediated response of T cells.\textsuperscript{52} In vacA, there are two families of signal sequences called s1 and s2, with variations such as s1a, s1b and s1c, and two alleles located in the middle region of the gene, m1 and m2.\textsuperscript{53} The vacA s1 \textit{H. pylori} strains are more virulent than s2 strains, and are more commonly observed in patients with PU and gastric carcinoma than in those with gastritis.\textsuperscript{53,54} In our population, 85.0 and 58.3\% of children with and without duodenal ulcer, respectively, are colonized by s1 strains.\textsuperscript{55}

The \textit{H. pylori} blood-group antigen-binding adhesin A (BabA) binds to Lewis b and H-1 antigens, expressed in the gastric mucosa. The adherence of the BabA-mediated bacterium seems to play a crucial role in the transfer of bacterial virulence factors, which cause injury to the gastric mucosa, either directly or as a result of the inflammatory response and/or autoimmunity.\textsuperscript{56} In addition, firmly adhered bacteria are less exposed to gastric acidity and are not eliminated by peristalsis.\textsuperscript{57} The presence of the babA2 gene, which encodes BabA, has been associated with duodenal ulcer in adults.\textsuperscript{47,58} In a study of our group, we demonstrated the presence of the gene in all \textit{H. pylori} strains that were evaluated, regardless of whether they were isolated from children with or without duodenal ulcer.\textsuperscript{59}

The adherence of the bacterium to the gastric mucosa is also mediated by the sialic acid-binding adhesin A (SabA) protein, which binds to glycoconjugate residues of sialic acid expressed on the surface of epithelial cells due to the inflammatory or neoplastic process. The expression of sialic acid, which seldom occurs in the healthy gastric mucosa, is induced by \textit{H. pylori} infection, contributing to its chronicity. SabA participates in the neutrophil activation by mechanisms that do not involve bacterial opsonization.\textsuperscript{60}

Genes that encode proteins in the outer membrane of the pathogen, such as outer inflammatory protein A (OipA) and adhering lipoprotein AB (AlpAB), have been associated with higher virulence of strains, although the functions of their products are unknown.\textsuperscript{61}

Recently, a probable \textit{H. pylori} virulence factor has been described, called duodenal ulcer promoting gene A (dupA). The dupA, also located in the bacterial genome region that encodes surface proteins, corresponds to the fusion of \textit{jhp0917} and \textit{jhp0918} genes, with the insertion of a cytosine (C) or thymine (T) base pair. On describing the gene, the authors found an association with duodenal ulcer in adults.\textsuperscript{52} These findings, however, have not been confirmed in Brazilian children and adults, thus indicating possible geographic differences.\textsuperscript{63}

**Genetic factors**

Genetic factors are implicated in the pathogenesis of PU. This disease usually affects children with family history of this disorder, and the concomitance between monozygotic twins is three times greater than among dizygotic twins.\textsuperscript{64}

Moreover, the disease is much more frequent among individuals with O blood type, which is equivalent to the Lewis b antigen. This higher frequency has been ascribed to the fact that the bacterial load is larger in these individuals, since, as previously mentioned, \textit{H. pylori} has an adhesin called BabA, which binds to the Lewis b antigens.\textsuperscript{56}

It should be underscored that the host’s genetic factors can also determine immunological and inflammatory response to the infection, and can thus contribute to the outcome of a severe disease. Recent studies have shown that polymorphisms in regions that stimulate genes that encode proinflammatory cytokines can change gene transcription, with consequent increase in cytokine expression.\textsuperscript{65,66} Thus, polymorphic alleles at positions -31 and -511 of the \textit{IL1B} gene represent phenotypes that release high amounts of IL-1\beta. Similarly, the polymorphic allele 2 of the \textit{IL1RN} gene, which encodes the IL-1 receptor antagonist (IL-1ra), also increases IL-1\beta production.\textsuperscript{65,66,67} These polymorphisms have been associated with a greater risk for gastric carcinoma.\textsuperscript{68-70} On the other hand, there are few studies on the role of these polymorphisms in the risk of PU. Recently, our group has demonstrated that the presence of polymorphic allele 2 of the IL1RN gene increases the risk for duodenal ulcer by 2.5 times in children.\textsuperscript{71} This increase is likely to cause more exuberant inflammation in the antrum, with a decrease in somatostatin levels and an increase in gastrin levels, followed by an increase in acid secretion by the parietal cells, predisposing to the development of PU. However, this association has not been observed in adults,\textsuperscript{72,73} neither in our population.\textsuperscript{74} These differences may indicate different etiopathogenic mechanisms for PU in children and adults.
**Clinical aspects**

The clinical symptoms of primary PU in children can vary considerably according to their ages. The disease has an insidious clinical course, alternating between symptomatic and asymptomatic periods.

Newborns and infants can have hemorrhage, visceral perforation, or both, as first manifestations of the disease, even in the absence of any triggers, such as stress, which is regarded as the major cause of PU in this age group. In children, injuries often occur in the stomach, as a single lesion, but they frequently develop as multiple, small and bleeding erosions. In children up to 6 years old, PU can initially present as nausea and vomiting, but hematemesis is the most common symptom, although it is difficult to establish the symptomatology. In school-aged children, older than 7 years, abdominal pain, albeit atypical and difficult to locate precisely, has been described in virtually all cases. In this age group, the most common symptoms include vomiting and bleeding, the latter of which is characterized either by hematemesis or melena. Older children and adolescents have similar symptoms to those of adults. Abdominal pain is usually epigastric, but can also be present in the right lower quadrant. It can be intermittent or, more rarely, continuous; it can also be cyclic, with remission periods that last weeks or months. There is no correlation with food intake, and it often occurs in early morning. Some authors have pointed out that variability is the most consistent aspect of pain caused by PU in children. In a study carried out in Brazil evaluating 43 children and adolescents aged 4 to 17 years, the authors demonstrated that abdominal pain was present in 90.7% of cases; that it was most frequently epigastric (79.5%); that it consisted of a burning sensation in 56.4% of children; that it improved with food intake in 51.3%; and that decreased appetite (74.4%) and vomiting (69.8%) were the symptoms most commonly associated with pain. Other symptoms, such as pyrosis, sialorrhea, sense of fullness, anorexia, weight loss, abdominal distension, eructation, meteorism and iron deficiency anemia seldom occur.

The differential diagnosis of primary PU should be established with clinical entities that cause vomiting, abdominal pain and/or upper gastrointestinal bleeding, such as parasitic diseases, peptic esophagitis, esophageal varices and/or gastric varices, Zollinger-Ellison syndrome, food intolerance, allergic gastroenteropathy, Crohn’s disease, pancreatitis, bile duct diseases, and gastritis (lymphocytic, hypertrophic or autoimmune), among others.

Secondary PU is characterized by more acute symptoms and, in most cases, upper gastrointestinal bleeding is the major complaint, accompanied or not by abdominal pain. The underlying clinical disease and the depth and extension of the ulcers determine the severity and prognosis of the bleeding event.

**Endoscopic aspects**

Contrast radiological examination of the stomach and duodenum has already been used for the diagnosis of ulcerated lesions before the advent of esophagastroduodenoscopy. However, even with the double contrast technique, which is more sensitive, results have not been satisfactory. Furthermore, it cannot be easily used in younger children, in addition to exposing them to radiation. Upper gastrointestinal endoscopy (UGIE) is the method of choice for the diagnosis of peptic ulcer disease, even in very young children. Even though it is invasive and costly, especially in children, because in most cases it is performed in a hospital under general anesthesia, this method is safe and reliable. In addition to establishing the diagnosis and locating the ulcer, the UGIE allows obtaining biopsy fragments for histopathological analysis and for *H. pylori* investigation. Moreover, modern videoendoscopes allow storing the images for later reassessments.

The most common endoscopic finding in children with *H. pylori* infection is a nodular lesion with a cobblestone pattern predominantly located in the antral mucosa, which is better visualized when covered by blood from the biopsy site.

PUs are continuity solutions of the gastrointestinal mucosa that extend through the muscularis mucosae, reaching into the submucosa and into the muscularis propria. Most of the time, it is a single lesion; however, there may be several lesions sometimes. In adults, gastric ulcers should be distinguished from neoplastic lesions. In children, malignant lesions are very rare, but the characteristics of the borders, base and mucosa around the lesion should be recognized by all endoscopists. In peptic lesions, usually round or oval-shaped, the base consists of granulation tissues, it is flat, smooth and regular, and often covered by a white or grayish white fibrinoid exudate. In the initial ulcer stages, fibrin is thick and contains necrotic debris or hematin deposition, and the borders are smooth, regular, clearly defined, raised, and a bit higher than the base. In the mucous membrane around the lesion, the terminal ends of the folds extend towards the borders in a regular fashion. Most gastric peptic ulcers are located in the lesser curvature, in the *incisura angularis*, in the lower third of the gastric body, proximally to the antrum and anteriorly to the pyloric region. In 50% of the cases, duodenal ulcers are located in the anterior wall of the bulb. The endoscopic aspect of the ulcer depends on the time at which it is observed, i.e., on its stage, according to the life cycle described by Sakita. This cycle is divided into three stages: an initial stage, called active (A-active), followed by an intermediate stage, in which the ulcer is in the process of healing (H-healing) and, finally, the last stage, in which the ulcer has scarred (S-scar). All of these stages, according to their
characteristics, are subdivided into other two stages. After healing of the duodenal ulcer, the bulb might show a deformed architecture and, in extreme cases, this can cause segmental stenosis.

**Diagnosis of H. pylori infection**

There are several methods for the diagnosis of *H. pylori* infection. The microbiological and histopathological methods, and molecular biology techniques for direct detection of the pathogen in the gastric mucosa, are considered invasive, since mucosal fragments are obtained through esophagogastroduodenoscopy. The noninvasive or indirect methods consist of detection of anti-*H. pylori* antibodies in serum, urine and saliva samples, detection of *H. pylori* antigens in stool samples, and of the carbon 13-labeled urea breath test, non-radioactive isotope.

It has been recommended that at least two tests be used for a more accurate diagnosis of the infection. It is also necessary that noninvasive methods be validated for the population to be assessed.

**Preformed urease test and H. pylori investigation in histological sections and stained smears**

Since bacterial load is lower in children, test sensitivity increases when at least two mucosal fragments are analyzed, one from the antrum and another one from the gastric corpus. There may be false-negative results due to the irregular distribution of the bacterium in the gastric mucosa or due to the use of antimicrobials or proton pump inhibitors (PPIs) in case of the urease test.

The accuracy of investigation in histological sections relies mainly on the pathologist’s experience. Carbol fuchsin staining has proved sensitive, simple and inexpensive for the detection of *H. pylori* in smears or histological sections.

**Culturing**

The isolation of *H. pylori* from gastric mucosal fragments is the most specific method for the diagnosis of this infection. It also allows detecting virulence factors and susceptibility to antimicrobials, enabling an improved therapy.

The use of at least two fragments from the gastric mucosa, one from the antrum and another one from the gastric body, adequate specimen transportation, use of a selective and indicator medium, and the team’s experience are essential for the successful isolation of *H. pylori*.

Despite the high specificity of this method, sensitivity rates range from 77.0 to 100%. Queiroz et al., in Brazil, found a sensitivity of 94.6%. Tissue culture of bacterial DNA can be performed using fluorescence in situ hybridization (FISH), with similar sensitivity to that of PCR.

*H. pylori* virulence factors, such as cagA and vacA, can be identified by several molecular biology methods, such as PCR, PCR followed by line probe assay (LPA), real-time PCR and reverse transcription PCR (rtPCR). Since there are regional variations in the sequence of genes that encode these factors, primers described in the literature must be tested for different populations. Amplification followed by sequencing is necessary to identify other *H. pylori* virulence genes, such as babA, dupA, sabA and oipa.

**Carbon 13-labeled urea breath test**

Studies with adults and with children older than 6 years have shown that the breath test has sensitivity and specificity higher than 95.0%.

Although some reports have described lower specificity for the carbon 13-labeled urea breath test in children aged less than 6 years, other studies have found a similar specificity to that observed in adults, regardless of the child’s age. Excellent results have been observed in our population, for children aged less than 6 years (sensitivity of 88.0% and specificity of 95.0%) and for older children as well (sensitivity of 100% and specificity of 98.0%).

The carbon 13-labeled urea breath test is currently regarded as the method of choice to assess therapeutic response in adults and in children.

False-negative results are obtained when the patient is on PPIs and antimicrobials that may decrease bacterial density. PPIs must be discontinued 15 days and antimicrobials 1 month prior to the test. On the other hand, the use of histamine-2 (H2) receptor antagonists and of antacids has a negligible interference with the test results; therefore, their use should be discontinued 48 hours before the test.

**Detection of H. pylori antigens in stool samples**

The detection of *H. pylori* in stool samples is achieved by an immunoenzyme assay using monoclonal or polyclonal antibodies; several kits are commercially available. Since it is a noninvasive test, it can also be used in epidemiological studies. There have been some reports of lower sensitivity of this method for the diagnosis of infection in children aged less than 6 years. Nevertheless, the test has high sensitivity and specificity rates (approximately 95.0%) in our population, even among children aged less than 6 years. It should be highlighted that appropriate transportation and maintenance of samples are crucial for successful results.
Gastrointestinal bleeding and the use of antimicrobials and of PPIs reduce the test sensitivity, which is not changed, however, by H2 receptor antagonists and antacids.

Immunochromatographic tests for the detection of antigens in the feces, recently released into the market, are easily applied and allow having the results within few minutes. Their sensitivity and specificity are similar to those obtained from immunoenzyme assays.

**Detection of anti-\textit{H. pylori} antibodies**

\textit{H. pylori} infection produces a cellular and humoral immune response in the host, which triggers the production of anti-\textit{H. pylori} antibodies (IgM, IgA and IgG). IgM antibodies can be detected very early on. IgA and IgG antibodies only have detectable levels approximately 3 weeks to 3 months after the onset of acute infection and can be detected for up to 2 years after bacterial eradication.

Among several available methods, the enzyme-linked immunosorbent assay (ELISA) is the most widely used, since it is quick, easy-to-use, reproducible, inexpensive, and highly accurate; several kits have been commercially available. However, it should not be used for the diagnosis of infection in children aged less than 12 years, because its sensitivity is too low in this age group (44.4% for children aged 2 to 6 years and 76.7% for those aged 7 to 11 years). As immunoenzyme assays for the detection of antibodies in the urine and saliva are even less sensitive and specific, they are not recommended for the diagnosis of infection in children. On the other hand, the sensitivity and specificity of the detection of anti-\textit{H. pylori} antibodies by immunoblotting are acceptable for the diagnosis in children. In our population, a sensitivity of 95.0% and a specificity of 86.0% have been reported for children aged 2 to 16 years.

**Treatment**

**Peptic ulcer associated with \textit{H. pylori} infection**

\textit{H. pylori} is the major cause of PU, and its eradication results in the cure of patients, being indicated for all children with active, recurrent, healed or complicated disease.

Even though there is no ideal therapeutic regimen, several treatments have been successfully used in adults, with eradication rates between 80 and 90%. The most efficient treatments include one PPI and two antimicrobials. At least one of the antimicrobials should be systemic, i.e., it should be excreted in active form into the gastric mucosa after being absorbed. There are few compounds with such quality, which include macrolides and imidazole derivatives (tinidazole or metronidazole). In Brazil, high eradication rates have been obtained with the use of PPIs, clarithromycin and furazolidone. Other antimicrobials include amoxicillin, metronidazole, tetracycline, bismuth and quinolones, which are often used as second-line treatments. However, there is a paucity of studies on the treatment of infection in children. In addition to assessing a small number of patients, these studies substantially differ in terms of design, drug dosage and length of treatment, making it difficult to choose the best treatment regimen for the eradication of the pathogen in children.

In Sweden, Tindberg et al. found eradication rates lower than 67.0% with therapeutic regimens containing azithromycin, tinidazole and lansoprazole. Better results were obtained by Kato et al. in Japan with treatments that included PPIs, amoxicillin and clarithromycin or metronidazole, which eradicated the pathogen in 77.4 and 87.5% of children, respectively. According to Oderda et al., triple regimens including bismuth, metronidazole and clarithromycin, or PPIs, amoxicillin and tinidazole, or PPIs, metronidazole and clarithromycin, for 1 to 2 weeks, yielded eradication rates greater than 85.0% in the treatment of children in Italy. Recently, Francavilla et al., in Italy, have obtained eradication rates of 97.5% by using a sequential regimen consisting of omeprazole and amoxicillin for 5 days, followed by omeprazole, clarithromycin and tinidazole for another 5 days. In Brazil, an eradication rate greater than 85% was observed in children treated with furazolidone, amoxicillin and metronidazole, given in three daily doses for 7 days. Differently from the results obtained for adults in industrialized countries, treatment regimens including PPIs, clarithromycin and amoxicillin were not efficient for the treatment of children in Brazil. Alternative regimens, containing other antimicrobials, should be used with caution. Quinolones are contraindicated for pediatric use, and tetracyclines cannot be used in children aged less than 8 years.

Resistance, especially to clarithromycin and to metronidazole, has been described, with rates that vary according to region. In our setting, clarithromycin resistance has amounted to 29.0%, whereas metronidazole resistance has reached 45.5%. The microbiological methods recommended to assess resistance include the E-test and agar dilution. Mutations that provide clarithromycin resistance (adenine-to-guanine transition at position 2142 or 2143, and adenine-to-cytosine transition at position 2142) in the gene that encodes RNA 23S can be directly investigated in the DNA of isolated bacteria or in the DNA obtained from the freshly collected tissue fragment, or kept frozen by PCR followed by restriction fragment length polymorphism analysis (PCR-RFLP), real-time PCR, LiPA or FISH.

**\textit{H. pylori}-negative peptic ulcer**

\textit{H2} receptor antagonists are safe and efficient drugs used for the healing of PU. They inhibit acid secretion, competing with the \textit{H2} receptors of parietal cells, and reduce
pepsinogen secretion. Oral cimetidine, in two doses of 20 to 30 mg/kg/day, and oral ranitidine, in two doses of 5 to 10 mg/kg/day, heal the ulcer in 80 to 90 and 80 to 100% of cases, respectively, after 8 weeks of treatment.17,124 
PPIs are the most potent acid-secretion blockers available on the market, and omeprazole is the drug pediatricians have more experience with. PPIs whose action is dose-dependent specifically block the H⁺-K⁺-ATPase of the apical membrane of the parietal cell, with consequent suppression of acid secretion. In case of younger children, unable to swallow an intact capsule, the contents should be removed from the capsule and mixed in an acidic medium, preventing the protective films from dissolving while traveling down through the esophagus. Omeprazole soluble in water and in fruit juice is already commercially available, making its administration to children a lot easier.30 The drug should be given in the morning, 30 minutes before breakfast.125 The dose ranges from 0.7 to 3.3 mg/kg/day, but it has not yet been clearly defined for pediatric patients.126 The total healing of ulcers is obtained in up to 100% of cases after 6 weeks. Individual response to intravenous omeprazole varies considerably, and persistent increase of pH levels above 4.0, is only observed in few patients.125 
Antacids can bring some benefits to the treatment of PU, but high doses are necessary to neutralize gastric acidity, making its administration more difficult, especially to younger children.16 Sucralfate has no effect on gastric acid secretion; however, it can contribute to the healing of ulcers by increasing the blood flow in the mucosa, as well as bicarbonate secretion and gastric mucus.16

H. pylori-negative bleeding peptic ulcer

Deep ulcers in the lesser curvature of the stomach or in the postero-inferior wall of the duodenal bulb are more likely to have severe bleeding, due to their vicinity to large vessels. Endoscopic stigmata of bleeding, described by Forrest et al., serve as a guide to endoscopic treatment and are useful indicators for the prognosis of bleeding. The endoscopic treatment of patients with active PU is indicated in special situations, such as in PU with active spurting bleeding (Forrest Ia) or oozing bleeding (Forrest Ib) and in those ulcers with visible vessel (Forrest IIa). The safest and most commonly used method of endoscopic hemostasis in the pediatric population in our setting consists of a local injection of an epinephrine 1:10,000 solution.127 Other methods include thermal coagulation with argon or Nd:Yag laser, and the mechanical method with placement of metal clips.127 The surgical treatment of patients with hemorrhagic PU is indicated in cases of uncontrollable bleeding, with severe hemodynamic consequences and unresponsiveness to clinical and endoscopic treatment.128

References
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