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# Particulars of the *Helicobacter pylori* Infection in Children

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Additional information is available at the end of the chapter

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## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is an important pathogen in human gastroenterology. *H. pylori* is commonly acquired during early childhood and it is more common among people in developing countries. Globally, over 50% of the population is infected with this bacteria, being practically evenly distributed between the two genders, in spite of a few studies showing a slight predisposition in males.

The clinical consequences of *H. pylori* infection in children are yet to be fully understood. *H. pylori* infection in children differs from the same infection in adults, both in terms of the percentage of infected individuals, symptoms, degree of complication towards peptic ulcer disease or malignancy, the gastric areas affected, the degree of compliance to therapeutic management or bacterial resistance to treatment.

## 2. Context

*Helicobacter pylori* (*H. pylori*) is a Gram - negative bacillus responsible for one of the most commonly diagnosed infections, namely gastritis, in humans worldwide. [1]

In 1983 Robin Warren, an Australian pathologist, described an S-shaped bacteria for the first time, that was found in the gastric mucosa. Together with Barry Marshall, they managed to isolate this micro-organism from biopsy samples taken during endoscopy, and called it *Campylobacter pyloridis*, to be called *H. pylori* later on. [2]

Although the presence of bacteria in the stomach had been known as early as the 19th century, these microbes were considered simply a consequence of gastric mucosa contamination from

food intake and not colonizing species in the true sense of the word. The current in thinking had been so controversial from the very beginning, that, about 30 years later, when *H. pylori* was discovered and proposed as the causative agent for gastritis and peptic ulcer disease, the scientific community rejected and even ridiculed the new theory. Survival of microbes in the acidic pH conditions of the stomach was considered impossible.

In one of the boldest scientific approaches of the last century, Barry Marshall self-administered an *H. pylori* dose in 1984. Although the researcher physician expected to develop peptic ulcer disease in the coming months, the symptoms emerged much sooner: only 3 days later, Marshall displayed dizziness, halitosis and vomiting, and in another 8 days, pangastritis was diagnosed endoscopically, meaning inflammation of a large areas of the stomach.

Shortly after the publication of results in Warren and Marshall's research, *H. pylori* was also detected in biopsy specimens taken during digestive endoscopy performed in children with chronic gastritis and / or duodenal ulcers; at the same time, resolution of gastric pathology in children was also demonstrated with bacterial eradication. [3] Overall, these discoveries have demonstrated the important role of *H. pylori* in gastric pathology both in adults and children.

The discovery of *H. pylori*, the demonstration of causality between the infection and gastric pathology and improvement of the bacteria eradication methodology increased the living quality for a large number of patients. If, in the past, peptic ulcer disease surgery used to be one of the most common forms of surgery performed, management of ulcers by eradication of *H. pylori* is so effective nowadays that very few patients require surgery. The merit of Warren and Marshall's pioneering research was awarded the Nobel Prize for medicine in 2005.

Goals of current and future research of *H. pylori* equally require better understanding of immune-pathogenics of gastric disease associated with *H. pylori* infection, clarification of modes of transmission, as well as improving the safety and effectiveness of vaccines for prevention of *H. pylori* infection.

Children are different from adults regarding *H. pylori* infection, in terms of the prevalence of the infection, the complication rate, the almost complete absence of gastric malignancy, age-specific issues, with diagnostic tests and medication as well as a higher rate of resistance to antibiotics. The former and other differences as well can explain why some of the recommendations for adults cannot be applied to children. [4]

### 3. Description of *H. pylori*

Phylogenetic classification of *H. pylori* is: *Helicobacter* genus, *Helicobacteraceae* family, *Campylobacteriales* order, *Proteobacteria* subdivision.

*H. pylori* is a Gram - negative type bacterium, able to colonize the gastric mucosa in the majority of the population in the context of very low pH and low partial pressure of oxygen (pO<sub>2</sub>). *H. pylori* has a curved shape and is 2-4 microns long and 1 micron wide. It displays 2-6 flagella of

about 3 microns in length, ensuring it high mobility. [5] Optimal development of this organism requires reduced O<sub>2</sub> pressure, high humidity, 37° C temperature and neutral pH. The metabolism of the microbe can process glucose but not any other sugars.

The bacterium displays a range of extraordinary adaptations needed for survival in the extreme conditions of the gastric environment. *H. pylori* is one of the most efficient animal species, capable of degrading urea. The abundance of the *urease* enzyme allows rapid urea hydrolysis in the gastric environment, with release of bicarbonate and ammonia, which neutralize the gastric pH and provide for the optimum conditions for bacterial life. At the same time, the ammonia generated is used in the metabolism of the bacterium for the synthesis of amino acids. [6] Initially, the *urease* enzyme is solely localized in the cytoplasm, however, in the case of exposure to acid *in vivo*, autolysis of the cell wall takes place and release of the enzyme, which is subsequently fixed on the *H. pylori* surface. At the same time, increased motility allows the bacterium to penetrate and become fixed in the layers of the gastric mucosa. [7]

Outside the host organism, however, *H. pylori* is fragile and unable to survive when stored at low and ultra-low temperatures as compared with other intestinal bacteria. Although healthy individuals' manner of infection of is not yet fully understood, it is assumed that transmission is largely by direct contact of individuals and less by contaminated objects.

#### 4. The rate of *H. pylori* infection

*H. pylori* infection global rate differs by region, ethnicity, age, and socio-economic level of the population. The percentage of infected individuals is higher in disadvantaged socio-economic categories and increases with age. Large infection percentages (about 80%) may be found in Asian countries, in Eastern and South-Eastern Europe, in Latin America, whereas much smaller percentages (about 40%) are characteristic to Western countries. [8-10]

Regardless of the geographic area analysed, one finds that *H. pylori* infection is usually acquired in early childhood both in developed and developing countries.

#### 5. Prevalence

Overall, about one third of the population is infected with *H. pylori*, and the frequency increases with age.

In general, the prevalence is higher in developing countries, and the infection is contacted at an early age. The incidence is 3-10% of the population every year in developing countries, as compared to 0.5% in developed countries. [11]

The prevalence of *H. pylori* infection is not only lower in industrialized countries than in developing countries, but the incidence of *H. pylori* infection, gastric cancer, peptic ulcer

disease and related diseases are also declining. Worldwide, more than 1 billion people are estimated to be infected with *H. pylori*. [4]

## 6. Possibility of transmission

*H. pylori* does not tolerate increased O<sub>2</sub> partial pressure, high temperatures or nutrients poor environments outside the host organism. In other words, *H. pylori* is excellently adapted to gastric existing parameters, but it is a fragile organism, non-viable outside the host. One study highlights the possibility for *Helicobacter pylori* infection from a water supply. For these reasons, although the exact *H. pylori* mode of transmission is not completely understood, the type of transmission is accepted by primarily direct contact of healthy individuals with an infected person. Transmission of infection may also be the result of transport vectors.

*H. pylori* isolated strains are found more often in staff performing endoscopies than the general population.

*H. pylori* has been isolated and cultivated from faeces, indicating the possibility of faecal-oral transmission. Also, *H. pylori* was found in the oral cavity in both saliva and the plaque, suggesting oral-oral transmission variant. Therefore, transmission of *H. pylori* can occur by oral-oral, faecal-oral transmission or a combination thereof. [12]

Horizontal transmission is favoured by overcrowding found in densely populated human communities. This version is the most likely in the case of infection transmission among family members. Thus, children of *H. pylori* infected mothers run an 8 times higher risk of acquiring the bacterium. [13]

## 7. Diagnosis of *H. pylori*

Correct diagnosis of *H. pylori* is possible through a wide range of working methods. However, the opportunity to diagnose *H. pylori* and the working method chosen should be evaluated according to the specificity of each case.

*H. pylori* infection generated symptoms is nonspecific, including abdominal pain, gastro-oesophageal reflux with or without heartburn, halitosis, vomiting or hematemesis.

Because symptoms caused by *H. pylori* are general (nonspecific), the *H. pylori* infection may overlap with another digestive or abdominally located disorder. Therefore, the primary purpose of investigating gastrointestinal symptoms should be elucidating their real ethyology and not just determining the presence of *H. pylori* infection. This consideration is especially important in the case of *H. pylori* infection in children under the age of 12, because the latter are unable to accurately describe the location, nature or intensity of their discomfort. [14]

Assessment of patients infected with *H. pylori* should pay particular attention to anorexia and weight loss, pallor or laboratory tests to identify anaemia, vomiting, abdominal pain or pain

associated with meals and night-time, as well as to any descriptions of gastrointestinal haemorrhage.

In children suspected of *H. pylori* infection, history should include the following:

- Abominable pain nature, location, frequency, duration, severity, exacerbation and alleviating factors;
- The intestinal transit and description of the stool;
- Appetite, diet, changes in weight;
- Halitosis, vomiting and description of the gastric material;
- Ulcer disease or gastrointestinal disorders (e.g. Crohn's disease) running in the family;
- Medications (on-prescription and OTC);
- Previous diagnostic tests and gastrointestinal tract specific therapy.

Physical examination of an asymptomatic *H. pylori* infected child usually ends in confusing results. In children with chronic gastritis, duodenal and peptic ulcer, important findings include epigastric tenderness or gastrointestinal bleeding (e.g., positive guaiac stools, tachycardia, pallor).

Children with peptic ulcer can develop complications (e.g., severe blood loss in the gastrointestinal tract, perforation, obstruction) and may show signs of hemodynamic instability or signs of acute abdomen. Children with long-term peptic ulcer caused by *H. pylori* may become anaemic from undetected and asymptomatic chronic bleeding. In such children, the following should be considered:

- The child's overall appearance;
- Assessment of perfusion, paying special attention to the child's mental status, heart rate, pulse as well as *refill of capillaries*.
- Evaluation of *the child's skin as well as* conjunctivae in order to check pallor.
- Careful cardiac and pulmonary scrutiny.
- Abdomen inspection, auscultation and palpating.
- Making a rectal exam and the guaiac test of the stool. [4]

For accurate diagnosis of *H. pylori* infection, several methods are available with varying degrees of accuracy:

### 7.1. Histopathological methods

Isolation and cultivation of *H. pylori* in biopsy specimens taken during endoscopy is the golden standard in diagnosing the infection. In addition, this method also has the advantage of providing information about tissue pathology as caused by *H. pylori* infection. Since distribution of *H. pylori* concentration on the gastric mucosa is not uniform but has rather the appear-



ance of distinct lower or higher concentration islands, taking at least 2 biopsies is recommended, one of the gastric body and the other from the antrum. [15]

## 7.2. Breath analysis

Diagnosis of *H. pylori* infection may also be performed by breath analysis after oral administration of a urea solution. If the urea used is provided with a  $^{13}\text{C}$ -labelled carbon atom, this isotope dosage can be performed, but the method is both very precise and demanding in terms of the equipment involved. Alternatively, unmarked urea can be administered to qualitatively detect the presence of *H. pylori* by identification of  $\text{NH}_3$  (ammonia) in the air expired. [4]

## 7.3. Immunological methods

*H. pylori* infection causes emergence of specific antibodies: anti-*H. pylori* antibodies (IgA and IgG) in serum, blood, urine and / or saliva. Although cheap and fast, detection of these antibodies is not relevant to assess the current status of infection or success of the eradication therapy. Because of immunological memory, antibodies may persist for months and years even in the host organism after eradication of the infection. [16-18]

## 7.4. Detection of antigens

Identification of *H. pylori* antigen in faeces is an accurate way of establishing the diagnosis, as a non-invasive method and easier to apply in children than administration of urea solution or endoscopy.

In addition, the method has the advantage that even after the passage of five days from sample harvest, diagnosing *H. pylori* is as accurate. Thus, sampling of biological material can be performed without the active participation of children and their visit to the medical centre, as the sample may be dispatched by courier. [4]

Colonization of gastric mucosa by *H. pylori* does not automatically mean onset of the disease, but the infection correlates with increased risk of infection during the onset of peptic ulcers and gastric cancer. The materialization of this risk depends on a summation of factors related to the genome of the bacterium, the host and environmental factors. [19]

A wide range of extra-gastrointestinal disorders are thought to be associated with *H. pylori* infection, e.g. otitis media, upper respiratory tract infections, periodontitis, food allergies, Sudden Infant Death Syndrome (SIDS). However, there is currently no convincing scientific evidence regarding the causal relationship between *H. pylori* infection and such disorders.

Symptoms associated with *H. pylori* infection may be absent even in some cases where the presence of *H. pylori* was proved by histological analysis. In other cases however, infection is followed by the occurrence of peptic ulcer and its complications. The general pathology of *H. pylori* includes phenomena such as dyspepsia and refractory anaemia. [15]

## 8. Incriminatory factors

To determine their causal relationship with *H. pylori* infection, epidemiological studies have addressed various factors such as a bacterial cause, the host, genetic and environmental factors. Data are related to the spread of infection from person to person (e. g. dental plaque), but the origin and the mode of transmission is incomplete known. [4]

*H. pylori* infection causes include the following:

- We can observe that the transmission of *H. pylori* is possible person to person.

Groups of infection are under observation, particularly within families of infected children. Possible routes are faecal-oral, oral-oral and gastro-oral. Mother to child transmission has been suggested in a study analysing DNA of *H. pylori* strains. [20] Studies have shown identical *H. pylori* strains in mothers and their younger children. Maternal symptoms of nausea and vomiting and pacifier use were associated with the risk of *H. pylori* infection in children.

Cervantes et al. participated a study performed at the US-Mexico border and they have shown that a younger brother is 4 times more prone to *H. pylori* infection if the mother was *H. pylori* infected, compared to an uninfected mother. Younger brothers are 8 times more likely to acquire the infection if an older brother had persistent *H. pylori* infection. [13]

Absence or poor personal hygiene may also play a role. Increase in *H. pylori* infection may be observed in developing countries, which may reflect the combined effects of poor living conditions, poor hygiene and overcrowded cities.

The status of *H. pylori* infection in the United States, a comparatively higher socio-economic setting, shows that the higher the social and economic level, the lower the incidence of *H. pylori* infection, a finding that may reflect also the same factors as those mentioned in the case of developing countries.

- In the clinical manifestations of *H. pylori* infection the bacterial factors may play an important role. Patients infected with *H. pylori* may have two basic phenotypes reported the presence or absence of cytotoxin vacuole.

Inflammation is more pronounced in people with cytotoxin - positive infection, confirmed at endoscopy, than in those infected with *H. pylori* cytotoxin - negative.

As far as bacterial factors are involved, presence of two fundamental phenotypes has been shown in *H. pylori* infected patients, i.e. vacuolating cytotoxin positive and negative, respectively. Endoscopy performed on cytotoxin-positive infected patients has proved inflammation more marked than in patients where the cytotoxin was absent.[13]

The significance of host dependent factors has been demonstrated by such observations as the fact that adults are less capable of solving acute infections than children.

A different such factor may be the presence of hypochlorhydria in the host, which allows specific *H. pylori* colonization of the stomach.

In addition, *H. pylori* may only persist if the metaplastic epithelium of the stomach is atrophied.[4]



- One study highlights the possibility for *H. pylori* infection from a water supply. [21]
- Transmission of infection may also be the result of transport vectors. [22]
- *H. pylori* isolated strains are found more often in staff performing endoscopies than the general population.

## 9. Pathophysiology

*H. pylori* organisms are spiral Gram - negative bacteria, highly mobile due to their multiple unipolar flagella. They are microaerophilic powerful urease producers. These organisms inhabit the mucus adjacent to the gastric mucosa.

Important adaptive features improve survival of the organism in an acidic environment include its shape and motility, its low oxygen needs, its adhesion molecules serving a feeding role in certain gastric cells and *urease* production. Bacterial *urease* converts urea to ammonia and bicarbonate, therefore neutralizing gastric acid and providing protection from a hostile environment. Some of the lipopolysaccharides of the organism mimic the Lewis blood group antigens structure. This molecular mimicry also helps the survival of *H. pylori* in the unfavourable gastric environment. [23]

*H. pylori* generates disease triggers, including *urease*, vacuolating cytotoxin, catalase and lipopolysaccharide (LPS). *Urease* is a potent antigen inducing increased production of immunoglobulin G and immunoglobulin A. Expression of vacuolating cytotoxin generating inflammatory cytokines may be associated with more pronounced inflammation and marked tendency of disease triggering.

The most important virulence factor in *H. pylori* infection is cytotoxin - associated antigen (CagA). A person infected with CagA -negative strains is likely to develop chronic gastritis and have little chance to develop peptic ulcer disease or gastric cancer.

On the other hand, infection with CagA -positive strains greatly increases the risk of peptic ulcer and gastric cancer. Movement of CagA protein into gastric epithelial cells leads to rearrangement of the host cytoskeleton, alters signalling cell and disturbs the cell cycle control. [24]

In children with *H. pylori* infection, who have peptic ulcer disease, *in situ* expression of CagA is increased and may play an important role in the pathogenesis of peptic ulcer disease. [25]

The bacteria *H. pylori* localises in the stomach, induces inflammatory cytokines formation and causes gastric inflammation. People with *H. pylori* gastritis associated with increased gastric acid gastritis are prone to peptic ulcer disease. [26] In contrast, people infected with *H. pylori* associated with corpus gastritis, with decreased gastric acid production are more prone to developing gastric atrophy (intestinal metaplasia and gastric adenocarcinoma).

The infection with *H. pylori* has been associated with iron deficiency anaemia. The two main assumptions underlying this theory are iron sequestration because of antral *H. pylori* infection and decrease of non-heme iron absorption caused by hypochlorhydria.

*H. pylori* infection and its association with gastric malignancies have been well described in several epidemiological studies. [27] However, the evolution from inflammation to cancer remains unclear.

There exists a model describing the progressive evolution of *H. pylori* infection to hypochlorhydria, chronic gastritis, atrophic gastritis, dysplasia, intestinal metaplasia and gastric cancer. [28, 29, 30, 31]

A newer hypothesis suggests that *H. pylori* infection may protect against self-inflammatory diseases such as asthma or inflammatory bowel disease. For instance, epidemiological data suggest that infection with *Helicobacter pylori* is less common in patients with inflammatory bowel disease, which leads to research for defining potential mechanisms underlying these clinical findings. [27]

## 10. Morbidity

Most *H. pylori* infected children are asymptomatic. Antral gastritis is the most common manifestation in children. Duodenal and gastric ulcers may be associated with *H. pylori* gastritis in adults, but is less common in children. The risk of gastric cancer, including non-Hodgkin lymphoma (i.e. associated to the lymphoid tissue mucosa MALT) and adenocarcinoma is increased in adults. [4]

The relationship between *H. pylori* gastritis and recurrent abdominal pain (RAP) is controversial. The incidence of *H. pylori* gastritis in patients with RAP is not significantly higher than the incidence of *H. pylori* infection in the general population. Although certain studies have shown an improvement in symptoms in children with RAP and *Helicobacter pylori* gastritis after eradication therapy for *H. pylori*, data from a recent double-blind controlled trial have not confirmed this finding. [32]

According to the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition no results were sufficiently reliable to support routine testing for *H. pylori* in children with RAP. [33]

Data published so far highlight an association between *H. pylori* infection and gastrointestinal symptoms in children, but no association has been found between RAP and *H. pylori* infection. Conflicting evidence has been found however concerning the association of *H. pylori* infection with epigastric pain. [34]

There are studies suggesting that *H. pylori* protects the human body from developing gastroesophageal reflux disease, while others affirm a causal association between them. Analysis of studies conducted in adults has found no association between *H. pylori* eradication and development of new cases of gastroesophageal reflux disease in dyspeptic patients. [35]

According to a pediatric retrospective study, there was a significantly higher prevalence of reflux esophagitis in *H. pylori* infected children. [36]

*H. pylori* infection was also associated with extraintestinal manifestations such as short stature, immune thrombocytopenic purpura and migraine, with different levels of causation. [37, 38]. This infection is also associated with coronary diseases, iron-deficiency anemia and hepatobiliary diseases among others. [39, 40, 41, 42, 43, 44]

## 11. Dissemination (population category)

The predominance *H. pylori* infection is increased in black, Hispanic, Asian, and Native American populations.

The infection with *H. pylori* affect more than a half of the world's population, which is acquired almost always within the first 5 years of life [45]. In the developed world, the prevalence rates vary from 1.2% to 12.2% [46-49]. In developing countries, the prevalence rates are much higher. The serological prevalence rates of *H. pylori* were 45% among Indian children [40,51]. In Bolivia and Alaska, at the age of 9 years, the seroprevalence was 70% and 69%, respectively [52]. The seroprevalence in preschoolers in Brazil was found to be 69.7% [53]. An age-related increase of the prevalence of *H. pylori*, irrespective of the economic state of the country, was observed by several independent studies across the world [47-51, 54, 55].

In a study of Prof Dr Sibille Koletzko et al [15] was presented that during the first years of life in both developing and industrialized countries the *H. pylori* infection is usually acquired. The epidemiology of *H. pylori* infection in children, in Europe and North America has changed in recent decades. In the northern and western European countries are founding low incidence rates, resulting in prevalence far below 10% in children and adolescents. In contrast, the infection is still common in certain geographic areas such as southern or eastern Europe, Mexico, and certain immigrant populations from South America, Africa, and most Asian countries, and aboriginal people in North America. The different prevalence of infection and the corresponding effect on health care resources in industrialized compared with developing countries require different recommendations with respect to testing and treating children. These guidelines apply only to children living in Europe and North America, but not to those living in other continents, particularly in developing countries with a high *H. pylori* infection rate in children and adolescents and with limited resources for health care [15].

Infection rates are similar in men and women alike.

Many study present that less than 10% of children under 12 years of age are infected in developed countries, but seropositivity increases with age, to a rate of 0.3-1% per year. Seropositivity studies in developed countries in adults showed a prevalence of 30-50%.

In the US, estimated prevalence is 20% for people under 30 and 50% for persons over 60. In developing countries, prevalence rates are much higher. *H. pylori* serological prevalence rates have been 15% and 46% for Gambian children under 20 months and 40-60 months, respectively. [56]

## 12. Laboratory methodology

An important study of Prof Dr Sibille Koletzko et al was presented by using the testing guidelines recently provided by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) for *H. pylori* infection in children [15]. These recommendations are:

- The primary purpose of clinical investigation of gastrointestinal symptoms is to determine the primary cause of the symptoms, and not the presence of *H. pylori* infection only.
- Diagnostic tests for *H. pylori* infection are not recommended in children with functional abdominal pain. Currently, in the absence of ulcer disease, there is insufficient evidence to justify a causal relationship between *H. pylori* gastritis and abdominal symptoms. Therefore, cases of abdominal pain consistent with diagnostic criteria for functional pain should not be investigated for *H. pylori*, unless upper endoscopy is conducted during diagnostic, in search of some organic disease.
- In children with first-degree relatives with gastric cancer, *H. pylori* testing may be considered.
- In children with refractory iron deficiency anaemia in whom other causes have been excluded, *H. pylori* testing can be considered.
- There is insufficient evidence that *H. pylori* infection is causally linked with otitis media, respiratory tract infections, periodontal diseases, food allergies, sudden infant death syndrome, idiopathic thrombocytopenic purpura and short stature.
- To confirm eradication in children selected with disease complicated by peptic ulcer or lymphoma and in children who remain symptomatic.

For diagnostic tests to be applied, the recommendations are as follows:

- For the diagnosis of *H. pylori* infection during esophagogastroduodenoscopy (EGD), it is recommended to obtain gastric biopsy samples (antrum and corpus gastritis).
- It is recommended that the initial diagnosis of *H. pylori* infection rely on positive histopathology examination and a rapid *urease* positive test or a positive culture.
- The <sup>13</sup>C - urea breath test (UBT) is a non-invasive test to determine successful eradication of *H. pylori*.
- A positive enzyme immunoassay (ELISA) for the detection of *H. pylori* antigen in the stool is a noninvasive test to determine whether *H. pylori* has been eradicated. Several methods are available for detection of the *H. pylori* antigen in stool, such as the enzyme immunoassay test (EIA) based on polyclonal or monoclonal antibodies and immunochromatographic tests (the so-called rapid tests).

Stool tests are generally much more convenient in children than UBT. Neither storage of evidence at room temperature for up to 5 days nor freezing them for months or even years

appears to influence the accuracy of the stool tests. So far, only EIA based on monoclonal antibodies has equalled UBT accuracy.

- Tests relying on antibody detection (IgG, IgA) against *H. pylori* in the blood serum, urine and saliva are not viable for use in the clinic setting.
- Physicians are recommended to wait for at least 2 weeks after end of the proton pump inhibitors (IPP) therapy and for 4 weeks after end of antibiotics before conducting biopsy and non-invasive tests (UBT, stool test) for *H. pylori*.

It should be noted that these guidelines only apply to children in Europe and North America, not in other continents, particularly developing countries, with a high rate of paediatric *H. pylori* infection and limited health resources.

#### **Another studies / tests**

- Imaging studies are not useful in the diagnosis of *H. pylori* infection. They can be useful in patients with complicated diseases (e.g., ulcer, gastric cancer, MALToma).
- Urea breath test: The patient ingests a test meal containing carbon-13 ( $^{13}\text{C}$ ) labelled urea, which is a nonradioactive isotope. *H. pylori* urease activity produces  $^{13}\text{C}$ -labelled carbon dioxide, detectable in the breath. A positive result confirms urease activity and *H. pylori* infection. This is a highly specific test, sensitive in patients over 6 years of age. It is useful to check eradication of *H. pylori* after treatment. Experience in children 5 years or younger, in infants particularly, is relatively limited and needs further validation.

#### **Detection of *Helicobacter pylori***

The procedure of choice for detecting gastritis, duodenitis and PUD in the paediatric population is upper endoscopy (EGD)

- EGD allows direct visualization of the mucosa, for locating the source of bleeding, to detect *H. pylori* by biopsy, culture and cytology analysis and DNA testing using PCR.
- In addition, a rapid test based on detection of urease activity (a *H. pylori* highly specific marker) may be performed. The test, called the *Campylobacter* test (CLO) allows diagnosis of *H. pylori* infection within 24 hours.
- Two modified urea rapid test kits are currently available on the market and reported as more accurate, with shorter reaction time and of better value for money than the CLO test.
- Endoscopy in children may reveal a nodular appearance in the gastric antrum resulting from lymphoid hyperplasia [34]. Approximately 50% of affected children have displayed endoscopic evidence of changes of *H. pylori* gastritis.

The appearance of an active ulcer is round or oval lesion in shape, the perforated base being smooth and white, with a red and oedematous surrounding mucosa. In *H. pylori* infection, the most common site for ulcer is the duodenal bulb.



Biopsy obtained from the prepiloric antrum has the highest yield in *H. pylori* infection. Often, tissue samples are also obtained from the body and the transition areas of the stomach, especially when the patient has recently taken acid suppressing medications.

- Endoscopic biopsy is indicated for the following reasons:
- Histological examination of gastric tissue;
- Rapid *urease* test (e.g. CLO test)
- Culture of organisms;
- PCR test for identification of *H. pylori* DNA
- Histological findings include infiltration of a substantial number of plasma cells and lymphocytes into the gastric mucosa and Giemsa, Diff-Quick visible bodies or haematoxylin and eosin. Sensitive colouring of a small number of bacteria is possible with a silver staining method such as Genta or Warthin-Starry.

### Stages

- Multiple stages in the progression of the disease are well described in the literature, although no stages system for *H. pylori* infection has been established.
- The first step is chronic gastritis, followed by a second step, atrophic gastritis. The third step is intestinal metaplasia, which can evolve to dysplasia. The last step in this process is gastric adenocarcinoma.
- This is a very slow process (which may take decades, for example), and can stop at any step because gastric cancer probably requires several other factors to grow, not just *H. pylori* infection.

### Treatment measures of *Helicobacter pylori* infection

Let us mention the new treatment rules recommended for the following patient groups [15]:

- In the presence of *H. pylori*-positive PUD, eradication of the microorganism is recommended.
- On detection of *H. pylori* infection by biopsy based methods in the absence of PUD, *H. pylori* treatment may be considered. The decision to treat *H. pylori* associated gastritis without duodenal or gastric ulcer is subject to the clinician's judgment and deliberation is undertaken with the patient and family, taking into account potential risks and benefits of treatment for the patient.
- In *H. pylori* infected children, whose next of kin suffer from gastric cancer, treatment can be offered.
- The "test - and-treat" strategy is not recommended for children. The main purpose of the tests is to diagnose the cause of the clinical symptoms.

Currently practiced therapeutic approach takes the following into account:



- *H. pylori* acquired resistance to antibiotics, which requires bacterial strain susceptibility testing to a certain class of antibiotics in geographic areas where resistance is seen in encountered in a percentage of patients;
- Success rate in eradication of infection is directly dependent on the dose and duration of medication administered. In practice however, this is less apparent because of lower compliance in long cures and because of adverse effects (vomiting, nausea, malaise) in high doses;
- Bismuth ( $\text{Bi}^{3+}$ ) salts preparations are effective but difficult to accept by children because of their bad taste;
- Therapeutic management aims not at eradication of *H. pylori* infection only but also at resolution of the pathology it determines (gastritis, reflux, dyspepsia etc.) and therefore triple therapy may be associated with prokinetics and hygienic-dietary regime to spare digestion;
- Unwanted side effects of the antibiotics cure can be reduced by administration of probiotic preparations that restore normal intestinal flora.

The following treatments should be implemented [15]:

- First line eradication regimens are: triple therapy with a PPI + amoxicillin + imidazole, or PPI + amoxicillin + clarithromycin + amoxicillin or bismuth salts + imidazole or sequential therapy. Sequential therapy involves dual therapy with a PPI and amoxicillin for 5 days, successively followed by five days of triple therapy (a PPI with clarithromycin and metronidazole / tinidazole). In fact, this scheme may be considered as quadruple therapy provided in a sequential manner. It is speculated that the initial use of amoxicillin reduces bacterial load and provides protection against resistance to clarithromycin.
- Clarithromycin antibiotic susceptibility testing is recommended prior to clarithromycin triple therapy in areas / populations definable as clarithromycin highly resistant (> 20%) to *H. pylori*.
- The recommended period for triple therapy is 7-14 days. Costs, compliance and adverse effects should be taken into account.
- A reliable non-invasive test for eradication is recommended at least 4-8 weeks after treatment.

In cases of treatment failure, the following 3 options are recommended:

- EGD with culture and sensitivity tests, including alternative antibiotics if not performed prior to standard treatment.
- *In situ* fluorescence hybridization (FISH) on paraffin-embedded biopsies, if clarithromycin susceptibility testing was not performed before standard therapy.
- Therapy changing by addition of an antibiotic, using various antibiotics, as well as addition of bismuth, and / or increase of the dose and / or treatment duration.

If not possible to perform a primary culture, the following regimens are suggested as second-line or rescue therapy [15]:

- Quadruple therapy consists of metronidazole + amoxicillin + PPI + bismuth. In most guidelines, quadruple therapy is the recommended second-line therapy, but this is a complicated regimen to administer. In addition, bismuth salts are not universally available.
- Triple therapy consists of PPI + levofloxacin (moxifloxacin) + amoxicillin. Regimen evaluation using fluoroquinolones, including levofloxacin, as second-line therapy in children is limited. In studies in adults, the treatment seems to be effective.

Although studies during ideal therapy duration for second-line treatment are not conclusive, a longer treatment duration is recommended, up to 14 days.

### Other procedures

- Surgical procedures are rarely needed in treatment of patients with *H. pylori* infection. However, the ulcer, surgery may be required for certain complications unresponsive to medical treatment, including difficult to treat abdominal pain, gastric outlet obstruction, perforation and severe bleeding.
- Consultations pediatric gastroenterologists: For evaluation, endoscopy and biopsy to confirm *Helicobacter pylori* infection and rule out other causes for abdominal pain or bleeding;
- Surgeon - For intervention in patients with severe or intractable pain or bleeding or patients with intestinal perforation or obstruction of the gastro-intestinal tract;
- Radiologist - For patients requiring upper gastrointestinal imaging with contrast-enhanced studies.

### Hygienic-dietary regime

A sparing digestive hygienic-dietary regime is recommended, including meals and snacks every 3-4 hours with correct chewing and avoidance of food aggressors. Foods such as fruit juices and certain dairy products may have a modest bacteriostatic effect on *H. pylori*. Active principles (sulforaphane and indole-3-carbinol) of the Brassicaceae family are also included here.

- Two randomized, placebo-controlled studies have evaluated the effect of probiotic food as an adjunct to standard triple therapy for eradication of *H. pylori* infection in children and have had conflicting results [58, 59].
- In a recent prospective study in adults, it was suggested that the addition of vitamin C to a regimen of *H. pylori* with amoxicillin, metronidazole, and bismuth can significantly increase the *H. pylori* eradication rate [60].

### 13. Medicines used in *H. pylori* eradication therapy [61-73]

#### Antibiotics, beta-lactamases

Beta-lactamases used to treat *H. pylori* infected patients are stable in an acidic environment, binding to proteins in bacterial cell walls, inducing direct lysis in the wall, and inhibiting cell wall synthesis.

Amoxicillin (Amoxil<sup>®</sup>, Polymox<sup>®</sup>, Trimox<sup>®</sup>, Wymox<sup>®</sup>)

Bacterially active against *Helicobacter pylori*. Available as GTT 50mg/ml; susp.125, 200, 250, or 400mg/5ml; caps 250 and 500 mg chewable tablets and 125, 200, 250, or 400mg.

#### Antibiotics, macrolides

Macrolides used to treat *H. pylori* infection are stable in the stomach, entering the bacterial cell, binding to receptors on the ribosomal subunits and inhibiting bacterial protein synthesis.

**Clarithromycin (Biaxin<sup>®</sup>, Fromilid<sup>®</sup>)**

This displays bactericidal activity against *H. pylori* antimicrobial spectrum similar to that of erythromycin but stable in acid and with fewer adverse gastrointestinal effects. Available as 125 or 250mg/5ml granules for suspension and 250 or 500 mg film-coated tablets.

#### Antibiotics, antiprotozoans

Used in the treatment of *H. pylori* infected patients, this antibiotic generates intracellular products affecting bacterial DNA.

**Metronidazole (Flagyl<sup>®</sup>, Protostat<sup>®</sup>)**

Metronidazole diffuses well into all tissues, is stable in an acidic environment, and provides bactericidal activity against *H. pylori*. Available as ex tempore 50 sau100mg/5ml suspension, 250 or 500mg tablets and 375 mg capsules.

#### Antibiotics, tetracyclines

Tetracyclines bind to ribosomal subunits and inhibit protein synthesis of susceptible bacteria. Use in paediatric patients should be limited in cases where other antibiotic regimens fail.

**Tetracycline hydrochloridum (Achromycin<sup>®</sup>, Sumycin<sup>®</sup>, Terramycin<sup>®</sup>)**

Bacteriostatic but may be bactericidal in high concentrations. Also available as 250 or 500mg tablets, 100, 250, or 500 mg capsules, and 125mg/5ml suspension.

#### H<sup>2</sup> receptor antagonists

H<sub>2</sub> receptors are located on acid-producing parietal cells. Blocking the action of the histamine suppresses gastric acid secretion.

**Ranitidine (ranitidinum) or Famotidine (famotidinum)**

H<sub>2</sub> antagonists prescribed for 8 weeks, when most *H. pylori* associated ulcers are cured. H<sub>2</sub> blockers have no antibacterial effect, therefore antibiotics should be used to eradicate *H.*

*pylori*. Available as 15mg/ml syrup, 75, 150, or 300 mg tablets, as well as effervescent tablets 150mg.

### Proton Pump Inhibitors

This class of medicinal products includes acid inhibitors more potent than H<sub>2</sub> receptor antagonists; they block the secretion of gastric acid proton pump (Na<sup>+</sup> / H<sup>+</sup> -ATP-ase), the final common path of the secretion. This class is recommended as part of a regimen of medications in symptomatic patients with *H. pylori* infection. Similar to H<sub>2</sub>-receptor blocking treatment, proton pump inhibitor (PPI) treatment only does not eliminate the *H. pylori* infection, but increases the bacteriostatic activity against *H. pylori*.

Examples of trade names depending on the active substance:

- Omeprazole: Omeprazole<sup>®</sup>, Prilosec<sup>®</sup>, Omez<sup>®</sup>, Omeran<sup>®</sup>, Ulto<sup>®</sup> (available within 10, 20 or 40 mg per tablet)
- Esomeprazole: Nexium<sup>®</sup>, Emanera<sup>®</sup>, Helide<sup>®</sup>, Esomeprazole Sandoz<sup>®</sup> (20 or 40 mg)
- Pantoprazole: Controlo<sup>®</sup>, Nolpaza<sup>®</sup> (20 or 40 mg per tablet)
- Lansoprazol: Prevacid<sup>®</sup>, Lanzul<sup>®</sup> 30mg

Proton Pump Inhibitors are potent gastric acid blockers. For best effectiveness, to be administered before the first meal of the day. Enteric film-coated granules in capsules, they ensure adequate bioavailability. For children unable to swallow whole capsules, the grains are opened and put in acid substances (e.g. apple juice), which is preferable to administer to the lower bioavailability suspension. Available as 10 or 20 mg SR capsules and granules for suspension *per os* 20 or 40 mg/package.

### Lansoprazole (Prevacid<sup>®</sup>)

Potent gastric acid blocker. Best administered just before the first meal of the day. Enteric film-coated granules in capsules, ensuring adequate bioavailability. For children unable to swallow the intact capsules, granules are placed in acid substances (e.g., applesauce or apple juice), preferable to the administration of lower bioavailable suspension. Available as capsules with 15 or 30 mg retard release and 15 mg or 30mg/package granules for suspension *per os*. [75-85]

### Bismuth

Bismuth subsalicylate and bismuth subcitrate have complementary effects with most antimicrobials. Bismuth disrupts enzymatic activity in bacterial cell walls. Bismuth is particularly effective in the lysis of the cell wall of the microorganism when close to the gastric epithelium and relatively inaccessible to most antimicrobial agents.

### Bismuth subsalicylate (Pepto-Bismol<sup>®</sup>)

These lyse bacterial cell walls, prevent microorganism adhesion to epithelium and inhibit *urease*.

Available as 262 mg chewable tablets (bismuth subsalicylate) and 262mg or 525mg/15ml solution.

Bismuth subcitrate (De - Nol®) acts similarly. The patient should be warned against normal black stools during the treatment administration.

### Patient care

In children with *H. pylori* and complications of the peptic ulcer disease (PUD), including bleeding, severe pain, perforation, or obstruction, care must include the following [86-106]:

- Attention to the airway, breathing and circulatory status
- Monitoring of fluid resuscitation, with consideration for transfusion
- Careful nasogastric lavage in stabilization of upper gastro-intestinal bleeding
- Antacid therapy with proton pump inhibitors (PPIs), maximum dosage
- Appropriate consultation with specialists in endoscopy or other procedures
- In children with stress-induced PUD, the treatment of the severe disease or traumatic injury
- additional outpatient care includes monitoring the patient's symptoms, assessment of patient tolerance to treatment regimen, and follow-up tests to confirm the effectiveness of the treatment. The tests should be conducted at least 6 weeks and preferably 3 months after treatment.

### Outpatient treatment of patients

- Patients should avoid all irritating drugs, including anti-inflammatory drugs (NSAIDs), aspirin, and preparations with corticosteroid
- It is necessary for the treatment of iron deficiency anaemia.

### Prophylactic measures

- The transmission mode of *H. pylori* infection is not fully understood.
- Data from epidemiological studies suggest that the following measures may be helpful to reduce transmission:
- Policies supporting improvement of living conditions, particularly in developing countries;
- For all patients with chronic symptoms of the gastro-intestinal tract, appropriate reference for definitive diagnosis and treatment, which may also help to prevent exposure of family members and close contacts.[103-111]
- *H. pylori* infection vaccines: several studies performed with *urease* -based vaccines have shown limited efficacy in humans. Vaccines based on recombinant CagA-VacA-0AP proteins display good immunogenicity of CagA - based cow - 0AP good immunogenicity and safety profile in phase I, but no subsequent efficacy studies have been reported. No further results from clinical trials on *H. pylori* vaccines have been reported in recent years. Currently, there is no authorised anti - *H. pylori* vaccine [74].

### *H. pylori* Complications

- PUD - perforation, gastrointestinal bleeding

- Iron deficiency anaemia
- Malignancies of:- The gastric mucosa associated to lymphoid tissue (MALT) - Adenocarcinoma of the gastric corpus, and the antrum
- Gastric outlet obstruction
- Increased sensitivity to enteric infections such as salmonella and giardiasis because of *H. pylori*-induced hypochlorhydria [92, 96]

## 14. Prospects study

1. Prospects for the eradication of *H. pylori* infection with multidrug therapy are good, with up to 95% reported efficacy rates.
2. Treatment is often unsuccessful because of lack of patient compliance and antibiotic resistance.
3. When cleaning is completed, long-term reinfection rates are low. Among children living in developing countries or among families with infected members, reinfection rates may be increased.
4. In this moment, the nature of *H. pylori* infection transmission is not fully understood. Therefore, the ability to implement appropriate preventive measures to control the infection is limited.
5. The theory concerning *H. pylori* person-to-person transmission, supported by data from epidemiological studies, may prove useful in promoting policies to improve the living and hygiene conditions and reduce crowdedness.
6. The true effect of educational authorities to reduce transmission of *H. pylori* in the patient's family (e.g., teaching children about proper hygiene and toilet practices) is unknown. However, such efforts may be part of a sensible approach to reducing the transmission of all infection pathogens in the infection of the gastrointestinal tract [109-111].

## 15. Conclusions

The infection with *H. pylori* is a common problem in pediatric practice and its origin is related with poor socio-economic conditions. Only a small number of children with well-defined clinical syndromes are benefited at present from testing and treatment.

The first line eradication regimens are triple therapy with a PPI, amoxicillin and imidazole, or PPI, amoxicillin, clarithromycin and amoxicillin or bismuth salts and imidazole or sequential therapy.



Each country may need to be adapted the recommendations guidelines to national health care systems, because certain tests or treatment regimens may not be available and /or reimbursed by health insurance programs.

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